3M Corporate Toxicology and Regulatory Services

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December 5, 2006

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EPA East – Room 6428 Attn: Section 8(e)
Office of Pollution Prevention and Toxics
US EPA
1200 Pennsylvania Avenue NW
Washington DC 20460-0001

RE: TSCA 8(e) Substantial Risk Notice on: isopropylmorpholine (CASRN 1004-14-4 and 1331-24-4).

To Whom It May Concern:

In October of this year 3M notified the EPA that preliminary data had been received for a 28 day repeat dose oral toxicity study in rats conducted on isopropylmorpholine (CASRN 1004-14-4 and 1331-24-4), a research and development chemical that 3M purchases from a supplier. Possible signs of neurotoxicity, including tremors and muscle twitching, were observed in most high dose animals (150 mg/kg/day) at the end of the treatment period. The final report for this study is enclosed.

For reference, 3M has previously submitted studies on this chemical. These previous submissions are assigned Docket No. 8EHQ-06-16525.

If you have any questions, or if we can provide any further information, please contact me at 651-737-1374.

Sincerely,

Deanna J. Luebker

8EHQ-06-16525

Deanna J. Luebker, MS, PhD
3M TSCA 8(e) Coordinator

Enclosure

CONTAIN NO CBI

8907000053

REPORT

Study Title

REPEATED DOSE 28-DAY ORAL TOXICITY STUDY WITH MTDID 7144 BY DAILY GAVAGE IN THE RAT, FOLLOWED BY A 14-DAY RECOVERY PERIOD

Author

Drs. F.M. van Otterdijk

Study completion date

16 November 2006

Test Facility

NOTOX B.V.
Hambakenwetering 7
5231 DD 's-Hertogenbosch
The Netherlands

Laboratory Project Identification

NOTOX Project 458966
NOTOX Substance 163134/B
3M MTDID Number 7144
3M Study ID Number 06-054

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2. STATEMENT OF GLP COMPLIANCE

NOTOX B.V., 's-Hertogenbosch, The Netherlands

The study described in this report has been correctly reported and was conducted in compliance with:

The Organization for Economic Cooperation and Development (OECD) Good Laboratory Practice Guidelines (1997),

which essentially conforms to:

The United States Food and Drug Administration Good Laboratory Practice Regulations.

The United States Environmental Protection Agency Good Laboratory Practice Regulations.

The sponsor is responsible for Good Laboratory Practice (GLP) compliance for all test substance information unless determined by NOTOX.

The GLP statement for the delegated phase Histopathology is included in Appendix 5 of this report.

NOTOX B.V.

Drs. F.M. van Otterdijk
Study Director

Date: 16 November 2006

Drs. M.S. Teunissen
Section Head Toxicology

Date: 16 November 2006

3. LEAD QUALITY ASSURANCE STATEMENT

NOTOX B.V., 's-Hertogenbosch, The Netherlands

This report was inspected by the NOTOX Quality Assurance Unit to confirm that the methods and results accurately and completely reflect the raw data.

The dates of Quality Assurance inspections are given below.
During the on-site process inspections procedures applicable to this type of study were inspected

The reporting date is the date of reporting to the Study Director. The QAU report was then forwarded to the Test Facility Management.

Type of inspections	Phase/Process	Start inspection date	End inspection date	Reporting date
Study	Protocol	09-Jun-06	09-Jun-06	09-Jun-06
	Exposure Dosing oral	07-Jul-06	07-Jul-06	07-Jul-06
	Amendment 1 of Protocol	07-Jul-06	07-Jul-06	07-Jul-06
	Amendment 2 of Protocol	07-Aug-06	07-Aug-06	07-Aug-06
	Amendment 3 of Protocol	19-Oct-06	19-Oct-06	19-Oct-06
	Report	25-Oct-06	01-Nov-06	01-Nov-06
	Amendment 4 of Protocol	08-Nov-06	08-Nov-06	08-Nov-06
	Amendment 5 of Protocol	13-Nov-06	13-Nov-06	13-Nov-06
Process	**Test substance unit** Test substance handling	10-Apr-06	11-Apr-06	11-Apr-06
	SPF unit Test substance handling Exposure Observation/Measurement Specimen handling	18-Apr-06	24-Apr-06	24-Apr-06
	Clinical pathology unit Observation/Measurement Specimen handling	08-May-06	11-May-06	11-May-06
	Histology unit Specimen handling	14-Jun-06	23-Jun-06	23-Jun-06
	Pathology unit Observation/Measurement	12-Jun-06	15-Jun-06	15-Jun-06
	Analytical and physical chemistry Test substance handling Observation/Measurement	22-May-06	30-May-06	02-Jun-06

The Quality Assurance programme for the delegated phase was performed by the Quality Assurance appointed by the test site management and a Quality Assurance statement is included in Appendix 5 of this report.

Head of Quality Assurance
C.J. Mitchell B.Sc.

Date: ...16-11-06.....

4. SUMMARY

Repeated dose 28-day oral toxicity study with MTDID 7144 by daily gavage in the rat, followed by a 14-day recovery period.

The study was based on the following guidelines:
- EC Directive 96/54/EC, B.7 Repeated Dose (28 days) Toxicity (oral), 1996.
- OECD 407, Repeated Dose 28-day Oral Toxicity Study in Rodents, 1995.
- Japanese Chemical Substances Control Law 1987, Notification of Nov. 21 2003 by MHLW (No. 1121002), METI (No. 2) and ME (No. 031121002).
- OPPTS 870.3050, Repeated dose 28-day oral toxicity study in rodents. Office of Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-00-366, 2000.

Based on the results of a 5-day range finding study, the dose levels for the 28-day toxicity study were selected to be 0, 15, 50 and 150 mg/kg/day.

The test substance was administered daily for 28 days by oral gavage to SPF-bred Wistar rats. One control group and three treated groups were tested, each consisting of 5 males and 5 females. An extra 5 animals per sex in the control and high dose group were allowed 14 days of recovery.
Chemical analyses of formulations were conducted once during the study to assess accuracy, homogeneity and stability over 5 hours.
The following parameters were evaluated: clinical signs daily; functional observation tests; body weight and food consumption weekly; clinical pathology and macroscopy at termination; organ weights and histopathology on a selection of tissues.

4.1. Results

Accuracy, homogeneity and stability over 5 hours of formulations of test substance in Milli-U water were demonstrated by analyses.

Findings in the kidneys consisted of an increased severity and incidence of cortical hyaline droplets in high dose males at the end of the treatment period. The hyaline droplets were considered to represent alpha$_{2\mu}$globulin, a normal protein in male rats which undergoes re-absorption in the proximal cortical tubules[4]. A range of chemicals are known to increase hyaline droplet formation. If hyaline droplets exceed the physiological capacity of the tubular epithelium, tubular cell degeneration may result. There was some evidence for this in high dose males in the form of a slight increase in severity of corticomedullary tubular basophilia along with a single occurrence of granular casts. This protein is not present in higher mammals, including man[4]. Following the recovery period the incidence and severity of the above findings were similar in control and high dose animals.

The slightly higher liver weight of high dose animals along with a slight increase in alanine aminotransferase activity was not associated with any morphological evidence of hepatocytotoxicity. Therefore, these alterations were considered not to be of an adverse nature. A range of other changes in clinical biochemistry parameters were noted at 150 mg/kg/day, including increased potassium levels and reduced chloride levels. Whilst these changes were still within the normal variation encountered for this strain of rats, these were considered to be related to treatment with the test substance and may in case of males be indicative of a functional deficit of the kidneys. These changes had recovered during the recovery phase.
At 50 mg/kg/day, only slightly higher cholesterol levels and slightly lower chloride levels were apparent, which could not be associated with morphological abnormalities. Also taking into account that these clinical biochemistry changes were of a minor nature, and appeared reversible in nature at 150 mg/kg/day, these changes at 50 mg/kg/day were considered to be of no toxicological relevance.

Tremors and muscle twitching were shown by most high dose animals, but only at the end of the treatment period. Functional observation tests revealed no treatment-related abnormalities that would support these signs. Incidentally, cases of flat/hunched posture, abdominal swelling, a pale appearance, lethargy, ptosis, squeaking, hypothermia and salivation were observed during treatment. Apart from a slightly reduced motor activity for high dose males, there were no observations/measurements that would support these clinical observations. However, considering the incidence and nature of these observations these were considered to be related to treatment. These signs resolved during the recovery period.

There were no changes at performance of functional observations, body weight and food consumption measurements, or alterations during haematological investigations and macroscopic examination that were considered to be an effect of treatment.

4.2. Conclusion

Based on these results, a No Observed Adverse Effect Level (NOAEL) for MTDID 7144 of 50 mg/kg/day was established.

5. INTRODUCTION

5.1. Preface

This is a multi-site study. The study was performed according to the OECD Consensus document Number 13 *The Application of the OECD Principles of GLP to the Organization and Management of Multi-Site studies.*

Information concerning the delegated phase Histopathology is given in appendix 5.

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Test Facility	NOTOX B.V. Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands

Study Plan		Experimental starting date	: 09 June 2006 (allocation)
	Pilot study	Treatment	: 14 June 2006 to 21 June 2006
		Necropsy	: 21 June 2006
	Main study	Treatment	: 07 July 2006 to 03 August 2006
		Blood sampling	: 04 August 2006 (All groups) 18 August 2006 (Recovery groups)
		Necropsy	: 04 August 2006 (Main groups) 18 August 2006 (Recovery groups)
		Experimental completion date	: 18 August 2006 (end of in-life phase)

5.2. Aim of the study

The nature and purpose of this repeated dose toxicity study was to assess the toxic potential of the test substance when administered to rats by daily oral gavage for a period of 28 days, followed by a 14-day recovery period. A No Observed Adverse Effect Level (NOAEL) was evaluated.
This study should provide part of a rational basis for toxicological risk assessment in man. The oral route was selected as it is a possible route of human exposure during manufacture, handling or use of the test substance.

5.3. Guidelines

As required by the Dutch Act on Animal Experimentation (February 1997), the study protocol was reviewed and agreed by the Animal Welfare Officer and the Ethical Committee of NOTOX (DEC NOTOX 97-03-15). The study procedures described in this report were based on the following guidelines:

1. European Community (EC) Council Directive 96/54/EC, Annex IV.D, replacing EC Directive 67/548/EEC, Part B : Methods for the Determination of Toxicity and other Health Effects; B.7: "Repeated Dose (28 days) Toxicity (oral)". Official Journal of the European Communities No. L248, September 1996.

2. Organisation for Economic Co-operation and Development (OECD), OECD Guidelines for Testing of Chemicals. Section 4, Health Effects, No. 407: "Repeated Dose 28-day Oral Toxicity Study in Rodents", Paris Cedex, 27 July 1995.

3. Japanese Chemical Substances Control Law 1987 according to the notification of November 21, 2003 by Ministry of Health, Labor and Welfare (No. 1121002), Ministry of Economy, Trade and Industry (No. 2) and Ministry of Environment (No. 031121002).

4. United States Environmental Protection Agency (EPA). Health Effects Test Guidelines, OPPTS 870.3050, Repeated dose 28-day oral toxicity study in rodents. Office of Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-00-366. July 2000.

5.4. Storage and retention of records and materials

Records and materials pertaining to the study including protocol, raw data, specimens (except specimens requiring refrigeration or freezing) and the final report are retained in the NOTOX archives for a period of at least 10 years after finalization of the report. After this period, the sponsor will be contacted to determine whether raw data and specimens should be returned to them, retained or destroyed on their behalf.

Those specimens requiring refrigeration or freezing will be retained by NOTOX for as long as the quality of the specimens permits evaluation but no longer than three months after finalization of the report.

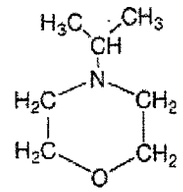
NOTOX will retain a test substance sample until the expiry date, but no longer than 10 years after finalization of the report. After this period the sample will be destroyed.

Storage and retention of records and materials to be retained by the test sites are described in the applicable appendices.

6. MATERIALS AND METHODS

6.1. Test Substance

6.1.1. Test substance information

Identification	MTDID 7144
Structure	
Molecular formula	$C_7H_{15}NO$
Molecular weight	129.2
CAS Number	1004-14-4
Description	Clear colourless liquid
Batch	6B601
Purity	≈ 99.68%
Test substance storage	At room temperature in the dark
Stability under storage conditions	Stable
Expiry date	24 May 2007 (allocated by NOTOX, 1 year after receipt of the test substance)

6.1.2. Study specific test substance information

Specific Gravity	0.9146
pH	10.7 at concentration of 10%
Stability in vehicle:	
• Water	At least 96 hours
Solubility in vehicle:	
• Water	Yes, >10 %

6.1.3. Test Substance Preparation

Vehicle	Water (Milli-U) (Millipore Corporation, Bedford, USA)
Rationale for vehicle	Based on trial formulations performed at NOTOX and on information from the sponsor.
Method of formulation	Prior to formulation the test substance was filtered. Formulations (w/w) were prepared daily within 4 hours (within 5 hours on day 11) prior to dosing and were homogenized to a visually acceptable level. Adjustment was made for specific gravity of the test substance.
Storage conditions	At ambient temperature.

6.1.4. Chemical Analysis of Dose Preparations

Samples of formulations prepared for use on day 6 were analysed to check stability over 5 hours, homogeneity (highest and lowest concentration) and accuracy of preparations (all concentrations). The analytical method used was based on the results of a separate project for the development and validation of the analytical method (NOTOX project 459056).

6.2. Test System

Test System	Rat: Wistar Crl:(WI) BR (outbred, SPF-Quality). Recognised by international guidelines as the recommended test system (e.g. EPA, FDA, OECD, EC). Source: Charles River Deutschland, Sulzfeld, Germany.
Age at Start of Treatment	Approximately 7 weeks.
Number of animals	30 males, 30 females (females were nulliparous and non-pregnant).
Randomisation	Prior to commencement of treatment, by computer-generated random algorithm according to body weight, with all animals within ± 20% of the sex mean.
Identification	Earmark and tattoo.
Health inspection	A health inspection was performed prior to commencement of treatment to ensure that the animals are in a good state of health.

6.3. Allocation

Group	Dose level mg/kg/day	Number of animals		Animal numbers	
		Males	Females	Males	Females
1 Main group	0 (vehicle)	5	5	1-5	31-35
1 Recovery group	0 (vehicle)	5	5	6-10	36-40
2 Main group	15	5	5	11-15	41-45
3 Main group	50	5	5	16-20	46-50
4 Main group	150	5	5	21-25	51-55
4 Recovery group	150	5	5	26-30	56-60

The dose levels were selected on the basis of a 5-day dose range finding study (NOTOX Project 458977). A summary of the results is included in this report (see Appendix 3).

6.4. Animal Husbandry

Room number	Room 12 (during the recovery phase animals were housed in room 6).
Conditions	Animals were housed in a controlled environment, in which optimal conditions were considered to be approximately 15 air changes per hour, a temperature of 21.0 ± 3.0°C (actual range: 20.8 – 23.1°C), a relative humidity of 30-70% (actual range: 39 - 89%) and 12 hours artificial fluorescent light and 12 hours darkness per day. Cleaning procedures in the room might have caused the temporary fluctuations above the optimal maximum level of 70% for relative humidity. Temporary fluctuations from the light/dark cycle (with a maximum of 1 hour) occurred due to performance of functional observations in the room. Based on laboratory historical data, these fluctuations were considered not to have affected the study integrity.
Accommodation	Group housing of 5 animals per sex in Macrolon plastic cages (MIV type, height 18 cm; during overnight activity monitoring individual housing in MIII type; height 15 cm.) with sterilized sawdust as bedding material (Woody-Clean type 3/4, Tecnilab-BMI BV, Someren, The Netherlands) and paper as cage-enrichment (Enviro-dri, Tecnilab-BMI BV, Someren, The Netherlands). No cage-enrichment was provided during overnight activity monitoring. Certificates of analysis are examined and then retained in the NOTOX archives. Acclimatization period was at least 5 days before start of treatment under laboratory conditions.

Diet	Free access to pelleted rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany). Each batch is analysed for nutrients and contaminants are analysed on a regular basis. Results are examined and archived.
Water	Free access to tap water. Certificates of analysis (performed quarterly) were examined and archived.

Results of analysis for ingredients and/or contaminants of diet, bedding, paper and water were assessed and did not reveal any findings that were considered to have affected study integrity.

6.5. Treatment

Method	Oral gavage, using a stainless steel stomach tube. Formulations were placed on a magnetic stirrer during dosing.
Frequency	Once daily for at least 28 days, 7 days per week, approximately the same time each day with a maximum of 4 hours difference between the earliest and latest dose. Animals were dosed up to the day prior to necropsy of the Main group animals.
Dose volume	20 ml/kg body weight. Actual dose volumes were calculated weekly according to the latest body weight.
Recovery	14 days.

6.6. Observations

Mortality / Viability	At least twice daily.
Clinical signs	At least once daily, detailed clinical observations were made in all animals. Once prior to start of treatment and on a weekly basis thereafter (except inadvertently on days 8 and 22), this was also performed outside the home cage in a standard arena. On days 8 and 14 of the recovery phase, an arena observation was conducted The symptoms were graded according to fixed scales and the time of onset, degree and duration were recorded: Maximum grade 1: grade 0 = absent, grade 1 = present Maximum grade 3 or 4: grade 1 = slight, grade 2 = moderate, grade 3 = severe, grade 4 = very severe
Functional Observations	During week 4 of treatment, the following tests were performed on all animals (abbreviations mentioned in the respective tables indicated between brackets): - hearing ability (HEARING), pupillary reflex (PUPIL L/R), static righting reflex (STATIC R) and grip strength (GRIP) (Score 0 = normal/present, score 1 = abnormal/absent). - motor activity test (recording period: 12 hours during overnight for individual animals, using a computerized monitoring system, Pearson Technical Services, Debenham, Stowmarket, England). Since no treatment-related effects during functional observation tests were seen in week 4, these tests were not repeated in week 6.
Body weights	Treatment period: on days 1, 8, 15, 22 and 28. Recovery period: on days 1, 8 and 14.
Food consumption	Weekly.
Water consumption	Subjective appraisal was maintained during the study, but no quantitative investigation introduced as no effect was suspected.

6.7. Clinical Laboratory Investigations

Blood samples were collected from all animals under iso-flurane anaesthesia (Abbott Laboratories Ltd., Zwolle, The Netherlands) between 7.00 and 10.30 a.m, immediately prior to scheduled *post mortem* examination at the end of the treatment and recovery period. The animals were fasted overnight (with a maximum of 20 hours) before blood sampling, but water was provided. Blood samples were drawn from the retro-orbital sinus and collected into tubes (Greiner Bio-One, Bad Haller, Austria) prepared with EDTA for haematological parameters (0.5 ml), with citrate for clotting tests (0.9 ml) and Li-heparin treated tubes for clinical biochemistry parameters (0.5 ml). The following parameters were determined:

Parameter	Abbreviation	Unit
Haematology [a]		
White blood cells	WBC	10^9/l
Differential leucocyte count neutrophils, lymphocytes, monocytes, eosinophils, basophils		%WBC
Red blood cells		10^{12}/l
Reticulocytes		%RBC
Red blood cell distribution width	RDW	%
Haemoglobin		mmol/l
Haematocrit		l/l
Mean corpuscular volume	MCV	fl
Mean corpuscular haemoglobin	MCH	fmol
Mean corpuscular haemoglobin concentration	MCHC	mmol/l
Platelets		10^9/l
Clotting Potential [b]		
Prothrombin time	PT	s
Activated Partial thromboplastin time	APTT	s
Clinical Biochemistry [c]		
Alanine aminotransferase	ALAT	U/l
Aspartate aminotransferase	ASAT	U/l
Alkaline phosphatase	ALP	U/l
Total Protein		g/l
Albumin		g/l
Total Bilirubin		µmol/l
Urea		mmol/l
Creatinine		µmol/l
Glucose		mmol/l
Cholesterol		mmol/l
Sodium		mmol/l
Potassium		mmol/l
Chloride		mmol/l
Calcium		mmol/l
Inorganic Phosphate	Inorg. Phos	mmol/l

[a] Instrumentation: ADVIA 120 (Bayer Diagnostics).
[b] Instrumentation: STA Compact (Roche Diagnostics).
[c] Instrumentation: Olympus AU400 (Goffin Meyvis).

6.8. Pathology

6.8.1. Necropsy

All animals surviving to the end of the observation period were deeply anaesthetised using isoflurane vapour (Abbott Laboratories Ltd., Zwolle, The Netherlands) and subsequently exsanguinated. All animals assigned to the study were necropsied and descriptions of all macroscopic abnormalities recorded. Samples of the following tissues and organs were collected from all animals at necropsy and fixed in a neutral phosphate buffered 4% formaldehyde solution (Klinipath, Duiven, The Netherlands):

Identification marks: not processed
Adrenal glands
Aorta
Brain [cerebellum, mid-brain, cortex]
Caecum
Cervix
(Clitoral gland)
Colon
Duodenum
Epididymides
(Eyes with optic nerve [if detectable] and Harderian gland)
(Female mammary gland area)
(Femur including joint)
Heart
Ileum
Jejunum
Kidneys
(Larynx)
(Lacrimal gland, exorbital)
Liver
Lung, infused with formalin
Lymph nodes - mandibular, mesenteric
(Nasopharynx)
Oesophagus
Ovaries
Pancreas
Peyer's patches [jejunum, ileum] if detectable
Pituitary gland
(Preputial gland)
Prostate gland
Rectum
(Salivary glands - mandibular, sublingual)
Sciatic nerve
Seminal vesicles
(Skeletal muscle)
(Skin)
Spinal cord -cervical, midthoracic, lumbar
Spleen
Sternum with bone marrow
Stomach
Testes
Thymus
Thyroid including parathyroid [if detectable]
(Tongue)
Trachea
Urinary bladder
Uterus
Vagina
All gross lesions

Tissues mentioned within brackets were not examined microscopically as there were no signs of toxicity or target organ involvement.

6.8.2. Organ Weights

The following organ weights (and terminal body weight) were recorded from the animals on the scheduled day of necropsy:

Adrenal glands
Epididymides
Kidneys
Testes
Brain
Heart
Liver
Spleen
Thymus

6.8.3. Histotechnology

All organ and tissue samples, as defined under Histopathology (following), were processed, embedded and cut at a thickness of 2-4 micrometers and stained with haematoxylin and eosin (Klinipath, Duiven, The Netherlands).

6.8.4. Histopathology

The delegated phase was performed by the Principal Investigator for Histopathology (see appendix 5).

6.9. Electronic data capture

Observations/measurements in the study were recorded electronically using the following programme(s):
- REES version 1.5 (REES Scientific, Trenton, NJ, USA): Environmental monitoring.
- TOXDATA version 8.0 (NOTOX B.V., 's-Hertogenbosch, The Netherlands): Mortality / Clinical signs / Body weights / Food consumption / Organ weights.
- MAMS version 6.2 (Pearson Technical Services, Suffolk, Great Britain): Motor activity measurement
- Advia 120 Version V.3.1.8.0.MS (Bayer Diagnostics, Mijdrecht, The Netherlands): Haematology
- Sta Compact version 1.06.06 (Stago Instruments, Gennevilliers, France): Clotting parameters
- Olympus AU 400 version 6 (Goffin-Meyvis, Etten-Leur, The Netherlands): Clinical laboratory investigations
- Empower version 5.00 (Waters, Milford, MA, USA): Formulation analysis

6.10. Interpretation

The following statistical methods were used to analyze the data:

- If the variables could be assumed to follow a normal distribution, the Dunnett-test[1] (many-to-one t-test) based on a pooled variance estimate was applied for the comparison of the treated groups and the control groups for each sex.
- The Steel-test[2] (many-to-one rank test) was applied when the data could not be assumed to follow a normal distribution.
- The exact Fisher-test[3] was applied to frequency data.

All tests were two-sided and in all cases $p < 0.05$ was accepted as the lowest level of significance. Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables. Test statistics were calculated on the basis of exact values for means and pooled variances. Individual values. means and standard deviations may have been rounded off before printing. Therefore. two groups may display the same printed means for a given parameter, yet display different test statistics values.

6.11. List of deviations

6.11.1. List of protocol deviations

1. Inadvertently, no terminal body weight was recorded for animal no. 5.
   Evaluation: Sufficient data were available for evaluation.
2. On days 8 and 22 of the treatment phase, no arena observation was conducted.
   On days 8 and 14 of the recovery phase, an arena observation was conducted.
   Evaluation: Sufficient data were available for evaluation of the study results.
3. On day 11, the formulations were prepared within 5 hours instead of within 4 hours prior to dosing.
   Evaluation: Formulations were stable for at least 5 hours.

The study integrity was not adversely affected by the deviations.

6.11.2. List of standard operating procedures deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

7. RESULTS

7.1. Chemical Analysis of Dose Preparations (see also APPENDIX 4)

Test substance formulations in Milli-U water were noted as stable for at least 5 hours and formed a homogeneous suspension at the concentrations tested. Analysis of the accuracy of dose preparations revealed values within the range of 80 % to 111 % of nominal. These results were in line with the results of the procedural recovery samples. Therefore, accuracy of dose preparations was considered acceptable for formulations of this type.

7.2. Observations

7.2.1. Mortality

No mortality occurred during the study period.

7.2.2. Clinical Signs

Tremors and muscle twitching were shown by most high dose animals at the end of the treatment period. One high dose female additionally showed flat/hunched posture, abdominal swelling, a pale appearance, lethargy, ptosis, squeaking and hypothermia during treatment. Also, a hunched posture was also noted for another high dose female, whilst salivation was incidentally noted among a few high dose animals during treatment. These signs resolved during the recovery period.

Incidental findings that were noted included rales, chromodacryorrhoea, scabs and wounds. These findings are commonly noted in rats of this age and strain and housed and treated under the conditions in this study and considered of no toxicological significance. No clinical signs were observed in control animals, males at 50 mg/kg/day and females at 15 mg/kg/day.

7.2.3. Functional Observations

Motor activity was slightly reduced in males at 150 mg/kg/day, achieving level of statistical significance for total low sensor counts.

The variation in motor activity noted among other groups was similar to control variations. Hearing ability, pupillary reflex, static righting reflex and grip strength were normal in all animals.

7.2.4. Body Weights

No toxicologically significant changes in body weight were noted.

The statistically significant reduction of body weight gain of high dose males in week 2 of treatment was of a very slight nature, and resolved as treatment progressed. This slight change was therefore considered to be of no toxicological relevance.
The statistically significant higher body weight gain of females on day 1 of the recovery period was considered to have occurred by chance and to be of no toxicological significance. Other (individual) variations in body weight occurred at a similar degree between treated and control animals.

7.2.5. Food Consumption

Food consumption before or after allowance for body weight was similar between treated and control animals.

7.3. Clinical Laboratory Investigations

7.3.1. Haematology

No toxicologically relevant changes in haematology parameters were apparent.

Any minor statistically significant changes observed at the end of the treatment period were within the normal range for rats of this age and strain and/or occurred in the absence of a dose-related response. In males, these changes included a higher relative neutrophil count and prothrombin time (PT) and a lower mean corpuscular haemoglobin (MCH) level at 150 mg/kg/day, a lower relative eosinophil count at 50 mg/kg/day, and a lower haemoglobin level and haematocrit and a higher partial thromboplastin time (APTT) at 15 mg/kg/day. In females, these alterations comprised a higher relative neutrophil and monocyte count at 150 mg/kg/day, a lower relative lymphocyte count at 50 and 150 mg/kg/day, and a higher red blood cell count and haematocrit level at 150 mg/kg/day.
Changes achieving a level of statistical significance at the end of the recovery period in high dose males were absent at the end of the treatment period, and were also within the range of values to be expected for rats of this age and strain. These changes consisted of a higher red cell distribution width (RDW), and a lower haemoglobin and haematocrit level. Also taking into account that other red blood cell parameters were similar to control levels, there was no indication of an adverse effect on red blood cell turn over.

7.3.2. Clinical Biochemistry

The following statistically significant changes distinguished treated from control rats at the end of the treatment period:

- Increased alanine aminotransferase activity (ALAT) in males and females at 150 mg/kg/day,
- Reduced creatinine level in females at 150 mg/kg/day,
- Increased cholesterol level in females at 50 and 150 mg/kg/day,
- Reduced sodium level in females at 150 mg/kg/day,
- Increased potassium level in males and females at 150 mg/kg/day,
- Reduced chloride level in males at 50 and 150 mg/kg/day, and in females at 150 mg/kg/day,
- Increased calcium level in females at 150 mg/kg/day,
- Increased inorganic phosphate level in males at 150 mg/kg/day.

With exception of alanine aminotransferase activity all means were within the normal range of values encountered for rats of this age and strain. At the end of the recovery phase the above changes were not apparent.

The statistically significant higher glucose level of females at 50 mg/kg/day and the statistically significant lower inorganic phosphate level of females at 15 mg/kg/day occurred in the absence of a dose-related response. No toxicological significance was ascribed to these changes.

7.4. Pathology

7.4.1. Macroscopic Examination

Macroscopic observations at necropsy did not reveal any alterations that were considered to have arisen as a result of treatment.

Incidental findings among control and/or treated animals included pelvic dilation of the kidneys, fluid in the uterus and a sore on the back of the neck. These findings are occasionally seen among rats used in these types of studies. In the absence of a dose-related distribution these were considered changes of no toxicological significance. No macroscopic abnormalities were noted in control males, and males at 15 and 50 mg/kg/day.

7.4.2. Organ Weights

Liver to body weight ratio of males at 150 mg/kg/day was slightly increased at the end of the treatment period, achieving a level of statistical significance. Liver weight of one high dose female was also increased, but the mean did not achieve a level of statistical significance.

Other organ weights and organ to body weight ratios of treated animals were considered to be similar to those of control animals.

7.4.3. Microscopic Examination (see also APPENDIX 5)

Treatment related microscopic findings were recorded in the kidneys of male rats. At the end of the main study cortical hyaline droplets were noted at increased severity and incidence in high dose males. Associated with this finding was a minimal degree of granular cast in one high dose male and a slightly increased severity of corticomedullary tubular basophilia in two high dose males. These findings had resolved during the recovery phase

All other microscopic findings were within the range of background pathology encountered in Wistar rats of this age and strain and occurred at similar incidences and severity in both control and treated rats.

8. CONCLUSIONS

Wistar rats were treated with MTDID 7144 for 28 consecutive days by oral gavage at dose levels up to 150 mg/kg/day.

Findings in the kidneys consisted of an increased severity and incidence of cortical hyaline droplets in high dose males at the end of the treatment period. The hyaline droplets were considered to represent alpha$_{2\mu}$globulin, a normal protein in male rats which undergoes re-absorption in the proximal cortical tubules[4]. A range of chemicals are known to increase hyaline droplet formation. If hyaline droplets exceed the physiological capacity of the tubular epithelium, tubular cell degeneration may result. There was some evidence for this in high dose males in the form of a slight increase in severity of corticomedullary tubular basophilia along with a single occurrence of granular casts. This protein is not present in higher mammals, including man[4]. Following the recovery period the incidence and severity of the above findings were similar in control and high dose animals.

The slightly higher liver weight of high dose animals along with a slight increase in alanine aminotransferase activity was not associated with any morphological evidence of hepatocytotoxicity. Therefore, these alterations were considered not to be of an adverse nature. A range of other changes in clinical biochemistry parameters were noted at 150 mg/kg/day, including increased potassium levels and reduced chloride levels. Whilst these changes were still within the normal variation encountered for this strain of rats, these were considered to be related to treatment with the test substance and may in case of males be indicative of a functional deficit of the kidneys. These changes had recovered during the recovery phase. At 50 mg/kg/day, only slightly higher cholesterol levels and slightly lower chloride levels were apparent, which could not be associated with morphological abnormalities. Also taking into account that these clinical biochemistry changes were of a minor nature, and appeared reversible in nature at 150 mg/kg/day, these changes at 50 mg/kg/day were considered to be of no toxicological relevance.

Tremors and muscle twitching were shown by most high dose animals, but only at the end of the treatment period. Functional observation tests revealed no treatment-related abnormalities that would support these signs. Incidentally, cases of flat/hunched posture, abdominal swelling, a pale appearance, lethargy, ptosis, squeaking, hypothermia and salivation were observed during treatment. Apart from a slightly reduced motor activity for high dose males, there were no observations/measurements that would support these clinical observations. However, considering the incidence and nature of these observations these were considered to be related to treatment. These signs resolved during the recovery period.

There were no changes at performance of functional observations, body weight and food consumption measurements, or alterations during haematological investigations and macroscopic examination that were considered to be an effect of treatment.

Based on these results, a No Observed Adverse Effect Level (NOAEL) for MTDID 7144 of 50 mg/kg/day was established.

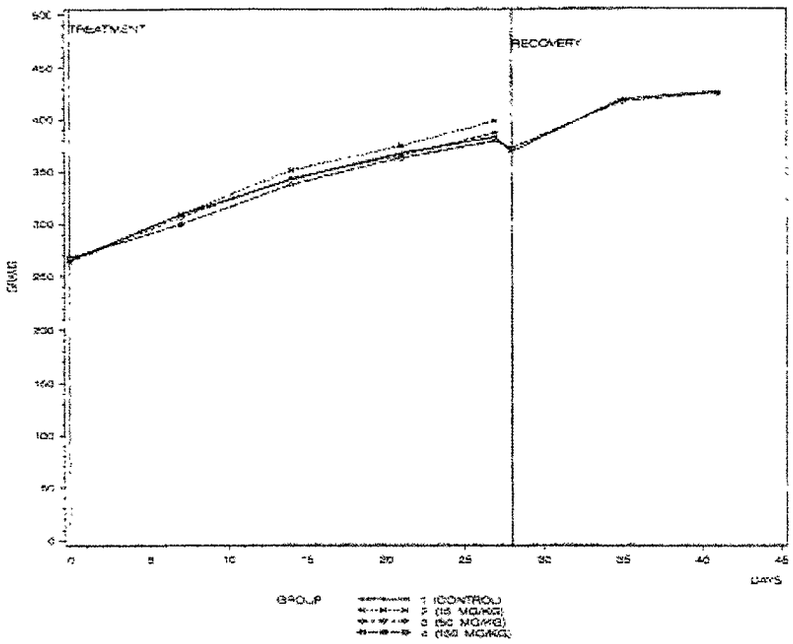
9. REFERENCES

1 C.W. Dunnett, A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Stat. Assoc. 50, 1096-1121 (1955).
2 R.G. Miller, Simultaneous Statistical Inference, Springer Verlag, New York (1981).
3 R.A. Fisher, Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).
4 Alden, CL and Frith CH. Urinary System, Ch. 15, pp 315-387. *In: Handbook of Toxicologic Pathology* Eds. Haschek WM and Rousseaux CG. Academic Press, San Diego (1991).

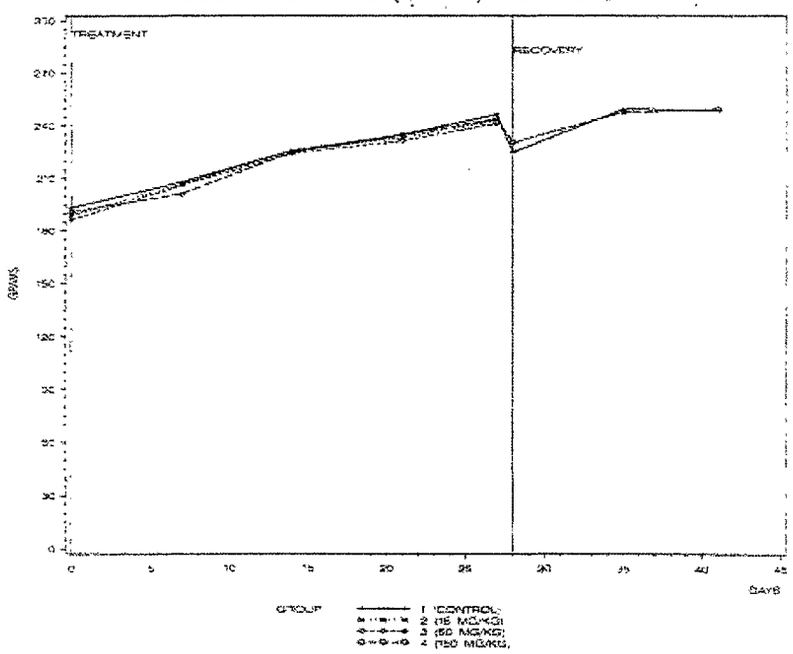
APPENDIX 1

FIGURES AND SUMMARY TABLES

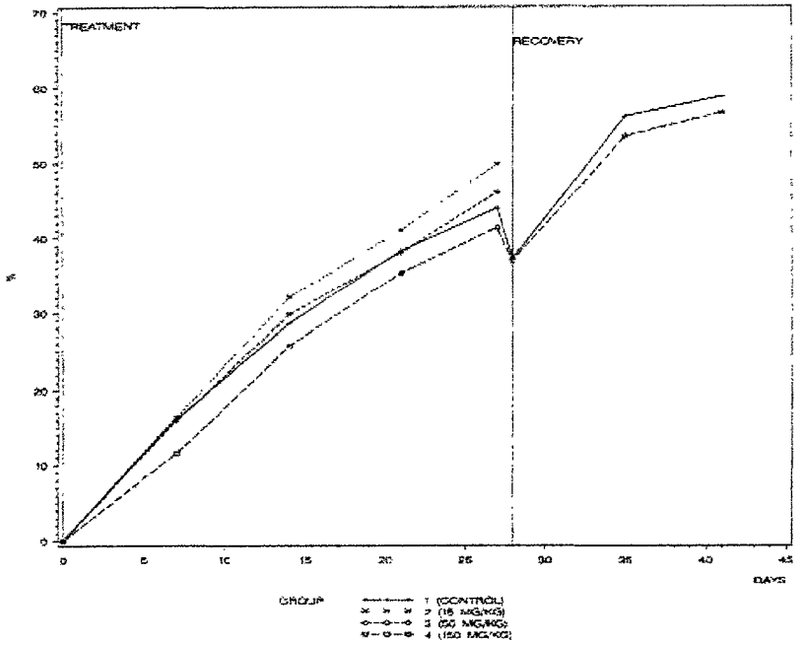
BODY WEIGHTS (GRAM) MALES



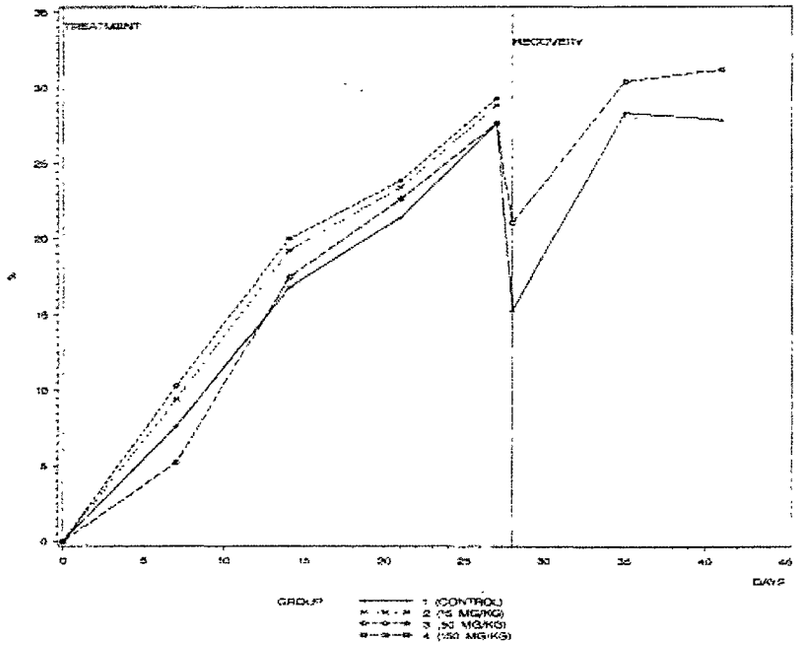
BODY WEIGHTS (GRAM) FEMALES



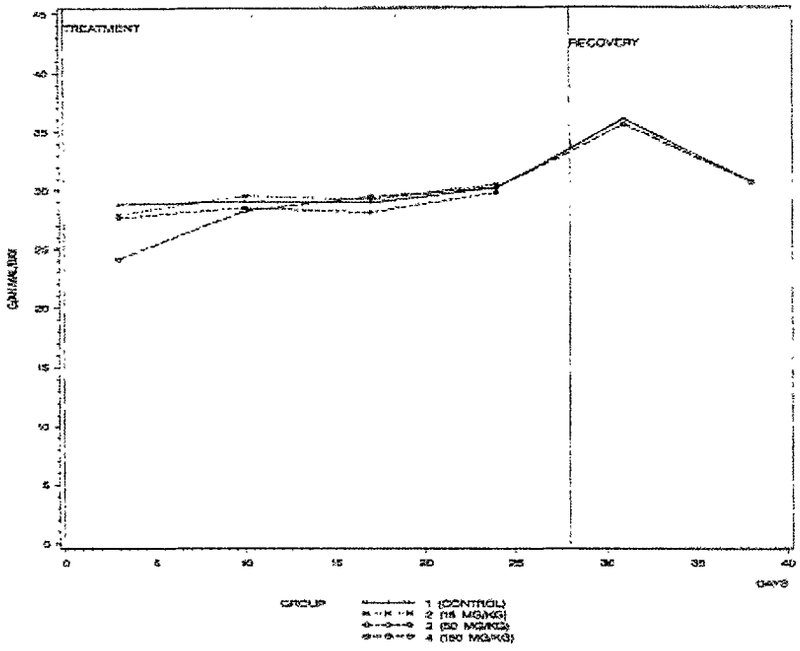
BODY WEIGHT GAIN (%) MALES



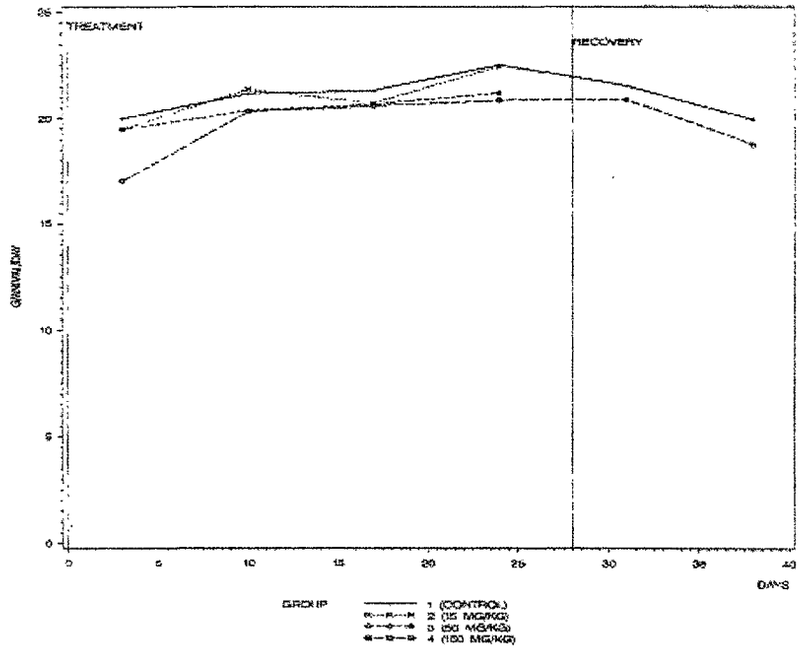
BODY WEIGHT GAIN (%) FEMALES



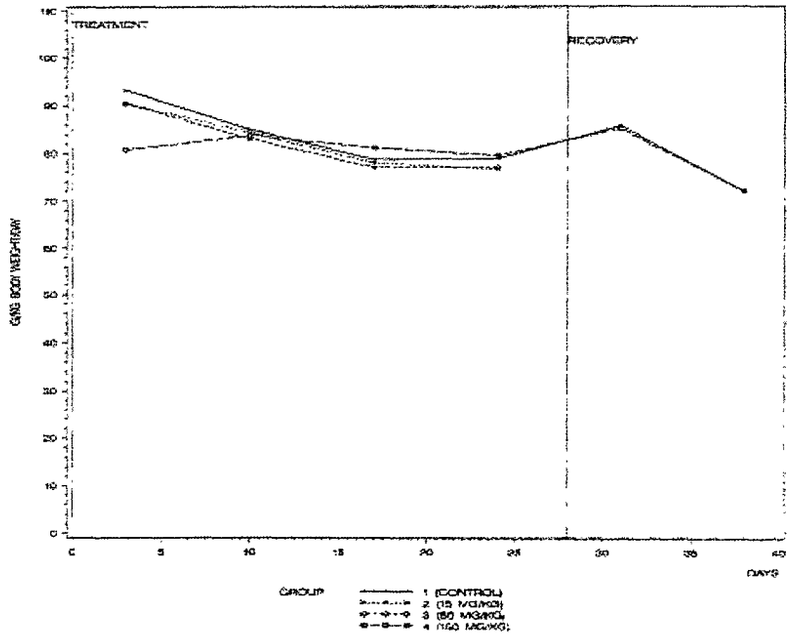
FOOD CONSUMPTION (G/ANIMAL/DAY) MALES



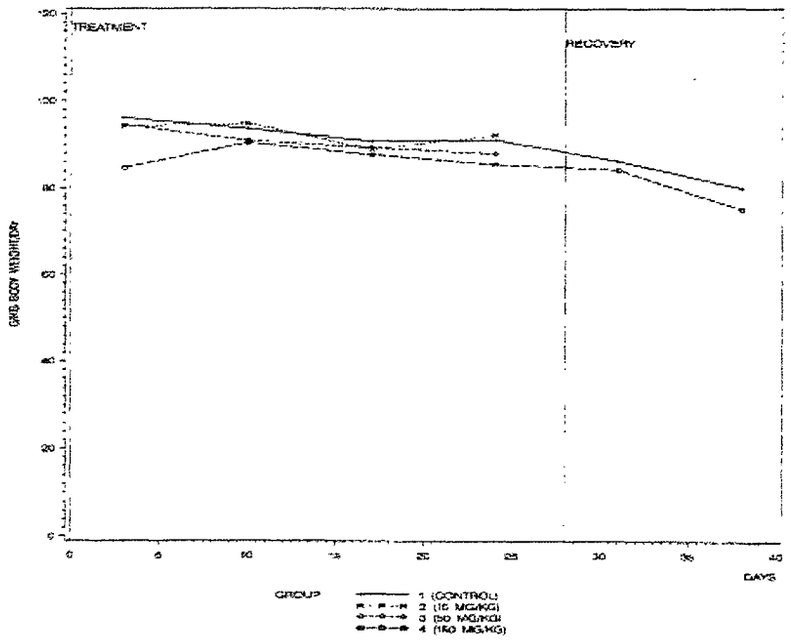
FOOD CONSUMPTION (G/ANIMAL/DAY) FEMALES



RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) MALES



RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) FEMALES



CLINICAL SIGNS SUMMARY
MALES

SIGN (MAX. GRADE) (LOCATION)		TREATMENT WEEK: 1 DAY: 1234567	4 1234567	RECOVERY 1 1234567
GROUP 1 (CONTROL)				
No clinical signs noted				
GROUP 2 (15 MG/KG)				
Breathing				
Rates (3)	G:		111	
	%:		222	
GROUP 3 (50 MG/KG)				
No clinical signs noted				
GROUP 4 (150 MG/KG)				
Spasms				
Tremor (3)	G:			2
	%:			A
Muscle twitching (1)	G:			1
	%			A
Secretion / excretion				
Salivation (3)	G:		1	
	%:		1	
Chromodacryorrhoea (3) (Snout)	G:	1		
	%:	1		

FEMALES

SIGN (MAX. GRADE) (LOCATION)		TREATMENT WEEK: 1 DAY 1234567	4 1234567	RECOVERY 1 1234567
GROUP 1 (CONTROL)				
No clinical signs noted				
GROUP 2 (15 MG/KG)				
No clinical signs noted				
GROUP 3 (50 MG/KG)				
Skin / fur / plumage				
Scabs (3)	G:	111	1111111111	
(Neck)	%:	222	2222222224	
Wound (3)	G:	1111		
(Neck)	%:	2222		
GROUP 4 (150 MG/KG)				
Behavior				
Lethargy (3)	G:	1		
	%:	1		
Spasms				
Tremor (3)	G:			1
	%:			9
Muscle twitching (1)	G:			1
	%:			9
Posture				
Flat posture (1)	G:	1	111	1
	%:	1	111	1
Hunched posture (1)	G:		1111111111	11111
	%:		1111111111	22222

G: Median value of the highest individual daily grades
%: Percent of affected animals (0=less than 5%, 1=between 5% and 15%....., A=more than 95%)
.: Observation performed, sign not present

CLINICAL SIGNS SUMMARY
FEMALES

```
                                TREATMENT                RECOVERY
SIGN (MAX. GRADE)        WEEK: 1.....................4......1............
(LOCATION)               DAY:  123456712345671234567123456712345671234567

GROUP 4 (150 MG/KG)
Skin / fur / plumage
  Swelling (4)           G:    .............111111111111111111111.......
    (Abdomen)            %:    ........ ....111111111111111222222.......
Secretion / excretion
  Salivation (3)         G     .......1.........111.1111..1.............
                         %:    .......1.........122.1111..1... ..........
  Chromodacryorrhoea (3) G:    .................1..........................
    (Snout)              %:    .................1..........................
Various
  Pale (3)               G     ....................111...................
                         %     ....................111...................
  Ptosis (3)             G     ............111.....111...11.............
                         %:    ............111.....111...12.............
  Squeaking (1)          G:    ............111.111111111111111..........
                         %:    ............111.111111111112222..........
  Hypothermia (1)        G:    ............1.............................
                         %:    ............1.............................
```

G: Median value of the highest individual daily grades
%: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%)
.: Observation performed, sign not present

FUNCTIONAL OBSERVATIONS SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
AT WEEK 4					
HEARING	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
PUPIL L	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
PUPIL R	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
STATIC R	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
GRIP	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10

FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
AT WEEK 4					
HEARING	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
PUPIL L	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
PUPIL R	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
STATIC R	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10
GRIP	MEDIAN	0	0	0	0
SCORE 0/1	N	10	5	5	10

+/++ Steel-test significant at 5% (+) or 1% (++) level

MOTOR ACTIVITY MEASUREMENTS SUMMARY
MALES
WEEK 4

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
total high sensor count	MEAN	4873	ND	2428	1903
	ST.DEV	5528		1074	726
	N	10		5	10
total low sensor count	MEAN	5491	ND	5292	4579 *
	ST.DEV	993		755	659
	N	10		5	10

ND No data for group 2 due to a technical error

FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
total high sensor count	MEAN	3958	2778	1643	3938
	ST DEV	3670	1219	472	6208
	N	10	5	5	10
total low sensor count	MEAN	6037	5452	4559	4614
	ST.DEV	2331	1189	1158	1696
	N	10	5	5	10

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHTS (GRAM) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAY 1	MEAN	266	265	264	268
WEEK 1	ST.DEV	13.5	14.6	18.7	13.5
	N	10	5	5	10
DAY 8	MEAN	309	309	306	299
WEEK 2	ST.DEV	15.5	16.8	23.1	19.2
	N	10	5	5	10
DAY 15	MEAN	342	350	343	337
WEEK 3	ST.DEV	17.0	24.4	30.5	19.0
	N	10	5	5	10
DAY 22	MEAN	367	374	365	363
WEEK 4	ST.DEV	20.3	26.0	37.0	19.4
	N	10	5	5	10
DAY 28	MEAN	383	398	386	379
WEEK 4	ST.DEV	23.0	30.0	41.8	25.3
	N	10	5	5	10
RECOVERY					
DAY 1	MEAN	369			372
WEEK 1	ST.DEV	28.6			19.7
	N	5			5
DAY 8	MEAN	419			417
WEEK 2	ST.DEV	29.8			22.4
	N	5			5
DAY 14	MEAN	427			425
WEEK 2	ST.DEV	36.8			20.6
	N	5			5

FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAY 1	MEAN	193	189	187	191
WEEK 1	ST.DEV	12.9	7.5	16.5	10.5
	N	10	5	5	10
DAY 8	MEAN	208	207	206	201
WEEK 2	ST.DEV	15.1	4.9	17.8	14.3
	N	10	5	5	10
DAY 15	MEAN	226	225	224	225
WEEK 3	ST.DEV	20.2	6.8	19.2	18.4
	N	10	5	5	10
DAY 22	MEAN	235	233	231	235
WEEK 4	ST.DEV	22.1	8.1	21.5	18.4
	N	10	5	5	10
DAY 28	MEAN	247	243	241	244
WEEK 4	ST.DEV	21.9	4.3	21.1	20.6
	N	10	5	5	10

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHTS (GRAM) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
RECOVERY					
DAY 1	MEAN	225			230
WEEK 1	ST.DEV	12.1			19.8
	N	5			5
DAY 8	MEAN	250			248
WEEK 2	ST.DEV	8.0			22.4
	N	5			5
DAY 14	MEAN	249			250
WEEK 2	ST.DEV	10.1			30.8
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHT GAIN (%) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	10	5	5	10
DAY 8	MEAN	16	16	16	12 **
WEEK 2	ST.DEV	1.7	3.1	1.4	3.8
	N	10	5	5	10
DAY 15	MEAN	29	32	30	26
WEEK 3	ST.DEV	3.3	4.2	4.3	3.3
	N	10	5	5	10
DAY 22	MEAN	38	41	36	35
WEEK 4	ST.DEV	4.1	5.0	5.4	4.4
	N	10	5	5	10
DAY 28	MEAN	44	50	46	41
WEEK 4	ST.DEV	3.7	5.6	6.7	5.6
	N	10	5	5	10
RECOVERY					
DAY 1	MEAN	37			37
WEEK 1	ST.DEV	4.5			3.7
	N	5			5
DAY 8	MEAN	56			54
WEEK 2	ST.DEV	4.8			3.8
	N	5			5
DAY 14	MEAN	59			57
WEEK 2	ST.DEV	7.2			3.4
	N	5			5

FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	10	5	5	10
DAY 8	MEAN	8	9	10	5
WEEK 2	ST.DEV	5.4	4.0	1.4	3.4
	N	10	5	5	10
DAY 15	MEAN	17	19	20	17
WEEK 3	ST.DEV	6.8	2.3	3.0	5.0
	N	10	5	5	10
DAY 22	MEAN	21	23	24	23
WEEK 4	ST.DEV	7.0	6.0	1.6	5.0
	N	10	5	5	10
DAY 28	MEAN	28	29	29	28
WEEK 4	ST.DEV	5.6	4.6	1.3	5.0
	N	10	5	5	10

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHT GAIN (%) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
RECOVERY					
DAY 1	MEAN	15			21 *
WEEK 1	ST.DEV	1.7			4.6
	N	5			5
DAY 8	MEAN	28			30
WEEK 2	ST.DEV	4.2			6.5
	N	5			5
DAY 14	MEAN	28			31
WEEK 2	ST.DEV	4.5			10.4
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAYS 1-6	MEAN	29	28	28	24
WEEKS 1-2	ST.DEV	0.9	---	---	0.9
	N (CAGE)	2	1	1	2
DAYS 8-15	MEAN	29	30	28	28
WEEKS 2-3	ST.DEV	0.8	---	---	0.5
	N (CAGE)	2	1	1	2
DAYS 15-22	MEAN	29	29	28	29
WEEKS 3-4	ST.DEV	1.2	---	---	0.1
	N (CAGE)	2	1	1	2
DAYS 22-28	MEAN	30	30	30	30
WEEK 4	ST.DEV	1.1	---	---	0.7
	N (CAGE)	2	1	1	2
MEAN OF MEANS OVER TREATMENT	MEAN	29	29	28	28
RECOVERY					
DAYS 1-8	MEAN	36			36
WEEKS 1-2	ST.DEV	---			---
	N (CAGE)	1			1
DAYS 8-14	MEAN	31			31
WEEK 2	ST.DEV	---			---
	N (CAGE)	1			1
MEAN OF MEANS OVER RECOVERY	MEAN	33			33

FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAYS 1-8	MEAN	20	19	19	17
WEEKS 1-2	ST.DEV	1.7	---	---	0.9
	N (CAGE)	2	1	1	2
DAYS 8-15	MEAN	21	21	20	20
WEEKS 2-3	ST.DEV	1.9	---	---	0.3
	N (CAGE)	2	1	1	2
DAYS 15-22	MEAN	21	21	21	21
WEEKS 3-4	ST.DEV	1.1	---	---	0.6
	N (CAGE)	2	1	1	2
DAYS 22-28	MEAN	23	22	21	21
WEEK 4	ST.DEV	1.3	---	---	0.2
	N (CAGE)	2	1	1	2
MEAN OF MEANS OVER TREATMENT	MEAN	21	21	20	20
RECOVERY					
DAYS 1-8	MEAN	22			21
WEEKS 1-2	ST.DEV	---			---
	N (CAGE)	1			1
DAYS 8-14	MEAN	20			19
WEEK 2	ST.DEV	---			---
	N (CAGE)	1			1

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

	GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
RECOVERY				
MEAN OF MEANS				
OVER RECOVERY MEAN	21			20

RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAYS 1-8	MEAN	93	90	90	81
WEEKS 1-2	ST.DEV	0.7	---	---	0.4
	N (CAGE)	2	1	1	2
DAYS 8-15	MEAN	85	84	83	84
WEEKS 2-3	ST.DEV	0.5	---	---	1.5
	N (CAGE)	2	1	1	2
DAYS 15-22	MEAN	79	78	77	81
WEEKS 3-4	ST.DEV	2.4	---	---	2.3
	N (CAGE)	2	1	1	2
DAYS 22-28	MEAN	79	77	77	80
WEEK 4	ST.DEV	0.6	---	---	1.1
	N (CAGE)	2	1	1	2
MEAN OF MEANS OVER TREATMENT	MEAN	84	82	82	81
RECOVERY					
DAYS 1-8	MEAN	86			85
WEEKS 1-2	ST.DEV	---			---
	N (CAGE)	1			1
DAYS 8-14	MEAN	72			72
WEEK 2	ST.DEV	---			---
	N (CAGE)	1			1
MEAN OF MEANS OVER RECOVERY	MEAN	79			79

FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
TREATMENT					
DAYS 1-8	MEAN	96	94	94	85
WEEKS 1-2	ST.DEV	5.4	---	---	3.4
	N (CAGE)	2	1	1	2
DAYS 8-15	MEAN	94	95	91	90
WEEKS 2-3	ST.DEV	5.3	---	---	0.1
	N (CAGE)	2	1	1	2
DAYS 15-22	MEAN	91	89	89	88
WEEKS 3-4	ST.DEV	1.4	---	---	0.7
	N (CAGE)	2	1	1	2
DAYS 22-28	MEAN	91	92	88	85
WEEK 4	ST.DEV	3.0	---	---	0.9
	N (CAGE)	2	1	1	2
MEAN OF MEANS OVER TREATMENT	MEAN	93	93	91	87
RECOVERY					
DAYS 1-8	MEAN	86			84
WEEKS 1-2	ST.DEV	---			---
	N (CAGE)	1			1
DAYS 8-14	MEAN	80			75
WEEK 2	ST.DEV	---			---
	N (CAGE)	1			1

RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
RECOVERY					
MEAN OF MEANS					
OVER RECOVERY	MEAN	83			80

HAEMATOLOGY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
WBC	MEAN	12.0	11.9	12.8	12.1
10E9/l	ST.DEV	1.6	2.4	3.0	2.7
	N	10	5	5	10
Neutrophils	MEAN	14.7	11.8	15.8	19.5 +
%WBC	ST.DEV	3.5	2.6	4.3	4.3
	N	10	5	5	10
Lymphocytes	MEAN	80.0	84.0	79.1	75.5
%WBC	ST.DEV	3.5	3.0	5.2	4.8
	N	10	5	5	10
Monocytes	MEAN	3.2	3.1	3.8	3.2
%WBC	ST.DEV	0.7	1.7	1.5	0.8
	N	10	5	5	10
Eosinophils	MEAN	1.8	0.8	0.8 ++	1.5
%WBC	ST.DEV	0.6	0.8	0.5	0.3
	N	10	5	5	10
Basophils	MEAN	0.3	0.2	0.3	0.3
%WBC	ST.DEV	0.2	0.2	0.2	0.1
	N	10	5	5	10
Red blood cells	MEAN	8.33	8.09	8.31	8.54
10E12/l	ST.DEV	0.30	0.47	0.19	0.36
	N	10	5	5	10
Reticulocytes	MEAN	2.2	2.1	2.0	2.0
%RBC	ST.DEV	0.2	0.3	0.3	0.3
	N	10	5	5	10
RDW	MEAN	12.0	12.4	12.2	12.5
%	ST.DEV	0.4	0.5	0.4	0.4
	N	10	5	5	10
Haemoglobin	MEAN	9.6	9.1 *	9.2	9.4
mmol/l	ST.DEV	0.2	0.3	0.4	0.3
	N	10	5	5	10
Haematocrit	MEAN	0.469	0.448 *	0.456	0.462
l/l	ST.DEV	0.013	0.016	0.016	0.012
	N	10	5	5	10
MCV	MEAN	56.3	55.4	54.9	54.2
fl	ST.DEV	1.9	2.2	2.4	1.5
	N	10	5	5	10
MCH	MEAN	1.15	1.13	1.11	1.10 *
fmol	ST.DEV	0.04	0.06	0.04	0.03
	N	10	5	5	10
MCHC	MEAN	20.38	20.43	20.24	20.32
mmol/l	ST.DEV	0.36	0.29	0.35	0.26
	N	10	5	5	10
Platelets	MEAN	906	986	1008	1037
10E9/l	ST.DEV	164	273	226	183
	N	10	5	5	10
PT	MEAN	16.3	17.1	16.6	17.1
s	ST.DEV	0.8	1.0	0.4	0.4
	N	9	4	5	8
APTT	MEAN	13.7	16.3 *	15.1	15.3
s	ST DEV	1.1	2.7	1.6	1.0
	N	9	4	5	8

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

HAEMATOLOGY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
WBC	MEAN	11.5			10.8
10E9/l	ST.DEV	1.1			3.2
	N	5			5
Neutrophils	MEAN	18.2			20.6
%WBC	ST.DEV	3.4			6.0
	N	5			5
Lymphocytes	MEAN	75.6			73.9
%WBC	ST.DEV	4.5			5.7
	N	5			5
Monocytes	MEAN	4.2			3.9
%WBC	ST.DEV	0.4			0.3
	N	5			5
Eosinophils	MEAN	1.7			1.4
%WBC	ST.DEV	1.1			0.5
	N	5			5
Basophils	MEAN	0.3			0.2
%WBC	ST.DEV	0.2			0.1
	N	5			5
Red blood cells	MEAN	8.44			8.30
10E12/l	ST.DEV	0.34			0.09
	N	5			5
Reticulocytes	MEAN	2.7			3.0
%RBC	ST.DEV	0.2			0.3
	N	5			5
RDW	MEAN	13.0			14.2 *
%	ST.DEV	0.4			0.7
	N	5			5
Haemoglobin	MEAN	9.6			9.2 *
mmol/l	ST.DEV	0.3			0.1
	N	5			5
Haematocrit	MEAN	0.467			0.444 *
l/l	ST.DEV	0.013			0.014
	N	5			5
MCV	MEAN	55.5			53.5
fl	ST.DEV	2.7			1.4
	N	5			5
MCH	MEAN	1.13			1.10
fmol	ST.DEV	0.06			0.02
	N	5			5
MCHC	MEAN	20.48			20.65
mmol/l	ST.DEV	0.19			0.39
	N	5			5
Platelets	MEAN	931			957
10E9/l	ST.DEV	138			177
	N	5			5
PT	MEAN	18.0			17.1
s	ST.DEV	0.6			0.8
	N	5			3
APTT	MEAN	17.3			14.5
s	ST.DEV	1.8			2.9
	N	5			3

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HAEMATOLOGY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
WBC	MEAN	7.0	7.2	7.2	8.9
10E9/l	ST.DEV	1.2	2.5	1.8	2.0
	N	10	5	5	10
Neutrophils	MEAN	9.7	16.8	17.2	15.3 +
%WBC	ST.DEV	2.1	6.9	4.7	5.7
	N	10	5	5	10
Lymphocytes	MEAN	85.8	78.5	77.7 ++	78.4 ++
%WBC	ST.DEV	2.4	6.3	5.2	6.4
	N	10	5	5	10
Monocytes	MEAN	2.3	2.7	3.0	4.0 ++
%WBC	ST.DEV	0.9	0.7	1.4	1.4
	N	10	5	5	10
Eosinophils	MEAN	2.0	1.7	1.8	2.0
%WBC	ST.DEV	0.4	0.5	0.2	0.5
	N	10	5	5	10
Basophils	MEAN	0.3	0.2	0.2	0.3
%WBC	ST.DEV	0.1	0.2	0.1	0.1
	N	10	5	5	10
Red blood cells	MEAN	7.57	7.75	7.54	7.98 **
10E12/l	ST.DEV	0.26	0.13	0.21	0.34
	N	10	5	5	10
Reticulocytes	MEAN	2.5	2.4	2.8	2.1
%RBC	ST.DEV	0.6	0.3	0.9	0.3
	N	10	5	5	10
RDW	MEAN	12.1	12.3	12.3	12.2
%	ST.DEV	0.6	0.4	0.5	0.6
	N	10	5	5	10
Haemoglobin	MEAN	8.6	8.7	8.5	8.9
mmol/l	ST.DEV	0.3	0.3	0.2	0.3
	N	10	5	5	10
Haematocrit	MEAN	0.420	0.423	0.421	0.437 *
l/l	ST.DEV	0.012	0.012	0.013	0.014
	N	10	5	5	10
MCV	MEAN	55.5	54.5	55.8	54.7
fl	ST.DEV	1.4	2.1	1.3	1.4
	N	10	5	5	10
MCH	MEAN	1.14	1.12	1.13	1.12
fmol	ST.DEV	0.04	0.04	0.04	0.04
	N	10	5	5	10
MCHC	MEAN	20.46	20.53	20.24	20.39
mmol/l	ST.DEV	0.37	0.30	0.24	0.35
	N	10	5	5	10
Platelets	MEAN	964	983	979	1026
10E9/l	ST.DEV	136	133	149	137
	N	10	5	5	10
PT	MEAN	16.8	16.5	16.5	16.2
s	ST.DEV	0.6	0.7	0.5	0.7
	N	10	5	5	10
APTT	MEAN	14.8	15.0	15.9	15.0
s	ST.DEV	2.1	1.2	1.4	1.6
	N	10	5	5	10

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HAEMATOLOGY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
WBC	MEAN	7.7			6.6
10E9/l	ST.DEV	2.3			1.7
	N	5			5
Neutrophils	MEAN	10.3			14.0
%WBC	ST.DEV	3.3			1.8
	N	5			5
Lymphocytes	MEAN	84.8			80.4
%WBC	ST.DEV	3.3			2.8
	N	5			5
Monocytes	MEAN	2.7			3.5
%WBC	ST.DEV	0.9			1.3
	N	5			5
Eosinophils	MEAN	1.9			1.8
%WBC	ST.DEV	0.2			0.6
	N	5			5
Basophils	MEAN	0.3			0.3
%WBC	ST.DEV	0.0			0.1
	N	5			5
Red blood cells	MEAN	7.85			7.85
10E12/l	ST.DEV	0.44			0.28
	N	5			5
Reticulocytes	MEAN	2.3			2.2
%RBC	ST.DEV	0.6			0.4
	N	5			5
RDW	MEAN	13.3			13.4
%	ST.DEV	0.6			0.6
	N	5			5
Haemoglobin	MEAN	9.0			8.8
mmol/l	ST.DEV	0.5			0.2
	N	5			5
Haematocrit	MEAN	0.441			0.427
l/l	ST.DEV	0.026			0.013
	N	5			5
MCV	MEAN	56.2			54.4
fl	ST.DEV	1.9			1.1
	N	5			5
MCH	MEAN	1.14			1.12
fmol	ST.DEV	0.05			0.04
	N	5			5
MCHC	MEAN	20.36			20.60
mmol/l	ST.DEV	0.35			0.30
	N	5			5
Platelets	MEAN	1085			1049
10E9/l	ST.DEV	105			208
	N	5			5
PT	MEAN	18.1			18.1
s	ST.DEV	0.9			1.0
	N	5			5
APTT	MEAN	14.3			15.5
s	ST.DEV	1.4			1.7
	N	5			5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
ALAT	MEAN	43.4	39.0	37.5	59.6 **
U/l	ST.DEV	5.9	8.8	5.0	13.4
	N	10	5	5	10
ASAT	MEAN	77.6	75.1	72.1	82.9
U/l	ST.DEV	6.8	9.6	7.3	14.6
	N	10	5	5	10
ALP	MEAN	120	104	97	129
U/l	ST.DEV	23	16	10	13
	N	10	5	5	10
Total protein	MEAN	62.6	60.4	61.0	61.5
g/l	ST.DEV	1.6	2.3	2.3	2.1
	N	10	5	5	10
Albumin	MEAN	30.9	29.9	29.8	30.3
g/l	ST.DEV	0.7	1.1	1.1	0.8
	N	10	5	5	10
Total bilirubin	MEAN	2.9	3.1	2.6	3.0
umol/l	ST.DEV	0.3	0.4	0.4	0.3
	N	10	5	5	10
Urea	MEAN	6.1	5.4	6.4	7.1
mmol/l	ST.DEV	1.3	0.7	1.2	1.3
	N	10	5	5	10
Creatinine	MEAN	40.0	37.5	38.9	40.3
umol/l	ST.DEV	1.5	1.2	2.8	2.3
	N	10	5	5	10
Glucose	MEAN	7.65	8.82	9.00	8.23
mmol/l	ST.DEV	1.58	1.52	1.41	1.01
	N	10	5	5	10
Cholesterol	MEAN	1.87	1.76	2.00	1.86
mmol/l	ST.DEV	0.34	0.20	0.46	0.37
	N	10	5	5	10
Sodium	MEAN	135.1	134.5	134.9	134.4
mmol/l	ST.DEV	0.9	0.7	1.0	1.2
	N	10	5	5	10
Potassium	MEAN	4.08	4.28	4.20	4.46 **
mmol/l	ST.DEV	0.19	0.24	0.20	0.21
	N	10	5	5	10
Chloride	MEAN	99	99	97 **	95 **
mmol/l	ST.DEV	1	0	1	1
	N	10	5	5	10
Calcium	MEAN	2.72	2.69	2.74	2.74
mmol/l	ST.DEV	0.03	0.04	0.06	0.06
	N	10	5	5	10
Inorg.Phos	MEAN	2.19	2.12	2.27	2.33 *
mmol/l	ST.DEV	0.09	0.16	0.10	0.14
	N	10	5	5	10

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
ALAT	MEAN	46.5			40.8
U/l	ST.DEV	2.8			5.5
	N	5			5
ASAT	MEAN	78.8			86.6
U/l	ST.DEV	8.2			7.9
	N	5			5
ALP	MEAN	108			103
U/l	ST.DEV	16			6
	N	5			5
Total protein	MEAN	61.8			60.7
g/l	ST.DEV	2.5			2.6
	N	5			5
Albumin	MEAN	31.0			30.4
g/l	ST.DEV	1.3			1.2
	N	5			5
Total bilirubin	MEAN	2.8			2.9
umol/l	ST.DEV	0.4			0.3
	N	5			5
Urea	MEAN	5.5			5.1
mmol/l	ST.DEV	1.1			1.0
	N	5			5
Creatinine	MEAN	40.0			39.1
umol/l	ST.DEV	1.5			1.1
	N	5			5
Glucose	MEAN	7.22			7.41
mmol/l	ST.DEV	0.70			1.06
	N	5			5
Cholesterol	MEAN	1.94			1.87
mmol/l	ST.DEV	0.27			0.54
	N	5			5
Sodium	MEAN	135.7			135.8
mmol/l	ST.DEV	1.5			0.6
	N	5			5
Potassium	MEAN	4.04			4.14
mmol/l	ST.DEV	0.18			0.15
	N	5			5
Chloride	MEAN	99			100
mmol/l	ST.DEV	1			1
	N	5			5
Calcium	MEAN	2.75			2.74
mmol/l	ST.DEV	0.06			0.04
	N	5			5
Inorg.Phos	MEAN	2.09			2.09
mmol/l	ST.DEV	0.14			0.17
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
ALAT	MEAN	35.5	44.2	37.8	56.6 **
U/l	ST.DEV	6.5	8.4	6.3	14.8
	N	10	5	5	10
ASAT	MEAN	74.5	77.8	69.2	76.8
U/l	ST.DEV	8.6	11.0	4.6	11.1
	N	10	5	5	10
ALP	MEAN	73	84	83	89
U/l	ST.DEV	13	24	10	15
	N	10	5	5	10
Total protein	MEAN	60.5	61.2	61.0	60.5
g/l	ST.DEV	2.2	2.3	2.5	2.6
	N	10	5	5	10
Albumin	MEAN	30.9	30.6	30.6	30.3
g/l	ST.DEV	1.2	1.2	1.2	1.5
	N	10	5	5	10
Total bilirubin	MEAN	3.1	2.9	2.9	3.2
umol/l	ST.DEV	0.4	0.3	0.7	0.5
	N	10	5	5	10
Urea	MEAN	6.5	5.5	6.3	6.7
mmol/l	ST.DEV	0.7	0.7	0.7	1.5
	N	10	5	5	10
Creatinine	MEAN	42.4	40.9	42.2	39.0 **
umol/l	ST.DEV	1.9	1.7	2.7	1.8
	N	10	5	5	10
Glucose	MEAN	8.11	8.98	10.05 *	9.16
mmol/l	ST.DEV	1.18	1.49	1.89	1.03
	N	10	5	5	10
Cholesterol	MEAN	1.53	1.84	1.97 *	2.00 **
mmol/l	ST.DEV	0.37	0.32	0.23	0.24
	N	10	5	5	10
Sodium	MEAN	134.4	133.9	135.4	133.2 *
mmol/l	ST.DEV	0.6	0.9	1.0	1.2
	N	10	5	5	10
Potassium	MEAN	3.75	3.76	3.82	4.09 *
mmol/l	ST.DEV	0.28	0.15	0.05	0.26
	N	10	5	5	10
Chloride	MEAN	100	100	102	97 **
mmol/l	ST.DEV	2	1	2	2
	N	10	5	5	10
Calcium	MEAN	2.59	2.58	2.58	2.71 **
mmol/l	ST.DEV	0.05	0.05	0.05	0.07
	N	10	5	5	10
Inorg.Phos	MEAN	2.00	1.65 **	1.85	2.08
mmol/l	ST.DEV	0.14	0.21	0.20	0.16
	N	10	5	5	10

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
ALAT	MEAN	42.0			35.6
U/l	ST.DEV	15.9			9.1
	N	5			5
ASAT	MEAN	72.4			72.3
U/l	ST.DEV	4.9			8.9
	N	5			5
ALP	MEAN	62			62
U/l	ST.DEV	16			16
	N	5			5
Total protein	MEAN	61.7			63.3
g/l	ST.DEV	2.9			4.9
	N	5			5
Albumin	MEAN	32.0			32.6
g/l	ST.DEV	1.3			2.8
	N	5			5
Total bilirubin	MEAN	3.8			3.1
umol/l	ST.DEV	0.6			0.7
	N	5			5
Urea	MEAN	6.3			6.0
mmol/l	ST.DEV	0.7			0.6
	N	5			5
Creatinine	MEAN	46.3			42.2
umol/l	ST.DEV	4.7			1.6
	N	5			5
Glucose	MEAN	7.71			7.39
mmol/l	ST.DEV	1.35			0.91
	N	5			5
Cholesterol	MEAN	1.63			1.68
mmol/l	ST.DEV	0.64			0.36
	N	5			5
Sodium	MEAN	135.5			135.2
mmol/l	ST.DEV	1.5			1.0
	N	5			5
Potassium	MEAN	3.81			3.70
mmol/l	ST.DEV	0.11			0.24
	N	5			5
Chloride	MEAN	101			100
mmol/l	ST.DEV	1			2
	N	5			5
Calcium	MEAN	2.60			2.59
mmol/l	ST.DEV	0.12			0.08
	N	5			5
Inorg.Phos	MEAN	1.77			1.81
mmol/l	ST.DEV	0.09			0.22
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

MACROSCOPIC FINDINGS SUMMARY
MALES

	GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT				
Animals examined	5	5	5	5
Animals without findings	5	5	5	4
Animals affected	0	0	0	1
Kidneys				
Pelvic dilation	0	0	0	1
END OF RECOVERY				
Animals examined	5			5
Animals without findings	5			5

FEMALES

	GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT				
Animals examined	5	5	5	5
Animals without findings	5	4	3	5
Animals affected	0	1	2	0
Uterus				
Contains fluid	0	1	1	0
Skin				
Sore(s)	0	0	1	0
END OF RECOVERY				
Animals examined	5			5
Animals without findings	2			2
Animals affected	3			3
Uterus				
Contains fluid	3			3

/ ## Fisher's Exact test significant at 5% (#) or 1% (##) level

ORGAN WEIGHTS (GRAM) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
BODY W.	MEAN	353	372	362	358
(GRAM)	ST.DEV	7	27	39	24
	N	4	5	5	5
BRAIN	MEAN	2.06	2.06	2.03	2.01
(GRAM)	ST.DEV	0.07	0.10	0.10	0.06
	N	5	5	5	5
HEART	MEAN	1.112	1.151	1.097	1.090
(GRAM)	ST.DEV	0.053	0.166	0.173	0.099
	N	5	5	5	5
LIVER	MEAN	10.12	10.68	10.64	11.34
(GRAM)	ST.DEV	0.73	1.25	1.57	1.14
	N	5	5	5	5
THYMUS	MEAN	0.411	2.316	0.401	0.386
(GRAM)	ST.DEV	0.041	4.203	0.061	0.102
	N	5	5	5	5
KIDNEYS	MEAN	2.68	2.68	2.93	3.15
(GRAM)	ST.DEV	0.16	0.84	0.11	0.39
	N	5	5	5	5
ADRENALS	MEAN	0.068	0.057	0.063	0.063
(GRAM)	ST.DEV	0.010	0.012	0.008	0.004
	N	5	5	5	5
SPLEEN	MEAN	0.838	0.866	0.841	0.800
(GRAM)	ST.DEV	0.139	0.121	0.098	0.120
	N	5	5	5	5
TESTES	MEAN	3.59	3.62	3.58	3.69
(GRAM)	ST.DEV	0.18	0.08	0.33	0.25
	N	5	5	5	5
EPIDIDYMIDES	MEAN	1.087	1.128	1.035	1.112
(GRAM)	ST.DEV	0.151	0.120	0.070	0.132
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN WEIGHTS (GRAM) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
BODY W.	MEAN	408			405
(GRAM)	ST.DEV	36			25
	N	5			5
BRAIN	MEAN	2.09			2.06
(GRAM)	ST.DEV	0.07			0.07
	N	5			5
HEART	MEAN	1.247			1.239
(GRAM)	ST.DEV	0.163			0.095
	N	5			5
LIVER	MEAN	11.27			11.14
(GRAM)	ST.DEV	1.89			1.53
	N	5			5
THYMUS	MEAN	0.385			0.348
(GRAM)	ST.DEV	0.040			0.040
	N	5			5
KIDNEYS	MEAN	2.87			2.98
(GRAM)	ST.DEV	0.43			0.32
	N	5			5
ADRENALS	MEAN	0.060			0.065
(GRAM)	ST.DEV	0.007			0.011
	N	5			5
SPLEEN	MEAN	0.971			0.862
(GRAM)	ST.DEV	0.079			0.060
	N	5			5
TESTES	MEAN	3.73			3.62
(GRAM)	ST.DEV	0.27			0.23
	N	5			5
EPIDIDYMIDES	MEAN	1.309			1.359
(GRAM)	ST.DEV	0.105			0.115
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
BODY W.	MEAN	353	372	362	358
(GRAM)	ST.DEV	7	27	39	24
	N	4	5	5	5
BRAIN	MEAN	0.58	0.56	0.57	0.56
(%)	ST.DEV	0.01	0.04	0.05	0.03
	N	4	5	5	5
HEART	MEAN	0.311	0.309	0.302	0.304
(%)	ST.DEV	0.012	0.031	0.022	0.012
	N	4	5	5	5
LIVER	MEAN	2.82	2.86	2.93	3.17 *
(%)	ST.DEV	0.23	0.14	0.15	0.20
	N	4	5	5	5
THYMUS	MEAN	0.117	0.663	0.110	0.108
(%)	ST.DEV	0.012	1.223	0.007	0.030
	N	4	5	5	5
KIDNEYS	MEAN	0.76	0.71	0.81	0.88
(%)	ST.DEV	0.06	0.20	0.07	0.06
	N	4	5	5	5
ADRENALS	MEAN	0.019	0.015	0.018	0.018
(%)	ST.DEV	0.003	0.003	0.003	0.002
	N	4	5	5	5
SPLEEN	MEAN	0.236	0.232	0.233	0.224
(%)	ST.DEV	0.044	0.021	0.020	0.032
	N	4	5	5	5
TESTES	MEAN	1.00	0.98	0.99	1.03
(%)	ST.DEV	0.04	0.07	0.09	0.05
	N	4	5	5	5
EPIDIDYMIDES	MEAN	0.307	0.303	0.289	0.312
(%)	ST.DEV	0.047	0.022	0.035	0.040
	N	4	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
BODY W.	MEAN	408			405
(GRAM)	ST.DEV	36			25
	N	5			5
BRAIN	MEAN	0.52			0.51
(%)	ST.DEV	0.05			0.03
	N	5			5
HEART	MEAN	0.305			0.306
(%)	ST.DEV	0.020			0.011
	N	5			5
LIVER	MEAN	2.75			2.74
(%)	ST.DEV	0.23			0.25
	N	5			5
THYMUS	MEAN	0.095			0.086
(%)	ST.DEV	0.015			0.013
	N	5			5
KIDNEYS	MEAN	0.70			0.73
(%)	ST.DEV	0.06			0.04
	N	5			5
ADRENALS	MEAN	0.015			0.016
(%)	ST.DEV	0.001			0.003
	N	5			5
SPLEEN	MEAN	0.239			0.214
(%)	ST.DEV	0.016			0.025
	N	5			5
TESTES	MEAN	0.92			0.89
(%)	ST.DEV	0.11			0.04
	N	5			5
EPIDIDYMIDES	MEAN	0.323			0.335
(%)	ST.DEV	0.042			0.022
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN WEIGHTS (GRAM) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
BODY W	MEAN	234	225	222	236
(GRAM)	ST.DEV	29	8	21	18
	N	5	5	5	4
BRAIN	MEAN	1.94	1.91	1.87	1.95
(GRAM)	ST.DEV	0.09	0.05	0.05	0.07
	N	5	5	5	5
HEART	MEAN	0.831	0.793	0.795	0.829
(GRAM)	ST.DEV	0.027	0.036	0.029	0.059
	N	5	5	5	5
LIVER	MEAN	6.67	7.03	7.27	7.73
(GRAM)	ST.DEV	0.81	0.63	0.63	1.23
	N	5	5	5	5
THYMUS	MEAN	0.333	0.295	0.322	0.316
(GRAM)	ST.DEV	0.073	0.090	0.071	0.056
	N	5	5	5	5
KIDNEYS	MEAN	1.89	1.88	1.82	1.92
(GRAM)	ST.DEV	0.26	0.07	0.11	0.22
	N	5	5	5	5
ADRENALS	MEAN	0.090	0.089	0.084	0.076
(GRAM)	ST.DEV	0.004	0.010	0.015	0.007
	N	5	5	5	5
SPLEEN	MEAN	0.690	0.566	0.675	0.628
(GRAM)	ST.DEV	0.147	0.091	0.065	0.090
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN WEIGHTS (GRAM) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
BODY W.	MEAN	235			232
(GRAM)	ST.DEV	9			21
	N	5			5
BRAIN	MEAN	1.90			1.82
(GRAM)	ST.DEV	0.06			0.09
	N	5			5
HEART	MEAN	0.811			0.791
(GRAM)	ST.DEV	0.037			0.043
	N	5			5
LIVER	MEAN	6.89			6.63
(GRAM)	ST.DEV	0.63			0.66
	N	5			5
THYMUS	MEAN	0.281			0.308
(GRAM)	ST.DEV	0.035			0.128
	N	5			5
KIDNEYS	MEAN	1.76			1.78
(GRAM)	ST.DEV	0.11			0.20
	N	5			5
ADRENALS	MEAN	0.084			0.076
(GRAM)	ST.DEV	0.007			0.017
	N	5			5
SPLEEN	MEAN	0.588			0.566
(GRAM)	ST.DEV	0.066			0.075
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF TREATMENT					
BODY W.	MEAN	234	225	222	236
(GRAM)	ST.DEV	29	8	21	18
	N	5	5	5	4
BRAIN	MEAN	0.84	0.85	0.85	0.83
(%)	ST.DEV	0.08	0.03	0.07	0.09
	N	5	5	5	4
HEART	MEAN	0.360	0.353	0.359	0.358
(%)	ST.DEV	0.042	0.022	0.023	0.026
	N	5	5	5	4
LIVER	MEAN	2.86	3.13	3.28	3.32
(%)	ST.DEV	0.11	0.26	0.30	0.48
	N	5	5	5	4
THYMUS	MEAN	0.141	0.131	0.145	0.134
(%)	ST.DEV	0.018	0.039	0.031	0.025
	N	5	5	5	4
KIDNEYS	MEAN	0.81	0.84	0.82	0.84
(%)	ST.DEV	0.03	0.04	0.05	0.06
	N	5	5	5	4
ADRENALS	MEAN	0.039	0.040	0.038	0.034
(%)	ST.DEV	0.004	0.005	0.006	0.003
	N	5	5	5	4
SPLEEN	MEAN	0.294	0.251	0.305	0.278
(%)	ST.DEV	0.042	0.039	0.031	0.045
	N	5	5	5	4

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 15 MG/KG	GROUP 3 50 MG/KG	GROUP 4 150 MG/KG
END OF RECOVERY					
BODY W.	MEAN	235			232
(GRAM)	ST.DEV	9			21
	N	5			5
BRAIN	MEAN	0.81			0.79
(%)	ST.DEV	0.05			0.06
	N	5			5
HEART	MEAN	0.345			0.344
(%)	ST.DEV	0.014			0.038
	N	5			5
LIVER	MEAN	2.93			2.87
(%)	ST.DEV	0.22			0.21
	N	5			5
THYMUS	MEAN	0.120			0.131
(%)	ST.DEV	0.017			0.047
	N	5			5
KIDNEYS	MEAN	0.75			0.77
(%)	ST.DEV	0.04			0.08
	N	5			5
ADRENALS	MEAN	0.036			0.033
(%)	ST.DEV	0.004			0.007
	N	5			5
SPLEEN	MEAN	0.251			0.244
(%)	ST.DEV	0.032			0.017
	N	5			5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

APPENDIX 2

INDIVIDUAL DATA TABLES

MORTALITY DATA
MALES

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
GROUP 1 (CONTROL)			
1	04AUG06	07JUL06	03AUG06
2	04AUG06	07JUL06	03AUG06
3	04AUG06	07JUL06	03AUG06
4	04AUG06	07JUL06	03AUG06
5	04AUG06	07JUL06	03AUG06
6	18AUG06	07JUL06	03AUG06
7	18AUG06	07JUL06	03AUG06
8	18AUG06	07JUL06	03AUG06
9	18AUG06	07JUL06	03AUG06
10	18AUG06	07JUL06	03AUG06
GROUP 2 (15 MG/KG)			
11	04AUG06	07JUL06	03AUG06
12	04AUG06	07JUL06	03AUG06
13	04AUG06	07JUL06	03AUG06
14	04AUG06	07JUL06	03AUG06
15	04AUG06	07JUL06	03AUG06
GROUP 3 (50 MG/KG)			
16	04AUG06	07JUL06	03AUG06
17	04AUG06	07JUL06	03AUG06
18	04AUG06	07JUL06	03AUG06
19	04AUG06	07JUL06	03AUG06
20	04AUG06	07JUL06	03AUG06
GROUP 4 (150 MG/KG)			
21	04AUG06	07JUL06	03AUG06
22	04AUG06	07JUL06	03AUG06
23	04AUG06	07JUL06	03AUG06
24	04AUG06	07JUL06	03AUG06
25	04AUG06	07JUL06	03AUG06
26	18AUG06	07JUL06	03AUG06
27	18AUG06	07JUL06	03AUG06
28	18AUG06	07JUL06	03AUG06
29	18AUG06	07JUL06	03AUG06
30	18AUG06	07JUL06	03AUG06

FEMALES

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
GROUP 1 (CONTROL)			
31	04AUG06	07JUL06	03AUG06
32	04AUG06	07JUL06	03AUG06
33	04AUG06	07JUL06	03AUG06
34	04AUG06	07JUL06	03AUG06
35	04AUG06	07JUL06	03AUG06
36	18AUG06	07JUL06	03AUG06
37	18AUG06	07JUL06	03AUG06
38	18AUG06	07JUL06	03AUG06
39	18AUG06	07JUL06	03AUG06
40	18AUG06	07JUL06	03AUG06
GROUP 2 (15 MG/KG)			
41	04AUG06	07JUL06	03AUG06
42	04AUG06	07JUL06	03AUG06
43	04AUG06	07JUL06	03AUG06
44	04AUG06	07JUL06	03AUG06
45	04AUG06	07JUL06	03AUG06

MORTALITY DATA
FEMALES

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
GROUP 3 (50 MG/KG)			
46	04AUG06	07JUL06	03AUG06
47	04AUG06	07JUL06	03AUG06
48	04AUG06	07JUL06	03AUG06
49	04AUG06	07JUL06	03AUG06
50	04AUG06	07JUL06	03AUG06
GROUP 4 (150 MG/KG)			
51	04AUG06	07JUL06	03AUG06
52	04AUG06	07JUL06	03AUG06
53	04AUG06	07JUL06	03AUG06
54	04AUG06	07JUL06	03AUG06
55	04AUG06	07JUL06	03AUG06
56	18AUG06	07JUL06	03AUG06
57	18AUG06	07JUL06	03AUG06
58	18AUG06	07JUL06	03AUG06
59	18AUG06	07JUL06	03AUG06
60	18AUG06	07JUL06	03AUG06

CLINICAL SIGNS
MALES

SIGN (MAX. GRADE) (LOCATION)		TREATMENT WEEK: 1	4	RECOVERY 1
	DAY:	1234567123456712345671234567123456712345671234567		
GROUP 1 (CONTROL)				
ANIMAL 1				
No clinical signs noted				
ANIMAL 2				
No clinical signs noted				
ANIMAL 3				
No clinical signs noted				
ANIMAL 4				
No clinical signs noted				
ANIMAL 5				
No clinical signs noted				
ANIMAL 6				
No clinical signs noted				
ANIMAL 7				
No clinical signs noted				
ANIMAL 8				
No clinical signs noted				
ANIMAL 9				
No clinical signs noted				
ANIMAL 10				
No clinical signs noted				
GROUP 2 (15 MG/KG)				
ANIMAL 11				
No clinical signs noted				
ANIMAL 12				
Breathing				
Rales (3)	G:	111	.....	
ANIMAL 13				
No clinical signs noted				
ANIMAL 14				
No clinical signs noted				
ANIMAL 15				
No clinical signs noted				
GROUP 3 (50 MG/KG)				
ANIMAL 16				
No clinical signs noted				
ANIMAL 17				
No clinical signs noted				
ANIMAL 18				
No clinical signs noted				
ANIMAL 19				
No clinical signs noted				
ANIMAL 20				
No clinical signs noted				
GROUP 4 (150 MG/KG)				
ANIMAL 21				
Spasms				
Tremor (3)	G:	.....	.....	2
Muscle twitching (1)	G:	.....	.....	1
ANIMAL 22				
Spasms				
Tremor (3)	G:	.....	.....	2
Muscle twitching (1)	G:	.....	.....	1
ANIMAL 23				
Spasms				
Tremor (3)	G:	.....	.....	2
Muscle twitching (1)	G:	.....	.....	1

G: Highest daily grades
. Observation performed, sign not present

CLINICAL SIGNS
MALES

SIGN (MAX. GRADE) (LOCATION)		TREATMENT WEEK: 1	4	RECOVERY 1
	DAY:	1234567123456712345671234567123456712345671234567		
GROUP 4 (150 MG/KG)				
ANIMAL 24				
Spasms				
Tremor (3)	G.	.....		2
Muscle twitching (1)	G.	.....		1
ANIMAL 25				
Spasms				
Tremor (3)	G.	.....		2
Muscle twitching (1)	G.	.....		1
ANIMAL 26				
Spasms				
Tremor (3)	G.	.....		1.....
Muscle twitching (1)	G:	.....		1.....
Secretion / excretion				
Chromodacryorrhoea (3) (Snout)	G:	.....1.....		.....
ANIMAL 27				
Spasms				
Tremor (3)	G:	.....		1.....
Muscle twitching (1)	G:	.....		1.....
Secretion / excretion				
Salivation (3)	G:	.....1.....		.....
ANIMAL 28				
Spasms				
Tremor (3)	G:	.....		1.....
Muscle twitching (1)	G:	.....		1.....
ANIMAL 29				
Spasms				
Tremor (3)	G.	.....		1.....
Muscle twitching (1)	G:	.....		1.....
ANIMAL 30				
Spasms				
Tremor (3)	G.	.....		1.....
Muscle twitching (1)	G:	.....		1.....

FEMALES

SIGN (MAX. GRADE) (LOCATION)		TREATMENT WEEK: 1	4	RECOVERY 1
	DAY:	1234567123456712345671234567123456712345671234567		
GROUP 1 (CONTROL)				
ANIMAL 31				
No clinical signs noted				
ANIMAL 32				
No clinical signs noted				
ANIMAL 33				
No clinical signs noted				
ANIMAL 34				
No clinical signs noted				
ANIMAL 35				
No clinical signs noted				
ANIMAL 36				
No clinical signs noted				
ANIMAL 37				
No clinical signs noted				
ANIMAL 38				
No clinical signs noted				

G. Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
FEMALES

SIGN (MAX. GRADE) (LOCATION)		TREATMENT WEEK: 1	4	RECOVERY 1
	DAY:	1234567123456712345671234567123456712345671234567		
GROUP 1 (CONTROL)				
ANIMAL 39				
No clinical signs noted				
ANIMAL 40				
No clinical signs noted				
GROUP 2 (15 MG/KG)				
ANIMAL 41				
No clinical signs noted				
ANIMAL 42				
No clinical signs noted				
ANIMAL 43				
No clinical signs noted				
ANIMAL 44				
No clinical signs noted				
ANIMAL 45				
No clinical signs noted				
GROUP 3 (50 MG/KG)				
ANIMAL 46				
Skin / fur / plumage				
Scabs (3)	G:			1
(Neck)				
ANIMAL 47				
Skin / fur / plumage				
Scabs (3)	G:	111	1111	1111111
(Neck)				
Wound (3)	G:	1111		
(Neck)				
ANIMAL 48				
No clinical signs noted				
ANIMAL 49				
No clinical signs noted				
ANIMAL 50				
No clinical signs noted				
GROUP 4 (150 MG/KG)				
ANIMAL 51				
No clinical signs noted				
ANIMAL 52				
Spasms				
Tremor (3)	G:			1
Muscle twitching (1)	G			1
ANIMAL 53				
Spasms				
Tremor (3)	G			1
Muscle twitching (1)	G:			1
Secretion / excretion				
Salivation (3)	G	111	1111	1
ANIMAL 54				
Spasms				
Tremor (3)	G:			1
Muscle twitching (1)	G:			1
Secretion / excretion				
Salivation (3)	G.	11		
ANIMAL 55				
Spasms				
Tremor (3)	G:			1
Muscle twitching (1)	G.			1

G: Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
FEMALES

SIGN (MAX. GRADE)		TREATMENT	RECOVERY
(LOCATION)	WEEK	1	4	1
	DAY:	123456712345671234567123456712345671234567	
GROUP 4 (150 MG/KG)			
ANIMAL 56			
Behavior			
Lethargy (3)	G:	1	
Spasms			
Tremor (3)	G:	1	
Muscle twitching (1)	G:	1	
Posture			
Flat posture (1)	G:	1	111 1
Hunched posture (1)	G.	1111	
Skin / fur / plumage			
Swelling (4) (Abdomen)	G:	1111111111111111111111	
Secretion / excretion			
Salivation (3)	G.	1	
Chromodacryorrhoea (3) (Snout)	G:	1	
Various			
Pale (3)	G.	111	
Ptosis (3)	G	111	111 11
Squeaking (1)	G:	111	111111111111111
Hypothermia (1)	G:	1	
ANIMAL 57			
Spasms			
Tremor (3)	G:	1	
Muscle twitching (1)	G:	1	
ANIMAL 58			
Spasms			
Tremor (3)	G	1	
Muscle twitching (1)	G.	1	
ANIMAL 59			
Spasms			
Tremor (3)	G:	1	
Muscle twitching (1)	G	1	
Posture			
Hunched posture (1)	G:	111111111111	
ANIMAL 60			
Spasms			
Tremor (3)	G.	1	
Muscle twitching (1)	G	1	

G. Highest daily grades
.: Observation performed sign not present

FUNCTIONAL OBSERVATIONS
MALES
AT WEEK 4

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP SCORE 0/1
GROUP 1 (CONTROL)					
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
8	0	0	0	0	0
9	0	0	0	0	0
10	0	0	0	0	0
GROUP 2 (15 MG/KG)					
11	0	0	0	0	0
12	0	0	0	0	0
13	0	0	0	0	0
14	0	0	0	0	0
15	0	0	0	0	0
GROUP 3 (50 MG/KG)					
16	0	0	0	0	0
17	0	0	0	0	0
18	0	0	0	0	0
19	0	0	0	0	0
20	0	0	0	0	0
GROUP 4 (150 MG/KG)					
21	0	0	0	0	0
22	0	0	0	0	0
23	0	0	0	0	0
24	0	0	0	0	0
25	0	0	0	0	0
26	0	0	0	0	0
27	0	0	0	0	0
28	0	0	0	0	0
29	0	0	0	0	0
30	0	0	0	0	0

FEMALES
AT WEEK 4

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP SCORE 0/1
GROUP 1 (CONTROL)					
31	0	0	0	0	0
32	0	0	0	0	0
33	0	0	0	0	0
34	0	0	0	0	0
35	0	0	0	0	0
36	0	0	0	0	0
37	0	0	0	0	0
38	0	0	0	0	0
39	0	0	0	0	0
40	0	0	0	0	0

FUNCTIONAL OBSERVATIONS
FEMALES
AT WEEK 4

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP SCORE 0/1
GROUP 2 (15 MG/KG)					
41	0	0	0	0	0
42	0	0	0	0	0
43	0	0	0	0	0
44	0	0	0	0	0
45	0	0	0	0	0
GROUP 3 (50 MG/KG)					
46	0	0	0	0	0
47	0	0	0	0	0
48	0	0	0	0	0
49	0	0	0	0	0
50	0	0	0	0	0
GROUP 4 (150 MG/KG)					
51	0	0	0	0	0
52	0	0	0	0	0
53	0	0	0	0	0
54	0	0	0	0	0
55	0	0	0	0	0
56	0	0	0	0	0
57	0	0	0	0	0
58	0	0	0	0	0
59	0	0	0	0	0
60	0	0	0	0	0

MOTOR ACTIVITY TEST
MALES
WEEK 4

Animal number	Location of sensor	Counts per sample period (hour) 1	2	3	4	5	6	7	8	9	10	11	12	Total
GROUP 1 (CONTROL)														
1	High	271	320	620	332	278	169	141	123	3	240	359	127	2983
1	Low	558	469	726	592	481	760	409	333	295	261	661	465	6010
2	High	1085	1311	1504	1006	2154	401	76	1683	47	1443	6413	3180	20303
2	Low	777	448	496	317	95	358	63	779	46	443	887	35	4744
3	High	240	273	587	154	356	2	12	355	45	221	262	118	2625
3	Low	602	552	698	229	501	14	61	530	158	680	486	200	4711
4	High	305	320	654	910	649	640	109	498	80	405	603	887	6060
4	Low	428	410	560	714	478	538	158	1662	116	524	580	1615	7783
5	High	306	175	48	528	287	142	366	154	18	91	413	162	2690
5	Low	363	506	396	680	232	456	520	521	148	423	751	266	5262
6	High	238	324	286	504	289	53	101	387	168	272	318	66	3006
6	Low	786	294	467	529	622	74	268	608	371	509	713	223	5464
7	High	269	281	417	338	227	386	265	97	267	267	401	12	3227
7	Low	448	397	709	765	520	426	423	47	546	365	687	30	5363
8	High	130	127	492	183	185	8	230	156	39	23	279	124	1976
8	Low	297	396	684	286	335	71	531	263	143	138	697	401	4242
9	High	170	228	579	271	211	108	82	354	151	159	599	95	3007
9	Low	572	307	531	738	350	216	131	782	120	417	917	82	5163
10	High	345	183	583	319	272	161	400	113	60	159	243	19	2857
10	Low	850	378	764	576	647	441	635	390	212	572	684	16	6165
GROUP 2 (15 MG/KG)														
11	High	No data for group 2 due to a technical error.												
11	Low													
12	High													
12	Low													
13	High													
13	Low													
14	High													
14	Low													
15	High													
15	Low													
GROUP 3 (50 MG/KG)														
16	High	145	278	131	277	303	41	104	7	32	122	228	35	1703
16	Low	364	548	209	682	710	146	292	204	112	344	694	340	4645
17	High	230	299	324	70	359	414	31	216	205	328	492	92	3060
17	Low	685	260	389	156	635	838	25	121	404	333	879	294	5019
18	High	723	361	368	412	495	208	114	334	287	249	426	14	3991
18	Low	1019	617	363	650	664	371	80	438	279	243	587	44	5355
19	High	234	6	212	61	101	66	269	0	9	52	332	64	1406
19	Low	936	136	559	179	389	497	611	149	220	215	704	282	4879
20	High	155	88	194	371	214	214	4	131	163	99	246	99	1978
20	Low	703	233	482	715	526	357	930	223	982	269	609	534	6563

MOTOR ACTIVITY TEST
MALES
WEEK 4

Animal number	Location of sensor	Counts per sample period (hour) 1	2	3	4	5	6	7	8	9	10	11	12	Total
GROUP 4 (150 MG/KG)														
21	High	155	56	80	126	41	125	1	14	18	58	102	1	776
21	Low	326	320	279	149	321	480	4	351	111	305	674	80	3400
22	High	107	76	112	96	42	86	267	56	32	175	136	281	1466
22	Low	523	628	549	310	264	387	488	618	115	601	394	493	5370
23	High	108	126	11	129	113	93	96	52	15	55	123	64	984
23	Low	585	468	223	493	457	534	422	379	62	633	507	367	5130
24	High	169	210	362	363	304	430	21	165	302	412	321	2	3061
24	Low	360	200	530	569	348	311	87	322	323	650	629	17	4346
25	High	296	127	175	433	363	297	311	87	97	29	372	111	2698
25	Low	677	296	329	607	640	737	454	274	193	102	697	152	5158
26	High	92	57	138	261	163	93	62	170	74	241	381	122	1854
26	Low	430	263	333	322	213	314	372	835	443	618	700	398	5241
27	High	93	135	200	226	105	82	9	45	94	209	373	126	1697
27	Low	67	455	794	460	168	247	7	265	412	520	716	393	4504
28	High	233	12	152	576	319	2	21	50	93	229	277	223	2187
28	Low	655	130	333	811	400	57	244	396	124	569	751	228	4698
29	High	244	74	288	222	79	332	16	20	197	105	172	70	1819
29	Low	504	416	481	510	172	453	193	169	426	276	294	105	3999
30	High	272	324	474	349	100	21	201	362	107	73	204	0	2485
30	Low	492	408	488	315	152	113	380	513	270	256	542	8	3939

MOTOR ACTIVITY TEST
FEMALES
WEEK 4

Animal number	Location of sensor	Counts per sample period (hour) 1	2	3	4	5	6	7	8	9	10	11	12	Total
GROUP 1 (CONTROL)														
31	High	207	134	193	207	99	26	76	38	5	177	116	170	1448
31	Low	692	527	403	568	218	102	233	202	65	478	498	563	4549
32	High	337	337	470	761	1254	1371	1329	1475	972	446	243	291	9286
32	Low	689	604	664	1019	1629	1415	1586	1607	1485	656	372	646	12372
33	High	184	109	194	386	387	124	5	138	55	252	248	192	2274
33	Low	533	294	459	1074	797	682	90	597	288	731	674	294	6513
34	High	370	57	362	217	88	13	58	175	167	247	230	376	2360
34	Low	668	196	822	321	252	42	96	336	382	679	583	778	5155
35	High	434	8	77	413	298	157	41	133	281	227	221	193	2483
35	Low	1010	56	194	772	728	366	67	222	649	528	419	350	5361
36	High	4213	1526	660	894	597	146	79	897	236	652	1398	816	12114
36	Low	756	552	275	812	410	162	33	976	412	772	557	68	5785
37	High	431	144	117	45	162	0	7	63	24	88	126	81	1288
37	Low	908	265	567	131	389	30	48	352	181	410	629	489	4399
38	High	467	211	222	159	14	265	0	132	281	138	166	142	2197
38	Low	802	489	419	375	11	596	0	93	442	429	493	554	4703
39	High	354	567	441	400	346	391	58	346	128	198	176	234	3639
39	Low	773	530	343	471	451	426	58	577	406	330	485	452	5302
40	High	410	5	185	130	344	265	12	61	116	156	340	465	2489
40	Low	1047	65	575	712	418	392	115	248	423	893	646	700	6234
GROUP 2 (15 MG/KG)														
41	High	497	309	313	389	514	536	616	337	260	236	168	390	4565
41	Low	680	550	584	584	608	726	881	687	423	417	417	700	7257
42	High	184	136	104	66	401	212	10	63	246	278	193	336	2231
42	Low	611	203	445	217	757	445	14	135	672	444	499	1274	5716
43	High	223	111	137	238	251	126	5	120	306	276	174	146	2117
43	Low	448	201	375	673	468	216	16	55	483	401	291	422	4049
44	High	260	418	300	884	161	290	0	39	183	593	236	85	3449
44	Low	630	560	203	1159	193	382	7	37	823	657	452	276	5379
45	High	184	12	61	214	220	191	0	18	219	90	161	158	1528
45	Low	393	189	361	1037	472	492	33	122	454	487	456	363	4859
GROUP 3 (50 MG/KG)														
46	High	273	28	159	202	112	15	155	12	1	1	216	184	1358
46	Low	431	131	564	318	374	88	383	34	24	66	502	378	3293
47	High	285	99	254	162	329	186	59	0	42	213	208	0	1837
47	Low	408	413	623	404	1068	621	201	41	294	869	616	55	5613
48	High	247	90	382	435	208	29	109	323	72	242	148	1	2286
48	Low	411	325	642	787	416	78	276	400	346	472	356	23	4534
49	High	221	194	46	317	240	0	0	2	113	250	260	44	1687
49	Low	1023	514	136	992	560	115	31	36	326	970	693	424	5822
50	High	198	15	137	92	81	86	0	20	189	164	0	63	1045
50	Low	567	77	478	405	321	196	18	107	436	660	19	247	3531

MOTOR ACTIVITY TEST
FEMALES
WEEK 4

Animal number	Location of sensor	Counts per sample period (hour) 1	2	3	4	5	6	7	8	9	10	11	12	Total
GROUP 4 (150 MG/KG)														
51	High	295	116	47	96	265	59	133	0	3	73	63	27	1177
51	Low	684	339	209	515	497	322	376	90	131	357	248	130	3898
52	High	5310	2907	2017	743	1597	1791	1263	1122	633	1048	1428	1282	21141
52	Low	650	688	675	604	747	1207	930	553	489	358	635	550	8086
53	High	181	232	44	100	156	42	52	11	127	145	157	155	1402
53	Low	757	259	207	179	377	309	542	21	336	161	432	371	3951
54	High	190	251	302	421	269	625	104	233	259	428	250	261	3593
54	Low	341	443	555	527	314	341	118	249	281	397	477	232	4275
55	High	246	82	86	121	157	103	1	4	2	27	34	17	880
55	Low	548	202	138	323	257	497	70	74	52	197	255	152	2765
56	High	301	26	72	8	36	16	21	37	0	115	127	0	763
56	Low	1336	264	330	32	454	385	258	171	83	395	641	115	4464
57	High	600	632	630	613	642	424	217	295	337	267	244	28	5329
57	Low	847	775	801	821	619	650	421	416	506	317	462	192	6827
58	High	313	352	157	651	36	10	42	103	398	2	33	59	2136
58	Low	404	235	164	375	33	42	71	311	557	18	115	210	2535
59	High	352	244	181	39	78	0	24	116	35	54	96	123	1342
59	Low	1288	496	626	165	335	0	131	403	189	319	634	317	4903
60	High	450	66	106	57	108	58	4	139	165	147	135	160	1615
60	Low	553	419	219	334	248	164	121	216	255	529	944	418	4440

BODY WEIGHTS (GRAM)
MALES

	TREATMENT					RECOVERY		
DAYS	1	8	15	22	28	1	8	14
WEEKS	1	2	3	4	4	1	2	2
ANIMAL								
GROUP 1 (CONTROL)								
1	260	302	341	371	382	---	---	---
2	246	289	321	346	359	---	---	---
3	266	303	338	363	371	---	---	---
4	265	307	343	374	374	---	---	---
5	278	319	339	368	388	---	---	---
6	278	326	372	403	416	395	455	476
7	262	308	337	353	372	351	398	400
8	287	329	360	386	417	386	437	446
9	245	283	314	332	347	327	381	383
10	270	323	352	378	400	384	425	428
GROUP 2 (15 MG/KG)								
11	282	325	370	390	414			
12	246	295	330	353	369			
13	276	321	377	407	438			
14	256	287	321	344	368			
15	266	316	354	377	399			
GROUP 3 (50 MG/KG)								
16	242	283	315	329	346			
17	287	337	373	405	429			
18	278	323	379	405	434			
19	263	300	327	346	366			
20	250	288	321	340	357			
GROUP 4 (150 MG/KG)								
21	252	268	304	325	335	---	---	---
22	262	281	323	354	367	---	---	---
23	248	287	319	346	355	---	---	---
24	285	307	343	362	375	---	---	---
25	275	319	352	385	411	---	---	---
26	273	304	341	364	380	358	406	413
27	254	286	326	352	363	346	387	399
28	287	329	368	390	416	395	446	453
29	274	316	353	375	397	381	417	428
30	270	294	341	372	390	380	429	434

FEMALES

	TREATMENT					RECOVERY		
DAYS	1	8	15	22	28	1	8	14
WEEKS	1	2	3	4	4	1	2	2
ANIMAL								
GROUP 1 (CONTROL)								
31	165	179	192	198	204	---	---	---
32	194	214	218	233	248	---	---	---
33	194	216	238	240	258	---	---	---
34	199	228	249	254	269	---	---	---
35	206	225	260	279	288	---	---	---
36	194	196	216	230	242	223	248	254
37	201	219	236	246	249	236	260	261
38	177	198	209	217	225	205	238	234
39	206	201	214	231	248	232	253	251
40	196	204	226	220	248	228	251	246

BODY WEIGHTS (GRAM)
FEMALES

	TREATMENT					RECOVERY		
DAYS	1	8	15	22	28	1	8	14
WEEKS	1	2	3	4	4	1	2	2
ANIMAL								
GROUP 2 (15 MG/KG)								
41	194	202	234	243	249			
42	177	203	215	231	239			
43	187	206	225	231	245			
44	193	214	227	239	245			
45	195	209	226	222	239			
GROUP 3 (50 MG/KG)								
46	204	221	235	253	261			
47	174	192	209	212	225			
48	196	216	237	241	252			
49	195	219	241	246	256			
50	165	182	198	205	213			
GROUP 4 (150 MG/KG)								
51	193	205	227	239	242	---	---	---
52	189	187	201	219	232	---	---	---
53	210	222	256	264	282	---	---	---
54	188	209	233	249	251	---	---	---
55	181	191	217	221	232	---	---	---
56	192	200	229	242	251	244	268	267
57	183	191	208	221	232	221	241	236
58	199	216	235	237	253	240	254	244
59	175	178	199	203	206	200	213	211
60	202	214	242	251	262	247	265	292

BODY WEIGHT GAIN (%)
MALES

	TREATMENT					RECOVERY		
DAYS	1	8	15	22	28	1	8	14
WEEKS	1	2	3	4	4	1	2	2
ANIMAL								
GROUP 1 (CONTROL)								
1	0	16	31	43	47	---	---	---
2	0	17	30	41	46	---	---	---
3	0	14	27	36	39	---	---	---
4	0	16	29	41	41	---	---	---
5	0	15	22	32	40	---	---	---
6	0	17	34	45	50	42	64	71
7	0	18	29	35	42	34	52	53
8	0	15	25	34	45	34	52	55
9	0	16	28	36	42	33	56	56
10	0	20	30	40	48	42	57	59
GROUP 2 (15 MG/KG)								
11	0	15	31	38	47			
12	0	20	34	43	50			
13	0	16	37	47	59			
14	0	12	25	34	44			
15	0	19	33	42	50			
GROUP 3 (50 MG/KG)								
16	0	17	30	36	43			
17	0	17	30	41	49			
18	0	16	36	46	56			
19	0	14	24	32	39			
20	0	15	28	36	43			
GROUP 4 (150 MG/KG)								
21	0	6	21	29	33	---	---	---
22	0	7	23	35	40	---	---	---
23	0	16	29	40	43	---	---	---
24	0	8	20	27	32	---	---	---
25	0	16	28	40	49	---	---	---
26	0	11	25	33	39	31	49	51
27	0	13	28	39	43	36	52	57
28	0	15	28	36	45	38	55	58
29	0	15	29	37	45	39	52	56
30	0	9	26	38	44	41	59	61

FEMALES

	TREATMENT					RECOVERY		
DAYS	1	8	15	22	28	1	8	14
WEEKS	1	2	3	4	4	1	2	2
ANIMAL								
GROUP 1 (CONTROL)								
31	0	8	16	20	24	---	---	---
32	0	10	12	20	28	---	---	---
33	0	11	23	24	33	---	---	---
34	0	15	25	28	30	---	---	---
35	0	9	26	35	40	---	---	---
36	0	1	11	19	25	15	28	31
37	0	9	17	22	24	17	29	30
38	0	12	18	23	27	16	34	32
39	0	-2	4	12	20	13	23	22
40	0	3	14	11	25	15	27	24

BODY WEIGHT GAIN (%)
FEMALES

	TREATMENT					RECOVERY		
DAYS	1	8	15	22	28	1	8	14
WEEKS	1	2	3	4	4	1	2	2
ANIMAL								
GROUP 2 (15 MG/KG)								
41	0	4	21	25	28			
42	0	15	21	31	35			
43	0	10	20	24	31			
44	0	11	18	24	27			
45	0	7	16	14	23			
GROUP 3 (50 MG/KG)								
46	0	8	15	24	28			
47	0	10	20	22	29			
48	0	10	21	23	29			
49	0	12	24	26	31			
50	0	10	20	24	29			
GROUP 4 (150 MG/KG)								
51	0	6	18	24	25	---	---	---
52	0	-1	6	16	23	---	---	---
53	0	6	22	26	34	---	---	---
54	0	11	24	32	34	---	---	---
55	0	6	20	22	28	---	---	---
56	0	4	19	26	31	27	40	39
57	0	4	14	21	27	21	32	29
58	0	9	18	19	27	21	28	23
59	0	2	14	16	18	14	22	21
60	0	6	20	24	30	22	31	45

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

	TREATMENT				RECOVERY	
DAYS	1-8	8-15	15-22	22-28	1-8	8-14
WEEKS	1-2	2-3	3-4	4	1-2	2
CAGE						
GROUP 1 (CONTROL)						
1	28	28	28	29	---	---
2	29	30	30	31	36	31
GROUP 2 (15 MG/KG)						
3	28	30	29	30		
GROUP 3 (50 MG/KG)						
4	28	28	28	30		
GROUP 4 (150 MG/KG)						
5	24	28	29	30	---	---
6	25	29	29	31	36	31

FEMALES

	TREATMENT				RECOVERY	
DAYS	1-8	8-15	15-22	22-28	1-8	8-14
WEEKS	1-2	2-3	3-4	4	1-2	2
CAGE						
GROUP 1 (CONTROL)						
7	21	23	22	23	---	---
8	19	20	21	22	22	20
GROUP 2 (15 MG/KG)						
9	19	21	21	22		
GROUP 3 (50 MG/KG)						
10	19	20	21	21		
GROUP 4 (150 MG/KG)						
11	18	21	21	21	---	---
12	16	20	20	21	21	19

RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY)
MALES

	TREATMENT				RECOVERY	
DAYS	1-8	8-15	15-22	22-28	1-8	8-14
WEEKS	1-2	2-3	3-4	4	1-2	2
CAGE						
GROUP 1 (CONTROL)						
1	93	85	77	78	---	---
2	94	85	80	79	86	72
GROUP 2 (15 MG/KG)						
3	90	84	78	77		
GROUP 3 (50 MG/KG)						
4	90	83	77	77		
GROUP 4 (150 MG/KG)						
5	80	85	83	80	---	---
6	81	83	80	79	85	72

FEMALES

	TREATMENT				RECOVERY	
DAYS	1-8	8-15	15-22	22-28	1-8	8-14
WEEKS	1-2	2-3	3-4	4	1-2	2
CAGE						
GROUP 1 (CONTROL)						
7	100	97	92	93	---	---
8	92	90	90	89	86	80
GROUP 2 (15 MG/KG)						
9	94	95	89	92		
GROUP 3 (50 MG/KG)						
10	94	91	89	88		
GROUP 4 (150 MG/KG)						
11	87	90	88	85	---	---
12	82	90	87	86	84	75

HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	WBC 10E9/l	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
1	13.6	10 3	84 5	3.4	1.3
2	12.7	11.0	82.0	4 0	3.0
3	10 7	10 5	85 0	2.0	2.2
4	11.9	15.9	78 6	3.6	1.6
5	14.6	19.8	73.8	3 5	2.4
6	10.9	12.4	81 4	4.0	1.9
7	12 3	16 4	77.3	3.8	2.1
8	13 2	15 4	80 4	2.7	1.2
9	11 4	19.0	77.0	3 0	1.0
10	8 9	16.1	79 5	2 4	1.6
GROUP 2 (15 MG/KG)					
11	9.0	12.0	86.0	2 0	0.0
12	13.6	9 8	86.8	2 0	1.0
13	10.8	14.0	80.0	6 0	0.0
14	15.0	14.6	81.6	2.4	1.2
15	11.3	8.7	85.7	3.2	1.9
GROUP 3 (50 MG/KG)					
16	14.3	12 3	83.9	2.2	1 1
17	9.7	13 6	81.3	3.5	1.3
18	9.8	13.4	82.5	2.8	0 9
19	13.6	17.0	77.0	6.0	0 0
20	16.6	22.9	71.0	4 7	0.9
GROUP 4 (150 MG/KG)					
21	9 6	18.6	77.1	3 0	1.1
22	13.5	27.5	66.4	4.2	1 4
23	18.1	17 6	77 3	3.5	1.2
24	12.2	20 3	74.4	3.7	1.2
25	11.7	17.2	78.5	1.9	2.2
26	11.4	22.2	71.8	4.0	1 5
27	12.4	23.3	71.2	3 6	1 7
28	7.6	16.3	78.5	3.5	1.7
29	13.3	11.9	83.5	2 7	1.5
30	11.5	19.9	76.1	2 1	1.7

MALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 1 (CONTROL)					
1	0.4	8.04	2.5	12 0	9.3
2	0.0	8.01	2.2	12.2	9 4
3	0.3	8.77	1.7	11.5	9.7
4	0.3	8.61	2.2	12.8	9.7
5	0.5	8.19	2.2	11 7	9.6
6	0.4	8.49	2.0	11 7	9.7
7	0.4	7.93	2.4	11.7	9.7
8	0.3	8 17	2.3	11.8	9.6
9	0 0	8.47	2.0	12.6	9.5
10	0.3	8.64	2 3	12 3	9.4

HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 2 (15 MG/KG)					
11	0.0	8.44	2.3	12.7	9.2
12	0 3	8 05	2 3	13 0	9.2
13	0 0	7 37	2 2	11.8	9.0
14	0 2	8 03	2 1	12.3	8.8
15	0.4	8.58	1 6	12.0	9.5
GROUP 3 (50 MG/KG)					
16	0 4	8 49	1.8	12.3	9.2
17	0 4	8 07	2.3	11.9	9.3
18	0 3	8.50	1.7	12.2	9.3
19	0 0	8.33	1.8	11.9	9 7
20	0.4	8 17	2 3	12.8	8 7
GROUP 4 (150 MG/KG)					
21	0.3	9 24	1 9	12.3	10.0
22	0 4	8 14	1.9	12.3	9.3
23	0.4	8 52	1 9	11.9	9.6
24	0.4	9.15	1.8	12.3	9.5
25	0.2	8 41	2 1	12 2	9.7
26	0.5	8.46	1.8	13.3	9.2
27	0.2	8.33	2.6	12.7	9.2
28	0.2	8.28	2.4	12.9	9.1
29	0.4	8 44	1.7	12.2	9 2
30	0.3	8.44	2.1	12.5	9.2

MALES
END OF TREATMENT

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 1 (CONTROL)					
1	0.449	55.9	1 16	20.77	1171
2	0 461	57.6	1.17	20.30	891
3	0 491	56 0	1 11	19.87	1057
4	0 463	53 8	1 12	20.84	895
5	0 456	55 7	1 17	20.94	638
6	0 483	56 8	1.15	20.16	969
7	0 476	60 1	1.23	20.43	1010
8	0.474	58 0	1 17	20.18	828
9	0.474	56 0	1 12	20.02	669
10	0.462	53 5	1 09	20.31	936
GROUP 2 (15 MG/KG)					
11	0.451	53.5	1 08	20 26	907
12	0.460	57.1	1.15	20.07	1193
13	0 431	58 4	1 22	20 86	579
14	0 431	53 6	1.10	20.43	978
15	0.465	54 2	1 11	20 53	1274
GROUP 3 (50 MG/KG)					
16	0.447	52 7	1 08	20 50	1210
17	0.459	56 9	1 16	20.34	869
18	0 450	52.9	1.09	20.60	973
19	0.483	57 9	1 16	20 03	726
20	0.441	54 0	1 07	19.74	1261

HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 4 (150 MG/KG)					
21	0.484	52.4	1.08	20.64	922
22	0.456	56.0	1.14	20.30	1184
23	0.468	54.9	1.13	20.52	1405
24	0.474	51.8	1.04	20.11	946
25	0.472	56.1	1.15	20.53	1222
26	0.463	54.8	1.09	19.87	922
27	0.462	55.5	1.11	19.98	835
28	0.445	53.8	1.10	20.36	949
29	0.450	53.4	1.09	20.35	1106
30	0.449	53.2	1.09	20.55	883

MALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
1	16.7	12.9
2	15.7	13.6
3	16.5	12.1
4	16.9	14.1
5	15.5	12.5
6	16.9	15.2
7	16.4	13.3
8	---	---
9	15.1	14.0
10	17.4	15.3
GROUP 2 (15 MG/KG)		
11	16.7	15.4
12	18.1	19.2
13	---	---
14	16.0	13.0
15	17.7	17.6
GROUP 3 (50 MG/KG)		
16	16.5	15.0
17	17.2	14.6
18	16.8	14.7
19	16.0	17.8
20	16.6	13.6
GROUP 4 (150 MG/KG)		
21	---	---
22	16.6	14.4
23	17.1	14.7
24	16.5	14.5
25	17.0	16.0
26	17.1	16.6
27	---	---
28	17.5	14.8
29	16.9	16.7
30	17.8	14.7

HAEMATOLOGY
MALES
END OF RECOVERY

ANIMAL	WBC 10E9/l	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
6	11.9	16.8	76.1	4.8	1.9
7	11.9	21.3	71.3	4.0	3.0
8	12.4	19.1	74.4	4.3	1.9
9	11.9	13.0	83.0	4.0	0.0
10	9.6	20.8	73.4	3.9	1.7
GROUP 4 (150 MG/KG)					
26	11.5	22.6	71.3	3.9	1.9
27	10.7	26.8	68.1	3.8	1.0
28	6.4	14.7	79.6	3.5	2.0
29	15.3	13.7	80.4	4.4	1.1
30	10.0	25.0	70.0	4.0	1.0

MALES
END OF RECOVERY

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 1 (CONTROL)					
6	0.4	8.62	2.9	12.6	9.9
7	0.4	8.23	2.6	12.8	10.0
8	0.4	8.15	2.7	12.6	9.5
9	0.0	8.23	3.0	13.6	9.2
10	0.3	8.95	2.5	13.2	9.4
GROUP 4 (150 MG/KG)					
26	0.3	8.41	2.7	15.1	9.3
27	0.3	8.35	3.1	14.1	9.3
28	0.3	8.16	3.0	14.6	9.1
29	0.3	8.27	2.8	13.1	9.0
30	0.0	8.31	3.4	14.2	9.2

MALES
END OF RECOVERY

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 1 (CONTROL)					
6	0.474	55.0	1.14	20.79	1044
7	0.486	59.0	1.21	20.53	1090
8	0.464	56.9	1.16	20.39	804
9	0.451	54.8	1.11	20.32	784
10	0.462	51.7	1.05	20.37	932
GROUP 4 (150 MG/KG)					
26	0.460	54.8	1.11	20.30	1078
27	0.459	55.0	1.11	20.18	881
28	0.436	53.4	1.12	20.91	1072
29	0.431	52.1	1.08	20.80	1076
30	0.435	52.3	1.10	21.05	679

HAEMATOLOGY
MALES
END OF RECOVERY

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
6	17.2	15.5
7	18.6	18.4
8	18.1	19.3
9	17.6	15.2
10	18.6	18.1
GROUP 4 (150 MG/KG)		
26	---	---
27	16.3	11.6
28	17.2	14.5
29	17.9	17.3
30	---	---

FEMALES
END OF TREATMENT

ANIMAL	WBC 10E9/l	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
31	7.1	11.9	83.4	2.1	2.4
32	7.3	6.9	88.9	1.7	2.2
33	6.5	9.0	86.5	2.1	2.0
34	8.8	12.2	85.0	1.5	1.2
35	7.5	8.0	85.6	3.6	2.4
36	8.0	7.0	89.2	1.5	2.1
37	7.9	9.1	86.9	2.0	1.9
38	6.6	12.9	81.0	4.1	1.8
39	5.5	9.6	85.8	1.7	2.6
40	4.7	10.1	85.4	2.2	1.7
GROUP 2 (15 MG/KG)					
41	8.5	7.3	87.5	2.5	2.3
42	5.2	25.6	71.0	1.7	1.3
43	10.9	16.0	80.0	3.0	1.0
44	6.2	20.8	74.3	2.9	1.7
45	5.0	14.3	79.9	3.5	2.1
GROUP 3 (50 MG/KG)					
46	6.5	12.2	81.8	3.6	2.1
47	10.3	16.5	79.0	2.8	1.5
48	6.5	22.3	70.4	5.2	1.9
49	7.1	13.2	82.8	2.0	1.9
50	5.7	21.7	74.7	1.6	1.8
GROUP 4 (150 MG/KG)					
51	9.8	12.7	83.1	2.1	1.7
52	10.5	11.8	82.9	3.0	1.9
53	9.9	10.9	83.0	4.3	1.5
54	6.9	13.6	78.4	5.0	2.5
55	8.3	10.0	83.4	4.1	2.2
56	7.0	22.5	67.5	7.0	3.0
57	10.0	23.0	70.7	4.2	2.1
58	6.2	24.8	70.1	2.9	1.8
59	7.7	11.7	83.3	2.9	1.9
60	12.8	11.7	81.8	4.4	1.6

HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 1 (CONTROL)					
31	0.2	7.94	2.8	12.0	8.9
32	0.3	7.12	2.4	11.4	8.4
33	0.3	7.41	2.7	12.0	8.7
34	0.2	7.40	2.8	12.4	8.4
35	0.4	8.02	1.5	11.6	9.0
36	0.2	7.67	1.8	11.6	8.1
37	0.1	7.47	2.2	11.6	8.9
38	0.2	7.53	3.8	13.6	8.4
39	0.2	7.61	2.6	12.5	8.7
40	0.6	7.54	2.7	11.9	8.6
GROUP 2 (15 MG/KG)					
41	0.3	7.90	1.9	12.8	9.0
42	0.3	7.73	2.7	12.3	8.7
43	0.0	7.58	2.2	11.9	9.0
44	0.4	7.71	2.7	11.9	8.5
45	0.2	7.85	2.3	12.5	8.3
GROUP 3 (50 MG/KG)					
46	0.3	7.26	1.7	11.5	8.6
47	0.3	7.60	4.0	12.5	8.7
48	0.3	7.81	2.8	12.7	8.7
49	0.1	7.44	2.1	13.0	8.1
50	0.1	7.60	3.3	11.7	8.5
GROUP 4 (150 MG/KG)					
51	0.4	8.19	1.9	12.6	9.1
52	0.3	8.01	2.0	11.7	9.3
53	0.4	7.67	1.9	11.6	8.9
54	0.4	8.50	2.1	12.0	9.3
55	0.4	8.14	2.0	12.7	9.0
56	0.1	7.30	2.4	12.5	8.4
57	0.1	7.98	1.9	12.0	8.6
58	0.4	7.87	2.8	13.5	8.5
59	0.3	8.32	1.5	11.5	8.9
60	0.4	7.84	2.2	11.9	9.1

FEMALES
END OF TREATMENT

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 1 (CONTROL)					
31	0.434	54.7	1.12	20.47	878
32	0.398	55.9	1.18	21.17	807
33	0.422	57.0	1.17	20.49	886
34	0.409	55.3	1.13	20.46	994
35	0.436	54.3	1.12	20.65	1038
36	0.411	53.5	1.06	19.73	1220
37	0.435	58.2	1.19	20.36	1178
38	0.418	55.5	1.12	20.20	1040
39	0.417	54.7	1.14	20.77	904
40	0.421	55.8	1.14	20.46	895

HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 2 (15 MG/KG)					
41	0.431	54.5	1.14	20.86	863
42	0.426	55.0	1.12	20.36	930
43	0.433	57.2	1.18	20.68	963
44	0.422	54.7	1.10	20.09	948
45	0.403	51.3	1.06	20.66	1210
GROUP 3 (50 MG/KG)					
46	0.415	57.2	1.18	20.64	1209
47	0.432	56.9	1.15	20.23	1011
48	0.432	55.3	1.11	20.10	802
49	0.402	54.0	1.09	20.19	921
50	0.423	55.7	1.12	20.04	954
GROUP 4 (150 MG/KG)					
51	0.448	54.7	1.11	20.25	1204
52	0.452	56.4	1.16	20.65	865
53	0.427	55.7	1.16	20.87	1009
54	0.459	53.9	1.09	20.25	977
55	0.442	54.3	1.10	20.34	998
56	0.419	57.3	1.15	20.10	1073
57	0.426	53.4	1.08	20.20	1275
58	0.420	53.3	1.08	20.22	1024
59	0.444	53.4	1.07	19.95	817
60	0.431	54.9	1.15	21.02	1022

FEMALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
31	18.1	15.4
32	17.0	13.4
33	17.3	13.3
34	17.4	19.0
35	16.4	13.8
36	16.5	12.7
37	16.7	15.5
38	16.4	17.6
39	15.9	12.8
40	16.6	14.2
GROUP 2 (15 MG/KG)		
41	16.4	16.9
42	16.0	14.7
43	17.7	15.3
44	16.1	14.6
45	16.4	13.6
GROUP 3 (50 MG/KG)		
46	17.0	16.4
47	16.4	14.1
48	16.0	15.0
49	17.0	15.9
50	16.1	17.9

HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 4 (150 MG/KG)		
51	16.2	16.0
52	16.1	16.4
53	16.4	14.0
54	16.3	14.6
55	16.4	16.0
56	16.3	14.9
57	17.5	16.1
58	15.2	13.7
59	15.1	11.5
60	16.1	16.9

FEMALES
END OF RECOVERY

ANIMAL	WBC 10E9/l	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
36	7.9	8.6	86.6	2.3	2.1
37	8.8	6.3	89.0	2.8	1.6
38	10.8	10.9	82.8	4.3	1.7
39	5.5	15.2	80.5	2.0	2.0
40	5.3	10.4	85.1	2.2	1.9
GROUP 4 (150 MG/KG)					
56	5.3	15.6	76.7	5.4	2.0
57	6.1	13.9	82.2	2.2	1.4
58	5.9	16.0	78.3	2.9	2.6
59	6.3	11.8	83.3	2.6	1.9
60	9.6	12.8	81.6	4.2	1.1

FEMALES
END OF RECOVERY

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 1 (CONTROL)					
36	0.4	7.91	2.1	13.7	8.5
37	0.3	7.54	2.7	12.8	9.1
38	0.3	8.45	1.8	13.9	9.7
39	0.3	7.33	3.1	13.7	8.4
40	0.3	8.04	1.5	12.6	9.1
GROUP 4 (150 MG/KG)					
56	0.3	7.40	1.6	12.6	8.7
57	0.2	7.81	2.2	13.1	8.6
58	0.3	7.87	2.2	14.1	8.7
59	0.4	8.14	2.5	13.8	8.9
60	0.3	8.02	2.7	13.4	9.1

HAEMATOLOGY
FEMALES
END OF RECOVERY

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 1 (CONTROL)					
36	0.427	54.0	1.07	19.82	1204
37	0.447	59.3	1.21	20.46	1056
38	0.476	56.3	1.15	20.44	1111
39	0.407	55.5	1.15	20.77	1131
40	0.448	55.8	1.13	20.32	923
GROUP 4 (150 MG/KG)					
56	0.415	56.1	1.18	20.96	1047
57	0.416	53.3	1.10	20.59	1076
58	0.423	53.8	1.11	20.56	852
59	0.441	54.1	1.09	20.14	891
60	0.440	54.9	1.14	20.75	1379

FEMALES
END OF RECOVERY

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
36	19.4	14.7
37	18.6	16.3
38	17.6	12.6
39	17.8	13.6
40	17.3	14.4
GROUP 4 (150 MG/KG)		
56	16.9	15.4
57	19.0	15.3
58	17.1	13.0
59	18.6	16.0
60	18.7	17.7

CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	ALAT U/l	ASAT U/l	ALP U/l	Total protein g/l	Albumin g/l
GROUP 1 (CONTROL)					
1	35.7	81.1	129	62.4	31.4
2	50.8	79.8	135	63.0	30.9
3	39.6	76.4	90	63.3	31.3
4	32.9	74.9	109	61.8	31.2
5	49.1	85.5	116	65.9	31.2
6	42.6	72.0	98	61.0	30.0
7	48.9	79.4	169	62.5	31.6
8	42.7	70.0	123	63.5	31.6
9	46.4	89.2	126	62.3	30.5
10	44.8	67.7	101	59.8	29.7
GROUP 2 (15 MG/KG)					
11	32.3	69.9	88	64.1	31.4
12	33.2	73.7	123	58.6	30.3
13	52.2	90.9	101	61.4	30.0
14	44.0	75.5	119	59.0	28.9
15	33.5	65.7	91	59.0	28.8
GROUP 3 (50 MG/KG)					
16	31.6	67.8	88	60.1	29.0
17	43.5	73.5	87	62.7	30.9
18	41.2	69.5	95	62.9	30.8
19	37.8	84.0	110	61.9	30.1
20	33.5	65.6	106	57.5	28.4
GROUP 4 (150 MG/KG)					
21	58.4	89.4	111	61.4	30.3
22	65.7	75.1	136	62.1	30.8
23	80.3	77.3	140	61.1	30.9
24	69.5	84.7	115	59.0	30.2
25	54.4	65.4	146	62.4	30.3
26	38.0	88.9	114	59.8	29.9
27	75.3	117.2	140	64.6	31.0
28	59.8	78.4	136	62.6	30.4
29	44.0	84.4	116	63.9	30.8
30	51.0	67.7	136	57.7	28.1

MALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 1 (CONTROL)					
1	2.5	5.8	41.9	6.60	1.99
2	2.7	7.9	38.3	6.49	1.78
3	3.3	5.9	38.3	7.24	1.33
4	2.8	5.7	41.2	5.96	1.42
5	3.0	5.0	39.0	6.86	1.97
6	2.7	7.1	39.0	8.64	2.14
7	3.5	6.1	40.5	8.43	1.90
8	2.7	5.0	39.0	10.76	2.26
9	3.0	4.4	40.5	6.18	2.30
10	2.8	8.2	42.6	9.34	1.56

CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 2 (15 MG/KG)					
11	3.4	4.6	36.9	7.53	1.89
12	3.1	4.7	36.2	9.91	1.57
13	3.4	6.1	38.3	10.78	1.96
14	3.0	6.0	39.0	7.23	1.53
15	2.5	5.7	36.9	8.67	1.85
GROUP 3 (50 MG/KG)					
16	2.8	4.7	34.8	8.61	1.74
17	2.6	6.7	39.7	9.33	2.14
18	2.5	8.0	40.5	9.79	2.26
19	3.1	5.9	41.9	6.79	2.52
20	1.9	6.7	37.6	10.48	1.34
GROUP 4 (150 MG/KG)					
21	2.8	8.2	44.7	7.90	1.85
22	2.8	7.5	39.0	8.06	1.80
23	2.6	9.8	39.7	7.54	1.89
24	3.6	5.5	38.3	7.05	1.38
25	3.1	7.0	38.3	9.04	1.86
26	2.8	6.0	39.0	7.39	1.28
27	3.3	6.6	43.3	7.19	2.39
28	2.7	6.0	39.0	9.10	1.66
29	3.0	7.6	42.6	8.85	2.37
30	3.1	6.8	39.0	10.14	2.13

MALES
END OF TREATMENT

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 1 (CONTROL)					
1	133.9	3.85	98	2.72	2.26
2	134.6	4.09	100	2.71	2.18
3	135.2	3.98	99	2.73	2.10
4	136.2	3.83	100	2.66	2.15
5	134.6	4.11	99	2.79	2.21
6	135.3	4.26	100	2.71	2.27
7	134.6	4.28	99	2.72	2.22
8	135.0	4.26	99	2.75	2.02
9	137.2	3.86	100	2.71	2.17
10	134.8	4.31	98	2.71	2.32
GROUP 2 (15 MG/KG)					
11	134.8	4.11	99	2.72	2.19
12	134.8	4.25	99	2.69	1.86
13	133.5	4.69	98	2.71	2.19
14	135.3	4.16	99	2.63	2.28
15	134.1	4.18	99	2.72	2.09
GROUP 3 (50 MG/KG)					
16	136.2	3.93	98	2.74	2.19
17	133.9	4.39	96	2.82	2.33
18	135.1	4.40	97	2.76	2.40
19	135.5	4.13	98	2.69	2.28
20	133.9	4.14	98	2.68	2.17

CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 4 (150 MG/KG)					
21	134.3	4.53	94	2.76	2.27
22	133.2	4.93	94	2.83	2.24
23	132.1	4.39	95	2.81	2.18
24	135.8	4.33	96	2.73	2.22
25	134.2	4.35	95	2.78	2.32
26	136.1	4.31	96	2.62	2.56
27	134.5	4.72	95	2.74	2.33
28	133.4	4.32	94	2.72	2.41
29	135.0	4.37	94	2.70	2.57
30	135.2	4.30	96	2.70	2.19

MALES
END OF RECOVERY

ANIMAL	ALAT U/l	ASAT U/l	ALP U/l	Total protein g/l	Albumin g/l
GROUP 1 (CONTROL)					
6	48.5	77.1	102	64.6	32.3
7	48.8	76.3	132	62.7	32.2
8	42.4	75.9	102	63.4	31.4
9	44.8	93.0	113	59.7	29.7
10	48.0	71.6	91	58.5	29.6
GROUP 4 (150 MG/KG)					
26	31.9	90.0	103	60.5	31.4
27	42.1	88.3	108	62.5	30.5
28	47.1	84.1	107	62.2	30.8
29	42.3	74.7	93	61.9	30.9
30	40.5	95.9	102	56.3	28.3

MALES
END OF RECOVERY

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 1 (CONTROL)					
6	2.6	6.5	40.3	7.36	1.90
7	3.4	5.2	39.6	7.47	1.88
8	2.6	4.4	38.8	7.83	2.19
9	3.1	4.4	38.8	6.00	2.20
10	2.5	6.8	42.5	7.43	1.54
GROUP 4 (150 MG/KG)					
26	3.3	4.4	40.3	7.74	1.07
27	3.1	4.1	39.6	6.09	2.10
28	2.8	4.7	38.8	6.63	1.58
29	2.5	6.6	39.6	7.83	2.43
30	3.0	5.5	37.4	8.78	2.18

CLINICAL BIOCHEMISTRY
MALES
END OF RECOVERY

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 1 (CONTROL)					
6	135.6	4.03	98	2.78	2.29
7	135.8	4.18	99	2.78	2.03
8	135.8	4.06	100	2.82	1.90
9	137.6	3.75	100	2.69	2.10
10	133.5	4.18	98	2.68	2.14
GROUP 4 (150 MG/KG)					
26	136.1	4.33	100	2.67	2.16
27	136.0	4.02	101	2.73	1.82
28	136.4	4.04	99	2.76	2.18
29	135.9	4.02	99	2.78	2.25
30	134.8	4.28	100	2.74	2.05

FEMALES
END OF TREATMENT

ANIMAL	ALAT U/l	ASAT U/l	ALP U/l	Total protein g/l	Albumin g/l
GROUP 1 (CONTROL)					
31	38.0	69.7	55	62.2	32.6
32	33.1	71.9	76	59.8	30.6
33	33.9	82.9	67	58.1	29.3
34	27.8	87.5	84	61.5	31.5
35	38.3	81.6	84	61.8	30.3
36	30.9	68.8	65	57.4	29.0
37	37.4	63.6	80	64.5	32.3
38	29.2	84.1	92	60.4	31.5
39	37.6	68.7	50	61.6	31.7
40	50.8	65.9	77	58.0	29.8
GROUP 2 (15 MG/KG)					
41	44.0	74.4	112	63.3	32.4
42	34.9	80.3	85	61.3	30.7
43	54.2	85.9	101	58.3	29.5
44	37.2	60.4	66	63.5	30.7
45	50.9	87.9	55	59.7	29.5
GROUP 3 (50 MG/KG)					
46	37.6	63.1	84	58.3	29.6
47	39.6	73.1	76	63.9	32.5
48	43.0	73.5	72	63.3	31.6
49	27.2	65.7	86	59.1	29.7
50	41.6	70.8	98	60.2	30.6
GROUP 4 (150 MG/KG)					
51	86.5	82.7	80	61.3	30.6
52	63.6	81.3	79	58.4	28.8
53	56.1	75.1	89	58.7	29.0
54	41.7	73.5	108	61.3	30.4
55	48.3	74.0	75	61.6	30.1
56	33.5	55.9	93	65.3	33.6
57	52.2	69.7	77	56.6	29.1
58	55.7	74.3	79	63.3	32.2
59	58.3	81.4	88	58.1	30.1
60	70.0	99.6	119	60.5	29.2

CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 1 (CONTROL)					
31	3.6	5.9	42.6	7.64	1.20
32	3.3	7.2	43.3	6.98	1.49
33	3.1	5.7	41.2	8.61	1.45
34	2.5	6.3	46.1	9.23	1.17
35	3.4	6.7	41.2	6.85	2.10
36	2.6	7.0	41.9	7.63	0.93
37	3.0	5.6	41.2	9.95	1.78
38	3.2	7.9	44.0	7.33	1.45
39	2.8	6.0	43.3	7.11	1.88
40	3.3	6.2	39.0	9.78	1.84
GROUP 2 (15 MG/KG)					
41	3.1	6.3	41.9	9.03	1.98
42	3.0	4.6	39.7	8.51	2.10
43	3.3	5.6	39.0	7.89	1.38
44	2.7	5.9	43.3	11.52	2.10
45	2.6	5.0	40.5	7.95	1.66
GROUP 3 (50 MG/KG)					
46	2.5	6.8	43.3	10.38	1.74
47	4.1	6.4	40.5	8.49	1.94
48	2.8	6.1	46.1	12.03	2.28
49	2.5	7.1	41.9	7.72	1.76
50	2.8	5.2	39.0	11.62	2.11
GROUP 4 (150 MG/KG)					
51	2.9	6.1	36.2	8.67	1.98
52	2.7	7.5	41.9	9.71	1.83
53	2.8	7.0	37.6	8.91	2.29
54	3.4	5.7	39.0	7.89	2.15
55	3.1	5.4	39.0	7.78	2.28
56	3.5	10.2	39.0	8.61	2.12
57	3.4	6.1	38.3	9.68	1.63
58	2.8	5.5	41.2	11.00	2.10
59	3.8	7.7	40.5	8.97	1.60
60	2.7	5.9	36.9	10.34	2.01

FEMALES
END OF TREATMENT

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 1 (CONTROL)					
31	133.9	3.25	100	2.62	1.70
32	133.5	3.71	98	2.59	2.04
33	133.9	3.66	101	2.56	1.96
34	134.8	3.56	101	2.52	1.86
35	134.5	3.58	97	2.63	2.05
36	135.5	3.93	101	2.61	2.14
37	134.0	3.97	99	2.62	2.16
38	135.0	3.61	102	2.48	1.97
39	135.0	4.06	102	2.61	2.00
40	134.0	4.19	101	2.65	2.12

CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 2 (15 MG/KG)					
41	134.7	3.92	100	2.66	1.91
42	134.1	3.59	101	2.57	1.49
43	134.3	3.89	100	2.60	1.85
44	132.3	3.76	100	2.53	1.50
45	134.1	3.62	101	2.54	1.50
GROUP 3 (50 MG/KG)					
46	135.2	3.84	102	2.53	1.66
47	135.8	3.76	101	2.63	2.17
48	134.1	3.88	101	2.65	1.81
49	135.7	3.79	106	2.54	1.74
50	135.2	3.85	101	2.56	1.89
GROUP 4 (150 MG/KG)					
51	133.6	4.28	98	2.73	2.08
52	132.8	4.13	100	2.55	1.88
53	134.3	4.15	98	2.72	2.12
54	131.1	4.22	95	2.73	2.04
55	134.0	4.00	96	2.74	2.12
56	131.0	4.58	95	2.79	2.25
57	133.9	4.01	97	2.71	2.14
58	133.0	3.79	98	2.75	1.76
59	134.2	4.07	97	2.64	2.29
60	133.9	3.63	96	2.73	2.15

FEMALES
END OF RECOVERY

ANIMAL	ALAT U/l	ASAT U/l	ALP U/l	Total protein g/l	Albumin g/l
GROUP 1 (CONTROL)					
36	27.0	71.5	53	58.6	30.6
37	43.4	66.7	55	64.6	32.4
38	43.2	80.1	61	64.1	33.5
39	29.4	73.3	44	62.7	32.9
40	67.0	70.5	77	58.6	30.6
GROUP 4 (150 MG/KG)					
56	23.8	58.8	39	70.8	37.1
57	28.8	80.9	61	58.9	30.5
58	43.8	76.3	58	65.4	33.1
59	37.2	68.1	66	60.5	31.3
60	44.2	77.6	84	60.7	30.3

FEMALES
END OF RECOVERY

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 1 (CONTROL)					
36	3.5	6.0	47.6	6.43	0.56
37	3.8	5.4	51.2	9.67	2.08
38	4.7	6.5	40.3	6.53	1.50
39	3.4	6.3	49.7	7.60	2.02
40	3.4	7.4	42.5	8.33	2.00

CLINICAL BIOCHEMISTRY
FEMALES
END OF RECOVERY

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 4 (150 MG/KG)					
56	4.1	7.1	43.2	6.35	2.23
57	3.1	5.0	41.0	6.80	1.39
58	2.2	5.9	43.9	7.28	1.75
59	3.3	6.5	43.2	8.69	1.33
60	3.0	5.4	39.6	7.84	1.71

FEMALES
END OF RECOVERY

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 1 (CONTROL)					
36	137.6	3.94	102	2.41	1.64
37	135.2	3.81	100	2.65	1.76
38	136.5	3.79	100	2.67	1.89
39	134.3	3.64	103	2.56	1.79
40	134.0	3.86	101	2.69	1.75
GROUP 4 (150 MG/KG)					
56	133.7	3.66	98	2.75	1.46
57	134.9	3.67	103	2.56	1.31
58	135.6	4.08	102	2.77	1.82
59	135.6	3.66	100	2.67	1.78
60	136.2	3.41	99	2.72	1.70

MACROSCOPIC FINDINGS
MALES
ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
1		No findings noted	Scheduled necropsy, 04Aug2006
2		No findings noted	Scheduled necropsy, 04Aug2006
3		No findings noted	Scheduled necropsy, 04Aug2006
4		No findings noted	Scheduled necropsy, 04Aug2006
5		No findings noted	Scheduled necropsy, 04Aug2006
6		No findings noted	Scheduled necropsy, 18Aug2006
7		No findings noted	Scheduled necropsy, 18Aug2006
8		No findings noted	Scheduled necropsy, 18Aug2006
9		No findings noted	Scheduled necropsy, 18Aug2006
10		No findings noted	Scheduled necropsy, 18Aug2006
GROUP 2 (15 MG/KG)			
11		No findings noted	Scheduled necropsy, 04Aug2006
12		No findings noted	Scheduled necropsy, 04Aug2006
13		No findings noted	Scheduled necropsy, 04Aug2006
14		No findings noted	Scheduled necropsy, 04Aug2006
15		No findings noted	Scheduled necropsy, 04Aug2006
GROUP 3 (50 MG/KG)			
16		No findings noted	Scheduled necropsy, 04Aug2006
17		No findings noted	Scheduled necropsy, 04Aug2006
18		No findings noted	Scheduled necropsy, 04Aug2006
19		No findings noted	Scheduled necropsy, 04Aug2006
20		No findings noted	Scheduled necropsy, 04Aug2006
GROUP 4 (150 MG/KG)			
21		No findings noted	Scheduled necropsy, 04Aug2006
22	Kidneys	Pelvic dilation.	Scheduled necropsy, 04Aug2006
23		No findings noted	Scheduled necropsy, 04Aug2006
24		No findings noted	Scheduled necropsy, 04Aug2006
25		No findings noted	Scheduled necropsy, 04Aug2006
26		No findings noted	Scheduled necropsy, 18Aug2006
27		No findings noted	Scheduled necropsy, 18Aug2006
28		No findings noted	Scheduled necropsy, 18Aug2006
29		No findings noted	Scheduled necropsy, 18Aug2006
30		No findings noted	Scheduled necropsy, 18Aug2006

FEMALES
ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
31		No findings noted	Scheduled necropsy, 04Aug2006
32		No findings noted	Scheduled necropsy, 04Aug2006
33		No findings noted	Scheduled necropsy, 04Aug2006
34		No findings noted	Scheduled necropsy, 04Aug2006
35		No findings noted	Scheduled necropsy, 04Aug2006
36	Uterus	Contains fluid.	Scheduled necropsy, 18Aug2006
37	Uterus	Contains fluid.	Scheduled necropsy, 18Aug2006
38		No findings noted	Scheduled necropsy, 18Aug2006
39	Uterus	Contains fluid.	Scheduled necropsy, 18Aug2006
40		No findings noted	Scheduled necropsy, 18Aug2006
GROUP 2 (15 MG/KG)			
41		No findings noted	Scheduled necropsy, 04Aug2006
42		No findings noted	Scheduled necropsy, 04Aug2006
43		No findings noted	Scheduled necropsy, 04Aug2006
44		No findings noted	Scheduled necropsy, 04Aug2006
45	Uterus	Contains fluid.	Scheduled necropsy, 04Aug2006

MACROSCOPIC FINDINGS
FEMALES
ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 3 (50 MG/KG)			
46		No findings noted	Scheduled necropsy, 04Aug2006
47	Skin	Back of the neck: sore(s).	Scheduled necropsy, 04Aug2006
48		No findings noted	Scheduled necropsy, 04Aug2006
49	Uterus	Contains fluid.	Scheduled necropsy, 04Aug2006
50		No findings noted	Scheduled necropsy, 04Aug2006
GROUP 4 (150 MG/KG)			
51		No findings noted	Scheduled necropsy, 04Aug2006
52		No findings noted	Scheduled necropsy, 04Aug2006
53		No findings noted	Scheduled necropsy, 04Aug2006
54		No findings noted	Scheduled necropsy, 04Aug2006
55		No findings noted	Scheduled necropsy, 04Aug2006
56		No findings noted	Scheduled necropsy, 18Aug2006
57	Uterus	Contains fluid.	Scheduled necropsy, 18Aug2006
58		No findings noted	Scheduled necropsy, 18Aug2006
59	Uterus	Contains fluid.	Scheduled necropsy, 18Aug2006
60	Uterus	Contains fluid.	Scheduled necropsy, 18Aug2006

ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)	THYMUS (GRAM)
GROUP 1 (CONTROL)					
1	361	2.06	1.108	9.87	0.429
2	345	1.96	1.036	10.68	0.349
3	352	2.06	1.153	8.98	0.461
4	353	2.06	1.090	10.26	0.417
5	---	2.16	1.171	10.78	0.401
GROUP 2 (15 MG/KG)					
11	387	2.22	1.380	11.62	0.416
12	345	2.05	1.078	9.28	9.834
13	406	2.05	1.241	12.13	0.439
14	345	1.96	0.942	9.57	0.478
15	377	2.01	1.116	10.82	0.415
GROUP 3 (50 MG/KG)					
16	323	2.01	0.859	9.26	0.372
17	404	2.20	1.225	12.49	0.482
18	405	2.02	1.296	12.16	0.449
19	342	2.03	1.090	9.27	0.356
20	336	1.91	1.015	10.02	0.345
GROUP 4 (150 MG/KG)					
21	325	1.98	0.927	10.13	0.338
22	362	2.02	1.111	12.37	0.350
23	349	1.99	1.114	11.05	0.562
24	364	1.96	1.100	10.47	0.300
25	390	2.12	1.198	12.69	0.381

MALES
END OF TREATMENT

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)	TESTES (GRAM)	EPIDIDYMIDES (GRAM)
GROUP 1 (CONTROL)					
1	2.42	0.056	0.837	3.46	1.150
2	2.86	0.060	0.751	3.62	0.944
3	2.69	0.078	0.687	3.46	0.939
4	2.69	0.079	1.054	3.54	1.297
5	2.72	0.069	0.859	3.89	1.107
GROUP 2 (15 MG/KG)					
11	3.16	0.075	0.933	3.52	1.033
12	2.73	0.045	0.856	3.55	1.047
13	3.25	0.054	1.029	3.73	1.318
14	1.21	0.049	0.717	3.66	1.067
15	3.03	0.063	0.796	3.65	1.177
GROUP 3 (50 MG/KG)					
16	2.89	0.052	0.716	3.27	0.938
17	2.98	0.062	0.906	3.83	1.017
18	3.06	0.062	0.914	3.71	1.042
19	2.96	0.066	0.916	3.92	1.046
20	2.76	0.074	0.754	3.19	1.134

Table 8 Individual Animal Microscopic Findings

Codes and symbols in table heading:

m Males

f Females

Codes and symbols in animal lines:

p Planned main sacrifice

r Planned recovery sacrifice

Grading system used in finding lines:

0 finding not present

1 minimal

2 slight

3 moderate

4 severe

5 very severe

x present

Only organs/groups with **findings** are listed in the table

Test Item : MTDID 7144
Test System 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
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Table 7 Incidence All Microscopic Findings - Main

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	5	5	5	5	5	5	5	5
Bone Marrow - sternal								
number examined	5			5	5			5
Thymus								
number examined	5			5	5			5
Mesenteric Lymph Node								
number examined	5			5	5			5
Mandibular Lymph Nodes								
number examined	5			5	5			5
Plasmacytosis	0			1	0			0
Skin								
number examined							1	
Epidermal inflammation, ulcerative							1	
Bone - sternum								
number examined	5			5	5			5

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Table 7 Incidence All Microscopic Findings - Main

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	5	5	5	5	5	5	5	5
Uterus								
number examined					5	1	1	5
Proestrus epithelium					0	0	1	0
Estrus epithelium					0	1	0	0
Cyst(s)					1	0	0	0
Uterus - cervix								
number examined					5			5
Vagina								
number examined					5			5
Pituitary Gland								
number examined	5			5	5			5
Thyroid Glands								
number examined	5			5	5			5
Follicular hypertrophy/ hyperplasia, diffuse	1			0	0			0
Parathyroid Glands								
number examined	5			5	5			5
Adrenal Glands								
number examined	5			5	5			5
Inflammation, lymphoid	0			0	2			3
Vacuolation, multifocal in r. fasciculata	1			0	0			0
Spleen								
number examined	5			5	5			5
Hemosiderin pigment	0			0	3			1
Hemopoietic foci, primarily erythroid	4			5	3			3

Test item : MTDID 7144
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Table 7 Incidence All Microscopic Findings - Main

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	5	5	5	5	5	5	5	5
Kidneys								
number examined	5	5	5	5	5			5
Pelvic dilation	0	0	0	1	0			0
Hyaline droplets, cortical	4	2	5	5	0			0
Granular cast(s)	0	0	0	1	0			0
Inflammation, lymphoid	1	1	0	0	0			1
Tubular basophilia, corticomedullary	1	2	2	3	1			1
Tubular basophilia, outer stripe medulla, diffuse	1	0	0	0	0			0
Urinary Bladder								
number examined	5			5	5			5
Testes								
number examined	5			5				
Epididymides								
number examined	5			5				
Prostate Gland								
number examined	5			5				
Inflammation, lymphoid	1			2				
Seminal Vesicles								
number examined	5			5				
Ovaries								
number examined					5			5
Cyst(s)					1			0
Cyst, luteal					1			0

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Table 7 Incidence All Microscopic Findings - Main

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	5	5	5	5	5	5	5	5
Stomach								
number examined	5			5	5			5
Squamous cyst	1			0	0			0
Duodenum								
number examined	5			5	5			5
Jejunum								
number examined	5			5	5			5
Ileum								
number examined	5			5	5			5
Peyer's Patches (GALT								
number examined	5			5	5			5
Cecum								
number examined	5			5	5			5
Colon								
number examined	5			5	5			5
Rectum								
number examined	5			5	5			5
Liver								
number examined	5			5	5			5
Inflammation, granulocytic/ mononuclear	4			3	5			4
Pancreas								
number examined	5			5	5			5

Test item : MTDID 7144
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Table 7 Incidence All Microscopic Findings - Main

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	5	5	5	5	5	5	5	5
Brain								
number examined	5			5	5			5
Spinal Cord - cervical								
number examined	5			5	5			5
Spinal Cord - midthoracic								
number examined	5			5	5			5
Spinal Cord - lumbar								
number examined	5			5	5			5
Sciatic Nerve								
number examined	5			5	5			5
Myelin fragmentation	0			1	2			1
Heart								
number examined	5			5	5			5
Inflammation, lymphoid	1			0	0			0
Aorta								
number examined	5			5	5			5
Trachea								
number examined	5			5	5			5
Lungs								
number examined	5			5	5			5
Alveolar inflammation, lymphocytic	1			1	0			0
Osseous metaplasia	0			1	0			0
Esophagus								
number examined	5			5	5			5
Myodegeneration, focal	1			0	1			1

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Table 6 Statistical Analyses Selected Microscopic Findings – Recovery

SEX:		MALE				
DOSE GROUP:		1	2	3	4	Trend
Kidneys						
Hyaline droplets, cortical	n	2	0	0	1	
	N	5	0	0	5	
	%	40.00	*	*	20.00	
	Min	0	0	0	0	
	Max	2	0	0	1	
	Ex P		N.S.	N.S.	N.S.	
	KW P		N.S.	N.S.	N.S.	N.S.
Kidneys						
Tubular basophilia, corticomedullary	n	4	0	0	3	
	N	5	0	0	5	
	%	80.00	*	*	60.00	
	Min	0	0	0	0	
	Max	2	0	0	2	
	Ex P		N.S.	N.S.	N.S.	
	KW P		N.S.	N.S.	N.S.	N.S.

n = number affected
Min = minimum grade
Ex = Fisher's exact
P = probability value
(+) = p <0.1

+ = p <0.05
+++ = p <0.001

N = number in sample
Max = maximum grade
KW = Kruskal-Wallis
N.S = p not significant
++ = p <0.01

Test item : MTDID 7144
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Table 5 Incidence Selected Microscopic Findings with Grades – Recovery

SEX:	MALE			
DOSE GROUP:	1	2	3	4
number of animals	5			5
Kidneys				
number examined	5			5
Hyaline droplets, cortical				
(minimal)	1			1
(slight)	1			0
Total	**2**			**1**
Tubular basophilia, corticomedullary				
(minimal)	3			1
(slight)	1			2
Total	**4**			**3**

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Table 4 Statistical Analyses Selected Microscopic Findings – Main

SEX:		MALE				
DOSE GROUP:		1	2	3	4	Trend
Kidneys						
hyaline droplets, cortical	n	4	2	5	5	
	N	5	5	5	5	
	%	80.00	40.00	100.00	100.00	
	Min	0	0	2	3	
	Max	2	2	2	3	
	Ex P		N.S.	N.S.	N.S.	
	KW P		N.S.	(+)	+	N.S.
Kidneys						
Granular cast(s)	n	0	0	0	1	
	N	5	5	5	5	
	%	0.00	0.00	0.00	20.00	
	Min	0	0	0	0	
	Max	0	0	0	1	
	Ex P		N.S.	N.S.	N.S.	
	KW P		N.S.	N.S.	N.S.	N.S.
Kidneys						
Tubular basophilia, corticomedullary	n	1	2	2	3	
	N	5	5	5	5	
	%	20.00	40.00	40.00	60.00	
	Min	0	0	0	0	
	Max	1	1	1	2	
	Ex P		N.S.	N.S.	N.S.	
	KW P		N.S.	N.S.	N.S.	N.S.

n = number affected
Min = minimum grade
Ex = Fishers exact
P = probability value
(+) = p <0.1

+ = p <0.05
+++ = p <0.001

N = number in sample
Max = maximum grade
KW = Kruskal-Wallis
N.S = p not significant
++ = p <0.01

Table 3 Incidence Selected Microscopic Findings with Grades – Main

SEX:	MALE			
DOSE GROUP:	1	2	3	4
number of animals	5	5	5	5
Kidneys				
number examined	5	5	5	5
Hyaline droplets, cortical				
(minimal)	3	1	0	0
(slight)	1	1	5	0
(moderate)	0	0	0	5
Total	**4**	**2**	**5**	**5**
Granular cast(s)				
(minimal)	0	0	0	1
Tubular basophilia, corticomedullary				
(minimal)	1	2	2	1
(slight)	0	0	0	2
Total	**1**	**2**	**2**	**3**

Test item . MTDID 7144
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Table 2 Incidence All Macroscopic Findings – Recovery

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	5			5	5			5
Uterus								
Contains fluid					3			3

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Table 1 Incidence All Macroscopic Findings – Main

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	5	5	5	5	5	5	5	5
Kidneys								
Pelvic dilation	0	0	0	1	0	0	0	0
Uterus								
Contains fluid					0	1	1	0
Skin								
Sores	0	0	0	0	0	0	1	0

Reference

1. Alden, CL and Frith CH. Urinary System, Ch. 15, pp 315-387. *In: Handbook of Toxicologic Pathology* Eds. Haschek WM and Rousseaux CG. Academic Press, San Diego. 1991.

Conclusions

Morphologic alterations following the administration of **MTDID 7144** by once daily gavage to Wistar rats at doses up to 150 mg/kg for twenty eight days, were noted in the ***kidneys*** of male rats.

Findings in the ***kidneys*** consisted of an increased severity to moderate of *cortical hyaline droplets* in group 4 (150 mg/kg/day) males at the end of the ***main*** study. The *hyaline droplets* were considered to represent alpha$_{2\mu}$globulin, a normal protein in male rats which undergoes re-absorption in the proximal cortical tubules (ref. 1). A range of chemicals are known to increase hyaline droplet formation. If hyaline droplets exceed the physiological capacity of the tubular epithelium, tubular cell degeneration may result. There was some evidence for this in group 4 in the form of a slight increase in severity of *corticomedullary tubular basophilia* along with a single occurrence of *granular casts*. This protein is not present in higher mammals, including man (ref 1). Following the recovery period the incidence and severity of the above findings were similar in control and group 4 rats.

The NOAEL may be regarded as 50 mg/kg/day for males and 150 mg/kg/day for females.

Results

Mortality

All rats survived the scheduled duration of the study.

Macroscopic Findings

The few recorded macroscopic findings were considered to be spontaneous in nature and did not distinguish treated animals from the controls at either sacrifice.

Microscopic Findings

Treatment related microscopic findings were recorded in the ***kidneys*** of male rats. At the end of the ***main*** study *cortical hyaline droplets* were noted at minimal or slight severity in four group 1 (0 mg/kg/day, control), two group 2 (15 mg/kg/day) and all five group 3 (50 mg/kg/day) rats compared with a moderate severity seen in all five group 4 (1000 mg/kg/day) males. Associated with this finding was a minimal degree of *granular cast* in one group 4 animal and a slight increase in severity to slight of *corticomedullary tubular basophilia* recorded in two group 4 rats. The incidence of *cortical hyaline droplets* in group 4 achieved statistical significance $p < 0.05$ (Kruskal-Wallis). Although the slight increase in this finding in group 3 had a p value of <0.1, this was considered not biologically relevant as the incidence and severity were within historical control ranges for this strain of rat. Following the recovery period the incidence and severity of the above findings were similar in control and group 4 rats.

The remainder of the microscopic findings recorded at either sacrifice were within the range of background pathology encountered in Wistar rats of this age and occurred at similar incidences and severity in both control and treated rats

Materials and Methods

Data Compilation

The animal data and macroscopic findings were electronically transferred from the necropsy raw data files of NOTOX into the computer system of Propath GmbH where the microscopic findings were recorded by the undersigned pathologist using on-line input.

Macroscopic findings are presented in summary in Table 1 - Incidence All Macroscopic Findings – Main and Table 2 - Incidence All Macroscopic Findings – Recovery and in full descriptive terms in Table 10 - Individual Animal Data Records Wherever possible, macroscopic findings were correlated with a microscopic finding.

Microscopic findings are listed for each animal along with severity grades in Table 8 - Individual Animal Microscopic Findings and summarized in Table 7 - Incidence All Microscopic Findings - Main. They are further given in full descriptive terms in Table 10 - Individual Animal Data Records. Histologic changes were described according to their distribution and morphologic character and were graded for severity on a scale of 1 – 5 (see key Table 8 - Individual Animal Microscopic Findings)

Selected microscopic findings were subjected to statistical analysis and the results are presented in Table 4 - Statistical Analyses Selected Microscopic Findings – Main and Table 6 - Statistical Analyses Selected Microscopic Findings – Recovery.

Archiving

The final pathology report (original hardcopy), all histologic slides, dispatch list(s) and a copy of the electronic records and final pathology report as captured by the appropriate software (on CD-ROM) will be sent to NOTOX B.V. to archive. Any other documents and electronic data covered by GLP, will be archived by Propath GmbH according to company standard operating procedures.

Materials and Methods

Study Design

Dose group	Dose mg/kg MTDID 7144	Number of rats				Animal Numbers			
		males		females		males		females	
		main	recovery	main	recovery	main	recovery	main	recovery
1	0	5	5	5	5	1-5	6-10	31-35	36-40
2	15	5		5		11-15		41-45	
3	50	5		5		16-20		46-50	
4	150	5	5	5	5	21-25	26-30	51-55	56-60

Administration of the Test Item

The test item was administered once daily by gavage for 28 days. Rats of the control group 1 received the vehicle, water (Milli-U), alone.

Necropsy and Histopathology

At the end of the assigned study period, the rats were killed by exsanguination following anesthesia by isoflurane. Complete necropsies were performed on all rats. Representative tissue samples of the following organs were preserved in 4% phosphate buffered neutral formaldehyde solution (10% formalin). Following fixation, organs (except those listed in brackets) from group 1 and 4 rats of the main study and all organs with macroscopic abnormalities from all rats, were trimmed, processed and embedded in paraffin wax. Sections were cut at a thickness of 2-4 micrometers and stained with hematoxylin and eosin. Numbers of sections made are given in parentheses.

> Adrenal glands (2), aorta (1), bone – sternum (1) [and femur including joint]; bone marrow - sternal (1), brain (3), [clitoral glands], epididymides (4), esophagus (1), [eyes with optic nerve and Harderian glands]; heart (1), [identification marks], kidneys (2), [lacrimal glands - exorbital], large intestine (3) - cecum, colon and rectum; [larynx], liver (2), lungs (2), lymph nodes - mandibular (2) and mesenteric (1); [female mammary gland area], [nasopharynx], ovaries (2), pancreas (1), pituitary gland (1), [preputial glands], prostate gland (1), [salivary glands – mandibular and sublingual]; sciatic nerve (1), seminal vesicles (2), [skeletal muscle], [skin], small intestine (3)- duodenum, jejunum and ileum with Peyer's patches; spinal cord (3)- cervical, midthoracic and lumbar; spleen (1), stomach (1), testes (2), thymus (1), thyroid glands (2) with parathyroid glands (2), [tongue], trachea (1), urinary bladder (1), uterus with uterine cervix (4) vagina (1) and all organs or tissues with macroscopic abnormalities.

Following examination of the above tissues, sections of ***kidneys*** from male animals of the intermediate dose groups of the main study – groups 2 and 3 and the recovery animals, were prepared and examined.

The sections were examined by light microscopy in August/September, 2006.

Test item	: MTDID 7144	NOTOX no. :	458966
Test System	: 28-Day Gavage 14-Day Rec. Study in Rats	Propath no. :	06031
Sponsor	: 3M Corporate Toxicology - Regulatory Services	Date :	20.Oct.2006

Summary

Pathomorphologic examination was performed on 60 Wistar rats (30 males, 30 females) which had been subjected to a 28-day oral (gavage) toxicity study with the test item **MTDID 7144**.

For pathology assessment the rats were assigned to four dose groups. The test item was administered once daily by gavage at doses of 15, 50 and 150 mg/kg (dose groups 2, 3 and 4 respectively). Dose groups 1 and 4 contained ten males and ten females (five animals of each sex assigned to a 14-day post treatment recovery period); groups 2 and 3, five animals of each sex. The rats of the control group 1 received the vehicle, water (Milli-U), alone.

All rats were necropsied. Histopathologic examination was performed on an extensive list of organs and tissues from group 1 and 4 rats of the ***main*** allocation, as well as ***kidneys*** from all males and gross lesions from all rats.

All rats survived the scheduled duration of the study.

There were no treatment related macroscopic findings at necropsy

Treatment related microscopic findings were present in the ***kidneys*** of male rats and consisted of an increased severity to moderate of *cortical hyaline droplets* in group 4 (150 mg/kg/day) males at the end of the ***main*** study along with a slight increase in severity of *corticomedullary tubular basophilia* and a single occurrence of *granular casts*. The *hyaline droplets* were considered to represent alpha$_{2\mu}$globulin, a normal protein in male rats which undergoes re-absorption in the proximal cortical tubules and if present in excess, may lead to tubular cell degeneration.

Following the ***recovery*** period the incidence and severity of the above findings were similar in control and group 4 rats.

The NOAEL may be regarded as 50 mg/kg/day for males and 150 mg/kg/day for females.

Quality Assurance Statement

The facilities of Propath GmbH are periodically (4x/year) inspected by the Quality Assurance Unit (CERTUS Quality Assurance Services GmbH). This report was inspected by the Quality Assurance Unit (CERTUS).

The respective dates are given below:

Inspection type	Date(s) of inspection	Date(s) of reporting
Facility based inspection (latest):	30.08.2006	30.08.2006
Report inspection:	09,16.10.2006	18.10.2006

The findings were reported to the test facility (Propath) management (only inspection of test facility (test site) Propath), the principal investigator, the study director, the management of the test facility of the study director and the "lead QA".

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

A. Brüggen
QA Inspector

Date: 20.10.2006

CERTUS Quality Assurance Services GmbH
CH-4125 Riehen, Switzerland
QAU of Propath GmbH

Test item	: MTDID 7144	NOTOX no. :	458966
Test System	: 26-Day Gavage 14-Day Rec Study in Rats	Propath no. :	06031
Sponsor	: 3M Corporate Toxicology - Regulatory Services	Date :	20.Oct.2006

Statement of Compliance

The undersigned hereby declares, that the histopathology data in this report were compiled by him, and that they reflect accurately the primary data records. This report, consisting of 72 pages, was created by the computer system of Propath GmbH.

This study phase was conducted in compliance with:

Swiss Ordinance relating to Good Laboratory Practice, adopted May 18th, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final].

which essentially conform to:

The United States Food and Drug Administration Good Laboratory Practice Regulations and

The United States Environmental Protection Agency Good Laboratory Practice Regulations.

Jeffrey Th. Wilson, Dr.med vet. BVSc, MSc, MRCVS
Principal Investigator - Toxicologic Pathologist

Date: 20.10.06

Propath GmbH
CH-4133 Pratteln, Switzerland

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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APPENDIX 5

REPORT FOR DELEGATED PHASE HISTOPATHOLOGY

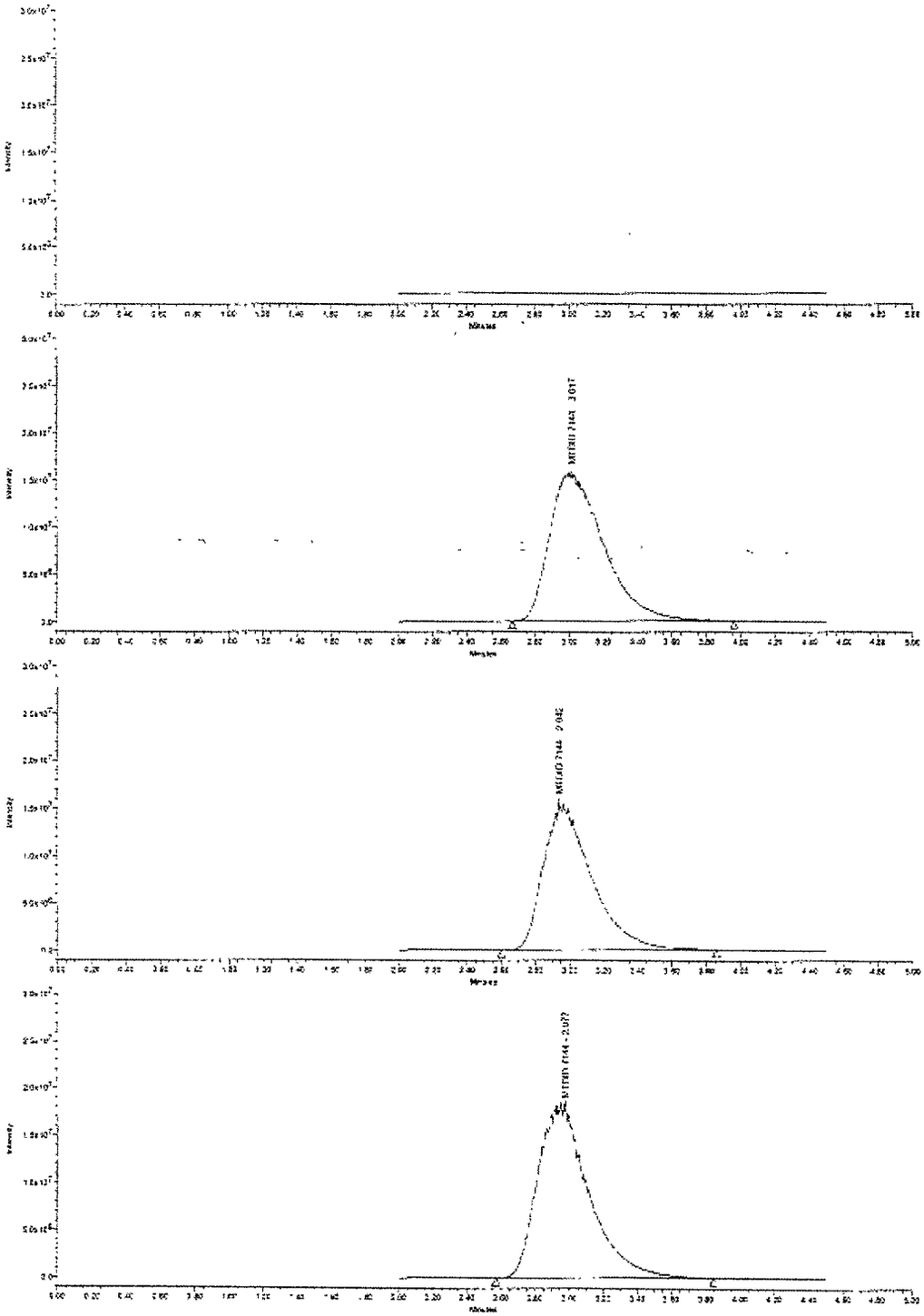

Figure 2 HPLC-MS chromatograms from top to bottom of samples from Group 1 [res. id. 1702; dilution factor 5], Group 2 [res. id. 1706; dilution factor 5], Group 3 [res. id. 1735; dilution factor 17] and Group 4 [res. id. 1726; dilution factor 50].

FIGURES

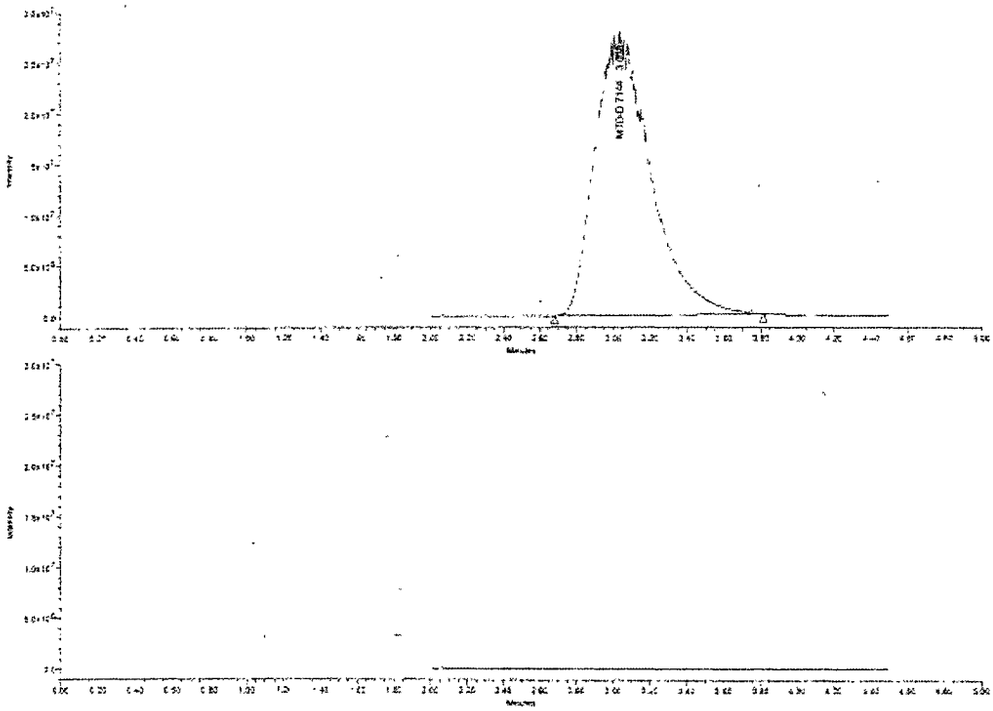

Figure 1 **HPLC-MS chromatograms of a 5.01 mg/l calibration solution [top; res. id. 1691] and blank 50/50 (v/v) methanol/Milli-Q water [bottom; res. id. 1778].**

Table 2 Accuracy and homogeneity test for the formulations prepared during treatment

Group	Date of analysis [dd-mm-yy]	Sample position	Concentration [mg/g]		Accuracy	Homogeneity (coefficient of variation)
			Target	Analysed	[%]	[%]
1	12-07-06	50% height	0.00	n.d.	n.a.	
				n.d.	n.a.	
2	12-07-06	90% height	0.750	0.701	93	
				0.660	88	
		50% height	0.750	0.696	93	2.4
				0.678	90	
		10% height	0.750	0.703	94	
				0.694	93	
3	12-07-06	50% height	2.50	2.00	80	
				2.33	93	
4	12-07-06	90% height	7.51	7.43	99	
				8.11	108	
		50% height	7.51	7.75	103	4.1
				8.34	111	
		10% height	7.51	7.86	105	
				7.71	103	

Table 3 Stability test for the formulations prepared during treatment

Group	Date of analysis [dd-mm-yy]	Concentration analysed [mg/g]		Relative diff. [%]
		t=0 [1]	t=5 hours	
2	12-07-06	0.689	0.625 [2]	-9.3
4	12-07-06	7.87	7.34 [3]	-6.7

[1] Mean of six samples at t=0 taken at 10%, 50% and 90% height. For individual results see Table 2.
[2] Mean of two samples at t=5 hours taken at 50% height. Individual results were 0.619 and 0.630 mg/g.
[3] Mean of two samples at t=5 hours taken at 50% height. Individual results were 7.73 and 6.95 mg/g.

TABLES

Table 1 Procedural recovery samples

Date of preparation [dd-mm-yy]	Date of analysis [dd-mm-yy]	Concentration nominal [mg/g]	Concentration analysed [mg/g]	Recovery [%]	Mean recovery (coefficient of variation) [%]
12-07-06	12-07-06	0.500	0.486	97	92
		0.500	0.445	89	(3.7)
		0.500	0.459	92	
		0.499	0.461	92	
		0.500	0.444	89	
12-07-06	12-07-06	10.7	11.5	107	106
		10.4	10.2	98	(4.9)
		9.79	10.4	106	
		14.5	15.5 [1]	107	
		11.5	13.0 [1]	112	

[1] Obtained by extrapolation of the calibration curve.

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Table 10 Individual Animal Data Records

Animal No: 59
SEX: Female
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS

Uterus Proestrus epithelium present (correlates to GROSS finding)

Animal No: 60

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

Uterus Contains fluid

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus Proestrus epithelium present (correlates to GROSS finding)

Table 10 Individual Animal Data Records

Animal No: 57
SEX: Female
DOSE GROUP: Group 4, 150 mg/kg/day

MACROSCOPIC FINDINGS
(continued)

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus — Estrus epithelium present (correlates to GROSS finding)

Animal No: 58

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 59

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

Uterus — Contains fluid

No abnormalities were found in any of the other tissues examined

Table 10 Individual Animal Data Records

Animal No: 55
SEX: Female
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Caecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 56

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 57

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

Uterus Contains fluid

Test item : MTDID 7144
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Table 10 Individual Animal Data Records

Animal No: 54
SEX: Female
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Liver, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 55

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Inflammation, lymphoid (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Spleen	Hemosiderin pigment (minimal) Hemopoietic foci, primarily erythroid (slight)

Number of Sections less than protocol for Parathyroid Gland/1 (0).

Test item : MTDID 7144
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Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 53
SEX: Female
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (slight)
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Spleen, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 54

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Inflammation, lymphoid (slight)
Adrenal Gland/2	Inflammation, lymphoid (minimal)
Esophagus	Myodegeneration, focal (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)

Table 10 Individual Animal Data Records

Animal No: 52
SEX: Female
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS

Adrenal Gland/1	Inflammation, lymphoid (minimal)
Adrenal Gland/2	Inflammation, lymphoid (minimal)
Kidney/1	Inflammation, lymphoid (minimal) Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Sciatic Nerve	poor section

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Spleen, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 53

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

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Table 10 Individual Animal Data Records

Animal No: 51
SEX: Female
DOSE GROUP: Group 4, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (minimal)
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 52

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

Test Item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Date : 20.Oct.2006

Table 10 Individual Animal Data Records

Animal No: 29
SEX: Male
DOSE GROUP: Group 4, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Tubular basophilia, corticomedullary (minimal)

Kidney/2 Tubular basophilia, corticomedullary (slight)

Animal No: 30

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (minimal)
Tubular basophilia, corticomedullary (minimal)

Kidney/2 Hyaline droplets, cortical (minimal)

Test item : MTDID 7144
Test System 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 27
SEX: Male
DOSE GROUP: Group 4, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 16/08/06

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Kidney/1, Kidney/2.

Animal No: 28

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 16/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Tubular basophilia, corticomedullary (minimal)

Kidney/2 Tubular basophilia, corticomedullary (slight)

Table 10 Individual Animal Data Records

Animal No: 28
SEX: Male
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS

Kidney/1	Hyaline droplets, cortical (moderate)
Kidney/2	Hyaline droplets, cortical (moderate)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Prostate Gland	Inflammation, lymphoid (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 26

MACROSCOPIC FINDINGS

Days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Kidney/1, Kidney/2.

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 24
SEX: Male
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS

Kidney/1	Hyaline droplets, cortical (moderate) Tubular basophilia, corticomedullary (slight)
Kidney/2	Hyaline droplets, cortical (moderate)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)
	Number of Sections less than protocol for Parathyroid Gland/1 (0).
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 25

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

Test item : MTDID 7144
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Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 23
SEX: Male
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS

Kidney/1	Hyaline droplets, cortical (moderate) Granular cast(s) (minimal) Tubular basophilia, corticomedullary (minimal)
Kidney/2	Hyaline droplets, cortical (moderate) Tubular basophilia, corticomedullary (slight)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Osseous metaplasia (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 24

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 22
SEX: Male
DOSE GROUP: Group 4, 150 mg/kg/day

MICROSCOPIC FINDINGS
'continued'

Mandibular Lymph Node/2	Plasmacytosis (moderate)
Prostate Gland	Inflammation, lymphoid (slight)
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Liver, Mandibular Lymph Node/1, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 23

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

Test item : MTDID 7144
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Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 21
SEX: Male
DOSE GROUP: Group 4, 180 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Liver, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 22

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

Kidneys — Pelvic dilation

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Kidney/1 — Pelvic dilation present (correlates to GROSS finding)
Hyaline droplets, cortical (moderate)

Kidney/2 — Hyaline droplets, cortical (moderate)

Lungs — Alveolar inflammation, lymphocytic (minimal)

Table 10 Individual Animal Data Records

Animal No: 50
SEX: Female
DOSE GROUP: Group 3, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 21
SEX: Male
DOSE GROUP: Group 4, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1	Hyaline droplets, cortical (moderate) Tubular basophilia, corticomedullary (minimal)
Kidney/2	Hyaline droplets, cortical (moderate)
Spleen	Hemopoietic foci, primarily erythroid (minimal)

Table 10 Individual Animal Data Records

Animal No: 49
SEX: Female
DOSE GROUP: Group 3, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 49

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

Uterus Contains fluid

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus Proestrus epithelium present (correlates to GROSS finding)

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Table 10 Individual Animal Data Records

Animal No: 46
SEX: Female
DOSE GROUP: Group 3, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 47

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

Skin back of the neck Scre(s)

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Skin Epidermal inflammation, ulcerative (slight) (correlates to GROSS finding)

Test item : MTDID 7144
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Table 10 Individual Animal Data Records

Animal No: 19
SEX: Male
DOSE GROUP: Group 3, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (minimal)
Tubular basophilia, corticomedullary (minimal)

Kidney/2 Hyaline droplets, cortical (slight)

Animal No: 20

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (minimal)

Kidney/2 Hyaline droplets, cortical (slight)

Test Item MTDID 7144
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Table 10 Individual Animal Data Records

Animal No: 17
SEX: Male
DOSE GROUP: Group 3, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (slight)
Tubular basophilia, corticomedullary (minimal)

Kidney/2 Hyaline droplets, cortical (slight)

Animal No: 18

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (minimal)

Kidney/2 Hyaline droplets, cortical (slight)

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
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Table 10 Individual Animal Data Records

Animal No: 45
SEX: Female
DOSE GROUP: Group 2, 15 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

Uterus — Contains fluid

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus — Estrus epithelium present (correlates to GROSS finding)

Animal No: 16
SEX: Male
DOSE GROUP: Group 3, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 — Hyaline droplets, cortical (slight)

Kidney/2 — Hyaline droplets, cortical (slight)

Table 10 Individual Animal Data Records

Animal No: 42
SEX: Female
DOSE GROUP: Group 2, 15 mg/kg/day

MACROSCOPIC FINDINGS
(continued)

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 43

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 44

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Test item MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
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Table 10 Individual Animal Data Records

Animal No: 15
SEX: Male
DOSE GROUP: Group 2, 15 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Kidney/1, Kidney/2.

Animal No: 41
SEX: Female

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Animal No: 42

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

Table 10 Individual Animal Data Records

Animal No: 13
SEX: Male
DOSE GROUP: Group 2. 15 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (minimal)

Kidney/2 Hyaline droplets, cortical (minimal)

Animal No: 14

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Kidney/1, Kidney/2.

Table 10 Individual Animal Data Records

Animal No: 11
SEX: Male
DOSE GROUP: Group 2, 15 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (slight)
Tubular basophilia, corticomedullary (minimal)

Kidney/2 Hyaline droplets, cortical (slight)

Animal No: 12

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Inflammation, lymphoid (minimal)
Tubular basophilia, corticomedullary (minimal)

No abnormalities found in: Kidney/2.

Table 10 Individual Animal Data Records

Animal No: 39
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

Uterus Contains fluid

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus Estrus epithelium present (correlates to GROSS finding)

Animal No: 40

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Test item	MTDID 7144	NOTOX no.	458966
Test System	28-Day Gavage 14-Day Rec Study in Rats	Propath no.	06031
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Table 10 Individual Animal Data Records

Animal No: 37
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

Uterus Contains fluid

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus Estrus epithelium present (correlates to GROSS finding)

Animal No: 38

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

No tissues examined

Table 10 Individual Animal Data Records

Animal No: 35
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Spleen, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 36

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

Uterus — Contains fluid

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus — Estrus epithelium present (correlates to GROSS finding)

Table 10 Individual Animal Data Records

Animal No: 34
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Spleen, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 35

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Inflammation, lymphoid (slight)
Adrenal Gland/2	Inflammation, lymphoid (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 33
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 34

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1	Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Ovary/1	Cyst, luteal (minimal)
Sciatic Nerve	Myelin fragmentation (minimal)

Table 10 Individual Animal Data Records

Animal No: 33
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus, Uterus - cervix, Vagina.

Animal No: 33

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (minimal)
Ovary/1	Cyst(s) present simple in oviduct
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemosiderin pigment (minimal) Hemopoietic foci, primarily erythroic (slight)

Table 10 Individual Animal Data Records

Animal No: 31
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

Uterus — Cyst(s) present

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix, Vagina.

Animal No: 32

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/06/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Esophagus — Myodegeneration, focal (minimal)

Liver — Inflammation, granulocytic/mononuclear (minimal)

Spleen — Hemosiderin pigment (minimal)
Hemopoietic foci, primarily erythroid (slight)

Number of Sections less than protocol for Parathyroid Gland/1 (0).

Table 10 Individual Animal Data Records

Animal No: 10
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1	Hyaline droplets, cortical (minimal) Tubular basophilia, corticomedullary (minimal)
Kidney/2	Hyaline droplets, cortical (minimal)

Animal No: 51
SEX: Female

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Inflammation, lymphoid (minimal)
Adrenal Gland/2	Inflammation, lymphoid (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Spinal Cord - cervical	Only cauda equina in section
Spleen	Hemosiderin pigment (minimal) Hemopoietic foci, primarily erythroid (minimal)

Table 10 Individual Animal Data Records

Animal No: 8
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (minimal)
Tubular basophilia, corticomedullary (slight)

Kidney/2 Hyaline droplets, cortical (slight)
Tubular basophilia, corticomedullary (minimal)

Animal No: 9

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Kidney/1, Kidney/2.

Table 10 Individual Animal Data Records

Animal No: 6
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Tubular basophilia, corticomedullary (minimal)

Kidney/2 Tubular basophilia, corticomedullary (minimal)

Animal No: 7

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned recovery
necropsy status : planned recovery
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 18/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Tubular basophilia, corticomedullary (minimal)

No abnormalities found in: Kidney/2.

Test item : MTDID 7144
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Table 10 Individual Animal Data Records

Animal No: 5
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Esophagus	Myodegeneration, focal (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)
Thyroid Gland/1	Follicular hypertrophy/hyperplasia, diffuse (minimal)
Thyroid Gland/2	Follicular hypertrophy/hyperplasia, diffuse (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Liver, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Trachea, Urinary Bladder.

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 10 Individual Animal Data Records

Animal No: 4
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS
(continued)

No findings noted

MICROSCOPIC FINDINGS

Heart	Inflammation, lymphoid (minimal)
Kidney/1	Hyaline droplets, cortical (minimal) Tubular basophilia, corticomedullary (minimal)
Kidney/2	Hyaline droplets, cortical (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Alveolar inflammation, lymphocytic (minimal)
Prostate Gland	Inflammation, lymphoid (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Ileum, Jejunum, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Table 10 Individual Animal Data Records

Animal No: 3
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1 Hyaline droplets, cortical (minimal)

Liver Inflammation, granulocytic/mononuclear (slight)

Number of Sections less than protocol for Parathyroid Gland/1 (0).

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Spleen, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 4

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

Table 10 Individual Animal Data Records

Animal No: 2
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (minimal)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (minimal)
Kidney/1	Hyaline droplets, cortical (slight) Inflammation, lymphoid (minimal) Tubular basophilia, outer stripe medulla, diffuse (moderate)
Kidney/2	Hyaline droplets, cortical (slight) Inflammation, lymphoid (slight) Tubular basophilia, outer stripe medulla, diffuse (moderate)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)
	No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Test item : MTDID 7144
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Table 10 Individual Animal Data Records

Animal No: 1
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 28
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 07/07/06
date of end of treatment: 03/08/06
date of necropsy : 04/08/06

No findings noted

MICROSCOPIC FINDINGS

Kidney/1	Hyaline droplets, cortical (minimal)
Kidney/2	Hyaline droplets, cortical (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)
Stomach	Squamous cyst (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Test item : MTDID 7144
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Table 9 Animal Data List

Females

ANIMAL NUMBER	SEX M/F	FINAL STATE	TEST DAYS	FIRST DAY	LAST DAY	DATE NECROPSY
DOSE GROUP 1						
31	f	p	28	07/07/06	03/08/06	04/08/06
32	f	p	28	07/07/06	03/08/06	04/08/06
33	f	p	28	07/07/06	03/08/06	04/08/06
34	f	p	28	07/07/06	03/08/06	04/08/06
35	f	p	28	07/07/06	03/08/06	04/08/06
36	f	r	28	07/07/06	03/08/06	18/08/06
37	f	r	28	07/07/06	03/08/06	18/08/06
38	f	r	28	07/07/06	03/08/06	18/08/06
39	f	r	28	07/07/06	03/08/06	18/08/06
40	f	r	28	07/07/06	03/08/06	18/08/06
DOSE GROUP 2						
41	f	p	28	07/07/06	03/08/06	04/08/06
42	f	p	28	07/07/06	03/08/06	04/08/06
43	f	p	28	07/07/06	03/08/06	04/08/06
44	f	p	28	07/07/06	03/08/06	04/08/06
45	f	p	28	07/07/06	03/08/06	04/08/06
DOSE GROUP 3						
46	f	p	28	07/07/06	03/08/06	04/08/06
47	f	p	28	07/07/06	03/08/06	04/08/06
48	f	p	28	07/07/06	03/08/06	04/08/06
49	f	p	28	07/07/06	03/08/06	04/08/06
50	f	p	28	07/07/06	03/08/06	04/08/06
DOSE GROUP 4						
51	f	p	28	07/07/06	03/08/06	04/08/06
52	f	p	28	07/07/06	03/08/06	04/08/06
53	f	p	28	07/07/06	03/08/06	04/08/06
54	f	p	28	07/07/06	03/08/06	04/08/06
55	f	p	28	07/07/06	03/08/06	04/08/06
56	f	r	28	07/07/06	03/08/06	18/08/06
57	f	r	28	07/07/06	03/08/06	18/08/06
58	f	r	28	07/07/06	03/08/06	18/08/06
59	f	r	28	07/07/06	03/08/06	18/08/06
60	f	r	28	07/07/06	03/08/06	18/08/06

Test item MTDID 7144
Test System . 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no 458966
Propath no. 06031
Date : 20.Oct.2006

Table 9 Animal Data List

Males

ANIMAL NUMBER	SEX M/F	FINAL STATE	TEST DAYS	FIRST DAY	LAST DAY	DATE NECROPSY
DOSE GROUP 1						
1	m	p	28	07/07/06	03/08/06	04/08/06
2	m	p	28	07/07/06	03/08/06	04/08/06
3	m	p	28	07/07/06	03/08/06	04/08/06
4	m	p	28	07/07/06	03/08/06	04/08/06
5	m	p	28	07/07/06	03/08/06	04/08/06
6	m	r	28	07/07/06	03/08/06	18/08/06
7	m	r	28	07/07/06	03/08/06	18/08/06
8	m	r	28	07/07/06	03/08/06	18/08/06
9	m	r	28	07/07/06	03/08/06	18/08/06
10	m	r	28	07/07/06	03/08/06	18/08/06
DOSE GROUP 2						
11	m	p	28	07/07/06	03/08/06	04/08/06
12	m	p	28	07/07/06	03/08/06	04/08/06
13	m	p	28	07/07/06	03/08/06	04/08/06
14	m	p	28	07/07/06	03/08/06	04/08/06
15	m	p	28	07/07/06	03/08/06	04/08/06
DOSE GROUP 3						
16	m	p	28	07/07/06	03/08/06	04/08/06
17	m	p	28	07/07/06	03/08/06	04/08/06
18	m	p	28	07/07/06	03/08/06	04/08/06
19	m	p	28	07/07/06	03/08/06	04/08/06
20	m	p	28	07/07/06	03/08/06	04/08/06
DOSE GROUP 4						
21	m	p	28	07/07/06	03/08/06	04/08/06
22	m	p	28	07/07/06	03/08/06	04/08/06
23	m	p	28	07/07/06	03/08/06	04/08/06
24	m	p	28	07/07/06	03/08/06	04/08/06
25	m	p	28	07/07/06	03/08/06	04/08/06
26	m	r	28	07/07/06	03/08/06	18/08/06
27	m	r	28	07/07/06	03/08/06	18/08/06
28	m	r	28	07/07/06	03/08/06	18/08/06
29	m	r	28	07/07/06	03/08/06	18/08/06
30	m	r	28	07/07/06	03/08/06	18/08/06

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
Propath no. : 06031
Date : 20.Oct.2006

Table 8 Individual Animal Microscopic Findings

Females
Group 4

	51 f	52 f	53 f	54 f	55 f	56 f	57 f	58 f	59 f	60 f
necropsy status	p	p	p	p	p	r	r	r	r	r
Sciatic Nerve										
Myelin fragmentation	1	0	0	0	0					
Esophagus										
Myodegeneration, focal	0	0	0	1	0					
Liver										
Inflammation, granulocytic/mononuclear	1	1	2	0	1					
Kidneys										
Inflammation, lymphoid	0	1	0	0	0					
Tubular basophilia, corticomedullary	0	1	0	0	0					
Uterus										
Proestrus epithelium	0	0	0	0	0		0		x	x
Estrus epithelium	0	0	0	0	0		x		0	0
Adrenal Glands										
Inflammation, lymphoid	0	1	0	2	1					
Spleen										
Hemosiderin pigment	0	0	0	0	1					
Hemopoietic foci, primarily erythroid	1	0	0	1	2					

Test Item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 8 Individual Animal Microscopic Findings

Females
Group 3

	46	47	48	49	50
	f	f	f	f	f
necropsy status	p	p	p	p	p
Uterus					
Proestrus epithelium				x	
Skin					
Epidermal inflammation, ulcerative		2			

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
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Date : 20.Oct.2006

Table 8 Individual Animal Microscopic Findings

Females
Group 2

	41	42	43	44	45
	f	f	f	f	f
necropsy status	p	p	p	p	p
Uterus					
Estrus epithelium					x

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 8 Individual Animal Microscopic Findings

Females
Group 1

	31	32	33	34	35	36	37	38	39	40
	f	f	f	f	f	f	f	f	f	f
Necropsy Status	p	p	p	p	p	r	r	r	r	r
Sciatic Nerve										
Myelin fragmentation	0	0	1	1	0					
Esophagus										
Myodegeneration, focal	0	1	0	0	0					
Liver										
Inflammation, granulocytic/mononuclear	1	1	1	1	1					
Kidneys										
Tubular basophilia, corticomedullary	0	0	0	1	0					
Ovaries										
Cyst(s)	0	0	x	0	0					
Cyst, luteal	0	0	0	1	0					
Uterus										
Estrus epithelium	0	0	0	0	0	x	x		x	
Cystic,	x	0	0	0	0	0	0		0	
Adrenal Glands										
Inflammation, lymphoid	1	0	0	0	2					
Spleen										
Hemosiderin pigment	1	1	1	0	0					
Hemopoietic foci, primarily erythroid	1	2	2	0	0					

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
Propath no : 06031
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Table 8 Individual Animal Microscopic Findings

Males
Group 4

	21 m	22 m	23 m	24 m	25 m	26 m	27 m	28 m	29 m	30 m
necropsy status	p	p	p	p	p	r	r	r	r	r
Sciatic Nerve										
Myelin fragmentation	0	1	0	0	0					
Lungs										
Alveolar inflammation, lymphocytic	0	1	0	0	0					
Osseous metaplasia	0	0	1	0	0					
Liver										
Inflammation, granulocytic/mononuclear	0	0	1	1	1					
Kidneys										
Pelvic dilation	0	x	0	0	0	0	0	0	0	0
Hyaline droplets, cortical	3	3	3	3	3	0	0	0	0	1
Granular casts	0	0	1	0	0	0	0	0	0	0
Tubular basophilia, corticomedullary	1	0	2	2	0	0	0	2	2	1
Prostate Gland										
Inflammation, lymphoid	0	2	0	0	1					
Spleen										
Hemopoietic foci, primarily erythroid	1	1	1	1	1					
Mandibular Lymph Nodes										
Plasmacytosis	0	3	0	0	0					

Test item MTDID 7144
Test System . 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 8 Individual Animal Microscopic Findings

Males
Group 3

	16 m	17 m	18 m	19 m	20 m
necropsy status	p	p	p	p	p
Kidneys					
hyaline droplets, cortical	2	2	2	2	2
tubular basophilia, corticomedullary	1	1	0	1	0

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
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Table 8 Individual Animal Microscopic Findings

Males
Group 2

	11 m	12 m	13 m	14 m	15 m
necropsy status	p	p	p	p	p
Kidneys					
Hyaline droplets, cortical	2	0	1	0	0
Inflammation, lymphoid	0	1	0	0	0
Tubular basophilia, corticomedullary	1	1	0	0	0

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

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Table 8 Individual Animal Microscopic Findings

Males
Group 1

	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m
necropsy status	p	p	p	p	p	r	r	r	r	r
Heart										
Inflammation, lymphoid	0	0	0	1	0					
Lungs										
Alveolar inflammation, lymphocytic	0	0	0	1	0					
Esophagus										
Myodegeneration, focal	0	0	0	0	1					
Stomach										
Squamous cyst	1	0	0	0	0					
Liver										
Inflammation, granulocytic/mononuclear	1	1	2	1	0					
Kidneys										
Hyaline droplets, cortical	1	2	1	1	0	0	0	2	0	1
Inflammation, lymphoid	0	2	0	0	0	0	0	0	0	0
Tubular basophilia, corticomedullary	0	0	0	1	0	1	1	2	0	1
Tubular basophilia, outer stripe medulla, diffuse	0	3	0	0	0	0	0	0	0	0
Prostate Gland										
Inflammation, lymphoid	0	0	0	1	0					
Thyroid Glands										
Follicular hypertrophy/ hyperplasia, diffuse	0	0	0	0	1					

Test item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
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Table 8 Individual Animal Microscopic Findings

Males
Group 1

	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m
necropsy status	p	p	p	p	p	r	r	r	r	r
Heart										
Inflammation, lymphoid	0	0	0	1	0					
Lungs										
Alveolar inflammation, lymphocytic	0	0	0	1	0					
Esophagus										
Myodegeneration, focal	0	0	0	0	1					
Stomach										
Squamous cyst	1	0	0	0	0					
Liver										
Inflammation, granulocytic/mononuc.ear	1	1	2	1	0					
Kidneys										
Hyaline droplets, cortical	1	2	1	1	0	0	0	2	0	1
Inflammation, lymphoid	0	2	0	0	0	0	0	0	0	0
Tubular basophilia, corticomedullary	0	0	0	1	0	1	1	2	0	1
Tubular basophilia, outer stripe medulla, diffuse	0	3	0	0	0	0	0	1	0	0
Prostate Gland										
Inflammation, lymphoid	0	0	0	1	0					
Thyroid Glands										
Follicular hypertrophy/ hyperplasia, diffuse	0	0	0	0	1					

Test Item : MTDID 7144
Test System : 28-Day Gavage 14-Day Rec. Study in Rats
Sponsor : 3M Corporate Toxicology - Regulatory Services

NOTOX no. : 458966
Propath no. : 06031
Date : 20.Oct.2006

Table 8 Individual Animal Microscopic Findings

Males
Group 1

	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m
necropsy status	p	p	p	p	p	r	r	r	r	r
Adrenal Glands										
Vacuolation, multifocal in z. fasiculata	0	1	0	0	0					
Spleen										
Hemopoietic foci, primarily erythroid	1	1	0	2	1					

ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)
GROUP 1 (CONTROL)					
1	361	0.57	0.307	2.73	0.119
2	345	0.57	0.300	3.10	0.101
3	352	0.58	0.328	2.55	0.131
4	353	0.58	0.309	2.91	0.118
5	---	---	---	---	---
GROUP 2 (15 MG/KG)					
11	387	0.57	0.357	3.00	0.107
12	345	0.59	0.312	2.69	2.850
13	406	0.51	0.306	2.99	0.108
14	345	0.57	0.273	2.77	0.139
15	377	0.53	0.296	2.87	0.110
GROUP 3 (50 MG/KG)					
16	323	0.62	0.266	2.87	0.115
17	404	0.54	0.303	3.09	0.119
18	405	0.50	0.320	3.00	0.111
19	342	0.59	0.319	2.71	0.104
20	336	0.57	0.302	2.98	0.103
GROUP 4 (150 MG/KG)					
21	325	0.61	0.285	3.12	0.104
22	362	0.56	0.307	3.42	0.097
23	349	0.57	0.319	3.17	0.161
24	364	0.54	0.302	2.88	0.082
25	390	0.54	0.307	3.25	0.098

MALES
END OF TREATMENT

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMIDES (%)
GROUP 1 (CONTROL)					
1	0.67	0.016	0.232	0.96	0.319
2	0.83	0.017	0.218	1.05	0.274
3	0.76	0.022	0.195	0.98	0.267
4	0.76	0.022	0.299	1.00	0.367
5	---	---	---	---	---
GROUP 2 (15 MG/KG)					
11	0.82	0.019	0.241	0.91	0.267
12	0.79	0.013	0.248	1.03	0.303
13	0.80	0.013	0.253	0.92	0.325
14	0.35	0.014	0.208	1.06	0.309
15	0.80	0.017	0.211	0.97	0.312
GROUP 3 (50 MG/KG)					
16	0.89	0.016	0.222	1.01	0.290
17	0.74	0.015	0.224	0.95	0.252
18	0.75	0.015	0.226	0.92	0.257
19	0.86	0.019	0.268	1.15	0.306
20	0.82	0.022	0.224	0.95	0.338

ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)	TESTES (GRAM)	EPIDIDYMIDES (GRAM)
GROUP 4 (150 MG/KG)					
21	2.58	0.061	0.698	3.44	1.135
22	3.51	0.069	0.952	3.55	1.042
23	3.04	0.061	0.735	3.55	0.955
24	3.12	0.064	0.907	4.01	1.311
25	3.52	0.059	0.708	3.90	1.119

MALES
END OF RECOVERY

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)	THYMUS (GRAM)
GROUP 1 (CONTROL)					
6	454	2.10	1.429	13.91	0.333
7	384	2.01	1.089	10.09	0.362
8	425	2.18	1.412	11.78	0.435
9	363	2.14	1.113	8.91	0.411
10	414	2.05	1.190	11.66	0.385
GROUP 4 (150 MG/KG)					
26	387	2.15	1.152	9.67	0.396
27	374	2.00	1.120	9.81	0.337
28	436	2.11	1.293	12.31	0.333
29	411	2.05	1.302	10.79	0.381
30	418	2.00	1.327	13.14	0.295

MALES
END OF RECOVERY

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)	TESTES (GRAM)	EPIDIDYMIDES (GRAM)
GROUP 1 (CONTROL)					
6	3.48	0.070	0.982	3.42	1.302
7	2.52	0.052	0.917	4.05	1.373
8	3.18	0.058	1.100	3.97	1.400
9	2.56	0.056	0.898	3.53	1.338
10	2.62	0.066	0.960	3.67	1.133
GROUP 4 (150 MG/KG)					
26	2.71	0.067	0.818	3.53	1.435
27	2.57	0.076	0.907	3.44	1.183
28	3.22	0.070	0.787	3.92	1.476
29	3.07	0.047	0.818	3.80	1.314
30	3.32	0.065	0.981	3.41	1.385

ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMIDES (%)
GROUP 4 (150 MG/KG)					
21	0.79	0.019	0.215	1.06	0.349
22	0.97	0.019	0.263	0.98	0.288
23	0.87	0.017	0.211	1.02	0.274
24	0.86	0.018	0.249	1.10	0.360
25	0.90	0.015	0.182	1.00	0.287

MALES
END OF RECOVERY

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)
GROUP 1 (CONTROL)					
6	454	0.46	0.315	3.06	0.073
7	384	0.52	0.284	2.63	0.094
8	425	0.51	0.332	2.77	0.102
9	363	0.59	0.307	2.45	0.113
10	414	0.49	0.287	2.82	0.093
GROUP 4 (150 MG/KG)					
26	387	0.55	0.298	2.50	0.102
27	374	0.53	0.299	2.62	0.090
28	436	0.48	0.297	2.82	0.076
29	411	0.50	0.317	2.62	0.093
30	418	0.48	0.317	3.14	0.071

MALES
END OF RECOVERY

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMIDES (%)
GROUP 1 (CONTROL)					
6	0.77	0.015	0.216	0.75	0.287
7	0.66	0.014	0.239	1.05	0.358
8	0.75	0.014	0.259	0.93	0.329
9	0.71	0.015	0.247	0.97	0.369
10	0.63	0.016	0.232	0.89	0.274
GROUP 4 (150 MG/KG)					
26	0.70	0.017	0.211	0.91	0.371
27	0.69	0.020	0.243	0.92	0.316
28	0.74	0.016	0.181	0.90	0.339
29	0.75	0.011	0.199	0.92	0.320
30	0.79	0.016	0.235	0.82	0.331

ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)	THYMUS (GRAM)
GROUP 1 (CONTROL)					
31	188	1.80	0.793	5.57	0.222
32	232	1.98	0.823	6.28	0.297
33	240	1.96	0.861	6.73	0.368
34	238	1.93	0.854	7.03	0.383
35	270	2.03	0.822	7.74	0.396
GROUP 2 (15 MG/KG)					
41	236	1.98	0.806	7.25	0.341
42	216	1.92	0.788	7.15	0.258
43	224	1.90	0.802	6.37	0.428
44	226	1.85	0.737	7.91	0.201
45	220	1.90	0.834	6.48	0.245
GROUP 3 (50 MG/KG)					
46	245	1.94	0.828	7.14	0.320
47	205	1.81	0.780	6.64	0.238
48	232	1.85	0.784	8.32	0.282
49	234	1.91	0.822	7.22	0.426
50	196	1.85	0.759	7.03	0.343
GROUP 4 (150 MG/KG)					
51	236	2.01	0.890	9.43	0.308
52	---	1.95	0.779	7.24	0.317
53	257	1.96	0.895	8.54	0.296
54	238	1.84	0.776	6.99	0.405
55	212	2.01	0.807	6.44	0.253

FEMALES
END OF TREATMENT

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)
GROUP 1 (CONTROL)			
31	1.55	0.086	0.504
32	1.84	0.087	0.800
33	2.00	0.095	0.746
34	1.81	0.089	0.564
35	2.26	0.095	0.835
GROUP 2 (15 MG/KG)			
41	1.94	0.091	0.617
42	1.92	0.104	0.514
43	1.95	0.092	0.701
44	1.81	0.081	0.485
45	1.80	0.078	0.511
GROUP 3 (50 MG/KG)			
46	1.92	0.108	0.721
47	1.75	0.070	0.734
48	1.78	0.074	0.651
49	1.96	0.081	0.696
50	1.71	0.089	0.573

ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)
GROUP 4 (150 MG/KG)			
51	2.17	0.082	0.562
52	1.68	0.065	0.537
53	2.15	0.079	0.618
54	1.83	0.077	0.765
55	1.81	0.079	0.660

FEMALES
END OF RECOVERY

ANIMAL	BODY W (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)	THYMUS (GRAM)
GROUP 1 (CONTROL)					
36	236	1.85	0.826	6.33	0.225
37	248	1.90	0.804	7.24	0.282
38	222	1.98	0.751	6.15	0.300
39	234	1.96	0.847	7.08	0.317
40	236	1.84	0.826	7.63	0.282
GROUP 4 (150 MG/KG)					
56	252	1.76	0.742	6.69	0.519
57	219	1.88	0.769	6.00	0.328
58	230	1.86	0.776	7.37	0.244
59	204	1.69	0.816	5.91	0.186
60	254	1.90	0.851	7.19	0.262

FEMALES
END OF RECOVERY

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)
GROUP 1 (CONTROL)			
36	1.64	0.092	0.493
37	1.84	0.077	0.562
38	1.64	0.081	0.609
39	1.78	0.092	0.606
40	1.87	0.079	0.672
GROUP 4 (150 MG/KG)			
56	1.58	0.056	0.628
57	1.78	0.084	0.522
58	1.82	0.066	0.499
59	1.62	0.075	0.517
60	2.09	0.099	0.664

ORGAN/BODY WEIGHT RATIOS (%)
FEMALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)
GROUP 1 (CONTROL)					
31	188	0.96	0.422	2.96	0.118
32	232	0.85	0.355	2.70	0.128
33	240	0.82	0.359	2.80	0.153
34	236	0.81	0.359	2.95	0.161
35	270	0.75	0.304	2.87	0.147
GROUP 2 (15 MG/KG)					
41	236	0.84	0.342	3.07	0.144
42	216	0.89	0.365	3.31	0.119
43	224	0.85	0.358	2.85	0.191
44	228	0.81	0.323	3.47	0.088
45	220	0.86	0.379	2.94	0.111
GROUP 3 (50 MG/KG)					
46	245	0.79	0.338	2.91	0.131
47	205	0.88	0.380	3.24	0.116
48	232	0.80	0.338	3.58	0.122
49	234	0.82	0.351	3.08	0.182
50	196	0.94	0.387	3.59	0.175
GROUP 4 (150 MG/KG)					
51	236	0.85	0.377	4.00	0.131
52	---	---	---	---	---
53	257	0.76	0.348	3.32	0.115
54	238	0.77	0.326	2.94	0.170
55	212	0.95	0.381	3.04	0.119

FEMALES
END OF TREATMENT

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)
GROUP 1 (CONTROL)			
31	0.83	0.046	0.268
32	0.79	0.038	0.345
33	0.83	0.040	0.311
34	0.76	0.037	0.237
35	0.84	0.035	0.309
GROUP 2 (15 MG/KG)			
41	0.82	0.039	0.261
42	0.89	0.048	0.238
43	0.87	0.041	0.313
44	0.80	0.036	0.213
45	0.82	0.035	0.232
GROUP 3 (50 MG/KG)			
46	0.78	0.044	0.294
47	0.85	0.034	0.358
48	0.77	0.032	0.261
49	0.84	0.035	0.297
50	0.87	0.045	0.292

ORGAN/BODY WEIGHT RATIOS (%)
FEMALES
END OF TREATMENT

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)
GROUP 4 (150 MG/KG)			
51	0.92	0.035	0.238
52	---	---	---
53	0.84	0.031	0.240
54	0.77	0.032	0.321
55	0.85	0.037	0.311

FEMALES
END OF RECOVERY

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)
GROUP 1 (CONTROL)					
36	236	0.78	0.350	2.68	0.095
37	248	0.76	0.324	2.92	0.114
38	222	0.89	0.338	2.77	0.135
39	234	0.84	0.362	3.02	0.135
40	236	0.78	0.350	3.23	0.119
GROUP 4 (150 MG/KG)					
56	252	0.70	0.294	2.66	0.206
57	219	0.86	0.351	2.74	0.150
58	230	0.81	0.337	3.20	0.106
59	204	0.83	0.400	2.90	0.091
60	254	0.75	0.335	2.83	0.103

FEMALES
END OF RECOVERY

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)
GROUP 1 (CONTROL)			
36	0.69	0.039	0.209
37	0.74	0.031	0.227
38	0.74	0.036	0.274
39	0.76	0.039	0.259
40	0.79	0.033	0.285
GROUP 4 (150 MG/KG)			
56	0.63	0.022	0.249
57	0.81	0.038	0.238
58	0.79	0.029	0.217
59	0.79	0.037	0.253
60	0.82	0.039	0.261

KEY TO MISSING VALUES/REMARKS CLINICAL LABORATORY INVESTIGATIONS

End of Treatment

Haematology:		
Animal(s):		
8, 13, 21, 27	—	= Citrate sample clotted
2, 9, 11, 13, 19, 43		Differential leucocyte count was also performed manually because of an abnormal plot in the automated count
11		Manual differential leucocyte count revealed that 1% of neutrophils were band cells.

End of Recovery

Haematology:		
Animal(s):		
26, 30	—	= Citrate sample clotted
9, 30		Differential leucocyte count was also performed manually because of an abnormal plot in the automated count
30		Manual differential leucocyte count revealed that 1 % of neutrophils were band cells.

APPENDIX 3

SUMMARY OF DOSE RANGE FINDING STUDY

NOTOX Project (Range Finding) 458977

Materials and methods

If not mentioned otherwise, test system, procedures and techniques were identical to those used during the main study.

Number of rats/group	3 females (allocated at random and identified by ear- and tailmark)
Age	Approximately 6 weeks
Duration of treatment	8 days (14-21 June 2006)
Dose levels [1]	100, 500 and 1000 mg/kg body weight/day
Dose volume [2]	20 ml/kg body weight/day
Vehicle	Milli-U water

[1] Dose levels were based on the results of the acute oral toxicity study (NOTOX project 458911)
[2] Dose volume selected to achieve a lower dose concentration, based on anticipated local irritating effects of the test substance.

Observations	Clinical signs:	At least once daily.
	Mortality:	At least twice daily.
	Body weights:	On days 1 and 8.
	Food consumption:	Over days 1-8.
Pathology	Necropsy:	All animals. No organs were fixed.
	Organ weights:	Terminal body weight, kidney and liver weight.

Results

Parameter	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Mortality	No mortality.	All animals sacrificed for ethical reasons on day 2.	All animals found dead on day 1.
Clinical appearance	No clinical signs noted.	Tremors, plat posture, uncoordinated movements, piloerection, pale appearance and/or ptosis (all animals)	No clinical signs noted.
Body weight	Normal.	a	a
Food consumption	Normal.	a	a
Macroscopic examination	No abnormalities noted.	Isolated red foci on the glandular mucosa of the stomach (one animal).	Several red foci on the glandular mucosa of the stomach (one animal).
Organ weights	Liver and kidney weights considered to be normal.	a	a

a) Not essessed; animals found dead/sacrificed on days 1/2.

Conclusion

Based on the results of this range finding study and in consultation with the sponsor, dose levels selected for the main study (28 days toxicity study) were: 15, 50 and 150 mg/kg body weight/day.

APPENDIX 4

ANALYTICAL REPORT

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2. REPORT APPROVAL

PRINCIPAL SCIENTIST: Ir. M.J.C. Brekelmans
(Analytical Chemistry)

Date: November 02, 2006

3. SUMMARY

The purpose of this part of the study was to determine the accuracy of preparation, homogeneity and stability of the test substance in formulations (Milli-U water).

The concentrations analysed in the formulations of Group 2, Group 3 and Group 4 were between 80% and 111% of target. Since these results were in line with the results of the procedural recovery samples, accuracy of preparation was considered to be acceptable. No test substance was detected in the Group 1 formulations.

The formulations of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation < 10%).

Formulations at the entire range were stable for at least 5 hours when stored at room temperature under normal laboratory light conditions.

4. INTRODUCTION

4.1. Preface

Study plan (analytical study)	Start	: 11 July 2006
	Completion	: 12 July 2006

4.2. Aim of the study

The purpose of the analytical study was to determine the accuracy of preparation, homogeneity and stability of the test substance in formulations (Milli-U water).

5. MATERIALS AND METHODS

5.1. Reagents

Milli-Q water	Tap water purified by a Milli-Q water purification system (Millipore, Bedford, MA, USA)
Methanol	VWR International, Leuven, Belgium
Ammonia solution 25%	Merck, Darmstadt, Germany
Milli-Q water pH 11	Milli-Q water adjusted to pH 11 using ammonia solution 25%

All reagents were of analytical grade purity, unless specified otherwise.

5.2. Samples

Accuracy, homogeneity and stability were determined for formulations prepared during treatment.

Duplicate samples (approximately 500 mg), which were taken from the formulations using a pipette, were accurately weighed into volumetric flasks of 25 ml. For determination of accuracy, samples were taken at 50% height or at 90%, 50% and 10% height. The latter set of samples was also used for the determination of the homogeneity of the formulations. For determination of stability, additional samples were taken at 50% height [1].

The flasks were filled up to the mark with 50/50 (v/v) methanol/Milli-Q water. The solutions were further diluted with 50/50 (v/v) methanol/Milli-Q water to obtain concentrations within the calibration range.

[1] Because at t=0 samples were taken at 10% 50%, and 90% height, the mean concentration of these samples was used as t=0 value for calculation of stability.

5.3. Analytical method

5.3.1. Analytical conditions

Quantitative analysis was based on the analytical method validated for the test substance during NOTOX project 459056.

Analytical conditions:

Column	
Stationary phase	Xterra MS C18
Dimensions	100 mm × 2.1 mm i.d.; dp = 3.5 µm
Brand	Waters, Milford, MA, USA
Mobile phase	50/50 (v/v) methanol/Milli-Q water at pH 11
Flow	0.2 ml/min
Injection volume	10 µl
Detection	MS detection using a ZQ 2000 mass spectrometer (Waters, Milford, MA, USA)
Ionisation source	ESI^-
Acquisition	selected ion recording (SIR) at m/z 130 amu
Cone voltage	30 V
Quantitation on mass	130 amu

5.3.2. Preparation of the calibration solutions

Stock- and spiking solutions
Stock and/or spiking solutions of the test substance were prepared in methanol at concentrations of 3184 and 4908 mg/l.

Calibration solutions
Calibration solutions in the concentration range 0.501 – 5.01 mg/l were prepared from two stock solutions. The end solution of the calibration solutions was 50/50 (v/v) methanol/Milli-Q water.

Procedural recovery samples
Blank vehicle (approximately 500 mg) was spiked with the test substance at a nominal concentration of approximately 0.5 or 10 mg/g using a spiking solution or pure test substance, respectively. The accuracy samples were treated as described in paragraph 5.2 'Samples'. Nominal concentrations were not corrected for the spiking volume.

5.3.3. Sample injections

Calibration solutions were injected in duplicate. Test samples and procedural recovery samples were analysed by single injection.

5.4. Electronic data capture

System control, data acquisition and data processing were performed using the following programme:
- Empower version 5.00 (Waters, Milford, MA, USA).

5.5. Formulas

Response (R) — Peak area test substance [units]

Calibration curve

$$R = a\,C_N^2 + b\,C_N + c$$

where:
C_N = nominal concentration [mg/l]
a = quadratic regression factor [units × (l/mg)^2]
b = linear regression factor [units × l/mg]
c = intercept [units]

Analysed concentration (C_A)

$$C_A = \frac{-b + \sqrt{b^2 - 4\,a \times (c - R)}}{2\,a} \times \frac{V \times d}{w} \quad [mg/g]$$

where:
w = weight sample [mg]
V = volume volumetric flask [ml]
d = dilution factor

Recovery

$$\frac{C_A}{C_N} \times 100\%$$

where:
C_N = nominal concentration [mg/g]

Accuracy

$$\frac{C_A}{C_T} \times 100\%$$

where:
C_T = target concentration [mg/g]

Relative difference (relative diff.)

$$\frac{\text{mean conc. } t = 5 - \text{mean conc. } t = 0}{\text{mean concentration } t = 0} \times 100\%$$

where:
t = time of sampling [hours]

5.6. Specifications

Preparation of formulations was considered acceptable if the measured concentration levels were between 90% and 110% of the target concentrations and if the coefficient of variation was < 10%. Additionally, formulations were considered to be stable if the relative difference between the t=0 and t=5-hour samples was < 10%.

6. RESULTS

6.1. Calibration curves

A calibration curve was constructed using five concentrations. For each concentration, two responses were used. Quadratic regression analysis was performed using the least squares method with a 1/concentration^2 weighting factor. The coefficient of correlation (r) was > 0.99.

HPLC-MS chromatograms of a test substance solution and blank solution are shown in Figure 1.

6.2. Samples

6.2.1. Procedural recovery samples

The results for the procedural recovery samples are given in Table 1.

Mean recoveries of the procedural recovery samples were 92% and 106%. Because the criterion that mean recoveries should be between 70% and 110% was met, the results for the test samples were accepted.

6.2.2. Test samples

The results of the test samples are given in Tables 2 and 3. Figure 2 shows HPLC-MS chromatograms of samples from Group 1, Group 2, Group 3 and Group 4 taken at 50% height.

In the Group 1 formulations, no test substance was detected. The concentrations analysed in formulations of Group 2, Group 3 and Group 4 were between 80% and 111% of target. Since these results were in line with the results of the procedural recovery samples, accuracy of preparation was considered to be acceptable.

The formulations of Group 2 and Group 4 were homogeneous (2.4% and 4.1% coefficient of variation, respectively).

Analysis of Group 2 and Group 4 formulations after 5 hours of storage at room temperature and light yielded a relative difference of -9.3% and -6.7%, respectively. Therefore, the samples were considered stable at room temperature and under normal laboratory light conditions for at least 5 hours.