Phenyl-Substituted Methicones

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EXPERT PANEL MEETING
September 26-27, 2022

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 18, 2022

SUBJECT: Diphenyl Dimethicone, Phenyl Methicone, Phenyl Trimethicone and Trimethylsiloxyphenyl Dimethicone

Anonymous. 2004. 13-Week toxicity study by oral route (gavage) in rats (mixture containing 15% Diphenyl Dimethicone).

Anonymous. 2006. Clinical study for the verification of the absence of sensitising potential and of the good cutaneous compatibility of a cosmetic test article, by repeated cutaneous applications under occlusive patch on 112 (or 111) healthy adult subjects (product contains 2% Diphenyl Dimethicone).

Anonymous. 2003. Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA) (test material contains 15% Diphenyl Dimethicone).

Anonymous. 2009. Repeated insult patch test (Marzulli and Maibach Method) (test material contains 0.2% Phenyl Methicone).

Anonymous. 2009. Repeated insult patch test (test material contains 28.67% Phenyl Trimethicone).

Anonymous. 2011. Repeated insult patch test (test material contains 38.006% Trimethylsiloxyphenyl Dimethicone).

[redacted]

[redacted]

[redacted]

STUDY TITLE
13-WEEK TOXICITY STUDY
BY ORAL ROUTE (GAVAGE) IN RATS

Mixture containing Diphenyl Dimethicone at 15%

[redacted]

EXPERIMENTAL COMPLETION DATE
04 September 2003

DATE OF ISSUE
13 october 2004

[redacted]

Volume 1

[redacted]

CONTENTS

[redacted]

STATEMENT OF THE STUDY DIRECTOR

The study was conducted in compliance with the following Good Laboratory Practice regulations:

- OECD Principles on Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98) 17,
- 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 harmonization 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 (OJ No. L 77 of 23.3.1999),
- Décret N° 98-1312 du 31 décembre 1998 concernant les Bonnes Pratiques de Laboratoire (Journal Officiel du 1er janvier 1999), Ministère de l'Economie, des Finances et de l'Industrie,
- US Environmental Protection Agency, Federal Register, 40 CFR Part 792; Toxic Substances Control Act; Good Laboratory Practice Standards, August 17, 1989 (and subsequent amendments).

The study was conducted in compliance with Animal Health regulation, in particular:

- Council Directive No. 86/609/EEC of 24th November 1986 on the harmonization of laws, regulations or administrative provisions relating to the protection of animals used for experimental or other scientific purposes.

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained during the performance of the study.

[redacted]

[redacted]

STATEMENT OF QUALITY ASSURANCE UNIT

Type of inspection	Dates		
	Inspection	Reported to Study Director (*)	Reported to Management (*)
Study plan	26 May 2003	27 May 2003	28 May 2003
Study	02 June 2003	04 June 2003	04 June 2003
Study	31 July 2003	04 August 2003	21 August 2003
Study	01 August 2003	04 August 2003	07 August 2003
Study	01 August 2003	04 August 2003	07 August 2003
Study	01 August 2003	04 August 2003	08 August 2003
Study	31 March 2004	02 April 2004	20 April 2004
Study	01 April 2004	02 April 2004	28 April 2004
Report	31 March 2004	02 April 2004	12 May 2004

In addition to the above-mentioned inspections, at about the same time as this study described in the present report, process-based and routine facility inspections of critical procedures relevant to this study were also made by the Quality Assurance Unit.
The findings of these inspections were reported to the Study Director and to [redacted]

The inspections were performed in compliance with [redacted] procedures and Principles of Good Laboratory Practice.

The reported methods and procedures were found to describe those used and the results to constitute an accurate and complete reflection of the study raw data.

[redacted]

(*) The dates indicated correspond to the dates of signature of audit reports by Study Director and Management.

SUMMARY

The objective of this study was to evaluate the potential toxicity of the test item, [redacted], following daily oral administration (gavage) to rats for 13 weeks.

Methods

Three treated groups of 10 male and 10 female Sprague-Dawley rats received the test item, [redacted] daily by gavage at 5, 20 or 80 mg/kg/day for 13 weeks. An additional group of 10 males and 10 females received the vehicle alone (10% Solutol® HS 15 in purified water) and acted as a control group.
The animals were checked daily for mortality and clinical signs. Detailed clinical observations were carried out weekly, and a functional observation battery (including motor activity) was performed at the end of the treatment period. Body weight and food consumption were recorded weekly. Ophthalmological examination was performed before the beginning of the treatment period on all animals and at the end of the treatment period for control animals and those given 80 mg/kg/day. Hematological, blood biochemical investigations and urinalysis were performed at the end of the treatment period.
On completion of the treatment period, the animals were killed and submitted to a complete macroscopic *post-mortem* examination. Designated organs were weighed and selected tissue specimens were preserved. A microscopic examination was performed on selected tissues of control animals and those given 80 mg/kg/day, and on macroscopic lesions and liver of all animals.

Results

Mortality
There were no deaths related to treatment with the test item.

Clinical signs
There were no clinical signs of toxicological significance.
Ptyalism was noted in animals given 20 and 80 mg/kg/day; this is a common sign noted when test item is administered by gavage and it was therefore not considered as an adverse effect.

Detailed clinical observation and functional observation battery (FOB)
The detailed clinical observation, functional observation battery and motor activity revealed no perturbation of the autonomic or physiological functions in any treated group.

Body weight and food consumption
The body weight and food consumption were unaffected by treatment with the test item.

Ophthalmology
There were no ophthalmological findings at the end of the treatment period.

Hematology
Higher prothrombin time was noted in males given 80 mg/kg/day (+3.8 s when compared to controls).

Blood biochemistry
There were no differences of toxicological significance between control and treated animals.

Urinalysis
There were no relevant qualitative or quantitative differences between control and treated animals at any dose-level.

Organ weights
When compared to controls, higher liver weight was noted in females given 5 and 20 mg/kg/day (+11 and +16% in relative weight, respectively) and in animals given 80 mg/kg/day (+24 and +31% in relative weight, in males and females, respectively).

Macroscopic examination
Liver enlargement was noted in few males given 80 mg/kg/day.

Microscopic examination
Minimal to moderate hepatocellular hypertrophy was observed in almost all animals given 80 mg/kg/day.

Conclusion

The test item, [redacted] was administered daily to Sprague-Dawley rats by gavage at 5, 20 or 80 mg/kg/day for 13 weeks.
There were no deaths related to [redacted] no clinical signs of toxicological significance or effects on body weight and food consumption at any dose-level. No salient differences were noted among hematological and blood biochemistry parameters, apart from a slightly higher prothrombin time in males given 80 mg/kg/day.
The main finding related to treatment with the test item was seen at microscopic examination of the liver in animals given 80 mg/kg/day; hepatocellular hypertrophy was observed in animals given this high dose-level, correlated with higher liver weight at necropsy. A slightly higher liver weight was also noted in females given 5 or 20 mg/kg/day, but in the absence of associated histopathological findings, these slight changes were considered to be of no toxicological significance.
Consequently, under the conditions of the study, the No Observed Adverse Effect Level (NOAEL) was established at 20 mg/kg/day.

1. INTRODUCTION

1.1 OBJECTIVE

The objective of this study was to evaluate the potential toxicity of the test item, [redacted], following daily oral administration (gavage) to rats for 13 weeks.

The rat was chosen because it is a rodent species commonly accepted by regulatory authorities for this type of study, and the Sprague-Dawley strain was selected since background data from previous studies are available at our laboratory.
The oral route was selected since it is an anticipated route of secondary human exposure.
[redacted]

1.2 REGULATORY COMPLIANCE

The study was designed to comply with the following guidelines:
. Commission Directive 87/302, B 26, 30 May 1988,
. OECD Guideline No. 408, 21 September 1998.

2. MATERIALS AND METHODS

2.1 TEST AND CONTROL ITEMS

2.1.1 Identification

2.1.1.1 Test item

[redacted]

. Description : colorless viscous liquid
. Container : two plastic containers
. Date of receipt : 26 February 2003
. Storage conditions : at room temperature and protected from light.

An analytical certificate is presented in Appendix 1.
Characterization of the test item, which appropriately defines the tested batch, is under the responsibility of the Sponsor.

2.1.1.2 Vehicle

. Name: 10% Solutol® HS 15 in purified water

Solutol® HS 15 corresponds to polyethylene glycol 660 hydroxystearate.

The vehicle was prepared using:
. Solutol® HS 15, batch No. 591768, supplied by Laserson (Etampes, France),
. purified water, obtained by reverse osmosis using a Milli-Ro 8 plus apparatus (Millipore SA, Saint-Quentin en Yvelines, France).

2.1.2 Dosage form preparation

The test item was administered as a suspension in the vehicle; the test item was mixed with the required quantity of vehicle.

The required amount of Solutol® HS 15 was weighed, transferred to a beaker and heated to 70°C. Then, the Solutol® HS 15 was added to the required amount of the test item. The test item and Solutol® HS 15 were mixed together and heated up to 70°C.
When a clear phase was obtained, the prewarmed purified water (50-70°C) was added slowly in order to achieve the required concentrations of test item and then mixed using a magnetic stirrer.
The test item dosage forms were prepared on a weekly basis (according to the stability data) and stored at room temperature, protected from light prior to use.

2.1.3 Chemical analysis of the dosage forms

All the analyses were performed by [redacted] after validation of the analytical method provided by the Sponsor.

2.1.3.1 Homogeneity

Before the start of treatment, dosage forms were prepared, under conditions representative of those of the study as follows:

. a dosage form at 0.5 mg/mL,
. a dosage form at 1 and 8 mg/mL,
. a dosage form at 10 mg/mL.

From each dosage form, duplicate samples were taken at three different levels of the container (top, middle, bottom) on day 0 (just after preparation for all concentrations) and on day 9 (for 0.5 mg/mL and 8 mg/mL) after storage at +4°C. Samples were analyzed for concentration of the test item to evaluate the homogeneity.

Due an analytical problem, the homogeneity for 10 mg/mL was checked on day 1, instead of day 0.

2.1.3.2 Stability

Each dosage form prepared for homogeneity analysis was stored at 4°C, protected from light and sampled after 0, 4 and 9 days storage.

The aliquot sampled on day 4 was analyzed immediately after sampling (for 1 and 10 mg/mL), or stored frozen at -20°C pending analysis on last sampling occasion when all samples were assayed (for 0.5 and 8 mg/mL).

In each case, the mean result of the homogeneity analysis was taken as the initial value for the stability test.

2.1.3.3 Concentration

The concentration of samples taken from each dosage form (including the control) prepared for use in weeks 1, 4, 8 and 13 was determined.

2.2 TEST SYSTEM

2.2.1 Animals

Number: 88 rats (44 males and 44 females) were received at [redacted] on 27 May 2003.

Strain and Sanitary status: Sprague-Dawley, Crl CD® (SD) IGS BR, *Cesarian Obtained, Barrier Sustained-Virus Antibody Free* (COBS-VAF®).

Breeder: Charles River Laboratories France, l'Arbresle, France.

Age/Weight: on the first day of treatment, the animals were approximately 6 weeks old and had a mean body weight of 208 g (range: 172 g to 235 g) for the males and 171 g (range: 153 g to 201 g) for the females.

Receipt: on arrival, the animals were given a clinical examination to ensure that they were in good condition.

Acclimation: a 7-day acclimation period to the conditions of the study preceded the beginning of the treatment period. A larger number of animals than necessary was acclimated to permit selection and/or replacement of individuals.

Allocation to groups: during the acclimation period, the required number of animals (40 males and 40 females) was selected according to body weight and clinical condition and allocated to the groups (by sex), according to a computerized stratification procedure, so that the average body weight of each group was similar.

Identification: each animal was identified by an individual ear tattoo. At the beginning of the study, each animal received a unique [redacted]identity number.

2.2.2 Environmental conditions

From arrival at [redacted] the animals were housed in a barriered rodent unit, under specific pathogen free (SPF) standard laboratory conditions.
The animal room conditions are set as follows:

- temperature : 22 ± 2°C
- relative humidity : 50 ± 20%
- light/dark cycle : 12h/12h (7:00 - 19:00)
- ventilation : approximately 12 cycles/hour of filtered, non-recycled air.

The corresponding instrumentation and equipment are checked and calibrated at regular intervals. The temperature and relative humidity are recorded continuously and the records checked daily and filed.
The animal room was disinfected before the arrival of the animals and cleaned regularly thereafter.

2.2.3 Housing

The animals were housed in suspended wire-mesh cages (43.0 x 21.5 x 18.0 cm) and each cage contained two rats of the same sex and group. A metal tray, containing autoclaved sawdust (SICSA, Alfortville, France), was placed under each cage.
The cages were placed in numerical order on the racks. On a monthly basis, all the racks were moved clockwise around the room, rack by rack. In this way, for each group, identical exposure to environmental conditions was achieved.

2.2.4 Food and water

The animals had free access to A04 C pelleted maintenance diet (batch Nos. 30407, 30423, 30514 and 30616 - SAFE, Villemoisson, Epinay-sur-Orge, France) distributed weekly. The diet formula is presented in Appendix 3.
The animals had free access to bottles containing tap water (filtered with a 0.22 µm filter).

2.2.5 Contaminant analyses

The batches of diet and sawdust were analyzed by the suppliers for composition and contaminant levels.
Bacterial and chemical analyses of water are performed regularly by external laboratories. These analyses include the detection of possible contaminants (pesticides, heavy metals and nitrosamines).

No contaminants were present in the diet, drinking water or sawdust at levels which may be expected to interfere with or prejudice the outcome of the study.

2.3 TREATMENT

2.3.1 Treatment groups

Rationale for dose-level selection

[redacted]

The treatment groups are detailed in the following table:

Group	Number of animals	Dose-level (mg/kg/day)	Animal number
1	10 males 10 females		C24681 to C24686, C24688 to C24690, and C24721 C24751 to C24760
2	10 males 10 females	5	C24691 to C24700 C24761 to C24770
3	10 males 10 females	20	C24701 to C24710 C24771 to C24780
4	10 males 10 females	80	C24711 to C24720 C24781 to C24790

2.3.2 Duration

The dosage forms were administered daily for a period of 92 or 93 days, according to the necropsy schedule.
Day 1 corresponds to the first day of the treatment period.

2.3.3 Administration

The oral route was selected since it is an anticipated route of secondary human exposure.
The dosage forms were administered by gavage using a plastic syringe fitted with a metal gavage tube, once a day, at approximately the same time.
The quantity of dosage form administered to each animal was adjusted according to the most recently recorded body weight.
A constant dosage-volume of 10 mL/kg/day was used.
Control animals (group 1) received the vehicle alone.
The dosage forms were stirred continuously throughout the dosing procedure.

2.4 CLINICAL EXAMINATIONS

2.4.1 Morbidity and mortality

Each animal was checked at least twice a day, including weekends and public holidays, for mortality or signs of morbidity during the treatment period.

2.4.2 General clinical signs

Each animal was observed at least once a day, at approximately the same time, for the recording of clinical signs during the treatment period.

2.4.3 Detailed clinical observations

Detailed clinical observations were made on all animals outside the home cage, in a standard arena, once before the beginning of the treatment period and then once a week until the end of the study.
Observations included (but not limited to) changes in the skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g. lachrymation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypes (e.g. excessive grooming, repetitive circling) or bizarre behavior (e.g. self-mutilation, walking backwards) were also recorded.

2.4.4 Functional Observation Battery (FOB)

All animals were evaluated in week 12 (before the blood sampling - see § Laboratory Investigations).
This included a detailed clinical examination, measurement of reactivity to manipulation or to different stimuli and motor activity.
The animals were randomized.
All animals were observed in the cage, in the hand and in the standard arena.
The following parameters were assessed and graded:

- "touch escape" or ease of removal from the cage,
- in the hand: fur appearance, salivation, lachrymation, piloerection, exophthalmia, reactivity to handling, pupil size (presence of myosis or mydriasis),
- in the standard arena (two-minute recording): grooming, palpebral closure, defecation, urination, tremors, twitches, convulsions, gait, arousal (hypo-and hyper-activity), posture, stereotypes, behavior, breathing, ataxia and hypotonia.

Then, the following parameter measurements, reflexes and responses were recorded:

- touch response,
- forelimb grip strength,
- pupil reflex,
- visual stimulus,
- auditory startle reflex,
- tail pinch response,
- righting reflex,
- landing foot splay,
- rectal temperature.

Motor activity of all animals was measured by automated infra-red sensor equipment over a 15-minute period.

2.4.5 Body weight

The body weight of each animal was recorded once before allocation of the animals to groups, on the first day of treatment, and then once a week until the end of the study.

2.4.6 Food consumption

The quantity of food consumed by the animals of each cage was recorded once a week, over a 7-day period, during the study.
Food consumption was calculated per animal and per day. When one of the two animals from the same cage died, the number of days for which that animal was present in the cage was taken into consideration for the calculation of the food consumption.

2.4.7 Ophthalmology

Ophthalmological examinations were performed on all animals before the beginning of the treatment period and on animals of the control and high-dose groups on one occasion at the end of the treatment period.
The pupils of the animals were dilated with tropicamide (Mydriaticum®, Merck Sharp & Dohme - Chibret, Paris, France). After assessment of the corneal reflex (by instillation of tropicamide), the appendages, optic media and fundus were examined by indirect ophthalmoscopy.

2.5 LABORATORY INVESTIGATIONS

2.5.1 Blood and urine collection

Blood samples were taken from the orbital sinus of the animals (before the daily treatment) under isoflurane anesthesia and collected into tubes containing the appropriate anticoagulant (see following tables).
Prior to blood sampling and during urine collection, the animals were deprived of food.
For urine collection, the animals were individually placed in metabolism cages for an overnight period of at least 14 hours. The urine was collected in the presence of thymol crystals.

2.5.2 Hematology

2.5.2.1 Peripheral blood

The following parameters were determined for all animals at the end of the treatment period.

Parameter	Apparatus/Method	Unit
EDTA tubes		
Erythrocytes (RBC)	Bayer Diagnostics H1 Hematology Analyzer/laser	T/L
Hemoglobin (HB)	Bayer Diagnostics H1 Hematology Analyzer/Drabkin	g/dL
Mean cell volume (MCV)	Bayer Diagnostics H1 Hematology Analyzer/laser	fL
Packed cell volume (PCV)	Bayer Diagnostics H1 Hematology Analyzer/calculated	L/L
Mean cell hemoglobin concentration (MCHC)	Bayer Diagnostics H1 Hematology Analyzer/calculated/ laser	g/dL
Mean cell hemoglobin (MCH)	Bayer Diagnostics H1 Hematology Analyzer/calculated	pg
Thrombocytes (PLAT)	Bayer Diagnostics H1 Hematology Analyzer/laser	G/L
Leucocytes (WBC)	Bayer Diagnostics H1 Hematology Analyzer/ peroxidase cytochemistry/laser morphometry	G/L
Differential white cell count with cell morphology	Bayer Diagnostics H1 Hematology Analyzer/ peroxidase cytochemistry/laser morphometry (a)	
. neutrophils (N)		G/L
. eosinophils (E)		G/L
. basophils (B)		G/L
. lymphocytes (L)		G/L
. monocytes (M)		G/L
Reticulocytes (RETIC) (b)	Bright cresyl blue staining	
Sodium citrate tubes		
Prothrombin time (PT)	ACL 300/Thromboplastin (IL France)	s

(a): blood smears were prepared from all sampled animals. If the samples were not accepted by the H1 Analyzer, a microscopic evaluation was performed after May Grünwald Giemsa staining.

(b): blood smears were prepared from all sampled animals. The reticulocyte count was not determined.

2.5.2.2 Bone marrow

Bone marrow smears were prepared at necropsy from the femoral bone of all animals killed on completion of the treatment period.

Parameter	Method
Bone marrow differential cell count	May Grünwald Giemsa staining

In the absence of effect on hematology parameters, the bone marrow differential cell count was not determined.

2.5.3 Blood biochemistry

The following parameters were determined for all animals at the end of the treatment period.

Parameter	Apparatus/Method	Unit
Lithium heparin tubes		
Sodium (Na^+)	Hitachi 717 / Selective electrode (Roche)	mmol/L
Potassium (K^+)	Hitachi 717 / Selective electrode (Roche)	mmol/L
Chloride (Cl^-)	Hitachi 717 / Selective electrode (Roche)	mmol/L
Calcium (Ca^{++})	Hitachi 717 / Ortho-cresolphthalein (Roche)	mmol/L
Inorganic phosphorus (I.PHOS)	Hitachi 717 / Phosphomolybdic reaction (Roche)	mmol/L
Glucose (GLUC)	Hitachi 717 / GOD-PAP (Roche)	mmol/L
Urea (UREA)	Hitachi 717 / Urease UV (Roche)	mmol/L
Creatinine (CREAT)	Hitachi 717 / Jaffé without deproteinization (Roche)	µmol/L
Total bilirubin (TOT.BIL)	Hitachi 717 / Jendrassik (Roche)	µmol/L
Total proteins (PROT)	Hitachi 717 / Biuret (Roche)	g/L
Albumin (ALB)	Hitachi 717 / Bromocresol green (Roche)	g/L
Albumin/globulin ratio (A/G)	Hitachi 717 / Calculated	
Cholesterol (CHOL)	Hitachi 717 / CHOD-PAP (Roche)	mmol/L
Triglycerides (TRIG)	Hitachi 717 / GPO-PAP (Roche)	mmol/L
Alkaline phosphatase (ALP)	Hitachi 717/ DGKC Standard/30°C (Roche)	IU/L
Aspartate aminotransferase (ASAT)	Hitachi 717 IFCC Standard/30°C (Roche)	IU/L
Alanine aminotransferase (ALAT)	Hitachi 717 IFCC Standard/30°C (Roche)	IU/L

2.5.4 Urinalysis

The following parameters were determined for all animals at the end of the treatment period.

Parameter	Apparatus/Method	Unit
Quantitative parameters		
Volume (VOLUME)		mL
pH (pH)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	
Specific gravity (SP.GRAV)	Refractometer (x 1000)	
Semi-quantitative parameters		
Proteins (PROT)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	(a)
Glucose (GLUC)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	(a)
Ketones (CETO)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	(a)
Bilirubin (BILI)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	(a)
Nitrites (NITR)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	(a)
Blood (BLOOD)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	(a)
Urobilinogen (UROB)	Clinitek 500 / 10-Multistix SG test strips (Bayer)	(a)
Cytology of sediment	Microscopic	
. leucocytes (WBC)		(a)
. erythrocytes (RBC)		(a)
. cylinders (CYLIN)		(a)
. magnesium ammonium phosphate crystals (AMM.PH)		(a)
. calcium phosphate crystals (CAL.PH)		(a)
. calcium oxalate crystals (CAL.OX.)		(a)
. cells (CELLS)		(a)
Qualitative parameters		
Appearance (APP)		(a)
Color (COLOR)		(a)

(a): see key or grading of cell frequency in Appendix with individual values.

2.6 PATHOLOGY

2.6.1 Sacrifice

On completion of the treatment period, after at least 14 hours fasting, all surviving animals were asphyxiated by carbon dioxide and killed by exsanguination.

2.6.2 Organ weights

The body weight of all animals killed at the end of the treatment period was recorded before sacrifice, and the organs specified in the Tissue Procedure Table were weighed wet as soon as possible after dissection.
The ratio of organ weight to body weight (recorded immediately before sacrifice) was calculated.

2.6.3 Macroscopic *post-mortem* examination

A complete macroscopic *post-mortem* examination was performed on all study animals. This included examination of the external surfaces, all orifices, the cranial cavity, the external surfaces of the brain and spinal cord, the thoracic, abdominal and pelvic cavities with their associated organs and tissues and the neck with its associated organs and tissues.

2.6.4 Preservation of tissues

For all study animals, the tissues specified in the Tissue Procedure Table were preserved in 10% buffered formalin (except for the eyes and Harderian glands which were fixed in Davidson's fixative, and the testes and epididymides which were preserved in Bouin's fluid).

2.6.5 Preparation of histological slides

All tissues required for microscopic examination were embedded in paraffin wax, sectioned at a thickness of approximately 4 microns and stained with hematoxylin-eosin (except testes and epididymides which were stained with hematoxylin/PAS).

2.6.6 Microscopic examination

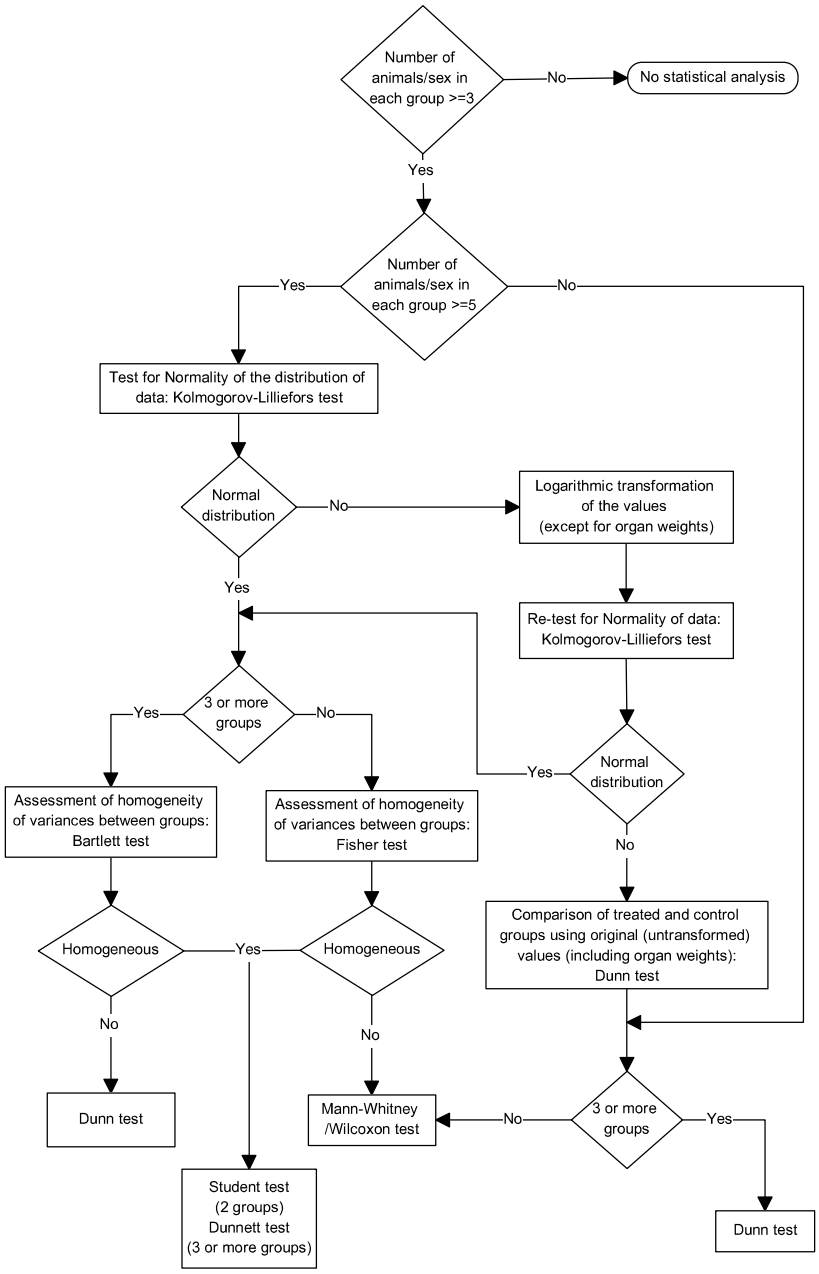
A microscopic examination was performed on:
. all tissues listed in the Tissue Procedure Table for animals of the control and high-dose groups (groups 1 and 4),
. all macroscopic lesions and liver of the animals of the low- and intermediate-dose groups (groups 2 and 3).

TISSUE PROCEDURE TABLE

Organs	Organ weights	Preservation of tissues	Microscopic examination
Macroscopic lesions		X	X
Adrenals	X	X	X
Aorta		X	X
Brain (including medulla/pons cerebellar and cerebral cortex)	X	X	X
Cecum		X	X
Colon		X	X
Duodenum		X	X
Epididymides	X	X	X
Esophagus		X	X
Eyes with Harderian glands		X	X
Femoral bone with articulation		X	
Heart	X	X	X
Ileum		X	X
Jejunum		X	X
Kidneys	X	X	X
Liver	X	X	X
Lungs with bronchi		X	X
Lymph nodes (mandibular and mesenteric)		X	X
Mammary glands/area		X	X
Ovaries	X	X	X
Pancreas		X	X
Pituitary gland		X	X
Prostate		X	X
Rectum		X	X
Salivary glands (sublingual and submandibular)		X	X
Sciatic nerve		X	X
Seminal vesicles		X	X
Skeletal muscle		X	
Skin		X	X
Spinal cord (cervical, thoracic and lumbar)		X	X
Spleen	X	X	X
Sternum with bone marrow		X	X
Stomach with forestomach		X	X
Testes	X	X	X
Thymus	X	X	X
Thyroids with parathyroids	X	X	X
Tongue		X	
Trachea		X	X
Urinary bladder		X	X
Uterus (horns and cervix)	X	X	X
Vagina		X	X

2.7 STATISTICAL ANALYSIS

The following sequence was used for the statistical analyses of body weight, food consumption, hematology, blood biochemistry, urinalysis and organ weight data:



2.8 ARCHIVING

The following study materials are retained in the archives of [redacted] for 10 years after the end of the *in vivo* phase of the study:

. Study plan and amendments,
. raw data,
. correspondence,
. final report and possible amendments,
. tissues in preservative, blocks and histological slides,
. hematological slides,
. sample of the test item.

On completion of this period, the archived study materials will be returned to the Sponsor, or may be archived at [redacted] for a further period.
The total duration of archiving (depending on regulations) is the responsibility of the Sponsor.
In addition, raw data not specific to the study, including but not limited to certificates of analyses for food, water and sawdust and records of environmental data and equipment calibration are also archived at [redacted] for at least 30 years.
At the end of the utilization, all remaining test item (excluding the archive sample) is returned to the Sponsor.

2.9 CHRONOLOGY OF THE STUDY

The chronology of the study is summarized as follows:

Procedure	Date	Study day
Study plan approved by:		
. Study Director	28 May 2003	
. Study Monitor	4 June 2003	
Experimental starting date (first day of acclimation period)	27 May 2003	-7
. Pre-identification and weighing	28 May 2003	-6
. Randomization and identification	30 May 2003	-4
. Ophthalmology	2 June 2003	-1
First day of treatment period	3 June 2003	1
Weeks 12/13		
. Motor activity	21 August 2003	80
. Functional observation battery		
- males	21 August 2003	80
- females	22 August 2003	81
. Ophthalmology	26 August 2003	85
. Laboratory investigations	28 August 2003	87
First day of necropsy	3 September 2003	93
Experimental completion date (day of necropsy of last animal)	4 September 2003	94

2.10 STUDY PLAN ADHERENCE

The study was performed in accordance with Study plan [redacted] and subsequent amendments, with the following deviations from the agreed Study plan:

. some fluctuations in relative humidity and room temperature were noted outside of the range specified in the study plan during the study,
. chemical analyses of the preparations:
  - due to an analytical problem at the concentration of 10 mg/mL on day 0, the stability and homogeneity were also determined accordingly at the concentration of 8 mg/mL, and the homogeneity at 10 mg/mL was checked on day 1,
  - there was no reliant stability data at 0.5 and 8 mg/mL after 4 days of storage due to an analytical problem. However, the stability data were satisfactory after 9 days of storage,
. preservation of tissues: the pituitary gland for control female C24758 and the pancreas for control female C24751 were not preserved, by error.

These deviations were not considered to have compromised the validity or integrity of the study.

3. RESULTS

3.1 CHEMICAL ANALYSIS OF THE DOSAGE FORMS (Appendix 2)

3.1.1 Homogeneity

The results of the analyses demonstrated the homogeneity of each dosage form analyzed just after preparation (0.5, 1, 8 and 10 mg/mL) or after 9 days storage (0.5 and 8 mg/mL).
Furthermore, there was a satisfactory correspondence between the nominal and the measured concentrations of the test item in the vehicle.

3.1.2 Stability

The results of the analyses demonstrated a satisfactory stability of the same dosage forms stored for 9 days at +4°C, protected from light.

3.1.3 Concentration

Throughout the study, a satisfactory agreement was observed between the nominal and actual concentrations of the test item in the administered dosage forms since the deviations from nominal concentration were in an acceptable range of ± 10%.

3.2 CLINICAL EXAMINATIONS

3.2.1 Mortality (Appendix 4)

No deaths occurred during the study among animals receiving the test item.
One control female was found dead on day 22. No clinical signs were recorded prior to death. At necropsy, foamy contents were noted in lungs and trachea. At microscopic examination, marked acute bronchopneumonia was noted. Consequently, the cause of death was considered to be an accidental aspiration of the dosage form, probably related to misdosing.

3.2.2 Clinical signs (Tables 1 and 2, Appendix 5)

Ptyalism was noted with higher incidence in animals given 20 and 80 mg/kg/day (generally from week 5 or 6). Although this finding was considered to be test item-related, it is a common sign noted when the test item is administered by gavage and consequently, it is not considered as an adverse effect.
The other clinical signs observed (including scabs, area of hair loss or scattered hair) were noted in single animals and/or without dose-relationship. Consequently, they were not attributed to treatment with the test item.

3.2.3 Detailed clinical observation, functional observation battery (FOB) and motor activity (Tables 3 to 5, Appendix 6)

The detailed clinical observation, functional observation battery and motor activity revealed no perturbation of the autonomic or physiological functions in any treated group.

3.2.4 Body weight (Figures 1 and 2, Tables 6 and 7, Appendix 7)

The mean body weight gain was similar in control and treated animals throughout the treatment period.

3.2.5 Food consumption (Tables 8 and 9, Appendix 8)

The food consumption was not affected by treatment with the test item in any treated group.

3.2.6 Ophthalmology (Appendix 9)

There were no ophthalmological findings at the end of the treatment period.

3.3 LABORATORY INVESTIGATIONS

3.3.1 Hematology (Tables 10 and 11, Appendix 10)

Higher mean prothrombin time was noted in males given 80 mg/kg/day (19.5 s *vs.* 15.7 s in controls). Although not statistically significant, as 6/10 values were higher than the control values and than the historical background data, this was attributed to treatment with the test item.
When compared to controls, a lower mean leucocyte count (statistically significant) was noted in females given 5, 20 and 80 mg/kg/day (7.55, 6.35 and 5.26 G/L, respectively, vs. 9.61 G/L in controls). This was essentially due to a lower mean lymphocyte count (5.61, 4.61 and 4.01 G/L, respectively, vs. 7.59 G/L in controls). The individual values of treated animals remained within the range of or close to our historical background data, whereas the individual values of the control group were in the upper limit of this range (see Appendix 15; leucocyte: 3.75-11.91 G/L, lymphocyte: 3.20-10.33 G/L). Consequently, this finding was considered to be of no toxicological significance.

The other statistically significant differences from controls (including prothrombin time) were slight, without dose-relationship, lacked a similar trend in the two sexes and/or with the individual values within the range of our historical background data. Consequently, these differences were considered to be without relationship to treatment with the test item.

3.3.2 Blood biochemistry (Tables 12 and 13, Appendix 11)

Higher mean cholesterol level was noted in females given 80 mg/kg/day (2.5 mmol/L *vs.* 1.8 mmol/L). As all the individual values were within the range of our historical background data (1.3-3.5 mmol/L), this difference was considered to be without toxicological significance.
The other statistically significant differences from controls (including electrolyte levels, albumin/globulin ratio) were slight, without dose-relationship, lacked a similar trend in the two sexes and/or with the individual values within the range of our historical background data. Consequently, these differences were not considered to be of toxicological significance.

3.3.3 Urinalysis (Tables 14 and 15, Appendix 12)

There was no relevant qualitative or quantitative difference between control and treated animals at any dose-level.

3.4 PATHOLOGY

3.4.1 Organ weights (Table 16, Appendix 13)

The main difference in organ weights (expressed in % from controls) for treated animals were observed in the liver as indicated below:

	Males			Females		
Dose-level (mg/kg/day)	5	20	80	5	20	80
- Liver						
. absolute	-1	-2	+22**	+17*	+18**	+30**
. relative	+2	+3	+24**	+11*	+16**	+31**

Statistically significant from controls: * $p<0.05$; ** $p<0.01$.

In females given 5 and 20 mg/kg/day, the higher liver weights were attributed to treatment with the test item, but this change was considered without toxicological significance since not related to relevant microscopic changes.

The higher absolute and relative liver weights in animals given 80 mg/kg/day was considered to be treatment-related and well correlated with the hepatocellular hypertrophy noted among these animals (see § Microscopic examination).

Some other differences were observed in the mean weights of other organs, particularly adrenals, thymus, thyroids and uterus. As these differences in the mean weights were the contribution of a few individuals, not dose-related or were minor, and did not correlate with histopathological abnormalities, they were considered to be without toxicological significance.

3.4.2 Macroscopic *post-mortem* examination (Table 17, Appendix 14)

Enlargement of the liver was noted in 3/10 males given 80 mg/kg/day and correlated with higher liver weights and with minimal or slight hepatocellular hypertrophy. Consequently, this finding was considered to be related to treatment with the test item.

The few other macroscopic *post-mortem* observations noted were not dose-related and/or were those commonly recorded spontaneously in the untreated laboratory rat of this strain and age. They were thus considered to be without toxicological significance.

3.4.3 Microscopic examination (Tables 18 to 20, Appendix 14)

The treatment-related microscopic findings were noted in the liver as follows:

Incidence and severity of microscopic changes in the liver

	Males				Females			
Dose-level (mg/kg/day)	0	5	20	80	0	5	20	80
Hepatocellular hypertrophy	0/10	0/10	0/10	8/10 (1.5)	0/10	0/10	0/10	10/10 (1.7)

( ): mean severity.

Minimal to moderate hepatocellular hypertrophy was observed in 8/10 males and 10/10 females given 80 mg/kg/day, and generally correlated with a higher liver weight.
However, there were no histopathologic abnormalities indicative of cytoplasmic/nuclear degenerative/necrotic changes. Consequently, the hepatocellular hypertrophy most probably represents a demand for increased liver function at such high dose-level.
Hepatocellular hypertrophy was not found in any animals of group 2 (5 mg/kg/day) or group 3 (20 mg/kg/day).

In the pancreas, focal chronic inflammation of Langerhans islets was observed in 3/10 males given 80 mg/kg/day. Although not common, this finding can be found spontaneously in the untreated laboratory rat of this strain. Taking into consideration its low severity (minimal or slight) and its absence in the treated females, this finding was considered to be without toxicological significance.

All the other microscopic observations encountered (especially in the heart, kidneys, liver, lungs and pancreas) were minor and/or not dose-related and were those which are commonly recorded spontaneously in the untreated laboratory rat of this strain and age. Consequently, they were considered to be without relationship to treatment with the test item.

4. CONCLUSION

The test item, [redacted], was administered daily to Sprague-Dawley rats by gavage at 5, 20 or 80 mg/kg/day for 13 weeks.
There were no deaths related to [redacted], no clinical signs of toxicological significance or effects on body weight and food consumption at any dose-level. No salient differences were noted among hematological and blood biochemistry parameters, apart from a slightly higher prothrombin time in males given 80 mg/kg/day.
The main finding related to treatment with the test item was seen at microscopic examination of the liver in animals given 80 mg/kg/day; hepatocellular hypertrophy was observed in animals given this high dose-level, correlated with higher liver weight at necropsy. A slightly higher liver weight was also noted in females given 5 or 20 mg/kg/day, but in the absence of associated histopathological findings, these slight changes were considered to be of no toxicological significance.
Consequently, under the conditions of the study, the No Observed Adverse Effect Level (NOAEL) was established at 20 mg/kg/day.

5. BIBLIOGRAPHICAL REFERENCES

Bartlett M.S. (1937) A test for heterogeneity of variances. Proc. Roy. Soc. Amer. 160: 268-282.

Dunn J.O. (1964) Multiple comparisons using rank sums. Technometrics 6 (3): 241-252.

Dunnett C.W. (1955) A multiple comparison procedure for comparing several treatments with a control. J. Am. Stat. Assoc.: 1096-1121.

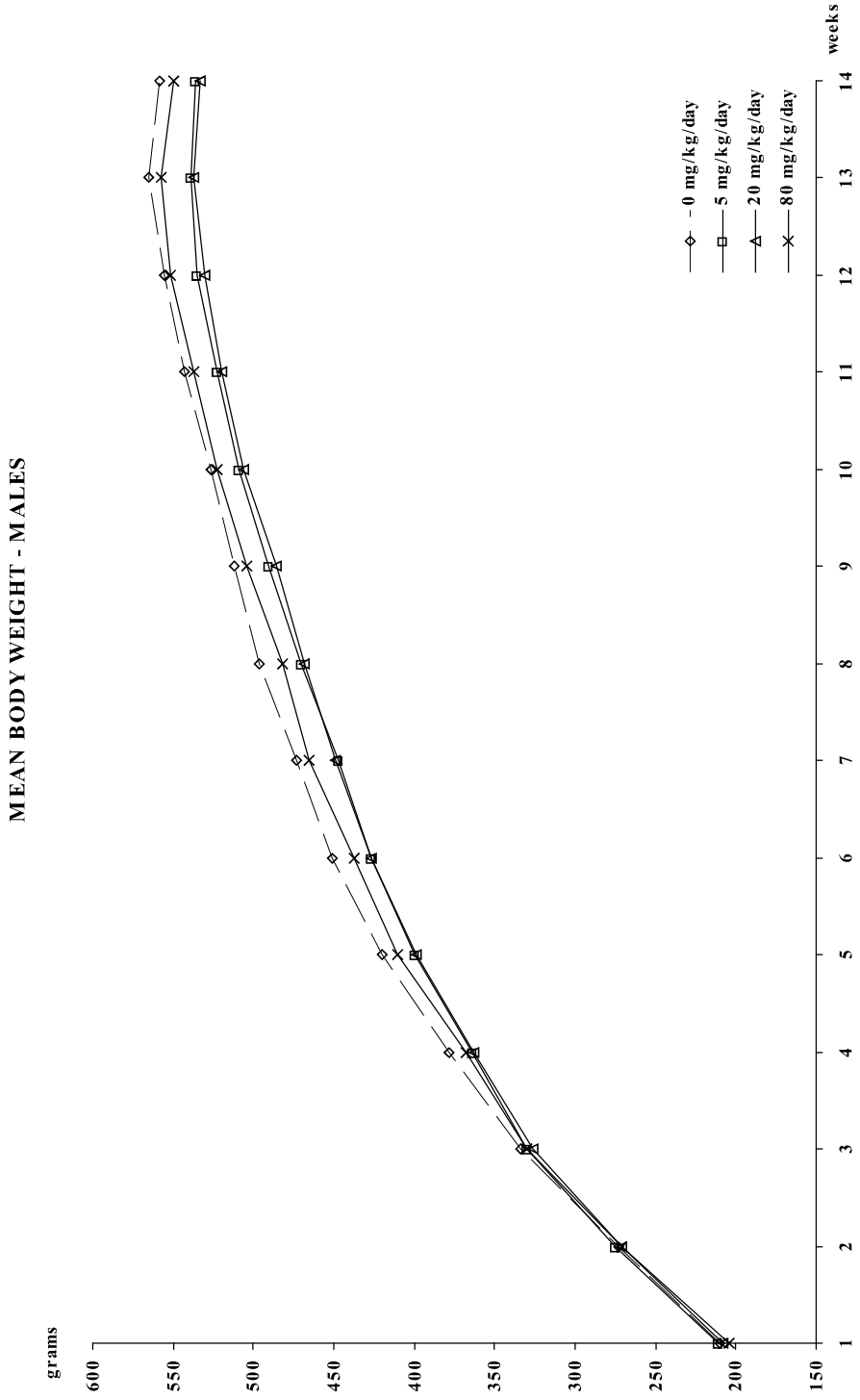
Fisher R.A. (1934) Statistical methods for research workers (5th ed). Edinburgh: Oliver and Boyd.

Lilliefors H.W. (1967) Normality test for samples of unknown mean and variances. J. Am. Stat. Assoc. 62: 399-402.

Mann H.B. and Whitney D.R. (1947) On a test of whether one of two random variables is stochastically larger than the other. Ann. Math. Statist. 18: 50-60.

Student W.S. (1908) The probable error of a mean. Biometrika 6: 1-25.

Figure 1


MEAN BODY WEIGHT - MALES
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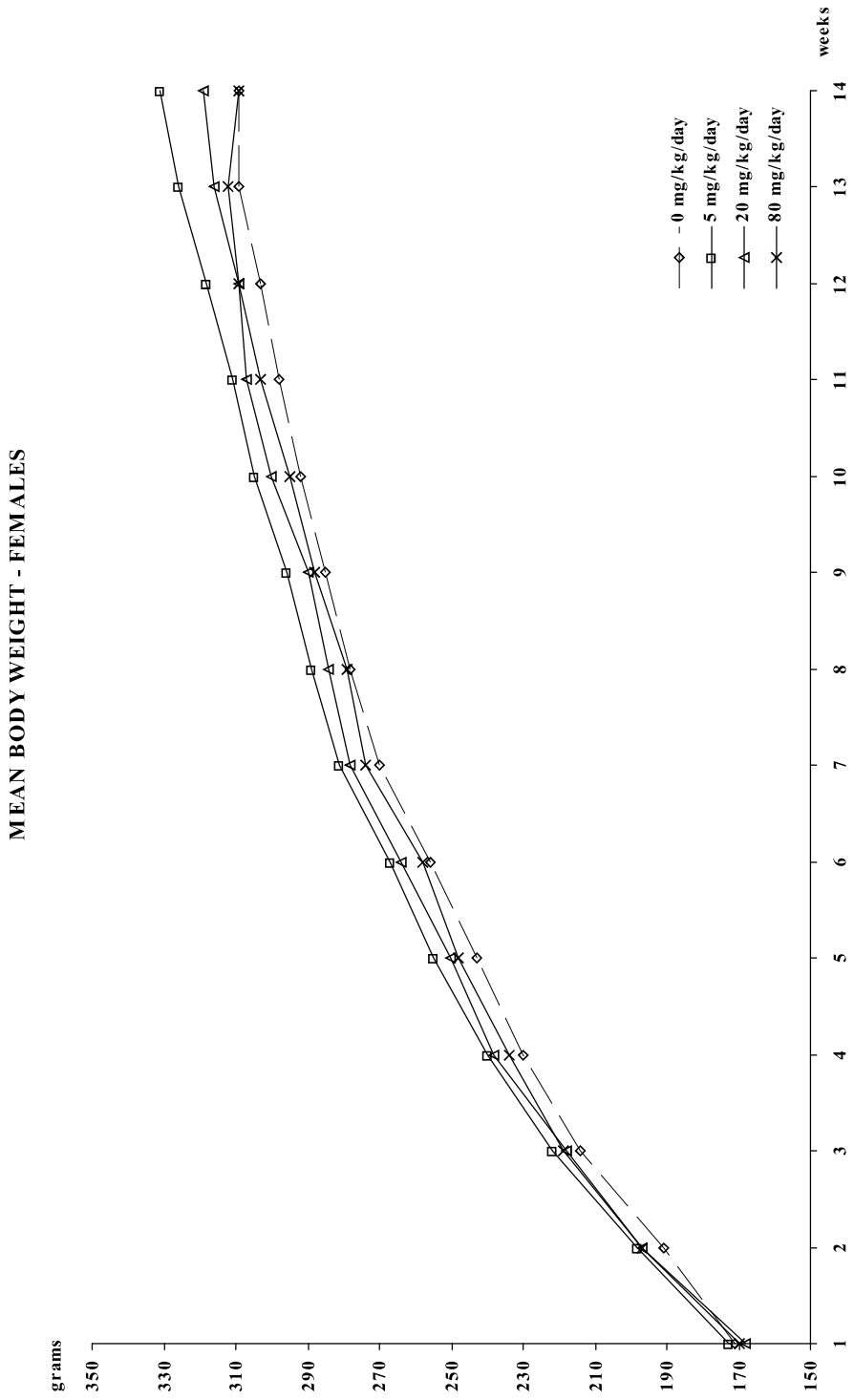
550
500
450
400
350
300
250
200
150
1
2
3
4
5
6
7
8
9
10
11
12
13
14
weeks
0 mg/kg/day
5 mg/kg/day
20 mg/kg/day
80 mg/kg/day

Figure 2


MEAN BODY WEIGHT - FEMALES
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290
270
250
230
210
190
170
150
1
2
3
4
5
6
7
8
9
10
11
12
13
14
weeks
0 mg/kg/day
5 mg/kg/day
20 mg/kg/day
80 mg/kg/day

CLINICAL SIGNS (SUMMARY TABLE)

Table: 1

Sex: male
Period: Week 1 to 14

Dose (mg/kg/d)	0		5		20		80	
Observations	No	%	No	%	No	%	No	%
Swollen / left ear	0	0	0	0	0	0	1	10
Chromodacryorrhea	0	0	0	0	1	10	1	10
Chromorhinorrhea	0	0	1	10	0	0	0	0
Ptyalism	2	20	3	30	6	60	10	100
Regurgitation	0	0	1	10	0	0	0	0
Nodosities / left eyelid	0	0	0	0	1	10	0	0
Area of hair loss / right forelimb	1	10	0	0	2	20	0	0
Area of hair loss / left forelimb	1	10	1	10	1	10	0	0
Scattered hair	0	0	0	0	1	10	0	0
Scabs / head	1	10	0	0	1	10	0	0
Scabs / left ear	0	0	0	0	0	0	1	10
Scabs / back	0	0	0	0	0	0	2	20
Scabs / left forelimb	0	0	0	0	0	0	1	10
Abnormal growth of teeth (cut regularly)	1	10	0	0	0	0	0	0
No clinical history	6	60	6	60	2	20	0	0

CLINICAL SIGNS (SUMMARY TABLE)

Table: 2

Sex: female
Period: Week 1 to 14

Dose (mg/kg/d)	0		5		20		80	
Observations	No	%	No	%	No	%	No	%
Chromodacryorrhea	0	0	0	0	0	0	1	10
Ptyalism	0	0	0	0	2	20	8	80
Regurgitation	0	0	1	10	0	0	1	10
Nodosities / right eyelid	0	0	0	0	0	0	1	10
Area of hair loss / head	1	10	0	0	0	0	1	10
Area of hair loss / dorsal region (neck)	0	0	0	0	0	0	1	10
Area of hair loss / right forelimb	4	40	4	40	1	10	2	20
Area of hair loss / left forelimb	5	50	4	40	1	10	2	20
Scattered hair	0	0	1	10	2	20	1	10
Scabs / head	1	10	0	0	1	10	1	10
No clinical history	5	50	5	50	6	60	1	10

Table: 3

SUMMARY OF MOTOR ACTIVITY

Sex: male
Week 12

		Dose-level (mg/kg/day)			
		0	5	20	80
	n	10	10	10	10
Movements within the front of the cage	Mean	78	69	78	80
	SD	34	17	30	35
	Mean/1 min	5	5	5	5
	SD/1min	2	1	2	2
Back and forth movements	Mean	39	38	43	36
	SD	16	10	14	7
	Mean/1 min	3	3	3	2
	SD/1min	1	1	1	0
Movements within the back of the cage	Mean	63	67	78	80
	SD	28	15	37	31
	Mean/1 min	4	4	5	5
	SD/1min	2	1	2	2
Vertical movements	Mean	119	113	114	111
	SD	33	29	32	19
	Mean/1 min	8	8	8	7
	SD/1min	2	2	2	1

Table: 4

SUMMARY OF MOTOR ACTIVITY

Sex: female
Week 12

		Dose-level (mg/kg/day)			
		0	5	20	80
	n	9	9	9	9
Movements within the front of the cage	Mean	86	106	94	88
	SD	17	25	28	24
	Mean/1 min	6	7	6	6
	SD/1min	1	2	2	2
Back and forth movements	Mean	45	48	52	44
	SD	9	14	15	7
	Mean/1 min	3	3	3	3
	SD/1min	1	1	1	0
Movements within the back of the cage	Mean	88	86	105	78
	SD	25	29	37	15
	Mean/1 min	6	6	7	5
	SD/1min	2	2	2	1
Vertical movements	Mean	129	132	144	123
	SD	34	23	37	26
	Mean/1 min	9	9	10	8
	SD/1min	2	2	2	2

Touch escape

Table: 5

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Touch escape

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Fur appearance

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Fur appearance

Table: 5 (Continued)

Sex: female	
Week	12
Dose: 0 mg/kg/day	
Score 0	6
Score 1	3
n	9
Dose: 5 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 20 mg/kg/day	
Score 0	7
Score 1	3
n	10
Dose: 80 mg/kg/day	
Score 0	7
Score 1	3
n	10

Salivation

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Salivation

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Lacrimation

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Lacrimation

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Piloerection

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Piloerection

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Pupil size

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 1	10
n	10
Dose: 5 mg/kg/day	
Score 1	10
n	10
Dose: 20 mg/kg/day	
Score 1	10
n	10
Dose: 80 mg/kg/day	
Score 1	10
n	10

Pupil size

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 1	9
n	9
Dose: 5 mg/kg/day	
Score 1	10
n	10
Dose: 20 mg/kg/day	
Score 1	10
n	10
Dose: 80 mg/kg/day	
Score 1	10
n	10

Exophthalmos

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Exophthalmos

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Reactivity to handling

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Reactivity to handling

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Grooming

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 80 mg/kg/day	
Score 0	9
Score 1	1
n	10

Grooming

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Palpebral closure

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Palpebral closure

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Tremors

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Tremors

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Twitches

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Twitches

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Clonic convulsions

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Clonic convulsions

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Tonic convulsions

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Tonic convulsions

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Hypoactivity

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Hypoactivity

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Hyperactivity

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Hyperactivity

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Ataxia

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Ataxia

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Hypotonia

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Hypotonia

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Gait

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Gait

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Posture

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Posture

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Stereotypy

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Stereotypy

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Behavior

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Behavior

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Breathing

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Breathing

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Defecation

Table: 5 (Continued)

Sex: male	
Week	12
Dose: 0 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 5 mg/kg/day	
Score 0	8
Score 1	2
n	10
Dose: 20 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Defecation

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Urination

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	7
Score 1	3
n	10
Dose: 5 mg/kg/day	
Score 0	7
Score 1	3
n	10
Dose: 20 mg/kg/day	
Score 0	5
Score 1	5
n	10
Dose: 80 mg/kg/day	
Score 0	7
Score 1	3
n	10

Urination

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	5
Score 1	4
n	9
Dose: 5 mg/kg/day	
Score 0	9
Score 1	1
n	10
Dose: 20 mg/kg/day	
Score 0	4
Score 1	6
n	10
Dose: 80 mg/kg/day	
Score 0	7
Score 1	3
n	10

Touch response

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Touch response

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

visual stimulus response

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

visual stimulus response

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Pupillary reflex

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Pupillary reflex

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Auditory startle reflex

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Auditory startle reflex

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Tail pinch response

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Tail pinch response

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Righting reflex

Table: 5 (Continued)

Sex: male	
Week	12
Dose: 0 mg/kg/day	
Score 0	10
n	10
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Righting reflex

Table: 5 (Continued)

Sex: female	
Week	12
Dose: 0 mg/kg/day	
Score 0	9
n	9
Dose: 5 mg/kg/day	
Score 0	10
n	10
Dose: 20 mg/kg/day	
Score 0	10
n	10
Dose: 80 mg/kg/day	
Score 0	10
n	10

Landing foot splay (mm)

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Mean	111
SD	25
Dose: 5 mg/kg/day	
Mean	100
SD	21
Dose: 20 mg/kg/day	
Mean	108
SD	25
Dose: 80 mg/kg/day	
Mean	97
SD	20

Landing foot splay (mm)

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Mean	90
SD	15
Dose: 5 mg/kg/day	
Mean	86
SD	12
Dose: 20 mg/kg/day	
Mean	88
SD	18
Dose: 80 mg/kg/day	
Mean	83
SD	13

Forelimbs grips strength

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Score 2	10
n	10
Dose: 5 mg/kg/day	
Score 2	10
n	10
Dose: 20 mg/kg/day	
Score 0	1
Score 2	9
n	10
Dose: 80 mg/kg/day	
Score 2	10
n	10

Forelimbs grips strength

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Score 2	9
n	9
Dose: 5 mg/kg/day	
Score 2	10
n	10
Dose: 20 mg/kg/day	
Score 2	10
n	10
Dose: 80 mg/kg/day	
Score 2	10
n	10

Rectal temperature (°C)

Table: 5 (Continued)

Sex: male

Week	12
Dose: 0 mg/kg/day	
Mean	37.5
SD	0.6
Dose: 5 mg/kg/day	
Mean	37.6
SD	0.7
Dose: 20 mg/kg/day	
Mean	38.0
SD	0.7
Dose: 80 mg/kg/day	
Mean	37.6
SD	0.4

Rectal temperature (°C)

Table: 5 (Continued)

Sex: female

Week	12
Dose: 0 mg/kg/day	
Mean	38.8
SD	0.4
Dose: 5 mg/kg/day	
Mean	38.7
SD	0.6
Dose: 20 mg/kg/day	
Mean	38.7
SD	0.4
Dose: 80 mg/kg/day	
Mean	38.7
SD	0.6

BODY WEIGHT
(mean values - g)

Table: 6

Sex: Male

Dose (mg/kg/d)		0	5	20	80
Week					
-1	M (1)	151	152	152	152
	SD	15.4	14.1	13.1	13.8
	n	10	10	10	10
1	M (1)	210	211	208	204
	SD	16.2	17.1	14.6	18.3
	n	10	10	10	10
2	M (1)	273	275	271	271
	SD	17.9	17.3	13.0	17.7
	n	10	10	10	10
3	M (1)	334	330	326	330
	SD	21.8	21.2	11.6	18.7
	n	10	10	10	10
4	M (1)	378	364	363	368
	SD	29.2	26.7	15.9	21.0
	n	10	10	10	10
5	M (1)	420	400	399	410
	SD	31.8	29.0	19.8	24.1
	n	10	10	10	10
6	M (1)	451	427	427	437
	SD	33.7	31.5	21.1	26.9
	n	10	10	10	10
7	M (1)	473	447	449	465
	SD	34.9	38.1	24.2	28.8
	n	10	10	10	10
8	M (3)	496	470	468	482
	SD(K)	37.9	39.6	29.1	28.6
	n	10	10	10	10
9	M (1)	512	491	486	504
	SD	34.7	40.7	27.4	30.8
	n	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

BODY WEIGHT
(mean values - g)

Table: 6 (continued)

Sex: Male

Dose (mg/kg/d)		0	5	20	80
Week					
10	M (1)	526	509	506	523
	SD	38.8	42.9	30.7	31.8
	n	10	10	10	10
11	M (1)	543	523	520	537
	SD	38.4	43.0	32.7	33.1
	n	10	10	10	10
12	M (1)	555	535	530	552
	SD	46.9	43.5	32.4	34.2
	n	10	10	10	10
13	M (1)	565	539	537	557
	SD	44.7	46.3	34.9	33.2
	n	10	10	10	10
14	M (1)	558	536	533	550
	SD	44.6	46.2	34.2	30.4
	n	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

BODY WEIGHT
(mean values - g)

Table: 7

Sex: Female

Dose (mg/kg/d)		0	5	20	80
Week					
-1	M (1)	140	143	140	141
	SD	8.4	8.9	6.9	7.6
	n	10	10	10	10
1	M (1)	171	173	168	170
	SD	13.2	12.0	7.8	7.4
	n	10	10	10	10
2	M (1)	191	198	197	197
	SD	14.5	15.2	9.2	10.3
	n	10	10	10	10
3	M (1)	214	222	218	219
	SD	20.2	17.1	11.2	14.7
	n	10	10	10	10
4	M (1)	230	240	238	234
	SD	20.7	18.2	11.6	18.1
	n	9	10	10	10
5	M (1)	243	255	250	248
	SD	23.1	24.4	13.0	17.3
	n	9	10	10	10
6	M (1)	256	267	264	258
	SD	22.0	25.0	16.3	17.9
	n	9	10	10	10
7	M (1)	270	281	278	274
	SD	24.9	27.3	14.5	17.6
	n	9	10	10	10
8	M (1)	278	289	284	279
	SD	27.7	26.8	14.3	18.2
	n	9	10	10	10
9	M (1)	285	296	290	288
	SD	26.6	31.0	16.2	18.3
	n	9	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

BODY WEIGHT
(mean values - g)

Table: 7 (continued)

Sex: Female

Dose (mg/kg/d)		0	5	20	80
Week					
10	M (1)	292	305	300	295
	SD	28.0	32.2	20.0	22.2
	n	9	10	10	10
11	M (1)	298	311	307	303
	SD	29.0	33.4	25.1	21.1
	n	9	10	10	10
12	M (1)	303	318	309	309
	SD	29.5	31.0	17.2	20.2
	n	9	10	10	10
13	M (1)	309	326	316	312
	SD	25.1	31.6	15.6	20.4
	n	9	10	10	10
14	M (1)	309	331	319	309
	SD	26.8	32.6	20.5	22.9
	n	9	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

FOOD CONSUMPTION
(mean values - g/animal/day)

Table: 8

Sex: Male

Dose (mg/kg/d) Week		0	5	20	80
1	M (1)	27.0	27.2	28.3	27.4
	SD	1.77	2.79	1.57	1.18
	n	5	5	5	5
2	M (1)	29.9	29.0	31.0	30.0
	SD	0.94	2.69	2.15	1.13
	n	5	5	5	5
3	M (1)	29.9	28.2	29.7	29.1
	SD	1.76	3.32	1.98	0.68
	n	5	5	5	5
4	M (1)	30.2	28.2	29.4	30.0
	SD	1.86	3.02	0.96	1.46
	n	5	5	5	5
5	M (1)	30.5	28.5	29.0	28.8
	SD	1.86	2.85	1.00	0.93
	n	5	5	5	5
6	M (1)	29.6	27.6	28.2	29.1
	SD	1.40	2.90	1.68	1.42
	n	5	5	5	5
7	M (1)	28.7	26.8	27.5	27.5
	SD	1.01	2.49	2.14	0.80
	n	5	5	5	5
8	M (1)	29.0	27.5	27.5	28.4
	SD	1.15	2.56	2.19	0.67
	n	5	5	5	5
9	M (1)	28.3	27.4	28.3	30.0
	SD	1.55	2.37	2.05	0.97
	n	5	5	5	5
10	M (1)	28.5	27.1	28.1	28.8
	SD	1.00	2.14	2.27	0.69
	n	5	5	5	5

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

FOOD CONSUMPTION
(mean values - g/animal/day)

Table: 8 (continued)

Sex: Male

Dose (mg/kg/d)		0	5	20	80
Week					
11	M (1)	28.4	26.7	27.3	28.6
	SD	1.40	1.77	1.45	0.54
	n	5	5	5	5
12	M (1)	28.6	27.6	28.0	28.9
	SD	1.09	2.80	1.68	0.60
	n	5	5	5	5
13	M (1)	24.3	23.1	24.2	23.8
	SD	1.23	1.84	1.58	0.80
	n	5	5	5	5

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

FOOD CONSUMPTION
(mean values - g/animal/day)

Table: 9

Sex: Female

Dose (mg/kg/d) Week		0	5	20	80
1	M (1)	18.0	18.8	18.7	18.7
	SD	0.82	0.86	1.50	1.34
	n	5	5	5	5
2	M (1)	19.4	20.6	19.5	20.0
	SD	1.09	1.00	1.19	1.61
	n	5	5	5	5
3	M (1)	20.3	21.6	20.3	20.2
	SD	1.82	0.70	1.44	1.70
	n	5	5	5	5
4	M (1)	20.4	21.4	20.9	20.4
	SD	1.14	1.11	1.52	1.33
	n	5	5	5	5
5	M (1)	21.3	21.2	20.6	20.5
	SD	1.86	1.04	1.45	1.35
	n	5	5	5	5
6	M (1)	22.0	21.2	20.6	21.0
	SD	2.41	0.88	0.83	1.19
	n	5	5	5	5
7	M (1)	21.3	20.8	20.1	20.0
	SD	2.09	0.84	0.59	1.59
	n	5	5	5	5
8	M (1)	21.1	21.1	20.5	21.0
	SD	0.52	0.34	1.09	0.98
	n	5	5	5	5
9	M (3)	23.8	23.4	22.3	21.2
	SD	2.99	2.15	2.30	2.03
	n	5	4	5	5
10	M (1)	20.8	20.5	19.4	19.5
	SD	2.63	0.92	0.98	1.97
	n	5	5	5	5

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

FOOD CONSUMPTION
(mean values - g/animal/day)

Table: 9 (continued)

Sex: Female

Dose (mg/kg/d)		0	5	20	80
Week					
11	M (1)	20.9	19.1	19.2	20.1
	SD	0.83	3.66	1.41	1.20
	n	5	5	5	5
12	M (3)	24.7	19.7	21.5	25.8
	SD	6.87	6.52	0.56	7.29
	n	5	5	3	5
13	M (3)	22.2	20.3	20.5	23.8
	SD	6.14	7.50	1.91	5.72
	n	5	3	4	5

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

HEMATOLOGY
(mean values)

Table: 10

Sex: Male
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
WBC	M (1)	11.30	11.06	10.49	9.86
G/L	SD	2.560	1.540	1.987	2.305
	n	10	10	10	10
RBC	M (1)	8.43	8.45	8.35	8.14
T/L	SD	0.255	0.469	0.266	0.267
	n	10	10	10	10
HB	M (1)	15.5	15.4	15.3	15.0
g/dL	SD	0.33	0.63	0.54	0.56
	n	10	10	10	10
PCV	M (3)	0.43	0.43	0.43	0.42
L/L	SD(K)	0.011	0.018	0.016	0.011
	n	10	10	10	10
MCV	M (1)	51.1	50.6	51.3	52.1
fL	SD	2.30	1.36	1.34	2.32
	n	10	10	10	10
MCH	M (1)	18.3	18.2	18.3	18.5
pg	SD	0.69	0.59	0.41	0.92
	n	10	10	10	10
MCHC	M (1)	35.9	36.0	35.7	35.5
g/dL	SD	0.42	0.49	0.39	0.49
	n	10	10	10	10
PLAT	M (1)	898	941	904	1026
G/L	SD	145.9	172.6	104.3	195.7
	n	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

HEMATOLOGY
(mean values)

Table: 10 (continued)

Sex: Male
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
N	M (1)	1.58	1.81	1.83	2.01
G/L	SD	0.440	0.515	0.629	0.726
	n	10	10	10	10
E	M (1)	0.23	0.24	0.18	0.20
G/L	SD	0.094	0.086	0.063	0.066
	n	10	10	10	10
B	M (3)	0.02	0.02	0.02	0.01
G/L	SD(K)	0.012	0.010	0.010	0.007
	n	10	10	10	10
L	M (1)	9.09	8.58	8.13	7.38
G/L	SD(L)	2.286	1.399	1.535	1.952
	n	10	10	10	10
M	M (1)	0.39	0.42	0.34	0.26 *
G/L	SD	0.105	0.090	0.097	0.082
	n	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

HEMATOLOGY
(mean values)

Table: 10 (continued)

Sex: Male
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
PT	M (3)	15.7	16.7	17.0	19.5
s	SD	0.80	1.48	2.23	5.25
	n (B)	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

HEMATOLOGY
(mean values)

Table: 11

Sex: Female
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
WBC	M (1)	9.61	7.55 *	6.35 **	5.26 **
G/L	SD(L)	1.788	2.404	1.546	0.970
	n	9	10	9	9
RBC	M (1)	7.43	7.41	7.38	7.26
T/L	SD	0.326	0.225	0.448	0.336
	n	9	10	9	9
HB	M (3)	14.2	14.5	14.1	13.9
g/dL	SD(K)	0.58	0.52	1.01	0.74
	n	9	10	9	9
PCV	M (1)	0.39	0.40	0.40	0.38
L/L	SD	0.015	0.013	0.030	0.021
	n	9	10	9	9
MCV	M (1)	52.7	54.1	53.6	53.2
fL	SD	0.94	2.12	1.97	1.25
	n	9	10	9	9
MCH	M (1)	19.1	19.6	19.1	19.2
pg	SD	0.29	0.71	0.71	0.47
	n	9	10	9	9
MCHC	M (3)	36.2	36.2	35.7 **	36.1
g/dL	SD(K)	0.45	0.29	0.26	0.36
	n	9	10	9	9
PLAT	M (1)	860	872	926	873
G/L	SD	117.5	146.7	162.5	154.0
	n	9	10	9	9

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

HEMATOLOGY
(mean values)

Table: 11 (continued)

Sex: Female
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
N	M (1)	1.45	1.40	1.37	0.98
G/L	SD(L)	0.390	0.494	0.751	0.175
	n	9	10	9	9
E	M (1)	0.28	0.29	0.19	0.13 *
G/L	SD(L)	0.181	0.284	0.134	0.077
	n	9	10	9	9
B	M (3)	0.01	0.01	0.01	0.00 *
G/L	SD(K)	0.011	0.009	0.007	0.004
	n	9	10	9	9
L	M (1)	7.59	5.61 **	4.61 **	4.01 **
G/L	SD	1.510	1.763	0.856	0.940
	n	9	10	9	9
M	M (1)	0.28	0.24	0.18	0.15 *
G/L	SD	0.129	0.129	0.061	0.056
	n	9	10	9	9

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

HEMATOLOGY
(mean values)

Table: 11 (continued)

Sex: Female
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
PTs	M (1)	14.9	13.2 **	13.2 **	12.5 **
	SD(L)	1.28	1.12	0.48	0.47
	n	9	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

BLOOD BIOCHEMISTRY
(mean values)

Table: 12

Sex: Male
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
Na+	M (1)	145.0	146.2	147.2 **	145.3
mmol/L	SD	1.58	0.55	0.81	1.11
	n	10	10	10	10
K+	M (1)	3.79	4.04	3.90	4.11 *
mmol/L	SD(L)	0.181	0.152	0.188	0.426
	n	10	10	10	10
Cl-	M (1)	101.3	103.2 **	103.5 **	102.9 *
mmol/L	SD	1.38	0.88	1.20	1.25
	n	10	10	10	10
Ca++	M (1)	2.88	2.83	2.81 *	2.87
mmol/L	SD	0.059	0.055	0.051	0.085
	n	10	10	10	10
I.PHOS	M (1)	2.32	2.28	2.21	2.20
mmol/L	SD	0.087	0.112	0.074	0.167
	n	10	10	10	10
GLUC	M (1)	6.22	6.69	6.40	6.62
mmol/L	SD	0.589	0.609	0.792	0.521
	n	10	10	10	10
UREA	M (1)	4.5	4.7	4.8	4.9
mmol/L	SD	0.54	0.79	0.53	0.67
	n	10	10	10	10
CREAT	M (1)	40	40	41	40
µmol/L	SD	3.1	3.8	3.9	3.6
	n	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

BLOOD BIOCHEMISTRY
(mean values)

Table: 12 (continued)

Sex: Male
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
PROT	M (1)	77	76	77	78
g/L	SD	3.6	2.1	1.9	3.6
	n	10	10	10	10
ALB	M (3)	42	41	42	41
g/L	SD(K)	2.0	1.9	1.7	1.6
	n	10	10	10	10
A/G	M (1)	1.22	1.16	1.18	1.16
	SD	0.105	0.078	0.088	0.123
	n	10	10	10	10
TOT.BIL.	M	2	2	1	1
µmol/L	SD(K)	0.6	0.5	0.4	0.3
	n	10	10	10	10
CHOL	M (1)	1.5	1.3	1.4	1.7
mmol/L	SD	0.41	0.25	0.27	0.45
	n	10	10	10	10
TRIG	M (1)	0.83	0.89	0.67	0.72
mmol/L	SD	0.302	0.321	0.344	0.272
	n	10	10	10	10
ALP	M (1)	176	170	169	141
IU/L	SD	47.4	29.0	29.6	22.4
	n	10	10	10	10
ASAT	M (1)	55	52	53	50
IU/L	SD(L)	12.8	15.2	10.0	13.0
	n	10	10	10	10
ALAT	M (1)	27	30	30	27
IU/L	SD	6.1	9.1	8.5	5.1
	n	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

BLOOD BIOCHEMISTRY
(mean values)

Table: 13

Sex: Female
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
Na+	M (1)	143.8	145.6 *	146.0 **	145.3 *
mmol/L	SD	0.86	1.37	1.27	1.53
	n	9	10	10	10
K+	M (1)	3.77	3.77	3.79	3.66
mmol/L	SD	0.222	0.210	0.390	0.289
	n	9	10	10	10
Cl-	M (1)	102.8	103.6	104.1	103.7
mmol/L	SD	1.06	1.47	1.16	1.74
	n	9	10	10	10
Ca++	M (1)	2.90	2.96	2.88	2.90
mmol/L	SD	0.079	0.079	0.116	0.091
	n	9	10	10	10
I.PHOS	M (1)	1.90	1.89	1.82	1.64 *
mmol/L	SD	0.163	0.308	0.143	0.189
	n	9	10	10	10
GLUC	M (1)	6.54	6.60	6.93	7.33
mmol/L	SD	0.614	0.640	1.196	1.112
	n	9	10	10	10
UREA	M (1)	5.8	5.5	6.3	6.3
mmol/L	SD(L)	0.28	0.86	1.11	0.94
	n	9	10	10	10
CREAT	M (1)	46	47	50	46
µmol/L	SD	5.5	3.1	4.7	3.7
	n	9	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

BLOOD BIOCHEMISTRY
(mean values)

Table: 13 (continued)

Sex: Female
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
PROT	M (1)	79	85	82	84
g/L	SD	4.6	6.3	5.9	5.0
	n	9	10	10	10
ALB	M (1)	49	51	49	48
g/L	SD	4.4	3.8	3.8	2.8
	n	9	10	10	10
A/G	M (1)	1.68	1.49 *	1.48 **	1.34 **
	SD	0.210	0.142	0.089	0.102
	n	9	10	10	10
TOT.BIL.	M	3	2	1	1
µmol/L	SD(K)	0.7	0.5	0.3	0.3
	n	9	10	10	10
CHOL	M (1)	1.8	1.9	2.2	2.5 **
mmol/L	SD	0.44	0.36	0.36	0.41
	n	9	10	10	10
TRIG	M (1)	0.51	0.54	0.42	0.43
mmol/L	SD	0.171	0.157	0.147	0.101
	n	9	10	10	10
ALP	M (1)	94	93	82	58 *
IU/L	SD(L)	23.8	52.0	45.0	10.7
	n	9	10	10	10
ASAT	M (1)	65	58	53	40 **
IU/L	SD(L)	26.1	18.0	23.8	7.3
	n	9	10	10	10
ALAT	M (3)	28	28	19	18
IU/L	SD(L)	13.7	16.9	3.1	3.9
	n (B)	9	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

URINALYSIS
(mean values)

Table: 14

Sex: Male
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
VOLUME	M (1)	18	15	15	12
mL	SD	10.2	8.4	10.7	4.2
	n	10	10	10	10
SP.GRAV	M (3)	1023	1026	1028	1031
-	SD(K)	10.3	9.8	9.8	6.6
	n	10	10	10	10
pH	M	7.2	6.9	7.0	7.0
-	SD(K)	0.47	0.53	0.24	0.24
	n	10	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

URINALYSIS
(mean values)

Table: 15

Sex: Female
Time: Week 13

Dose (mg/kg/d)		0	5	20	80
VOLUME	M (1)	8	13	10	9
mL	SD(L)	6.4	6.1	6.0	5.3
	n	9	10	10	10
SP.GRAV	M (3)	1034	1023	1026	1030
-	SD(K)	13.3	11.6	10.7	9.3
	n	9	10	10	10
pH	M (3)	6.3	6.4	6.5	6.5
-	SD(K)	0.36	0.46	0.53	0.37
	n	9	10	10	10

Significance of the difference between treated and control groups
* P<0.05
** P<0.01
(1) : Dunnett test
(2) : Mann-Whitney test
(3) : Dunn test

Sample distribution-relative tests

(B) Bartlett test P<0.01
(F) Fisher test P<0.01
(K) Kolmogorov-Smirnov test P<0.01
(L) Logarithmic transformation
\- Statistics excluded group

Table: 16

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-------------------------------------------------------------------------
SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS
STATUS AT NECROPSY:  K0
SEX: MALE
-------------------------------------------------------------------------

            DOSE GROUP:     1         2         3         4
ORGAN       NO.ANIMALS:    10        10        10        10
-------------------------------------------------------------------------
ADRENAL GLANDS        n:   10        10        10        10
      MEAN WEIGHT  (g): 0.05710   0.05500   0.05790   0.05820
      SD              :   0.007     0.009     0.011     0.009
      MEAN % BODY     : 0.01093   0.01097   0.01152   0.01123
      SD              :   0.001     0.002     0.002     0.002
.........................................................................
BRAIN                 n:   10        10        10        10
      MEAN WEIGHT  (g):    2.13      2.09      2.12      2.09
      SD              :   0.077     0.090     0.117     0.053
      MEAN % BODY     : 0.40699   0.41326   0.42228   0.40241
      SD              :   0.030     0.040     0.034     0.030
.........................................................................
EPIDIDYMIDES          n:   10        10        10        10
      MEAN WEIGHT  (g):    1.56      1.55      1.54      1.57
      SD              :   0.079     0.131     0.174     0.150
      MEAN % BODY     : 0.29769   0.30718   0.30682   0.30273
      SD              :   0.024     0.046     0.042     0.037
.........................................................................
FINAL BODY WEIGHT     n:   10        10        10        10
      MEAN WEIGHT  (g):   525.5     508.5     502.7     520.5
      SD              :   44.47     45.40     32.43     31.20
.........................................................................
HEART                 n:   10        10        10        10
      MEAN WEIGHT  (g):    1.70      1.71      1.61      1.76
      SD              :   0.199     0.162     0.156     0.177
      MEAN % BODY     : 0.32310   0.33634   0.32103   0.33896
      SD              :   0.031     0.027     0.032     0.034
.........................................................................
KIDNEYS               n:   10        10        10        10
      MEAN WEIGHT  (g):    3.67      3.51      3.41      3.52
      SD              :   0.287     0.307     0.230     0.283
      MEAN % BODY     : 0.70010   0.69274   0.68067   0.67623
      SD              :   0.047     0.058     0.048     0.052
.........................................................................



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No statistically significant weight differences noted between treated
groups and controls

                                                25580 / PDS PATHDATA SYSTEM TM
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Table: 16 (continued)

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------------------------------------------------------------------------
SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS
STATUS AT NECROPSY:  K0
SEX: MALE
------------------------------------------------------------------------

            DOSE GROUP:     1         2         3         4
ORGAN       NO.ANIMALS:    10        10        10        10
------------------------------------------------------------------------
LIVER                 n:   10        10        10        10
      MEAN WEIGHT  (g):   14.32     14.13     13.99     17.49**
      SD              :    2.24      1.60      1.31      2.50
      MEAN % BODY     :    2.72      2.78      2.79      3.37##
      SD              :   0.274     0.150     0.227     0.486
........................................................................
SPLEEN                n:   10        10        10        10
      MEAN WEIGHT  (g): 0.78360   0.81560   0.83950   0.83510
      SD              :   0.107     0.089     0.105     0.072
      MEAN % BODY     : 0.14909   0.16095   0.16702   0.16101
      SD              :   0.017     0.017     0.018     0.017
........................................................................
TESTES                n:   10        10        10        10
      MEAN WEIGHT  (g):    3.53      3.43      3.45      3.68
      SD              :   0.279     0.229     0.295     0.362
      MEAN % BODY     : 0.67611   0.68060   0.68942   0.71111
      SD              :   0.076     0.080     0.077     0.097
........................................................................
THYMUS                n:   10        10        10        10
      MEAN WEIGHT  (g): 0.32130   0.34400   0.31290   0.29710
      SD              :   0.061     0.068     0.057     0.073
      MEAN % BODY     : 0.06138   0.06773   0.06225   0.05661
      SD              :   0.012     0.013     0.010     0.011
........................................................................
THYROID GLANDS        n:   10        10        10        10
      MEAN WEIGHT  (g): 0.02290   0.02490   0.02730   0.02790*
      SD              :   0.004     0.004     0.004     0.005
      MEAN % BODY     : 0.00436   0.00491   0.00545*  0.00538*
      SD              :   0.001     0.001     0.001     0.001
........................................................................



---------
#/##):DUNN'S TEST AT 5% (#) OR 1% (##) LEVEL
*/**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL
Assigned control group(s) : 1,
```

Table: 16 (continued)

```
-----------------------------------------------------------------------
SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS
STATUS AT NECROPSY:  K0
SEX: FEMALE
-----------------------------------------------------------------------

            DOSE GROUP:     1         2         3         4
ORGAN       NO.ANIMALS:    10        10        10        10
-----------------------------------------------------------------------
ADRENAL GLANDS       n:     9        10        10        10
      MEAN WEIGHT  (g): 0.06478   0.07960** 0.07100   0.06190
      SD             :   0.009     0.012     0.011     0.008
      MEAN % BODY    : 0.02273   0.02631   0.02438   0.02179
      SD             :   0.004     0.004     0.004     0.003
.......................................................................
BRAIN                n:     9        10        10        10
      MEAN WEIGHT  (g):    1.94      1.96      1.90      1.93
      SD             :   0.055     0.080     0.065     0.076
      MEAN % BODY    : 0.67856   0.64975   0.65337   0.68111
      SD             :   0.051     0.061     0.043     0.059
.......................................................................
FINAL BODY WEIGHT    n:     9        10        10        10
      MEAN WEIGHT  (g):   286.9     304.0     292.3     284.9
      SD             :   24.75     31.06     17.54     20.42
.......................................................................
HEART                n:     9        10        10        10
      MEAN WEIGHT  (g):    1.04      1.08      1.12      1.07
      SD             :   0.084     0.131     0.141     0.083
      MEAN % BODY    : 0.36476   0.35713   0.38419   0.37706
      SD             :   0.021     0.032     0.048     0.038
.......................................................................
KIDNEYS              n:     9        10        10        10
      MEAN WEIGHT  (g):    2.03      2.14      2.05      1.99
      SD             :   0.132     0.165     0.103     0.186
      MEAN % BODY    : 0.70981   0.70875   0.70244   0.70118
      SD             :   0.060     0.063     0.051     0.063
.......................................................................
LIVER                n:     9        10        10        10
      MEAN WEIGHT  (g):    8.01      9.36*     9.44**   10.41**
      SD             :   0.708     0.884     0.758      1.30
      MEAN % BODY    :    2.79      3.09*     3.24**    3.65**
      SD             :   0.136     0.264     0.263     0.322
.......................................................................


---------
*/**):DUNNETT'S TEST BASED ON POOLED VARIANCES AT 5% (*) OR 1% (**) LEVEL
Assigned control group(s) : 1,
```

Table: 16 (continued)

```
------------------------------------------------------------------------
SUMMARY TABLE OF BODY/ORGAN WEIGHTS AND STATISTICS
STATUS AT NECROPSY:  K0
SEX: FEMALE
------------------------------------------------------------------------

            DOSE GROUP:      1         2         3         4
ORGAN       NO.ANIMALS:     10        10        10        10
------------------------------------------------------------------------
OVARIES               n:     9        10        10        10
      MEAN WEIGHT  (g): 0.13233   0.13650   0.12840   0.13470
      SD              :   0.019     0.015     0.018     0.022
      MEAN % BODY     : 0.04661   0.04521   0.04410   0.04733
      SD              :   0.009     0.006     0.007     0.007
........................................................................
SPLEEN                n:     9        10        10        10
      MEAN WEIGHT  (g): 0.62067   0.66710   0.62280   0.59600
      SD              :   0.100     0.095     0.073     0.110
      MEAN % BODY     : 0.21695   0.22035   0.21326   0.20913
      SD              :   0.035     0.029     0.023     0.036
........................................................................
THYMUS                n:     9        10        10        10
      MEAN WEIGHT  (g): 0.30367   0.30660   0.28630   0.24240
      SD              :   0.071     0.080     0.096     0.045
      MEAN % BODY     : 0.10560   0.10051   0.09747   0.08584
      SD              :   0.024     0.022     0.030     0.019
........................................................................
THYROID GLANDS        n:     9        10        10        10
      MEAN WEIGHT  (g): 0.02122   0.02080   0.02140   0.02000
      SD              :   0.007     0.004     0.004     0.003
      MEAN % BODY     : 0.00739   0.00687   0.00732   0.00702
      SD              :   0.002     0.001     0.001     0.001
........................................................................
UTERUS                n:     9        10        10        10
      MEAN WEIGHT  (g): 0.57867   0.62860   0.74480   0.63380
      SD              :   0.092     0.112     0.390     0.196
      MEAN % BODY     : 0.20260   0.20711   0.25768   0.22323
      SD              :   0.034     0.033     0.143     0.067
........................................................................



---------
No statistically significant weight differences noted between treated
groups and controls

                                                25580 / PDS PATHDATA SYSTEM TM
```

Table: 17

NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0 MALE

ORGAN/FINDING	DOSE GROUP:	1	2	3	4
	ANIM.EXAM.:	10	10	10	10
EARS					
- ENLARGED		-	-	-	1
KIDNEYS					
- DILATED PELVIS		1	-	-	-
- IRREGULAR COLOR		-	1	-	-
LIVER					
- ACCENTUATED LOBULAR PATTERN		-	-	-	1
- ENLARGED		-	-	-	3
- REDUCED IN SIZE		-	-	-	1
THYMUS					
- REDDISH COLOR		-	-	1	-

Table: 17 (continued)

```
-------------------------------------------------------------------------
NUMBER OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS                            FEMALE
-------------------------------------------------------------------------
                       DOSE GROUP:   1    2    3    4
ORGAN/FINDING          ANIM.EXAM.:  10   10   10   10
-------------------------------------------------------------------------
LIVER                             :
- ACCENTUATED LOBULAR PATTERN     :   -    -    1    1
- FOCI GREYISH/WHITISH            :   -    3    -    2
- FOCI YELLOWISH                  :   -    -    1    -
.........................................................................
LUNGS                             :
- FOAMY CONTENTS                  :   1    -    -    -
- REDDISH COLOR                   :   1    -    -    -
.........................................................................
SKIN                              :
- ALOPECIA                        :   -    1    -    -
- SCABS                           :   1    -    1    -
.........................................................................
THYMUS                            :
- REDDISH COLOR                   :   2    -    1    -
.........................................................................
TRACHEA                           :
- FOAMY CONTENTS                  :   1    -    -    -
.........................................................................
UTERUS                            :
- DILATATION                      :   -    1    2    1
- SEROUS CONTENTS                 :   -    -    1    1
.........................................................................

                                                25580 / PDS PATHDATA SYSTEM TM
```

Table: 18

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX	:				MALE
DOSE GROUP	:	1	2	3	4
NO.ANIMALS	:	10	10	10	10
ADRENAL GLANDS	:	10	-	-	10
- Vacuol.Cortical cell	:	-	-	-	3
EARS	:	-	-	-	1
- Chondropathy	:	-	-	-	1
EPIDIDYMIDES	:	10	-	-	10
- Inters.Mono.Cel.Agg.	:	-	-	-	1
- Spermatic granuloma	:	-	-	-	1
HARDERIAN GLANDS	:	10	-	-	10
- Deg./Nec.Myopat.R-O.	:	4	-	-	5
- Inters.Mono.Cel.Agg.	:	4	-	-	3
- Necrotizing Inflamm.	:	2	-	-	-
- Subacute Dacryoaden.	:	-	-	-	2
HEART	:	10	-	-	10
- Degen.cardiomyopathy	:	4	-	-	4
- Inters.Mono.Cel.Agg.	:	-	-	-	2
JEJUNUM	:	10	-	-	10
- Mineralization Galt	:	1	-	-	-
KIDNEYS	:	10	1	-	10
- Aci.Glob.Cor.Tub.Ep.	:	4	-	-	8
- Tubular Basophilia	:	1	1	-	6
- Tub.dil.flat.epith.	:	-	-	-	1
- Proteinaceous casts	:	1	-	-	-
- Peritubular Fibrosis	:	1	1	-	5
- Inters.Mono.Cel.Agg.	:	7	-	-	6
- Mineralization	:	-	-	-	2
- Dilated Pelvis	:	1	-	-	-

Table: 18 (continued)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0, INCL. DEATHS					
SEX :					MALE
DOSE GROUP:	1	2	3	4	
NO.ANIMALS:	10	10	10	10	
LIVER :	10	10	10	10	
- Mononuclear Cel.Agg.:	10	10	10	10	
- Granulocyte Infiltr.:	2	-	-	-	
- Vacuolated Hepatocy.:	8	1	2	6	
- Tension Lipidosis :	-	1	-	-	
- Area Coag.Hepat.Nec.:	1	-	-	1	
- Hepatocel.Hypertrop.:	-	-	-	8	
- Biliary Proliferat. :	5	-	1	4	
- Green.Pi.Lad.Kup.Ce.:	1	-	-	2	
- Accessory lobe :	1	-	-	-	
- Capsular thickening :	-	-	-	1	
LUNGS :	10	-	-	10	
- Chron.Inters.Pneumo.:	3	-	-	2	
- Foamy Alveol.Macro. :	5	-	-	5	
- Alveolar hemorrhage :	2	-	-	-	
- Granulocyte Infiltr.:	1	-	-	2	
- Miner.vascular wall :	-	-	-	3	
MANDIBUL. LYMPH NODE :	10	-	-	10	
- Histiocytosis :	10	-	-	10	
- Plasmocytosis :	10	-	-	10	
- Mastocytosis :	10	-	-	10	
- Granulocyt.Infiltr. :	6	-	-	5	
- Prom.Reticular Cells:	1	-	-	2	
- Lymphoid Depletion :	1	-	-	-	
- Lymphoid Cel.Hyperp.:	-	-	-	1	
MESENT. LYMPH NODE :	10	-	-	10	
- Histiocytosis :	10	-	-	10	
- Plasmocytosis :	3	-	-	8	
- Mastocytosis :	7	-	-	4	
- Granulocyte infiltr.:	7	-	-	8	
- Sinusal hemorrhage :	2	-	-	-	

Table: 18 (continued)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0, INCL. DEATHS					
SEX :					MALE
DOSE GROUP:	1	2	3	4	
NO.ANIMALS:	10	10	10	10	
PANCREAS :	10	-	-	10	
- Inters.Infl.Cel.Inf.:	2	-	-	3	
- Inters.Mono.Cel.Agg.:	3	-	-	2	
- Acinar Cell Deg/Nec.:	3	-	-	4	
- Vacuolat.Acinar Cel.:	7	-	-	5	
- Acinar Cell Degranu.:	1	-	-	1	
- Ch.Infl.Islet.Lang. :	-	-	-	3	
- Yellow.Pig.Lad.Macr.:	-	-	-	3	
PARATHYROID GLANDS :	8	-	-	8	
- Development. Cyst(S):	1	-	-	-	
- Interstitial fibros.:	1	-	-	-	
PROSTATE :	10	-	-	10	
- Inters.Mono.Cel.Agg.:	7	-	-	3	
STERNUM :	10	-	-	10	
- Lipoid tissue :	10	-	-	10	
- Adequate cellularity:	10	-	-	10	
STOMACH :	10	-	-	10	
- Dilated Glands :	4	-	-	2	
- Submuc.inflamm.cells:	4	-	-	2	
TESTES :	10	-	-	10	
- Degener.germ.epith. :	6	-	-	7	
THYMUS :	10	-	1	10	
- Interstit.hemorrhage:	1	-	1	1	
THYROID GLANDS :	10	-	-	10	
- Development. Cyst(s):	2	-	-	5	
- Ectopic Thymus :	1	-	-	-	
- Inters.Mono.Cel.Agg.:	-	-	-	1	
TRACHEA :	10	-	-	10	
- Dilated glands :	6	-	-	6	

Table: 18 (continued)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0, INCL. DEATHS					
SEX :					FEMALE
DOSE GROUP:	1	2	3	4	
NO.ANIMALS:	10	10	10	10	
ADRENAL GLANDS :	10	-	-	10	
- Sinusoidal Ectasia :	1	-	-	-	
- Cortical Necrosis :	1	-	-	-	
EYES :	10	-	-	10	
- Infl.Cel.Inf.,R.Ocu.:	1	-	-	-	
HARDERIAN GLANDS :	10	-	-	10	
- Deg./Nec.Myopat.R-O.:	6	-	-	6	
- Inters.Mono.Cel.Agg.:	2	-	-	-	
- Necrotizing Inflamm.:	4	-	-	4	
HEART :	10	-	-	10	
- Degen.cardiomyopathy:	5	-	-	1	
- Inters.Mono.Cel.Agg.:	1	-	-	1	
- Epicarditis :	1	-	-	-	
KIDNEYS :	10	-	-	10	
- Tubular Basophilia :	1	-	-	1	
- Tub.dil.flat.epith. :	1	-	-	-	
- Peritubular Fibrosis:	1	-	-	1	
- Inters.Mono.Cel.Agg.:	3	-	-	1	
- Mineralization :	1	-	-	1	
LIVER :	10	10	10	10	
- Mononuclear Cel.Agg.:	9	7	7	10	
- Vacuolated Hepatocy.:	8	8	3	9	
- Tension Lipidosis :	3	3	2	4	
- Area Coag.Hepat.Nec.:	1	-	-	-	
- Hepatocel.Hypertrop.:	-	-	-	10	
- Biliary Proliferat. :	6	-	-	8	
- Green.Pi.Lad.Kup.Ce.:	1	-	-	-	
- Perivascular fibros.:	-	1	-	1	
- Megakaryocytosis :	1	-	-	3	

Table: 18 (continued)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX	:				FEMALE
DOSE GROUP	:	1	2	3	4
NO.ANIMALS	:	10	10	10	10
LUNGS	:	10	-	-	10
- Chron.Inters.Pneumo.	:	2	-	-	2
- Acute Bronchopneumo.	:	1	-	-	-
- Alveolitis	:	-	-	-	1
- Foamy Alveol.Macro.	:	2	-	-	1
- Alveolar hemorrhage	:	1	-	-	1
- Granulocyte Infiltr.	:	1	-	-	3
MANDIBUL. LYMPH NODE	:	10	-	-	10
- Histiocytosis	:	10	-	-	10
- Plasmocytosis	:	10	-	-	10
- Mastocytosis	:	9	-	-	9
- Granulocyt.Infiltr.	:	9	-	-	9
- Black.Pig-Lad.Macro.	:	1	-	-	-
MESENT. LYMPH NODE	:	10	-	-	10
- Histiocytosis	:	10	-	-	10
- Plasmocytosis	:	4	-	-	10
- Mastocytosis	:	6	-	-	2
- Granulocyte infiltr.	:	9	-	-	10
- Prom.Reticular Cells	:	3	-	-	2
OVARIES	:	10	-	-	10
- Proestrus	:	2	-	-	2
- Estrus	:	3	-	-	1
- Metestrus	:	3	-	-	5
- Diestrus	:	2	-	-	2
- Luteal Cyst(S)	:	-	-	-	1
PANCREAS	:	9	-	-	10
- Inters.Mono.Cel.Agg.	:	1	-	-	-
- Acinar Cell Deg/Nec.	:	3	-	-	2
- Vacuolat.Acinar Cel.	:	1	-	-	1
PARATHYROID GLANDS	:	9	-	-	8
- Interstitial fibros.	:	-	-	-	2

Table: 18 (continued)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX :				FEMALE
DOSE GROUP:	1	2	3	4
NO.ANIMALS:	10	10	10	10
PITUITARY GLAND :	9	-	-	10
- Development. Cyst(S):	1	-	-	-
SKIN :	10	1	1	10
- Ulceration :	1	-	1	-
- Empty hair follicles:	-	1	-	-
- Acanthosis :	1	1	1	-
- Hyperkeratosis :	1	1	1	-
STERNUM :	10	-	-	10
- Lipoid tissue :	10	-	-	10
- Adequate cellularity:	10	-	-	10
STOMACH :	10	-	-	10
- Dilated Glands :	2	-	-	-
- Submuc.inflamm.cells:	2	-	-	4
THYMUS :	10	-	1	10
- Interstit.hemorrhage:	2	-	1	-
- Cyst(S) :	1	-	1	1
THYROID GLANDS :	10	-	-	10
- Development. Cyst(s):	6	-	-	6
- Ectopic Thymus :	-	-	-	2
TRACHEA :	10	-	-	10
- Dilated glands :	5	-	-	1
UTERUS :	10	1	2	10
- Proestrus :	2	-	-	2
- Estrus :	3	-	-	1
- Metestrus :	3	-	-	5
- Diestrus :	2	-	-	2
- Dilated Lumen :	-	1	2	1

Table: 18 (continued)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS

SEX	:				FEMALE
DOSE GROUP:	1	2	3	4	
NO.ANIMALS:	10	10	10	10	
VAGINA	: 10	-	-	10	
- Proestrus	: 2	-	-	2	
- Estrus	: 3	-	-	1	
- Metestrus	: 3	-	-	5	
- Diestrus	: 2	-	-	2	
- Mucific.Vagin.Epith.	: 2	-	-	1	

Table: 19

```
-------------------------------------------------------------------------
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-------------------------------------------------------------------------
            SEX       :                                            MALE
            DOSE GROUP:    1    2    3    4
            NO.ANIMALS:   10   10   10   10
-------------------------------------------------------------------------
LIVER                 :   10   10   10   10
- Hepatocel.Hypertrop.
             GRADE  1 :    -    -    -    5
             GRADE  2 :    -    -    -    2
             GRADE  3 :    -    -    -    1

       TOTAL AFFECTED :    -    -    -    8
       MEAN  SEVERITY :    -    -    -  1.5
-------------------------------------------------------------------------
```

Table: 19 (continued)

```
-------------------------------------------------------------------------
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. DEATHS
-------------------------------------------------------------------------
            SEX       :                                          FEMALE
            DOSE GROUP:    1    2    3    4
            NO.ANIMALS:   10   10   10   10
-------------------------------------------------------------------------
LIVER                 :   10   10   10   10
- Hepatocel.Hypertrop.
             GRADE  1 :    -    -    -    3
             GRADE  2 :    -    -    -    7

       TOTAL AFFECTED :    -    -    -   10
       MEAN  SEVERITY :    -    -    -  1.7
-------------------------------------------------------------------------
```

Table: 20

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 1, MALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24683
KIDNEYS	
- 01: Right: dilated pelvis.	- Dilated pelvis, unilateral,grade 3.

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 1, FEMALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24753
LUNGS	
- 01: Foamy contents, reddish color.	- Acute bronchopneumonia, by regurgitation/aspiration,grade 4.
TRACHEA	
- 01: Foamy contents.	- NOTHING ABNORMAL DISCOVERED.
	ANIMAL NO: C24756
SKIN	
- 01: Head region: scabs, several, up to 0.3 cm in diameter, (a).	- Ulceration, superficial, few small foci,grade 2.
THYMUS	
- 01: Right lobe: reddish color.	- Interstitial hemorrhage, multifocal,grade 2.
	ANIMAL NO: C24759
THYMUS	
- 01: Left lobe: reddish color.	- Interstitial hemorrhage,grade 4.

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 2, MALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24695
KIDNEYS	
- 01: Irregular color.	- NOTHING ABNORMAL DISCOVERED.

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 2, FEMALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24762
LIVER	
- 01: Median lobe sulcus: focus greyish/whitish, approx 0.2 cm in diameter.	- Tension lipidosis, one focus,grade 3.
	ANIMAL NO: C24765
UTERUS	
- 01: Both horns: dilatation.	- Dilated lumen,grade 2.
	ANIMAL NO: C24768
LIVER	
- 01: Median lobe sulcus: focus greyish/whitish, approx 0.3 cm in diameter.	- Perivascular fibrosis, one subcapsular area,grade 1.
	ANIMAL NO: C24769
LIVER	
- 01: Median lobe sulcus: focus greyish/whitish, approx 0.3 cm in diameter.	- Tension lipidosis, one focus,grade 3.
SKIN	
- 01: Foreleg(s): right, alopecia, approx 1.5 cm long, approx 0.5 cm wide, (a).	- Empty hair follicles, one focus,grade 1.

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 3, MALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24706
THYMUS	
- 01: Reddish color.	- Interstitial hemorrhage, multifocal,grade 2.

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 3, FEMALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24772
UTERUS	
- 01: Both horns: dilatation, serous contents.	- Dilated lumen,grade 4.
	ANIMAL NO: C24774
LIVER	
- 01: Accentuated lobular pattern.	- NOTHING ABNORMAL DISCOVERED.
- 02: Median lobe sulcus: focus yellowish, approx 0.3 cm in diameter.	- Tension lipidosis, one small focus,grade 1.
	ANIMAL NO: C24778
SKIN	
- 01: Head region: scabs, several, up to 0.2 cm in diameter, (a).	- Ulceration, superficial, some foci,grade 3.
THYMUS	
- 01: Right lobe: reddish color.	- Interstitial hemorrhage, a few foci,grade 2.
	ANIMAL NO: C24779
UTERUS	
- 01: Both horns: dilatation.	- Dilated lumen,grade 1.

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 4, MALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24715
LIVER	
- 01: Enlarged.	- Hepatocellular hypertrophy, few foci,grade 1.
	ANIMAL NO: C24716
EARS	
- 01: Left: enlarged.	- Chondropathy, a wide area in the pinna, unilateral,grade 4.
	ANIMAL NO: C24717
LIVER	
- 01: Accentuated lobular pattern.	- NOTHING ABNORMAL DISCOVERED.
	ANIMAL NO: C24718
LIVER	
- 01: Enlarged.	- Hepatocellular hypertrophy, a few areas,grade 2.
	ANIMAL NO: C24719

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY	DOSE GROUP 4, MALE
NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
LIVER	
- 01: Median lobe: adhesion together	- Capsular thickening, fibro-vascular, one focus,grade 2
- 02: Left lateral lobe: reduced in size.	- NOTHING ABNORMAL DISCOVERED.
- 03: Caudate lobe, right lateral lobe, right papillary process, left papillary process: enlarged.	- Hepatocellular hypertrophy, several areas,grade 3.

Table: 20 (continued)

CORRELATION TABLE: NECROPSY - MICROSCOPY — DOSE GROUP 4, FEMALE

NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
	ANIMAL NO: C24781
LIVER	
- 01: Median lobe sulcus: focus greyish/whitish, approx 0.3 cm in diameter.	- Tension lipidosis, one focus,grade 3.
	ANIMAL NO: C24782
UTERUS	
- 01: Both horns: dilatation, serous contents.	- Dilated lumen,grade 4.
	ANIMAL NO: C24784
LIVER	
- 01: Accentuated lobular pattern.	- NOTHING ABNORMAL DISCOVERED.
	ANIMAL NO: C24788
LIVER	
- 01: Median lobe sulcus: focus greyish/whitish, approx 0.2 cm in diameter.	- Tension lipidosis, one focus,grade 3.

[redacted]

REPORT : SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

[redacted]

CLINICAL STUDY FOR THE CLINICAL STUDY FOR THE VERIFICATION OF THE ABSENCE OF THE SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS COMPATIBILITY OF A COSMETIC TEST ARTICLE, BY REPEATED EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 112 (OR 111) HEALTHY ADULT SUBJECTS
(modified Marzulli and Maibach method)

contains 2% Diphenyl Dimethicone

[redacted]

TABLE OF CONTENTS

[redacted]

SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

[redacted]

CLINICAL STUDY FOR THE VERIFICATION OF THE ABSENCE OF THE SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS COMPATIBILITY OF A COSMETIC TEST ARTICLE, BY REPEATED EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 112 (OR 111) HEALTHY ADULT SUBJECTS (modified Marzulli and Maibach method)

SUBJECTS

143 subjects of both sexes, healthy adults, were recruited and selected after a general medical examination taking into account the inclusion and non-inclusion criteria, as well as the prohibition and restriction concepts defined in the study protocol : 119 came to [redacted] on the starting day of treatment.

113 panellists were then finally included by the Investigators on the basis of a clinical examination specific to the study, carried out just before its start, after signature of, among other things, the compensation modes form and of the informed consent statement : one of them abandoned before the first reading and another during the induction period (abandons not linked to the test article applications).

Analysis of the results was made from a selection of :
- 112 subjects for the evaluation of Primary Cutaneous Irritation,
- 111 subjects for the evaluation of cumulative irritation and of cutaneous sensitisation,
composed of 99 (or 98) women and 13 men, from 18 to 69 years old.

PROTOCOL

The protocol of the irritation and sensitisation study was divided up into 3 distinct periods :

- Induction period : during which the "preparing" or "sensitising" contacts between epidermis and test article may occur, which will possibly induce the allergical process without showing evidence of any clinical manifestation of hypersensitivity :

. 9 consecutive applications, to the same area, of about 0.02 ml per subject, of the test article as supplied, by occlusive epicutaneous route (Finn Chambers on Scanpor) for about 48 hours or for the first 3 week-ends 72 hours, to the skin of the back of the panellists.

- Rest period : or incubation period during which the cells' transformations possibly go on, leading to the modification of reactivity :

. 13 days without any application.

- "Challenge" phase : corresponding to the contact between the epidermis and the test article applied during the induction period and which aim is to reveal a clinical manifestation of induced immunological hypersensitivity :

. single application of about 0.02 ml, per subject, of the test article as supplied, by epicutaneous occlusive route for about 48 hours, on 2 areas of the skin of the back of the panellists (i.e., the same area as the one used for the induction and on an untreated symetrical area).

The cutaneous reaction, control of the primary and cumulative irritations, was evaluated by the macroscopic examination of the reactions possibly observed 15 to 30 minutes after removal of each patch corresponding to the induction period (scales provided by the Sponsor).

The cutaneous reaction, control of the sensitisation, was evaluated by the macroscopic examination of the reactions possibly noted, at least 30 minutes and about 48 hours after removal of the patches corresponding to the "challenge" application (scales provided by the Sponsor).

These examinations were performed by comparison to the reactions possibly obtained with a patch alone (without test article), applied in parallel under the same conditions, as a "negative" control.

Analysis and interpretation of the results were performed depending on the data obtained under the experimental conditions adopted :

- As regards evaluation of the sensitising potential, an erythema, of intensity higher or equal to 2 during the challenge, with or without palpable lesions, must be evaluated the following days to note whether the reaction diminishes or increases in order to specify between an allergic or irritant reaction. A rapid reduction in the reaction indicates an irritation (reaction decrescendo). A reaction, with infiltration/oedeme, that persists and/or increases over time generally indicates reaction of an allergic type (reaction crescendo).

- As regards cutaneous compatibility, this analysis was completed by the calculation of the Mean Irritation Index (M.I.I.) equal to the total of the quotations of the 9 readings corresponding to the induction, divided by the number of panellists included in this study and by the number of readings performed (maximum M.I.I. = 4).

[redacted]

RESULTS AND CONCLUSION

- Percentage of panellists having presented with one or several well visible to severe irritation reactions (score ≥ 2), during the induction : = **0%**

The Mean Irritation Index (M.I.I.), obtained during the induction was equal to 0.01, and compared to the one obtained with the control (patch alone, without any product) applied under the same conditions, thus enabled to classify arbitrarily the applications of the test article as "non irritant".

No pathological irritation, nor sensitisation reaction significant of a cutaneous intolerance was noted.

- Percentage of the sensitisation reactions observed = **0%**

No cutaneous **sensitisation** reaction was noted.

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of this test article, under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitisation.

QUALITY CONTROL

[redacted]

The quality control of the clinical studies, is carried out periodically. It is designed to ensure that all critical phases (investigational product applications and examinations or measurements) of a particular study type are controlled, at least once a quarter, for the studies carried out during this time period. Dates of these quality controls and study type concerned are given below.

The results of these quality controls were reported to the Dermatologist Investigators and to the General Management.

Types of study	Dates of quality controls	Dates of reports to the Dermatologist Investigators	Dates of reports to the General Management
. Identical study :	21 February 2006	22 February 2006	1st March 2006
. Raw data :	Induction : 6 March 2006	7 March 2006	14 March 2006
	Challenge : 23 March 2006	24 March 2006	31 March 2006

[redacted]

	Date of quality control	Date of report to the Dermatologist Investigators	Date of report to the General Management
Report (vs. compiled data):	28 June 2006	28 June 2006	28 June 2006

Signature : [redacted]

Date : 4/07/06

1. STUDY OBJECTIVE

The main aim of this study is to confirm that the application of cosmetic products, in 100 healthy adult subjects, under maximised application conditions, according to the modified Marzulli and Maibach method, does not lead to any delayed contact allergic reactions and its second objective is to evaluate, during the induction period, their irritant potential.

2. STUDY RELEVANCE

Cutaneous allergy is an individual phenomenon, of immune origin, which triggering requires 3 stages :

. penetration of the foreign substance (hapten) into the skin and forming of the allergen ;

. development of the immune reaction ;

. triggering of the reaction, by a new application of the allergenic molecule to the skin.

These 3 stages are thus required to check the absence of sensitising potential of a test article, and are at the root of the method described by Marzulli and Maibach *(protocol in compliance with the note of 4 August 1997 of the "Répression des Fraudes" to the "Fédération des Industries de la Parfumerie") :* repeated applications of the test article, by occlusive epicutaneous route, for 48 or 72 hours and for 3 consecutive weeks (induction stage), followed by a rest period and by a new application under occlusion, for 48 hours (challenge stage, during which cutaneous macroscopic examinations are performed according to the International Contact Dermatitis Research Group scale : I.C.D.R.G.).

The realisation of this trial under medical control, on a limited number of people thus enables to complete the data relative to the safety of a product by studying it under maximised exposure conditions.

The maximisation of the test conditions (occlusivity, leaving time, etc …) moreover enables to determine better the substances with a very weak allergenic potential

3. PRINCIPLE

- Induction period : during which the "preparing" or "sensitising" contacts between epidermis and test article may occur, which will possibly induce the allergical process without showing evidence of any clinical manifestation of hypersensitivity :

. 9 consecutive applications, to the same area, of about 0.02 ml or g, per subject, of the test article, by occlusive epicutaneous route (Finn Chambers on Scanpor) for about 48 hours or for the first 3 week-ends 72 hours, to the skin of the back of 100 healthy adult panellists, of both sexes.

- Rest period : or incubation period during which the cells' transformations possibly go on, leading to the modification of reactivity :

. 13 days without any application.

- "Challenge" phase : corresponding to the contact between the epidermis and the test article applied during the induction period and which aim is to reveal a clinical manifestation of induced immunological hypersensitivity :

. single application of about 0.02 ml or g, per subject, of the test article, by epicutaneous occlusive route for 48 hours, on 2 areas on the skin of the back of the panellists (i.e., the same area as the one used for the induction and on an untreated symmetrical area).

The cutaneous reaction, control of the primary and cumulative irritations, is evaluated by the macroscopic examination of the reactions possibly observed 15 to 30 minutes after removal of each patch corresponding to the induction period.

The cutaneous reaction, control of the sensitisation, is evaluated by the macroscopic examination of the reactions possibly noted, at least 30 minutes and about 48 hours after removal of the patches corresponding to the "challenge" application.

These examinations were performed by comparison to the reactions possibly obtained with a patch alone (without test article), or if necessary with a vehicle known as neutral, non irritant, non sensitising and non comedogenic, applied in parallel under the same conditions, as a "negative" control.

Analysis and interpretation of the results were performed depending on the data obtained under the experimental conditions adopted.

4. SUBJECTS

4.1. Principle of recruitment, selection and inclusion

The procedure for recruitment, selection and inclusion of the subjects who accepted to participate in this study, after informed consent, was elaborated to grant them clear and precise information, enabling them to appraise the aim and the consequences of their consent.

This procedure included in particular :
- a preliminary interview during which they were explained in particular the objective and the protocol of the study, the study timetable, the compensation modes, as well as the constraints linked to the study and the foreseeable risks even in case of stop of the study before its normal end ;
- the signature of an informed consent statement by the panellist : he could thus make his decision completely freely taking into account the conditions proposed ;
- the notification of his taking over by the insurances in civil liability subscribed independently by the Sponsor and [redacted] once the subject has been definitively admitted in the study by the Investigator.

The panellists recruited for this study were selected on the basis of the inclusion and non-inclusion criteria, as well as the prohibition and restriction concepts defined in the protocol.

The final inclusion of the subjects was determined by the Dermatologist, from a pre-study medical auto-questionnaire and from a clinical medical examination specific to the study, performed just before its start.

4.2. Inclusion criteria

- Origin : Caucasian.
- Justification for origin : the white colour of Caucasian people's skin enables easier evaluation of cutaneous reactions.

- Age : adults from 18 to 70 years.

- Sex : male and female.

- Health condition : it corresponded to the selection criteria defined in the procedures of [redacted] Bulgarie, in order to eliminate, as much as possible, the subjects incurring "risks" or presenting with redhibitory affections for the clinical studies performed by [redacted] These criteria were evaluated on the basis of questionnaires and clinical examinations listed in the protocol.

- Female subjects : having taken the necessary precautions to make sure not to be pregnant at least 3 months before the beginning of the study, during the whole study, and 3 months after the end of the study.

- Subjects able to justify a fixed abode.

- Subjects capable of giving their written consent.

- Understanding of the Bulgarian language : subjects informed of the test modalities, able to read the documents they were presented with and to hold to what they were explained.

- Subjects affiliated to a medical security organisation.

4.3. Non-inclusion criteria

- Subjects not presenting with the above-mentioned inclusion criteria.

- Subjects not having respected :
. the prohibition concerning the simultaneous acceptance of several biomedical research projects without direct benefit to the individual,
. the grace period during which a person may not be involved in any other biomedical research projects without direct benefit to the individual.

- Subjects having participated in a solar protection factor test in the last 4 to 8 weeks and/or in a sensitisation trial and/or in photo-irritation or photo-sensitisation studies in the last 3 months.

- Subjects deprived from liberty by a judiciary or administrative decision, sick subjects in an emergency situation.

- Under age or of age subjects protected by law, as well as those admitted in sanitary or social facilities.

- Subjects having refused to give their agreement by signing the informed consent statement.

- Subjects having undergone organ excision (kidney, lung, spleen, liver…), an organ transplant, a skull concussion with extended loss of consciousness since less than 5 years ago or with present after-effects.

- Subjects, either pregnant or breastfeeding mothers, or not using medically acceptable contraceptive methods.

- Subjects having :
. *the following disorders :* cardiovascular, pulmonary, digestive, neurologic, psychiatric, genital, urinary, haematological, endocrine, having a redhibitory aspect for the study concerned ;
. *an immunological deficit ;*
. *a background of drug intolerance* (local or general anaesthetics), and intolerance to cosmetics, to body hygiene or household products, to clothes, to products used at work such as rosin, rubber (gloves, adhesive tapes, plasters), nickel, aluminium ... ;
. *a background of contact allergies :*
. *immediate allergic reactions being presently treated :* asthma, periodic spasmodic rhinitis, conjunctivitis ;
. *cutaneous marks* on the experimental area which could interfere with the evaluation of the skin reactions (pigmentary disorders, scars, hyperpilosity, too many ephelis and naevi, sunburn…) ;
. *a febrile illness :* more than 24 hours of fever in the 8 days prior to the test article application.

- Subjects having been or presently being in the course of a long-term treatment, in particular with antihistamine, steroids, Betablockers (including collyrium), antibiotics, immuno-suppressor treatment (cyclosporine) and/or desensitisation.

-Subjects having had a treatment containing acid vitamin A or its derivatives since less than the 3 months prior to the start of the study.

- Subjects who were vaccinated in the 3 weeks preceding the start of the study or who plan on being vaccinated during the course of the study.

- Subject presenting with a cutaneous hyperactivity or a dermopathy.

- Subject having a severe reactivity to plasters or micropores.

- Subjects having a recently insolated skin, or having undergone heliotherapy in the month preceding the start of the study.

- Subjects smoking more than 10 cigarettes a day and/or having an excessive daily consumption of alcohol and not accepting to restrict these during the two days prior to the start of the study and throughout its whole duration

4.4. Prohibition and Restriction

For all the time of the applications (thus excepted during the rest period), the panellists could not dampen the treated area or apply plasters or practice a sport which could lead to an excessive perspiration. They could not use other products on the body (except for water and soap or the usual cleansing product) during the study. The use of medicine or a vaccination had to be reported to the Investigator, the latter being the only one to judge of the preservation or the exclusion of the panel.
The subjects could not be re-included in a test of the same type during the 3 months following the end of the test. However, the subjects who did not present with any cutaneous intolerance during the trial could be re-included one month after the end of the test for trials aiming to check the good compatibility or efficacy of other products (single patch test, in-use test, repeated applications "in open").

4.5. Number of subjects

This study was performed in an exclusive selection of :
- 112 subjects for the evaluation of Primary Cutaneous Irritation,
- 111 subjects for the evaluation of cumulative irritation and of cutaneous sensitisation.

Justification : sensitisation being an individual phenomenon, of immune origin, the test being performed under medical control and maximised conditions, this number corresponds to a minimum acceptable number, to put into evidence the sensitising potential of a test article.

4.6. Recording

The subjects were registered in the order of their inclusion, this being made progressively as they arrived.

5. CLINICAL STUDY (EXPERIMENTAL DESIGN)

5.1. Application

5.1.1. Application area

The applications of the test article were performed on a surface of about 50 mm² (8 mm in diameter) on the one hand, for the induction on the left side of the spine, and on the other hand, for the challenge phase on one side and the other of the spine (induction area and "blank" area), between the hips and shoulders. These areas had been submitted beforehand to a specific examination, at the occasion of the final inclusion **by the Dermatologist Investigator**, that is to say just before the start of the study on D1, **as well as on D36** (before the application of the challenge stage), in order to keep only surfaces free from any macroscopic trace of irritation or from any abnormality which could interfere with the interpretation of the results.

5.1.2. Preparation of the application area

The surface defined above was previously cleaned with distilled water, then dried with cotton-wool cellulose paper.

5.1.3. Patches

The applications of the test article were performed under occlusive patches (epitest : Finn Chambers on Scanpor, delivered by Promédica) during the whole study. The "Finn Chamber" makes an isolation chamber which ensures a good occlusion limited to the application area of the test article : it is composed of an 8 mm-diameter aluminium cupule covering a contact surface of 50 mm².

Each cupule is individually mounted onto an adhesive tape (Scanpor : Norgesplaster A/S Norway) applied in order to create the same pressure on the whole cupule.

Being under semi-liquid form, the test article was directly put into the cupule which was filled to 2/3 of its volume.

5.1.4. Dose level and concentration

- About 0.02 ml, per subject, of the test article as supplied, measured with an automatic micropipette (Eppendorf Multipipette : 10 to 100 µl).

- Justification for the dose level : it is the capacity of the cupule indicated by the manufacturer of the "Finn Chambers on Scanpor".

5.1.5. Administration routes

- Route : local epicutaneous

- Justification for the route : normal route of use and propitious to the induction of a sensitisation.

5.1.6. Application modalities

5.1.6.1. Induction period

- Application area : back, between the hips and the shoulders, on the left side of the spine and always on the same area.

- Test articles applied : the previously identified patches were carefully applied to the skin of the back, using several "ribbons" composed of 2 parallel rows, having a number of several isolation chambers corresponding to the number of test articles.
A "Small Finn Chambers" patch alone (without test article) was also affixed under the same conditions to act as a negative control.

- Frequency and administration time : 9 applications spread out over 3 weeks as follows :

1st week	:	Day 1 (Tuesday : 1st application), Day 3 (Thursday), Day 5 (Saturday),
2nd week	:	Day 8 (Tuesday), Day 10 (Thursday), Day 12 (Saturday),
3rd week	:	Day 15 (Tuesday), Day 17 (Thursday), Day 19 (Saturday).

- Duration of exposure : about 48 hours (1st, 2nd, 4th, 5th, 7th and 8th application) or 72 hours (3rd, 6th and 9th application). During the last patch removal, the application area of each product was marked off on the skin (using transparent cards with anatomic marks), in order to find the precise areas for the "challenge".

5.1.6.2. Rest period

The subjects were not submitted to any application from Day 23 (Wednesday) to Day 35 (Monday) inclusive, i.e. for a 13 day period.

5.1.6.3. "Challenge" phase

- Application area : back, between the hips and the shoulders, on the left and right side of the spine, on the same area as the one for the induction, precisely marked off, as well as on a symmetric area (on the right of the spine), having never received any product.

- Test articles applied : the test articles (left and right side of the spine), as well as one patch alone (without test article) applied under the same conditions, to act as "negative" control.

- Frequency and administration time point : single application on Day 36 (Tuesday).

- Duration of exposure : about 48 hours.

5.1.6.4. Supplementary "challenge" phase (particular case)

In the case of a doubtful clinical reaction during the challenge phase, or in order to confirm a positive reaction, or to try to determine the raw material(s) which could be the origin of these reactions, a single application under occlusive patch will be performed during 48 hours on the back, on an area having never received any product, in the 3 to 6 weeks following the application of the challenge phase, in the subjects concerned. This application will be performed on the one hand, with the corresponding formula(e) and on the other hand, with declination products [raw materials or "preparations" going into this (these) product(s)].

5.1.7. Security

If the adhesive of the patch provokes an intolerance leading to the stop of the applications to the concerned area, the bandage is not applied to the same site as the one used for the previous application, but to a site located near it.

When, during the induction and as of the 2nd application, a clear sign of intolerance (moderate to severe erythema : score ≥ 2) is observed on the application area of a test article, when removing the patches, its application is done on another site, located close to the previous one and the readings are performed on the 1st site until reversibility of the effects and on the 2nd site until the end of the induction (the changing of area can only be performed once). If an intolerance sign reappears on this 2nd site, the case is immediately discussed with the Sponsor and the application is interrupted until the "challenge" phase.

If the product turns out to be very irritant, the Sponsor is informed of this in order to examine another study protocol (application in open, reduction of the leaving time…).

In the case where there is suspicion of an allergic type of reaction, the product is not applied again and the case is discussed, in the shortest delay with the Sponsor.

The decision of reapplying or not the product during the challenge stage is taken by both the Investigator and the Sponsor.

A photograph is taken and sent to the Sponsor in the case of a marked reaction (induction or challenge).

If the applications provoke a severe or unforeseeable intolerance, the panellist must immediately inform the Clinical Investigator : this one will proceed, in the shortest delay, to a medical examination and [redacted]

5.2. Observations and clinical examinations

5.2.1. Reading times

The cutaneous examinations were performed on the one hand, during the induction, about 15 to 30 minutes after removal of the patches of the test articles, in order to appraise their possible irritation potential and on the other hand, at least 30 minutes and about 48 hours after removal of the patches corresponding to the "challenge" stage (i.e. on D38 and D40 : examinations performed by the Dermatologist) to evaluate their possible sensitising potential.

Special attention was paid to the reading carried out after the 1st application (D3), in order to check the irritant potential of the test articles applied, under the above-mentioned conditions.

In all cases, during the challenge stage, any late cutaneous reaction on the test area, after the reading at time point 96 hours (that is to say 48 hours after the removal), must be reported by the subject who must come back to the laboratory for an evaluation of the site by the Investigator.

If the supplementary challenge study is realised, the cutaneous examinations will be performed 2, 3 and 4 days after the new application. If necessary, the readings will continue each day until complete disappearance of the reactions.

5.2.2. Evaluation of the cutaneous irritation and of the sensitising potential

The cutaneous readings were always performed under the same conditions, in particular as regards the lighting ("day light" lamp).

The cutaneous reactions possibly observed during the induction and the "challenge" stage were evaluated, for each subject and for each product, according to the 3 following scales (provided by the Sponsor of the Study) :

(E) Erythema

No erythema 0
Slight-slightly pinkish erythema 1
Moderate-well defined erythema..... 2
Severe erythema 3
Caustic effect – erosive and/or necrotic aspect 4

(A) Scale of the International Contact Dermatitis Research Group : I.C.D.R.G.

No reaction* 0
Slightly positive reaction : erythema, infiltration, possibly papule..... 1 (+)
Strongly positive reaction : erythema, infiltration, papule, vesicles ..... 2 (++)
Very severely positive reaction : intense erythema, infiltration,
coalescent vesicles leading to the forming of a bullae ..... 3 (+++)

* *no reaction according to the I.C.D.R.G.*
for the doubtful reactions (±), read the Erythema column.

N.B. : the results which are listed in this report correspond to the ones obtained by the difference between the area on which were applied the test articles and the one of the "negative" control.

(M) Supplementary mentions / other reactions

H = Homogeneous infiltration / oedema from 1 to 3 [1 = slight ; 2 = moderate ; 3 = severe]
P = Papule (precise the number)
V = Vesicle (precise the number)
B = Bullae (precise the number)
Pe = Petechies
S = Spreading beyond the patch area (infiltration or erythema)
SV = Soap effect
F = Fissuring
D = Desquamation
Dr = Dryness
C = Skin coloration – hyperpigmentation
HY = Hypopigmentation
FR = Follicular reaction
NA = Non applied product
T = Tape reaction
I = Itching at the test site
* = Free comments
N9G = No 9th reading
CR = Exudation and/or surface encrustation

X = The following patch is not applied ; indication of the residual reactions between brackets
- = Absent subject
MU = Make-up patch

5.3. Data analysis and interpretation of the results

Analysis and interpretation of the results were performed according to the data obtained under the experimental conditions adopted.

5.3.1. Sensitising potential

For the analysis of the sensitising potential, only the subjects having participated in the challenge stage and having respected the protocol were taken into account.
The interpretation of the sensitising potential was made from results in compliance to the I.C.D.R.G. scale (see chapter. 5.2.2.).
An erythema, which intensity is superior or equal to 2 during the challenge stage, with or without oedema, must be evaluated in the following days to note if the reaction diminishes or increases, in order to precise if the reaction observed is of allergic or irritative type. A reaction which develops itself and lasts in time is generally significant of an allergic reaction.

5.3.2. Cutaneous compatibility

All the subjects included were taken into account for the analysis of the cutaneous compatibility, whatever the number of times they visited the Investigator, during the induction stage.

This analysis was completed by the calculation of the Mean Irritation Index (M.I.I.), equal to the sum of the quotations of the 9 readings corresponding to the induction divided by the number of panellists included in this study and the number of readings performed :

$$\text{M.I.I.} = \frac{\Sigma \text{ quotations of the 9 readings (all the subjects)}}{\text{Number of subjects x 9 (readings)}}$$

For this index calculation, it was defined that :

. if a subject is absent for an examination, the quotation of the day of absence is identical to the one of the day before ;

. if an application is stopped because of a too severe reaction, the maximum quotation (4) is attributed on the day following the stop of the test article application for the considered area and this, until the end of the tolerance test ;

. if the applications are stopped for any other reason, the quotations of the subject are excluded of the indices calculation.

The M.I.I. thus obtained enabled arbitrary classification of the test articles as follows (taking into account the reactions and the M.I.I. calculated on the control area) :

M.I.I.	**Classification of the test article**
lower than 0.25	non-irritant
0.25 to 1 not included	slightly irritant
1 to 2 not included	moderately irritant
2 to 3 not included	very irritant
3 to 4	very severely irritant

6. REGULATIONS, CONFIDENTIALITY AND LEGAL FORMALITIES

6.1. Regulations

This study was performed in agreement with the most recent recommendations of the World Medical Association (Declaration of Helsinki 1964, amended in Tokyo, 2004) and the Good Clinical Practices published by I.C.H. (CPMP/ICH/135/95).

6.2. Confidentiality

Any information regarding the health condition of the panellists and the results of the clinical examinations, performed before the start of the study, for their recruitment, their selection and inclusion, are submitted to the rules of the medical secrecy : under no circumstance can this information be communicated to the Sponsor.

To ensure preservation of the subjects' anonymity, they were identified by a code number using 5 letters, corresponding to the first 3 letters of their surname, then the first 2 letters of their first Christian name, and for the study, by a number corresponding to their inclusion order in the test.

At the end of the study, the page called "Subject Identification Form", in which are mentioned notably the name and address of the subject, was removed from the study notebook and destroyed.

The investigators and any person collaborating in the trials are submitted to the rules of the professional secrecy concerning, among others, the nature of the test articles, the trials, the people undergoing them and the results obtained.

6.3. Legal formalities

6.3.1. Subscription of insurance by the Sponsor

The Sponsor subscribed an insurance (contract nº 481B) to guarantee its civil liability vis-à-vis the subjects: Zurich International (France), General Liability policy nº 07020319G.

6.3.2. Information and informed consent

An information sheet was given to each subject, in order to inform him of, in particular :
- the aim of the research, its methodology and its duration ;
- the constraints linked to the study and the foreseeable risks, including in case of stop of the research before its normal end ;
- the non-inclusion period, the amount of the compensation, the possibility for the panellist to check the exactitude of the data contained in his medical file and their subsequent destruction.

This information enabled the subject to sign an informed participation consent, with full knowledge of the facts.

6.3.3. Data recording and archiving

All handwritten data were immediately transcribed in laboratory notebooks constituted, paginated and stapled before the start of the study.

[redacted]

Once this period is over, the Sponsor is contacted regarding its archives. No archive destroying will be done without the written agreement from the Sponsor.

[redacted]

7. PROTOCOL COMPLIANCE

Analysis of the results was carried out on a panel of 112 (or 111) subjects, instead of the 100 stated in the protocol.

This deviation is not considered to have affected, in a notable way, the quality or the interpretation of the results obtained.

8. BIBLIOGRAPHICAL REFERENCE

Marzulli F.N. and Maibach H.I.
Contact allergy, predictive testing in man.
Contact Dermatitis, 1976, 2,1 – 17

- I.C.H. Topic E6 = Guideline for good clinical practice - May 1, 1996

- I.C.D.R.G. = The International Contact Dermatitis Research Group. Fregert S. Manuel of Contact Dermatitis 2nd Edition

- Declaration of Helsinki adopted by the 18th world medical assembly in Helsinki, Finland, in June 1964, and amended by the 29th world medical assembly in Tokyo, Japan, in October 1975, by the 35th world medical assembly in Venice, Italy, in October 1983, by the 41st world medical assembly in Hong Kong, in September 1989, in Somerset West, Republic of South Africa, in 1996, in Edinburgh, Scotland in October 2000, and in Washington, USA, in 2002, and in Tokyo, Japan in 2004.

9. RESULTS

See the detailed results which are listed in the appendix (Tables I to V).

10. DISCUSSION AND CONCLUSION

- Percentage of panellists having presented with one or several well visible to severe irritation reactions (score ≥ 2), during the induction : = **0%**

The Mean Irritation Index (M.I.I.), obtained during the induction was equal to 0.01, and compared to the one obtained with the control (patch alone, without any product) applied under the same conditions, thus enabled to classify arbitrarily the applications of the test article as "non irritant".

No pathological irritation, nor sensitisation reaction significant of a cutaneous intolerance was noted.

- Percentage of the sensitisation reactions observed = **0%**

No cutaneous **sensitisation** reaction was noted.

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of this test article, under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitisation.

APPENDIX 1

RESULTS

TABLE II

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE CONTROL

ALLERGY [A] AND IRRITATION [E]

CONTROL : cupule alone, without test article.

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																											Σ QUOT.	
	DAYS																												
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
01	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
02	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
03	0	0	-	0	0	-	0	0	-	0	1	-	0	1	-	0	1	-	0	0	-	0	0	-	0	0	-	0	3
04	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
05	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
06	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
07	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
08	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
09	0	0	-	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
10	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
11	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
12	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
13	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
14	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
15	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
16	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
17	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
18	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
19	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
20	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
21	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
22	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
23	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
24	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
25	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE II (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE CONTROL

ALLERGY [A] AND IRRITATION [E]

CONTROL : cupule alone, without test article.

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																											Σ QUOT.	
	DAYS																												
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
26	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
27	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
28	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
29	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
30	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
31	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
32	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
33	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
34	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	1
35	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
36	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
37	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
38	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
39	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
40	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
41	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
42	0	0	-	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	/	/	/	/	/	/	/	/	/	/	/
43	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
44	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
45	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
46	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
47	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
48	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
49	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
50	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE II (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE CONTROL

ALLERGY [A] AND IRRITATION [E]

CONTROL : cupule alone, without test article.

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																											Σ QUOT.	
	DAYS																												
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
51	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
52	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
53	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
54	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
55	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
56	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
57	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
58	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
59	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
60	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
61	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
62	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
63	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
64	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
65	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
66	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
67	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
68	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
69	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
70	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
71	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
72	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
73	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
74	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
75	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE II (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE CONTROL

ALLERGY [A] AND IRRITATION [E]

CONTROL : cupule alone, without test article.

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																											Σ QUOT.	
	DAYS																												
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
76	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
77	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
78	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
79	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
80	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
81	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
82	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
83	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
84	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
85	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
86	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
87	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
88	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
89	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
90	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
91	0	0	-	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
92	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
93	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
94	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
95	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
96	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
97	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
98	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
99	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
100	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE II (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE CONTROL

ALLERGY [A] AND IRRITATION [E]

CONTROL : cupule alone, without test article.

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																										Σ QUOT.	
	DAYS																											
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
102	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
103	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
104	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
105	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
106	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
107	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
108	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
109	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
110	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
111	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
112	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
113	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TOTAL = 11
M.I.I. = 0.01

SUPPLEMENTARY MENTION [M] :

/ = Abandon during the study.

OTHER OBSERVATION : Nothing to report.

TABLE III

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

INVESTIGATIONAL PRODUCT : [redacted]

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																											Σ QUOT.	
	DAYS																												
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
01	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
02	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
03	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
04	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
05	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
06	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
07	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
08	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
09	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
10	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
11	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
12	0	0	-	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
13	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
14	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
15	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
16	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
17	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
18	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
19	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
20	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
21	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
22	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
23	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
24	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
25	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE III (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

INVESTIGATIONAL PRODUCT : [redacted]

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																										Σ QUOT.	
	DAYS																											
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
26	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
27	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
28	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
29	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
30	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
31	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
32	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
33	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
34	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
35	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
36	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
37	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
38	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
39	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
40	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
41	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
42	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	/	/	/	/	/	/	/	/	/	/	/
43	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
44	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
45	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
46	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
47	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	1
48	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
49	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
50	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE III (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

INVESTIGATIONAL PRODUCT : [redacted]

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																											Σ QUOT.	
	DAYS																												
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
51	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
52	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
53	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
54	0	0	-	0	0	-	0	1	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1
55	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
56	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
57	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
58	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
59	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
60	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
61	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
62	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
63	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
64	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
65	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
66	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
67	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
68	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
69	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
70	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
71	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
72	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	1	-	0	1	-	0	0	-	0	2
73	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
74	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
75	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE III (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE INVESTIGATIONAL PRODUCT

A L L E R G Y [A] A N D I R R I T A T I O N [E]

INVESTIGATIONAL PRODUCT : [redacted]

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																											Σ QUOT.	
	DAYS																												
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
76	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
77	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
78	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
79	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
80	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
81	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
82	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
83	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
84	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
85	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
86	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
87	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
88	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
89	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
90	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
91	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
92	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
93	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
94	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
95	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
96	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
97	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
98	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
99	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
100	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TABLE III

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE INDUCTION PERIOD FOR THE INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

INVESTIGATIONAL PRODUCT : [redacted]

VOL. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																										Σ QUOT.	
	DAYS																											
	3			5			8			10			12			15			17			19			22				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
102	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
103	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
104	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
105	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
106	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
107	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
108	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
109	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
110	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
111	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
112	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
113	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0

TOTAL = 5
M.I.I. = 0.01

SUPPLEMENTARY MENTION [M] :

/ = Abandon during the study.

OTHER OBSERVATION : Nothing to report.

TABLE IV

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE CONTROL

S E N S I T I S A T I O N

CONTROL : cupule alone, without test article.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
01	0	0	-	0	0	-	0	0	-	0	0	-	-
02	0	0	-	0	0	-	0	0	-	0	0	-	-
03	0	0	-	0	0	-	0	0	-	0	0	-	-
04	0	0	-	0	0	-	0	0	-	0	0	-	-
05	0	0	-	0	0	-	0	0	-	0	0	-	-
06	0	0	-	0	0	-	0	0	-	0	0	-	-
07	0	0	-	0	0	-	0	0	-	0	0	-	-
08	0	0	-	0	0	-	0	0	-	0	0	-	-
09	0	0	-	0	0	-	0	0	-	0	0	-	-
10	0	0	-	0	0	-	0	0	-	0	0	-	-
11	0	0	-	0	0	-	0	0	-	0	0	-	-
12	0	0	-	0	0	-	0	0	-	0	0	-	-
13	0	0	-	0	0	-	0	0	-	0	0	-	-
14	0	0	-	0	0	-	0	0	-	0	0	-	-
15	0	0	-	0	0	-	0	0	-	0	0	-	-
16	0	0	-	0	0	-	0	0	-	0	0	-	-
17	0	0	-	0	0	-	0	0	-	0	0	-	-
18	0	0	-	0	0	-	0	0	-	0	0	-	-
19	0	0	-	0	0	-	0	0	-	0	0	-	-
20	0	0	-	0	0	-	0	0	-	0	0	-	-
21	0	0	-	0	0	-	0	0	-	0	0	-	-
22	0	0	-	0	0	-	0	0	-	0	0	-	-
23	0	0	-	0	0	-	0	0	-	0	0	-	-
24	0	0	-	0	0	-	0	0	-	0	0	-	-
25	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE CONTROL

S E N S I T I S A T I O N

CONTROL : cupule alone, without test article.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
26	0	0	-	0	0	-	0	0	-	0	0	-	-
27	0	0	-	0	0	-	0	0	-	0	0	-	-
28	0	0	-	0	0	-	0	0	-	0	0	-	-
29	0	0	-	0	0	-	0	0	-	0	0	-	-
30	0	0	-	0	0	-	0	0	-	0	0	-	-
31	0	0	-	0	0	-	0	0	-	0	0	-	-
32	0	0	-	0	0	-	0	0	-	0	0	-	-
33	0	0	-	0	0	-	0	0	-	0	0	-	-
34	0	0	-	0	0	-	0	0	-	0	0	-	-
35	0	0	-	0	0	-	0	0	-	0	0	-	-
36	0	0	-	0	0	-	0	0	-	0	0	-	-
37	0	0	-	0	0	-	0	0	-	0	0	-	-
38	0	0	-	0	0	-	0	0	-	0	0	-	-
39	0	0	-	0	0	-	0	0	-	0	0	-	-
40	0	0	-	0	0	-	0	0	-	0	0	-	-
41	0	0	-	0	0	-	0	0	-	0	0	-	-
43	0	0	-	0	0	-	0	0	-	0	0	-	-
44	0	0	-	0	0	-	0	0	-	0	0	-	-
45	0	0	-	0	0	-	0	0	-	0	0	-	-
46	0	0	-	0	0	-	0	0	-	0	0	-	-
47	0	0	-	0	0	-	0	0	-	0	0	-	-
48	0	0	-	0	0	-	0	0	-	0	0	-	-
49	0	0	-	0	0	-	0	0	-	0	0	-	-
50	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE CONTROL

S E N S I T I S A T I O N

CONTROL : cupule alone, without test article.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
51	0	0	-	0	0	-	0	0	-	0	0	-	-
52	0	0	-	0	0	-	0	0	-	0	0	-	-
53	0	0	-	0	0	-	0	0	-	0	0	-	-
54	0	0	-	0	0	-	0	0	-	0	0	-	-
55	0	0	-	0	0	-	0	0	-	0	0	-	-
56	0	0	-	0	0	-	0	0	-	0	0	-	-
57	0	0	T	0	0	T	0	0	-	0	0	-	-
58	0	0	-	0	0	-	0	0	-	0	0	-	-
59	0	0	-	0	0	-	0	0	-	0	0	-	-
60	0	0	-	0	0	-	0	0	-	0	0	-	-
61	0	0	-	0	0	-	0	0	-	0	0	-	-
62	0	0	-	0	0	-	0	0	-	0	0	-	-
63	0	0	-	0	0	-	0	0	-	0	0	-	-
64	0	0	-	0	0	-	0	0	-	0	0	-	-
65	0	0	-	0	0	-	0	0	-	0	0	-	-
66	0	0	-	0	0	-	0	0	-	0	0	-	-
67	0	0	-	0	0	-	0	0	-	0	0	-	-
68	0	0	-	0	0	-	0	0	-	0	0	-	-
69	0	0	-	0	0	-	0	0	-	0	0	-	-
70	0	0	-	0	0	-	0	0	-	0	0	-	-
71	0	0	-	0	0	-	0	0	-	0	0	-	-
72	0	0	-	0	0	-	0	0	-	0	0	-	-
73	0	0	-	0	0	-	0	0	-	0	0	-	-
74	0	0	-	0	0	-	0	0	-	0	0	-	-
75	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE CONTROL

S E N S I T I S A T I O N

CONTROL : cupule alone, without test article.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
76	0	0	T	0	0	T	0	0	-	0	0	-	-
77	0	0	-	0	0	-	0	0	-	0	0	-	-
78	0	0	-	0	0	-	0	0	-	0	0	-	-
79	0	0	-	0	0	-	0	0	-	0	0	-	-
80	0	0	-	0	0	-	0	0	-	0	0	-	-
81	0	0	T	0	0	T	0	0	-	0	0	-	-
82	0	0	-	0	0	-	0	0	-	0	0	-	-
83	0	0	-	0	0	-	0	0	-	0	0	-	-
84	0	0	-	0	0	-	0	0	-	0	0	-	-
85	0	0	-	0	0	-	0	0	-	0	0	-	-
86	0	0	-	0	0	-	0	0	-	0	0	-	-
87	0	0	-	0	0	-	0	0	-	0	0	-	-
88	0	0	-	0	0	-	0	0	-	0	0	-	-
89	0	0	-	0	0	-	0	0	-	0	0	-	-
90	0	0	T	0	0	T	0	0	-	0	0	-	-
91	0	0	-	0	0	-	0	0	-	0	0	-	-
92	0	0	-	0	0	-	0	0	-	0	0	-	-
93	0	0	-	0	0	-	0	0	-	0	0	-	-
94	0	0	-	0	0	-	0	0	-	0	0	-	-
95	0	0	-	0	0	-	0	0	-	0	0	-	-
96	0	0	-	0	0	-	0	0	-	0	0	-	-
97	0	0	-	0	0	-	0	0	-	0	0	-	-
98	0	0	-	0	0	-	0	0	-	0	0	-	-
99	0	0	-	0	0	-	0	0	-	0	0	-	-
100	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE CONTROL EXAMINATIONS

S E N S I T I S A T I O N

CONTROL : cupule alone, without test article.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
102	0	0	-	0	0	-	0	0	-	0	0	-	-
103	0	0	T	0	0	T	0	0	-	0	0	-	-
104	0	0	-	0	0	-	0	0	-	0	0	-	-
105	0	0	-	0	0	-	0	0	-	0	0	-	-
106	0	0	-	0	0	-	0	0	-	0	0	-	-
107	0	0	-	0	0	-	0	0	-	0	0	-	-
108	0	0	-	0	0	-	0	0	-	0	0	-	-
109	0	0	-	0	0	-	0	0	-	0	0	-	-
110	0	0	T	0	0	T	0	0	-	0	0	-	-
111	0	0	-	0	0	-	0	0	-	0	0	-	-
112	0	0	T	0	0	T	0	0	-	0	0	-	-
113	0	0	-	0	0	-	0	0	-	0	0	-	-

SUPPLEMENTARY MENTION [M] :

T = Tape reaction.

OTHER OBSERVATION : Nothing to report.

TABLE V

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE INVESTIGATIONAL PRODUCT

S E N S I T I S A T I O N

INVESTIGATIONAL PRODUCT : [redacted]
as supplied.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
01	0	0	-	0	0	-	0	0	-	0	0	-	-
02	0	0	-	0	0	-	0	0	-	0	0	-	-
03	0	0	-	0	0	-	0	0	-	0	0	-	-
04	0	0	-	0	0	-	0	0	-	0	0	-	-
05	0	0	-	0	0	-	0	0	-	0	0	-	-
06	0	0	-	0	0	-	0	0	-	0	0	-	-
07	0	0	-	0	0	-	0	0	-	0	0	-	-
08	0	0	-	0	0	-	0	0	-	0	0	-	-
09	0	0	-	0	0	-	0	0	-	0	0	-	-
10	0	0	-	0	0	-	0	0	-	0	0	-	-
11	0	0	-	0	0	-	0	0	-	0	0	-	-
12	0	0	-	0	0	-	0	0	-	0	0	-	-
13	0	0	-	0	0	-	0	0	-	0	0	-	-
14	0	0	-	0	0	-	0	0	-	0	0	-	-
15	0	0	-	0	0	-	0	0	-	0	0	-	-
16	0	0	-	0	0	-	0	0	-	0	0	-	-
17	0	0	-	0	0	-	0	0	-	0	0	-	-
18	0	0	-	0	0	-	0	0	-	0	0	-	-
19	0	0	-	0	0	-	0	0	-	0	0	-	-
20	0	0	-	0	0	-	0	0	-	0	0	-	-
21	0	0	-	0	0	-	0	0	-	0	0	-	-
22	0	0	-	0	0	-	0	0	-	0	0	-	-
23	0	0	-	0	0	-	0	0	-	0	0	-	-
24	0	0	-	0	0	-	0	0	-	0	0	-	-
25	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE INVESTIGATIONAL PRODUCT

S E N S I T I S A T I O N

INVESTIGATIONAL PRODUCT : [redacted]
as supplied.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
26	0	0	-	0	0	-	0	0	-	0	0	-	-
27	0	0	-	0	0	-	0	0	-	0	0	-	-
28	0	0	-	0	0	-	0	0	-	0	0	-	-
29	0	0	-	0	0	-	0	0	-	0	0	-	-
30	0	0	-	0	0	-	0	0	-	0	0	-	-
31	0	0	-	0	0	-	0	0	-	0	0	-	-
32	0	0	-	0	0	-	0	0	-	0	0	-	-
33	0	0	-	0	0	-	0	0	-	0	0	-	-
34	0	0	-	0	0	-	0	0	-	0	0	-	-
35	0	0	-	0	0	-	0	0	-	0	0	-	-
36	0	0	-	0	0	-	0	0	-	0	0	-	-
37	0	0	-	0	0	-	0	0	-	0	0	-	-
38	0	0	-	0	0	-	0	0	-	0	0	-	-
39	0	0	-	0	0	-	0	0	-	0	0	-	-
40	0	0	-	0	0	-	0	0	-	0	0	-	-
41	0	0	-	0	0	-	0	0	-	0	0	-	-
43	0	0	-	0	0	-	0	0	-	0	0	-	-
44	0	0	-	0	0	-	0	0	-	0	0	-	-
45	0	0	-	0	0	-	0	0	-	0	0	-	-
46	0	0	-	0	0	-	0	0	-	0	0	-	-
47	0	0	-	0	0	-	0	0	-	0	0	-	-
48	0	0	-	0	0	-	0	0	-	0	0	-	-
49	0	0	-	0	0	-	0	0	-	0	0	-	-
50	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE INVESTIGATIONAL PRODUCT

S E N S I T I S A T I O N

INVESTIGATIONAL PRODUCT : [redacted]
as supplied.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
51	0	0	-	0	0	-	0	0	-	0	0	-	-
52	0	0	-	0	0	-	0	0	-	0	0	-	-
53	0	0	-	0	0	-	0	0	-	0	0	-	-
54	0	0	-	0	0	-	0	0	-	0	0	-	-
55	0	0	-	0	0	-	0	0	-	0	0	-	-
56	0	0	-	0	0	-	0	0	-	0	0	-	-
57	0	0	T	0	0	T	0	0	-	0	0	-	-
58	0	0	-	0	0	-	0	0	-	0	0	-	-
59	0	0	-	0	0	-	0	0	-	0	0	-	-
60	0	0	-	0	0	-	0	0	-	0	0	-	-
61	0	0	-	0	0	-	0	0	-	0	0	-	-
62	0	0	-	0	0	-	0	0	-	0	0	-	-
63	0	0	-	0	0	-	0	0	-	0	0	-	-
64	0	0	-	0	0	-	0	0	-	0	0	-	-
65	0	0	-	0	0	-	0	0	-	0	0	-	-
66	0	0	-	0	0	-	0	0	-	0	0	-	-
67	0	0	-	0	0	-	0	0	-	0	0	-	-
68	0	0	-	0	0	-	0	0	-	0	0	-	-
69	0	0	-	0	0	-	0	0	-	0	0	-	-
70	0	0	-	0	0	-	0	0	-	0	0	-	-
71	0	0	-	0	0	-	0	0	-	0	0	-	-
72	0	1	-	0	0	-	0	0	-	0	0	-	-
73	0	0	-	0	0	-	0	0	-	0	0	-	-
74	0	0	-	0	0	-	0	0	-	0	0	-	-
75	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE INVESTIGATIONAL PRODUCT

S E N S I T I S A T I O N

INVESTIGATIONAL PRODUCT : [redacted]
as supplied.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E](0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
76	0	0	T	0	0	T	0	0	-	0	0	-	-
77	0	0	-	0	0	-	0	0	-	0	0	-	-
78	0	0	-	0	0	-	0	0	-	0	0	-	-
79	0	0	-	0	0	-	0	0	-	0	0	-	-
80	0	0	-	0	0	-	0	0	-	0	0	-	-
81	0	0	T	0	0	T	0	0	-	0	0	-	-
82	0	0	-	0	0	-	0	0	-	0	0	-	-
83	0	0	-	0	0	-	0	0	-	0	0	-	-
84	0	0	-	0	0	-	0	0	-	0	0	-	-
85	0	0	-	0	0	-	0	0	-	0	0	-	-
86	0	0	-	0	0	-	0	0	-	0	0	-	-
87	0	0	-	0	0	-	0	0	-	0	0	-	-
88	0	0	-	0	0	-	0	0	-	0	0	-	-
89	0	0	-	0	0	-	0	0	-	0	0	-	-
90	0	0	T	0	0	T	0	0	-	0	0	-	-
91	0	0	-	0	0	-	0	0	-	0	0	-	-
92	0	0	-	0	0	-	0	0	-	0	0	-	-
93	0	0	-	0	0	-	0	0	-	0	0	-	-
94	0	0	-	0	0	-	0	0	-	0	0	-	-
95	0	0	-	0	0	-	0	0	-	0	0	-	-
96	0	0	-	0	0	-	0	0	-	0	0	-	-
97	0	0	-	0	0	-	0	0	-	0	0	-	-
98	0	0	-	0	0	-	0	0	-	0	0	-	-
99	0	0	-	0	0	-	0	0	-	0	0	-	-
100	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V (con't)

RESULTS OF OBSERVATIONS AND CLINICAL EXAMINATIONS DURING THE CHALLENGE PHASE FOR THE INVESTIGATIONAL PRODUCT

S E N S I T I S A T I O N

INVESTIGATIONAL PRODUCT : [redacted]
as supplied.

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (lack of sensitisation)
	at least 30 minutes						(about) 48 h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
102	0	0	-	0	0	-	0	0	-	0	0	-	-
103	0	0	T	0	0	T	0	0	-	0	0	-	-
104	0	0	-	0	0	-	0	0	-	0	0	-	-
105	0	0	-	0	0	-	0	0	-	0	0	-	-
106	0	0	-	0	0	-	0	0	-	0	0	-	-
107	0	0	-	0	0	-	0	0	-	0	0	-	-
108	0	0	-	0	0	-	0	0	-	0	0	-	-
109	0	0	-	0	0	-	0	0	-	0	0	-	-
110	0	0	T	0	0	T	0	0	-	0	0	-	-
111	0	0	-	0	0	-	0	0	-	0	0	-	-
112	0	0	T	0	0	T	0	0	-	0	0	-	-
113	0	0	-	0	0	-	0	0	-	0	0	-	-

SUPPLEMENTARY MENTION [M] :

T = Tape reaction.

OTHER OBSERVATION : Nothing to report.

[redacted]

[redacted]

TEST ITEM
71582

STUDY TITLE
EVALUATION OF SKIN SENSITIZATION POTENTIAL IN MICE USING THE LOCAL LYMPH NODE ASSAY (LLNA)

contains 15% Diphenyl Dimethicone

[redacted]

DATE OF ISSUE
22 July 2003

[redacted]

[redacted]

[redacted]

CONTENTS

STATEMENT OF THE STUDY DIRECTOR

The study was performed in compliance with the principles of Good Laboratory Practice as described in:

- OECD Principles on Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98) 17.
- Décret N° 98-1312 du 31 décembre 1998 concernant les Bonnes Pratiques de Laboratoire (Journal Officiel du 1er janvier 1999), Ministère de l'Economie, des Finances et de l'Industrie.
- 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 harmonization 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 (OJ No. L 77 of 23.3.1999).

The study was also conducted in compliance with the following Animal Health regulations:

- Council Directive 86/609/EEC of 24th November 1986 on the harmonization of laws, regulations or administrative provisions relating to the protection of animals used for experimental or other scientific purposes.
- Guidance document on the recognition, assessment, and use of clinical signs as humane endpoints for experimental animals used in safety evaluation, OECD Environmental Health and Safety Publications, No. 19.

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained during the performance of the study.

This study was performed at CIT, BP 563, 27005 Evreux, France.

Toxicology [redacted] 18 July 2003

OTHER SCIENTIST INVOLVED IN THIS STUDY

[redacted]

[redacted]

STATEMENT OF QUALITY ASSURANCE UNIT

Type of inspections	Dates		
	Inspections	Reported to Study Director (*)	Reported to Management (*)
Study plan	19 February 2003	19 February 2003	19 February 2003
Report	23 June 2003	30 June 2003	1 July 2003

[redacted]

[redacted]

(*) The dates indicated correspond to the dates of signature of audit reports by Study Director and Management.

SUMMARY

The aim of this study was to evaluate the potential of the test item [redacted] to induce delayed contact hypersensitivity using the murine Local Lymph Node Assay (LLNA).
This study was conducted in compliance with the principles of Good Laboratory Practice Regulations.

Methods

Twenty-eight female CBA/J mice were allocated to seven groups of four animals each:
- five treated groups receiving the test item [redacted] the concentration of 2.5, 5, 10, 25 or 50%,
- one negative control group receiving the vehicle (mixture acetone/olive oil (4/1, v/v)),
- one positive control group receiving the reference item, α-hexylcinnamaldehyde (HCA), a moderate sensitizer, at the concentration of 25% in AOO (4/1, v/v).

The test item, vehicle or reference item was applied over the ears (25 µL per ear) for three consecutive days (days 1, 2 and 3). After 2 days of resting, the proliferation of the lymph node cells in the lymph node draining the application site was measured by incorporation of tritiated methyl thymidine (day 6). The obtained values were used to calculate stimulation indices (SI).

The irritant potential of the test item was assessed in parallel by measurement of ear thickness on days 1, 2, 3 and 6.

Results

The test item was freely soluble in the first recommended vehicle, acetone/olive oil (4/1, v/v). A homogenous dosage form was obtained whatever the proportion.

Systemic clinical signs and mortality
Two out of four animals given the test item at the concentration of 10% were found dead on day 3; sedation was recorded prior to death. In addition, 1/4 animals given the test item at the concentration of 50% was found dead on day 6; piloerection, dyspnea, sedation and round back were observed prior to death.
As no evidence of a dose relationship was observed and as no clinical signs and no mortality were noted in the other treated groups, these deaths were not attributed to the treatment with the test item.

Local irritation
No cutaneous reactions and no noteworthy increases in ear thickness were observed in the animals of the treated groups when compared to the vehicle control group.

Proliferation assay
No positive lymphoproliferative response (SI > 3) was noted at any tested concentration.
In the treated groups, the incorporation of tritiated methyl thymidine was slightly lower than that observed in the vehicle control group and a slight tendency to a dose-related decrease in this incorporation was noted.

The results are presented in the following table:

Treatment	Concentration (%)	Signs of local irritation	Stimulation Index (SI)
Test item	2.5	no	0.71
Test item	5	no	0.79
Test item	10	no	0.70
Test item	25	no	0.61
Test item	50	no	0.39
HCA	25	-	11.16

Conclusion

Under our experimental conditions, the test item [redacted] does not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay.

1. INTRODUCTION

The aim of this study was to evaluate the potential of the test item [redacted] to induce delayed contact hypersensitivity, using the murine Local Lymph Node Assay (LLNA).

This study was based on the design adopted by ICCVAM (Interagency Coordination Committee on the Validation of Alternative Methods, ICCVAM 1999) and ECETOC (Technical Report No. 78 Skin sensitization Testing: Methodological Considerations, Brussels, December 1999), with the addition of the evaluation of local irritation.

The study has been designed to comply with the following guideline:
. OECD Guideline No. 429, 24th April 2002.

2. MATERIAL AND METHODS

2.1 TEST MATERIALS

2.1.1 Test item

. [redacted]
. description: colorless liquid
. containers: two plastic flasks
. date of receipt: 26 February 2002
. storage conditions: at room temperature and protected from light.

Data relating to the characterisation of the test item are documented in an analytical certificate (presented in appendix 1) provided by the Sponsor.

2.1.2 Vehicle

The vehicle used was a mixture acetone/olive oil (4/1, v/v): acetone, batch No. 0124359 (Fisher, Maurepas, France) and olive oil, batch No. 050K6072 (Sigma, Saint-Quentin-Fallavier, France).

2.1.3 Dosage form preparations

The test item was prepared in the vehicle at the chosen concentrations. The concentrations were expressed in % (v/v).
All dosage form preparations were made freshly on the morning of administration and any unused material was discarded that same day.

2.1.4 Other materials

2.1.4.1 Reference item

The reference item was α-hexylcinnamaldehyde (HCA), batch No. 13102MO (Aldrich, Saint-Quentin-Fallavier, France), dissolved in a mixture acetone/olive oil (4/1, v/v) at the concentration of 25% (v/v).
The preparation was made freshly on the morning of administration and any unused material was discarded that same day.

2.1.4.2 Reactive used for the proliferation assay

The reactive used for the proliferation assay was [^{3}H] methyl-thymidine (^{3}H-TdR), batch No. B478 (Amersham, Les Ulis, France).

Three days before the injections, the required quantity of ^{3}H-TdR was diluted in 0.9% NaCl (20 µCi in 250 µL of 0.9% NaCl per animal). The obtained solution was stored at +4°C and protected from light before use.

2.2 TEST SYSTEM

2.2.1 Animals

Species, strain and sex:	CBA/J mouse, nulliparous and non-pregnant females.
Reason for this choice:	species generally accepted by regulatory authorities for this type of study. Females have been chosen since this sex is recommended by regulatory authorities for this type of study.
Breeder:	Janvier, Le Genest-Saint-Isle, France.
Number:	28 females.
Age/weight:	on the first day of treatment, the animals were approximately 9 weeks old and had a mean body weight ± standard deviation of 17.6 ± 1.8 g.
Acclimation:	at least 5 days before the beginning of the study.
Allocation:	on day 1, animals were assigned to the treatment groups by hand procedure.
Identification :	individually by a number on the tail.

2.2.2 Environmental conditions

The conditions in the animal room were set as follows:

- temperature: 22 ± 2°C
- relative humidity: 30 to 70%
- light/dark cycle: 12 h/12 h
- ventilation: approximately 12 cycles/hour of filtered, non-recycled air.

The temperature and relative humidity were under continuous control and recording. The records were checked daily and filed. In addition to these daily checks, the housing conditions and corresponding instrumentation and equipment are verified and calibrated at regular intervals. The animals were housed individually in disposable crystal polystyrene cages (22.00 cm x 8.50 cm x 8.00 cm).

Each cage contained autoclaved sawdust (SICSA, Alfortville, France).

Sawdust is analysed by the supplier for composition and contaminant levels.

2.2.3 Food and water

All animals had free access to A04 C pelleted diet [redacted] and tap water (filtered using a 0.22 micron filter) contained in bottles.
Each batch of food is analyzed by the supplier for composition and contaminant levels.
The diet formula is presented in appendix 2.

Bacteriological and chemical analyses of water, including the detection of possible contaminants (pesticides, heavy metals and nitrosamines) are performed regularly by external laboratories. The results of these analyses are archived at [redacted].

No contaminants are known to be present in the diet, drinking water or sawdust at levels which may be expected to interfere with or prejudice the outcome of the study.

2.3 TREATMENT

2.3.1 Study design

The concentrations of test item were selected according to the criteria specified in the International Guideline and on the basis of the results of the solubility assay.

The study design was as follows:

Groups	Number of animals	Treatment	Concentration (%)
1	4 females	Vehicle	0
2	4 females	Test item	2.5
3	4 females	Test item	5
4	4 females	Test item	10
5	4 females	Test item	25
6	4 females	Test item	50
7	4 females	HCA	25

2.3.2 Administration of the dosage forms

On days 1, 2 and 3, a dose-volume of 25 µL of the control or dosage form preparations was applied to the dorsal surface of both ears, using an adjustable pipette fitted with a plastic tip.
In order to avoid licking and to ensure an optimized application of the test materials, the animals were placed under light isoflurane anesthezia during the administration.
No massage was performed but the tip was used to spread the preparation over the application sites. No rinsing was performed between each application.

2.4 CLINICAL EXAMINATIONS

2.4.1 Clinical signs, morbidity and mortality

The animals were observed at least once a day during the study for clinical signs, signs of morbidity or mortality.

2.4.2 Body weight

The animals were weighed individually on the first day of the study (day 1) and on the day of sacrifice (day 6).

2.4.3 Ear thickness measurements and recording of local reactions

Ear thickness measurements and recording of local reactions were performed in order to assess any possible irritant effect of the test item, as possible irritancy may be involved in false positive lymphoproliferative responses.

On days 1, 2 and 3 (before application) as well as on day 6 (after sacrifice), the thickness of the left ear of each animal of the vehicle control and treated groups was measured using a micrometer.
Any irritation reaction (erythema and oedema) was recorded in parallel. Any other observation (coloration, presence of residual test item,…) was noted.

The irritation level of the test item was determined according to the following table:

% increase in ear thickness between day 1 and day 3 or 6	Irritation level	Interpretation
< 10%	I	Non-irritant
10 - 30%	II	Slightly irritant
> 30%	III	Irritant

2.5 PROLIFERATION ASSAY

2.5.1 Intravenous injection of ^{3}H-TdR and sampling of auricular lymph nodes

Lymph node cell proliferative responses were measured as described by Kimber and Dearman (1991). On day 6, all animals of all groups received a single intravenous injection of 250 µL of 0.9% NaCl containing 20 µCi of ^{3}H-TdR (specific activity of 25 Ci/mmol), via the tail vein. Approximately 5 hours later, the animals were killed by cervical dislocation and the auricular lymph nodes were excised. The lymph nodes were pooled for each experimental group.

2.5.2 Preparation of auricular lymph node cell suspensions and determination of proliferation

For each experimental group, a single cell suspension of auricular lymph node cells (ALNC) was prepared by mechanical dissagregation in Petri dishes with the plunger of a syringe. Cell suspensions were washed with 15 mL of 0.9% NaCl and pellets obtained were re-suspended in 0.9% NaCl for numeration of lymphocytes (cellularity) and determination of their viability by exclusion of Trypan blue. Each cell suspension was then centrifuged and pellets were precipitated with 3 mL of 5% (w/v) trichloroacetic acid (TCA) in purified water at +4°C overnight. After a last centrifugation, the pellets were precipitated with 1 mL of 5% TCA. Three mL of Ultima Gold^{xR} scintillation fluid (Packard) were added in order to measure incorporation of ^{3}H-TdR using β-scintillation counting.
The results were expressed as disintegrations/mn (dpm) per node.
Stimulation Indices (SI) were calculated according to the following formula:

$$SI = \frac{\text{dpm of treated group / node}}{\text{dpm of control group / node}}$$

The same calculation was made for the positive control group.

2.5.3 Interpretation of results

The test item was considered as a skin sensitizer when the SI for a dose group is ≥ 3. Other relevant criteria such as cellularity, radioactivity levels and ear thickness were also taken into account for the interpretation of results.

2.5.4 Determination of the EC_3 value

The EC_3 value (theoretical concentration resulting in a SI value of 3) was determined by linear interpolation of points on the dose-response curve, immediately above and below the 3-fold threshold. The equation used for calculation of EC_3 was:

$$EC_3 = c + [(3 - d)/(b-d)] \times (a - c)$$

Where a = the lowest concentration giving stimulation > 3; b = the actual stimulation index caused by a; c = the highest concentration failing to produce a stimulation index of 3; and d = the actual stimulation index caused by c.

2.6 ARCHIVING

The following study materials are archived [redacted] for 10 years after the end of the *in vivo* phase of the study:

- Study plan and possible amendments,
- raw data,
- correspondence,
- final report and possible amendments.

[redacted]

2.7 CHRONOLOGY OF THE STUDY

The chronology of the study is summarized as follow:

Procedure	Date
Experimental starting date (first day of treatment)	19 March 2003
Experimental completion date (Day of injection of ^{3}H-TdR and ALNC collection)	24 March 2003

2.8 STUDY PLAN ADHERENCE

The study was performed in accordance with the Study plan No. 25412 TSS and subsequent amendments. There were no deviations from the agreed Study plan.

3. RESULTS

3.1 CHOICE OF THE VEHICLE

The test item was freely soluble in the first recommended vehicle, acetone/olive oil (4/1, v/v).
A homogeneous dosage form preparation was obtained whatever the proportion.

3.2 CLINICAL EXAMINATIONS

3.2.1 Systemic clinical signs and mortality

Two out of four animals given the test item at the concentration of 10% were found dead on day 3; sedation was recorded prior to death. In addition, 1/4 animals given the test item at the concentration of 50% was found dead on day 6; piloerection, dyspnea, sedation and round back were observed prior to death.
As no evidence of a dose relationship was observed and as no clinical signs and no mortality were noted in the other treated groups, these deaths were not attributed to the treatment with the test item.

3.2.2 Body weight

The body weight change of the treated animals was similar to that of controls (table 4).

3.2.3 Local irritation

No cutaneous reactions and no noteworthy increases in ear thickness were observed at any of the tested concentration (tables 2 and 3).

3.3 PROLIFERATION ASSAY

Results of proliferation assay are presented in table 1.

The quantity of cells obtained in each group was satisfactory and the cellularity correlated with incorporation of ^{3}H-TdR. The cell viability was higher than 80% in each group.

In the positive control group given HCA at the concentration of 25%, an increase in cellularity and a stimulation index exceeding the threshold value of 3 (SI = 11.16) were noted. The study was therefore considered valid.

No positive lymphoproliferative response (SI > 3) was noted at any tested concentration.
In the treated groups, the incorporation of tritiated methyl thymidine was slightly lower than that observed in the vehicle control group and a slight tendency to a dose-related decrease in this incorporation was noted.

4. CONCLUSION

Under our experimental conditions, the test item [redacted] does not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay.

Table 1: Study results

Groups	1	2	3	4	5	6	7
Concentrations (%)	0 (Acetone/Olive oil)	2.5	5	10	25	50	HCA at 25%
Cell count – viable	94	86	110	48	97	34	218
Cell count – dead	4	6	8	5	10	3	16
Viability (%)	95.92	93.48	93.22	90.57	90.65	91.89	93.16
Amount of cells (x 10^6 cells)	4.70	4.30	5.50	2.40	4.85	1.70	21.80
Cellularity index		0.91	1.17	0.51	1.03	0.36	4.64
Number of nodes per group	8	8	8	4	8	6	8
Disintegrations per minute per group (dpm)	672.21	475.43	529.85	236.89	410.13	199.01	7499.39
Disintegrations per minute per node (dpm)	84.03	59.43	66.23	59.22	51.27	33.17	937.42
Stimulation index (SI)		0.71	0.79	0.70	0.61	0.39	11.16
Increase in ear thickness (% between day 1 and day 6)	7.45	4.17	9.47	4.44	12.90	4.26	
EC3 value		NC					

$$\text{Viability} = \frac{\text{viable cells}}{\text{viable cells + dead cells}} \times 100$$

$$\text{Cellularity index} = \frac{\text{amount of cells (x } 10^6 \text{ cells) in the treated group}}{\text{amount of cells (x } 10^6 \text{ cells) in the vehicle group}}$$

$$\text{Stimulation index} = \frac{\text{dpm of treated group}}{\text{dpm of control group}}$$

EC3 value = theorical concentration resulting in a SI value of 3

NC = not calculable

Table 2: Evaluation of cutaneous reactions

Groups	Sex	Test item	Animals	Days			
				1	2	3	6
1	Female	AOO	21	0	0	0	0
			22	0	0	0	0
			23	0	0	0	0
			24	0	0	0	0
2	Female	[redacted] 2.5%	25	0	0	0	0
			26	0	0	0	0
			27	0	0	0	0
			28	0	0	0	0
3	Female	[redacted] 5%	29	0	0	0	0
			30	0	0	0	0
			31	0	0	0	0
			32	0	0	0	0
4	Female	[redacted] 10%	33	0	0	0	0
			34	0	0		
			35	0	0	0	0
			36	0	0		
5	Female	[redacted] 25%	37	0	0	0	0
			38	0	0	0	0
			39	0	0	0	0
			40	0	0	0	0
6	Female	[redacted] 50%	41	0	0	0	0
			42	0	0	0	
			43	0	0	0	0
			44	0	0	0	0

0 = No erythema
AOO = Acetone / Olive oil
Animals found dead during the study not mentioned

Table 3: Ear thickness measurements (mm)

Groups	Sex	Test item	Animals	Days						
				1	2	d1	3	d2	6	d3
1	Female	AOO	21	0.24	0.23	-0.01	0.24	0.00	0.25	0.01
			22	0.24	0.23	-0.01	0.24	0.00	0.26	0.02
			23	0.23	0.22	-0.01	0.23	0.00	0.25	0.02
			24	0.23	0.22	-0.01	0.23	0.00	0.25	0.02
			M	0.24	0.23	-0.01	0.24	0.00	0.25	0.02
			SD	0.01	0.01	0.00	0.01	0.00	0.00	0.00
			% (*)			-4.26		0.00		7.45
2	Female	[redacted] 2.5%	25	0.23	0.23	0.00	0.23	0.00	0.25	0.02
			26	0.24	0.24	0.00	0.24	0.00	0.25	0.01
			27	0.25	0.24	-0.01	0.24	-0.01	0.25	0.00
			28	0.24	0.24	0.00	0.24	0.00	0.25	0.01
			M	0.24	0.24	0.00	0.24	0.00	0.25	0.01
			SD	0.01	0.01	0.01	0.01	0.01	0.00	0.01
			% (*)			-1.04		-1.04		4.17
3	Female	[redacted] 5%	29	0.24	0.24	0.00	0.25	0.01	0.27	0.03
			30	0.24	0.24	0.00	0.25	0.01	0.26	0.02
			31	0.24	0.23	-0.01	0.23	-0.01	0.27	0.03
			32	0.23	0.23	0.00	0.23	0.00	0.24	0.01
			M	0.24	0.24	0.00	0.24	0.00	0.26	0.02
			SD	0.01	0.01	0.00	0.01	0.01	0.01	0.01
			% (*)			-1.05		1.05		9.47

M = Mean
SD = Standard Deviation
(*) = Percentage of ear thickness increase compared to day 1
d1 = Difference of ear thickness between day 2 and day 1
d2 = Difference of ear thickness between day 3 and day 1
d3 = Difference of ear thickness between day 6 and day 1
AOO = Acetone / Olive oil

Table 3 (continued)

Groups	Sex	Test item	Animals	Days						
				1	2	d1	3	d2	6	d3
4	Female	[redacted] 10%	33	0.22	0.21	-0.01	0.22	0.00	0.23	0.01
			34	0.22	0.22	0.00				
			35	0.24	0.25	0.01	0.24	0.00	0.25	0.01
			36	0.22	0.23	0.01				
			M	0.23	0.23	0.00	0.23	0.00	0.24	0.01
			SD	0.01	0.02	0.01	0.01	0.00	0.01	0.00
			% (*)			1.11		0.00		4.44
5	Female	[redacted] 25%	37	0.22	0.22	0.00	0.22	0.00	0.26	0.04
			38	0.25	0.24	-0.01	0.24	-0.01	0.27	0.02
			39	0.25	0.25	0.00	0.24	-0.01	0.28	0.03
			40	0.21	0.21	0.00	0.22	0.01	0.24	0.03
			M	0.23	0.23	0.00	0.23	0.00	0.26	0.03
			SD	0.02	0.02	0.01	0.01	0.01	0.02	0.01
			% (*)			-1.08		-1.08		12.90
6	Female	[redacted] 50%	41	0.24	0.24	0.00	0.25	0.01	0.25	0.01
			42	0.23	0.22	-0.01	0.22	-0.01		
			43	0.25	0.25	0.00	0.24	-0.01	0.26	0.01
			44	0.22	0.22	0.00	0.22	0.00	0.23	0.01
			M	0.24	0.23	0.00	0.23	0.00	0.25	0.01
			SD	0.01	0.02	0.01	0.02	0.01	0.02	0.00
			% (*)			-1.06		-1.06		4.26

M = Mean
SD = Standard Deviation
(*) = Percentage of ear thickness increase compared to day 1
d1 = Difference of ear thickness between day 2 and day 1
d2 = Difference of ear thickness between day 3 and day 1
d3 = Difference of ear thickness between day 6 and day 1
Animals found dead during the study not mentioned

Table 4: Individual and mean body weight and body weight gain (g)

Groups	Sex	Animals	Days		
			1	(1)	6
1	Female	21	17.8	1.7	19.5
		22	19.6	1.1	20.7
		23	16.4	3.6	20.0
		24	16.5	1.0	17.5
		M	17.6	1.9	19.4
		SD	1.5	1.2	1.4
2	Female	25	17.2	2.0	19.2
		26	19.3	0.7	20.0
		27	16.6	2.4	19.0
		28	21.2	0.1	21.3
		M	18.6	1.3	19.9
		SD	2.1	1.1	1.0
3	Female	29	19.3	0.6	19.9
		30	20.3	1.1	21.4
		31	18.2	1.9	20.1
		32	17.6	1.4	19.0
		M	18.9	1.3	20.1
		SD	1.2	0.5	1.0
4	Female	33	17.9	1.3	19.2
		34	16.1		
		35	18.6	1.8	20.4
		36	14.8		
		M	16.9	1.6	19.8
		SD	1.7	0.4	0.8

(1) = Body weight gain
M = Mean
SD = Standard Deviation
Animals found dead during the study not mentioned

Table 4 (continued)

Groups	Sex	Animals	Days		
			1	(1)	6
5	Female	37	15.7	0.0	15.7
		38	18.6	0.2	18.8
		39	18.7	0.1	18.8
		40	15.2	4.8	20.0
		M	17.1	1.3	18.3
		SD	1.9	2.4	1.8
6	Female	41	18.8	0.8	19.6
		42	15.4		
		43	20.5	-0.1	20.4
		44	14.9	1.7	16.6
		M	17.4	0.8	18.9
		SD	2.7	0.9	2.0
7	Female	45	17.6	1.2	18.8
		46	15.6	1.6	17.2
		47	15.7	1.6	17.3
		48	17.6	1.7	19.3
		M	16.6	1.5	18.2
		SD	1.1	0.2	1.1

(1) = Body weight gain
M = Mean
SD = Standard Deviation
Animal found dead during the study not mentioned

APPENDICES

1. Analytical certificate

[redacted]

BULLETIN D'ANALYSE

[redacted]

ESSAIS	RESULTATS	NORMES OU VALEUR ATTENDUE	REFERENCES 71582/04
ASPECT	Liquide visqueux limpide Incolore	Liquide visqueux limpide à légèrement trouble incolore à jaune pâle	1
SOLUBILITES à 25°C eau (1g+10mL) :	Non miscible	Non miscible	1
Spectre IR (20min à 60°C sur étalé sur Irtran)	Conforme	Caractéristique	1 annexe 1
Extrait sec à 105°C (g%g)	14,8	13,0- 16,0	1
Viscosité cinématique à 25°C (mm^2/s) (produit brut)	2900	1000 - 3000	1

CONCLUSION : **PRODUIT CONFORME**

[redacted]

Références : 1 : Spécification DGT-CI
2 : Dossier Analytique DGT-CI
3 : Dossier Fournisseur
4 : Documents autres

[redacted]

[redacted] or Quote

Final Report

Repeated Insult Patch Test
(Marzulli and Maibach Method)

test material contains 0.2% Phenyl Methicone

CLIENT: [redacted]

ATTENTION:

TEST MATERIAL:

REPORT DATE: November 13, 2009

[redacted]

[redacted] uote

Good Clinical Practice
Quality Assurance Audit Statement

[redacted]

Start Date: September 14, 2009

Completion Date: October 23, 2009

The clinical study listed above was conducted in accordance with [redacted] Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

[redacted]

[redacted]

FINAL REPORT

REPEATED INSULT PATCH TEST
MARZULLI AND MAIBACH

PURPOSE

The purpose of this study was to confirm that the application of a cosmetic product to volunteer subjects, under maximized conditions of exposure, does not induce delayed contact sensitization.

INVESTIGATIVE SITE

[redacted]

TEST MATERIAL

[redacted]

Test Material	Test Condition	Patch Type
[redacted]	Test as received/ Switch to semi-occlusive patch in case of reaction	Occlusive Finn Chamber*/ Do not patch adjacent to [redacted]

[redacted]

STUDY DATES

This study was initiated on September 14, 2009 and was completed on October 23, 2009.

* Finn Chamber on Scanpore (Allerderm Laboratories, Inc., Petaluna, CA)

[redacted]

PANEL SELECTION

Each subject was assigned a permanent [redacted] identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Panelist Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following inclusion criteria were selected for study participation.

- Male and female subjects between the ages of 18 and 70;
- Subjects who have completed a Panelist Profile/Medical History Form;
- Subjects in general good health as determined by the Panelist Profile/Medical History Form;
- Subjects who do not exhibit any skin diseases that might be confused with a skin reaction from the test material;
- Subjects willing to sign an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects";
- Subjects who have signed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;
- Females who are not pregnant or lactating;
- Subjects who demonstrate dependability and intelligence in following directions;
- Subjects who are not currently using any systemic or topical corticosteroids, anti-inflammatory drugs, sympathomimetics, antihistamines and/or immunosuppressive medication;
- Subjects who do not have any known allergies to cosmetics, skin care products or topical related drugs as related to the product(s) being tested;
- Subjects who agree to refrain from participating simultaneously in other biomedical studies.

[redacted]

TEST METHOD

Prior to the application of the patch, the test area was wiped with distilled water and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back, between the scapulae and the waist, lateral to the midline.

The test material was applied to the same site three times per week (Monday, Wednesday, and Friday) for a total of nine applications. However, the schedule may have been modified to accommodate inclement weather, holidays, or missed applications. At the discretion of the Study Director, the test material may have been applied on two consecutive days during the Induction Phase or a makeup day may have been added at the end of the Induction Phase.

Each site was marked with a gentian violet surgical marker to ensure the continuity of patch application. The patches were removed by a [redacted] clinician after 48 hours, with the exception of patches applied on Friday. Friday patches were removed by the subject, after approximately 48 hours, on Sunday. Each site was evaluated for dermal reactions just prior to the application of the next patch, according to the dermal scoring system.

If at any time during the Induction Phase of the study a test site was observed to exhibit an evaluation score of "++" or greater, the application of test material to this site was moved to an adjacent virgin site, and, at the discretion of the Study Director, the patch type and/or test condition may have been changed. The new adjacent site, referenced as an alternate site, was scored for all Induction Phase study visits subsequent to a 48-hour test material exposure at the alternate site. The original patch application location was evaluated and scored until the reaction resolved and/or until the final study visit. At the discretion of the Study Director, patch sites with scores less than a ++ may have been changed to a new test site location.

If a "++" reaction or greater occurred on the changed site, patching with the test material was discontinued for the remainder of the Induction Phase, but the subject was challenged on the appropriate day of the study.

At the discretion of the Study Director, any subject exhibiting a significant reaction at the beginning of the Induction Phase may have been classified as “pre-sensitized” to an ingredient(s) contained in the test material product and may have been discontinued from further patching of the test material.

During the course of the study, all sites graded a “+” or greater were confirmed by a second clinician.

[redacted]

TEST METHOD (Continued)

Approximately 10 to 14 days following the Induction Phase, challenge patches were applied to the original test site and a virgin site on the back, following the same procedure described for the Induction Phase. Alternate test sites, which were assigned during the Induction Phase for patch type changes, were also patched during the Challenge Phase with the same patch type as for the Induction Phase. After 48 hours, patches on the original and virgin sites were removed by a [redacted] clinician, and the sites were evaluated and scored. Subjects were required to return for additional evaluations of the test sites at 72 and 96 hours after application.

All test sites were evaluated and scored according to the following grading system during the Induction and Challenge Phases of the study:

Dermal Score

- = No reaction

? = Minimal or doubtful response, slightly different from surrounding normal skin

\+ = Definite erythema, No edema

++ = Definite erythema, Definite edema

+++ = Definite erythema, Definite edema and vesiculation

RESULTS

This study was initiated with 112 subjects. Five subjects discontinued study participation for reasons unrelated to the test material. A total of 107 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 107 subjects and under the conditions of this study, the sample identified as [redacted] did not demonstrate a potential for eliciting dermal irritation or sensitization.

[redacted]

REFERENCES

Marzulli, F. N. and Maibach, H. I. 1973. *Antimicrobials: Experimental contact sensitization in man. J. Soc. Cosmet. Chem.* 24:399-421

Marzulli. F. N. and Maibach, H. I. 1974a. *Status of topical parabens: Skin hypersensitivity. Int. J. Dermatol.* 13:397-399

Marzulli, F. N. and Maibach, H. I. 1974b. The use of graded concentrations in studying skin sensitizers: Experimental contact sensitization in man. *Food Cosmet. Toxicol. 12:219-227. Human Patch Tests, Proc. Sci. Sect. Toilet Goods Assoc*., 19:46-49, 1953.

[redacted]

[redacted]

TABLE I

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	Discontinued										
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	?	-	-	Discontinued								
15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	-	Discontinued											
18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
26	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-
30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
32	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37	-	-	-	-	-	-	?	-	-	-	-	-	-	-	-
38	-	-	-	-	Discontinued										
39	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
43	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
47	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
49	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-
50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
51	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
53	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
54	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
55	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
56	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
57	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
58	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
59	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
60	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
61	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
64	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
66	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
68	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
69	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
70	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
71	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
74	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
76	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-
77	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
78	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
79	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
80	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
81	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
82	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
84	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
85	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
86	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
87	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
88	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
89	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
90	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
91	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
92	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
93	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
94	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
95	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
96	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
97	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
98	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
99	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent

[redacted]

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material:	[redacted]

	Induction Scores									**Challenge Scores**					
										48 Hours		**72 Hours**		**96 Hours**	
Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**O**	**V**	**O**	**V**	**O**	**V**
101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-
103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
104	-	-	-	?	-	-	-	-	-	-	-	-	-	-	-
105	-	-	Discontinued												
106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
109	-	-	-	-	-	-	?	-	-	-	-	-	-	-	-
110	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-
111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent

[redacted]

REPEATED INSULT PATCH TEST

test material contains 28.67% Phenyl Trimethicone

[redacted]

CONDUCTED FOR:

[redacted]

DATE OF ISSUE:

September 24, 2009

[redacted]

TABLE OF CONTENTS

APPENDICES

[redacted]

[redacted]

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

[redacted]

TITLE OF STUDY

Repeated Insult Patch Test

SPONSOR

[redacted]

STUDY MATERIAL

[redacted]

DATE STUDY INITIATED

July 22, 2009

DATE STUDY COMPLETED

September 3, 2009

DATE OF ISSUE

September 24, 2009

INVESTIGATIVE PERSONNEL

[redacted]

[redacted]

SUMMARY

One (1) study material, [redacted], was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using a semi-occlusive repeated insult patch study. Two hundred three (203) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to [redacted]

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of [redacted] Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. were males or females, 18 to 70 years of age, in general good health;
2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
3. were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. had completed a medical screening procedure; and
5. had read, understood, and signed an informed consent agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. had psoriasis and/or active atopic dermatitis/eczema;
4. were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. were participating in another study or had been recruited to participate in another study concurrently.

3.1.3 Informed Consent

A properly executed informed consent document was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2] Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1*	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

DAY	ACTIVITIES
1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

DAY	ACTIVITIES
1-6	Same as Week 2

WEEK 4

DAY	ACTIVITIES
1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU patches
3	Staff graded MU induction sites at MU visit
4-7	Rest period

WEEK 5

DAY	ACTIVITIES
1-7	Rest period

* Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday. Study flow could be altered if a holiday occurred during the study.

[redacted]

WEEK 6

DAY	ACTIVITIES
1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

SYMBOL		REACTION
-	=	No reaction
?	=	Minimal or doubtful response, slightly different from surrounding normal skin
+	=	Definite erythema, no edema
++	=	Definite erythema, definite edema
+++	=	Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E	=	Marked/severe erythema
S	=	Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p	=	Papular response > 50%
pv	=	Papulovesicular response > 50%
D	=	Damage to epidermis: oozing, crusting and/or superficial erosions
I	=	Itching
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Not applied
NP	=	Not patched (due to reaction achieved)
N9G	=	No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting [redacted] requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : [redacted]
Amount Applied : 0.2 g
Special Instructions : Volatilized for 30 minutes prior to patch application.

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by [redacted] On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the sponsor. Material was applied in an amount proportionate to the patch type or as requested by the sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The

reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a [redacted] facility in a secured room accessible only to [redacted] employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the sponsor's review on the premises of [redacted]

7.0 RESULTS AND DISCUSSION

Two hundred thirty-nine (239) subjects between the ages of 18 and 70 were enrolled and 203 subjects completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).

The following table summarizes subject enrollment and disposition.

Number enrolled:		239
Number discontinued:		36
Lost to follow-up:	32	
Voluntary withdrawal:	4	
Number completed:		203

Source: Table 1, Appendix I

There were no adverse events reported.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

[redacted]

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to [redacted]

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145

Marzulli FN, Maibach HI. Contact allergy: predictive testing in man. Contact Dermatitis 1976; 2:1.

Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

APPENDIX I

SUMMARY TABLES

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	122
Subjects completed induction phase	105 (86.1)
Subjects completed all phases	104 (85.2)
Total subjects discontinued	18 (14.8)
Lost to follow-up	16 (13.1)
Voluntary withdrawal	2 (1.6)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

[redacted]

[redacted]

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	54 (44.3)
N (%) 45 to 64	58 (47.5)
N (%) 65 and up	10 (8.2)
Mean (SD)	44.9 (14.0)
Median	46.5
Range	18.0 to 70.8
Gender	
N (%) Male	38 (31.1)
N (%) Female	84 (68.9)
Race	
Asian	1 (0.8)
Black	14 (11.5)
Caucasian	79 (64.8)
Hispanic	28 (23.0)

See data listing 2 for further detail.

[redacted]

[redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

[redacted]

	Induction Reading										Challenge Phase		
Response	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Make Up**	**48hr**	**72hr**	**96hr(*)**
-	111	108	110	108	104	103	103	99	102	34	104	104	
Total evaluable	111	108	110	108	104	103	103	99	102	34	104	104	
Number absent	3	6	3	4	6	6	3	7	3		0	0	
Number discontinued	8	8	9	10	12	13	16	16	17		18	18	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=105)

Response	**n(%) Subjects**
-	105 (100.0%)

(*) when required

Key to Symbols:
- = No reaction ? = Minimal or doubtful response, slightly / different from surrounding normal skin
+ = Definite erythema, no edema ++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation
D = Damage to epidermis: oozing, crusting and/or superficial erosions
p = Papular response >50%

[redacted]

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	117
Subjects completed induction phase	100 (85.5)
Subjects completed all phases	99 (84.6)
Total subjects discontinued	18 (15.4)
Lost to follow-up	16 (13.7)
Voluntary withdrawal	2 (1.7)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

[redacted]

[redacted]

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	49 (41.9)
N (%) 45 to 64	63 (53.8)
N (%) 65 and up	5 (4.3)
Mean (SD)	45.8 (12.5)
Median	46.3
Range	18.5 to 70.0
Gender	
N (%) Male	35 (29.9)
N (%) Female	82 (70.1)
Race	
Amer Ind	1 (0.9)
Asian	1 (0.9)
Black	2 (1.7)
Caucasian	61 (52.1)
Hispanic	52 (44.4)

See data listing 2 for further detail.

[redacted]

[redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

[redacted]

	Induction Reading										Challenge Phase		
Response	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Make Up**	**48hr**	**72hr**	**96hr(*)**
-	102	104	104	98	98	100	101	96	100	17	98	99	
?	0	0	0	0	0	0	0	0	0	0	1	0	
Total evaluable	102	104	104	98	98	100	101	96	100	17	99	99	
Number absent	4	1	1	5	4	1	0	4	0		0	0	
Number discontinued	11	12	12	14	15	16	16	17	17		18	18	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=100)

Response	**n(%) Subjects**
-	100 (100.0%)

(*) when required

Key to Symbols:
- = No reaction ? = Minimal or doubtful response, slightly / different from surrounding normal skin
+ = Definite erythema, no edema ++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation
D = Damage to epidermis: oozing, crusting and/or superficial erosions
p = Papular response >50%

[redacted]

APPENDIX II

DATA LISTINGS

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
002	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
003	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
004	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
005	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
006	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
007	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
008	07/27/09	07/27/09	--	07/31/09	I0	L	5
009	07/27/09	07/27/09	--	07/31/09	I0	L	5
010	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
011	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
012	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
013	07/27/09	07/27/09	--	08/05/09	I2	L	10
014	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
015	07/27/09	07/27/09	--	08/17/09	I8	L	22
016	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
017	07/27/09	07/27/09	--	07/31/09	I0	L	5
018	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
019	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
020	07/27/09	07/27/09	--	08/10/09	I4	L	15
021	07/27/09	07/27/09	--	08/12/09	I6	L	17
022	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
023	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
024	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
025	07/27/09	07/27/09	--	08/31/09	I9	S	36
026	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
027	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
028	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
029	07/27/09	07/27/09	--	07/31/09	I0	L	5
030	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
031	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
033	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
034	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
035	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
036	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
037	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
038	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
039	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
040	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
041	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
042	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
043	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
044	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
045	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
046	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
047	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
048	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
049	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
050	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
051	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
052	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
053	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
054	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
055	07/27/09	07/27/09	--	08/12/09	I6	L	17
056	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
057	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
058	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
059	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
060	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
061	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
062	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
064	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
065	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
066	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
067	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
068	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
069	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
070	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
071	07/27/09	07/27/09	--	08/14/09	I6	L	19
072	07/27/09	07/27/09	--	07/31/09	I0	L	5
073	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
074	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
075	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
076	07/27/09	07/27/09	08/31/09	09/03/09	C	C	39
077	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
078	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
079	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
080	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
081	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
082	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
083	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
084	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
085	07/31/09	07/31/09	--	08/12/09	I3	L	13
086	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
087	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
088	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
089	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
090	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
091	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
092	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
093	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
095	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
096	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
097	07/31/09	07/31/09	--	08/05/09	I0	L	6
098	07/31/09	07/31/09	--	08/03/09	I0	S	4
099	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
100	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
101	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
102	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
103	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
104	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
105	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
106	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
107	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
108	07/31/09	07/31/09	--	08/14/09	I5	L	15
109	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
110	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
111	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
112	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
113	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
114	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
115	07/31/09	07/31/09	--	08/05/09	I0	L	6
116	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
117	07/31/09	07/31/09	--	08/14/09	I4	L	15
118	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
119	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
120	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
121	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35
122	07/31/09	07/31/09	08/31/09	09/03/09	C	C	35

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	-	-	-	-	-	-		-	-	
008	X	X	X	X	X	X	X	X	X		X	X	
009	X	X	X	X	X	X	X	X	X		X	X	
010	-	-	-	-	-	-	-	-	-		-	-	
011	-	-	-	X	-	-	-	-	-	-	-	-	
012	-	-	-	-	-	-	-	-	N9G		-	-	
013	-	-	X	X	X	X	X	X	X		X	X	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	X	-	-	-	-	-	-	X		X	X	
016	-	-	-	-	-	-	-	-	-		-	-	
017	X	X	X	X	X	X	X	X	X		X	X	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	-	-	-	-		-	-	
020	-	-	-	-	X	X	X	X	X		X	X	
021	-	-	-	-	X	-	X	X	X		X	X	
022	X	-	-	-	-	-	-	-	-	-	-	-	
023	-	-	-	-	-	-	-	X	-	-	-	-	

Key to Symbols:
- = No reaction ? = Minimal or doubtful response, slightly different from surrounding normal skin
+ = Definite erythema, no edema ++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation
N9G = No ninth grading NA = Not applied NP = Not patched due to reaction achieved
X = Reading not performed due to missed visit or subject discontinuation
D = Damage to epidermis: oozing, crusting and/or superficial erosions
p = Papular response >50% NR=Data not recorded
MU = Make-up reading for missed induction visit

(*) When required

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	-	-	-	-	X	-	-	X	X	
026	-	-	-	-	-	X	-	-	-	-	-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	X	-	-	-	-	-	-	-	-	-	-	
029	X	X	X	X	X	X	X	X	X		X	X	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	-	-	X	-	-	-	-	-	-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	N9G		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	X	-	-	-	-	-	-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	X	-	-	-	-	-	-	-	-	-	-	

(*) When required

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	X	-	-	-	-	-	
049	-	-	-	-	X	-	-	-	-	-	-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	X	-	-	-	-	
052	-	-	-	-	-	-	-	-	-		-	-	
053	-	-	X	-	-	-	-	-	-	-	-	-	
054	-	-	-	-	X	-	-	-	-	-	-	-	
055	-	-	-	X	-	-	X	X	X		X	X	
056	-	-	-	-	-	-	-	X	-	-	-	-	
057	-	-	-	-	-	-	-	X	-	-	-	-	
058	-	-	-	-	-	-	-	-	-		-	-	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	-	-	-	-	-	-	X	-	-	-	-	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	-	-	-	-	-	N9G		-	-	
063	-	-	-	-	-	-	-	X	-	-	-	-	
064	-	-	-	-	-	-	-	-	-		-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	-	-	-	-		-	-	
067	-	-	-	-	-	-	X	-	-	-	-	-	
068	-	-	-	-	-	-	-	-	-		-	-	
069	-	-	X	-	-	-	-	-	-	-	-	-	

(*) When required

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	X	-	-	-	-	-	-	-	-	
071	-	-	-	-	-	-	X	X	X		X	X	
072	X	X	X	X	X	X	X	X	X		X	X	
073	-	-	-	-	-	-	-	-	-		-	-	
074	X	-	-	-	-	-	-	-	-	-	-	-	
075	-	-	-	-	-	-	-	-	-		-	-	
076	X	-	-	-	-	-	-	-	-	-	-	-	
077	-	-	-	-	-	-	-	-	-		-	-	
078	-	-	-	-	-	X	-	-	-	-	-	-	
079	-	-	-	-	-	-	-	-	-		-	-	
080	-	-	-	-	-	-	-	-	-		-	-	
081	-	-	-	-	-	-	-	-	-		-	-	
082	-	-	X	-	-	-	-	-	-	-	-	-	
083	-	-	-	-	-	-	-	-	-		-	-	
084	-	X	-	-	-	-	-	-	-	-	-	-	
085	-	-	-	X	X	X	X	X	X		X	X	
086	-	-	-	-	-	-	-	-	-		-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	-	-	-	-	-	-	-	-		-	-	
089	-	-	-	-	-	-	-	-	-		-	-	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	-	-	-	-	-	-	-	-		-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	-	-	-	-	-	-	-	-		-	-	
095	-	-	-	-	-	-	-	-	-		-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	X	X	X	X	X	X	X	X	X		X	X	
098	X	X	X	X	X	X	X	X	X		X	X	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	-	-		-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	-	-	-	-	-		-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	-	-	-	-	-	-	-	-		-	-	
105	-	-	-	-	-	-	-	-	-		-	-	
106	-	-	-	-	-	-	-	-	-		-	-	
107	-	-	-	-	-	-	X	-	-	-	-	-	
108	-	X	-	-	-	X	X	X	X		X	X	
109	-	-	-	-	-	X	-	-	-	-	-	-	
110	-	-	-	-	-	-	-	-	-		-	-	
111	-	-	-	-	-	X	-	-	-	-	-	-	
112	-	X	-	-	-	-	-	-	-	-	-	-	
113	-	-	-	-	X	-	-	-	-	-	-	-	
114	-	-	-	-	-	X	-	-	-	-	-	-	
115	X	X	X	X	X	X	X	X	X		X	X	
116	-	-	-	X	-	-	-	-	-	-	-	-	
117	-	-	-	-	X	X	X	X	X		X	X	
118	-	-	-	-	-	-	-	-	-		-	-	
119	-	-	-	-	-	X	-	-	-	-	-	-	
120	-	-	-	-	-	-	-	-	-		-	-	
121	-	-	-	-	-	-	-	-	-		-	-	
122	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
002	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
003	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
004	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
005	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
006	07/22/09	07/22/09	--	07/27/09	I0	L	6
007	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
008	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
009	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
010	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
011	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
012	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
013	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
014	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
015	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
016	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
017	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
018	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
019	07/22/09	07/22/09	--	07/27/09	I0	L	6
020	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
021	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
022	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
023	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
024	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
025	07/22/09	07/22/09	--	07/31/09	I3	S	10
026	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
027	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
028	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
029	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
030	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
031	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	07/22/09	07/22/09	--	08/05/09	I4	L	15
033	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
034	07/22/09	07/22/09	--	07/27/09	I0	L	6
035	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
036	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
037	07/22/09	07/22/09	--	07/27/09	I0	L	6
038	07/22/09	07/22/09	--	07/27/09	I0	L	6
039	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
040	07/22/09	07/22/09	--	07/27/09	I0	L	6
041	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
042	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
043	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
044	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
045	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
046	07/22/09	07/22/09	--	07/27/09	I0	L	6
047	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
048	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
049	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
050	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
051	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
052	07/22/09	07/22/09	--	08/24/09	I9	L	34
053	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
054	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
055	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
056	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
057	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
058	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
059	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
060	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
061	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
062	07/22/09	07/22/09	--	07/31/09	I3	S	10

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
064	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
065	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
066	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
067	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
068	07/22/09	07/22/09	--	07/27/09	I0	L	6
069	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
070	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
071	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
072	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
073	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
074	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
075	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
076	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
077	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
078	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
079	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
080	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
081	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
082	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
083	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
084	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
085	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
086	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
087	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
088	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
089	07/22/09	07/22/09	--	07/27/09	I0	L	6
090	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
091	07/22/09	07/22/09	--	07/29/09	I1	L	8
092	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
093	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
095	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
096	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
097	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
098	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
099	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
100	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
101	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
102	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
103	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
104	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
105	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
106	07/22/09	07/22/09	--	08/05/09	I5	L	15
107	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
108	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
109	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
110	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
111	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
112	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
113	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
114	07/22/09	07/22/09	08/24/09	08/27/09	C	C	37
115	07/22/09	07/22/09	--	08/10/09	I7	L	20
116	07/22/09	07/22/09	--	07/27/09	I0	L	6
117	07/22/09	07/22/09	--	07/27/09	I0	L	6

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading 1	2	3	4	5	6	7	8	9	MU	Challenge Phase 48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	-	-	-	-	-	-	-		?	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	X	X	X	X	X	X	X	X	X		X	X	
007	X	-	-	-	-	-	-	-	-	-	-	-	
008	-	-	-	-	X	-	-	-	-	-	-	-	
009	-	-	-	X	-	-	-	-	-	-	-	-	
010	-	-	-	-	-	-	-	-	-		-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	X	-	-	-	-	-	-	-	-	-	-	-	
013	-	-	-	-	-	-	-	-	-		-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	X	-	-	-	-	-	-	-	-	-	-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	X	X	X	X	X	X	X	X	X		X	X	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		-	-	
023	-	-	-	-	-	-	-	-	-		-	-	

Key to Symbols:
- = No reaction ? = Minimal or doubtful response, slightly different from surrounding normal skin
+ = Definite erythema, no edema ++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation
N9G = No ninth grading NA = Not applied NP = Not patched due to reaction achieved
X = Reading not performed due to missed visit or subject discontinuation
D = Damage to epidermis: oozing, crusting and/or superficial erosions
p = Papular response >50% NR=Data not recorded
MU = Make-up reading for missed induction visit

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	X	X	X	X	X	X		X	X	
026	X	-	-	-	-	-	-	-	-	N9G	-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	-	-	-	-		-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	X	X	X	X	X		X	X	
033	-	-	-	-	-	-	-	-	-		-	-	
034	X	X	X	X	X	X	X	X	X		X	X	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	X	X	X	X	X	X	X	X	X		X	X	
038	X	X	X	X	X	X	X	X	X		X	X	
039	-	-	-	-	X	-	-	-	-	-	-	-	
040	X	X	X	X	X	X	X	X	X		X	X	
041	-	-	-	-	-	-	-	X	-	-	-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	X	-	-	-	-	-	-	-	
046	X	X	X	X	X	X	X	X	X		X	X	

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	-	-		X	X	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	-	-	-	-	-	-		-	-	
056	-	-	-	X	-	-	-	-	-	-	-	-	
057	-	-	-	-	-	-	-	-	-		-	-	
058	-	-	-	-	-	-	-	-	-		-	-	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	-	X	-	-	-	-	-	-	-	-	-	
061	-	-	-	-	-	-	-	X	-	-	-	-	
062	-	-	-	X	X	X	X	X	X		X	X	
063	-	-	-	-	-	-	-	-	-		-	-	
064	-	-	-	-	-	-	-	-	-		-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	-	-	-	-		-	-	
067	-	-	-	-	-	-	-	-	-		-	-	
068	X	X	X	X	X	X	X	X	X		X	X	
069	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	-	-		-	-	
071	-	-	-	-	-	-	-	-	-		-	-	
072	-	-	-	-	-	-	-	-	-		-	-	
073	-	-	-	-	-	-	-	-	-		-	-	
074	-	-	-	-	-	-	-	-	-		-	-	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	-	-	-	-	-	-	-	-		-	-	
077	-	-	-	-	-	-	-	-	-		-	-	
078	-	-	-	-	-	-	-	-	-		-	-	
079	-	-	-	-	-	-	-	-	-		-	-	
080	-	-	-	-	-	-	-	-	-		-	-	
081	-	-	-	-	-	-	-	-	-		-	-	
082	-	-	-	-	-	-	-	-	-		-	-	
083	-	-	-	-	-	-	-	-	-		-	-	
084	-	-	-	-	-	-	-	-	-		-	-	
085	-	-	-	-	-	-	-	X	-	-	-	-	
086	-	-	-	-	-	-	-	-	-		-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	-	-	-	-	-	-	-	-		-	-	
089	X	X	X	X	X	X	X	X	X		X	X	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	X	X	X	X	X	X	X	X		X	X	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	X	-	-	-	-	-	-	-	-	-	-	
095	-	-	-	-	-	-	-	-	-		-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	-	-	-	-	-	-	-	-	-		-	-	
098	-	-	-	-	-	-	-	-	-		-	-	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	X	-	-	-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	X	-	-	-	-	-	-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	-	-	X	-	-	-	-	-	-	-	-	
105	-	-	-	X	-	-	-	-	-	-	-	-	
106	-	-	-	X	-	X	X	X	X		X	X	
107	-	-	-	-	-	-	-	-	-		-	-	
108	-	-	-	-	-	-	-	-	-		-	-	
109	-	-	-	-	-	-	-	-	-		-	-	
110	-	-	-	-	-	-	-	-	-		-	-	
111	-	-	-	-	-	-	-	-	-		-	-	
112	-	-	-	-	-	-	-	-	-		-	-	
113	-	-	-	-	-	-	-	-	-		-	-	
114	-	-	-	-	-	-	-	-	-		-	-	
115	-	-	-	-	-	X	-	X	X		X	X	
116	X	X	X	X	X	X	X	X	X		X	X	
117	X	X	X	X	X	X	X	X	X		X	X	

(*) When required

[redacted]

[redacted]

REPEATED INSULT PATCH TEST

test material contains 38.006% Trimethylsiloxyphenyl Dimethicone

[redacted]

[redacted]

DATE OF ISSUE:

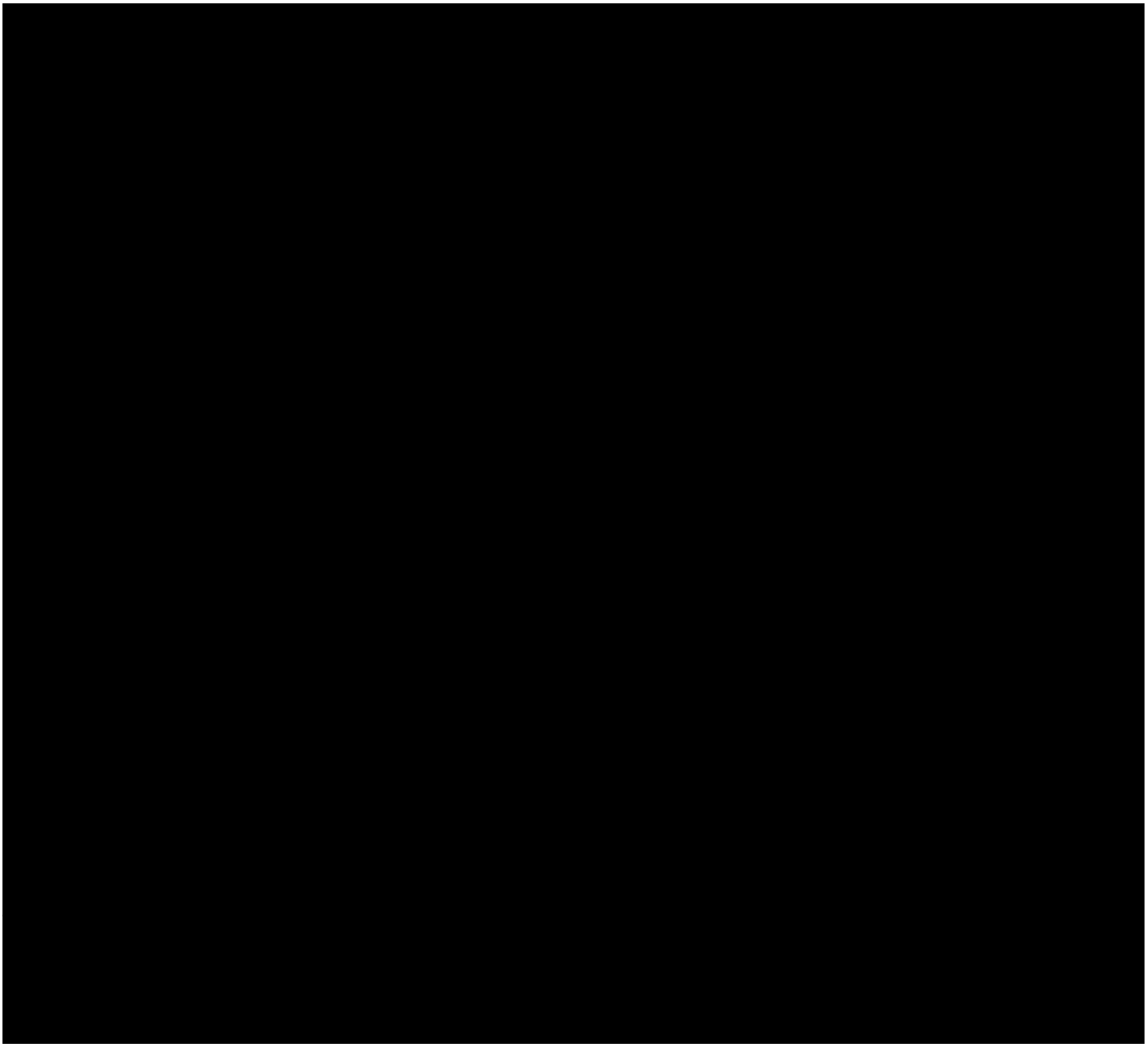
June 15, 2011

[redacted]

[redacted]

TABLE OF CONTENTS

APPENDICES



STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

[redacted]

TITLE OF STUDY

Repeated Insult Patch Test

SPONSOR

[redacted]

STUDY MATERIAL

[redacted]

DATE STUDY INITIATED

April 11, 2011

DATE STUDY COMPLETED

May 26, 2011

DATE OF ISSUE

June 15, 2011

[redacted]

[redacted]

SUMMARY

One (1) study material, Formula No. [redacted] was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using a semi-occlusive repeated insult patch study. Two hundred five (205) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to Formula No. [redacted]

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of [redacted] Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 to 70 years of age, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

[redacted]

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. Were participating in another study or had been recruited to participate in another study concurrently.

3.1.3 Informed Consent

A properly executed informed consent document was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2]

Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

[redacted]

24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1[3]	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

DAY	ACTIVITIES
1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

DAY	ACTIVITIES
1-6	Same as Week 2

WEEK 4

DAY	ACTIVITIES
1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU patches
3	Staff graded MU induction sites at MU visit
2-7	Rest Period

WEEK 5

DAY	ACTIVITIES
1-7	Rest Period

[3] Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday. Study flow could be altered if a holiday occurred during the study.

[redacted]

WEEK 6

DAY	ACTIVITIES
1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

SYMBOL		REACTION
-	=	No reaction
?	=	Minimal or doubtful response, slightly different from surrounding normal skin
+	=	Definite erythema, no edema
++	=	Definite erythema, definite edema
+++	=	Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E	=	Marked/severe erythema
S	=	Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p	=	Papular response > 50%
pv	=	Papulovesicular response > 50%
D	=	Damage to epidermis: oozing, crusting and/or superficial erosions
I	=	Itching
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Not applied
NP	=	Not patched (due to reaction achieved)
N9G	=	No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting [redacted] strict certification requirements to standardize the assignment of response grades.

[redacted]

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : [redacted]
Amount Applied : 0.2 g
Special Instructions : Volatilized for 30 minutes prior to patch application.

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by [redacted] On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The

[redacted]

reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a [redacted] facility in a secured room accessible only to [redacted] employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the sponsor's review on the premises of [redacted]

7.0 RESULTS AND DISCUSSION

Two hundred twenty-seven (227) subjects between the ages of 18 and 71 were enrolled. This is a deviation from the protocol-specified age range of 18 to 70 years. This deviation did not affect the validity of the study. Two hundred five (205) subjects completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition.

Number enrolled:		227
Number discontinued:		22
Lost to follow-up:	11	
Voluntary withdrawal:	10	
Protocol violation: (Crohn's Disease)	1	
Number completed:		205

Source: Table 1, Appendix I

There were no adverse events reported on either study.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

[redacted]

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to Formula No. [redacted]

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145.

Marzulli FN, Maibach HI. Contact allergy: predictive testing in man. Contact Dermatitis 1976; 2:1.

Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980:41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

APPENDIX I

SUMMARY TABLES

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	108
Subjects completed induction phase	104 (96.3)
Subjects completed all phases	103 (95.4)
Total subjects discontinued	5 (4.6)
Lost to follow-up	1 (0.9)
Voluntary withdrawal	4 (3.7)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

[redacted]

[redacted]

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	36 (33.3)
N (%) 45 to 64	50 (46.3)
N (%) 65 and up	22 (20.4)
Mean (SD)	50.9 (14.4)
Median	52.9
Range	18.3 to 71.0
Gender	
N (%) Male	27 (25.0)
N (%) Female	81 (75.0)
Race	
Black	1 (0.9)
Caucasian	5 (4.6)
Hispanic	102 (94.4)

See data listing 2 for further detail.

[redacted]

[redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

[redacted]

	Induction Reading										Challenge Phase		
Response	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Make Up**	**48hr**	**72hr**	**96hr(*)**
-	106	107	105	103	104	104	102	103	104	6	103	103	
Total evaluable	106	107	105	103	104	104	102	103	104	6	103	103	
Number absent	1	0	1	3	2	1	3	1	0		0	0	
Number discontinued	1	1	2	2	2	3	3	4	4		5	5	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=104)

Response	**n(%) Subjects**
-	104 (100.0%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

[redacted]

[redacted]

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	119
Subjects completed induction phase	105 (88.2)
Subjects completed all phases	102 (85.7)
Total subjects discontinued	17 (14.3)
Lost to follow-up	10 (8.4)
Voluntary withdrawal	6 (5.0)
Protocol violation	1 (0.8)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

[redacted]

[redacted]

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	38 (31.9)
N (%) 45 to 64	70 (58.8)
N (%) 65 and up	11 (9.2)
Mean (SD)	47.8 (13.0)
Median	50.4
Range	18.5 to 70.4
Gender	
N (%) Male	35 (29.4)
N (%) Female	84 (70.6)
Race	
Asian	3 (2.5)
Black	15 (12.6)
Caucasian	84 (70.6)
Hispanic	17 (14.3)

See data listing 2 for further detail.

[redacted]

[redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

[redacted]

	Induction Reading										Challenge Phase		
Response	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Make Up**	**48hr**	**72hr**	**96hr(*)**
-	110	99	109	105	106	108	104	104	105	22	103	102	
Total evaluable	110	99	109	105	106	108	104	104	105	22	103	102	
Number absent	3	12	2	5	4	1	3	2	0		0	0	
Number discontinued	6	8	8	9	9	10	12	13	14		16	17	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=105)

Response	**n(%) Subjects**
-	105 (100.0%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

[redacted]

[redacted]

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

APPENDIX II

DATA LISTINGS

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
002	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
003	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
004	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
005	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
006	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
007	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
008	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
009	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
010	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
011	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
012	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
013	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
014	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
015	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
016	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
017	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
018	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
019	04/11/11	04/11/11	--	04/25/11	I5	S	15
020	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
021	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
022	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
023	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
024	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
025	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
026	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
027	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
028	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
029	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
030	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
031	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
033	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
034	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
035	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
036	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
037	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
038	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
039	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
040	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
041	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
042	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
043	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
044	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
045	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
046	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
047	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
048	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
049	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
050	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
051	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
052	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
053	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
054	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
055	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
056	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
057	04/11/11	04/11/11	--	04/29/11	I7	L	19
058	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
059	04/11/11	04/11/11	--	04/13/11	I0	S	3
060	04/11/11	04/11/11	--	04/20/11	I2	S	10
061	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
062	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
064	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
065	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
066	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
067	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
068	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
069	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
070	04/11/11	04/11/11	--	05/17/11	I9	S	37
071	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
072	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
073	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
074	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
075	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
076	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
077	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
078	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
079	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
080	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
081	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
082	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
083	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
084	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
085	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
086	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
087	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
088	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
089	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
090	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
091	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
092	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
093	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
095	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
096	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
097	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
098	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
099	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
100	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
101	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
102	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
103	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
104	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
105	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
106	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
107	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40
108	04/11/11	04/11/11	05/17/11	05/20/11	C	C	40

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	-	-	-	-	-	-		-	-	
008	-	-	-	-	-	-	-	-	-		-	-	
009	-	-	-	-	-	-	-	-	-		-	-	
010	-	-	-	-	-	-	-	-	-		-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	-	-	-	-	-	-	-	-		-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	-	-	-	-	-	-	-	-	-		-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	X	X	X	X		X	X	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		-	-	
023	-	-	-	-	-	-	-	-	-		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	X	-	-	N9G	-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	-	-	-	-	-	-	-		-	-	
027	-	-	-	-	-	-	X	-	-	N9G	-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	-	-	-	-		-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	-	-	-	-	-	-	-		-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	-	X	-	-	-	-	-	-	-	-	

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

	Induction Reading										Challenge Phase		
Subject No.	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	X	-	-	-	-	-	-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	-	-		-	-	
053	-	-	-	X	-	-	-	-	-	-	-	-	
054	-	-	-	X	-	-	-	-	-	-	-	-	
055	-	-	X	-	-	-	-	-	-	N9G	-	-	
056	-	-	-	-	-	-	-	-	-		-	-	
057	-	-	-	-	X	-	-	X	X		X	X	
058	-	-	-	-	-	-	-	-	-		-	-	
059	X	X	X	X	X	X	X	X	X		X	X	
060	-	-	X	X	X	X	X	X	X		X	X	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	-	-	-	-	-	-		-	-	
063	-	-	-	-	-	-	-	X	-	N9G	-	-	
064	-	-	-	-	-	-	-	-	-		-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	-	-	-	-		-	-	
067	-	-	-	-	-	-	-	-	-		-	-	
068	-	-	-	-	-	-	-	-	-		-	-	
069	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	-	-		X	X	
071	-	-	-	-	-	-	-	-	-		-	-	
072	-	-	-	-	-	-	-	-	-		-	-	
073	-	-	-	-	-	-	-	-	-		-	-	
074	-	-	-	-	-	-	-	-	-		-	-	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	-	-	-	-	-	-	-	-		-	-	
077	-	-	-	-	-	-	-	-	-		-	-	
078	-	-	-	-	-	-	-	-	-		-	-	
079	-	-	-	-	-	-	-	-	-		-	-	
080	-	-	-	-	-	-	X	-	-	N9G	-	-	
081	-	-	-	-	-	-	-	-	-		-	-	
082	-	-	-	-	-	-	-	-	-		-	-	
083	-	-	-	-	-	-	-	-	-		-	-	
084	-	-	-	-	-	-	-	-	-		-	-	
085	-	-	-	-	-	-	-	-	-		-	-	
086	-	-	-	-	-	-	-	-	-		-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	-	-	-	-	-	-	-	-		-	-	
089	-	-	-	-	-	-	-	-	-		-	-	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	-	-	-	-	-	-	-	-		-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	-	-	-	-	-	-	-	-		-	-	
095	-	-	-	-	-	-	-	-	-		-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	-	-	-	-	-	-	-	-	-		-	-	
098	-	-	-	-	-	-	-	-	-		-	-	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	-	-		-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	-	X	-	-	-	-	-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	-	-	-	-	-	-	-	-		-	-	
105	X	-	-	-	-	-	-	-	-	-	-	-	
106	-	-	-	-	-	-	-	-	-		-	-	
107	-	-	-	-	-	-	-	-	-		-	-	
108	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
002	04/18/11	04/18/11	--	04/29/11	I5	S	12
003	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
004	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
005	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
006	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
007	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
008	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
009	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
010	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
011	04/18/11	04/18/11	--	04/25/11	I1	L	8
012	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
013	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
014	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
015	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
016	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
017	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
018	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
019	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
020	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
021	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
022	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
023	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
024	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
025	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
026	04/18/11	04/18/11	05/23/11	05/25/11	I9	S	38
027	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
028	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
029	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
030	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
031	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
033	04/18/11	04/18/11	--	05/09/11	I8	L	22
034	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
035	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
036	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
037	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
038	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
039	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
040	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
041	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
042	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
043	04/18/11	04/18/11	--	04/20/11	I0	S	3
044	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
045	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
046	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
047	04/18/11	04/18/11	--	04/22/11	I0	L	5
048	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
049	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
050	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
051	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
052	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
053	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
054	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
055	04/18/11	04/18/11	--	04/22/11	I0	S	5
056	04/18/11	04/18/11	--	04/29/11	I3	L	12
057	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
058	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
059	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
060	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
061	04/18/11	04/18/11	--	04/22/11	I0	L	5
062	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
064	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
065	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
066	04/18/11	04/18/11	05/23/11	05/26/11	C1	L	39
067	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
068	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
069	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
070	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
071	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
072	04/18/11	04/18/11	--	05/04/11	I6	L	17
073	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
074	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
075	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
076	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
077	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
078	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
079	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
080	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
081	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
082	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
083	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
084	04/18/11	04/18/11	--	04/25/11	I1	L	8
085	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
086	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
087	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
088	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
089	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
090	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
091	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
092	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
093	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	**Screened**	**1st Applic**	**Chall Applic**	**Ended**	**Last Reading #**	**Completion Status**	**Days in Study**
094	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
095	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
096	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
097	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
098	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
099	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
100	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
101	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
102	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
103	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
104	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
105	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
106	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
107	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
108	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
109	04/18/11	04/18/11	--	05/04/11	I6	L	17
110	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
111	04/18/11	04/18/11	--	04/22/11	I0	S	5
112	04/18/11	04/18/11	--	05/06/11	I7	L	19
113	04/18/11	04/18/11	05/23/11	05/26/11	C	C	39
114	04/20/11	04/20/11	05/23/11	05/26/11	C	C	37
115	04/20/11	04/20/11	--	05/23/11	I9	S	34
116	04/20/11	04/20/11	05/23/11	05/26/11	C	C	37
117	04/20/11	04/20/11	05/23/11	05/26/11	C	C	37
118	04/20/11	04/20/11	--	04/22/11	I0	V	3
119	04/20/11	04/20/11	05/23/11	05/26/11	C	C	37

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	X	-	-	-	-	-	-	
002	-	-	-	-	-	X	X	X	X		X	X	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	X	-	-	-	-	
007	-	-	-	-	-	-	-	-	-		-	-	
008	-	-	-	-	-	-	-	-	-		-	-	
009	-	-	-	-	-	-	X	-	-	-	-	-	
010	-	X	-	-	-	-	-	-	-	-	-	-	
011	-	X	X	X	X	X	X	X	X		X	X	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	X	-	-	-	-	-	-	-	-	-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	-	-	-	-	-	-	-	-	-		-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	-	-	-	-		-	-	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		-	-	
023	-	-	-	-	-	-	-	-	-		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	X	-	-	-	-	-	-	-	N9G	-	-	
026	-	X	-	-	-	-	-	-	-	-	X	X	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	-	-	-	-		-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	X	-	-	-	-	X		X	X	
034	-	X	-	-	-	-	-	-	-	-	-	-	
035	-	X	-	-	-	-	-	-	-	-	-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	-	-	-	-	-	-	-		-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	X	X	X	X	X	X	X	X	X		X	X	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	X	X	X	X	X	X	X	X	X		X	X	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	-	-		-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	X	-	-	-	-	-	-	-	-	-	
055	X	X	X	X	X	X	X	X	X		X	X	
056	-	-	-	X	X	X	X	X	X		X	X	
057	-	-	-	-	-	-	-	-	-		-	-	
058	-	-	-	X	-	-	-	-	-	-	-	-	
059	X	-	-	-	-	-	-	-	-	-	-	-	
060	-	-	-	-	-	-	-	-	-		-	-	
061	X	X	X	X	X	X	X	X	X		X	X	
062	-	-	-	-	-	-	-	-	-		-	-	
063	-	-	-	-	-	-	-	-	-		-	-	
064	-	X	-	-	-	-	-	-	-	-	-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	-	-	-	-		-	X	
067	-	-	-	-	-	-	-	X	-	-	-	-	
068	-	-	-	-	-	-	-	-	-		-	-	
069	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	X	-	-	-	-	-	-	-	-	-	-	
071	-	-	-	-	-	-	-	-	-		-	-	
072	-	-	-	X	-	-	X	X	X		X	X	
073	-	-	-	-	X	-	-	-	-	-	-	-	
074	-	-	-	-	-	-	-	-	-		-	-	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	X	-	-	-	-	-	-	-	-	-	-	
077	-	-	-	-	-	-	-	-	-		-	-	
078	-	-	-	-	-	-	-	-	-		-	-	
079	-	-	-	-	-	-	-	-	-		-	-	
080	-	-	-	-	X	-	-	-	-	-	-	-	
081	-	X	-	-	-	-	-	-	-	-	-	-	
082	-	-	-	-	-	-	-	-	-		-	-	
083	-	-	-	-	-	-	-	-	-		-	-	
084	-	X	X	X	X	X	X	X	X		X	X	
085	-	-	-	-	-	-	-	-	-		-	-	
086	-	-	-	-	-	-	-	-	-		-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	-	-	-	-	-	-	-	-		-	-	
089	-	-	-	-	X	-	-	-	-	-	-	-	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	-	-	-	-	-	-	-	-		-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required

[redacted]

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	-	-	X	-	-	-	-	-	-	-	-	
095	-	-	-	-	-	-	-	-	-		-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	-	-	-	-	-	-	-	-	-		-	-	
098	-	-	-	-	-	-	-	-	-		-	-	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	-	-		-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	X	-	-	-	-	-	-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	-	-	-	-	-	-	-	-		-	-	
105	-	-	-	-	-	-	-	-	-		-	-	
106	-	-	-	-	-	-	-	-	-		-	-	
107	-	-	-	-	-	-	-	-	-		-	-	
108	-	-	-	-	-	-	-	-	-		-	-	
109	X	-	-	-	-	-	X	X	X		X	X	
110	-	X	-	-	-	-	-	-	-	-	-	-	
111	X	X	X	X	X	X	X	X	X		X	X	
112	-	X	-	-	-	-	-	X	X		X	X	
113	X	-	-	-	-	-	-	-	-	N9G	-	-	
114	-	-	-	-	-	-	X	-	-	N9G	-	-	
115	-	-	-	-	-	-	X	-	-	N9G	X	X	
116	-	-	-	-	-	-	-	-	-		-	-	
117	-	-	-	X	-	-	-	-	-	N9G	-	-	
118	X	X	X	X	X	X	X	X	X		X	X	
119	-	-	X	-	-	-	-	-	-	N9G	-	-	

(*) When required

[redacted]

[redacted]