

8EHQ-0902-14959

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September 4, 2002

To: TSCA §8(e) Distribution List

From: K. P. Plotzke - Chairperson, Substantial Risk Evaluation Committee  
(SREC)

Re: Supplemental Submission of Final Report to 8EHQ-01-14959 TSCA  
Section 8(e) Notification of Substantial Risk: Material 02675234 (DOW  
CORNING® 3-8214 Adhesion Promoter) Toxicity Study by Oral  
Administration to CD Rats for 4 weeks

Dow Corning is submitting the final report to EPA under TSCA Section 8(e) as  
supplemental information.

**Summary:**

In a previous TSCA Section 8(e) submission, Dow Corning provided EPA with  
the results from a four-week oral gavage study with administration of the test  
material (silicic acid, 1,2-ethanediyl ethyl ester) showing organ-specific effects on  
the kidneys that were significantly altered compared to control animals. These  
findings included increased kidney weights at 1000 mg/kg and histopathology  
findings consistent with signs of kidney toxicity at 1000 mg/kg/day and milder  
effects at 300 mg/kg/day. The No-Observed-Adverse-Effect-Level (NOAEL) for  
these organ-specific effects was considered to be 100 mg/kg/day. The final report  
confirms that material 02675234 produced evidence of kidney toxicity and that  
the NOAEL for these effects remained at 100 mg/kg/day.

**Actions:**

This note is being provided to you for informational purposes only. No other  
action is required on your part in response to this notification at this time.

An electronic copy of the more detailed TSCA Section 8(e) submission is  
attached:

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8EHQ-01-14959



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September 4, 2002

Document Control Office (7407)  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
Room G-099  
Attn: TSCA Section 8(e) Coordinator  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460

Re: Supplemental Submission of Final Report to 8EHQ-01-14959 TSCA  
Section 8(e) Notification of Substantial Risk: Material 02675234 Toxicity  
Study by Oral Administration to CD Rats for 4 weeks

Dear Sir:

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), as interpreted in the Statement of Interpretation and Enforcement Policy (40 FR 11110, 16 March 1978), Dow Corning is submitting the following recently issued final study report as a supplemental submission to our initial TSCA Section 8(e) notification of June 14, 2001 (8EHQ-01-14959).

**Chemical Substance:**

170424-65-4            Silicic acid, 1,2-ethanediyl ethyl ester

**Manufacturer:**

Dow Corning Corporation  
2200 West Salzburg Road  
Midland, Michigan 48686-0994

**Ongoing Study:**

MATERIAL 02675234 TOXICITY STUDY BY ORAL ADMINISTRATION TO  
CD RATS FOR 4 WEEKS

Dow Corning Corporation  
2001-I0000-50640  
May 7, 2002

## Summary:

In a previous TSCA Section 8(e) submission, Dow Corning provided EPA with the results from a four-week oral gavage study with the test material (silicic acid, 1,2-ethanediyl ethyl ester) showing organ-specific effects on the kidneys that were significantly altered compared to control animals. These findings included increased kidney weights at 1000 mg/kg and histopathology findings consistent with signs of kidney toxicity at 1000 mg/kg/day and milder effects at 300 mg/kg/day. The No-Observed-Adverse-Effect-Level (NOAEL) for these organ-specific effects was considered to be 100 mg/kg/day. The final report confirms that material 02675234 produced evidence of kidney toxicity and that the NOAEL for these effects remained at 100 mg/kg/day.

## Details:

The test material was administered by oral gavage in sesame oil to three groups of five male and five female CD rats for 29 days at dosages of 100, 300 or 1000 mg/kg/day. A concurrent control group received sesame oil. In total three animals, two males and one female, treated at 1000 mg/kg/day were either euthanized *in extremis* or found dead. One male (Group 4, 1000 mg/kg/day) was found dead on day 4 of treatment. This animal had no clinical signs prior to its death. A second male (Group 4, 1000 mg/kg/day) was killed *in extremis* on day 6 of treatment. Clinical signs observed in this animal prior to sacrifice included thin build, dark eyes, piloerection, hunched posture and fast respiration. Macroscopic examination of both of these male animals at necropsy revealed pale and enlarged kidneys, dark areas on the stomach and one animal with a hard aorta and pale areas on the heart. Microscopic examination revealed findings in the kidneys, heart, stomach, liver, colon and lungs. A female in Group 4 (1000 mg/kg/day) was killed *in extremis* on day 16 of treatment. Clinical signs observed prior to sacrifice included thin build, hunched posture, piloerection and reduced body temperature. Pale and enlarged kidneys were observed during macroscopic examination at necropsy.

Clinical signs observed for animals receiving 1000 mg/kg/day included thin build, reduced body temperature, piloerection, hunched posture and salivation after dosing. These signs were observed throughout the treatment period, however, not all animals were affected. These effects were considered secondary to the marked kidney damage observed in the animals in this dosage group. Further, there was a significant reduction in body weight gain, food consumption and food conversion efficiency in males and females receiving 1000 mg/kg/day throughout the treatment period when compared with the controls. These effects also could have contributed to the other clinical signs discussed above.

Total leukocyte counts, associated with high neutrophil and eosinophil counts, were elevated in males and females at the 1000 mg/kg/day dose. The myeloid to erythroid ratio in the bone marrow also was slightly higher in male and female animals treated at 1000 mg/kg/day when compared to the controls. Activated partial thromboplastin clotting times were shorter for the animals treated at 1000 mg/kg/day than in the controls.

Absolute and relative kidney weights were significantly increased in male and female animals administered 1000 mg/kg/day. Further, high blood urea and creatinine levels were observed in both sexes receiving 1000 mg/kg/day. Females treated at 1000 mg/kg/day had high spleen weights when compared with the controls.

A high incidence of enlarged and/or pale kidneys in males and females at 1000 mg/kg/day was observed during macroscopic examination of animals killed at the end of the treatment period. The kidneys of individual males at this dosage were noted to have cysts, contain calculus, and have a granular appearance or pelvic dilation.

Microscopic examination showed an increased incidence and/or severity of a number of inflammatory and degenerative/regenerative changes in the kidneys of animals given the test material at 300 mg/kg/day and above. These findings were considered related to administration of the test material.

The No-Observed-Adverse-Effect-Level (NOAEL) for these organ-specific effects was considered to be 100 mg/kg/day.

**Actions:**

These findings from the aforementioned study will be communicated to appropriate internal and external audiences including employees and customers.

If you have technical questions concerning this study, please contact Dr. Kathleen P. Plotzke, Director of Health and Environmental Sciences (989) 496-8046. If you require further general information regarding this submission, please contact Michael E. Thelen, Manager of U.S. EPA Regulatory Affairs, (989) 496-4168 or at the address provided herein.

Sincerely,



Laura L. Perkins  
Director of Environment, Health and Safety

DOW CORNING CORPORATION  
HEALTH & ENVIRONMENT SCIENCES  
TECHNICAL REPORT

HUNTINGDON LIFE SCIENCES LTD  
WOOLLEY ROAD  
ALCONBURY  
HUNTINGDON  
CAMBRIDGESHIRE  
PE28 4HS  
ENGLAND

**Report Number:** 2001-I0000-50640

**Title:** Material 02675234:  
Toxicity Study By Oral Administration To CD  
Rats For 4 Weeks

**Study Number:** 9547

**External Testing Facility Number:** DCN302 / 012512

**Test Substance:** Material 02675234

**Study Director:** M.A.B. Blee, B.Sc.

**Sponsor:** Dow Corning Corporation  
2200 W. Salzburg Road  
Midland, MI 48686-0994  
USA

**Sponsor Representative:** Michelle A. Kravat, B.S.

**Testing Facility:** Huntingdon Life Sciences Ltd  
Eye Research Centre  
Eye, Suffolk IP23 7PX  
England

**Study Completion Date:** 7 May 2002

**Security Statement:** This report may be reproduced and shared with any Dow Corning employee. Distribution outside the corporation must be approved by the Director of H.E.S. When this INTERNAL report is no longer needed, it may be placed in office waste baskets for destruction.

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Material 02675234  
Toxicity Study By Oral Administration To CD Rats For 4 Weeks

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### ABSTRACT

The test material was administered by oral gavage in sesame oil to three groups of five males and five female CD rats for 29 days at dosages of 100, 300 or 1000 mg/kg/day. A concurrent control group received sesame oil. In total three animals, two males and one female, treated at 1000 mg/kg/day were either euthanized *in extremis* or found dead. One male (Group 4, 1000 mg/kg/day) was found dead on day 4 of treatment. This animal had no clinical signs prior to its death. A second male (Group 4, 1000 mg/kg/day) was killed *in extremis* on day 6 of treatment. Clinical signs observed in this animal prior to sacrifice included thin build, dark eyes, piloerection, hunched posture and fast respiration. Macroscopic examination of both of these male animals at necropsy revealed pale and enlarged kidneys, dark areas on the stomach and one animal with a hard aorta and pale areas on the heart. Microscopic examination revealed findings in the kidneys, heart, stomach, liver, colon and lungs. A female in Group 4 (1000 mg/kg/day) was killed *in extremis* on day 16 of treatment. Clinical signs observed prior to sacrifice included thin build, hunched posture, piloerection and reduced body temperature. Pale and enlarged kidneys were observed during macroscopic examination at necropsy.

Clinical signs observed for animals receiving 1000 mg/kg/day included thin build, reduced body temperature, piloerection, hunched posture and salivation after dosing. These signs were observed throughout the treatment period, however, not all animals were affected. These effects were considered secondary to the marked kidney damage observed in the animals in this dosage group. Further, there was a significant reduction in bodyweight gain, food consumption and food conversion efficiency in males and females receiving 1000 mg/kg/day throughout the treatment period when compared with the controls. These effects also could have contributed to the other clinical signs discussed above.

Total leukocyte counts, associated with high neutrophil and eosinophil counts, were elevated in males and females at 1000 mg/kg/day dose. The myeloid to erythroid ratio in the bone marrow also was slightly higher in male and female animals treated at 1000 mg/kg/day when compared to the controls. Activated partial thromboplastin clotting times were shorter for the animals treated at 1000 mg/kg/day than in the controls.

Absolute and relative kidney weights were significantly increased in male and female animals administered 1000 mg/kg/day. Further high blood urea and creatinine levels were observed in both sexes receiving 1000 mg/kg/day. Females treated at 1000 mg/kg/day had high spleen weights when compared with the controls.

A high incidence of enlarged and/or pale kidneys in males and females at 1000 mg/kg/day was observed during macroscopic examination of animals killed at the end of the treatment period. The kidneys of individual males at this dosage were noted to have cysts, contain calculus, and have a granular appearance or pelvic dilation.

Microscopic examination showed an increased incidence and/or severity of a number of inflammatory and degenerative/regenerative changes in the kidneys of animals given the test material at 300 mg/kg/day and above. These findings were considered related to administration of the test material.

### Conclusion

It is concluded that administration of Material 02675234 to CD rats for a minimum of 28 days resulted in clear signs of toxicity at 1000 mg/kg/day and some signs of nephropathy at 300 mg/kg/day. The No-Observed-Adverse-Effect-Level (NOAEL) was considered to be 100 mg/kg/day.

Material 02675234  
Toxicity Study By Oral Administration To CD Rats For 4 Weeks

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**GLP COMPLIANCE STATEMENT**

This study was conducted in accordance with the following:

United States Environmental Protection Agency, (TSCA), Title 40 Code of Federal Regulations Part 792, Federal Register, 29 November 1983 and subsequent amendment Federal Register 17 August 1989.

OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98) 17.

The United Kingdom Good Laboratory Practice Regulations 1999 (Statutory Instrument No. 3106).

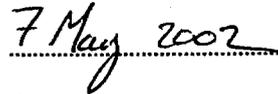
EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No L 77/8).

I certify that the information contained in this report is consistent with and supported by the raw data.

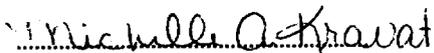
Minor deviations from protocol did not affect the integrity of the study.



M.A.B. Blee, B.Sc.  
Study Director  
Huntingdon Life Sciences Ltd.



Date



Sponsor Representative



Date

**QUALITY ASSURANCE STATEMENT**

The following have been inspected or audited in relation to this study

<b>Study Phase Inspected</b>	<b>Date of Inspection</b>	<b>Date of Reporting</b>
<b>Protocol Audit</b>	18 January 2001	18 January 2001
<b>Study Based Inspections</b>		
Dose preparation	24 January 2001	25 January 2001
Dosing and post dose observations	24 January 2001	25 January 2001
Necropsy	22 February 2001	22 February 2001
<b>Report Audit</b>	6 June 2001	6 June 2001
<b>Additional Report Audit</b>	6 February 2002	6 February 2002

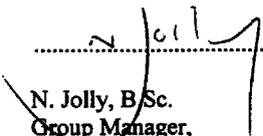
**Protocol:** An audit of the protocol for this study was conducted and reported to the Study Director and Company Management as indicated above.

**Study based inspections:** Inspections and audits of phases of this study were conducted and reported to the Study Director and Company Management as indicated above.

**Process based inspections:** At or about the time this study was in progress inspections and audits of other routine and repetitive procedures employed on this type of study were carried out. These were promptly reported to appropriate Company Management.

**Report Audit:** This report has been audited by the Quality Assurance Department. This audit was conducted and reported to the Study Director and Company Management as indicated above.

The methods, procedures and observations were found to be accurately described and the reported results to reflect the raw data.

  
.....  
N. Jolly, B.Sc.  
Group Manager,  
Department of Quality Assurance  
Huntingdon Life Sciences Ltd.

7 MAY 2002  
.....  
Date

Material 02675234  
Toxicity Study By Oral Administration To CD Rats For 4 Weeks

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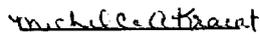
**APPROVAL SIGNATURES**

This report consists of Pages 1 through 238 including Tables 1-9 and Appendices 1-9.

M.A.B. Blee, B.Sc.  
Study Director,  
Department of Toxicological Sciences.

  
Date 7 May 2002

Michelle A. Kravat, B.S.,  
Sponsors' Representative,  
Dow Corning Corporation.

  
Date April 25, 2002

Material 02675234  
Toxicity Study By Oral Administration To CD Rats For 4 Weeks

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**STUDY INFORMATION**

Study initiation Date  
(Final protocol signed by the Study Director): 12 January 2001

Animals arrived: 10 January 2001

Experimental Initiation Date  
(treatment commenced): 24 January 2001

Experimental Termination Date  
(completion of laboratory work): 27 April 2001

Study Completion Date: 7 May 2002

Study Director: M.A.B. Blee, B.Sc.

Sponsor: Dow Corning Corporation

Sponsors' Representative: Michelle A. Kravat, B.S.

Study Personnel: Study Management -  
P. Aughton, B.Sc., D.A.B.T., Dip.R.C.Path., C.Biol.,  
M.I.Biol.  
Monitoring Toxicologist.  
M.A.B. Blee, B.Sc.  
Study Director.  
N. Chick, B.Sc.  
Study Supervisor.  
Quality Assurance -  
N. Jolly, B.Sc.  
Group Manager.  
Animal Resources -  
N. Plummer, M.I.A.T.,  
Registered Animal Technician,  
Animal Facility Manager.

Material 02675234  
Toxicity Study By Oral Administration To CD Rats For 4 Weeks

---

**STUDY INFORMATION - continued**

Study Personnel:

Pharmacy -

J. Wright, O.N.D.,  
Production Manager.

Formulation Chemistry -

A.D. Clemson, B.Sc., M.Sc., Ph.D., C.Chem., F.R.S.C.  
Scientific Manager.

Veterinary Examination -

P. Lee, B.V.Sc., M.R.C.V.S., D.V.S.M.  
Veterinary Officer.

Functional Observation Battery -

M.J. Collier, B.Sc.  
Senior Scientist, Neurobehavioural Studies.

Clinical Pathology -

J. Collard, A.I.B.M.S.  
Clinical Pathology Manager.

D. Crook, B.Sc., Ph.D.  
Data Quality/Logistics Manager.

Macropathology -

D.M. John, B.Sc., D.M.S.  
Head of Necropsy.

Pathology -

I. Taylor, B.Sc., D.I.B.T., C.Biol., M.I.Biol.  
Staff Pathologist

M.P. Brown, B.Sc., P.G.C.E., Ph.D., C.Biol., M.I.Biol.  
Consultant Pathologist

Archives -

A. Churchland, A.I.M.L.S.  
Archivist.

## INTRODUCTION

### Objective

The objective of this study was to assess the systemic toxic potential of Material 02675234 in a 4 week study in CD rats.

The study was conducted in accordance with the requirements of current, internationally recognised Good Laboratory Practice Standards and was designed to meet the requirements of the following guideline:

Organisation for Economic Co-operation and Development, Testing of Chemicals Guideline No. 407 (revised 1995).

### Justification for the test system

The CD rat was chosen because of the requirement for a rodent species by regulatory agencies and the availability of background data.

### Justification for the treatment regimen

The oral gavage route was selected to simulate the conditions of potential human exposure.

Dosages of 100, 300 and 1000 mg/kg/day were selected, based on results from an earlier study conducted by Huntingdon Life Sciences (Study No. DCN301/004814; DCC Study No. 9546). The duration of the study was selected by the Sponsor in accordance with the guideline.

### Study organisation

Testing facilities:

The principal laboratory was:

Huntingdon Life Sciences Ltd  
Eye Research Centre  
Eye  
Suffolk  
IP23 7PX  
England

The analysis described in the blood chemistry section of this report were performed by:

Huntingdon Life Sciences Ltd  
Huntingdon Research Centre  
Woolley Road  
Alconbury  
Huntingdon  
Cambridgeshire  
PE28 4HS  
England

#### **Animal welfare compliance statement**

This study complied with all applicable sections of the Animals (Scientific Procedures) Act 1986 of the United Kingdom and the associated Code of Practice for the Housing and Care of Animals used in Scientific Procedures issued under Section 21 of the Act. As required by condition 6 of the Project Licence issued under the Act (Appendix IV), the procedures used in this study were designed to avoid or minimise discomfort, distress and pain to animals.

#### **Archives**

The study protocol, all amendments/deviations, data, specimens, sample of the test substance, study related documents generated during the course of the study (collectively defined as the "materials") remain the property of the Sponsor.

Huntingdon Life Sciences Ltd. will retain the materials and the authorised final report in its archive (Eye Research Centre, Eye, Suffolk, England) for a period of 5 years from the date of issue of the final report. After such time, the Sponsor will be contacted and advice sought on the return, disposal or further retention of the "materials". If requested, Huntingdon Life Sciences will continue to retain the "materials" subject to a reasonable fee being agreed with the Sponsor. Under no circumstances will any item be discarded without the Sponsor's prior approval. The sample of the test substance will be retained in the archive at Huntingdon Life Sciences Ltd., Huntingdon Research Centre, Huntingdon, England and will be subject to the same conditions of retention as the other materials.

Other records not exclusive to this study, for example training records and certificates of analysis for food and water and general records for temperature and humidity and general maintenance work performed will be maintained and stored independently in the archives.

## MATERIALS AND METHODS

### DESIGN CONDITIONS

#### Animals

A total of 25 male and 25 female rats of the CD®(SD) IGS BR VAF/Plus™ strain, 26 to 30 days of age, were obtained from Charles River (UK) Limited, Margate, Kent, England. The females were nulliparous and non-pregnant.

The animals used on the study weighed 97 to 121 g five days after arrival. At commencement of treatment, the animals were approximately 40 to 44 days of age and weighed 134 to 217 g.

#### Identification

After random allocation to groups each animal was assigned a number and identified uniquely within the study by a tail tattoo. Tattoos were checked at regular intervals and renewed if necessary.

#### Quarantine (Acclimatisation)

The animals were allowed to acclimatise to the conditions described below for 14 days before commencement of treatment. During this time their health status was assessed by daily observation. Nine days before treatment commenced, the Study Director and a Veterinary Officer examined the animals and reviewed the acclimatisation data to confirm their good health.

#### Environmental control

Animals were housed inside a barriered rodent facility. The animal room exclusively contained the animals for the study. All personnel entering the facility were required to change into clean protective clothing. Each animal room was kept at positive pressure with respect to the outside by its own supply of filtered fresh air which passed to the atmosphere and was not recirculated. Target ranges within the study room were 19-23°C for temperature (actual range 20.5-23.5°C), 30-70% for relative humidity (actual range 50-64%) and at least 15 air changes per hour. Lighting was controlled by an electronic timer to provide a 12-hour light: 12 hour dark cycle (lights on at 06:00 hours GMT).

The facility was designed and operated to minimise the entry of external biological and chemical agents and to minimise the transference of such agents between rooms. Before each study the room was cleaned and disinfected with a bactericide.

Alarms were available to be activated if there was any failure of the ventilation system, or temperature limits were exceeded.

Periodic checks were made on the number of air changes in the animal rooms. Temperature and humidity were monitored daily. Contrary to the protocol the temperature and humidity were measured manually once per day. Humidity was measured using a Vaisala Hygrometer and temperature was measured using a min/max thermometer. The environmental conditions were measured accurately therefore this deviation was considered not have affected the integrity of the study. On one occasion (Day 8) the temperature of the room rose to 23.5°C. The condition of the animals was monitored throughout and they appeared to have been unaffected by this minor transient fluctuation in temperature. Temperatures were within the target ranges on all other occasions. This deviation from protocol was not considered to have affected the integrity of the study. The data are not presented, but are retained in the archives.

A stand-by electricity supply was available to be automatically brought into operation should the public supply fail.

#### **Animal accommodation**

The animals were housed one animal per cage. The cages used were RB3 cages from North Kent Plastic Cages Limited, Erith, Kent, England, which were made of a polypropylene body with a stainless steel mesh lid and floor. The cages were suspended above absorbent paper which was changed at appropriate intervals. Cages, cage-trays, food hoppers and water bottles were changed at appropriate intervals. The cage size was in compliance with UK Animal Welfare guidelines.

#### **Diet and water supply**

The animals were allowed free access, except overnight before routine blood sampling, to a pelleted rodent diet, Rat and Mouse No. 1 Maintenance Diet from Special Diet Services Ltd, Witham, Essex, England. This diet contained no added antibiotic or other chemotherapeutic or prophylactic agent. Weighed amounts of diet were provided at intervals during each week to each cage.

At the end of each treatment week the weight of uneaten food was recorded. The uneaten diet may have been included in that returned to the cage, after appropriate measurement.

Water taken from the public supply (Essex and Suffolk Water Company, Chelmsford, Essex, England), was available without restriction, via polycarbonate bottles fitted with sipper tubes. The water tap was drained for at least two minutes before use.

#### **Quality control of diet and water**

Each batch of diet was routinely analysed by the supplier for various nutritional components and chemical and microbiological contaminants. Supplier's analytical certificates were scrutinised and approved by the Divisional Manager, Laboratory Animal Technologies before any batch of diet was released for use.

The quality of the water supply is governed by regulations published by the Department of the Environment. Certificates of analysis were routinely received from the supplier.

Since the results of these various analyses did not provide evidence of contamination that might have prejudiced the study they are not presented, but certificates are retained in the archives.

No other specific contaminants that were likely to have been present in the diet or water were analysed, as none that may have interfered with or prejudiced the outcome of the study was known.

#### **Allocation to treatment groups**

On arrival animals were non-selectively assigned to cages and treatment groups. Using the sequence of cages in the battery, one animal was placed in each cage.

The Study Director and a Veterinary Officer observed the animals and reviewed the acclimatisation data to confirm their good health.

During the acclimatisation period all animals were weighed and two males with bodyweights at the extreme of the ranges were replaced with spare animals of suitable bodyweight from the same batch.

Material 02675234  
Toxicity Study By Oral Administration To CD Rats For 4 Weeks

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On the day that treatment commenced (before dosing) all animals were weighed to ensure that individual variations in bodyweight did not exceed  $\pm 20\%$  of the mean for each sex.

As far as was practicable the distribution of animals in the room was designed to minimise the effect of any spatially variable component of the environment. The distribution is shown in Figure 1.

#### Composition and identity of treatment groups

Animals were assigned to the groups as follows:

Group	Treatment	Dosage (mg/kg/day)#	Animal/cage numbers	
			Male	Female
1	Vehicle Control	0	11-15	21-25
2	Material 02675234	100	1-5	26-30
3	Material 02675234	300	16-20	36-40
4	Material 02675234	1000	6-10	31-35

# Expressed in terms of the test substance as supplied.

Cage labels, identifying the occupants by experiment, animal number, sex and treatment group, were colour-coded.

Because of the need for the Functional Observational Battery to be performed without knowledge of the treatment groups, the animal numbering system was such that it was not easy to identify a treatment group from the animal numbers.

## TREATMENT

### Test substance

The Sponsor supplied 1825 ml of Material 02675234 (supplied as Dow Corning ® 3-8214 Adhesion Promoter) Lot No. 0000545418, which was received at Huntingdon Life Sciences Ltd., Eye Research Centre, Eye, Suffolk, England on 29 November 2000. It was a clear colourless liquid. Based on the analysis by the Sponsor, documented in Dow Corning Study No. 9495, the test substance, as received, was regarded as 'pure' material and was representative.

Before use the characteristics which appropriately defined the batch from which the Material 02675234 for this study was drawn, were determined by the Sponsor. Stability of the Material 02675234 and methods of synthesis, fabrication or derivation were documented by the Sponsor.

The test substance was stored at room temperature. The test substance will remain stable under these conditions until expiration (expiry) date of this batch, 26 May 2001.

Before the consignment of the test material was used a 1 g representative sample was taken. This sample was placed in a well-closed glass container and stored in the archives at room temperature. The sample is held in the archives at Huntingdon Life Sciences Ltd, Eye, Suffolk, England.

A sample of the test substance has been retained by the Sponsor.

Residual test substance will be returned to the Sponsor on completion of all studies at the end of the program of work with Material 02675234.

Material 02675234  
Toxicity Study By Oral Administration To CD Rats For 4 Weeks

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All dosages and concentrations are expressed in terms of the material received.

The vehicle, sesame oil, was obtained from Sigma - Aldrich Company Ltd., Poole, Dorset, England. It was a golden coloured oil stored at room temperature. One batch was used on this study: Batch Number 30K0127 (arrival 24 and 30 January 2001). Another Batch was used for the trial preparation: Batch Number 89H0018 (Arrival 7 and 13 December 2000).

#### **Dosage form**

Material 02675234 was prepared for administration by adding a small quantity of the vehicle (sesame oil) to a pre-weighed amount of test substance and hand stirring to mix. Further quantities of vehicle were added to provide the required volume and the final product was mixed for five minutes using a magnetic stirrer.

All formulations were prepared freshly each day and administered within one hour of preparation.

#### **Quality control of dosage form (Appendix 8)**

Detailed records of compound usage were maintained.

A record of the weight of each formulation dispensed and the amount remaining after dosing was made. The balance was compared with the predicted usage as a check that the doses had been administered correctly. No significant discrepancy was found.

Before treatment commenced the suitability of the proposed mixing procedure was determined by a trial preparation. Samples of formulation were assayed as described below:

The distribution of the test material in the vehicle was assessed for the lowest and highest concentrations by analysing samples taken from three positions in the mix.

In addition, samples of each formulation prepared for administration in Week 1 of treatment were analysed for the test material.

The mean concentrations of Material 02675234 in formulations, prepared for dosing on Day 1 of treatment, ranged from 96.8 - 103 % of nominal concentrations and, considering the nature of the test material, these were considered satisfactory.

#### **Administration**

Animals received the test material or vehicle control formulations by gavage using a syringe and rubber catheter at a volume-dosage of 5 ml/kg bodyweight/day. All animals were dosed in sequence of cage-number within each group, once each day, for 29 days. The volume administered to each animal was calculated from the most recently recorded bodyweight.

Formulations were stirred for at least five minutes using a magnetic stirrer before and throughout the dosing procedure. Formulations were administered within one hour of preparation on every occasion.

#### **Duration of treatment**

All surviving animals were treated for 29 days and were sacrificed on Day 30.

## SERIAL OBSERVATIONS

All observations described below were performed in group number sequence, except where otherwise indicated.

### Signs

Animals were inspected at least twice daily for evidence of reaction to treatment or ill-health. The initial inspection was early in the working day and the second was during the afternoon, at least four hours later. Any deviations from normal were recorded at the time with respect to the nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate.

Further, thorough examinations were performed once each week. Each animal was removed from its cage and positively identified. The physical examination assessed changes from normal with particular reference to:

Stance and muscle tone	Ears
Quality of the coat and skin condition	Whiskers
Eye, visual examination of conjunctiva and eye rims	Urogenital region
Nose	Anal region
Teeth	

Daily during the first week of treatment and twice weekly during Weeks 2 to 4 (middle and end of each week) detailed observations were recorded before and after dosing; these observations were recorded at the following times in relation to dosing:

- Immediately before dosing.
- Immediately after dosing on return of the animal to its cage.
- On completion of dosing of each group.
- Between one and two hours after completion of dosing of all groups \*.
- As late as possible in the working day.

\* On Day 21 of study; this observation was omitted in error. The signs were recorded on completion of dosing of each group and at the end of the day. The duration of the signs was determined from the other occasions when post-dose observations were recorded. This deviation, therefore, was considered not to have affected the integrity of the study.

Further observations were made as part of neurobehavioural screening.

During the acclimatisation period, observations of the animals and their cages were recorded at least once per day.

### Mortality

Debilitated animals were observed carefully. Animals judged to be *in extremis* were euthanized. A complete necropsy was performed in all cases as described below.

### Bodyweight

Each animal was weighed five days after arrival, on the day that treatment commenced, at weekly intervals throughout the treatment period and before necropsy.

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Further weighings occurred as part of the neurobehavioural screening.

More frequent weighings were instituted, when appropriate, for animals displaying ill-health, so that the progress of the observed condition could be monitored (Appendix 2B).

#### **Food consumption**

The weight of food supplied to each animal, that remaining and an estimate of any spilled was recorded for each week throughout the treatment period. From these records the mean weekly consumption per animal was calculated.

#### **Food conversion efficiency**

Group mean food conversion efficiencies were calculated for each week of treatment.

### **FUNCTIONAL OBSERVATIONAL BATTERY**

All surviving animals were subjected to the procedures detailed below on the specified occasions. The functional observational battery was performed at approximately the same time of day on each occasion before dosing and the observer was unaware of the experimental group to which the animal belonged. The animals were not necessarily all tested on the same day but the number of animals were balanced across the groups on each day of testing. Any deviation from normal was recorded with respect to nature and, where appropriate, degree of severity. Further details on test procedures and definitions and results are documented in the Functional Observational Battery Report.

#### **In the hand and standard arena observations**

Observations were performed in the hand and then during a one minute period in a standard arena. Animals were examined before treatment commenced and once weekly throughout the treatment period.

After removal from the home cage the following parameters were assessed:

In the hand	Standard arena
Exophthalmos	Activity counts
Fur appearance	Level of arousal
Lacrimation	Convulsion
Piloerection	Defecation count
Reactivity to handling	Gait
Ease of removal from cage	Grooming
Salivation	Palpebral closure
Vocalisation on handling	Posture
	Rearing count
	Tremor
	Twitches
	Urination

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### Manipulations

Before commencement and during Week 4 of treatment the following measurements, reflexes, and responses were recorded:

- Approach response
- Auditory startle reflex
- Body temperature
- Bodyweight
- Grip strength - forelimbs and hindlimbs
- Landing footsplay
- Tail pinch response
- Pupil closure reflex
- Righting reflex
- Touch response

### Motor activity

Motor activity was measured before commencement and during Week 4 of treatment by automated infra-red sensor equipment (supplied by Pearson Technical Services, Debenham, Suffolk, England), recording individual animal activity over a one hour period.

### Haematology, peripheral blood

Blood samples were obtained on Day 30 of treatment following overnight starvation from all surviving animals. These samples were obtained following completion of the FOB tests.

Blood samples were withdrawn from the retro-orbital sinus under Isoflurane anaesthesia and were collected into EDTA as the anticoagulant. All samples were examined for the following:

Using a Technicon H-1 haematology analyser -

- Haematocrit (Hct)
- Haemoglobin concentration (Hb)
- Erythrocyte count (RBC)
- Mean cell haemoglobin (MCH)
- Mean cell haemoglobin concentration (MCHC)
- Mean cell volume (MCV)
- Total and differential<sup>†</sup> leucocyte count (WBC)
- Platelet count (Plt)

Abnormalities - the equipment identifies the following: anisocytosis (Anisocyto), microcytosis (Microcyto), macrocytosis (Macrocyto), hypochromasia (Hypochrom) and hyperchromasia (Hyperchrom).

<sup>†</sup> The equipment distinguishes neutrophils, lymphocytes, eosinophils, basophils, monocytes and a small proportion of large unstained cells (LUC). Large unstained cells are those that the H-1 haematology analyser is unable to clarify as belonging to any other classes.

Blood film - Romanowsky stain, examined by light microscopy. In cases where the H-1 haematology analyser generated positive findings for cell morphology, grossly elevated total white blood cell counts or abnormal "scattergrams," the blood film was used to corroborate or refute the morphological findings.

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Additional blood samples were taken into citrate anticoagulant and examined for:

Prothrombin time (PT) - after Quick (1966), J. Clin. Pathol. 45, 105.

Activated partial thromboplastin time (APTT) - after Proctor and Rapaport (1972), Am. J. Clin. Pathol. 36, 212.

#### **Haematology, bone marrow**

Bone marrow samples were obtained from the femur at the necropsy of all animals euthanized.

Smears from these samples were air-dried, fixed in methanol and stained using a Romanowsky procedure.

The smears from all animals sacrificed on completion of the scheduled treatment period were examined by counting 100 nucleated cells, after Dacie and Lewis, 1975 (in "Practical Haematology", 5th Edition, J + A Churchill, London).

The cells were classified as myeloid, erythroid or 'others' (where 'others' are all non-myeloid and non-erythroid cells, e.g. lymphoid). The myeloid to erythroid ratio was calculated using only myeloid and erythroid cells.

#### **Blood chemistry**

At the same time as the peripheral haematology, further blood samples were taken and collected into lithium heparin as anticoagulant. These samples were then centrifuged, separated and the resultant plasma was transported refrigerated to the Central Laboratory Services at Huntingdon Research Centre for analysis. Samples were analysed in the same sequence as for peripheral haematology. The plasma was examined for the following:

Alkaline phosphatase (Alk.phos) - "Optimised standard method" conforming to the recommendations of the Deutsche Gesellschaft für Klinische Chemie (D.G.K.C) Anon. Z. klin. Chem. u. klin Biochem. (1970) 8: 658 Anon. Z. klin. Chem. u. klin Biochem. (1972) 10: 182.

Alanine amino-transferase (ALT) - International Federation of Clinical Chemistry (I.F.C.C.) Recommendation Bergmeyer H U, Hørder M, Rej R. J. Clin. Chem. Clin. Biochem (1986) 24: 481-495.

Aspartate amino-transferase (AST) - International Federation of Clinical Chemistry (I.F.C.C.) Recommendation Bergmeyer H U, Hørder M, Rej R. J. Clin. Chem. Clin. Biochem (1986) 24: 497.

Gamma-glutamyl transpeptidase (gGT) - Persijn J P and W van der Slik. J. Clin. Chem. Clin. Biochem. (1976) 14: 421. Szasz G., Persijn J. P. et al. J. Clin. Chem. Clin. Biochem (1976) 12: 228.

Total bilirubin concentration (Bili.Total) - Wahlefeld A. W., Herz G., and Bernt E. Scand. J. clin. Lab. Invest. (1972) Vol 29, Suppl 126:Abstract 11.12.

Urea concentration (Urea) - after Talke H. and Schubert G. E. Klin. Wschr. (1965) 43: 174 - 175.

Creatinine concentration (Creat) - Seelig H. P., Wust H. Arztl Labor (1969) 15: 34. Bartels H. et al. Clin. Chim. Acta. (1972) 37:193. Foster-Swanson A., Swartzentruber M., Roberts P. et al. Clin. Chem. (1994) Abstract No 361.

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Glucose concentration (Gluc) - Schmidt F.H. Kiln. Wschr. (1961) 39:1244.

Total cholesterol concentration (Chol.Total) - Siedel J., et al. Clin. Chem. (1983) 29:1075. Katterman R., et al. Clin. Chem. Clin. Biochem. (1984) 22:245. Trinder P. Ann. Clin. Biochem. (1969) 6:24.

Total triglyceride concentration (Trig) - after Wahlefeld A. W., Bergermeyer H. U. eds. Methods of Enzymatic Analysis, 2<sup>nd</sup> English ed. New York, NY: Academic Press Inc., (1974) 1831. Siedel J., et al. AACC Meeting Abstract 34. Clin Chem. (1993) 39:1127.

Sodium (Na), potassium (K) and Chloride (Cl) - by indirect ion selective electrode on the Hitachi 917.

Calcium concentration (Ca Total) - Gindler E. M. King J. D. Am. J. Clin. Pathol. (1972) 58:376.

Inorganic phosphorus (Phos) - Henry R J. ed. Clinical Chemistry, 2<sup>nd</sup>. Ed. Hagerstown: Harper & Row (1974) 773.

Total protein concentration (Total Prot) - after Weichselbaum T. E. Am. J. Clin. Path. (1946) 16: 40.

Chemical albumin (Alb) - Doumas B. T. et al. Clin. Chim. Acta. (1987) 31: 87.

Albumin/globulin ratio (A/G Ratio) - calculated from total protein concentration and chemically analysed albumin concentration.

## **TERMINAL OBSERVATIONS**

### **Euthanasia**

Animals sacrificed during the study and those surviving until the end of the scheduled treatment period were euthanized by carbon dioxide inhalation.

The sequence in which the animals were euthanized after completion of the treatment was selected to allow satisfactory inter-group comparison.

### **Macroscopic pathology**

All animals euthanized and any found dead were subjected to a detailed necropsy.

The necropsy procedure included a review of the history of each animal and a detailed examination of the external features and orifices, the neck and associated tissues and the thoracic and abdominal cavities and their viscera. The requisite organs were weighed and external and cut surfaces of the organs and tissues were examined as appropriate. Abnormalities and interactions were noted and tissues which were found to be abnormal were preserved in 10% Neutral Buffered Formalin.

### **Organ weights**

The following organs, taken from each animal, were dissected free of adjacent fat and other contiguous tissue and the weights recorded. The weight of each organ was expressed as a percentage of the bodyweight recorded immediately before necropsy.

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Adrenals	Liver
Brain	Spleen
Epididymides	Testes
Heart	Thymus
Kidneys	

**Tissues preserved for histopathology**

Samples of the following tissues were preserved in 10% neutral buffered formalin, except the testes and epididymides which were placed in Bouin's fluid and subsequently retained in 70% industrial methylated spirit.

Adrenals	Prostate
Brain	Rectum
Caecum	Sciatic nerve, one only
Colon	Seminal vesicles
Duodenum	Spinal cord
Epididymides	Spleen
Heart	Stomach
Ileum (including Payer's patch)	Testes
Jejunum	Thymus
Kidneys	Thyroid with parathyroids
Liver	Trachea
Lungs (including bronchi)	Urinary bladder
Lymph nodes - mandibular	Uterus with cervix
- mesenteric	Vagina
Ovaries	

Femoral bone marrow smears, taken from all animals euthanized, were processed and examined as described in the haematology, bone marrow section.

Samples of any abnormal tissues were also retained for histopathological examination. In those cases where a lesion was not clearly delineated, contiguous tissue was fixed with the grossly affected region and sectioned as appropriate.

**Tissues preserved, but not examined**

Samples of the tissues listed below were not processed but are held in fixative against any future requirement for microscopic examination.

Aorta - thoracic	Pharynx
Eyes	Pituitary
Harderian glands	Salivary glands
Head	Sciatic nerve, one only
Mammary area - caudal	Skeletal muscle - thigh
Oesophagus	Skin (overlying mammary area)
Optic nerves	Sternum
Pancreas	Tongue

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### Histology

Tissue samples from the animals specified below were dehydrated, embedded in paraffin wax, sectioned at approximately four to five microns thickness and stained with haematoxylin and eosin, except the testes with were stained with Periodic Acid/Schiff (PAS).

The tissues subjected to histopathological processing included the following regions:

<b>Tissue</b>	<b>Regions examined</b>
Adrenals	: cortex and medulla
Brain	: cerebellum, cerebrum and midbrain
Heart	: including auricular and ventricular regions
Ileum	: including Payer's patch where possible
Kidneys	: including cortex, medulla and papilla regions
Liver	: section from all main lobes
Lungs	: section from two major lobes, including bronchi
Spinal cord	: transverse and longitudinal sections at the cervical level
Stomach	: keratinised, glandular and antrum
Thyroid	: including parathyroid in section, where possible
Uterus	: uterus section separate from cervix section

For bilateral organs sections of both the left and right organs were examined. A single section was prepared from each of the remaining tissues required for microscopic pathology.

### Microscopy

Microscopic examination was performed as follows:

- i. The tissues specified above were examined for all animals of Groups 1 and 4 sacrificed on completion of the scheduled treatment period and for all animals killed or dying during the study. The kidneys of all animals were examined following the findings observed in Group 4.
- ii. Tissues reported at macroscopic examination as being abnormal were examined for all animals.

Findings were either reported as "Present" or assigned a severity grade. In the latter case one of the following five grades was used – minimal, slight, moderate, marked or severe.

### DEFINITION OF "WEEK"

The first week of treatment started at midnight prior to treatment commencing and ended at midnight on the seventh day following. Subsequent experimental weeks were of the same duration.

The bodyweights recorded before dosing on the first day of study, however, are classified as the Week 0 bodyweights, relating to the number of weeks of treatment completed. Subsequent bodyweight recordings followed this pattern.

## TREATMENT OF DATA

This report contains serial observations pertaining to each week of treatment completed before commencement of the necropsies, together with signs data collected during the necropsy period. The only serial observations relating to the acclimatisation period included in this report are the pre-treatment functional observational battery findings.

Group mean values were calculated from the individual values presented in the appendices, unless otherwise specified below:

The death codes in the appendices have the following meaning:

- 7 Terminal sacrifice
- F Found dead
- K Euthanized *in extremis*

Throughout the tables the following abbreviations are used:

- N Number of animals examined.
- SD Standard deviation.

### Signs

Individual incidences in Appendix 1 are presented as the days on which the sign was observed, only animals with positive findings are reported. The total number of animals displaying each sign at any time during the treatment period is presented in Table 1A.

### Bodyweight

Group mean weight changes were calculated from the weight changes of individual animals. Bodyweights recorded during the acclimatisation period are not reported.

### Food consumption

Overall food consumption values were calculated from the weekly group mean values presented.

### Food conversion efficiency

The weekly group mean values presented here were calculated from unrounded cage values.

Overall group mean values were calculated from the overall bodyweight gain (Table 2B), divided by the total food consumed (Table 3), expressed as a percentage.

### Haematology

Differential leucocyte counts were determined automatically by counting the numbers of lymphocytes, neutrophils, monocytes, eosinophils, basophils and large unstained cells in the instrument sample.

The units for erythrocyte count, total and differential leucocyte count and platelet count represent the number of cells per litre of blood.

Blood films were examined for all animals.

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### Blood chemistry

Albumin to globulin (A/G) ratios were calculated as:

$$A/G = \frac{\text{Chemical albumin concentration}}{\text{Total protein} - \text{chemical albumin concentration}}$$

### Pathology

Tissues which could not be examined are specified in the appendix. The absence of a comment for a tissue scheduled for examination therefore indicates that the tissue was examined and found to be normal. In all tabular presentations of data the tissues specified in the protocol for histopathological examination precede other tissues.

### Statistical analysis

The significance of inter-group differences in haematology and blood chemistry was assessed by Student's t-test using a pooled error variance. Statistical significances for eosinophil, basophil, monocyte and large unstained cell counts are not reported as these data are not normally distributed.

For organ weights and bodyweight changes, homogeneity of variance was tested using Bartlett's test. Whenever this was found to be statistically significant a Behrens-Fisher test was used to perform pairwise comparisons, otherwise a Dunnett's test was used.

Inter-group differences in macroscopic pathology and histopathology were assessed using Fisher's Exact test.

Unless stated, group mean values or incidences for the treated groups were not significantly different from those of the Controls ( $p \leq 0.05$ ).

The functional observation battery numerical data were subjected to statistical analysis: activity and rearing in the standard arena, body temperature, bodyweight, landing footsplay, grip strength and motor activity. The following statistical analyses were performed:

If the data consisted predominantly of one particular value (relative frequency of the mode exceeds 75%), the proportion of animals with different values from the mode was analysed using Fisher's Exact test. Otherwise, Bartlett's test was performed to test for variance heterogeneity between groups. Where significant (1% level) heterogeneity was found, the data were logarithmically transformed and re-tested for heterogeneity. If no statistically significant heterogeneity of variance was detected (with or without logarithmic transformation), a one way analysis of variance was carried out. If the analysis of variance showed evidence (at the 5% level) of differences between the groups, Student's *t*-test was used to test for differences between treatment groups and the Control group. If heterogeneity was significant and could not be stabilised by logarithmic transformation, the Kruskal-Wallis test on ranks was performed on the untransformed data. If the Kruskal-Wallis test showed evidence (5% level) of differences between the groups, the Wilcoxon Rank-Sum test was used to test for differences between the treatment groups and the Control group.

**Statistical references**

FISHER, R.A. (1973) Statistical Methods of Research Workers, 14<sup>th</sup> edn., p.96. Hafner Publishing Company, New York, USA.

**(Fisher's Exact test)**

ARMITAGE, P (1971) Statistical Methods in Medical Research, p.189. Blackwell Scientific Publications, Oxford, UK.

**(One-way analysis of variance, t-test)**

COCHRAN, W.G. AND COX, G.M. (1957) Experimental Designs. 2<sup>nd</sup> edition. New York, USA:Wiley.

**("Behrens-Fisher" test)**

DUNNETT, C.W. (1955) A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association, **50**, 1096-1121.

**(Dunnnett's test)**

BARTLETT, M.S. (1937) Properties of sufficiency and statistical tests. Proceedings of the Royal Society. Series A, **160**, 268-282.

**(Bartlett's test)**

SNEDECOR, G.W. and COCHRAN, W.G. (1967) Statistical methods. 6<sup>th</sup> ed. The Iowa State University Press.

## DEVIATIONS FROM THE PROTOCOL

### **Blood chemistry sample volume**

Section 4.3.8 of the protocol states that a volume of 1.0ml of blood will be taken for blood chemistry investigations, however, it is practise at these laboratories to take 0.7ml, as this is sufficient for the investigations. A sample volume of 0.7ml was therefore taken. This deviation from protocol has no impact on the integrity of the study.

### **Environmental conditions**

Contrary to the protocol the temperature and humidity were measured manually once per day. Humidity was measured using a Vaisala Hygrometer and temperature was measured using a min/max thermometer. The environmental conditions were measured accurately therefore this deviation was considered not have affected the integrity of the study. On one occasion (Day 8) the temperature of the room rose to 23.5°C. The condition of the animals was monitored throughout and they appeared to have been unaffected by this minor transient fluctuation in temperature. Temperatures were within the target ranges on all other occasions. This deviation from protocol was not considered to have affected the integrity of the study. The data are not presented, but are retained in the archives.

### **Post-dose observations**

On Day 21 of study, the fourth post-dose observation, between 1 and 2 hours after completion of dosing all groups, was omitted in error. The signs were recorded at the end of dosing each group and at the end of the day and the duration of the signs was determined from the other occasions when post-dosing observations were recorded. This deviation, therefore, was considered not to have affected the integrity of the study.

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## RESULTS

### Mortality (Appendix 7A)

Male Number 8 in Group 4 (1000 mg/kg/day) was found dead on Day 4 of treatment. There were no clinical signs observed prior to its death. Macroscopic examination at necropsy revealed pale areas on the kidneys, a dark liver and a distended stomach. Microscopic examination revealed a number of findings in the kidneys including slight acute pyelonephritis, cortical tubular hyperplasia, collecting duct epithelial hyperplasia, multi-focal cortical mineralisation and slight focal necrosis.

Male Number 9 in Group 4 (1000 mg/kg/day) was killed *in extremis* on Day 6 of treatment. Signs observed prior to euthanasia included thin build, dark eyes, piloerection, hunched posture and fast respiration. Macroscopic examination at necropsy revealed pale and enlarged kidneys, dark areas on the stomach and a hard aorta with pale areas on the heart. Microscopic examination revealed a number of findings, most notable in the kidneys, heart, stomach, liver, colon and lungs. Findings in the kidneys included marked acute pyelonephritis and marked chronic interstitial nephritis. Marked myocarditis and marked myocardial mineralisation were recorded in the heart. Mineralisation was recorded in the stomach. Involution/atrophy of the thymus was recorded.

Female Number 33 in Group 4 (1000 mg/kg/day) was also killed *in extremis* on Day 16 of treatment. Signs observed prior to euthanasia included thin build, hunched posture, piloerection and reduced body temperature. Macroscopic examination at necropsy revealed pale and enlarged kidneys. Microscopic examination revealed a number of findings in the kidneys including marked acute pyelonephritis and marked chronic interstitial nephritis. Involution/atrophy of the thymus was also recorded.

### Signs (Tables 1A and 1B; Appendix 1)

Clinical signs observed for animals receiving 1000 mg/kg/day included thin build, reduced body temperature, piloerection, hunched posture and salivation after dosing. These signs were observed throughout the treatment period, however, not all animals were affected.

The appearance and behaviour of animals receiving 100 or 300 mg/kg/day were considered to have been unaffected by treatment.

### Bodyweight (Figures 2A and 2B; Tables 2A and 2B; Appendix 2)

Weekly group mean bodyweight gains were low for males and females receiving 1000 mg/kg/day throughout the treatment period and overall bodyweight gains for these animals were low when compared with the Controls (61% and 72% of the Control values respectively). Some individuals in this group were unaffected.

There were no clear dosage-related bodyweight effects at 100 or 300 mg/kg/day.

### Food consumption (Table 3; Appendix 3)

Group mean food consumption was lower than that for the Controls for males and females receiving 1000 mg/kg/day throughout the treatment period resulting in low total values (75% and 83% of the Control values respectively). Some individuals in this group were unaffected.

There were no clear dosage-related effects on food consumption at 100 or 300 mg/kg/day.

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**Food conversion efficiency (Table 4)**

Overall food conversion efficiency was low for males and females receiving 1000 mg/kg/day when compared with the Controls (81% and 86% of the Control values respectively).

There were no clear dosage-related effects for animals receiving 100 or 300 mg/kg/day.

**Functional observation battery (FUNCTIONAL OBSERVATIONAL BATTERY REPORT)**

**In the hand observations**

Animals receiving 1000 mg/kg/day showed a high incidence of piloerection at the weekly observation from Week 2 (females) or Week 3 (males) of treatment onwards.

**Arena observations**

Compared with Controls, activity and rearing scores for females receiving 1000 mg/kg/day were markedly reduced at these weekly observations, particularly during Weeks 2, 3 and 4 of treatment. The reduced number of males receiving 1000 mg/kg/day decreased the reliability of inter-group comparisons but, overall, activity and rearing scores for males in this group appeared to be unaffected. Occasional, slight whole body tremors were observed in one male receiving 1000 mg/kg/day at the Week 4 of observation.

**Manipulations**

Group mean body temperature values for animals receiving 1000 mg/kg/day were 0.6 °C lower than those of Controls at the observation occasion during Week 4 of treatment, with statistical significance being achieved in the females. All group mean values were, however, within the previously recorded Background Control Data range of values and in view of the reduced number of animals in this dosage group, an effect of treatment on body temperature could not be established with certainty.

The bodyweight of some individuals receiving 1000 mg/kg/day were markedly lower than those of Controls at the observation occasion during Week 4 of treatment but other individuals in the group were unaffected.

At the observation occasion during Week 4 of treatment, forelimb and hindlimb grip strength values for two males receiving 1000 mg/kg/day were reduced, compared with Controls, but these individuals also showed reduced bodyweights.

**Motor activity**

Compared with Controls, group mean high beam and low beam scores (rearing and cage floor activity respectively) for males receiving 1000 mg/kg/day were markedly reduced throughout the one-hour recording period at the observation occasion during Week 4 of treatment. Scores for females in all treated groups tended to be lower than those of Controls throughout the one-hour recording period but there was no consistent dosage-relationship. These differences could not be attributed with certainty to treatment as scores for Controls were atypically high, often falling outside of the Background Control Data range, and because of the reduced number of animals in this treatment group.

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**Haematology (Table 5; Appendix 4A)**

Haematology investigations on Day 30 revealed low haematocrit, haemoglobin concentrations and red blood cell counts for males and females at 1000 mg/kg/day when compared with the Controls. Values were also lower than the Controls for females which received 300 mg/kg/day. The males at this dosage were not clearly affected. High total white blood cell counts, associated with high neutrophil and eosinophil counts were recorded for males and females which received 1000 mg/kg/day, when compared with the Controls.

The activated partial thromboplastin clotting time (APTT) was shorter for the animals treated at 1000 mg/kg/day than in the Controls.

Other inter-group differences which attained statistical significance were either without dosage-relationship or restricted to a single sex and were, therefore, not considered to be attributable to treatment.

**Haematology, bone marrows (Appendix 4B)**

The myeloid to erythroid ratio was slightly high for animals treated at 1000 mg/kg/day when compared with the Controls. This increase was associated with a slightly higher myeloid series and a slightly low erythroid series in this group.

**Blood chemistry (Table 6; Appendix 5)**

Blood chemistry investigations revealed high urea and creatinine levels for males and females which received 1000 mg/kg/day when compared with the Controls.

Other inter-group differences which attained statistical significance were either without dosage-relationship or restricted to a single sex and were, therefore, not considered to be attributable to treatment.

**Organ weights (Tables 7A and 7B; Appendices 6A and 6B)**

Analysis of organ weights revealed high absolute and bodyweight-relative kidney weights for males and females which received 1000 mg/kg/day when compared with the Controls. Females treated at 1000 mg/kg/day had high spleen weights when compared with the Controls. Thymus weights were high for all treated female groups, however, there was no relationship to dosage.

**Macroscopic pathology (Table 8; Appendix 7B)**

Macroscopic examination at necropsy of animals euthanized at the end of the treatment period revealed a high incidence of enlarged and/or pale kidneys for males and females which had received 1000 mg/kg/day. The kidneys of individual males at this dosage were noted to have cysts, contain calculus, have a granular appearance or pelvic dilation.

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**Microscopic pathology** (Table 9; Appendix 7B)

Findings considered to be related to treatment were seen in the kidneys.

An increased incidence and/or severity of a number of inflammatory and degenerative/regenerative changes were evident in the kidneys of animals given Material 02675234 at 300 mg/kg/day or above (see text table 1).

Text table 1 – Kidney Changes – Animals killed at the end of the treatment period

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dosage (mg/kg/day)	0	100	300	1000	0	100	300	1000
<b>Kidneys</b>								
Number examined	5	5	5	3	5	5	5	4
<b>Cortical Tubular Basophilia</b>								
Minimal	1	2	2	0	0	1	3	0
Slight	0	0	2	0	0	0	0	1
Moderate	0	0	1	0	0	0	0	0
Marked	0	0	0	2	0	0	0	3
Total	1	2	5a	2	0	1	3	4b
<b>Acute Pyelonephritis</b>	0	0	2	3a	0	0	0	3a
<b>Tubular Dilatation</b>	0	0	3	3a	0	0	0	3a
<b>Chronic Interstitial Nephritis</b>	0	0	1	3a	0	0	0	3a
<b>Cortical Tubular Hyperplasia</b>	0	0	0	2	0	0	0	3a
<b>Collecting Duct Epithelial Hyperplasia</b>	0	0	0	2	0	0	0	3a
<b>Hyperplasia of Papillary Epithelium</b>	0	0	0	2	0	0	1	2

Significant when compared with Group 1 : a - p<0.05; b – p<0.01 (Fisher's Exact Test)

Two males and one female given Material 02675234 at 1000 mg/kg/day died or were euthanized during the treatment period. Kidney changes of the same type as those seen in animals euthanized at the end of the treatment period were evident in the kidneys of these animals.

## DISCUSSION AND CONCLUSION

Animals receiving Material 02675234 at 1000 mg/kg/day, showed clear signs of toxicity; one male and one female were euthanized *in extremis* and another male was found dead. Bodyweight, food consumption and food conversion efficiency were low in this group. Signs included piloerection, thin build, hunched posture, salivation and reduced rearing in the arena. Grip strength was reduced in two of the three surviving males receiving 1000 mg/kg/day, although this was probably associated with the low bodyweights of these two individuals. Decreased motor activity scores and body temperature values were also recorded in animals receiving 1000 mg/kg/day but because of atypically high Control group values and the reduced number of animals in the treated group, it was uncertain if these changes were treatment-related. None of the observed changes were considered to indicate specific action on the nervous system.

Haematological differences included low haematocrit, haemoglobin concentrations and red blood cell counts for animals treated at 1000 mg/kg/day and for females treated at 300 mg/kg/day. Linked to these changes were high myeloid to erythroid ratios in the bone marrow of animals treated at 1000 mg/kg/day which is seen when red cell formation is depressed.

Also at 1000 mg/kg/day, total white blood cell counts were higher than the Controls, associated with increases in neutrophil and eosinophil counts. Activated partial thromboplastin clotting times were shorter in this group than in the Controls.

Kidney weights were high for animals treated at 1000 mg/kg/day and the kidneys were enlarged and/or pale at macroscopic examination in this group. Microscopic findings were observed in the kidneys of animals treated at 300 or 1000 mg/kg/day. It is considered that these treatment-related changes were probably related to an obstructive nephropathy. The high levels of acute inflammatory cells present in the tubules, however, indicate that there may also be a local irritant effect in the kidneys. The presence of amorphous material in the ureter of one high dose male (with associated inflammation and epithelial hyperplasia), and the occurrence of refractile crystals in the tubular lumina of the kidneys of another male of the same dosage group suggests that the test material or a metabolite is being deposited in the urinary system. The lack of an inflammatory reaction in the urinary bladder of any animals, and the variable levels of change between kidneys in individual animals (for example, male number 18 in Group 3 (300 mg/kg/day) and female number 34 in Group 4 (1000 mg/kg/day) suggest that obstruction is taking place in the ureters and/or the kidney tubules. Basophilia is indicative of a regenerative response to injury of the cortical tubules, and in the most severely affected kidneys there is evidence of marked degenerative changes associated with marked basophilia of tubules. Basophilic cortical tubules also, however, occur spontaneously in the kidneys of young rats, and the occurrence of this finding at a minimal severity in animals of Group 2 (100 mg/kg/day) is considered to be a chance occurrence, and not related to treatment.

High blood urea and creatinine levels were recorded for animals treated at 1000 mg/kg/day. These findings were considered to be associated with the kidney damage seen in these animals.

One of the male decedent animals showed marked mineralisation of the cardiovascular system and gastro-intestinal tract. The presence of these changes was probably a significant factor in the early death of this animal. The relationship of these changes to treatment is, however, unclear. It is known that a marked impairment of kidney function can lead to secondary mineralisation of these tissues, but it is considered unlikely that this was the aetiology in this case. The duration of treatment (the animal was euthanized *in extremis* on Day 6 of the study), the level of mineralisation present, and the lack of a similar effect in animals surviving for the duration of the treatment period indicate that it is likely that the mineralisation was a pre-existing condition which contributed to the early demise of this animal.

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Changes in the male reproductive organs seen in decedent animals of the highest dosage group were considered to be related to the early death of these animals, and their consequent immaturity, and were not considered to be related to treatment.

It is concluded that administration of Material 02675234 by oral gavage to CD rats for a minimum of 28 days resulted in clear signs of toxicity at 1000 mg/kg/day and some signs of nephropathy at 300 mg/kg/day. The No-Observed-Adverse-Effect-Level (NOAEL) was considered to be 100 mg/kg/day.

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FIGURE 1

Cage arrangement in batteries

Group : 1 2 3 4  
 Compound : Control  
 Dosage (mg/kg/day) : 0 100 300 1000  
 - Material 02675234 -

Battery 1

4M	6	3M	17	2M	3	1M	14	14
3M	16	2M	2	1M	13	4M	10	10
2M	1	1M	12	4M	9	3M	20	20
1M	11	4M	8	3M	19	2M	5	5
4M	7	3M	18	2M	4	1M	15	15

Battery 2

4F	31	3F	37	2F	28	1F	24	24
3F	36	2F	27	1F	23	4F	35	35
2F	26	1F	22	4F	34	3F	40	40
1F	21	4F	33	3F	39	2F	30	30
4F	32	3F	38	2F	29	1F	25	25

Group/sex
Cage No.
Animal No.

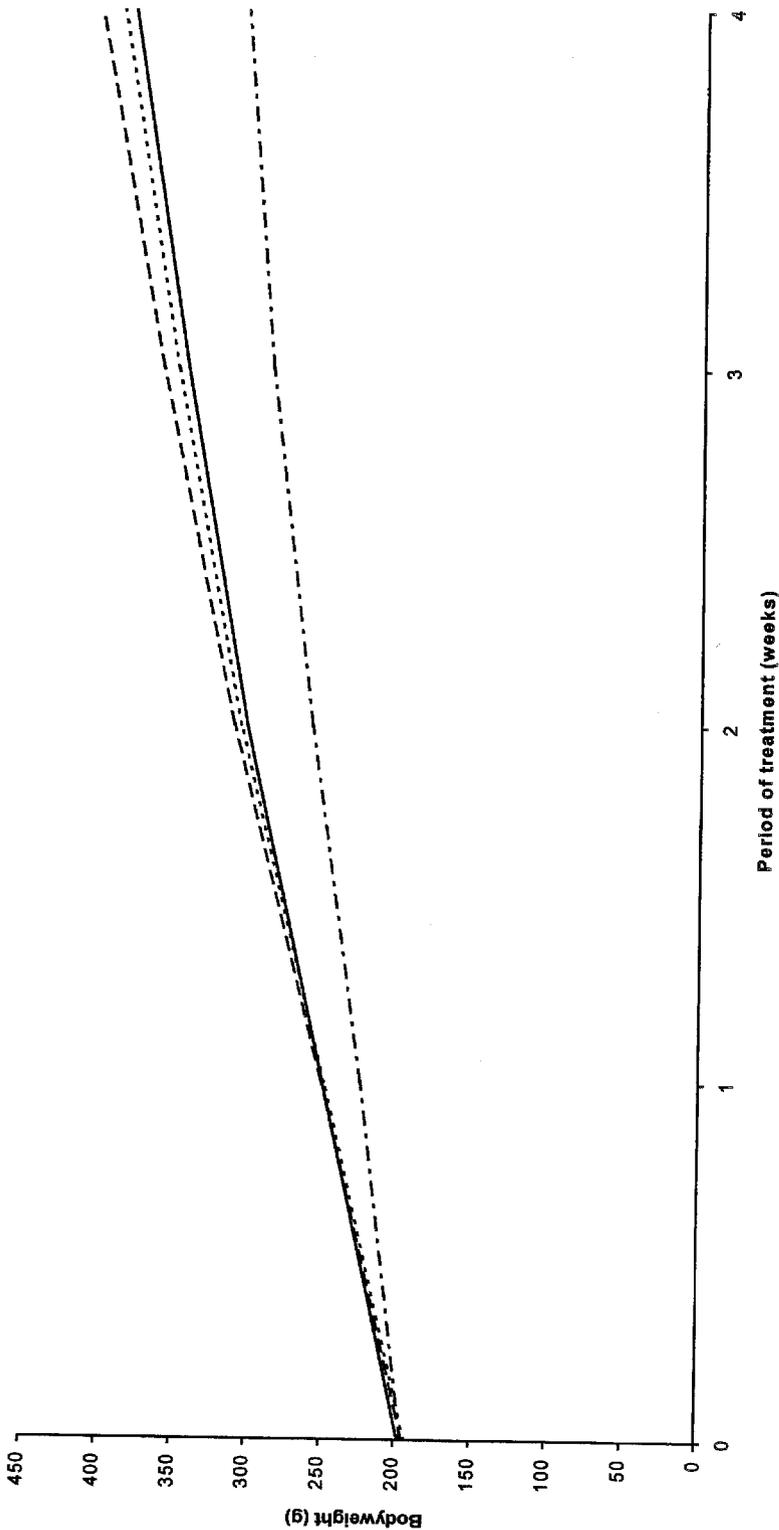
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FIGURE 2A

Group mean bodyweight versus period of treatment - males

Group	:	1	2	3	4
Compound	:	Control		- Material 02675234 -	
Dosage (mg/kg/day)	:	0	100	300	1000

— Group 1    - - - Group 2    ····· Group 3    - · - · - Group 4



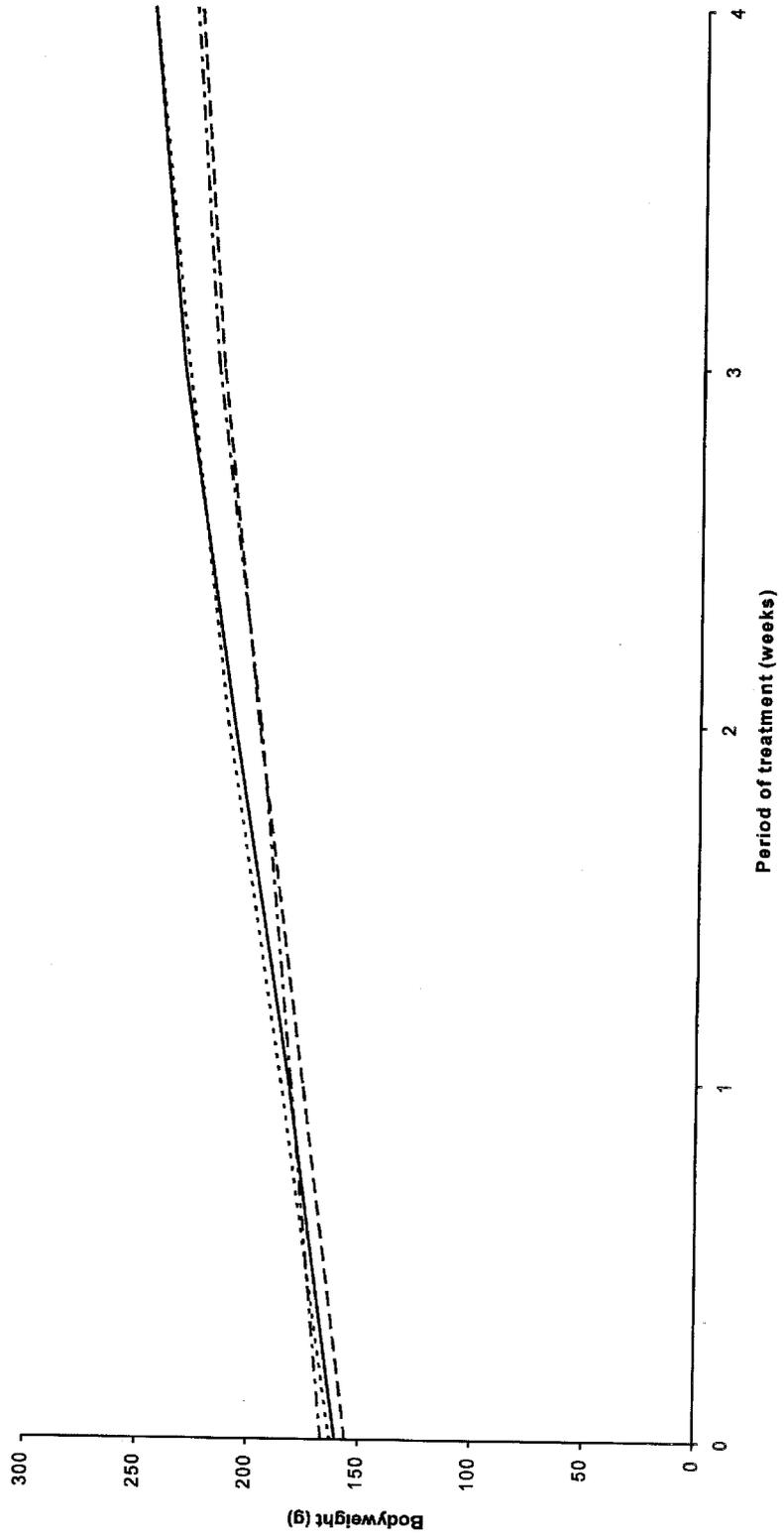
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FIGURE 2B

Group mean bodyweight versus period of treatment - females

Group	:	1	2	3	4
Compound	:	Control		- Material 02675234 -	
Dosage (mg/kg/day)	:	0	100	300	1000

— Group 1    - - - Group 2    ····· Group 3    - · - · - Group 4



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TABLE 1A  
 Signs - group distribution of observations

Group	1	2	3	4	NUMBER OF ANIMALS AFFECTED					
					1	2	3	4	5	
Compound	Control	Material 02675234 -	300	1000						
Dosage (mg/kg/day)	0	100	300	1000						
DAYS 1-30										
CATEGORY	SEX:				---MALE---		---FEMALE---			
KEYWORD	GROUP:	1	2	3	4	1	2	3	4	
QUALIFIER	NUMBER:	5	5	5	5	5	5	5	5	5
*** TOP OF LIST ***										
SKIN ABRASION										
DRY										
HEAD					0	1	0	0	0	0
DORSAL BODY SURFACE					0	1	0	0	0	0
BUILD (CONFORMATION)					0	0	0	3	0	0
THIN					0	0	0	3	0	0
BUILD (DEFORMITY)					0	0	0	1	0	0
SWOLLEN AREA					0	0	0	1	0	0
VENTRAL ABDOMEN					0	0	0	1	0	0
BEHAVIOUR					0	0	0	1	0	0
UNDERACTIVE					0	0	0	1	0	0
VOCALIZATION					0	0	0	0	0	1
BODY TEMPERATURE					0	0	0	2	0	0
REDUCED					0	0	0	2	0	0
COAT					0	0	0	3	0	0
PILORECTION					0	0	0	3	0	0
HAIRLOSS					0	0	1	0	0	0
RIGHT FORELIMB					0	1	0	0	0	0
HEAD					0	1	0	0	0	0
DORSAL BODY SURFACE					0	1	0	0	1	0
EYES					0	0	0	1	0	0
DARK					0	0	0	1	0	0
BOTH					0	0	0	1	0	0

Material 02675234  
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TABLE 1A - continued.  
 Signs - group distribution of observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

DAYS 1-30	NUMBER OF ANIMALS AFFECTED							
	--MALE--				--FEMALE--			
CATEGORY	1	2	3	4	1	2	3	4
KEYWORD	SEX: GROUP:							
QUALIFIER	5	5	5	5	5	5	5	5
QUALIFIER	NUMBER:							
MUSCLE REACTION	0	0	0	1	0	0	0	0
REDUCED BODY TONE	0	0	0	1	0	0	0	0
WHOLE BODY	0	0	0	3	0	0	0	4
POSTURE	0	0	0	1	0	0	0	0
HUNCHED	0	0	0	1	0	0	0	0
RESPIRATION	0	0	0	1	0	0	0	0
FAST	0	0	0	1	0	0	0	0
SKIN	0	1	0	0	0	0	0	0
ENCRUSTATION(S)	0	1	0	0	0	0	0	0
UPPER DORSAL THORAX	0	0	0	1	0	0	0	0
STAINING	0	0	0	1	0	0	0	0
FAECES	0	0	0	1	0	0	0	0
PERIANAL	0	0	0	1	0	0	0	0
BROWN	0	0	0	1	0	0	0	0
RIGHT FORELIMB	0	0	0	0	0	1	0	0
RIGHT ORBIT	0	0	0	0	0	0	0	1
SCROTUM	0	0	0	1	0	0	0	0
PINNA	0	0	0	0	0	0	0	1
HEAD	0	1	0	2	0	1	2	2
NOSE	0	0	0	0	1	0	0	0
MUZZLE	1	0	0	2	0	1	1	0
DORSAL BODY SURFACE	1	1	0	2	0	1	0	1
TAIL	0	0	0	0	0	0	0	0

\*\*\* END OF LIST \*\*\*

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 1B

Signs - group distribution of observations associated with dosing

Group Compound Dosage (mg/kg/day)	Day number	Group and sex/Animal number												
		1M	2M	3M	4M	1F	2F	3F	4F					
: 1	2													
: Control				3	4									
: 0	100			300	1000									
				- Material 02675234 -										
Sign														
Salivation	1													31
	4				9									
	10													
	14			18	6							38		
					7							40		
	17													
					10									
	21				6									
					7									
					10									

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 1B - continued

Signs - group distribution of observations associated with dosing

Group Compound Dosage (mg/kg/day)	1 Control 0	2 100	3 300	4 1000	Group and sex/Animal number									
					1M	2M	3M	4M	1F	2F	3F	4F		
Sign	Day number													
Salivation - continued	24					1	16	6						31
								7						34
								10						35
	29						16	6						34
							20	7						35
								10						

Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 1B - continued

Signs - group distribution of observations associated with dosing

Group Compound Dosage (mg/kg/day)	1 Control 0	2 100	3 - Material 02675234 - 300	4 1000	Group and sex/Animal number								
					1M	2M	3M	4M	1F	2F	3F	4F	
Sign	Day number												
Piloerection	4			9									31 35
	17			10									31 35
	21			6									31 35
	24			7									31 32 35
	29			10									31 34 35
Fast respiration	4			6									
				10									
Staining as a result of salivation	14			6									

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 2A

Bodyweight - group mean values (g)

Group Compound : 1 Control 2 3 4  
 Dosage (mg/kg/day) : 0 100 300 1000

SEX: -----MALE-----FEMALE-----

WEEK	SEX: MALE					SEX: FEMALE				
	1	2	3	4	5	1	2	3	4	5
0	N 197	5 194	5 192	5 195	5 160	5 160	5 155	5 162	5 166	5 166
	MEAN 15.5	12.3	10.1	10.3	10.5	10.5	12.7	8.5	5.6	5.6
1	N 250	5 251	5 249	3 225	5 183	5 183	5 177	5 186	5 182	5 182
	MEAN 21.9	19.8	15.3	47.1	12.6	12.6	13.0	10.2	21.6	21.6
2	N 303	5 311	5 307	3 259	5 209	5 209	5 198	5 212	5 197	5 197
	MEAN 28.1	22.5	13.6	78.9	15.2	15.2	15.3	13.8	28.3	28.3
3	N 344	5 361	5 351	3 287	5 233	5 233	5 215	5 231	4 217	4 217
	MEAN 31.2	20.2	17.8	110.7	16.9	16.9	13.3	11.0	37.7	37.7
4	N 381	5 403	5 388	3 306	5 248	5 248	5 226	5 248	4 229	4 229
	MEAN 29.6	21.9	12.9	125.6	21.0	21.0	15.5	17.9	37.9	37.9

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 2B

Bodyweight gain - group mean values (g)

Group Compound : 1 Control 2 3 4  
 - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

WEEK	SEX: MALE					FEMALE				
	1	2	3	4	5	1	2	3	4	5
0-1	N	5	5	5	3	5	5	5	5	5
	MEAN	53	57	57	30	23	21	24	15	15
	S.D.	8.3	8.6	5.9	35.9	6.5	3.0	4.7	16.6	16.6
1-2	N	5	5	5	3	5	5	5	5	5
	MEAN	52	60	58	34	26	21	25	15	15
	S.D.	7.6	3.1	4.6	32.5	3.5	5.6	5.3	12.8	12.8
2-3	N	5	5	5	3	5	5	5	4	4
	MEAN	41	49	44	28	24	17	19	18	18
	S.D.	5.2	5.2	15.0	39.0	2.2	2.7	5.5	6.7	6.7
3-4	N	5	5	5	3	5	5	5	4	4
	MEAN	37	43	38	18 a	15	11	17	11	11
	S.D.	6.2	3.4	7.9	15.0	5.1	6.5	7.6	3.9	3.9
0-4	N	5	5	5	3	5	5	5	4	4
	MEAN	183	209	196	111	88	71	85	63	63
	S.D.	18.5	10.9	9.4	112.1	14.1	13.1	15.7	33.5	33.5
As % of Control		-	114	107	61	-	81	97	72	72

Significant when compared with Group 1: a - p<0.05; b - p<0.01 S.D. - Standard deviation

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 3  
 Food consumption - group mean values (g/animal)

Group Compound	Material 02675234 -			
	Control	100	300	1000
Dosage (mg/kg/day)	0	100	300	1000
WEEK	SEX:			
	MALE		FEMALE	
	1	2	3	4
1	5	5	5	3
N	196	202	200	158
MEAN	26.5	20.2	18.7	66.0
S.D.				
2	5	5	5	3
N	197	208	206	148
MEAN	22.1	21.7	11.1	83.2
S.D.				
3	5	5	5	3
N	201	219	213	145
MEAN	16.7	14.9	17.9	98.7
S.D.				
4	5	5	5	3
N	197	219	221	142
MEAN	16.6	13.8	13.7	77.2
S.D.				
Total 1-4	791	848	840	593
As % of Control	-	107	106	75

WEEK	SEX:			
	MALE		FEMALE	
	1	2	3	4
1	5	5	5	5
N	136	129	135	123
MEAN	16.3	10.3	12.4	34.0
S.D.				
2	5	5	5	5
N	139	125	133	105
MEAN	11.6	11.7	11.3	44.1
S.D.				
3	5	5	5	4
N	145	138	146	124
MEAN	11.6	6.9	15.0	36.4
S.D.				
4	5	5	5	4
N	149	134	151	121
MEAN	12.4	10.1	24.3	33.5
S.D.				
Total 1-4	569	526	565	473
As % of Control	-	92	99	83

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 4  
 Food conversion efficiency - group mean values (%)

Group Compound Dosage (mg/kg/day)	Material 02675234 -			
	1 Control 0	2 100 300	3 300 1000	4
WEEK	SEX: -----MALE-----FEMALE-----			
	1	2	3	4
1	27.1	28.2	28.5	15.4
2	26.5	29.2	28.0	20.7
3	20.5	22.6	20.1	7.8
4	18.6	19.6	17.0	11.6
Overall 1-4	23.1	24.6	23.3	18.7

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 5

Haematology - group mean values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	Control		- Material 02675234 -		MCV fL	WBC x10 <sup>9</sup> /L	Neutr ophil x10 <sup>9</sup> /L	Lymph ocyte x10 <sup>9</sup> /L	
	1 Control	2 100	3 300	4 1000					
Group	Hct L/L	Hb g/dL	RBC x10 <sup>12</sup> /L	MCH pg	MCHC g/dL	MCV fL	WBC x10 <sup>9</sup> /L	Neutr ophil x10 <sup>9</sup> /L	Lymph ocyte x10 <sup>9</sup> /L
1M	Mean	16.1	8.25	19.5	34.2	57.1	15.21	1.82	12.53
	SD	0.0036	0.23	0.26	0.39	0.44	2.550	0.499	2.702
	n	5	5	5	5	5	5	5	5
2M	Mean	0.456	15.6	7.76 <sup>a</sup>	20.2	58.7	16.45	2.58	12.98
	SD	0.0115	0.23	0.285	0.69	2.13	3.547	2.258	1.537
	n	5	5	5	5	5	5	5	5
3M	Mean	0.462	15.9	8.03	19.8	57.5	14.37	2.40	10.98
	SD	0.0216	0.72	0.339	0.43	0.91	3.412	1.067	2.182
	n	5	5	5	5	5	5	5	5
4M	Mean	0.423 <sup>c</sup>	14.7 <sup>b</sup>	7.44 <sup>b</sup>	19.8	56.9	24.85 <sup>b</sup>	7.43 <sup>c</sup>	15.33
	SD	0.0136	0.42	0.278	0.55	2.05	4.840	0.352	3.500
	n	3	3	3	3	3	3	3	3

Significant when compared with Group 1: a - p<0.05; b - p<0.01; c - p<0.001.

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 5 – continued

Haematology - group mean values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control	2 100	3 300 - Material 02675234 -	4 1000			
Group	Eosinophil x10 <sup>-9</sup> /L	Basophil x10 <sup>-9</sup> /L	Monoocyte x10 <sup>-9</sup> /L	LUC x10 <sup>-9</sup> /L	Plt x10 <sup>-9</sup> /L	PT sec	APTT sec
1M	Mean	0.10	0.03	0.42	0.31	1040	20.1
	SD	0.041	0.015	0.118	0.064	244.8	1.75
	n	5	5	5	5	5	5
2M	Mean	0.11	0.03	0.41	0.33	1218	19.7
	SD	0.068	0.018	0.118	0.054	181.7	0.86
	n	5	5	5	5	5	5
3M	Mean	0.15	0.03	0.45	0.36	1197	20.2
	SD	0.073	0.016	0.161	0.082	88.4	0.18
	n	5	5	5	5	5	5
4M	Mean	0.91	0.06	0.63	0.49	1530 <sup>b</sup>	16.3 <sup>b</sup>
	SD	0.452	0.025	0.292	0.310	137.6	1.79
	n	3	3	3	3	3	3

Significant when compared with Group 1: b – p<0.01

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 5 – continued

Haematology - group mean values on Day 30 of the study

Group	1	2	3	4															
Compound	Control		- Material 02675234 -																
Dosage (mg/kg/day)	0	100	300	1000															
Group	Hct	Hb	RBC	MCH	MCHC	MCV	WBC	Neutr ophil x10 <sup>-9</sup> /L	Lymph ocyte x10 <sup>-9</sup> /L	Hct	Hb	RBC	MCH	MCHC	MCV	WBC	Neutr ophil x10 <sup>-9</sup> /L	Lymph ocyte x10 <sup>-9</sup> /L	
	L/L	g/dL	x10 <sup>-12</sup> /L	pg	g/dL	fL	x10 <sup>-9</sup> /L	x10 <sup>-9</sup> /L	x10 <sup>-9</sup> /L	L/L	g/dL	x10 <sup>-12</sup> /L	pg	g/dL	fL	x10 <sup>-9</sup> /L	x10 <sup>-9</sup> /L	x10 <sup>-9</sup> /L	
1F	Mean	16.1	7.69	20.9	35.2	59.6	13.03	0.91	11.42										
	SD	0.0068	0.27	0.53	0.29	1.37	3.433	0.263	3.006										
	n	5	5	5	5	5	5	5	5										
2F	Mean	0.436	15.3	7.77	19.7 <sup>b</sup>	56.1 <sup>b</sup>	13.97	1.36	11.83										
	SD	0.0131	0.46	0.166	0.31	0.97	2.479	0.746	2.199										
	n	5	5	5	5	5	5	5	5										
3F	Mean	0.421 <sup>a</sup>	14.8 <sup>a</sup>	7.37	20.1 <sup>a</sup>	57.2 <sup>a</sup>	11.90	1.91	9.35										
	SD	0.0123	0.40	0.193	0.35	1.10	1.835	1.160	1.392										
	n	5	5	5	5	5	5	5	5										
4F	Mean	0.415 <sup>a</sup>	14.4 <sup>b</sup>	7.28	19.8 <sup>b</sup>	56.9 <sup>a</sup>	19.50 <sup>a</sup>	4.29 <sup>b</sup>	13.81										
	SD	0.0484	1.64	0.671	0.70	1.89	5.612	2.657	3.188										
	n	4	4	4	4	4	4	4	4										

Significant when compared with Group 1: a - p<0.05; b - p<0.01

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 5 – continued

Haematology - group mean values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control	2 100	3 300 - Material 02675234 -	4 1000					
Group	Eosinophil x10-9/L	Basophil x10-9/L	Monoocyte x10-9/L	LUC x10-9/L	Plt x10-9/L	PT sec	APTT sec		
1F	Mean	0.18	0.03	0.25	1215	13.6	17.7		
	SD	0.049	0.009	0.076	110.9	0.37	0.47		
	n	5	5	5	5	5	5		
2F	Mean	0.15	0.02	0.31	1122	13.4	17.5		
	SD	0.021	0.011	0.151	243.0	0.40	1.80		
	n	5	5	5	5	5	5		
3F	Mean	0.18	0.02	0.22	1185	13.8	17.7		
	SD	0.108	0.008	0.094	109.2	0.88	0.69		
	n	5	5	5	5	4	4		
4F	Mean	0.52	0.04	0.46	1195	13.4	14.9 <sup>a</sup>		
	SD	0.257	0.014	0.150	317.6	0.30	2.59		
	n	4	4	4	4	3	3		

Significant when compared with Group 1: a - p<0.05

Material 02675234  
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TABLE 6

Blood chemistry - group mean values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1		2		3		4		
	Control	0	100	300	1000	- Material 02675234 -			
Group	Alk. Phos U/L	ALT U/L	AST U/L	gGT U/L	Bili. Total umol/L	Urea mmol/L	Creat umol/L	Gluc mmol/L	Chol Total mmol/L
1M	Mean	39	68	0	1	4.62	41	7.74	1.71
	SD	57.5	11.0	0.0	0.4	0.769	2.3	1.160	0.301
	n	5	5	5	5	5	5	5	5
2M	Mean	575	46	63	0	2	43	8.42	1.99
	SD	60.6	13.1	10.4	0.0	0.5	3.1	0.812	0.313
	n	5	5	5	5	5	5	5	5
3M	Mean	608	40	63	0	2	47	7.99	1.94
	SD	129.2	8.2	3.8	0.0	0.5	4.8	0.858	0.386
	n	5	5	5	5	5	5	5	5
4M	Mean	564	38	64	1 <sup>b</sup>	4 <sup>c</sup>	126 <sup>c</sup>	7.15	2.90 <sup>b</sup>
	SD	100.7	2.5	5.1	0.6	1.5	54.6	0.692	0.596
	n	3	3	3	3	3	3	3	3

Significant when compared with Group 1: b - p<0.01; c - p<0.001.

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 6 – continued

Blood chemistry - group mean values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control	2 100	3 300	4 1000	Trig mmol/L	Na mmol/L	K mmol/L	Cl mmol/L	Ca Total mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
1M	Mean	143	4.1	100	0.79	143	4.1	100	2.89	2.57	64	35	1.24
	SD	1.5	0.24	0.8	0.121	1.5	0.24	0.8	0.034	0.109	1.0	0.5	0.016
	n	5	5	5	5	5	5	5	5	5	5	5	5
2M	Mean	142	4.2	98 <sup>a</sup>	0.90	142	4.2	98 <sup>a</sup>	2.82	2.55	65	35	1.19
	SD	0.4	0.21	1.3	0.159	0.4	0.21	1.3	0.149	0.108	3.5	1.6	0.098
	n	5	5	5	5	5	5	5	5	5	5	5	5
3M	Mean	142	4.1	98 <sup>a</sup>	0.90	142	4.1	98 <sup>a</sup>	2.77 <sup>a</sup>	2.56	63	35	1.22
	SD	1.6	0.18	1.4	0.321	1.6	0.18	1.4	0.065	0.168	2.1	0.8	0.105
	n	5	5	5	5	5	5	5	5	5	5	5	5
4M	Mean	143	4.4	98 <sup>a</sup>	1.20 <sup>a</sup>	143	4.4	98 <sup>a</sup>	2.87	3.00	65	34	1.11 <sup>a</sup>
	SD	1.5	0.57	1.5	0.305	1.5	0.57	1.5	0.061	0.742	2.1	1.0	0.021
	n	3	3	3	3	3	3	3	3	3	3	3	3

Significant when compared with Group 1: a – p<0.05.

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 6 – continued

Blood chemistry - group mean values on Day 30 of the study

Group	1	2	3	4					
Compound	Control	- Material 02675234 -							
Dosage (mg/kg/day)	0	100	300	1000					
Group	Alk. Phos U/L	ALT U/L	AST U/L	gGT U/L	Bili. Total umol/L	Urea mmol/L	Creat umol/L	Gluc mmol/L	Chol Total mmol/L
1F	Mean	40	69	1	2	6.03	46	6.81	2.49
	SD	4.2	6.2	1.3	0.5	0.537	2.8	0.462	0.610
	n	5	5	5	5	5	5	5	5
2F	Mean	38	64	1	2	5.17	42	7.41	2.12
	SD	7.8	3.0	0.7	0.7	1.133	2.4	0.954	0.422
	n	5	5	5	5	5	5	5	5
3F	Mean	32	61	0	2	6.19	47	7.97 <sup>a</sup>	2.50
	SD	3.0	5.8	0.5	0.5	1.294	2.6	1.178	0.100
	n	5	5	5	5	5	5	5	5
4F	Mean	42	85	1	2	17.21 <sup>b</sup>	75 <sup>b</sup>	7.34	3.04
	SD	14.7	32.9	0.6	0.5	10.022	27.0	0.525	1.061
	n	4	4	4	4	4	4	4	4

Significant when compared with Group 1: a – p<0.05; b – p<0.01.

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

TABLE 6 – continued

Blood chemistry - group mean values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control	2 100	3 300	4 1000	Trig mmol/L	Na mmol/L	K mmol/L	Cl mmol/L	Ca Total mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
1F	Mean	143	4.2	100	2.84	2.38	67	37	1.24				
	SD	0.8	0.17	0.8	0.022	0.061	1.9	0.8	0.058				
	n	5	5	5	5	5	5	5	5	5	5	5	5
2F	Mean	143	3.8 <sup>a</sup>	100	2.73 <sup>b</sup>	2.05 <sup>a</sup>	64	36	1.30				
	SD	1.1	0.26	1.3	0.066	0.168	2.6	1.6	0.049				
	n	5	5	5	5	5	5	5	5	5	5	5	5
3F	Mean	142	3.9	100	2.71 <sup>b</sup>	2.08 <sup>a</sup>	64	35	1.23				
	SD	0.8	0.17	1.6	0.071	0.128	1.1	1.0	0.083				
	n	5	5	5	5	5	5	5	5	5	5	5	5
4F	Mean	142	4.6 <sup>a</sup>	100	2.80	2.39	65	35	1.16				
	SD	1.3	0.33	1.3	0.048	0.306	4.2	2.9	0.113				
	n	4	4	4	4	4	4	4	4	4	4	4	4

Significant when compared with Group 1: a – p<0.05; b – p<0.01.

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 7A

Absolute organ weights - group mean values (g) for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

SEX:	-MALE-				-FEMALE-			
	1	2	3	4	1	2	3	4
GROUP:	1	2	3	4	1	2	3	4
NUMBER:	5	5	5	5	5	5	5	5
TERMINAL BODY WEIGHT (g)								
	BEHREN'S - FISHER'S TEST				DUNNETT'S TEST			
N	5	5	5	5	5	5	5	5
MEAN	362.1	390.8	375.3	239.6	240.2	220.1	238.8	207.3
sd	33.6	18.1	10.0	109.9	19.6	13.2	15.5	40.5
BRAIN								
	BEHREN'S - FISHER'S TEST				DUNNETT'S TEST			
N	5	5	5	5	5	5	5	5
MEAN	2.02	1.97	2.00	1.91	1.90	1.82	1.81	1.79
sd	0.08	0.06	0.03	0.11	0.04	0.02	0.04	0.06
ADRENALS								
	BEHREN'S - FISHER'S TEST				DUNNETT'S TEST			
N	5	5	5	5	5	5	5	5
MEAN	0.051	0.061	0.065	0.078	0.063	0.066	0.078	0.066
sd	0.008	0.003	0.010	0.022	0.009	0.011	0.011	0.010
EPIDIDYMIDES								
	BEHREN'S - FISHER'S TEST				DUNNETT'S TEST			
N	5	5	5	5	5	5	5	5
MEAN	0.833	0.854	0.879	0.722	0.828	0.828	0.828	0.828
sd	0.063	0.040	0.050	0.131	0.057	0.057	0.057	0.125
HEART								
	BEHREN'S - FISHER'S TEST				DUNNETT'S TEST			
N	5	5	5	5	5	5	5	5
MEAN	1.323	1.463	1.277	1.081	0.942	0.878	0.948	0.835
sd	0.184	0.072	0.060	0.285	0.057	0.078	0.089	0.125

Significant when compared with Group 1: a - p<0.05; b - p<0.01

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 7A - continued.  
 Absolute organ weights - group mean values (g) for all animals

Group Compound Dosage (mg/kg/day)	1 Control 0		2 100		3 300		4 1000	
	1	2	3	4	5	6	7	8
SEX: ---MALE---FEMALE---								
GROUP NUMBER:	5	5	5	5	5	5	5	5
KIDNEYS								
N	5	5	5	5	5	5	5	5
MEAN	3.03	3.03	3.25	4.66 b	1.88	1.85	1.94	2.84
sd	0.26	0.34	0.60	0.24	0.06	0.06	0.15	0.89
LIVER								
N	5	5	5	5	5	5	5	5
MEAN	14.93	17.14	16.86	12.19	10.12	9.27	10.02	9.55
sd	0.66	1.76	1.12	3.42	1.36	0.43	0.89	2.04
SPLEEN								
N	5	5	5	5	5	5	5	5
MEAN	0.698	0.786	0.741	0.668	0.481	0.451	0.529	0.624 b
sd	0.056	0.085	0.085	0.144	0.068	0.066	0.056	0.043
TESTES								
N	5	5	5	5	5	5	5	5
MEAN	3.21	3.45	3.38	2.94	0	0	0	0
sd	0.26	0.17	0.17	0.29				
THYMOS								
N	5	5	5	5	5	5	5	5
MEAN	0.454	0.563	0.479	0.415	0.365	0.441	0.459	0.439
sd	0.078	0.131	0.074	0.276	0.066	0.057	0.074	0.097

Significant when compared with Group 1: a - p<0.05; b - p<0.01

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TABLE 7B

Organ weights relative to bodyweight - group mean values (%) for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

SEX:	---MALE---					---FEMALE---				
	1	2	3	4	5	1	2	3	4	5
GROUP:	5	5	5	5	5	5	5	5	5	5
NUMBER:	5	5	5	5	5	5	5	5	5	5
TERMINAL BODY WEIGHT (g)										
-----										
	BEHREN'S - FISHER'S TEST					DUNNETT'S TEST				
N :	5	5	5	5	5	5	5	5	5	5
MEAN :	362.1	390.8	375.3	239.6	240.2	220.1	238.8	207.3		
sd :	33.6	18.1	10.0	109.9	19.8	13.2	15.5	40.5		
-----										
BRAIN										
-----										
	BEHREN'S - FISHER'S TEST					DUNNETT'S TEST				
N :	5	5	5	5	5	5	5	5	5	5
MEAN :	0.562	0.506	0.533	0.711	0.794	0.829	0.759	0.829		
sd :	0.045	0.035	0.010	0.226	0.059	0.054	0.061	0.107		
-----										
ADRENALS										
-----										
	BEHREN'S - FISHER'S TEST					DUNNETT'S TEST				
N :	5	5	5	5	5	5	5	5	5	5
MEAN :	0.0142	0.0156	0.0174	0.0300	0.0266	0.0301	0.0326	0.0310		
sd :	0.0020	0.0008	0.0025	0.0141	0.0048	0.0036	0.0036	0.0088		
-----										
EPIDIDYMIDES										
-----										
	BEHREN'S - FISHER'S TEST					DUNNETT'S TEST				
N :	5	5	5	5	5	5	5	5	5	5
MEAN :	0.2319	0.2188	0.2341	0.2612	0	0	0	0		
sd :	0.0312	0.0144	0.0124	0.0565						
-----										
HEART										
-----										
	BEHREN'S - FISHER'S TEST					DUNNETT'S TEST				
N :	5	5	5	5	5	5	5	5	5	5
MEAN :	0.3646	0.3746	0.3402	0.3826	0.3937	0.3997	0.3969	0.3818		
sd :	0.0268	0.0164	0.0128	0.0495	0.0307	0.0349	0.0220	0.0336		

Significant when compared with Group 1: a - p<0.05; b - p<0.01

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TABLE 7B - continued

Organ weights relative to bodyweight - group mean values (%) for all animals

Group Compound Dosage (mg/kg/day)	SEX:			
	1	2	3	4
Control	0	100	300	1000
Material 02675234 -				

SEX:	MALE			FEMALE		
	1	2	3	1	2	3
GROUP NUMBER:	5	5	5	5	5	5

N	BEHREN'S - FISHER'S TEST			BEHREN'S - FISHER'S TEST		
	5	5	5	5	5	5
MEAN	0.837	0.775	0.864	1.745	0.787	0.840
sd	0.043	0.068	0.147	0.590	0.049	0.036

N	DUNNETT'S TEST			DUNNETT'S TEST		
	5	5	5	5	5	5
MEAN	4.150	4.384	4.497	4.311	4.200	4.196
sd	0.395	0.376	0.342	0.670	0.258	0.213

N	DUNNETT'S TEST			DUNNETT'S TEST		
	5	5	5	5	5	5
MEAN	0.1946	0.2011	0.1973	0.2391	0.2020	0.2051
sd	0.0296	0.0185	0.0210	0.0395	0.0372	0.0292

N	BEHREN'S - FISHER'S TEST			BEHREN'S - FISHER'S TEST		
	5	5	5	0	0	0
MEAN	0.895	0.885	0.900	1.094		
sd	0.137	0.046	0.036	0.340		

N	DUNNETT'S TEST			DUNNETT'S TEST		
	5	5	5	5	5	5
MEAN	0.1261	0.1445	0.1280	0.1338	0.1519	0.2001b
sd	0.0233	0.0346	0.0223	0.0364	0.0250	0.0175

Significant when compared with Group 1: a - p<0.05; b - p<0.01

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 8  
 Macropathology - group distribution of findings for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

ORGAN AND KEYWORD (S) OR PHRASE	NUMBER OF ANIMALS AFFECTED			
	1	2	3	4
** TOP OF LIST **	5	5	5	5
HEART	0	0	0	0
PALE AREA(S)	5	5	5	5
ILEUM/PEYERS	0	0	0	0
DARK	5	5	5	5
KIDNEYS	0	0	0	0
PALE AREA(S)	5	5	5	5
ENLARGED	0	0	0	0
PALE	0	0	0	0
PELVIC DILATION	0	0	0	0
GRANULAR	0	0	0	0
CYST(S)	0	0	0	0
CONTAINS CALCULUS (I)	0	0	0	0
UNILATERALLY ENLARGED	0	0	0	0
LIVER	5	5	5	5
DARK	0	0	0	0
PALE AREA(S)	0	0	0	0
LN MANDIBULAR	5	5	5	5
ENLARGED	0	0	0	0
CONGESTED	0	0	0	0
LUNGS & BRONCHI	5	5	5	5
DARK AREA(S)	1	0	0	0
SPLEEN	5	5	5	5
MISSHAPE	0	0	0	0

Significant when compared with Group 1: a - p<0.05

Material 02675234  
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TABLE 8 - continued  
 Macropathology - group distribution of findings for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

ORGAN AND KEYWORD (S) OR PHRASE	NUMBER OF ANIMALS - AFFECTED											
	MALE				FEMALE							
	1	2	3	4	1	2	3	4	1	2	3	4
STOMACH	5	5	5	5	5	5	5	5	5	5	5	5
DISTENDED	0	0	0	0	0	0	0	0	0	0	0	0
DARK AREA(S)	0	0	0	0	1	0	0	0	0	0	0	0
THYMUS	5	5	5	5	5	5	5	5	5	5	5	5
DARK AREA(S)	1	0	0	0	2	1	1	0	0	0	0	0
URINARY BLADDER	5	5	5	5	5	5	5	5	5	5	5	5
DISTENDED	0	0	0	0	1	0	0	0	0	0	0	0
UTERUS	0	0	0	0	0	0	0	0	5	5	5	5
FLUID DISTENTION	0	0	0	0	1	2	0	0	0	0	0	0
MISSHAPEN	0	0	0	0	0	0	0	0	0	0	0	1
AORTA	5	5	5	5	5	5	5	5	5	5	5	5
HARD	0	0	0	0	1	0	0	0	0	0	0	0
BONE MARROW	5	5	5	5	5	5	5	5	5	5	5	5
GRANULAR	0	0	0	0	1	0	0	0	0	0	0	0
LN RENAL	5	5	5	5	5	5	5	5	5	5	5	5
ENLARGED	0	0	0	0	2	0	0	0	0	0	0	1
MISCELLANEOUS	5	5	5	5	5	5	5	5	5	5	5	5
ANIMAL THIN	0	0	0	0	3	0	0	0	0	0	0	3
OPTIC NERVES	5	5	5	5	5	5	5	5	5	5	5	5
DARK AREA(S)	0	1	0	0	0	0	0	0	0	0	0	0
PITUITARY	5	5	5	5	5	5	5	5	5	5	5	5
CYST(S)	0	0	1	0	0	0	0	0	0	0	0	0

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TABLE 8 - continued  
 Macropathology - group distribution of findings for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

ORGAN AND KEYWORD(S) OR PHRASE	NUMBER OF ANIMALS AFFECTED							
	MALE				FEMALE			
	1	2	3	4	1	2	3	4
URETERS	5	5	5	5	5	5	5	5
DISTENDED	0	0	1	0	0	0	0	0
CONTAINS CALCULUS (I)	0	0	0	1	0	0	0	0
** END OF LIST **								

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 9  
 Histopathology - group distribution of findings for all animals

Group Compound Dosage (mg/kg/day)	1 Control	2 Material 02675234 - 100	3 300	4 1000	Schedule number: DCN 302								
					--- NUMBER OF ANIMALS AFFECTED ---				SEX: --- MALE --- FEMALE ---				
	5	5	5	5	5	5	5	5	5	5	5	5	5
ORGAN AND FINDING DESCRIPTION	1- -1-	2- -2-	3- -3-	4- -4-	5- -5-	5- -5-	5- -5-	5- -5-	5- -5-	5- -5-	5- -5-	5- -5-	5- -5-
** TOP OF LIST **	5	5	5	5	5	5	5	5	5	5	5	5	5
LUNGS & BRONCHI	5	0	0	5	5	0	0	0	0	0	0	0	5
--ALVEOLAR OSSEOUS METAPLASIA	0	0	0	1	1	0	0	0	0	0	0	0	0
--ALVEOLAR MACROPHAGES	0	0	0	1	1	0	0	0	0	0	0	0	0
--ALVEOLAR EPITHELIAL HYPERPLASIA	0	0	0	1	1	0	0	0	0	0	0	0	0
--ALVEOLAR HAEMORRHAGE	0	0	0	1	1	0	0	0	0	0	0	0	0
LIVER	5	0	0	5	5	0	0	1	5	0	0	0	0
--VASCULAR MINERALISATION	0	0	0	1	1	0	0	0	0	0	0	0	0
--FOCAL SINUSOIDAL LEUCOCYTES	0	0	0	0	0	0	0	0	0	0	0	0	1
KIDNEYS	5	5	5	5	5	5	5	5	5	5	5	5	5
--CORTICAL TUBULAR BASOPHILIA	1	2	5a	3	0	1	3	5b	0	0	0	0	0
--ACUTE PYELONEPHRITIS	0	0	2	5b	0	0	0	0	0	0	0	0	0
--TUBULAR DILATATION	0	0	3	4a	0	0	0	0	0	0	0	0	0
--CHRONIC INTERSTITIAL NEPHRITIS	0	0	1	4a	0	0	0	0	0	0	0	0	0
--CORTICAL TUBULAR HYPERPLASIA	0	0	0	4a	0	0	0	0	0	0	0	0	0
--COLLECTING DUCT EPITHELIAL HYPERPLASIA	0	0	0	4a	0	0	0	0	0	0	0	0	0
--HYPERPLASIA OF PAPILLARY EPITHELIUM	0	0	0	4a	0	0	0	0	0	0	0	0	0
--CORTICAL TUBULES WITH HYALINE DROPLETS	0	0	0	2	0	0	0	0	0	0	0	0	0
--HYDRONEPHROSIS	0	1	1	1	1	0	0	1	0	0	0	0	0
--CORTICAL MINERALISATION	0	0	0	2	0	0	0	0	0	0	0	0	0
--FOCAL NECROSIS	0	0	0	1	0	0	0	0	0	0	0	0	0
--VASCULAR MINERALISATION	0	0	0	1	0	0	0	0	0	0	0	0	0
--CORTICO-MEDULLARY MINERALISATION	0	0	0	0	0	0	0	0	0	0	0	0	0
--REFRACTILE CRYSTALS IN TUBULAR LUMINA	0	0	0	0	4	1	2	1	2	1	2	1	0
URINARY BLADDER	5	0	0	5	5	0	0	0	0	0	0	0	0
--REFUSED SEMINAL COLLOID PLUG	1	0	0	1	5	0	0	0	0	0	0	0	5
--TRANSITIONAL CELL HYPERPLASIA	0	0	0	1	0	0	0	0	0	0	0	0	0
HEART	5	0	0	5	5	0	0	0	0	0	0	0	0
--MYOCARDITIS	2	0	0	2	0	0	0	0	0	0	0	0	0

Significant when compared with Group 1: a - p<0.05; b - p<0.01

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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TABLE 9 - continued.  
 Histopathology - group distribution of findings for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

ORGAN AND FINDING DESCRIPTION	NUMBER OF ANIMALS - AFFECTED			
	MALE	MALE	FEMALE	FEMALE
GROUP: -1- -2- -3- -4- -5	-1- -2- -3- -4- -5	-1- -2- -3- -4- -5	-1- -2- -3- -4- -5	-1- -2- -3- -4- -5
** FROM PREVIOUS PAGE **	5	5	5	5
HEART	5	0	0	0
--MYOCARDIAL MINERALISATION	0	0	0	0
--VASCULAR MINERALISATION	0	0	0	0
THYMUS	5	0	0	0
--HAEMORRHAGE	1	0	0	0
--INVOLUTION/ATROPHY	0	0	0	0
--FOCAL MINERALISATION	0	0	0	0
LN MANDIBULAR	5	2	0	0
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS	1	0	0	0
--PLASMACYTOSIS	0	1	0	0
STOMACH	5	0	0	0
--MINERALISATION OF MUSCULARIS	0	0	0	0
--MUCOSAL MINERALISATION - GLANDULAR REGION	0	0	0	0
--SUBMUCOSAL MINERALISATION - NON-GLANDULAR REGION	0	0	0	0
--VASCULAR MINERALISATION	0	0	0	0
--DILATED GLANDS - GLANDULAR REGION	0	0	0	0
UTERUS	0	0	0	0
--LUMINAL DILATATION	0	0	0	0
--ATROPHY	0	0	0	0
AORTA	0	0	0	0
--MEDIAL MINERALISATION	0	0	0	0
PITUITARY	0	0	0	0
--DEVELOPMENTAL CYST(S)	0	0	0	0
OPTIC NERVES	0	1	0	0
--INFLAMMATION	0	1	0	0

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TABLE 9 - continued.  
 Histopathology - group distribution of findings for all animals

Group	1	2	3	4	Schedule number: DCN 302							
					--- NUMBER OF ANIMALS ---				AFFECTED ---			
Compound	Control	Material 02675234 -			MALE		FEMALE					
Dosage (mg/kg/day)	0	100	300	1000	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	5	5	5	5	5	5	5	5	5	5	5	5
ORGAN AND FINDING DESCRIPTION												
** FROM PREVIOUS PAGE **												
OPTIC NERVES	0	1	0	0	0	0	0	0	0	0	0	0
--HAEMORRHAGE	0	1	0	0	0	0	0	0	0	0	0	0
URETERS												
--TRANSITIONAL CELL HYPERPLASIA	0	0	1	1	0	0	0	0	0	0	0	0
--INFLAMMATION	0	0	0	1	0	0	0	0	0	0	0	0
--AMORPHOUS MATERIAL IN LUMEN	0	0	1	1	0	0	0	0	0	0	0	0
LN RENAL												
--SINUS HISTIOCYTOSIS	0	0	0	2	0	0	0	0	0	0	0	1
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS	0	0	0	2	0	0	0	0	0	0	0	0
** END OF LIST **	0	0	0	0	0	0	0	0	0	0	0	1

Material 02675234  
Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1

Signs - individual observations

Group : 1 2 3 4  
Compound : Control - Material 02675234 -  
Dosage (mg/kg/day) : 0 100 300 1000  
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ANIMAL DEATH WK OF NUMBER CODE DEATH	CATEGORY	GROUP: IM	DAYS 1-30
13 7 5	STAINING BROWN MUZZLE DORSAL BODY SURFACE		16, 23 2, 9

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1 - continued.

Signs - individual observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

CATEGORY GROUP: 2M

DAYS 1-30

ANIMAL DEATH WK OF KEYWORD  
 NUMBER CODE DEATH QUALIFIER

1	7	5	SKIN ABRASION DRY HEAD	16
			COAT HAIRLOSS HEAD	16
2	7	5	STAINING BROWN DORSAL BODY SURFACE	2
3	7	5	SKIN ABRASION DRY DORSAL BODY SURFACE COAT HAIRLOSS DORSAL BODY SURFACE SKIN ENCrustATION(S) UPPER DORSAL THORAX	16 16 23
4	7	5	STAINING BROWN HEAD	9, 16

Material 02675234  
Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1 - continued.

Signs - individual observations

Group : 1 2 3 4  
Compound : Control - Material 02675234 -  
Dosage (mg/kg/day) : 0 100 300 1000

-----  
CATEGORY GROUP: 5M DAYS 1-30  
ANIMAL DEATH WK OF KEYWORD  
NUMBER CODE DEATH QUALIFIER

19 7 5 COAT  
HAIRLOSS  
RIGHT FORELIMB 9

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1 - continued.  
 Signs - individual observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

GROUP: 4M

DAYS 1-30

CATEGORY  
 ANIMAL DEATH WK OF KEYWORD  
 NUMBER CODE DEATH QUALIFIER

6	7	5	BUILD (CONFORMATION) THIN BODY TEMPERATURE REDUCED COAT PILORECTION POSTURE HUNCHED STAINING BROWN SCROTUM HEAD MUZZLE	10-23, 30 10-12 10-23, 30 10-15 30 23 9-13
7	7	5	BUILD (DEFORMITY) SWOLLEN AREA VENTRAL ABDOMEN	8-10, 16
9	K	1	BUILD (CONFORMATION) THIN COAT PILORECTION EYES DARK BOTH POSTURE HUNCHED RESPIRATION FAST STAINING FACES PERIANAL BROWN MUZZLE	5-6 5-6 6 6 5-6 5-6 5-6 5-6 5

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APPENDIX 1 - continued.  
 Signs - individual observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

GROUP: 4M

DAYS 1-30

CATEGORY  
 ANIMAL DEATH WK OF KEYWORD  
 NUMBER CODE DEATH QUALIFIER

10	7	5	BUILD (CONFORMATION) THIN	10-30
			BEHAVIOUR	25-30
			UNDERACTIVE	10
			BODY TEMPERATURE	10-30
			REDUCED	24-30
			COAT	10-30
			PILOREACTION	10-30
			MUSCLE REACTION	10-30
			REDUCED BODY TONE	10-30
			WHOLE BODY	9-12
			POSTURE	
			HUNCHED	
			STAINING	
			BROWN	
			HEAD	

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1 - continued.

Signs - individual observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

CATEGORY GROUP: 1F

DAYS 1-30

ANIMAL DEATH WK OF KEYWORD  
 NUMBER CODE DEATH QUALIFIER

21	7	5	STAINING BROWN	DORSAL BODY SURFACE	9
22	7	5	STAINING BROWN	NOSE	30
25	7	5	COAT HAIRLOSS	DORSAL BODY SURFACE	16, 23, 30

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Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1 - continued.

Signs - individual observations

Group : 1 2 3 4  
Compound : Control - Material 02675234 -  
Dosage (mg/kg/day) : 0 100 300 1000

-----  
CATEGORY GROUP: 2F DAYS 1-30  
ANIMAL DEATH WK OF KEYWORD  
NUMBER CODE DEATH QUALIFIER

27 7 5 STAINING  
BROWN  
RIGHT FORELIMB 9  
HEAD 16  
MUZZLE 9, 16

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1 - continued.

Signs - individual observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/dsy) : 0 100 300 1000

GROUP: 3F

DAYS 1-30

CATEGORY  
 ANIMAL DEATH WK OF KEYWORD  
 NUMBER CODE DEATH QUALIFIER

36	7	5	BEHAVIOUR VOCALIZATION	9, 16, 23, 30
37	7	5	STAINING BROWN HEAD	23
40	7	5	STAINING BROWN HEAD MUZZLE	16, 23 16

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APPENDIX 1 - continued.

Signs - individual observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day): 0 100 300 1000

GROUP: 4F

DAYS 1-30

CATEGORY  
 ANIMAL DEATH WK OF KEYWORD  
 NUMBER CODE DEATH QUALIFIER

31	7	5	BUILD (CONFORMATION)	10-30
			THIN	
			BODY TEMPERATURE	
			REDUCED	10-12
			COAT	
			PILORECTION	10-30
			POSTURE	
			HUNCHED	10-15
32	7	5	STAINING	
			BROWN	
			RIGHT ORBIT	30
			FINNA	9, 16
			HEAD	23, 30
			TAIL	16, 23
33	K	3	BUILD (CONFORMATION)	
			THIN	16
			BODY TEMPERATURE	
			REDUCED	16
			COAT	
			PILORECTION	16
			POSTURE	
			HUNCHED	16
34	7	5	COAT	
			PILORECTION	10-13
			POSTURE	
			HUNCHED	10-13
			STAINING	
			BROWN	
			HEAD	2, 9-16, 23
			DORSAL BODY SURFACE	9-16

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 1 - continued.

Signs - individual observations

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

GROUP: 4F

DAYS 1-30

-----  
 CATEGORY KEYWORD DAYS 1-30  
 ANIMAL DEATH WK OF KEYWORD  
 NUMBER CODE DEATH QUALIFIER

35 7 5 BUILD (CONFORMATION)  
 THIN 10-30  
 BODY TEMPERATURE  
 REDUCED 10  
 COAT 10-15, 23-30  
 Piloerection  
 POSTURE  
 HUNCHED 10-15

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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Schedule number: DCN 302

APPENDIX 2A

Bodyweights - individual values (g)

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

GROUP	ANIMAL	WEEK				
		0	1	2	3	4
1M	11	175	215	255	291	332
	12	217	275	330	370	409
	13	202	257	308	356	382
	14	201	254	306	345	383
	15	191	252	314	360	398
2M	1	191	237	295	348	391
	2	203	267	332	374	415
	3	201	263	324	378	427
	4	202	265	325	372	412
	5	174	224	280	331	372
3M	16	209	274	328	376	409
	17	194	250	312	329	377
	18	187	244	304	359	390
	19	189	247	298	346	378
	20	184	232	293	343	388
4M	6	192	190	208	243	257
	7	210	279	350	413	448
	8	190				
	9	200				
	10	183	207	220	206	212

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 2A - continued.

Bodyweights - individual values (g)

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

GROUP	ANIMAL	WEEK 0	WEEK 1	WEEK 2	WEEK 3	WEEK 4
1F	21	169	202	232	258	279
	22	158	174	203	227	244
	23	146	170	192	212	220
	24	172	189	214	237	249
	25	155	179	204	229	246
2F	26	155	178	195	211	230
	27	163	188	216	231	246
	28	161	178	192	209	210
	29	165	185	209	226	235
	30	134	155	177	199	211
3F	36	165	189	222	242	263
	37	159	184	207	228	250
	38	165	181	200	217	223
	39	173	202	231	242	265
	40	150	175	199	225	236
4F	31	158	149	163	177	191
	32	166	195	224	248	263
	33	170	189	186	186	186
	34	172	203	229	252	260
	35	166	172	184	194	201

Material 02675234

Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 2B

Bodyweights - unscheduled individual values (g) for animals displaying ill-health

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

Group/ sex	Animal number	Day of study															
		0	7	8	9	10	11	12	13	14	15	16	17				
4M	6	192	190	-	183	201	203	209	202	208	220	221	229				
	7	210	279	292	306	-	-	-	-	350	-	-	-				
	10	183	207	-	212	218	221	225	223	220	212	211	211				
4F	31	158	149	-	144	151	155	158	158	163	169	168	173				
	34	172	203	-	207	213	216	222	223	229	-	-	-				
	35	166	172	-	162	174	176	180	172	184	174	181	183				

Group/ sex	Animal number	Day of study															
		18	19	20	21	22	23	24	25	26	27	28					
4M	6	238	240	239	243	251	-	-	-	-	-	-	257				
	7	-	-	-	413	-	-	-	-	-	-	-	448				
	10	203	206	205	206	206	204	204	209	209	209	209	212				
4F	31	171	178	183	177	185	184	178	186	189	191	191	191				
	34	-	-	-	252	-	-	-	-	-	-	-	260				
	35	183	189	191	194	195	200	202	195	190	204	204	201				

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 3

Food consumption - individual values (g/animal)

Group Compound : 1 Control : 2 100 : 3 300 : 4 1000  
 Dosage (mg/kg/day) : 0 : Material 02675234 -

GROUP	CAGE	WEEK			
		1	2	3	4
1M	11	149	162	174	176
	12	212	219	211	211
	13	205	193	207	186
	14	205	199	197	198
	15	211	212	217	215
2M	1	187	196	213	218
	2	229	238	237	229
	3	212	213	224	235
	4	204	212	221	207
	5	178	179	197	203
3M	16	231	221	221	220
	17	195	205	186	232
	18	201	201	218	205
	19	183	192	208	209
	20	190	213	234	237
4M	6	113	87	137	121
	7	234	243	248	227
	10	128	114	51	77

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 3 - continued.

Food consumption - individual values (g/animal)

GROUP	CASE	WEEK			
		1	2	3	4
1F	21	156	153	162	169
	22	130	132	139	147
	23	123	125	132	141
	24	151	150	151	137
	25	121	137	142	152
2F	26	142	132	147	144
	27	136	140	137	139
	28	124	120	135	136
	29	126	123	141	136
	30	116	110	128	118
	36	146	149	157	171
3F	37	123	136	156	171
	38	125	120	120	117
	39	149	137	149	162
	40	130	126	148	135
	67	66	66	91	92
4F	31	146	153	154	162
	32	129	95	158	134
	33	154	149	158	94
	34	120	61	95	
	35				

Material 02675234

Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4A

Haematology - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	Group Animal	Hct L/L	Hb g/dL	RBC x10 <sup>12</sup> /L	- Material 02675234 -				MCV fL	WBC x10 <sup>9</sup> /L	Neutr ophil x10 <sup>9</sup> /L	Lymph ocyte x10 <sup>9</sup> /L
					1 Control	2 100	3 300	4 1000				
1M	11	0.468	16.1	8.23	19.6	34.4	56.9	18.38	1.64	15.72		
	12	0.468	16.0	8.15	19.6	34.2	57.4	12.58	1.54	10.03		
	13	0.473	16.0	8.23	19.5	33.8	57.5	13.56	1.96	10.96		
	14	0.476	16.5	8.33	19.8	34.7	57.1	17.45	1.33	15.19		
	15	0.469	15.9	8.32	19.1	33.8	56.4	14.07	2.61	10.73		
2M	1	0.455	15.6	7.96	19.6	34.3	57.2	15.13	1.44	13.01		
	2	0.466	15.9	8.13	19.6	34.1	57.3	12.40	1.12	10.47		
	3	0.466	15.8	7.46	21.2	33.9	62.4	21.83	6.42	14.38		
	4	0.453	15.4	7.73	19.9	33.9	58.6	15.17	1.11	12.97		
	5	0.438	15.4	7.52	20.5	35.2	58.2	17.71	2.81	14.07		
3M	16	0.438	15.1	7.80	19.3	34.5	56.1	12.34	1.77	9.64		
	17	0.451	15.4	7.86	19.5	34.0	57.4	17.63	3.48	13.09		
	18	0.491	16.8	8.52	19.8	34.3	57.6	15.49	2.95	11.12		
	19	0.478	16.5	8.25	20.0	34.6	57.9	9.47	0.86	8.03		
	20	0.453	15.8	7.73	20.4	34.8	58.6	16.93	2.96	13.00		
4M	6	0.409	14.2	7.19	19.8	34.8	56.9	25.89	7.68	16.27		
	7	0.436	15.0	7.40	20.3	34.4	59.0	29.08	7.59	18.27		
	10	0.425	14.8	7.74	19.2	34.9	54.9	19.57	7.03	11.46		

Material 02675234

Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4A - continued

Haematology - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	Animal	1		2		3		4	
		Control	0	100	300	1000			
		Eosinophil x10 <sup>9</sup> /L	Basophil x10 <sup>9</sup> /L	Mono cyte x10 <sup>9</sup> /L	LUC x10 <sup>9</sup> /L	Plt x10 <sup>9</sup> /L	PT sec	APTT sec	
1M	11	0.07	0.03	0.55	0.37	1241	12.1	18.4	
	12	0.11	0.01	0.52	0.35	1224	13.5	20.9	
	13	0.07	0.02	0.30	0.24	803	14.1	21.3	
	14	0.10	0.05	0.43	0.35	744	13.7	21.9	
	15	0.17	0.02	0.30	0.24	1187	12.3	18.1	
2M	1	0.06	0.03	0.33	0.26	1516	11.8	20.9	
	2	0.09	0.01	0.41	0.29	1087	13.0	18.7	
	3	0.23	0.06	0.36	0.38	1063	13.5	20.1	
	4	0.08	0.03	0.61	0.37	1180	13.7	19.1	
	5	0.10	0.04	0.33	0.36	1243	13.4	19.8	
3M	16	0.08	0.02	0.43	0.39	1287	12.4	20.1	
	17	0.19	0.05	0.45	0.38	1053	13.7	20.4	
	18	0.24	0.04	0.72	0.41	1187	13.1	20.0	
	19	0.07	0.01	0.29	0.21	1216	13.0	20.4	
	20	0.16	0.04	0.38	0.39	1241	13.4	20.3	
4M	6	0.86	0.06	0.59	0.43	1515	14.4	15.3	
	7	1.38	0.08	0.94	0.83	1400	14.1	18.4	
	10	0.48	0.03	0.36	0.22	1674	14.1	15.3	

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4A – continued

Haematology - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control 0	2 100	3 - Material 02675234 - 300	4 1000	
Group Animal	Aniso cyto	Micro cyto	Macro cyto	Hypo chrom	Hyper chrom
1M	11	-	-	-	-
	12	-	-	-	-
	13	-	-	-	-
	14	-	-	-	-
	15	-	-	-	-
2M	1	-	-	-	-
	2	-	-	-	-
	3	-	-	-	-
	4	-	-	-	-
	5	-	-	-	-
3M	16	-	-	-	-
	17	-	-	-	-
	18	-	-	-	-
	19	-	-	-	-
	20	-	-	-	-
4M	6*	-	-	-	-
	7*	-	-	-	-
	10*	-	-	-	-

\* A few hypersegmented neutrophils present

Material 02675234

Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4A – continued

Haematology - individual values on Day 30 of the study

Group	Animal	Hct	Hb	RBC	MCH	MCHC	MCV	WBC	Neutr ophil x10 <sup>9</sup> /L	Lymph ocyte x10 <sup>9</sup> /L	- Material 02675234 -			
											1	2	3	4
Compound	Dosage (mg/kg/day)		Control	100	300	1000								
1F	21	0.452	16.0	7.57	21.1	35.4	59.7	14.23	0.94	12.50	1F	21	0.452	16.0
	22	0.467	16.5	7.67	21.5	35.4	60.8	13.69	0.94	11.95				
	23	0.459	15.9	7.72	20.6	34.7	59.5	9.11	0.70	7.94				
	24	0.462	16.3	7.64	21.3	35.2	60.5	10.34	0.66	9.12				
	25	0.451	15.9	7.87	20.2	35.3	57.3	17.79	1.32	15.58				
2F	26	0.449	15.7	7.98	19.7	35.1	56.3	15.90	0.75	14.50	2F	26	0.449	15.7
	27	0.446	15.6	7.80	20.0	34.9	57.2	16.20	2.55	12.48				
	28	0.427	14.8	7.55	19.6	34.7	56.6	13.04	0.79	11.60				
	29	0.439	15.6	7.84	19.9	35.5	56.0	14.56	1.60	12.15				
	30	0.418	14.8	7.66	19.2	35.3	54.6	10.14	1.13	8.42				
3F	36	0.423	15.1	7.36	20.5	35.7	57.4	12.39	3.69	7.99	3F	36	0.423	15.1
	37	0.436	15.2	7.40	20.5	34.9	58.9	14.76	2.43	11.32				
	38	0.410	14.4	7.20	20.0	35.2	56.9	10.32	1.02	8.78				
	39	0.429	15.1	7.67	19.7	35.2	56.0	10.31	1.52	8.41				
	40	0.407	14.4	7.20	20.0	35.4	56.6	11.73	0.91	10.25				
4F	31	0.352	12.3	6.32	19.5	35.0	55.6	25.92	5.33	18.41	4F	31	0.352	12.3
	32	0.445	15.5	7.59	20.5	34.9	58.6	13.61	1.09	11.67				
	34	0.460	15.9	7.85	20.3	34.6	58.5	16.20	3.43	11.65				
	35	0.404	14.0	7.36	19.0	34.6	55.0	22.27	7.31	13.52				

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4A – continued

Haematology - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control	2 100	3 - Material 02675234 - 300	4 1000			
Group Animal	Eosinophil x10 <sup>-9</sup> /L	Basophil x10 <sup>-9</sup> /L	Mono cyte x10 <sup>-9</sup> /L	LUC x10 <sup>-9</sup> /L	Plt x10 <sup>9</sup> /L	PT sec	APTT sec
1F	21	0.16	0.02	0.35	0.26	1280	17.4
	22	0.24	0.03	0.25	0.27	1228	18.3
	23	0.12	0.02	0.18	0.15	1168	17.3
	24	0.16	0.02	0.17	0.21	1054	17.5
	25	0.22	0.04	0.29	0.34	1344	18.2
2F	26	0.13	0.02	0.18	0.31	738	17.2
	27	0.16	0.04	0.57	0.40	1149	20.3
	28	0.15	0.02	0.23	0.25	1134	15.3
	29	0.12	0.03	0.31	0.34	1173	17.7
	30	0.17	0.01	0.28	0.14	1414	17.1
3F	36	0.10	0.02	0.33	0.27	1188	17.3
	37	0.35	0.03	0.31	0.32	1019	18.7
	38	0.21	0.02	0.14	0.16	1171	17.6
	39	0.08	0.01	0.13	0.16	1319	17.2
	40	0.16	0.03	0.20	0.18	1230	CTD
4F	31	0.85	0.06	0.65	0.62	1379	12.0
	32	0.24	0.03	0.33	0.27	1168	16.9
	34	0.43	0.03	0.35	0.32	759	CTD
	35	0.57	0.04	0.51	0.32	1474	13.1

CTD Clotted sample

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4A – continued

Haematology - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control 0	2 100	3 300	4 1000	
Group Animal	Aniso cyto	Micro cyto	Macro cyto	Hypo chrom	Hyper chrom
1F	21	-	-	-	-
	22	-	-	-	-
	23	-	-	-	-
	24	-	-	-	-
	25	-	-	-	-
2F	26	-	-	-	-
	27	-	-	-	-
	28	-	-	-	-
	29	-	-	-	-
	30	-	-	-	-
3F	36	-	-	-	-
	37	-	-	-	-
	38	-	-	-	-
	39	-	-	-	-
	40	-	-	-	-
4F	31*†	-	-	-	-
	32	-	-	-	-
	34	-	-	-	-
	35	-	-	-	-
		-	-	-	-

\* A few hypersegmented neutrophils present  
 † Slight hypochromasia

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4B

Haematology - individual and group mean bone marrow smear values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control	2 100	3 300	4 1000			
Group /sex	Animal	M:E Ratio	Total myeloid %	Total erythroid %	Other %	Incr. Myel	Decr. Eryth
1M	11	2.05	52.5	25.5	22.0		
	12	1.82	51.0	28.0	21.0		
	13	2.16	54.0	25.0	21.0		
	14	2.71	61.0	22.5	16.5		
	15	2.23	62.5	28.0	9.5		
Mean		2.19	56.2	25.8	18.0		
S.D.		0.328	5.20	2.31	5.21		
n		5	5	5	5		
2M	1	2.18	60.0	27.5	12.5		
	2	1.83	54.0	29.5	16.5		
	3	2.63	60.5	23.0	16.5		
	4	2.46	58.0	23.5	18.5		
	5	1.90	58.0	30.5	11.5		
Mean		2.20	58.1	26.8	15.1		
S.D.		0.346	2.56	3.42	2.97		
n		5	5	5	5		

Significant when compared with Group 1: a - p<0.05  
 S.D. Standard Deviation

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4B - continued

Haematology - individual and group mean bone marrow smear values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control 0	2 100	3 300	4 1000			
Group /sex	Animal	M:E Ratio	Total myeloid %	Total erythroid %	Other %	Incr. Myel	Decr. Eryth
3M	16	1.56	51.0	32.5	16.5		
	17	2.76	65.0	23.5	11.5		
	18	2.45	65.0	26.5	8.5		
	19	2.19	57.0	26.0	17.0		
	20	2.45	56.5	23.0	20.5		
Mean		2.28	58.9	26.3	14.8		
S.D.		0.451	6.05	3.78	4.76		
n		5	5	5	5		
4M	6	2.88	62.0	21.5	16.5		
	7	3.14	64.5	20.5	15.0		
	10	5.75	69.0	12.0	19.0	IMN	++
Mean		3.92 <sup>b</sup>	65.2 <sup>a</sup>	18.0 <sup>a</sup>	16.8		
S.D.		1.590	3.50	5.20	2.00		
n		3	3	3	3		

Significant when compared with Group 1: a – p<0.05; b – p<0.01

S.D. Standard Deviation

IMN Increase in mature neutrophils

++ Moderate decrease in erythroid series

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4B - continued

Haematology - individual and group mean bone marrow smear values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control	2 100	3 300	4 1000			
	- Material 02675234 -						
Group /sex	Animal	M:E Ratio	Total myeloid %	Total erythroid %	Other %	Incr. Myel	Decr. Eryth
1F	21	2.12	57.5	27.0	15.5		
	22	2.38	59.5	25.0	15.5		
	23	2.48	58.5	23.5	18.0		
	24	1.49	44.0	29.5	26.5		
	25	2.13	55.5	26.0	18.5		
Mean		2.12	55.0	26.2	18.8		
S.D.		0.385	6.32	2.25	4.52		
n		5	5	5	5		
2F	26	2.33	56.0	24.0	20.0		
	27	2.41	61.5	25.5	13.0		
	28	2.69	62.0	23.0	15.0		
	29	2.11	55.0	26.0	19.0		
	30	2.29	62.0	27.0	11.0		
Mean		2.37	59.3	25.1	15.6		
S.D.		0.212	3.49	1.60	3.85		
n		5	5	5	5		

Significant when compared with Group 1: a - p<0.05  
 S.D. Standard Deviation

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 4B - continued

Haematology - individual and group mean bone marrow smear values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	Material 02675234 -						
	1 Control	2 100	3 300	4 1000			
Group /sex	Animal	M:E Ratio	Total myeloid %	Total erythroid %	Other %	Incr. Myel	Decr. Eryth
3F	36	1.86	54.0	29.0	17.0		
	37	2.70	59.5	22.0	18.5		
	38	1.98	56.5	28.5	15.0		
	39	2.43	58.5	24.0	17.5		
	40	2.28	51.5	22.5	26.0		
Mean		2.25	56.0	25.2	18.8		
S.D.		0.339	3.28	3.33	4.22		
n		5	5	5	5		
4F	31	2.67	61.5	23.0	15.5		
	32	1.93	58.0	30.0	12.0		
	34	6.63	73.0	11.0	16.0	IMN	++
	35	6.95	80.0	11.5	8.5	IMN	++
	Mean		4.55 <sup>b</sup>	68.1 <sup>b</sup>	18.9 <sup>a</sup>	13.0	
S.D.		2.613	10.18	9.26	3.49		
n		4	4	4	4		

Significant when compared with Group 1: a - p<0.05; b - p<0.01

S.D. Standard Deviation

IMN Increase in mature neutrophils

++ Moderate decrease in erythroid series

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 5

Blood chemistry - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	- Material 02675234 -								
	1 Control	2 100	3 300	4 1000					
	Alk. Phos U/L	ALT U/L	AST U/L	gGT U/L	Bili. Total umol/L	Urea mmol/L	Creat umol/L	Gluc mmol/L	Chol Total mmol/L
1M	11 625	43	85	0	2	4.79	40	9.02	1.97
	12 503	36	60	0	1	5.50	42	6.17	1.74
	13 502	40	58	0	1	4.49	39	7.15	1.30
	14 570	40	73	0	1	3.41	41	8.70	1.54
	15 608	35	66	0	1	4.90	45	7.64	2.02
2M	1 635	49	64	0	2	5.96	39	8.29	2.49
	2 599	47	74	0	1	4.63	45	7.87	1.73
	3 551	65	73	0	1	4.76	40	8.11	1.92
	4 481	34	51	0	2	7.08	46	9.85	1.74
	5 608	33	55	0	2	4.77	44	8.00	2.08
3M	16 547	34	65	0	1	5.51	42	6.61	1.40
	17 621	43	63	0	2	7.93	48	8.53	2.09
	18 523	31	62	0	2	6.90	55	7.72	2.37
	19 827	52	57	0	2	6.73	45	8.35	2.15
	20 520	40	67	0	1	6.06	47	8.73	1.71
4M	6 632	41	68	1	4	25.68	138	6.52	2.86
	7 448	36	65	0	2	9.22	66	7.03	2.32
	10 611	38	58	1	5	35.07	173	7.89	3.51

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 5 – continued

Blood chemistry - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	1 Control 0	2 100	3 300	4 1000	Trig mmol/L	Na mmol/L	K mmol/L	Cl mmol/L	Ca Total mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
1M					0.83	141	4.4	99	2.91	2.49	65	36	1.24
					0.74	144	4.3	101	2.92	2.70	63	35	1.25
					0.64	143	4.0	100	2.86	2.66	64	35	1.21
					0.79	144	3.8	99	2.85	2.53	63	35	1.25
					0.97	145	4.1	100	2.92	2.45	65	36	1.24
2M					1.00	142	4.4	96	3.03	2.61	70	38	1.19
					0.67	143	4.0	99	2.84	2.39	62	35	1.30
					0.96	142	4.5	99	2.80	2.65	67	34	1.03
					1.07	142	4.2	97	2.61	2.62	64	35	1.21
					0.82	142	4.1	98	2.82	2.50	62	34	1.21
3M					0.57	143	4.1	100	2.72	2.71	65	36	1.24
					0.69	143	4.1	99	2.82	2.72	63	35	1.25
					1.37	142	3.8	97	2.85	2.42	66	34	1.06
					1.07	142	4.0	97	2.70	2.35	61	35	1.35
					0.80	139	4.3	97	2.74	2.59	62	34	1.21
4M					0.89	141	4.9	98	2.84	2.94	67	35	1.09
					1.50	143	3.8	99	2.83	2.29	63	33	1.10
					1.21	144	4.6	96	2.94	3.77	64	34	1.13

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 5 – continued

Blood chemistry - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	- Material 02675234 -								
	1 Control	2 100	3 300	4 1000					
Group Animal	Alk. Phos U/L	ALT U/L	AST U/L	gGT U/L	Bili. Total umol/L	Urea mmol/L	Creat umol/L	Gluc mmol/L	Chol Total mmol/L
1F	21	377	44	65	0	5.21	43	7.23	3.48
	22	334	42	74	0	5.88	44	6.02	2.68
	23	446	33	69	3	6.13	45	6.97	1.98
	24	334	41	62	0	6.66	47	6.85	2.18
	25	369	41	77	1	6.26	50	6.97	2.15
2F	26	347	45	67	1	5.18	42	8.72	2.64
	27	354	38	61	1	4.55	45	7.38	2.19
	28	347	25	66	0	4.06	39	6.04	1.48
	29	261	43	64	1	7.04	43	7.31	2.26
	30	401	37	60	2	5.01	40	7.60	2.03
3F	36	438	34	54	0	5.50	50	7.98	2.34
	37	465	29	62	0	5.47	47	9.77	2.56
	38	388	34	67	1	5.39	43	6.49	2.58
	39	356	28	56	1	6.15	48	7.62	2.47
	40	399	34	66	0	8.44	48	7.98	2.56
4F	31	592	34	66	1	24.10	96	8.12	4.17
	32	430	33	69	0	7.00	48	7.01	2.43
	34	421	64	134	0	10.37	55	7.05	1.88
	35	748	38	70	1	27.35	100	7.18	3.66

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 5 – continued

Blood chemistry - individual values on Day 30 of the study

Group Compound Dosage (mg/kg/day)	- Material 02675234 -								
	1 Control 0	2 100	3 300	4 1000					
Group Animal	Trig mmol/L	Na mmol/L	K mmol/L	Cl mmol/L	Ca Total mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
1F	21	0.78	142	4.1	100	2.85	70	38	1.19
	22	0.55	144	4.3	99	2.85	66	37	1.28
	23	0.40	143	4.3	101	2.85	66	36	1.20
	24	0.36	143	4.2	99	2.80	65	37	1.32
	25	0.63	142	3.9	100	2.85	66	36	1.20
2F	26	0.51	142	3.7	101	2.68	63	36	1.33
	27	0.68	144	3.7	100	2.75	65	37	1.32
	28	0.35	144	3.5	101	2.68	64	35	1.21
	29	0.79	142	3.8	98	2.84	67	38	1.31
	30	0.92	142	4.2	99	2.72	60	34	1.31
3F	36	0.53	141	3.8	99	2.79	65	35	1.17
	37	0.89	142	4.2	102	2.66	62	34	1.21
	38	0.46	143	3.8	100	2.63	64	34	1.13
	39	0.41	143	3.8	101	2.71	64	36	1.29
	40	0.28	142	3.9	98	2.78	63	36	1.33
4F	31	0.87	140	4.8	98	2.84	66	34	1.06
	32	0.55	142	4.4	101	2.74	65	37	1.32
	34	0.88	141	4.3	100	2.77	59	31	1.11
	35	0.89	143	5.0	100	2.83	69	37	1.16

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 6A  
 Absolute organ weights - individual values (g) for all animals

GROUP	ANIMAL	TERMINAL				BRAIN	ADRENALS	EPIDIDYMIUM	HEART	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
		1	2	3	4									
		Group	1	2	3									
		Compound	Control	- Material 02675234	-									
		Dosage (mg/kg/day)	0	100	300	1000								
			Schedule number: DCN 302											
IM	11	305.0	1.92	0.042	0.841	1.074	2.63	14.47	0.731	3.35	0.416			
	12	392.5	2.03	0.043	0.755	1.505	3.24	15.20	0.683	2.99	0.342			
	13	364.3	1.98	0.056	0.782	1.350	3.28	15.91	0.739	3.04	0.485			
	14	370.4	2.15	0.060	0.894	1.203	3.00	14.21	0.605	3.59	0.549			
	15	378.3	2.03	0.056	0.891	1.483	2.99	14.86	0.731	3.07	0.476			

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 6A - continued.  
 Absolute organ weights - individual values (g) for all animals

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Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

Schedule number: DCN 302

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	ADRENALS	EPIDIDYMIUM	HEART	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
2M	1	375.7	2.06	0.062	0.836	1.460	2.81	17.52	0.757	3.47	0.682
	2	398.2	1.89	0.058	0.891	1.564	3.00	15.09	0.710	3.41	0.376
	3	413.1	1.99	0.063	0.875	1.455	3.10	19.43	0.825	3.40	0.691
	4	398.2	1.94	0.065	0.791	1.476	3.56	17.95	0.915	3.72	0.504
	5	369.0	1.98	0.057	0.875	1.361	2.68	15.70	0.724	3.26	0.564

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APPENDIX 6A - continued.  
 Absolute organ weights - individual values (g) for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

Schedule number: DCN 302

GROUP	ANIMAL	TERMINAL	BODY WT (g)	BRAIN	ADRENALS	EPIDIDYMID	HEART	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
3M	16		386.0	2.04	0.076	0.900	1.346	3.14	15.75	0.843	3.39	0.370
	17		361.4	1.99	0.070	0.888	1.211	3.10	16.29	0.765	3.29	0.523
	18		383.9	2.03	0.065	0.941	1.268	4.27	17.15	0.775	3.60	0.450
	19		374.2	1.96	0.050	0.806	1.230	3.03	16.47	0.619	3.46*	0.489
	20		371.1	1.98	0.065	0.858	1.330	2.69	18.66	0.701	3.16	0.562

\* Organ weighed post-fixation.

Material 02675234  
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APPENDIX 6A - continued.

Absolute organ weights - individual values (g) for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

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Schedule number: DCN 302

GROUP	ANIMAL	TERMINAL	BODY WT (g)	BRAIN	ADRENALS	EPIDIDYMI	HEART	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
4M	6		247.4	1.80	0.102	0.750	0.956	4.39	10.06	0.614	3.21	0.248
	7		424.9	2.03	0.060	0.837	1.408	4.85	16.14	0.832	2.98	0.733
	8		170.4	NOT TAKEN								
	9		150.8	NOT TAKEN								
	10		204.6	1.90	0.071	0.580	0.880	4.74	10.37	0.559	2.63	0.263

Material 02675234  
 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 6A - continued  
 Absolute organ weights - individual values (g) for all animals

GROUP	ANIMAL	Group				BRAIN	ADRENALS	HEART	KIDNEYS	LIVER	SPLEEN	THYMUS
		1	2	3	4							
		: Control										
		- Material 02675234 -										
		Dosage (mg/kg/day)	0	100	300	1000						
Schedule number: DCN 302												
-----												
		TERMINAL										
		BODY WT (g)										
1F	21	268.8	1.96	0.060	0.985	1.90	11.82	0.426	0.388			
	22	236.2	1.89	0.051	0.887	1.91	9.26	0.472	0.310			
	23	216.7	1.91	0.064	0.961	1.78	8.58	0.447	0.281			
	24	249.1	1.87	0.066	1.001	1.94	11.21	0.462	0.414			
	25	230.2	1.86	0.076	0.878	1.89	9.72	0.598	0.433			
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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 6A - continued.  
 Absolute organ weights - individual values (g) for all animals

Group	Compound	Dosage (mg/kg/day)	Schedule number: DCN 302				TERMINAL								
			1	2	3	4	ANIMAL	BODY WT (g)	BRAIN	ADRENALS	HEART	KIDNEYS	LIVER	SPLEEN	TRIMUS
	Control	0													
	- Material 02675234 -														
			100	300	1000										
2F	26	218.6	1.85	0.060	0.968	1.80	8.84	0.396	0.391						
	27	238.3	1.81	0.078	0.836	1.89	9.70	0.482	0.488						
	28	213.2	1.81	0.070	0.867	1.80	9.50	0.544	0.424						
	29	226.8	1.79	0.073	0.943	1.92	9.55	0.451	0.513						
	30	203.5	1.83	0.051	0.778	1.82	8.78	0.383	0.390						

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 6A - continued.  
 Absolute organ weights - individual values (g) for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

Schedule number: DCN 302

GROUP	ANIMAL	TERMINAL									
		BODY WT (g)	BRAIN	ADRENALS	HEART	KIDNEYS	LIVER	SPLEEN	THYMUS		
3F	36	255.5	1.78	0.078	1.050	2.10	10.78	0.583	0.582		
	37	243.2	1.86	0.075	0.893	1.81	9.50	0.478	0.459		
	38	216.7	1.85	0.072	0.827	1.96	8.62	0.470	0.392		
	39	248.6	1.78	0.096	1.003	2.07	10.95	0.589	0.416		
	40	229.9	1.76	0.069	0.968	1.76	10.08	0.526	0.446		

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

APPENDIX 6A - continued.  
 Absolute organ weights - individual values (g) for all animals

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Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

Schedule number: DCN 302

GROUP	ANIMAL	TERMINAL BODY WT (g)	BRAIN	ADRENALS	HEART	KIDNEYS	LIVER	SPLEEN	THYMUS
4F	31	188.5	1.76	0.063	0.795	3.26	8.13	0.571	0.407
	32	247.3	1.83	0.061	0.981	1.86	10.03	0.657	0.522
	33	158.6	NOT TAKEN						
	34	251.4	1.85	0.059	0.877	2.86	12.24	0.660	0.511
	35	190.7	1.73	0.081	0.686	3.36	7.81	0.607	0.317

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 Toxicity Study by Oral Administration to CD Rats for 4 Weeks

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APPENDIX 6B  
 Organ weights relative to bodyweight - individual values (%) for all animals

Group : 1 2 3 4  
 Compound : Control - Material 02675234 -  
 Dosage (mg/kg/day) : 0 100 300 1000

Schedule number: DCN 302

GROUP	ANIMAL	TERMINAL									
		BODY WT (g)	BRAIN	ADRENALS	EPIDIDYIMID	HEART	KIDNEYS	LIVER	SPLEEN	TESTES	THYMUS
1M	11	305.0	0.631	0.0138	0.2757	0.3521	0.861	4.744	0.2397	1.098	0.1364
	12	392.5	0.518	0.0110	0.1924	0.3834	0.825	3.872	0.1740	0.761	0.0871
	13	364.3	0.543	0.0154	0.2147	0.3706	0.899	4.367	0.2029	0.835	0.1331
	14	370.4	0.579	0.0162	0.2414	0.3248	0.810	3.837	0.1633	0.970	0.1482
	15	378.3	0.538	0.0148	0.2355	0.3920	0.791	3.929	0.1932	0.811	0.1258