

January 7, 1997
U. S. Environmental Protection Agency
Dipropylene Glycol t-Butyl Ether
Page 2

response to the high levels of exposure to the test material. The minor degree of centrilobular hepatocyte enlargement in 4/5 cases in males only also was considered as a physiological adaptation. In the 90-day study, minimal centrilobular hepatocyte hypertrophy again was seen in male and female rats receiving 1000 mg/kg/day. However, recovery from this effect was complete following 4 weeks off-dose, providing further evidence of physiological adaptation.

The eosinophilic droplets, presumed to be α_2 microglobulin, in renal cortical tubular epithelia in 5/5 cases noted in the range-finding study also were observed with male rats in the 90-day study. As noted in our previous correspondence, this response is thought to be a condition specific to male rats and, therefore, not considered relevant to humans. The incidence of treatment-related renal changes seen in the 90-day study was less in male rats allowed a recovery period than in male rats at the end of treatment. This was considered to indicate partial reversibility of these renal changes.

The statistically significant decrease in lymphocytes and leukocytes reported in the preliminary analysis of results from high dose males only was confirmed in the final report from the 14-day study. This effect was not considered to be biologically significant, based on intra- and inter-group variations in the data. Preliminary and final results from the 90-day study confirmed that no clear dose-response was seen in these data at any dose level, and recovery group animals showed no differences from concurrent controls.

Increased adrenal weight and associated minimal increased width of the zona fasciculata seen in female rats at the high dose in the range-finding study also appeared in the 90-day study. These effects were not detected after the recovery period.

Under the EC criteria for classification and labelling of dangerous substances, the minimal effects seen in this study would not result in classification, indicating that DPTB would not be expected to present a significant risk to human health.

Sincerely,



D. C. Boyle

CC: Mr. Mark Howard
U. S. Environmental Protection Agency

Huntingdon

DIPROPYLENE GLYCOL T-BUTYL ETHER (DPTB)

**TOXICITY TO RATS BY REPEATED ORAL ADMINISTRATION FOR 13 WEEKS
INCORPORATING A NEUROTOXICITY SCREEN AND FOLLOWED BY A 4-WEEK
RECOVERY PERIOD**

Volume 1

DIPROPYLENE GLYCOL T-BUTYL ETHER (DPTB)
TOXICITY TO RATS BY REPEATED ORAL ADMINISTRATION FOR 13
WEEKS INCORPORATING A NEUROTOXICITY SCREEN AND FOLLOWED BY
A 4-WEEK RECOVERY PERIOD

Volume 1

Sponsor

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Newtown Square,
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PA 19073 - 2387,
U.S.A.

Testing facility

Huntingdon Life Sciences Ltd.,
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Report issued 17 December 1996

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COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

Good Laboratory Practice, The United Kingdom Compliance Programme, Department of Health & Social Security 1986 and subsequent revision, Department of Health 1989.

EC Council Directive, 87/18 EEC of 18 December 1986, (No. L 15/29).

Good Laboratory Practice in the testing of Chemicals OECD, ISBN 92-64-12367-9, Paris 1982, subsequently republished OECD Environment Monograph No. 45, 1992.

United States Environmental Protection Agency, (FIFRA), Title 40 Code of Federal Regulations Part 160, Federal Register, 29 November 1983 and subsequent amendment Federal Register 17 August 1989.

Japan Ministry of Agriculture, Forestry and Fisheries, 59 NohSan, Notification No. 3850, Agricultural Production Bureau, 10 August 1984.

Note: The animal arrival date (3 January 1996) was before the date on which the protocol was signed and issued (12 January 1996) however this point of non-compliance with GLP did not compromise the study.



Steven J. Crome, B.Sc., M.Sc.,
Study Director,
Huntingdon Life Sciences Ltd.

17 December 1996.

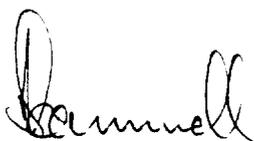
Date

QUALITY ASSURANCE STATEMENT

This report has been audited by Huntingdon Life Sciences Quality Assurance Department (Huntingdon). The methods, practices and procedures reported herein are an accurate description of those employed at Huntingdon during the course of the study. Observations and results presented in this final report form a true and accurate representation of the raw data generated during the conduct of the study at Huntingdon.

Inspections were made by the Quality Assurance Department of various phases of the study as conducted at Huntingdon and described in this report. The dates on which the inspections were made and the dates on which findings were reported to the Study Director and to Management, Huntingdon Life Sciences are given below.

Phase of Study	Date of Inspection	Date of Reporting
Protocol Review	-	17 January 1996
Pre-experimental Period	-	-
Experimental Period	22 - 23 January 1996	23 January 1996
	1 March 1996	13 March 1996
	11 April 1996	11 April 1996
	18 - 19 April 1996	19 April 1996
	16 May 1996	24 May 1996
	7 June 1996	7 June 1996
Date of reporting audit findings to the Study Director and Management		14 November 1996



Rod Scammell,
 Audit Team Supervisor,
 Department of Quality Assurance,
 Huntingdon Life Sciences Ltd.

17.12.96
 Date

RESPONSIBLE PERSONNEL

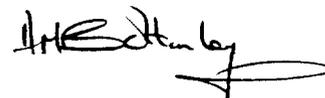
STUDY MANAGEMENT

Steven J. Crome, B.Sc., M.Sc.,
Study Director,
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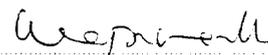
TOXICOLOGY

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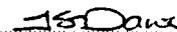
PATHOLOGY

Chirukandath Gopinath, B.V.Sc., M.V.Sc., Ph.D., F.R.C.Path.,
Director of Pathology.



FORMULATION ANALYSIS

I. Suzanne Dawe, M.Sc., C.Chem., M.R.S.C.,
Head, Formulation Analysis,
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NEUROTOXICOLOGY

Elizabeth W. Hughes, B.A., M.Sc.,
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SUMMARY

The test substance DPTB was administered by daily, oral gavage to groups of CrI:CD BR rats for a period of 13 weeks; control animals were concurrently dosed with vehicle (water) only. Fifty rats were dosed with DPTB at 1000 mg/kg/day: 10 males plus 10 females for toxicity evaluation (main group), 10 males plus 10 females for investigation of the reversibility of any treatment-related effects (recovery group: terminated after a four week respite from treatment) and 5 males plus 5 females for neurotoxicity/neuropathology evaluation. The vehicle control group was similarly constituted, whilst the intermediate and low dose groups comprised only 10 + 10 main group rats and 5 + 5 for neurotoxicology/neuropathology. Clinical signs, bodyweight and food intake were assessed throughout the study period; water intake was measured in Week 12 of the dosing period and again in Week 3 of the recovery period. Haematology investigations were undertaken during Weeks 5 and 13 of dosing and in Week 4 of recovery; biochemistry investigations were also undertaken on the first two of these occasions. Behavioural screening to assess neurotoxicity was performed in Weeks 4, 8 and 12 of dosing. All rats were necropsied at termination, with weighing of major organs and microscopic examination of collected tissues.

Mortalities

There were no deaths attributable to treatment. One control female died following blood sampling in Recovery Week 4.

Clinical signs

Noted in animals receiving 1000 mg/kg/day only - salivation after dosing, throughout the study at an incidence increasing with time; unsteady gait, collapsed posture, partially closed eyelids, body spasms and paddling of forelimbs from Weeks 8 - 12 onwards in a small proportion of animals. No treatment related signs were seen during the recovery period.

Bodyweight and food consumption

No treatment-related effects were apparent.

Water consumption

Water consumption was increased among males receiving 1000 mg/kg/day in Week 12 of dosing but this was not apparent in Week 3 of recovery.

Ophthalmoscopy and neurotoxicology

No treatment-related effects were apparent.

Haematology

Slight, but statistically significant reductions in white blood cell and lymphocyte counts were seen in Week 5 (males receiving 1000 mg/kg/day only) and 13 (both sexes receiving 1000 mg/kg/day, females only receiving 250 mg/kg/day) of the treatment period. Values recorded in the test animals were within historical control ranges, so the relationship between the observed reductions and treatment with DPTB is unclear, recovery group animals showed no differences from concurrent controls.

Biochemistry

Increases in group mean albumin and globulin levels (and, consequently, increased total protein) were noted in Weeks 5 and 13 for both sexes receiving 1000 mg/kg/day. These increased plasma protein concentrations were probably associated with the liver changes described below.

Terminal studies

Increased liver weights in both sexes receiving 1000 mg/kg/day were associated with macroscopically enlarged livers in males and minimal centrilobular hepatocyte hypertrophy in both sexes of rats killed after 13 weeks of treatment. Recovery was complete following 4 weeks off-dose.

Increased kidney weights were noted in both sexes receiving 1000 mg/kg/day and males only receiving 250 mg/kg/day, after 13 weeks of treatment. This was associated with an increased degree and incidence of cortical tubules with eosinophilic inclusions in males at all dose levels, a dose-related incidence of minimal basophilic cortical tubules in males at 250 or 1000 mg/kg/day, and cellular debris casts in small numbers of males at 250 or 1000 mg/kg/day. There were no microscopic changes in females. Increased kidney weights, and an increased incidence of minimal basophilic cortical tubules and cellular debris casts in cortical tubules were still apparent 4 weeks after the last treatment, but at a lower incidence indicating partial reversibility of the changes.

A raised incidence of minimally increased width of the zona fasciculata was seen in female rats receiving 1000 mg/kg/day, compared to female controls. This change was possibly related to the significantly increased mean adrenal weight (adjusted for bodyweight) seen in the same group of females.

Minimally increased width of the zona fasciculata was seen in a single male rat receiving 1000 mg/kg/day was comparable to that seen in one (female) control animal; it was not considered to be treatment-related. No microscopic changes were seen which might be related to the increased mean (bodyweight-adjusted) adrenal weights found in male rats receiving 250 or 1000 mg/kg/day.

Reversibility of these changes was complete after 4 weeks without treatment.

Conclusion

In this study 1000 mg/kg/day was a clear effect level, producing changes in the liver, adrenals and kidneys and (questionably) in white blood cell counts. As the changes seen in the male rat kidney were of a type not considered relevant to man and no other toxicologically significant changes were seen in animals given 250 mg/kg/day, this was a No Observed Adverse Effect Level in both sexes for oral administration of DPTB. Similar kidney changes in male rats have been seen following administration of a variety of substances (Swenberg 1993). These were also seen in males of the low dose group: hence no No Effect Level could be established. In contrast, 62.5 mg/kg/day was a clear NOEL for females. Under the EC criteria for classification and labelling of dangerous substances (Commission Directive 93/21/EEC of 27 April 1993), no classification or risk phrase is required for DPTB in respect of damage to health following prolonged exposure.

INTRODUCTION

The object of this study, performed at Huntingdon Life Sciences Ltd., England, was to assess the toxicity and the potential neurotoxicity of the test substance, DPTB, to rats by repeated oral administration over a period of 13 weeks followed by a 4-week recovery period.

The neurotoxicity component was designed in accordance with EPA FIFRA Pesticide Assessment Guidelines, Subdivision F, Addendum 10, Neurotoxicity, published March 1991, contained in NTIS PB91-154617 which is also applicable to neurotoxicity testing requirements for industrial chemicals under the Toxic Substances Act (TSCA).

Otherwise, this study was designed in accordance with EPA TOSCA Test Guidelines, 40 CFR Part 798 - Health Effects Testing Guidelines, September 27 1985, 798.2650, Oral Toxicity and Subsequent Revisions, May 20 1987/Dec 6 1988/May 16 1989 and with note for guidance concerning the application of the Annex of Directive 92/69/EEC and OECD Guideline for Testing of Chemicals No. 408. "Subchronic Oral Toxicity - Rodent" dated 12 May 1981.

The treatment levels were chosen by the Sponsor with reference to available toxicity data from a 14-day study (ARO 25/960403) performed at this laboratory.

The rat is a recognised species of choice for regulatory requirement and the strain was chosen on account of the availability of background data. Oral administration was chosen since this is a potential route of human exposure.

RELEVANT STUDY DATES

Protocol approval by:	
Study Director	12 January 1996
Management	12 January 1996
Study Sponsor	16 January 1996
Animals arrival at Huntingdon Life Sciences:	
	3 January 1996
Treatment commenced:	
	18 January 1996
Water consumption:	
Week 12	4 - 11 April 1996
Recovery Week 3	2 - 9 May 1996
Ophthalmoscopy:	
Pre-dose	9 January 1996
Week 13	16 April 1996
Neurobehavioural screening:	
Week 4	8 - 11 February 1996
Week 8	7 - 10 March 1996
Week 13	11 - 14 April 1996
Haematology and Biochemistry:	
Week 5	20 February 1996
Week 13	17 April 1996
Recovery Week 4*	15 May 1996
Terminal kill:	
	18 - 23 April 1996
Recovery kill:	
	16 May 1996

* Haematology only

TEST SUBSTANCE

Identity:	DPTB
Chemical name:	Dipropylene glycol t-butyl ether
Intended use:	Additive/solvent
Appearance:	Clear, colourless liquid
Storage conditions:	Room temperature, in the dark, under nitrogen
Batch no.:	HRC - 1095
Expiry date#:	Stated by the Sponsor to be stable for at least the duration of this study
Purity:	>97%
Date received:	17 November 1995
Stability of formulations:	15 days at 4°C

The Sponsor is responsible for characterisation and stability of the test substance

EXPERIMENTAL PROCEDURE

ANIMAL MANAGEMENT

A total of 99 male and 99 female CrI:CD BR rats, 26 - 28 days old, was received from Charles River Breeding Laboratories, Manston Road, Margate, Kent, England. The estimated age of those animals selected for the study was 6 weeks at the start of treatment and bodyweights were in the range 148 g to 207 g (males) and 133 g to 176 g (females).

On arrival, 5 males and 5 females selected at random were used for health check purposes. These animals were killed within 24 hours of arrival at Huntingdon Life Sciences and subjected to routine macroscopic examination. Lungs, liver, kidneys, spleen and heart were preserved in fixative, but not processed further. No macroscopic abnormalities were detected.

The remaining rats were housed individually at random in suspended cages with wire mesh floors, according to sex. Each cage measured 21 cm high, 26 cm wide and 27 cm deep.

Animal room temperature and relative humidity were maintained at 18°C to 24°C and 22 to 72% respectively. Although the humidity range exceeded that specified in the protocol this was not considered to have affected the integrity of the study. Permanent weekly recordings of these parameters were made and these are archived with all other data for this study. Artificial lighting was controlled to give 12 hours continuous light and 12 hours continuous light and 12 hours continuous dark per 24 hours.

All rats had free access to tap water and pelleted SDS Rat and Mouse No. 1 maintenance diet. There was no information available to the Study Director to indicate that any non-nutrient substance likely to influence the effect of the test substance was in the diet, or drinking water, both of which were routinely subjected to regular chemical analyses, results of which are lodged in Huntingdon Life Sciences Archives, Huntingdon.

After an acclimatisation period of eight days, each animal was weighed (Week -1) and the required number of Main and Neuropath group animals was selected by discarding those animals furthest from the mean bodyweight. The animals were then randomly assigned to cages, stratified by bodyweight. The appropriate number of cages were then allocated to each treatment group. This procedure assured that the initial group mean bodyweights were approximately equal. After a further 5 days, the required number of Recovery group animals were selected following the same procedure and using the bodyweights recorded at Week -1.

A total period of acclimatisation of seven days for Main and Neuropath groups and two days for Recovery groups was allowed between allocation of animals to groups and the commencement of treatment. During this period a review of animal health was undertaken by a veterinary officer. The spare animals were retained during this acclimatisation period to replace any rat showing signs of ill health. Animal no. 16 (Group 2♂) was replaced prior to the commencement of treatment due to absence of toes on a hindpaw. The replacement animal was designated number 1016. On the day after commencement of treatment the spare rats were discarded without further investigation.

Throughout the study the animals were housed in the Department of Rodent Toxicology, Barrièred Rodent Building No. 1, in Room 30 on arrival and in Room 27 from the day after arrival and throughout the study.

ANIMAL IDENTIFICATION

Group	Animal numbers					
	Main groups		Neuropath (Satellite) groups		Recovery groups	
	♂	♀	♂	♀	♂	♀
1	1 - 10	41 - 50	81 - 85	101 - 105	121 - 130	141 - 150
2	11 - 20†	51 - 60	86 - 90	106 - 110	-	-
3	21 - 30	61 - 70	91 - 95	111 - 115	-	-
4	31 - 40	71 - 80	96 - 100	116 - 120	131 - 140	151 - 160
Health check	161 - 165	166 - 170				

† Animal number 16 was replaced with animal number 1016 - see **ANIMAL MANAGEMENT**.

The rats were housed individually. Each cage was identified by a coloured label according to group, each label was uniquely numbered with cage and study number and the animal number was tattooed on the leg of each rat. The cages constituting each group were dispersed in batteries so that possible environmental influences arising from their spatial distribution were equilibrated, as far as possible, for all treatments.

PREPARATION OF FORMULATIONS

The test substance, DPTB, was weighed out and stirred in with the vehicle, distilled deionised water, using a magnetic stirrer. Once up to volume, the formulation was homogenised to thoroughly mix the test substance and vehicle together. Any samples required were taken whilst the formulation was being stirred magnetically. Each concentration was prepared by direct dilution, on a weekly basis, the concentrations being chosen to give a constant dosage volume of 10 ml/kg bodyweight. Following preparation, daily aliquots were decanted and stored in amber glass bottles, sealed with plastic screw caps lined with waxed card and stored at 4°C when not in use.

Group/ colour code	Dosage (mg/kg/day)	Concentration (mg/ml)	Dose volume (ml/kg)
1: White	Control	0	10
2: Yellow	62.5	6.25	10
3: Green	250	25	10
4: Red	1000	100	10

FORMULATION SAMPLING AND ANALYSIS

Prior to the commencement of the study, the proposed formulation procedure was checked by chemical analysis and it was confirmed that the method was acceptable and that formulations in a concentration range of 0.1 to 100 mg/ml were stable for 15 days at 4°C.

Samples of the solutions prepared for the first week and Week 11 of dosing (solutions were prepared on a weekly basis) were taken from all groups and were analysed to check the accuracy of preparation. In addition, contingency samples were taken in Week 13 and stored frozen but were not analysed. Chemical analysis was carried out by Huntingdon Life Sciences Department of Analytical Chemistry and results are appended to this report.

ADMINISTRATION OF FORMULATIONS

The test substance, DPTB, was administered as a solution in distilled, deionised water. Control animals received the vehicle alone. The animals were dosed, where possible, at approximately the same time each day using a suitably graduated syringe and a rubber catheter (Ch 8 or 10) inserted into the stomach. The dosage volume administered to each animal was calculated according to the most recent recorded bodyweight. A constant dosage volume of 10 ml/kg was used.

Treatment in this manner continued once a day, 7 days a week, for a total period of 13 weeks.

OBSERVATIONS

Dated and signed records of all activities relating to daily maintenance of the study within the animal unit, as well as the group observations and examinations outlined in this procedure, were recorded in the Study Day Book.

The following observations were made during the course of the study.

Clinical signs and mortality

Individual animals were observed at least once daily for any signs of behavioural changes, reaction to treatment or ill health. These examinations were performed each weekday, at suitable intervals after dosing. Daily for the first 4 weeks and subsequently weekly, they were palpated.

Dated and signed records of appearance, change and disappearance of clinical signs were maintained on clinical history sheets for individual animals.

Further checks were made early in each working day and again in the afternoon to look for dead or moribund animals. This allowed *post mortem* examination to be carried out during the working period of that day. At weekends and public holidays a similar procedure was followed except that the final check was carried out at approximately mid-day.

The rat which was found dead during the study was subjected to a detailed macroscopic examination and a full spectrum of tissue samples were preserved in the appropriate fixative (see **MORTALITY**).

Bodyweight

The weight of each rat was recorded at the time of allocation of animals to groups on the day of commencement of treatment, and once a week thereafter, including the day of sacrifice.

Animals designated for the functional observational battery were also weighed on each occasion of testing.

Food consumption

The quantity of food consumed by each rat was recorded on a weekly basis. Food intake per rat (g/rat/day) was calculated using the total amount of food given to and left by each rat in each group. The following formula was used:

$$\text{Food consumption (g/rat/day)} = \frac{\text{Total food given} - \text{Total food left}}{\text{Number of animal days} *}$$

The results using this formula (presented in Appendix 3) were subject to rounding to the nearest whole number.

To provide a more accurate measure of the food consumed by each animal in a group, the following formula was used for group mean calculation.

$$\text{Group mean consumption (g/rat/day)} = \frac{\text{Total food given to group} - \text{Total food left by group}}{\text{Number of animal days} * \text{ for the group}}$$

It is therefore inappropriate to attempt to calculate the stated group means (presented in Table 3) from the individual values in the appendix.

Efficiency of food utilisation

Food conversion ratios were calculated from the bodyweight and food consumption data as weight of food consumed per unit gain in bodyweight. The following formula was used:

$$\text{Food conversion ratio} = \frac{\text{Food consumed over the specified period}}{\text{Bodyweight gain over the specified period}}$$

The 'food consumed' was calculated as indicated in the **Food consumption** section and is not a mean of the individual cage means. The 'bodyweight gain' as calculated from the gain of each animal over the period specified and uses the mean gain in the formula.

* The term 'animal day' counts one animal day for each animal alive for a whole day. It is assumed that on the day of death an animal does not eat.

Water consumption (Main and Recovery groups)

Daily monitoring by visual appraisal of the water bottles was maintained throughout the study.

Water consumption was measured accurately, by weight, over daily periods during Week 12 and Week 16 (Week 3 of recovery) for individual animals.

Ophthalmoscopy

Before treatment commenced, the eyes of all animals were examined by means of a Keeler indirect ophthalmoscope. During Week 13 the eyes of all Main and Recovery animals in Groups 1 and 4 were examined.

Prior to examination, the pupils of each animal were dilated using a Tropicamide ophthalmic solution. During the dosing period, the examination was performed before administration of the daily dose.

Neurobehavioural screen (Main and Neuropath groups)

A functional observational battery and motor activity assessment were performed on a total of 10 animals/sex/group (5 Neuropath group animals/sex/group, and 5 Main group animals/sex/group).

The functional observational battery and motor activity assessment were performed at approximately the same time of day, before initiation of treatment and during the 4th, 8th and 13th week of treatment. Observations in Week 13 were performed prior to any laboratory investigations. Not all rats were tested in one day, but time of testing was balanced across the groups with observations performed prior to dosing of individual animals.

Details and results of the functional observational battery and motor activity assessment are appended to this report.

Laboratory investigations (Main and Recovery groups)

During Week 5 and 13, samples of blood were withdrawn, under light ether anaesthesia, from the orbital sinus of 5 Main group and 5 Recovery group animals in Groups 1 and 4 and all Main group rats from Groups 2 and 3. All Recovery group animals were similarly sampled for haematological investigations during Week 17 (Week 4 of recovery).

The blood samples collected were divided into tubes as follows:

- EDTA anticoagulant for haematological investigations
- Citrate anticoagulant for coagulation tests
- Heparin anticoagulant for biochemical tests

Food was removed overnight from animals to be sampled for laboratory investigations except from females for the repeat sampling for thrombotest performed during Week 17 (Week 4 of recovery).

The estimations performed on blood samples are listed below, together with an abbreviated title for use in Appendices and Tables), the methods and the units of measurement applicable at the time

Haematology

Units

The following estimations were performed using a Bayer-Technicon HIE haematology analyser:

Packed cell volume (PCV)		%
Haemoglobin (Hb)		g/dl
Red cell count (RBC)		$\times 10^{12}/l$
Absolute indices calculated as follows:		
Mean corpuscular haemoglobin concentration (MCHC)		g/dl
Hb (g/dl) $\times 100 \div$ PCV (%)		
Mean corpuscular volume (MCV)		fl
PCV (%) $\times 10 \div$ RBC ($\times 10^6/mm^3$)		
Mean corpuscular haemoglobin (MCH)		pg
Hb (g/dl) $\times 10 \div$ RBC ($\times 10^6/mm^3$)		
Total white cell count (WBC Total)		$\times 10^9/l$
Differential WBC count (Diff)		
Neutrophils	(N)	} $\times 10^9/l$
Lymphocytes	(L)	
Eosinophils	(E)	
Basophils	(B)	
Monocytes	(M)	
Large unstained cells	(LUC)	

Cell Morphology: abbreviations used for cell morphology are indicated below:

Anisocytosis	Anis
Microcytosis	Micro
Macrocytosis	Macro
Variation in colour	Var
Hypochromasia	Hypo
Hyperchromasia	Hyper
Left shift	LS
Atypical cells	Atyp
Blast cells	Blast
No abnormalities detected	-
Slight	+
Moderate	++
Marked	+++

	Units
Platelet count (Plts)	$\times 10^9/l$
Thrombotest (TT) - (Owren, P.A., 1959)	s

Biochemistry

The following parameters were analysed with an Hitachi 737 Clinical Chemistry analyser:

Total Protein	g/dl
Albumin (Alb)	g/dl
Globulin (Glob) - By subtraction Total protein (g/dl) minus Albumin (g/dl)	g/dl
Urea Nitrogen (Nitr)	mg/dl
Creatinine	mg/dl
Sodium (Na)	mEq/l
Potassium (K)	mEq/l
Calcium (Ca)	mEq/l
Inorganic Phosphorus (P)	mEq/l
Chloride (Cl)	mEq/l
Cholesterol (Chol) - (Enzymatic assay)	mg/dl
Alkaline phosphatase (AP) Reaction temperature 30°C	mU/ml
Total bilirubin	mg/dl
Glucose (Hexokinase mediated assay)	mg/dl
Glutamic-pyruvic transaminase (GPT), also known as 'alanine aminotransferase' Reaction temperature 30°C	mU/ml
Glutamic-oxaloacetic transaminase (GOT), also known as 'aspartate aminotransferase' Reaction temperature 30°C	mU/ml

	Units
	Units
γ Glutamyl transferase (γ GT) Reaction temperature 30°C	mU/ml
Ornithine carbamoyl transferase (OCT) (Cerioti G., 1973) Reaction temperature 37°C	mU/ml

TERMINAL STUDIES

Main and Recovery group

On completion of 13 weeks treatment, all surviving Main group rats were killed. Recovery group rats were killed after a further 4-week period without treatment.

As the terminal procedure took 2 days to complete for Main group animals, the dosing of individual treated animals continued until the day before they were killed. The duration of the dosing period, however, is reported as 13 weeks. The terminal procedures for Recovery group animals took one day.

All rats were killed by carbon dioxide asphyxiation and subjected to the necropsy procedure indicated below.

All superficial tissues were examined visually and by palpation and the cranial roof removed to allow observation of the brain, pituitary gland and cranial nerves. After ventral midline incision and skin reflection, all subcutaneous tissues were examined. The condition of the thoracic viscera were noted with due attention to the thymus, lymph nodes and heart.

The abdominal viscera were examined before and after removal, the urinary bladder was examined externally and by palpation. The gastrointestinal tract was examined as a whole and the stomach and caecum was incised and examined. The lungs were removed and all pleural surfaces examined under suitable illumination. The liver was sectioned at intervals of a few millimetres; the kidneys were incised and examined. Any abnormalities in the appearance and size of the gonads, adrenals, uterus, intra-abdominal lymph nodes and accessory reproductive organs were recorded.

The following organs from all animals killed at the scheduled sacrifice were dissected free of fat and weighed:

adrenals	liver	spleen
brain	ovaries	testes
epididymides	pituitary	thyroid
heart	prostate	uterus
kidneys	seminal vesicles	

Testes and epididymides were weighed individually and identified as left or right.

Preservation of tissues

Samples of all the tissues listed below from all animals were preserved in buffered 10% formalin (except eyes, which were preserved in Davidson's fixative and testes/epididymides which were fixed in Bouin's solution and then transferred to 70% alcohol).

adrenals*	heart*	skeletal muscle
alimentary tract*	kidneys*	skin
(oesophagus, stomach	larynx and pharynx	spinal column (to preserve
duodenum, jejunum,	liver*	and examine samples of
ileum, caecum, colon,	lungs* (all lobes and	spinal cord from cervical
and rectum)	mainstem bronchi)	level)
aorta*	lymph nodes* (cervical	spleen*
brain* (medullary,	and mesenteric)	sternum* (for bone and
cerebellar	mammary gland	marrow)
and cerebral sections)	other macroscopic	testes*
epididymides*	abnormalities*	thymus* (where present)
eyes	ovaries*	thyroid* (with parathyroids)
femur (with joint)	pancreas*	tongue
Harderian gland	pituitary*	trachea*
head (to preserve nasal	prostate*	urinary bladder*
cavity, paranasal sinuses,	salivary glands*	uterus* (corpus and cervix)
oral cavity, nasopharynx,	sciatic nerve*	vagina
middle ear, teeth,	seminal vesicles*	
lachrymal gland and		
Zymbal's gland)		

This extensive list of tissues preserved was intended to satisfy any possible future requirements for further examination of tissues.

Histopathological examination

The tissues indicated by * above were examined for all animals by light microscopy.

Prior to microscopic examination tissues were embedded in paraffin wax and sections cut at 4 micrometres and stained with haematoxylin and eosin.

Frozen sections of liver, previously fixed in formol calcium were cut on a cryostat at 12 micrometres and stained for fat using Oil Red O (ORO).

The macroscopic and microscopic findings are presented in Appendix 9 by an automated data collection system. Particular care was taken during tissue removal and processing to ensure recovery and sectioning of all protocol-scheduled tissues. Understandably, omissions or irregularities can occasionally occur, in rodents the most vulnerable tissues in this regard being parathyroid, thymus and male mammary gland. For each animal, any tissue so affected is listed as not seen. WNL (within normal limits) indicates that a macroscopically abnormal tissue was within normal limits upon histopathological examination.

The microscopic examination consisted of the following.

The specified list of tissues from all animals of the control group and high dosage group killed after 13 weeks of treatment.

Liver, adrenals, lungs and kidneys from all animals from the low and intermediate dosage levels (Groups 2 and 3) killed after 13 weeks of treatment.

Liver, adrenals and kidneys from all animals killed following 13 weeks of treatment and 4 weeks of recovery.

Any macroscopically abnormal tissue in any animal.

Neuropathology groups

On completion of 13 weeks of treatment, Neuropath group animals were killed. Terminal procedures took 6 days to complete. However, the duration of the treatment period is reported as 13 weeks.

All animals were perfused and tissue samples were taken, but neuropathological examination was restricted to the control and high dose groups.

Method of sacrifice and perfusion fixation: the animals were anaesthetised with sodium pentobarbital (i.p.) and perfused *in situ* with heparinised 0.7% sodium nitrite followed by a 1.5% glutaraldehyde: 4% paraformaldehyde solution. After perfusion, the cranial vault was removed and the brain removed, weighed and measured as detailed below. The skin was removed from the dorsal region and hindlimbs, and the sciatic, tibial and sural nerves were exposed. The spinal column and cord were fixed *in toto*, integral with the carcass overnight, in fixative-filled containers and held at 4°C.

Anatomical measurements: the brain was transected from the spinal cord above the first cervical spinal nerve, and the olfactory lobes were removed. The length between the rostral part of the cerebral hemispheres to the most caudal part of the cerebellum, and the width between the widest parts of the cerebral hemispheres were both measured.

Following overnight storage, tissues for each animal for paraffin wax H&E sections were taken and stored for at least 48 hours in buffered formalin. Peripheral nerve samples were taken and processed for epon/toluidine blue sections. The carcass was transferred to buffered formalin and stored at room temperature.

Light microscopic examination: brains, spinal cords, ganglia and dorsal and ventral root fibres of the perfused animals were processed for paraffin embedding, sectioned at approximately 5 - 6 micrometres and stained with haematoxylin and eosin. Peripheral nerves from the right side were embedded in epon, sectioned at approximately 2 micrometres and stained with toluidine blue.

Lesions were graded as to severity, where possible, into 4 categories (trace, minimal, moderate or marked).

The tissues for examination are shown below.

Paraffin wax/H&E sections

Forebrain (three levels) (1))	
Mid-brain (1))	
Cerebellum and pons (1))	6 sections of brain in total
Medulla oblongata (1))	

Spinal cord (cervical (C3-C6) and lumbar (L1-L4) swellings) (2)

Gasserian (trigeminal) ganglia

Dorsal root ganglia (one cervical and one lumbar level))	taken and processed as one
Dorsal root fibres (one cervical and one lumbar level) (3))	sample from each level
Ventral root fibres (one cervical and one lumbar level) (3))	

The dorsal and ventral root fibres and dorsal root ganglia examined in each case were one from any of C3 - C6 and one from any of L1 - L4.

Epon/Toluidine blue sections

Sciatic nerve (sciatic notch and mid-thigh) (2)

Sural nerve (at and just distal to knee) (2)

Tibial nerve (at and just distal to knee) (2)

- (1) Cross sections of these tissues were evaluated
- (2) Cross and longitudinal sections of these tissues were evaluated
- (3) Longitudinal sections of these tissues were evaluated

STATISTICAL ANALYSIS

All statistical analyses were carried out separately for males and females.

For all parameters the analyses were carried out using the individual animal as the basic experimental unit.

Food consumption data were analysed using cumulative cage totals, and bodyweight data were analysed using weight gains.

The following sequence of statistical tests was used for food consumption, bodyweight, clinical pathology and organ weight data.

If the data consisted predominantly of one particular value (relative frequency of the mode exceeds 75%), the proportion of animals with values different from the mode was analysed by Fisher's exact test (Fisher, 1973) followed by Mantel's test for a trend with proportion (Mantel, 1963), if appropriate. Otherwise, Bartlett's test (Bartlett, 1937) was applied to test for heterogeneity of variance between treatments. Where significant (at the 1% level) heterogeneity was found, a logarithmic transformation was tried to see if a more stable variance structure could be obtained.

If no significant heterogeneity was detected (or if a satisfactory transformation was found), a one-way analysis of variance was carried out. If significant heterogeneity of variance was present, and could not be removed by a transformation, the Kruskal-Wallis analysis of ranks was used (Kruskal, Wallis 1952/3).

Analyses of variance was followed by Student's *t* test and Williams' test for a dose-related response, although only the one thought most appropriate for the response pattern observed is reported (Williams 1971/2). The Kruskal-Wallis analyses were followed by the non-parametric equivalents of the *t* test and Williams' test (Shirley's test 1977)

The incidence of selected histopathological lesions was analysed using Fisher's Exact Test.

Analysis of behavioural data

Details of analysis of behavioural data are presented in the Behavioural Screening report which is appended to this report.

LOCATION OF STUDY RECORDS

All specimens, raw data and study related documents generated during the course of the study at Huntingdon Life Sciences, together with a copy of the final report have been lodged in the Huntingdon Life Sciences Ltd, Archives, Huntingdon, England.

Such specimens and records will be retained for a minimum period of 5 years from the date of issue of the final report. At the end of the 5-year retention period the Client will be contacted and advice sought on the future requirements. Under no circumstances will any item be discarded without the Client's knowledge.

Samples and data arising from any investigations made by the Sponsor, the findings of which are included in the Huntingdon Life Sciences final report, were retained and archived by the Sponsor.

PROCEDURES

The procedures used during the study were those documented in the relevant Huntingdon Life Sciences Procedures Manuals.

DEVIATIONS FROM PROTOCOL

The requirement for statistical analysis of Laboratory Investigations and organ weight data was omitted from the protocol in error, these analyses have, however, been included in this report.

RESULTS

MORTALITY

There was one unscheduled death on the study. Rat no. 149♀ (Group 1, Control) died during routine blood sampling procedures in Week 4 of the recovery period. No previous signs of ill health or behavioural change had been noted. Macroscopic *post mortem* examination revealed the smell of ether in the thoracic cavity and congested lungs. This death was considered to be a result of trauma during blood sampling. The loss of this control animal did not affect the assessment of the toxicity of DPTB.

CLINICAL SIGNS (Table, 1, Appendices 1, 9)

Clinical signs attributable to treatment were confined to animals receiving 1000 mg/kg/day only. These included:

salivation in all male and female animals immediately after dosing from Week 1 and throughout the 13 weeks of treatment at an incidence between 0 and 7 days per week and increasing with time.

unsteady gait, collapsed posture, partially closed eyelids, body spasms and paddling of forelimbs noted from Week 8 - 12 onwards in a small proportion of animals on generally 1 or 2 days per week (also 1 animal only in Week 5).

noisy respiration (possibly due to inhalation of saliva) in one animal of each sex on one day in Week 1.

No treatment-related clinical signs were noted during the recovery period.

BODYWEIGHT (Figures 1 and 2, Table 2, Appendix 2)

Overall mean bodyweight gain for all treated groups was comparable with concurrent control values during the 13-week treatment period.

During the recovery period to completion of Recovery Week 3, overall mean bodyweight gain for previously treated males was marginally higher than concurrent controls, however this difference is considered mainly attributable to individual biological variation and the smaller group size. Overall mean bodyweight gain for females during Recovery Weeks 0 - 3 was generally similar to controls. During Recovery Week 4 bodyweight losses were noted for all groups. These losses were considered attributable to the blood sampling procedure for haematological analysis and associated restriction of access to food performed during this week.

Group mean weight changes (g/rat) were as follows:

	Group/dosage (mg/kg/day)							
	1♂ 0	2♂ 62.5	3♂ 250	4♂ 1000	1♀ 0	2♀ 62.5	3♀ 250	4♀ 1000
Week 0 - 13	357	358	354	352	138	134	128	134
sd	65.3	40.2	28.7	46.9	26.7	20.5	19.0	20.7
% Control	-	100	99	99	-	97	93	97
Week R0 - R3	31			39+	16			14
sd	7.57			8.84	21.9			6.42
Week R3 - R4	-1.9			-2.1	-1.8			-4.4
sd	3.38			6.39	13.4			6.27
sd	Standard deviation							
+	$p < 0.05$ (Student's <i>t</i> test)							

FOOD CONSUMPTION (Table 3, Appendix 3)

During the 13 weeks of treatment individual weekly and overall cumulative food intake for all treated groups were generally comparable with concurrent controls.

During the 4-week recovery phase, mean food intake for males previously receiving 1000 mg/kg/day was marginally higher than concurrent controls, but this was thought to be attributable to normal variation. Mean food intake for previously treated females was comparable with controls throughout the 4-week recovery phase.

Group mean intake (g/rat) were as follows:

	Group/dosage (mg/kg/day)							
	1♂ 0	2♂ 62.5	3♂ 250	4♂ 1000	1♀ 0	2♀ 62.5	3♀ 250	4♀ 1000
Week 0 - 13	2961	3005	2987	2974	2118	2128	2034	2109
sd	287.7	207.2	193.6	242.3	223.8	261.9	197.7	201.8
% Control	-	101	101	100	-	100	96	100
Week R1 - R3	709			779+	544			533
sd	66.1			58.3	126.5			38.8
% Control	-			110	-			98
Week R4	214			236+	168			158
sd	23.0			16.5	23.4			11.8
% Control	-			110	-			94

sd Standard deviation

+ $p < 0.05$ (Student's *t* test)

FOOD CONVERSION RATIOS (Table 4)

Efficiency of food utilisation of all treated groups was similar to concurrent controls for all treated groups, for the period Week 1 to 13 and for previously treated males during the recovery period (Week R1 to R3). It was not possible to calculate FCRs during Week R4 due to the bodyweight losses during this week.

	Group/dosage (mg/kg/day)							
	1♂ 0	2♂ 62.5	3♂ 250	4♂ 1000	1♀ 0	2♀ 62.5	3♀ 250	4♀ 1000
Week 1 - 13	8.3	8.4	8.4	8.4	15.4	15.9	15.9	15.7
Week R1 - R3	22.7			19.8	34.1			38.2

WATER CONSUMPTION (Table 5, Appendix 4)

A slight, but statistically significant, increase in water consumption was noted among males receiving 1000 mg/kg/day during Week 12.

There was no other effect of treatment, or previous treatment, on overall mean water intake measured during the Week 12 of treatment or Week 3 of recovery.

	Group/dosage (mg/kg/day)							
	1♂ 0	2♂ 62.5	3♂ 250	4♂ 1000	1♀ 0	2♀ 62.5	3♀ 250	4♀ 1000
Main group								
Week 12	254	270	285	292*	219	223	209	236
sd	54.0	42.2	42.7	59.7	39.9	24.4	33.0	36.8
% Control	-	106	112	115	-	102	95	108
Recovery group								
Week R3	251			278	229			243
sd	37.3			49.8	45.8			43.4
% Control	-			111	-			106

sd Standard deviation

* $p < 0.05$ (Williams' test)

OPHTHALMOSCOPY (Appendix 5)

There were no abnormalities detected at predose assessment considered likely to prejudice the evaluation of any treatment-related effects.

There were no abnormalities detected during Week 13 in any animal.

NEUROTOXICITY ASSESSMENT (see appended report)

Treatment with DPTB for 13 weeks was not associated with any behavioural changes which were considered indicative of neurotoxicity.

HAEMATOLOGY (Table 6, Appendix 6)

Haematological investigations were performed in Weeks 5 and 13 of treatment and, due to the changes evident at these investigations, analysis was repeated for all animals in Week 4 of recovery. In Week R4 5/10 blood samples from control group females, collected into citrate anticoagulant tubes were clotted, consequently all females were re-bled one day later for measurement of Thrombotest (TT) alone.

In Week 5, a small but statistically significant reduction in mean total white blood cell counts (due to reduced lymphocyte counts) was seen in males receiving 1000 mg/kg/day compared to control values. In Week 13, a statistically significant reduction in mean total white blood cell and lymphocyte counts was evident for females only receiving 1000 or 250 mg/kg/day; however, these differences from controls were not dosage-related in degree. All values were well within the historical control range. Consequently no clear relationship between these apparent changes and treatment with DPTB was established.

Parameter	Week	Sex	Group/dosage (mg/kg/day)				Background ranges			
			0	62.5	250	1000	n	5%	50%	95%
Total white blood cells	5	♂	13.98	11.74	12.50	10.32**	27	8.61	13.73	20.52
		♀	10.62	9.40	7.97	9.37	26	3.98	10.03	13.30
	13	♂	13.33	12.16	12.52	11.76	101	9.82	13.67	20.53
		♀	9.00	8.59	6.48*	7.67*	100	5.18	8.75	13.69
Lymphocytes	5	♂	11.31	9.66	10.15	8.17**	27	6.45	11.26	16.31
		♀	9.09	7.95	6.57	7.73	26	3.26	8.10	10.81
	13	♂	9.93	10.02	9.68	9.04	101	7.70	10.94	14.96
		♀	7.56	7.23	5.39*	6.43*	100	3.91	7.09	11.96

* $p < 0.05$, ** $p < 0.01$ (Williams' test)

Background data drawn from studies performed June 1995 to July 1996 and based on rats aged 11 - 13 weeks old (Week 5 comparison) or 18 - 20 weeks old (Week 13 comparison). All units as per table.

In Week 13 a small but statistically significant decrease in packed cell volume (PCV) and red blood cell (RBC) count was evident for males receiving 1000 mg/kg/day. In comparison with the background data, the red blood cell count for controls is towards the upper end of the range while that for animals receiving 1000 mg/kg/day is similar to the 50 percentile; the PCV values are also within the background range. These differences from concurrent controls were not evident amongst similarly treated females. In the absence of any differences from the normal range, the differences seen in males are not thought to be related to treatment.

Parameter	Week	Sex	Group/dosage (mg/kg/day)				Background ranges			
			0	62.5	250	1000	n	5%	50%	95%
Red blood cells	5	♂	8.74	8.71	8.65	8.37	27	7.8	8.5	9.0
	13	♂	9.27	9.31	8.94	8.72**	110	8.2	8.9	9.6
	R4	♂	9.22	-	-	8.84 ⁺	110	8.2	8.9	9.6
PCV	5	♂	49.0	48.2	48.6	48.0	27	44	47	50
	13	♂	46.5	46.7	45.5	44.8*	110	43	46	50
	R4	♂	47.9	-	-	46.2 ⁺	110	43	46	50

* $p < 0.05$, ** $p < 0.01$ (William's test)

+ $p < 0.05$ (Student's *t* test)

Background data drawn from studies performed June 1995 to July 1996 and based on rats aged 11 - 13 weeks old (Week 5 comparison) or 18 - 20 weeks old (Week 13 and R4 comparisons). All units as per table.

In Week 4 of the recovery period, slight, but statistically significant, decreases in group mean packed cell volume (PCV), haemoglobin (Hb) and total red blood cell count (RBC) compared to control values were noted for male rats previously receiving 1000 mg/kg/day. The magnitude of these differences were similar to those evident in males at Week 13, so that all values were again well within the background ranges of the laboratory. Mean total white blood cell and lymphocyte counts for previously treated males and females were comparable with controls at the recovery phase investigations.

There were no other findings considered to be related to treatment at any dosage.

BIOCHEMISTRY (Table 7, Appendix 7)

Increased group mean albumin and globulin levels, and consequently total protein, were noted for both sexes receiving 1000 mg/kg/day in Week 5 and again in Week 13, statistical significance being attained in most cases and the degree of difference generally greater in Week 13. Although the majority of mean values were within the 5 - 95% of the range of background data, differences from concurrent controls were consistent between the sexes and with time suggesting relationship to treatment.

Group mean glucose levels were reduced for males receiving 1000 mg/kg/day in Week 5 and for both sexes at this dosage in Week 13. However, there was great variability in the individual values with considerable overlap between treated animals and controls and relationship to treatment is uncertain.

Parameter	Week	Sex	Group/dosage (mg/kg/day)				Background ranges			
			0	62.5	250	1000	n	5%	50%	95%
Total protein	5	♂	6.6	6.4	6.6	6.9*	35	6.1	6.5	7.6
		♀	6.6	6.8	7.0*	7.2**	33	5.5	6.4	7.3
	13	♂	6.8	6.8	7.0	7.5**	100	6.1	6.7	7.2
		♀	7.0	7.1	7.3	7.7**	100	6.2	6.8	7.9
Albumin	5	♂	3.1	3.0	3.1	3.2	55	2.7	3.1	4.4
		♀	3.3	3.3	3.4	3.5	53	2.7	3.2	4.9
	13	♂	3.1	3.1	3.1	3.3**	110	2.5	2.9	3.6
		♀	3.3	3.4	3.5	3.6*	110	2.9	3.3	4.3
Globulin	5	♂	3.5	3.4	3.6	3.7*	55	2.1	3.3	4.3
		♀	3.3	3.5	3.6*	3.7**	53	2.1	3.1	4.1
	13	♂	3.7	3.8	3.9	4.2**	110	3.3	3.8	4.3
		♀	3.7	3.6	3.8	4.1**	110	2.7	3.5	4.5
Glucose	5	♂	102	121	99	90*	49	94	115	142
		♀	106	102	110	102	109	98	126	156
	13	♂	124	132	112	103**	48	88	107	148
		♀	119	114	113	107*	108	90	118	144

* $p < 0.05$, ** $p < 0.01$ (William's test)

Background data drawn from studies performed June 1991 to November 1994 and based on rats aged 11 - 13 weeks old (Week 5 comparison) or 18 - 20 weeks old (Week 13 comparison) all units as per table (Statistics 1995).

Although a number of other statistically significant differences were apparent between treated groups and the controls, there were no clear dosage related trends or effects in all or most individuals and all differences were considered attributable to natural variation. Animal 32♂ (1000 mg/kg/day) showed particularly high values for GPT, GOT and OCT and a low chloride value in Week 13.

No investigations were performed on recovery animals.

ORGAN WEIGHTS (Table 8, Appendix 8)

Analysis of organ weights on completion of 13 weeks of treatment revealed significantly increased mean liver, adrenal and kidney weights for both sexes receiving 1000 mg/kg/day, following adjustment for bodyweight. These correlated with histopathological changes in the liver and adrenals for both sexes, the adrenals for females and the kidneys for males only. Males receiving 250 mg/kg/day also showed statistically significantly higher mean kidney and adrenal weights following adjustment for bodyweight, in comparison with concurrent controls. The difference in kidney weight correlated with histopathological change but no such changes were observed to account for the adrenal weight difference.

Parameter	Sex	Group/dosage (mg/kg/day)				Background ranges			
		0	62.5	250	1000	n	5%	50%	95%
Liver	♂	23.4	22.3	22.6	29.7	95	9.6	19.4	26.9
	♀	10.7	10.7	11.3	14.2	90	5.5	10.5	14.0
Adrenal	♂	65.0	67.1	73.5	75.9	95	33.4	52.8	73.5
	♀	73.3	76.4	77.9	91.8	90	34.9	63.5	95.7
Kidneys	♂	3.71	3.87	4.33	4.25	95	1.78	3.22	4.07
	♀	2.11	2.10	2.09	2.35	90	1.18	1.99	2.50

Statistical analysis was performed on bodyweight adjusted values and therefore not presented here.

Background data drawn from studies performed June 1991 to November 1994 and based on rats aged 18 - 20 weeks old. All units as per table (Statistics 1995).

Analysis of organ weights on completion of 4 weeks of recovery revealed slight, but not significantly, increased mean kidney weights, following adjustment for bodyweight, for males previously given 1000 mg/kg/day, correlating with histopathological change. Mean kidney weights for previously treated females were similar to concurrent controls. There was no effect on adrenal weight.

All other differences from controls were slight and did not attain statistical significance and therefore are not considered to be of toxicological importance.

MACROSCOPIC PATHOLOGY (Table 9, Appendix 9)

Macroscopic *post mortem* examination of animals killed following 13 weeks of treatment revealed enlargement of the liver in 5/10 males compared with 1/10 control group males. Enlargement of the adrenals was observed in 6/10 females receiving 1000 mg/kg/day in comparison with 2/10 females in the concurrent control group.

Macroscopic *post mortem* examination of animals killed following 4 weeks of recovery revealed no abnormalities or lesions which were considered to be attributable to previous treatment with DPTB.

The incidence and distribution of all other findings were considered to fall within the expected background range of macroscopic changes.

MICROSCOPIC PATHOLOGY (Table 10, Appendix 9)

Treatment-related changes

Terminal kill

Liver - Minimal centrilobular hepatocyte hypertrophy was seen in male and female rats receiving 1000 mg/kg/day. This change was associated with the significant increased mean liver weight, following adjustment for bodyweight, for both sexes in this treatment group.

Dosage level (mg/kg/day)	Male				Female			
	0	62.5	250	1000	0	62.5	250	1000
Minimal centrilobular hepatocyte hypertrophy	0	0	0	7**	0	0	0	7**
No. of livers examined	10	10	10	10	10	10	10	10

** $p < 0.01$ with Fisher's Exact Test

Kidneys - A dose-related increased degree and incidence of cortical tubules with eosinophilic inclusions was seen in male rats from all treated groups compared to male controls.

A dose-related incidence of minimal basophilic cortical tubules was seen in male rats receiving 250 and 1000 mg/kg/day.

Cortical tubules with cellular debris casts were seen in a small number of male rats receiving 250 and 1000 mg/kg/day.

These microscopic changes were associated with the significantly increased mean kidney weights, following adjustment for bodyweight, for male rats receiving 250 and 1000 mg/kg/day.

No microscopic changes were seen which might be related to the significantly increased kidney weights, following adjustment for bodyweight, recorded for female rats receiving 1000 mg/kg/day.

Dosage level (mg/kg/day)	Male			
	0	62.5	250	1000
Cortical tubules with eosinophilic inclusions				
Total	4	10**	10**	10**
Trace	1	0	0	0
Minimal	3	7	3	0
Moderate	0	3	7**	4*
Marked	0	0	0	6**
Minimal basophilic cortical tubules	0	0	5	8**
Cortical tubules with cellular debris casts	0	0	1	2
Number of kidneys examined	10	10	10	10

* $p < 0.05$, ** $p < 0.01$ with Fisher's Exact Test

Adrenals - A raised incidence of minimally increased width of the zona fasciculata was seen in female rats receiving 1000 mg/kg/day, compared to female controls. This change was possibly related to the significantly increased mean adrenal weight (adjusted for bodyweight) seen in the same group of females.

The minimally increased width of the zona fasciculata seen in a single male rat receiving 1000 mg/kg/day was comparable to that seen in one (female) control animal; it was not considered to be treatment-related. No microscopic changes were seen which might be related to the increased mean (bodyweight adjusted) adrenal weights found in male rats receiving 250 or 1000 mg/kg/day.

Dosage level (mg/kg/day)	Male				Female			
	0	62.5	250	1000	0	62.5	250	1000
Minimal increased width of zona fasciculata	0	0	0	1	1	0	0	6*
No. of adrenals examined	10	10	10	10	10	10	10	10

* $p < 0.05$ with Fisher's Exact Test

Recovery kill

Liver - Centrilobular hepatocyte hypertrophy was not detected after the recovery period.

Kidneys

The degree and incidence of cortical tubules with eosinophilic inclusions was considered to be comparable between male rats previously receiving 1000 mg/kg/day and corresponding male controls.

An increased incidence of minimal basophilic cortical tubules was still present in male rats previously receiving 1000 mg/kg/day compared to corresponding controls.

Cortical tubules with cellular debris casts were seen in one male rat previously receiving 1000 mg/kg/day.

The increased incidence of basophilic cortical tubules was considered to be associated with the significantly increased mean kidney weight, following adjustment for bodyweight, for males previously receiving 1000 mg/kg/day.

The incidence of treatment-related renal changes was less in male rats allowed a recovery period than in male rats at the end of treatment. This was considered to indicate partial reversibility of these renal changes.

Dosage level (mg/kg/day)	Male		
	0	1000	
Cortical tubules with eosinophilic inclusions	Total	7	7
	Trace	7	5
	Minimal	0	2
Minimal basophilic cortical tubules	1	5	
Cortical tubules with cellular debris casts	0	1	
No. of kidneys examined	10	10	

$p > 0.05$

Adrenals - Increased width of the zona fasciculata was not detected after the recovery period.

Incidental findings

All other microscopic findings in this study were considered of no toxicological importance.

Neuropathology

No microscopic changes were seen in any of the tissues examined from satellite animals used for the neurotoxicity screen.

DISCUSSION AND CONCLUSION

Three target organs were identified for effects of DPTB in this study - liver, adrenal and kidney. Increased liver weights associated with macroscopically enlarged livers and minimal centrilobular hepatocyte enlargement were accompanied by increases in plasma protein concentrations; there was no evidence of leakage of liver marker enzymes into plasma or pathological determinates of liver cell damage. Liver effects were confined to animals given 1000 mg/kg/day. Thus, the changes in the liver were considered to be an adaptive response related to metabolism of the test material and not a toxic change. Recovery was complete following 4 weeks off-dose.

In the adrenals, increased weights were noted in both sexes given 1000 mg/kg/day and males only receiving 250 mg/kg/day. Macroscopically enlarged adrenals were noted only in females given 1000 mg/kg/day. Microscopic pathology revealed minimal increased width of the zona fasciculata in 6/10 females dosed at 1000 mg/kg/day, but no changes attributed to treatment in males. Recovery in females was complete after 4 weeks without treatment. In the absence of pathological change, the aetiology of the increased adrenal weights in males is unknown; since there was no evidence of adverse functional or structural alteration, this effect is considered to be of no toxicological significance.

In the kidneys, effects other than organ weight increase at 1000 mg/kg/day were confined to males only and all three dosage levels showed similar changes, dose-related in incidence and degree. Eosinophilic inclusions, basophilic tubules and cellular debris casts in cortical tubules, allied to increased kidney weights are all changes suggestive of effects on α_2 microglobulin and protein recycling. Recovery was apparent but not complete following 4 weeks without treatment. These effects are a well known response to the administration of a variety of substances, and effects on α_2 microglobulin are known to be specific to the male rat. Thus they are not predictive of a hazard to human health.

Changes in white blood cell numbers among rats receiving 1000 mg/kg/day were not accompanied by any microscopic pathological changes in relevant tissues, were minimal in degree and were inconsistent between the Week 5 and 13 investigations. These changes (mean shifts of less than 30% from mean control values) are therefore of questionable toxicological significance.

In this study 1000 mg/kg/day was a clear effect level, producing changes in the liver, adrenals and kidneys and (questionably) in white blood cell counts. As the changes seen in the male rat kidney were of a type not considered relevant to man and no other, toxicologically significant, changes were seen in animals given 250 mg/kg/day, this was a No Observed Adverse Effect Level in both sexes for oral administration of DPTB. Similar kidney changes in male rats have been seen following administration of a variety of substances (Swenberg 1993). These were also seen in males of the low dose group; hence no No Effect Level could be established. In contrast, 62.5 mg/kg/day was a clear NOEL for females. Under the EC criteria for classification and labelling of dangerous substances (Commission Directive 93/21/EEC of 27 April 1993), no classification or risk phrase is required for DPTB in respect of damage to health following prolonged exposure.

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FIGURE 1
Bodyweights - Main, Neuropath and Recovery group mean values

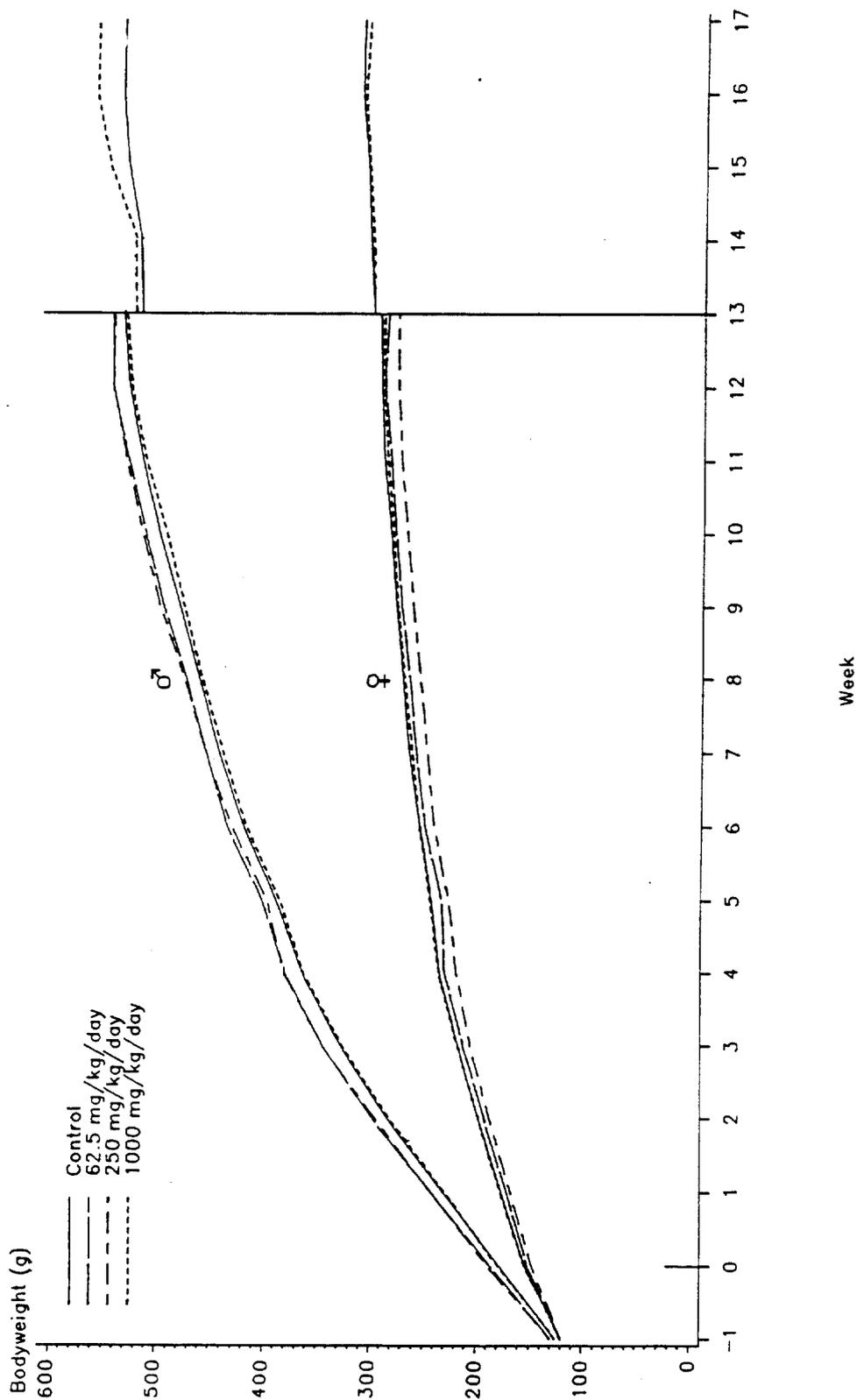


FIGURE 2
Bodyweights - Recovery group mean values

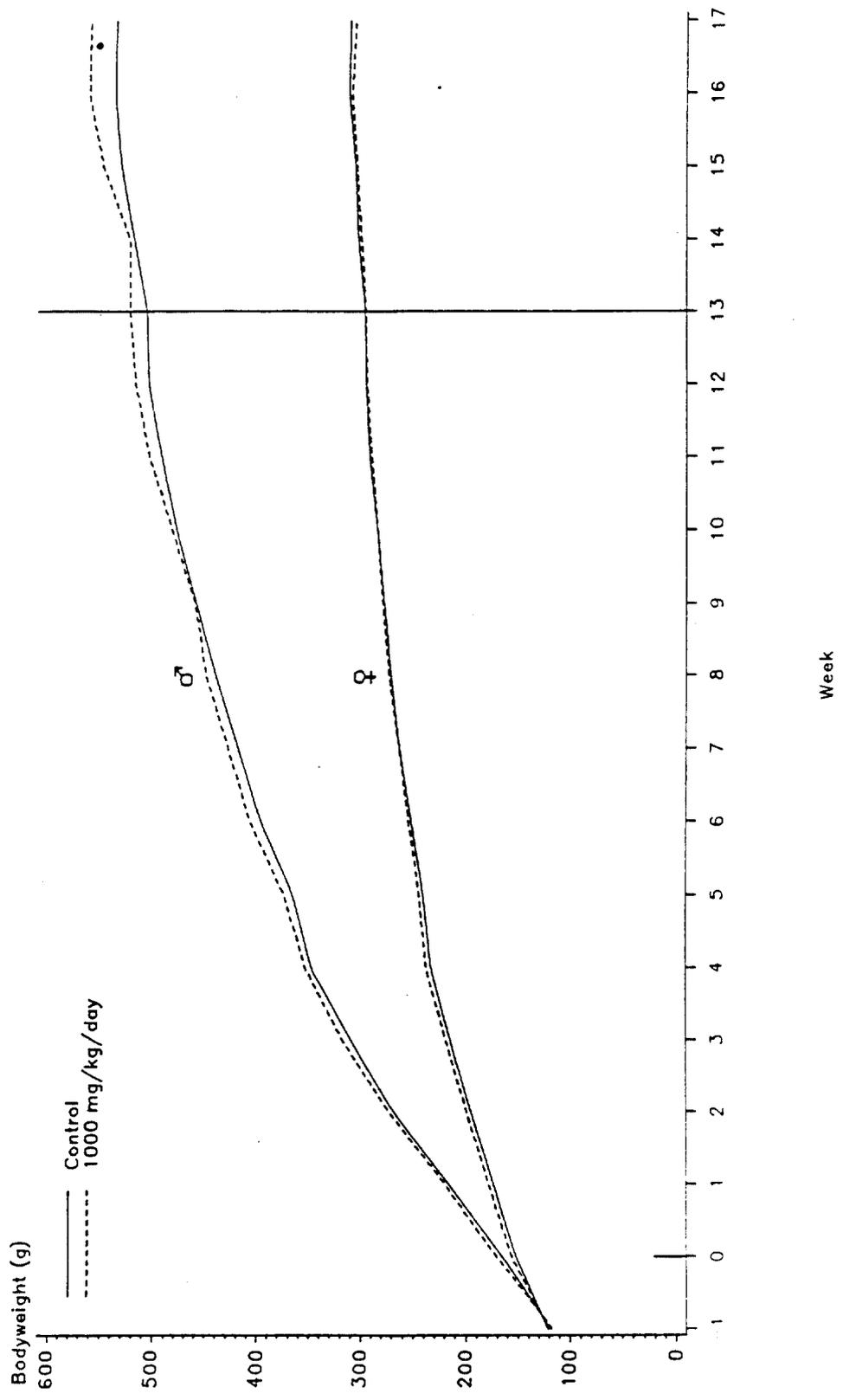


TABLE 1
Clinical signs after dosing (Main, Neuropath. and Recovery groups) -
group mean percentage incidence†

Group 4: 1000 mg/kg/day

Group/ sex	Week												
	1	2	3	4	5	6	7	8	9	10	11	12	13
	Salivation												
4♂	44	40	26	42	70	82	70	77	86	85	93	81	86
4♀	34	46	25	50	74	76	68	82	84	85	85	92	79
	Unsteady gait												
4♂	-	-	-	-	-	-	-	2	2	1	1	-	-
4♀	-	-	-	-	-	-	-	-	1	-	-	-	-
	Collapsed posture												
4♂	-	-	-	-	-	-	-	-	-	1	3	3	2
4♀	-	-	-	-	-	-	-	-	-	-	1	1	-
	Brown peri-oral staining												
4♂	-	-	-	-	-	-	-	-	-	-	-	1	1
	Partially closed eyelids												
4♂	-	-	-	-	-	-	-	-	-	-	4	2	2
4♀	-	-	-	-	-	-	-	-	-	-	1	5	1
	Body spasms												
4♂	-	-	-	-	-	-	-	-	-	-	-	1	9
4♀	-	-	-	-	-	-	-	-	-	-	-	-	2
	Paddling of forelimbs												
4♂	-	-	-	-	-	-	-	-	-	-	2	-	6
4♀	-	-	-	-	-	-	-	-	1	-	5	2	10
	Noisy respiration												
4♂	1	-	-	-	-	-	-	-	-	-	-	1	-
4♀	1	-	-	-	-	-	-	-	-	-	-	-	-

† Only Group 4 is shown: there was a low incidence of salivation for 2 Group 3 females but this is not presented in this table (see Appendix 9)

$$\text{percentage incidence} = \frac{\text{Total incidence}}{\text{Maximum possible incidence}} \times 100$$

Where total incidence = group total number of days sign observed

Maximum possible incidence = Number of animals × number of days dosed in the week

TABLE 2

Bodyweights - group mean values (g)

(Main, Neuropath and Recovery groups)

Week	Group and dosage (mg/kg/day)							
	1♂ Control	2♂ 62.5	3♂ 250	4♂ 1000	1♀ Control	2♀ 62.5	3♀ 250	4♀ 1000
-1	125	130	130	125	120	119	119	120
0	177	186	188	179	155	151	148	154
1	230	241	242	228	176	171	167	177
2	282	297	294	280	198	192	187	198
3	327	344	344	326	218	212	206	218
4	364	380	381	363	235	230	219	236
5	388	402	397	385	243	233	226	244
6	419	434	430	416	254	249	241	254
7	442	454	455	439	264	257	248	261
8	461	473	475	458	270	264	254	269
9	479	494	498	475	277	272	261	276
10	499	512	515	492	282	277	267	280
11	515	529	531	512	289	283	273	286
12	528	544	543	526	292	289	276	290
13	534	544	542	531	292	285	276	289
Gain 0 - 13	357	358	354	352	138	134	128	134
sd	65.3	40.2	28.7	46.9	26.7	20.5	19.0	20.7
% Control	-	100	99	99	-	97	93	97
R0	505			522	296			295
R1	518			522	303			300
R2	531			547	306			305
R3	537			561	312			309
R4	535			559	310			305
Gain R0 - R3	31.3			39.4	16.0			14.0
sd	7.6			8.8	21.9			6.4
Gain R3 - R4	-1.9			-2.1	-1.8			-4.4
sd	3.4			6.4	13.4			6.3

sd Standard deviation

R Recovery

+ $p < 0.05$ (Student's *t* test)

TABLE 3

Food consumption - group mean values (g/rat/week)

(Main, Neuropath and recovery groups)

Week	Group and dosage (mg/kg/day)							
	1♂ Control	2♂ 62.5	3♂ 250	4♂ 1000	1♀ Control	2♀ 62.5	3♀ 250	4♀ 1000
-1	178	186	187	179	158	152	150	155
1	202	217	216	203	164	160	156	161
2	210	212	207	206	164	160	156	162
3	236	245	219	232	172	165	165	173
4	219	227	226	222	161	158	154	158
5	222	225	223	222	162	165	154	160
6	238	239	233	236	174	176	168	166
7	240	240	245	239	170	174	166	168
8	238	239	244	242	168	171	162	168
9	235	241	247	238	164	167	156	164
10	234	234	239	232	159	164	153	160
11	237	238	241	242	160	161	153	163
12	230	233	235	236	157	163	154	159
13	220	215	214	224	143	145	137	148
Total 1 - 13	2961	3005	2987	2974	2118	2128	2034	2109
sd	287.7	207.2	193.6	242.3	223.8	261.9	197.7	201.8
% Control	-	101	101	100	-	100	96	100
R1	228			243	177			176
R2	238			268	180			178
R3	243			268	186			180
R4	214			236	168			158
Total R1 - R3	709			779 ⁺	544			533
sd	66.1			58.3	126.5			38.8
R3 - R4	214			236 ⁺	168			158
sd	23.0			16.5	23.4			11.8

sd Standard deviation

R Recovery

+ $P \leq 0.05$ (Student's *t* test)

TABLE 4

Food conversion ratios - group mean values

Week	Group and dosage (mg/kg/day)							
	1♂ Control	2♂ 62.5	3♂ 250	4♂ 1000	1♀ Control	2♀ 62.5	3♀ 250	4♀ 1000
1	3.8	3.9	4.1	4.1	7.7	8.2	8.1	7.3
2	4.0	3.8	3.9	4.0	7.5	7.6	7.8	7.6
3	5.2	5.2	4.4	5.2	8.6	8.3	8.9	8.7
4	6.1	6.4	6.1	6.0	9.6	8.9	11.7	8.8
5	9.1	10.2	13.8	10.0	19.5	57.0	20.1	19.3
6	7.6	7.3	7.1	7.5	15.5	10.8	12.0	16.1
7	10.6	12.0	9.8	10.7	16.9	20.7	23.7	24.0
8	12.8	12.9	12.4	12.5	27.9	27.2	25.3	22.1
9	12.7	11.3	10.6	13.8	23.6	20.2	21.2	23.2
10	11.9	13.1	14.0	13.8	30.7	30.6	28.4	39.7
11	14.4	14.4	15.4	12.0	23.1	30.5	23.6	26.3
12	17.8	15.5	18.6	16.9	56.1	26.2	48.5	41.6
13	41.7	2483.1	n/a	47.6	475.3	n/a	n/a	n/a
R1	18.2			640.6	24.9			34.4
R2	19.0			10.6	78.4			41.6
R3	39.3			19.4	28.6			39.2
R4	n/a			n/a	n/a			n/a
1 - 13	8.3	8.4	8.4	8.4	15.4	15.9	15.9	15.7
R1 - R3	22.7			19.8	34.1			38.2

R Recovery

n/a Insufficient bodyweight gain to give a meaningful ratio

Food conversion ratio = food consumption/bodyweight gain

TABLE 5

Water consumption - group mean values (g/rat/day)

Week 12 (Main and Recovery groups)

Day	Group and dosage (mg/kg/day)							
	1♂ Control	2♂ 62.5	3♂ 250	4♂ 1000	1♀ Control	2♀ 62.5	3♀ 250	4♀ 1000
1	33.3	34.2	36.0	37.0	27.5	29.2	26.1	31.1
2	38.2	41.4	42.0	44.8	32.8	33.8	31.7	34.2
3	35.1	37.9	38.8	40.3	29.8	31.6	27.4	32.0
4	36.6	36.4	43.4	41.2	30.9	31.4	30.0	32.6
5	36.7	40.1	39.9	43.1	32.0	31.8	31.0	34.0
6	35.7	39.2	40.5	42.3	31.0	30.5	29.8	34.6
7	38.6	41.1	44.8	43.7	35.6	34.4	32.7	38.0
Week 12	254	270	285	292*	219	223	209	236
sd	54.0	42.2	42.7	59.7	39.9	24.4	33.0	36.8
% Control	-	106	112	115	-	102	95	108

Week 16 (R3)

Day	Group and dosage (mg/kg/day)			
	1♂ Control	4♂ 1000	1♀ Control	4♀ 1000
1	35.5	39.1	30.6	32.2
2	35.4	40.4	32.8	34.2
3	37.0	42.1	34.3	38.2
4	36.7	40.2	33.0	34.5
5	36.0	39.4	32.4	36.2
6	34.9	38.8	31.7	31.8
7	35.6	37.9	34.4	35.8
Week 16	251	278	229	243
sd	37.3	49.8	45.8	43.4
% Control	-	111	-	106

sd Standard deviation

R Recovery

* $p \leq 0.05$ (Williams' test)

TABLE 6

Haematology - group mean values

Week 5

Group/ dosage mg/kg/day	PCV %	Hb g/dl	RBC $10^{12}/l$	MCHC g/dl	MCV fl	MCH pg	Plt $10^9/l$	TT s
1♂ Control	49.0	16.1	8.74	32.8	56.1	18.4	1110	24
2♂ 62.5	48.2	16.1	8.71	33.3	55.4	18.5	1109	24
3♂ 250	48.6	16.2	8.65	33.2	56.3	18.7	1134	24
4♂ 1000	48.0	15.7	8.37	32.6	57.3	18.7	1177	24
1♀ Control	47.4	16.2	8.52	34.1	55.7	19.0	1211	21
2♀ 62.5	47.2	16.0	8.37	33.9	56.4	19.2	1079	21
3♀ 250	46.2	15.8	8.33	34.2	55.5	19.0	1143	20
4♀ 1000	47.3	15.9	8.41	33.7	56.3	19.0	1171	20

No statistical significance ($p > 0.05$)

TABLE 6

(Haematology - continued)

Week 5

Group/ dosage mg/kg/day	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
1♂ Control	13.98	1.75	11.31	0.10	0.04	0.20	0.58
2♂ 62.5	11.74	1.32	9.66	0.08	0.04	0.23	0.41
3♂ 250	12.50	1.57	10.15	0.08	0.04	0.21	0.45
4♂ 1000	** 10.32	1.47	** 8.17	0.10	0.03	0.18	0.37
1♀ Control	10.62	0.98	9.09	0.09	0.03	0.14	0.29
2♀ 62.5	9.40	0.90	7.95	0.08	0.03	0.15	0.30
3♀ 250	7.97	1.01	6.57	0.07	0.02	0.10	0.20
4♀ 1000	9.37	1.10	7.73	0.10	0.03	0.16	0.26

** $p \leq 0.01$ (Williams' test)

TABLE 6

(Haematology - continued)

Week 13

Group/ dosage mg/kg/day	PCV %	Hb g/dl	RBC $10^{12}/l$	MCHC g/dl	MCV fl	MCH pg	Plt $10^9/l$	TT s
1♂ Control	46.5	16.2	9.27	34.9	50.2	17.6	1001	23
2♂ 62.5	46.7	16.4	9.31	35.1	50.2	17.6	1068	23
3♂ 250	45.5	16.1	8.94	35.4	50.9	18.0	1093	23
4♂ 1000	44.8*	15.7	8.72**	35.2	51.4	18.1	1157*	22
1♀ Control	44.3	15.9	8.44	35.9	52.5	18.9	1086	20
2♀ 62.5	44.1	15.8	8.23	35.9	53.6	19.2	996	19
3♀ 250	43.6	15.6	8.25	35.8	52.9	18.9	1057	19
4♀ 1000	44.2	15.8	8.34	35.7	53.0	18.9	1058	19

* $p \leq 0.05$, ** $p \leq 0.01$ (Williams' test)

TABLE 6

(Haematology - continued)

Week 13

Group/ dosage mg/kg/day	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
1♂ Control	13.33	2.46	9.93	0.17	0.03	0.33	0.40
2♂ 62.5	12.16	1.46	10.02	0.12	0.03	0.26	0.27
3♂ 250	12.52	2.21	9.68	0.14	0.03	0.23	0.23
4♂ 1000	11.76	2.08	9.04	0.14	0.03	0.23	0.25
1♀ Control	9.00	1.02	7.56	0.10	0.02	0.16	0.14
2♀ 62.5	8.59	0.93	7.23	0.11	0.02	0.17	0.14
3♀ 250	6.48*	0.82	5.39*	0.07	0.01	0.11	0.08*
4♀ 1000	7.67*	0.86	6.43*	0.09	0.02	0.16	0.12*

* $p \leq 0.05$ (Williams' test)

TABLE 6

(Haematology - continued)

Week R4

Group/ dosage mg/kg/day	PCV %	Hb g/dl	RBC $10^{12}/l$	MCHC g/dl	MCV fl	MCH pg	Plt $10^9/l$	TT s	TT# s
1♂ Control	47.9	16.5	9.22	34.5	52.0	17.9	976	24	-
4♂ 1000	46.2 ⁺	15.9 ⁺	8.84 ⁺	34.4	52.4	18.0	970	23	-
1♀ Control	45.7	16.0	8.27	34.9	55.3	19.3	1044	20	19
4♀ 1000	45.1	15.7	8.28	34.9	54.4	19.0	1029	20	20

+ $p \leq 0.05$ (Student's *t* test)

Repeated one day later due to 5/10 control samples being clotted at the original assessment

TABLE 6

(Haematology - continued)

Week R4

Group/ dosage mg/kg/day	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
1♂ Control	12.12	1.60	9.72	0.14	0.03	0.34	0.29
4♂ 1000	12.49	1.73	9.87	0.16	0.03	0.38	0.32
1♀ Control	8.52	1.04	6.91	0.13	0.02	0.27	0.15
4♀ 1000	8.70	1.07	7.07	0.12	0.02	0.27	0.15

No statistical significance ($p > 0.05$)

TABLE 7

Biochemistry - group mean values

Week 5

Group/ dosage mg/kg/day	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γ GT mU/ ml	OCT mU/ ml
		Total	Alb	Glob							
1♂ Control	102	6.6	3.1	3.5	14	0.5	370	26	64	1	1.8
2♂ 62.5	121	6.4	3.0	3.4	13	0.5	327	23	58	1	1.8
3♂ 250	99	6.6	3.1	3.6	14	0.5	300	24	62	1	2.4
4♂ 1000	* 90	* 6.9	3.2	* 3.7	13	0.6	321	24	57	1	2.4
1♀ Control	106	6.6	3.3	3.3	15	0.5	221	22	54	<1	2.1
2♀ 62.5	102	6.8	3.3	3.5	14	0.5	195	21	54	<1	3.6
3♀ 250	110	7.0	3.4	* 3.6	16	* 0.6	213	20	50	<1	2.7
4♀ 1000	102	** 7.2	3.5	** 3.7	14	* 0.5	185	22	* 48	<2	2.3

* $p \leq 0.05$, ** $p \leq 0.01$ (Williams' test)

TABLE 7

(Biochemistry - continued)

Week 5

Group/ dosage mg/kg/day	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
1♂ Control	0.1	146	3.8	5.7	5.1	102	71
2♂ 62.5	0.1	145	3.7	5.6	4.8	101	74
3♂ 250	0.1	145	3.8	5.7	4.8	101	77
4♂ 1000	0.1	147	3.8	5.7	5.2	** 99	74
1♀ Control	0.1	145	3.9	5.7	4.4	103	93
2♀ 62.5	<0.1	145	4.0	5.6	4.3	104	100
3♀ 250	<0.1	145	3.5	5.6	3.9*	103	104
4♀ 1000	<0.1	146*	3.6	5.8	4.2*	102	94

* $p \leq 0.05$ ** $p \leq 0.01$ (Williams' test)

TABLE 7

(Biochemistry - continued)

Week 13

Group/ dosage mg/kg/day	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γ GT mU/ ml	OCT mU/ ml
		Total	Alb	Glob							
1♂ Control	124	6.8	3.1	3.7	15	0.5	188	26	64	1	5.3
2♂ 62.5	132	6.8	3.1	3.8	15	0.6	178	24	56	1	5.0
3♂ 250	112	7.0	3.1	3.9	16	0.6	159	22	54	1	3.8
4♂ 1000	** 103	** 7.5	** 3.3	** 4.2	14	0.6	190	* 36	76	1	17.3
1♀ Control	119	7.0	3.3	3.7	15	0.5	107	34	77	<1	24.4
2♀ 62.5	114	7.1	3.4	3.6	15	0.5	92	26	61	<2	10.6
3♀ 250	113	7.3	3.5	3.8	16	0.5	94	21	52	<1	6.1
4♀ 1000	* 107	** 7.7	* 3.6	** 4.1	15	* 0.6	89	21	* 47	<1	4.4

* $p \leq 0.05$, ** $p \leq 0.01$ (Williams' test)

TABLE 7

(Biochemistry - continued)

Week 13

Group/ dosage mg/kg/day	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
1♂ Control	0.2	146	4.0	5.7	4.4	103	67
2♂ 62.5	0.2	146	3.6*	5.6	4.0**	102	77
3♂ 250	0.1	146	3.5*	5.6	3.9**	102*	86
4♂ 1000	0.1*	146	3.8*	5.9**	4.0**	100**	102**
1♀ Control	0.2	145	3.6	5.7	3.6	104	95
2♀ 62.5	0.2	145	3.8	5.6	3.6	105	104
3♀ 250	0.1	145	3.7	5.7	3.3	105	116
4♀ 1000	0.1	146	3.5	5.9*	3.5	103*	110

* $p \leq 0.05$, ** $p \leq 0.01$ (Williams' test)

TABLE 8

Organ weights - group mean values

Terminal kill

Group/ dosage mg/kg/day	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
Unadjusted values						
1♂ Control	549	2.04	14.5	24.0	1.70	23.4
2♂ 62.5	546	2.04	12.8	22.3	1.76	22.3
3♂ 250	528	2.06	13.7	23.9	1.73	22.6
4♂ 1000	515	2.03	14.0	24.4	1.72	29.7
Adjusted values						
1♂	-	2.03	14.1	23.6	1.66	22.5
2♂	-	2.03	12.5	22.0	1.73	21.5
3♂	-	2.06	13.7	24.1	1.75	23.0
4♂	-	2.05	14.6	25.0	1.77	31.0 ^{**}

^{**} $p \leq 0.01$ (Williams' test)

TABLE 8
(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Spleen g	Kidneys g	Adrenals mg	Prostate g	Testes g	Seminal Vesicles g	Epididymides g
Unadjusted values							
1♂ Control	0.95	3.71	65.0	0.959	3.41	1.56	1.259
2♂ 62.5	0.80	3.87	67.1	0.994	3.60	1.50	1.346
3♂ 250	0.83	4.33	73.5	1.104	3.82	1.49	1.269
4♂ 1000	0.81	4.25	75.9	0.953	3.52	1.44	1.326
Adjusted values							
1♂	0.87	3.59	63.4	-	-	1.49	-
2♂	0.77	3.78 **	65.9 *	-	-	1.45	-
3♂	0.83	4.39 **	74.2 **	-	-	1.51	-
4♂	0.84	4.42	77.9	-	-	1.52	-

** $p \leq 0.01$, * $p \leq 0.05$ (Williams' test)

TABLE 8

(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
Unadjusted values						
1♀ Control	280	1.90	14.7	14.9	1.07	10.7
2♀ 62.5	275	1.84	14.4	15.3	1.05	10.7
3♀ 250	274	1.86	14.7	16.1	1.07	11.3
4♀ 1000	273	1.85	14.7	16.4	1.08	14.2
Adjusted values						
1♀	-	1.89	14.5	14.6	1.06	10.4
2♀	-	1.84	14.4	15.4	1.05	10.7
3♀	-	1.86	14.8	16.2	1.07	11.3
4♀	-	1.85	14.8	16.6	1.08	14.3**

** $p \leq 0.01$ (Williams' test)

TABLE 8
(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Spleen g	Kidneys g	Adrenals mg	Uterus g	Ovaries mg
Unadjusted values					
1 ♀ Control	0.52	2.11	73.3	0.71	90.2
2 ♀ 62.5	0.56	2.10	76.5	0.65	90.8
3 ♀ 250	0.57	2.09	77.9	0.68	83.0
4 ♀ 1000	0.55	2.35	91.8	0.66	94.3
Adjusted values					
1 ♀	0.51	2.07	71.7	-	87.8
2 ♀	0.56	2.11	76.7	-	91.2
3 ♀	0.57	2.10	78.3	-	83.7
4 ♀	0.55	2.37	92.6	-	95.6

** $p \leq 0.01$ (Williams' test)

TABLE 8
(Organ weights - continued)

Recovery kill

Group/ dosage mg/kg/day	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
Unadjusted values						
1♂ Control	526	2.01	11.1	22.0	1.63	22.5
4♂ 1000	550	2.02	11.8	25.3	1.74	26.0
Adjusted values						
1♂	-	2.02	11.2	22.5	1.65	23.3
4♂	-	2.01	11.7	24.8	1.71	25.2

No statistical significance ($p > 0.05$)

Group/ dosage mg/kg/day	Spleen g	Kidneys g	Adrenals mg	Prostate g	Testes g	Seminal Vesicles g	Epididymides g
Unadjusted values							
1♂ Control	0.74	3.49	62.9	1.073	3.696	1.31	1.387
4♂ 1000	0.78	4.23	64.3	1.116	3.764	1.28	1.397
Adjusted values							
1♂	0.76	3.57	-	-	-	-	-
4♂	0.76	4.15 ⁺⁺	-	-	-	-	-

++ $p \leq 0.01$ (Student's *t* test)

TABLE 8
(Organ weights - continued)

Recovery kill

Group/ dosage mg/kg/day	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
Unadjusted means						
1 ♀ Control	298	1.84	13.7	20.0	1.09	12.2
4 ♀ 1000	297	1.90	13.6	19.7	1.06	12.0
Adjusted means						
1 ♀	-	1.84	13.7	20.0	1.09	12.1
4 ♀	-	1.90 ⁺	13.6	19.7	1.06	12.0

Group/ dosage mg/kg/day	Spleen g	Kidneys g	Adrenals mg	Uterus g	Ovaries mg
Unadjusted values					
1 ♀ Control	0.49	2.27	82.6	0.59	79.7
4 ♀ 1000	0.56	2.34	85.5	0.63	91.3
Adjusted values					
1 ♀	0.49	2.27	-	-	-
2 ♀	0.56	2.34	-	-	-

+ $p \leq 0.05$ (Student's *t* test)

TABLE 9
Macroscopic pathology incidence summary

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	10	10	10	10	10	10	10
Fur								
Stained	6	2	2	2	1	1	2	1
Coarse - dorsum	6	7	6	7	0	0	0	0
Encrusted	0	0	0	1	0	0	0	0
Skin								
Alopecia	2	0	1	0	2	4	0	0
Eyes								
Damaged	0	0	0	1	0	0	0	0
Tail								
Brown stained	3	0	0	1	0	0	0	0
Lymph Nodes - Cervical								
Enlarged	1	0	0	2	1	0	0	1
Lungs								
Petechiae	0	2	0	1	1	0	0	0
Pale subpleural focus/i	0	0	0	0	0	0	1	1
Congested	1	0	0	0	0	1	0	1
Liver								
Enlarged	1	1	0	0	0	0	0	0
Median cleft, pale subcapsular area/s	2	2	3	2	2	2	2	2
Lobe/s missing	0	0	1	0	0	0	0	0
Adhesions	0	0	1	0	0	0	1	0
Subcapsular cyst/s	0	0	1	0	0	0	0	0

TABLE 9
(Macroscopic pathology incidence summary - continued)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	10	10	10	10	10	10	10
Spleen								
Enlarged	1	0	0	0	0	0	0	0
Pale subcapsular area/s	1	0	0	0	0	0	0	0
Stomach Corpus Mucosa								
White nodule/s	1	0	0	0	0	0	0	0
Stomach Antrum Mucosa								
White nodule/s	1	2	2	3	3	1	5	3
Adrenals								
Enlarged	0	0	0	1	2	3	2	6
Kidneys								
Enlarged	0	1	1	2	0	0	0	0
Increased pelvic dilatation	0	0	0	1	0	0	1	1
Pale	0	0	1	0	0	0	0	0
Ureters								
Distended	0	0	0	0	0	0	0	1
Testes								
Enlarged	0	0	1	0	0	0	0	0
Small	1	1	0	0	0	0	0	0
Blue	1	1	1	0	0	0	0	0
White subnival striae	0	0	1	0	0	0	0	0
Epididymides								
Small	1	1	1	0	0	0	0	0

TABLE 9
(Macroscopic pathology incidence summary - continued)

Removal reason: Terminal	Group 1		Group 2		Group 3		Group 4		Group 1		Group 2		Group 3		Group 4	
	25	10	15	10	15	10	25	10	25	10	15	10	15	10	25	10
Animals on study Animals completed	25	10	15	10	15	10	25	10	25	10	15	10	15	10	25	10
	----- Males -----								----- Females -----							
Ovaries	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Fluid distension - periovarian sac/s	0	0	0	0	0	0	0	0	0	0	4	4	3	3	2	2
Uterus	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fluid distension	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skeletal Muscle	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mass/es	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Haemorrhage - periorbital region/s	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 9
Macroscopic pathology incidence summary

	Group		Group		Group	
	1	4	25	25	1	4
Removal reason: Recovery	---	Males	---	Females	---	---
Animals on study	25	25	25	25	25	25
Animals completed	10	10	9	10	9	10
Fur						
Stained	3	3	2	0	2	0
Coarse - dorsum	2	4	0	0	0	0
Skin						
Alopecia	0	1	0	1	0	1
Eyes						
Damaged	0	0	0	1	1	1
Congested	0	0	0	1	1	0
Incisors						
Broken	0	0	0	1	1	0
Missing	0	0	0	1	1	0
Overgrown	0	0	0	1	1	0
Lymph Nodes - Cervical						
Enlarged	0	2	0	0	0	2
Lungs						
Petechiae	1	4	0	0	0	0
Pale subpleural focus/i	0	0	0	2	2	4
Congested	1	0	0	0	0	0
Pale	0	0	0	0	0	1
Adipose Tissue						
Torioned nodule/s	1	0	0	0	0	0
Minimal	0	0	0	0	1	0

TABLE 9
(Macroscopic pathology incidence summary - continued)

	Group		Group		Group	
	1	4	1	4	1	4
Removal reason: Recovery						
	--- Males	---	--- Females	---		
Animals on study	25	25	25	25	25	25
Animals completed	10	10	9	10	9	10
Liver						
Enlarged	0	1	0	0	0	0
Median cleft, pale subcapsular area/s	3	2	1	1	1	1
Stomach Antrum Mucosa						
White nodule/s	1	1	2	0	0	0
Adrenals						
Enlarged	0	0	3	4	4	4
Kidneys						
Increased pelvic dilatation	1	0	1	0	0	0
Testes						
Asymmetrical	0	1	0	0	0	0
Ovaries						
No corpora lutea visible	0	0	2	0	0	0
Skeletal Muscle						
Haemorrhage - periorbital region/s	0	0	1	0	0	0

TABLE 10
Microscopic pathology incidence summary (Terminal kill)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study Animals completed	25 10	15 10	15 10	25 10	25 10	15 10	15 10	25 10
Trachea Examined No abnormalities detected	10 10	0 0	0 0	10 10	10 10	0 0	0 0	10 10
Lungs Examined No abnormalities detected Pneumonitis (Total) Minimal	10 9 0 0	10 7 1 1	10 10 0 0	10 9 1 1	10 9 1 1	7 2 2	10 0 0	10 9 1 1
Increased numbers of alveolar macrophages (Total) Minimal	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0
Vascular congestion (Total) Minimal	1 1	1 1	0 0	0 0	0 0	1 1	0 0	0 0
Aorta Examined No abnormalities detected	10 10	0 0	0 0	10 10	10 10	0 0	0 0	10 10
Heart Examined No abnormalities detected Myocarditis (Total) Minimal	10 5 3 3	0 0 0 0	0 0 0 0	10 6 4 4	10 10 0 0	0 0 0 0	0 0 0 0	10 10 0 0
Thymus Examined No abnormalities detected	10 10	0 0	0 0	10 10	10 10	0 0	0 0	10 10
Lymph Nodes - Cervical Examined No abnormalities detected	10 10	0 0	0 0	10 8	10 8	0 0	0 0	10 9

TABLE 10
(Microscopic pathology incidence summary (Terminal kill) - continued)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study Animals completed	25 10	15 10	15 10	25 10	25 10	15 10	15 10	25 10
Lymph Nodes - Cervical Increased cellularity - generalised (Total) Minimal	(Continued) 0 0	0 0	0 0	2 2	2 2	0 0	0 0	1 1
Lymph Nodes - Mesenteric Examined No abnormalities detected	10 10	0 0	0 0	10 10	10 10	0 0	0 0	10 10
Spleen Examined Trace Minimal Haemosiderosis (Total)	10 10 4 6 10	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	10 10 2 7 10	0 0 0 0 0	0 0 0 0 0	10 10 2 8 10
Trace Minimal Congestion (Total) Minimal	3 7 1 1	0 0 0 0	0 0 0 0	3 7 0 0	3 7 0 0	0 0 0 0	0 0 0 0	5 5 0 0
Liver Examined No abnormalities detected Hepatocyte hypertrophy - centriobular (Total) Minimal Sinusoidal dilatation/congestion (Total) Minimal Hepatocyte vacuolation - periportal (Total) Minimal	10 6 0 0 1 0 0	10 6 0 0 2 0 0	10 7 0 0 0 0 0	10 2 7 7 0 0 0	10 5 0 0 0 0 2	10 9 0 0 0 0 0	10 9 0 0 0 0 0	10 2 7 7 1 1 0 0

TABLE 10
(Microscopic pathology incidence summary (Terminal kill) - continued)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	10	10	10	10	10	10	10
(Continued)								
Liver								
Extramedullary haemopoiesis (Total)								
Minimal	2	1	1	1	3	1	1	1
Hepatocyte necrosis - focal (Total)	1	0	0	1	0	0	0	0
Minimal	1	0	0	1	0	0	0	0
Hepatocyte vacuolation - median cleft (Total)	0	1	1	1	0	0	0	0
Minimal	0	1	1	1	0	0	0	0
Capsular adhesion	0	0	1	0	0	0	1	0
Subcapsular cyst	0	0	1	0	0	0	0	0
Liver (ORO stain)								
Examined	10	10	10	10	10	10	10	10
No abnormalities detected	8	10	10	6	7	9	9	7
Periportal fat deposition (Total)	2	0	0	4	3	1	1	3
Trace	2	0	0	4	1	1	1	3
Minimal	0	0	0	0	2	0	0	0
Pancreas								
Examined	10	0	0	10	10	0	0	10
No abnormalities detected	10	0	0	10	10	0	0	10
Kidneys								
Examined	10	10	10	10	10	10	10	10
No abnormalities detected	5	0	0	0	10	10	9	7
Cortical tubules with eosinophilic inclusions (Total)	4	10	10	10	0	0	0	0
Trace	1	0	0	0	0	0	0	0
Minimal	3	7	3	0	0	0	0	0
Moderate	0	3	7	4	0	0	0	0
Marked	0	0	0	6	0	0	0	0
Minimal	0	0	5	8	0	0	0	0
Cortical tubules - basophilic (Total)	0	0	5	8	0	0	0	0

TABLE 10
(Microscopic pathology incidence summary (Terminal kill) - continued)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	10	10	10	10	10	10	10
(Continued)								
Kidneys	0	0	1	2	0	0	0	0
Cortical tubules with cellular debris casts (Total)	0	0	1	1	0	0	0	0
Trace	0	0	0	1	0	0	0	0
Minimal	0	0	1	0	0	0	0	0
Cortical tubules - dilated (Total)	0	0	1	0	0	0	0	0
Minimal	0	0	0	0	0	0	0	0
Pyelitis (Total)	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Dilatation of the renal pelvis (Total)	0	1	0	1	0	0	1	1
Minimal	0	0	0	1	0	0	0	0
Moderate	0	0	0	0	0	0	0	1
Interstitial inflammatory cell infiltration (Total)	1	0	1	0	0	0	0	1
Minimal	1	0	1	0	0	0	0	1
Free blood in renal pelvis	0	0	0	0	0	0	0	1
Urinary Bladder	10	0	0	10	10	0	0	10
Examined	8	0	0	7	10	0	0	10
No abnormalities detected	2	0	0	3	0	0	0	0
Intra-luminal plug of refluxed seminal colloid	0	0	0	0	0	0	0	0
Ureters	0	0	0	0	0	0	0	1
Examined	0	0	0	0	0	0	0	1
Luminal dilatation (Total)	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Uterus	0	0	0	0	10	4	3	10
Examined	0	0	0	0	6	0	0	7
No abnormalities detected	0	0	0	0	0	0	0	0

TABLE 10
(Microscopic pathology incidence summary (Terminal kill) - continued)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	10	10	10	10	10	10	10
Uterus	(Continued)							
Luminal dilatation (Total)	0	0	0	0	4	4	3	3
Minimal	0	0	0	0	4	4	3	3
Cervix	0	0	0	0	10	0	0	10
Examined	0	0	0	0	10	0	0	10
No abnormalities detected	0	0	0	0	10	0	0	10
Ovaries	0	0	0	0	10	1	0	10
Examined	0	0	0	0	10	1	0	10
No abnormalities detected	0	0	0	0	10	1	0	10
Prostate	10	0	0	10	0	0	0	0
Examined	8	0	0	9	0	0	0	0
No abnormalities detected	0	0	0	0	0	0	0	0
Focal interstitial lymphoid aggregations (Total)	2	0	0	1	0	0	0	0
Minimal	2	0	0	1	0	0	0	0
Seminal Vesicles	10	0	0	10	0	0	0	0
Examined	10	0	0	10	0	0	0	0
No abnormalities detected	10	0	0	10	0	0	0	0
Epididymides	10	1	1	10	0	0	0	0
Examined	9	0	0	10	0	0	0	0
No abnormalities detected	0	0	0	0	0	0	0	0
Reduced numbers of spermatozoa (Total)	1	1	0	0	0	0	0	0
Moderate	0	1	0	0	0	0	0	0
Marked	1	0	0	0	0	0	0	0
Abnormal spermatozoa absent	0	0	1	0	0	0	0	0
Testes	10	1	1	10	0	0	0	0
Examined	9	0	0	10	0	0	0	0
No abnormalities detected	9	0	0	10	0	0	0	0

TABLE 10
(Microscopic pathology incidence summary (Terminal kill) - continued)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study Animals completed	25 10	15 10	15 10	25 10	25 10	15 10	15 10	25 10
Testes	(Continued)							
Seminiferous tubular atrophy (Total)	1	1	1	0	0	0	0	0
Marked	1	1	1	0	0	0	0	0
Spermatocele in rete testis	0	0	1	0	0	0	0	0
Interstitial oedema (Total)	0	0	1	0	0	0	0	0
Moderate	0	0	1	0	0	0	0	0
Thyroids								
Examined	10	0	0	10	10	0	0	10
No abnormalities detected	10	0	0	10	10	0	0	10
Parathyroids								
Examined	10	0	0	8	8	0	0	9
Missing	0	0	0	2	2	0	0	1
No abnormalities detected	10	0	0	8	8	0	0	9
Adrenals								
Examined	10	10	10	10	10	10	10	10
No abnormalities detected	7	10	10	6	8	8	8	4
Sinusoidal dilatation (Total)	0	0	0	0	0	1	1	0
Minimal	0	0	0	0	0	2	1	0
Sinusoidal congestion (Total)	0	0	0	0	1	0	1	0
Minimal	0	0	0	0	1	0	1	0
Diffuse cellular vacuolation - zona fasciculata (Total)	3	0	0	3	0	0	0	0
Minimal	3	0	0	3	0	0	0	0
Increased width of zona fasciculata (Total)	0	0	0	1	1	0	0	6
Minimal	0	0	0	1	1	0	0	6
Pituitary								
Examined	10	0	0	10	10	0	0	10
No abnormalities detected	9	0	0	10	10	0	0	10

TABLE 10
(Microscopic pathology incidence summary (Terminal kill) - continued)

Removal reason: Terminal	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	10	10	10	10	10	10	10
(Continued)								
Pituitary Focal vacuolation - pars distalis (Total)	1	0	0	0	0	0	0	0
Minimal	1	0	0	0	0	0	0	0
Salivary Glands Examined	10	0	0	10	10	0	0	10
No abnormalities detected	10	0	0	10	10	0	0	10
Skeletal Muscle Examined	1	0	0	1	0	0	0	0
Fibroma (Benign)	1	0	0	1	0	0	0	0
Haemorrhage (Total)	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	0
Oesophagus Examined	10	0	0	10	10	0	0	10
No abnormalities detected	10	0	0	10	10	0	0	10
Stomach Examined	10	2	2	10	10	1	5	10
No abnormalities detected	10	1	0	8	8	0	0	7
Focus of ectopic non-glandular epithelium within the glandular mucosa	0	1	2	2	2	1	5	3
Duodenum Examined	10	0	0	10	10	0	0	10
No abnormalities detected	10	0	0	10	10	0	0	10
Jejunum Examined	10	0	0	10	10	0	0	10
No abnormalities detected	10	0	0	10	10	0	0	10
Ileum Examined	10	0	0	10	10	0	0	10
No abnormalities detected	10	0	0	10	10	0	0	10

TABLE 10
(Microscopic pathology incidence summary (Terminal kill) - continued)

Removal reason: Terminal	Group 1		Group 2		Group 3		Group 4		Group 1		Group 2		Group 3		Group 4	
	Males				Females											
Animals on study	25	15	15	10	25	10	25	10	25	15	15	10	15	10	25	10
Animals completed	10	10	0	0	0	0	10	10	10	10	0	0	0	0	10	10
Caecum Examined No abnormalities detected	10	10	0	0	0	0	10	10	10	10	0	0	0	0	10	10
Colon Examined No abnormalities detected	10	10	0	0	0	0	10	10	10	10	0	0	0	0	10	10
Rectum Examined No abnormalities detected	10	10	0	0	0	0	10	10	10	10	0	0	0	0	10	10
Nematodes in lumen	9	0	0	0	0	0	10	8	10	0	0	0	0	0	10	0
Eyes Examined Keratitis (Total) Moderate	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Uveitis (Total) Moderate	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Sciatic Nerve Examined No abnormalities detected	10	10	0	0	0	0	10	10	10	10	0	0	0	0	10	10
Brain Examined No abnormalities detected	10	10	0	0	0	0	10	10	10	10	0	0	0	0	10	10
Bone Marrow/sternum Examined No abnormalities detected	10	10	0	0	0	0	10	10	10	10	0	0	0	0	10	10

TABLE 10
Microscopic pathology incidence summary (Recovery kill)

Removal reason: Recovery	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
	25	15	15	25	25	15	15	25
Animals on study	10	0	0	10	9	0	0	10
Animals completed	10	0	0	10	9	0	0	10
Lungs								
Examined	2	0	0	4	2	0	0	4
No abnormalities detected	0	0	0	1	1	0	0	1
Increased numbers of alveolar macrophages (Total)	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Moderate	2	0	0	3	1	0	0	1
Minimal	2	0	0	3	1	0	0	3
Vascular congestion (Total)	0	0	0	0	0	0	0	0
Lymph Nodes - Cervical								
Examined	0	0	0	2	0	0	0	2
Increased cellularity - generalised (Total)	0	0	0	2	0	0	0	2
Minimal	0	0	0	2	0	0	0	2
Liver								
Examined	10	0	0	10	9	0	0	10
No abnormalities detected	9	0	0	7	4	0	0	7
Hepatocyte vacuolation - periportal (Total)	0	0	0	0	1	0	0	0
Minimal	0	0	0	0	1	0	0	0
Moderate	1	0	0	2	3	0	0	3
Minimal	1	0	0	2	3	0	0	3
Extramedullary haemopoiesis (Total)	0	0	0	0	0	0	0	0
Hepatocyte vacuolation - median cleft (Total)	0	0	0	1	1	0	0	0
Minimal	0	0	0	1	1	0	0	0
Liver (ORO stain)								
Examined	10	0	0	10	9	0	0	10
No abnormalities detected	8	0	0	10	5	0	0	10
Periportal fat deposition (Total)	2	0	0	0	4	0	0	0
Trace	2	0	0	0	3	0	0	0
Minimal	0	0	0	0	1	0	0	0
Kidneys								
Examined	10	0	0	10	9	0	0	10
No abnormalities detected	2	0	0	3	8	0	0	7

TABLE 10
(Microscopic pathology incidence summary (Recovery kill) - continued)

Removal reason: Recovery	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	0	0	10	9	0	0	10
(Continued)								
Kidneys								
Cortical tubules with eosinophilic inclusions (Total)	7	0	0	7	0	0	0	0
Trace	7	0	0	5	0	0	0	0
Minimal	0	0	0	2	0	0	0	0
Cortical tubules - basophilic (Total)	1	0	0	3	1	0	0	0
Trace	0	0	0	0	0	0	0	0
Minimal	1	0	0	3	0	0	0	0
Cortical tubules with cellular debris casts (Total)	0	0	0	5	0	0	0	0
Minimal	0	0	0	1	0	0	0	0
Dystrophic mineralisation (Total)	0	0	0	1	0	0	0	0
Trace	0	0	0	0	0	0	0	0
Minimal	0	0	0	0	0	0	0	0
Dilatation of the renal pelvis (Total)	1	0	0	0	0	0	0	0
Minimal	1	0	0	0	0	0	0	0
Mineralisation of pelvic/papillary epithelium (Total)	0	0	0	0	0	0	0	0
Trace	0	0	0	0	0	0	0	1
Ovaries								
Examined	0	0	0	0	2	0	0	0
Absence of corpora lutea	0	0	0	0	2	0	0	0
Testes								
Examined	0	0	0	1	0	0	0	0
Seminiferous tubular atrophy (Total)	0	0	0	1	0	0	0	0
Minimal	0	0	0	1	0	0	0	0
Interstitial oedema (Total)	0	0	0	1	0	0	0	0
Minimal	0	0	0	1	0	0	0	0
Adrenals								
Examined	10	0	0	10	9	0	0	10
No abnormalities detected	10	0	0	10	9	0	0	10

TABLE 10
(Microscopic pathology incidence summary (Recovery kill) - continued)

Removal reason: Recovery	Males				Females			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Animals on study	25	15	15	25	25	15	15	25
Animals completed	10	0	0	10	9	0	0	10
Skeletal Muscle	0	0	0	0	1	0	0	0
Examined	0	0	0	0	1	0	0	0
Haemorrhage (Total)	0	0	0	0	1	0	0	0
Moderate	0	0	0	0	1	0	0	0
Stomach	1	0	0	1	2	0	0	0
Examined	0	0	0	0	1	0	0	0
No abnormalities detected	1	0	0	1	1	0	0	0
Focus of ectopic non-glandular epithelium within the glandular mucosa	1	0	0	1	1	0	0	0
Eyes	0	0	0	0	2	0	0	1
Examined	0	0	0	0	2	0	0	1
Conjunctival haemorrhage, inflammation and oedema (Total)	0	0	0	0	2	0	0	1
Moderate	0	0	0	0	2	0	0	1
Adipose Tissue	1	0	0	0	0	0	0	0
Examined	1	0	0	0	0	0	0	0
Fat necrosis	1	0	0	0	0	0	0	0

TABLE 11
Neuropathology

Removal reason: Terminal	Group	Group	Group	Group
	1	4	1	4
	--- Males ---		-- Females --	
Animals on study	25	25	25	25
Animals completed	5	5	5	5
Forebrain/cerebrum				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Midbrain				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Cerebellum And Pons				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Medulla Oblongata				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Spinal Cord (C3-6)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Spinal Cord (L1-4)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Gasserian Ganglia				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Dorsal Root Ganglion (C)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Dorsal Root Ganglion (L)				
Examined	4	5	5	5
Missing	1	0	0	0
No abnormalities detected	4	5	5	5

TABLE 11
(Neuropathology - continued)

	Group	Group	Group	Group
Removal reason: Terminal	1	4	1	4
	--- Males ---		-- Females --	
Animals on study	25	25	25	25
Animals completed	5	5	5	5
Dorsal Root Fibres (C)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Dorsal Root Fibres (L)				
Examined	4	5	5	5
Missing	1	0	0	0
No abnormalities detected	4	5	5	5
Ventral Root Fibres (C)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Ventral Root Fibres (L)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Sciatic Nerve (Sciatic Notch)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Sciatic Nerve (Mid-thigh)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Sural Nerve				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
Tibial Nerve				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5

APPENDIX 1

Clinical signs after dosing

Group 4♂: 1000 mg/kg/day - Incidence of salivation noted immediately after dosing
(no. of days observed per week)

Animal no.	Week												
	1	2	3	4	5	6	7	8	9	10	11	12	13
	Main group												
31	4	2	2	3	2	5	5	5	6	5	7	4	6
32	5	2	3	1	7	6	6	6	6	5	7	4	7
33	2	4	2	2	5	5	5	6	6	6	7	5	6
34	6	3	2	-	3	6	5	6	7	7	6	6	7
35	2	3	2	3	6	6	5	7	5	7	7	6	7 [†]
36	1	1	2	2	5	7	6	5	6	6	6	5	5
37	2	1	2	3	4	5	6	7	6	6	6	6	5
38	2	2	3	1	3	6	5	3	4	6	7	4	5
39	5	1	2	2	4	6	3	4	5	6	7	6	5
40	3	2	1	2	6	7	4	6	6	6	6	7	7
	Neuropath group												
96	5	3	1	5	7	5	4	7	7	5	6	5	5
97	2	5	-	2	5	5	3	3	7	5	7	6	5
98	3	6	3	4	5	6	5	6	7	6	6	7	7 [†]
99	3	3	1	5	4	5	4	4	5	7	4	4	6
100	3	2	2	3	5	6	5	4	5	6	7	5	7
	Recovery group												
131	1	1	-	3	5	4	4	6	7	5	7	6	6
132	6	1	2	3	5	5	5	6	7	5	7	6	6
133	4	3	1	2	4	5	4	6	6	5	7	6	6
134	4	1	2	1	5	6	6	4	5	7	7	7	6
135	3	4	-	3	5	7	5	3	6	6	7	6	6
136	3	4	2	4	5	6	5	6	6	6	6	6	6
137	1	2	2	3	5	7	6	7	7	7	6	7	6
138	3	4	3	5	5	6	4	6	6	6	6	5	7
139	2	5	1	6	6	5	6	5	7	5	7	7	5
140	2	5	4	6	7	7	7	6	6	7	7	6	6

† Salivation noted up to 1 hour post dosing

APPENDIX 1

(Clinical signs after dosing - continued)

Group 4♀: 1000 mg/kg/day - Incidence of salivation noted immediately after dosing
(no. of days observed per week)

Animal no.	Week												
	1	2	3	4	5	6	7	8	9	10	11	12	13
	Main group												
71	1	4	1	4	6	6	5	7	6	6	7	5	7
72	-	4	-	3	5	5	5	6	6	6	7	7	5
73	1	3	1	4	6	5	4	5	5	7	6	7	5
74	1	3	-	1	5	5	6	6	5	7	4	7	5
75	2	2	1	4	5	4	4	5	6	5	6	7	5
76	3	2	-	3	4	5	5	7	5	7	5	7	7
77	4	2	-	5	4	5	4	4	6	6	7	7	6
78	3	3	3	3	4	5	3	7	7	4	6	6	7
79	-	1	3	4	3	6	4	4	6	5	5	6	5
80	3	4	5	3	5	6	6	4	6	6	6	6	4
	Neuropath group												
116	2	3	2	2	6	6	4	6	6	6	6	7	6
117	1	4	1	2	3	5	3	7	5	6	7	5	5
118	3	4	1	5	6	5	3	6	5	6	7	7	6
119	4	4	1	5	7	5	4	6	6	7	5	7	7
120	3	4	1	3	4	4	4	6	6	5	6	5	4
	Recovery group												
151	2	4	3	4	7	5	6	7	6	7	6	7	6
152	-	3	-	3	5	5	4	6	5	6	5	7	5
153	4	2	1	3	5	5	4	5	6	7	6	7	6
154	6	3	5	2	4	6	6	6	7	5	7	6	6
155	4	3	2	3	7	5	5	6	6	5	4	7	4
156	3	2	2	2	4	5	6	5	7	6	4	6	4
157	1	5	4	5	6	6	6	7	6	6	6	7	5
158	2	5	1	6	7	7	6	6	7	6	7	7	6
159	2	1	3	4	5	6	5	5	5	6	7	5	6
160	4	5	3	5	6	6	7	5	6	6	6	6	6

APPENDIX 1

(Clinical signs after dosing - continued)

Group 4♂ 1000 mg/kg/day - Post dosing - clinical sign (no. of days observed per week)#

Animal no.	Week												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Main group													
37	-	-	-	-	-	-	-	-	-	-	-	B(1)	P(1)
39	R(1)	-	-	-	-	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-	-	-	-	B(1) H(1)	J(1) H(1)
Neuropath group													
96	-	-	-	-	-	-	-	-	-	-	H(1)	-	P(1)
97	-	-	-	-	-	-	-	-	-	-	-	-	C(1) H(1) J(4) P(2)
98	-	-	-	-	-	-	-	-	U(1)	C(1) U(1)	U(1)	-	J(5) P(2)
99	-	-	-	-	-	-	-	-	-	-	-	-	P(2)
100	-	-	-	-	-	-	-	-	-	-	P(1)	C(1)	-
Recovery group													
131	-	-	-	-	-	-	-	-	U(1)	-	-	C(1) H(1) J(1)	-
132	-	-	-	-	J(1) C(1)	-	-	-	-	-	-	C(1)	P(1)
133	-	-	-	-	-	-	-	-	-	-	-	P(1)	-
134	-	-	-	-	-	-	-	-	-	-	P(1)	-	P(1)
135	-	-	-	-	-	-	-	-	-	-	-	C(1) H(1)	-
136	-	-	-	-	-	-	-	-	U(1)	-	C(1) H(2)	P(1)	C(1) H(1) J(1)
137	-	-	-	-	-	-	-	U(1)	U(1)	-	C(3) H(2)	J(1) B(1)	B(1) J(1)
138	-	-	-	-	-	-	-	-	-	-	C(1) H(2)	-	J(2)
139	-	-	-	-	-	-	-	U(1)	-	-	-	C(1)	-
140	-	-	-	-	-	-	-	U(1)	-	-	P(1)	H(1)	C(1) H(1) J(1)

Only affected individual as shown
 P Paddling of forelimbs
 U Unsteady gait
 C Collapsed posture

J Body spasms
 R Noisy respiration
 B Brown peri-oral staining
 H Partially closed eyelids

APPENDIX 1

(Clinical signs after dosing - continued)

Group 4 ♀ 1000 mg/kg/day - Post dosing - clinical sign (no. of days observed per week)#

Animal no.	Week												
	1	2	3	4	5	6	7	8	9	10	11	12	13
	Main group												
73	R(1)	-	-	-	-	-	-	-	-	-	-	H(1)	-
75	-	-	-	-	-	-	-	-	-	-	-	-	P(1)
77	-	-	-	-	-	-	-	-	U(1)	-	-	-	-
80	-	-	-	-	-	-	-	-	-	-	-	H(1)	-
												P(1)	-
	Neuropath group												
116	-	-	-	-	-	-	-	-	-	-	-	P(1)	-
117	-	-	-	-	-	-	-	-	-	-	-	P(2)	P(1)
118	-	-	-	-	-	-	-	-	-	-	-	P(1)	C(1) H(2) P(1)
119	-	-	-	-	-	-	-	-	-	-	-	C(1) P(1)	P(1)
120	-	-	-	-	-	-	-	-	-	-	-	-	P(1)
	Recovery group												
151	-	-	-	-	-	-	-	-	-	-	-	-	P(1) J(1) P(1)
152	-	-	-	-	-	-	-	-	-	-	-	-	P(3)
153	-	-	-	-	-	-	-	-	-	-	-	H(1) P(1)	J(1) P(2)
154	-	-	-	-	-	-	-	-	-	-	-	-	P(1)
155	-	-	-	-	-	-	-	-	-	-	-	H(1)	-
156	-	-	-	-	-	-	-	-	-	-	-	P(1)	P(1)
157	-	-	-	-	-	-	-	-	-	-	-	H(1)	J(1) P(2)
158	-	-	-	-	-	-	-	-	-	P(1)	-	P(1)	H(1) J(1)
159	-	-	-	-	-	-	-	-	-	-	-	P(2)	H(1) P(2)
160	-	-	-	-	-	-	-	-	-	-	-	H(1)	H(1) P(1)

Only affected individual as shown
 P Paddling of forelimbs
 U Unsteady gait
 C Collapsed posture

J Body spasms
 R Noisy respiration
 B Brown peri-oral staining
 H Partially closed eyelids

APPENDIX 2

Bodyweights - individual values (g)

(Main, Neuropath and Recovery groups)

Group 1♂: Control

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
1	123	182	234	280	317	351	357	385	402	412
2	127	184	235	291	339	376	389	425	436	457
3	127	191	238	301	348	398	405	437	468	491
4	130	189	247	293	354	390	416	461	490	517
5	132	183	226	270	303	331	337	362	384	392
6	133	192	250	310	357	390	421	455	478	495
7	136	200	245	306	343	377	406	427	448	455
8	138	197	262	315	390	403	443	508	538	551
9	139	195	257	318	371	413	449	478	502	525
10	142	190	272	315	403	414	481	527	545	572
81	112	156	195	240	274	317	353	377	407	427
82	121	169	217	272	302	338	362	389	405	429
83	122	187	251	312	355	401	432	460	493	503
84	129	171	205	243	285	320	367	386	407	416
85	138	189	251	310	347	388	423	442	470	477
121	110	151	196	244	281	318	335	364	388	411
122	113	148	181	223	256	291	298	319	337	352
123	115	172	239	294	353	404	421	472	499	529
124	115	155	199	251	298	339	359	397	411	426
125	116	165	216	268	309	345	356	390	417	443
126	117	163	216	274	312	344	358	381	394	414
127	118	169	217	263	290	316	332	347	359	370
128	119	170	215	282	340	382	415	445	483	507
129	120	174	221	273	314	350	373	397	410	428
130	147	186	264	313	346	395	414	454	484	521

APPENDIX 2

(Bodyweights - continued)

Group 1♂: Control

Animal number	Week								
	9	10	11	12	13	R1	R2	R3	R4
1	422	435	452	462	459				
2	476	491	521	533	545				
3	502	519	544	545	546				
4	549	573	581	602	604				
5	399	411	421	423	426				
6	511	531	554	567	587				
7	472	482	501	510	515				
8	582	609	630	651	655				
9	545	575	586	605	604				
10	596	627	647	669	664				
81	440	454	471	490	510				
82	439	457	469	476	491				
83	524	542	564	574	596				
84	442	475	500	515	528				
85	503	520	532	545	557				
121	424	438	449	462	462	467	477	479	479
122	364	379	387	402	389	408	419	423	422
123	552	574	586	607	593	613	625	633	625
124	440	459	473	484	464	486	501	504	503
125	465	490	500	508	512	525	531	545	542
126	428	451	467	479	488	502	515	524	528
127	386	402	408	419	431	437	453	452	453
128	529	557	577	596	608	618	634	638	635
129	444	459	480	484	490	502	508	517	511
130	548	567	587	601	618	621	643	651	650

R Recovery

APPENDIX 2

(Bodyweights - continued)

Group 2♂ 62.5 mg/kg/day

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
11	123	187	237	294	344	386	403	428	447	463
12	124	191	251	318	370	401	446	488	517	537
13	128	189	251	313	366	396	427	483	500	523
14	130	188	239	286	329	365	375	403	423	445
15	132	192	247	303	344	386	401	444	465	488
1016	122	179	229	294	337	361	374	407	423	451
17	134	181	256	325	379	413	429	459	483	493
18	138	195	266	318	368	410	417	439	458	474
19	139	195	233	285	334	378	383	424	437	459
20	140	197	257	312	364	395	412	446	480	501
86	117	160	202	253	294	330	360	382	405	425
87	120	166	212	263	304	334	362	390	412	431
88	128	180	235	290	340	375	408	443	460	471
89	131	192	251	295	341	372	404	425	433	445
90	138	193	252	304	349	392	423	453	471	487

APPENDIX 2
(Bodyweights - continued)

Group 2♂: 62.5 mg/kg/day

Animal number	Week				
	9	10	11	12	13
11	484	500	509	520	523
12	570	588	606	621	620
13	561	578	598	617	620
14	456	474	492	501	497
15	508	532	546	556	561
1016	475	500	516	542	533
17	531	546	571	593	579
18	483	509	524	546	531
19	476	491	504	523	510
20	514	538	559	567	562
86	447	454	470	481	486
87	450	474	491	507	520
88	495	522	538	552	564
89	457	462	471	486	492
90	507	514	534	541	558

APPENDIX 2

(Bodyweights - continued)

Group 3♂: 250 mg/kg/day

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
21	123	188	242	300	337	376	381	411	436	452
22	125	170	216	270	313	359	367	400	425	439
23	128	196	254	298	349	388	408	437	460	481
24	130	195	249	318	374	416	410	449	486	511
25	132	197	250	297	339	380	392	426	442	463
26	134	198	243	287	362	401	421	458	479	500
27	135	193	245	303	343	378	383	420	432	449
28	137	207	269	309	401	407	436	483	504	525
29	138	184	234	277	321	355	378	417	446	469
30	140	200	257	322	365	402	401	433	461	481
91	114	159	198	247	280	310	336	354	391	405
92	120	180	239	296	340	378	388	412	446	469
93	127	178	235	295	350	402	429	463	482	504
94	131	196	260	313	365	395	418	445	466	486
95	136	187	232	279	322	367	408	442	467	484

APPENDIX 2

(Bodyweights - continued)

Group 3♂: 250 mg/kg/day

Animal number	Week				
	9	10	11	12	13
21	479	497	512	524	520
22	458	472	480	489	485
23	505	529	544	556	548
24	532	549	551	570	564
25	481	495	503	515	511
26	523	544	558	576	564
27	468	487	501	519	522
28	551	559	581	586	579
29	491	507	530	542	538
30	509	510	532	550	546
91	426	443	456	466	474
92	489	511	533	543	550
93	531	548	566	572	574
94	511	532	551	565	572
95	515	544	562	575	590

APPENDIX 2

(Bodyweights - continued)

Group 4♂: 1000 mg/kg/day

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
31	123	169	214	260	301	342	348	367	399	415
32	124	182	222	268	302	339	339	361	386	402
33	128	185	241	295	344	388	406	431	461	487
34	131	166	197	242	285	314	320	348	369	386
35	132	189	238	293	331	372	388	418	439	459
36	133	190	249	280	308	324	358	391	409	434
37	135	197	258	315	362	395	421	454	482	489
38	136	192	238	299	345	393	412	456	483	498
39	138	178	219	271	330	364	395	421	438	454
40	140	198	256	325	375	406	442	494	520	540
96	117	163	204	261	304	341	367	390	404	420
97	117	176	235	297	358	405	439	484	513	538
98	129	198	247	294	332	364	397	413	436	448
99	132	187	240	287	332	385	418	451	474	497
100	136	191	255	299	352	392	425	458	479	498
131	110	158	209	271	324	365	381	420	438	465
132	113	165	213	259	301	338	348	391	417	440
133	115	166	209	257	302	344	357	396	420	445
134	116	158	206	259	297	328	339	370	380	401
135	116	179	235	298	351	398	419	456	480	500
136	117	175	228	290	336	388	413	447	473	494
137	118	181	230	277	325	360	387	414	432	443
138	119	174	216	264	307	320	344	364	381	394
139	120	183	230	287	339	374	410	437	462	483
140	121	174	222	264	295	325	347	374	393	420

APPENDIX 2

(Bodyweights - continued)

Group 4♂: 1000 mg/kg/day

Animal number	Week								
	9	10	11	12	13	R1	R2	R3	R4
31	438	451	469	482	481				
32	429	442	461	466	462				
33	506	524	539	553	544				
34	401	417	435	450	441				
35	477	484	505	522	497				
36	458	464	483	506	516				
37	516	524	546	555	574				
38	514	531	555	563	578				
39	472	488	502	516	520				
40	571	589	605	631	637				
96	435	445	468	485	496				
97	563	580	596	618	626				
98	459	469	486	506	514				
99	526	540	563	567	580				
100	525	540	562	572	591				
131	493	510	536	551	550	531	576	589	591
132	453	472	494	511	505	516	525	550	545
133	458	493	514	533	536	510	565	580	583
134	412	423	440	447	441	453	473	488	483
135	519	537	558	572	567	576	594	604	596
136	442	489	520	529	554	555	573	572	572
137	458	478	497	515	525	534	552	560	569
138	409	428	446	461	474	491	500	521	514
139	509	526	545	555	560	550	585	595	583
140	439	459	484	492	507	506	532	554	555

R Recovery

APPENDIX 2

(Bodyweights - continued)

Group 1♀: Control

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
41	113	144	157	182	199	211	212	225	226	236
42	114	146	168	184	201	220	227	236	248	261
43	114	154	176	200	221	243	246	260	270	274
44	113	146	165	181	205	218	221	236	254	254
45	118	161	188	206	229	246	251	254	263	275
46	119	158	177	198	214	229	250	264	274	274
47	121	157	174	197	211	227	233	238	244	244
48	122	155	166	185	200	209	221	243	243	246
49	123	173	207	237	252	273	288	300	312	317
50	123	163	184	202	219	243	253	269	272	285
101	108	140	160	178	201	215	226	234	244	249
102	121	154	185	213	238	250	260	270	283	280
103	122	164	185	213	245	261	268	279	288	291
104	123	156	176	198	214	220	229	237	250	249
105	137	168	191	218	248	269	279	290	304	311
141	108	133	150	161	175	189	194	197	214	219
142	108	146	170	198	225	240	241	260	274	276
143	108	139	154	172	189	202	202	216	225	226
144	124	158	183	200	225	254	254	268	279	291
145	126	162	187	210	229	254	263	281	279	296
146	126	159	177	203	222	232	239	247	255	261
147	127	156	174	206	225	250	259	270	284	299
148	127	154	178	189	200	220	236	243	245	257
149	128	168	197	222	249	272	286	289	303	311
150	130	151	170	193	207	220	232	247	272	273

APPENDIX 2

(Bodyweights - continued)

Group 1♀: Control

Animal number	Week								
	9	10	11	12	13	R1	R2	R3	R4
41	243	247	251	253	244				
42	262	269	266	273	271				
43	283	289	295	295	293				
44	268	270	275	281	274				
45	281	277	287	299	289				
46	283	289	296	298	300				
47	251	253	256	262	262				
48	255	258	264	262	268				
49	321	332	337	338	346				
50	298	299	313	320	313				
101	259	258	271	275	275				
102	290	298	294	292	299				
103	293	304	311	311	314				
104	252	257	257	260	262				
105	315	319	338	332	339				
141	226	225	234	240	235	244	252	253	244
142	287	297	300	306	297	307	319	317	311
143	226	238	238	235	227	208	187	189	219
144	301	306	323	332	332	338	344	354	342
145	303	308	322	326	319	336	329	341	347
146	261	270	277	273	273	282	282	286	284
147	303	307	315	318	332	345	358	371	350
148	269	269	271	277	286	296	297	303	305
149	322	324	328	336	344	347	346	350	346
150	278	294	314	309	317	331	344	358	356

R Recovery

APPENDIX 2

(Bodyweights - continued)

Group 2♀: 62.5 mg/kg/day

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
51	113	142	149	169	189	205	208	222	234	239
52	114	143	160	175	189	201	206	220	226	232
53	115	155	176	201	223	237	237	252	271	278
54	117	158	185	207	215	244	202	258	257	285
55	118	166	188	203	232	256	255	267	281	288
56	119	156	169	209	237	261	255	272	285	288
57	120	151	171	190	210	226	228	241	250	253
58	122	139	161	182	195	209	211	228	230	238
59	123	160	180	205	224	236	239	261	270	268
60	124	152	175	194	214	230	240	255	256	260
106	113	147	164	178	203	218	221	226	236	237
107	119	154	173	197	226	242	260	264	273	292
108	123	140	167	187	198	222	234	250	262	254
109	125	150	171	189	208	232	252	259	264	274
110	128	158	174	198	218	230	243	258	266	271

APPENDIX 2

(Bodyweights - continued)

Group 2♀: 62.5 mg/kg/day

Animal number	Week				
	9	10	11	12	13
51	239	245	253	256	249
52	241	242	243	247	242
53	278	291	289	298	285
54	297	308	303	320	309
55	291	292	308	308	298
56	296	300	312	320	305
57	264	266	275	280	268
58	238	244	252	260	253
59	283	290	292	295	292
60	272	279	276	287	283
106	251	252	266	268	262
107	299	295	309	317	315
108	263	278	277	283	309
109	289	290	294	305	304
110	280	288	292	290	302

APPENDIX 2

(Bodyweights - continued)

Group 3♀: 250 mg/kg/day

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
61	113	148	163	180	211	228	231	244	250	257
62	114	142	160	177	189	210	216	224	229	238
63	115	142	159	187	207	225	231	247	256	257
64	117	156	174	197	215	235	241	260	272	282
65	118	137	156	175	195	210	213	233	241	253
66	119	149	168	191	214	226	231	247	251	251
67	120	159	184	200	227	240	237	248	264	266
68	122	151	176	193	209	209	228	244	252	257
69	123	152	162	183	198	206	205	227	239	241
70	123	159	179	199	213	236	246	263	276	284
111	111	144	163	183	198	208	216	232	231	240
112	120	135	152	169	189	195	206	215	213	223
113	122	138	150	164	182	195	205	213	222	231
114	124	135	154	170	180	190	206	213	218	223
115	132	172	207	236	256	269	287	299	301	308

APPENDIX 2

(Bodyweights - continued)

Group 3♀: 250 mg/kg/day

Animal number	Week				
	9	10	11	12	13
61	266	265	272	270	264
62	242	247	251	257	258
63	262	272	274	285	272
64	296	294	295	305	303
65	259	263	271	269	267
66	261	269	273	274	271
67	273	272	286	288	276
68	268	276	272	282	284
69	239	247	257	255	257
70	301	305	301	305	313
111	252	245	249	256	256
112	228	231	234	241	247
113	222	247	258	258	263
114	232	237	266	252	256
115	319	330	339	349	350

APPENDIX 2

(Bodyweights - continued)

Group 4♀: 1000 mg/kg/day

Animal number	Week									
	-1	0	1	2	3	4	5	6	7	8
71	114	155	180	201	216	231	244	254	251	264
72	114	153	178	195	209	227	234	238	240	256
73	116	140	165	182	193	217	227	233	237	257
74	118	170	209	228	262	287	287	305	316	312
75	118	157	167	191	217	237	232	256	269	270
76	118	150	169	185	204	221	224	237	239	246
77	120	152	170	191	203	222	234	245	250	255
78	121	141	160	183	192	212	228	230	240	246
79	122	155	174	197	216	229	247	254	264	258
80	124	158	177	193	211	213	229	247	242	245
116	118	153	166	194	224	241	249	265	272	273
117	118	140	166	196	211	225	243	249	251	265
118	123	154	170	200	227	241	240	254	269	272
119	127	141	166	178	198	220	235	237	250	261
120	129	176	213	240	266	282	296	300	313	312
151	108	144	164	177	195	208	221	223	229	233
152	108	138	162	187	213	229	230	247	262	271
153	110	149	173	199	207	234	239	253	261	264
154	112	141	158	171	187	209	209	221	231	241
155	125	159	178	195	215	238	239	253	259	269
156	126	172	195	213	237	249	250	255	262	270
157	127	166	194	213	230	249	265	265	278	293
158	128	163	187	207	221	240	254	262	262	280
159	130	169	196	225	265	287	291	315	315	331
160	130	166	181	205	221	240	251	255	270	277

APPENDIX 2

(Bodyweights - continued)

Group 4♀: 1000 mg/kg/day

Animal number	Week								
	9	10	11	12	13	R1	R2	R3	R4
71	274	273	272	278	269				
72	268	267	266	271	272				
73	263	263	264	271	268				
74	336	340	354	357	341				
75	275	282	288	289	277				
76	247	259	255	264	265				
77	263	269	268	277	276				
78	253	264	267	275	268				
79	274	275	278	281	290				
80	247	254	267	262	267				
116	279	289	298	295	294				
117	270	274	278	282	287				
118	269	265	291	292	296				
119	264	265	272	276	276				
120	322	318	330	330	325				
151	235	239	246	250	247	253	263	259	258
152	275	282	293	294	283	303	295	296	301
153	276	280	278	283	283	286	294	303	297
154	246	253	260	258	258	267	275	280	275
155	276	279	291	295	291	294	306	306	301
156	277	283	291	300	300	307	311	322	313
157	300	301	309	314	319	312	324	329	322
158	281	287	285	298	300	296	298	300	296
159	346	350	353	362	371	379	373	383	366
160	280	287	296	293	301	307	309	315	320

R Recovery

APPENDIX 3

Food consumption - individual values (g/rat/week)

(Main, Neuropath and Recovery groups)

Group 1♂: Control

Week	Animal												
	1	2	3	4	5	6	7	8	9	10	81	82	83
-1	188	182	189	190	170	183	193	196	197	197	155	159	200
1	210	207	209	230	187	215	224	214	215	188	180	205	237
2	215	222	226	200	191	239	215	171	166	212	192	219	197
3	220	237	247	264	207	267	240	288	252	285	210	255	270
4	208	225	232	230	196	251	230	217	222	223	192	218	246
5	207	215	213	241	178	240	232	243	241	250	217	225	248
6	216	234	231	274	198	258	230	290	248	294	212	226	256
7	219	222	239	268	200	268	238	291	249	283	229	229	241
8	216	226	223	283	195	260	231	278	242	288	223	233	241
9	199	232	221	273	187	248	225	292	250	283	215	220	249
10	201	234	222	270	191	261	222	287	265	298	205	220	245
11	210	230	229	254	196	267	219	290	248	298	216	226	248
12	213	233	214	256	181	262	218	272	231	292	223	223	244
13	187	214	191	226	177	267	208	268	212	274	221	226	248

APPENDIX 3

(Food consumption - continued)

Group 1♂: Control

Week	Animal											
	84	85	121	122	123	124	125	126	127	128	129	130
-1	172	186	149	144	179	154	182	164	165	172	181	199
1	192	223	193	167	211	176	201	201	198	192	197	188
2	204	205	202	172	224	207	218	239	213	227	216	250
3	193	246	205	176	240	212	242	235	205	252	224	232
4	202	224	199	184	233	217	224	215	202	246	206	247
5	243	243	191	170	213	200	221	211	201	240	217	251
6	222	239	219	194	265	239	249	206	200	255	223	267
7	223	248	237	176	258	237	253	212	205	269	214	285
8	206	226	230	180	259	228	263	229	211	261	231	283
9	220	234	215	181	252	221	250	229	206	273	220	271
10	220	234	202	181	251	221	244	234	206	275	215	259
11	232	227	208	191	253	232	242	256	200	273	221	262
12	225	234	206	186	254	215	239	233	193	260	207	247
13	223	224	178	164	228	196	222	238	199	270	198	239
R1			211	212	251	239	237	225	195	244	217	252
R2			222	207	268	237	242	231	215	268	227	266
R3			215	205	269	235	271	252	212	273	228	265
R4			198	179	237	212	223	231	189	254	201	215

R Recovery

APPENDIX 3

(Food consumption - continued)

Group 2♂: 62.5 mg/kg/day

Week	Animal														
	11	12	13	14	15	1016	17	18	19	20	86	87	88	89	90
-1	188	192	194	186	192	176	195	196	187	195	165	180	170	191	187
1	215	231	239	215	219	213	237	240	196	226	180	206	198	235	211
2	204	213	208	218	203	242	225	205	205	212	193	219	214	198	218
3	249	259	263	221	251	250	271	254	234	251	222	236	235	238	240
4	237	228	238	208	239	226	238	239	228	243	194	211	238	212	231
5	229	244	248	187	230	201	246	231	193	214	202	236	228	236	245
6	229	275	283	215	264	241	255	231	226	245	201	224	232	226	238
7	233	277	283	220	255	246	249	232	218	248	209	240	224	232	230
8	242	277	284	224	261	239	244	227	226	244	219	231	222	217	231
9	236	281	291	215	255	245	262	227	228	252	216	237	229	210	233
10	223	277	286	206	250	245	251	220	230	243	205	223	220	206	217
11	231	274	272	213	250	245	248	231	234	247	209	240	228	212	236
12	229	267	272	209	248	242	240	241	217	237	198	234	223	217	227
13	218	230	244	178	230	202	201	214	182	217	200	254	224	212	223

APPENDIX 3

(Food consumption - continued)

Group 3♂: 250 mg/kg/day

Week	Animal														
	21	22	23	24	25	26	27	28	29	30	91	92	93	94	95
-1	190	167	202	183	196	198	192	192	187	191	157	189	174	200	189
1	217	183	226	224	236	215	229	209	207	223	178	229	208	246	210
2	217	200	194	219	212	220	201	202	207	212	184	205	223	198	205
3	265	206	256	248	240	288	243	99	223	244	212	241	241	254	214
4	232	217	240	234	226	231	228	235	212	244	177	232	234	233	221
5	216	194	249	187	212	249	209	242	213	228	199	227	242	229	242
6	228	223	250	246	240	262	238	185	233	246	201	229	232	242	247
7	254	218	252	258	233	256	238	269	256	254	208	246	242	239	252
8	257	221	274	250	235	259	229	267	240	254	200	250	240	246	238
9	268	217	272	243	223	260	236	278	246	255	206	244	257	246	249
10	253	209	275	241	225	264	235	247	223	235	191	249	248	232	264
11	240	211	266	243	218	257	244	256	244	256	195	239	247	237	261
12	243	208	258	216	226	266	234	240	237	255	201	238	229	226	244
13	216	186	223	199	198	220	204	221	200	212	201	236	221	220	246

APPENDIX 3

(Food consumption - continued)

Group 2♂: 62.5 mg/kg/day

Week	Animal														
	11	12	13	14	15	1016	17	18	19	20	86	87	88	89	90
-1	188	192	194	186	192	176	195	196	187	195	165	180	170	191	187
1	215	231	239	215	219	213	237	240	196	226	180	206	198	235	211
2	204	213	208	218	203	242	225	205	205	212	193	219	214	198	218
3	249	259	263	221	251	250	271	254	234	251	222	236	235	238	240
4	237	228	238	208	239	226	238	239	228	243	194	211	238	232	231
5	229	244	248	187	230	201	246	231	193	214	202	236	228	236	245
6	229	275	283	215	264	241	255	231	226	245	201	224	232	226	238
7	233	277	283	220	255	246	249	232	218	248	209	240	224	232	240
8	242	277	284	224	261	239	244	227	226	244	219	231	222	217	231
9	236	281	291	215	255	245	262	227	228	252	216	237	229	210	233
10	223	277	286	206	250	245	251	220	230	243	205	223	220	206	237
11	231	274	272	213	250	245	248	231	234	247	209	240	228	212	236
12	229	267	272	209	248	242	240	241	217	237	198	234	223	217	237
13	218	230	244	178	230	202	201	214	182	217	200	254	224	212	239

APPENDIX 3

(Food consumption - continued)

Group 3♂: 250 mg/kg/day

Week	Animal														
	21	22	23	24	25	26	27	28	29	30	91	92	93	94	95
-1	190	167	202	183	196	198	192	192	187	191	157	189	174	200	189
1	217	183	226	224	236	215	229	209	207	223	178	229	208	246	210
2	217	200	194	219	212	220	201	202	207	212	184	205	223	198	205
3	265	206	256	248	240	288	243	99	223	244	212	241	241	254	214
4	232	217	240	234	226	231	228	235	212	244	177	232	234	233	221
5	216	194	249	187	212	249	209	242	213	228	199	227	242	229	242
6	228	223	250	246	240	262	238	185	233	246	201	229	232	242	247
7	254	218	252	258	233	256	238	269	256	254	208	246	242	239	252
8	257	221	274	250	235	259	229	267	240	254	200	250	240	246	258
9	268	217	272	243	223	260	236	278	246	255	206	244	257	246	249
10	253	209	275	241	225	264	235	247	223	235	191	249	248	232	244
11	240	211	266	243	218	257	244	256	244	256	195	239	247	237	251
12	243	208	258	216	226	266	234	240	237	255	201	238	229	226	244
13	216	186	223	199	198	220	204	221	200	212	201	236	221	220	246

APPENDIX 3

(Food consumption - continued)

Group 4♂: 1000 mg/kg/day

Week	Animal												
	31	32	33	34	35	36	37	38	39	40	96	97	98
-1	174	184	201	170	186	183	196	196	168	182	161	172	184
1	193	205	221	171	207	224	222	202	178	215	182	205	227
2	201	217	213	180	219	232	211	205	193	193	209	230	207
3	211	222	243	200	218	221	242	263	223	212	239	263	242
4	214	226	237	183	214	188	230	237	215	240	217	246	223
5	185	191	223	163	211	214	234	247	246	247	225	248	233
6	197	192	257	196	246	236	238	254	216	272	214	285	231
7	218	203	249	209	232	244	249	250	223	250	223	287	238
8	220	209	259	206	236	241	243	251	240	257	214	289	237
9	210	213	247	199	240	252	245	256	229	266	210	284	225
10	207	212	246	200	274	245	234	239	204	259	214	271	213
11	221	216	250	205	232	248	242	256	221	273	221	265	229
12	208	212	240	211	233	240	237	240	230	255	216	276	245
13	189	195	207	180	195	242	244	243	204	255	215	267	232

APPENDIX 3

(Food consumption - continued)

Group 4♂: 1000 mg/kg/day

Week	Animal											
	99	100	131	132	133	134	135	136	137	138	139	140
-1	192	191	166	168	168	156	166	165	177	190	196	179
1	213	224	201	183	196	174	215	199	198	189	220	205
2	206	184	223	201	210	198	198	216	195	197	199	210
3	236	267	261	206	229	213	249	236	227	213	249	223
4	229	231	241	204	228	205	237	226	222	184	244	225
5	249	250	237	220	207	181	222	237	229	192	243	218
6	257	272	262	219	249	203	247	253	225	198	254	223
7	251	275	275	225	247	199	249	268	237	189	261	230
8	261	269	274	234	248	211	254	258	234	191	256	256
9	257	274	277	219	230	204	239	222	223	206	259	256
10	241	267	266	212	253	195	228	235	218	223	222	232
11	264	276	270	232	255	211	245	259	236	206	261	251
12	258	272	260	225	257	203	235	235	235	195	261	229
13	267	263	239	200	223	183	214	246	228	194	242	242
R1			254	231	249	226	250	250	252	216	254	253
R2			306	238	305	231	263	271	266	236	285	280
R3			300	248	286	243	265	276	262	242	285	272
R4			264	215	246	220	231	241	239	211	245	247

R Recovery

APPENDIX 3

(Food consumption - continued)

Group 1♀: Control

Week	Animal												
	41	42	43	44	45	46	47	48	49	50	101	102	103
-1	145	151	157	148	166	151	149	147	174	161	129	154	161
1	148	158	162	158	175	159	146	142	189	179	141	166	164
2	149	146	166	152	176	156	146	144	194	172	140	175	167
3	154	157	174	173	181	160	153	165	182	170	99	190	204
4	146	151	176	158	169	158	147	144	175	164	133	174	175
5	129	156	162	149	162	175	148	151	201	170	149	179	170
6	150	167	180	173	182	188	145	157	201	181	153	178	164
7	143	162	180	172	178	198	152	146	191	159	147	175	158
8	147	157	168	167	172	174	158	150	196	167	145	167	152
9	137	150	161	168	176	173	142	145	187	176	154	174	154
10	137	147	158	157	162	157	142	124	182	164	145	166	153
11	133	141	156	152	168	164	154	137	186	164	140	161	149
12	136	155	156	167	175	182	138	137	183	163	131	155	144
13	112	134	130	144	159	146	138	141	149	162	128	147	143

APPENDIX 3

(Food consumption - continued)

Group 19: Control

Week	Animal											
	104	105	141	142	143	144	145	146	147	148	149	150
-1	158	174	136	158	128	157	175	160	179	162	171	195
1	165	184	140	173	128	163	169	156	169	165	177	218
2	156	199	146	174	138	164	168	163	186	151	185	193
3	162	201	157	184	137	175	173	165	199	166	212	204
4	150	169	141	167	130	165	171	147	189	151	185	198
5	151	187	140	157	102	161	164	154	187	165	175	198
6	149	190	159	182	159	180	199	167	201	170	177	211
7	156	199	163	175	139	186	179	149	203	165	179	199
8	143	197	156	168	133	170	189	159	207	177	175	203
9	143	187	154	169	126	171	184	152	202	170	166	181
10	137	181	149	154	128	174	180	157	185	162	166	213
11	135	195	151	151	117	188	182	148	184	167	168	222
12	143	173	143	148	118	178	173	135	186	159	156	179
13	137	88	137	129	108	154	159	142	191	157	154	177
R1			162	161	108	188	198	166	218	172	168	233
R2			164	177	79	188	187	155	243	188	171	252
R3			163	173	97	184	210	165	250	195	177	251
R4			145	149	163	150	179	154	189	181	156	219

R Recovery

APPENDIX 3

(Food consumption - continued)

Group 29: 62.5 mg/kg/day

Week	Animal														
	51	52	53	54	55	56	57	58	59	60	106	107	108	109	110
-1	139	149	162	159	164	145	137	141	157	159	137	168	144	158	163
1	136	147	174	169	170	179	144	146	162	176	139	181	159	157	158
2	144	133	171	170	160	165	160	147	158	168	141	186	171	158	164
3	155	142	177	179	181	169	147	156	76	183	150	219	192	179	175
4	149	152	172	178	173	156	133	148	151	165	138	175	157	170	150
5	145	133	157	250	164	146	136	149	152	162	139	218	180	180	166
6	155	153	184	203	182	176	154	170	176	184	147	231	177	180	164
7	161	130	185	201	189	169	143	160	171	170	153	249	181	190	163
8	157	144	187	197	191	163	135	164	164	153	139	231	175	190	177
9	159	143	175	201	172	163	136	149	160	156	145	212	170	196	174
10	147	134	174	184	169	155	132	143	155	159	146	247	171	180	157
11	141	125	170	174	181	158	135	147	157	155	152	211	170	183	163
12	144	138	174	188	163	155	137	146	159	164	141	204	170	193	169
13	133	121	147	153	149	131	113	126	134	137	127	191	175	170	166

APPENDIX 3

(Food consumption - continued)

Group 3♀: 250 mg/kg/day

Week	Animal														
	61	62	63	64	65	66	67	68	69	70	111	112	113	114	115
-1	144	155	135	162	143	140	159	158	146	155	149	143	143	149	176
1	147	156	148	159	144	150	162	161	149	164	152	140	145	153	203
2	145	167	155	168	143	147	153	149	169	162	156	139	141	139	212
3	162	168	162	175	150	165	177	156	155	162	165	150	156	136	236
4	155	156	163	178	157	143	148	154	150	160	145	144	140	125	199
5	142	145	155	166	144	153	149	142	138	168	166	140	156	150	199
6	159	158	177	194	171	173	176	168	165	185	164	142	164	134	195
7	154	167	171	186	175	148	173	163	162	180	154	145	167	145	202
8	144	148	161	188	166	145	166	161	150	187	158	152	173	137	194
9	146	134	156	179	159	145	159	153	152	175	156	143	161	132	190
10	137	131	168	181	150	134	158	154	150	169	137	130	165	132	198
11	134	132	163	168	152	138	158	150	152	162	150	135	151	154	193
12	129	132	161	178	151	154	152	160	149	167	149	133	150	146	196
13	121	121	131	156	140	117	130	140	149	151	137	127	146	125	168

APPENDIX 3

(Food consumption - continued)

Group 4♀: 1000 mg/kg/day

Week	Animal												
	71	72	73	74	75	76	77	78	79	80	116	117	118
-1	153	160	131	177	160	148	158	145	149	148	159	148	147
1	170	167	136	201	147	160	162	166	155	153	154	156	141
2	157	176	135	200	155	155	161	153	164	148	161	160	154
3	174	176	156	211	163	155	171	139	154	165	189	191	176
4	163	173	143	203	164	154	160	134	148	140	158	162	144
5	152	160	140	190	150	137	166	151	160	157	169	188	148
6	189	157	147	205	169	150	165	144	166	164	172	171	159
7	174	175	150	203	180	152	168	144	168	134	168	171	162
8	180	177	152	213	159	151	169	145	147	147	170	189	151
9	169	170	142	213	157	140	159	139	157	146	173	173	158
10	155	159	138	196	155	147	155	140	145	152	nr	166	156
11	161	155	142	202	147	141	158	148	148	162	174	175	160
12	158	158	136	194	148	145	175	149	148	150	170	167	154
13	141	134	121	174	126	142	148	134	146	142	166	162	147

APPENDIX 3

(Food consumption - continued)

Group 4♀: 1000 mg/kg/day

Week	Animal											
	119	120	151	152	153	154	155	156	157	158	159	160
-1	143	176	147	143	155	133	164	170	167	159	167	164
1	166	190	155	152	164	135	159	176	173	157	176	159
2	151	204	140	155	163	132	166	171	168	167	186	166
3	174	198	153	169	159	147	179	173	173	178	238	166
4	153	174	143	154	155	135	159	155	162	158	195	159
5	174	189	144	155	142	136	143	161	169	162	193	166
6	166	190	148	174	162	146	170	151	164	164	207	158
7	189	195	166	182	164	144	170	150	173	164	210	157
8	182	180	148	183	161	145	159	158	171	172	210	169
9	173	184	155	171	159	142	174	150	171	161	200	155
10	173	180	138	172	152	145	170	151	171	166	200	149
11	179	181	137	172	151	145	181	159	170	173	197	157
12	170	172	141	161	149	138	164	158	157	169	201	152
13	169	162	130	142	135	123	146	144	165	157	195	148
R1			172	190	165	164	180	171	168	167	203	175
R2			161	179	176	176	185	174	171	176	209	174
R3			155	183	180	165	182	175	176	184	219	181
R4			146	163	154	137	160	154	153	162	178	170

R Recovery

APPENDIX 4

Water consumption - individual values (g/rat/day)

(Main and Recovery groups)

Group 1♂: Control

Week 12	Animal									
	1	2	3	4	5	6	7	8	9	10
Day										
1	26.0	48.0	34.0	22.0	32.0	47.0	25.0	37.0	25.0	41.0
2	26.0	52.0	37.0	34.0	32.0	56.0	41.0	33.0	30.0	42.0
3	25.0	51.0	23.0	38.0	28.0	47.0	33.0	40.0	21.0	41.0
4	26.0	63.0	37.0	34.0	31.0	47.0	35.0	30.0	29.0	50.0
5	29.0	59.0	34.0	29.0	29.0	49.0	33.0	38.0	29.0	48.0
6	25.0	54.0	34.0	41.0	29.0	48.0	30.0	37.0	21.0	34.0
7	30.0	58.0	29.0	35.0	30.0	54.0	36.0	39.0	37.0	55.0

Group 1♂: Control

Week 12	Animal									
	121	122	123	124	125	126	127	128	129	130
Day										
1	43.0	31.0	26.0	38.0	25.0	29.0	41.0	25.0	32.0	39.0
2	49.0	30.0	36.0	44.0	34.0	37.0	45.0	32.0	33.0	40.0
3	45.0	32.0	35.0	42.0	33.0	28.0	41.0	27.0	35.0	36.0
4	44.0	33.0	35.0	44.0	24.0	28.0	39.0	29.0	36.0	37.0
5	48.0	35.0	32.0	43.0	28.0	31.0	35.0	46.0	22.0	36.0
6	42.0	34.0	22.0	55.0	35.0	33.0	34.0	32.0	36.0	37.0
7	45.0	33.0	35.0	43.0	32.0	36.0	42.0	22.0	37.0	43.0

APPENDIX 4

(Water consumption - continued)

Group 2♂: 62.5 mg/kg/day

Week 12	Animal									
	11	12	13	14	15	1016	17	18	19	20
Day 1	33.0	34.0	38.0	27.0	40.0	38.5	27.0	41.0	24.0	39.0
2	44.0	44.0	44.0	29.0	41.0	40.1	42.0	54.0	35.0	41.0
3	48.0	38.0	35.0	31.0	39.0	39.9	30.0	49.0	26.0	43.0
4	36.0	37.0	36.0	30.0	39.0	33.5	31.0	49.0	28.0	44.0
5	40.0	39.0	36.0	30.0	47.0	36.9	37.0	53.0	33.0	49.0
6	40.0	40.0	34.0	28.0	43.0	38.7	40.0	49.0	30.0	49.0
7	45.0	38.0	38.0	28.0	46.0	43.7	40.0	49.0	39.0	44.0

Group 3♂: 250 mg/kg/day

Week 12	Animal									
	21	22	23	24	25	26	27	28	29	30
Day 1	39.0	31.0	44.0	38.0	37.0	36.0	33.0	37.0	36.0	29.0
2	43.0	33.0	53.0	50.0	44.0	46.0	26.0	41.0	38.0	46.0
3	42.0	33.0	49.0	46.0	38.0	39.0	29.0	38.0	34.0	40.0
4	44.0	33.0	49.0	48.0	40.0	45.0	34.0	46.0	36.0	59.0
5	40.0	33.0	51.0	43.0	38.0	44.0	29.0	38.0	37.0	46.0
6	43.0	33.0	48.0	42.0	39.0	47.0	32.0	43.0	34.0	44.0
7	47.0	32.0	53.0	50.0	42.0	51.0	32.0	46.0	36.0	59.0

APPENDIX 4

(Water consumption - continued)

Group 4♂: 1000 mg/kg/day

Week 12	Animal									
	31	32	33	34	35	36	37	38	39	40
1	32.0	32.0	42.0	42.0	44.0	35.0	33.0	35.0	32.0	37.0
2	36.0	41.0	46.0	42.0	45.0	44.0	45.0	44.0	41.0	47.0
3	35.0	32.0	44.0	40.0	43.0	38.0	42.0	42.0	32.0	38.0
4	37.0	26.0	46.0	39.0	48.0	46.0	40.0	35.0	34.0	40.0
5	37.0	36.0	42.0	34.0	44.0	47.0	44.0	46.0	45.0	48.0
6	38.0	36.0	42.0	42.0	47.0	37.0	39.0	41.0	32.0	36.0
7	36.0	32.0	49.0	35.0	44.0	46.0	35.0	41.0	38.0	56.0

Group 4♂: 1000 mg/kg/day

Week 12	Animal									
	131	132	133	134	135	136	137	138	139	140
1	35.0	36.0	36.0	34.0	32.0	41.0	36.0	27.0	61.0	38.0
2	41.0	41.0	40.0	34.0	40.0	57.0	44.0	29.0	84.0	55.0
3	35.0	41.0	44.0	29.0	35.0	51.0	37.0	27.0	71.0	49.0
4	40.0	45.0	41.0	29.0	32.0	55.0	44.0	28.0	70.0	49.0
5	47.0	43.0	40.0	33.0	37.0	54.0	41.0	32.0	77.0	35.0
6	39.0	50.0	40.0	39.0	40.0	56.0	44.0	29.0	63.0	55.0
7	56.0	43.0	44.0	32.0	41.0	46.0	50.0	30.0	66.0	54.0

APPENDIX 4

(Water consumption - continued)

Group 1♀: Control

Week 12	Animal									
	41	42	43	44	45	46	47	48	49	50
1	25.0	19.0	28.0	29.0	33.0	26.0	19.0	20.0	38.0	22.0
2	31.0	29.0	29.0	33.0	35.0	28.0	23.0	28.0	41.0	30.0
3	28.0	19.0	28.0	35.0	34.0	23.0	23.0	22.0	33.0	24.0
4	29.0	25.0	23.0	39.0	31.0	28.0	20.0	24.0	37.0	30.0
5	28.0	25.0	31.0	43.0	27.0	31.0	26.0	30.0	37.0	17.0
6	28.0	21.0	33.0	36.0	33.0	33.0	27.0	25.0	35.0	28.0
7	30.0	24.0	34.0	33.0	37.0	29.0	28.0	27.0	30.0	30.0

Group 1♀: Control

Week 12	Animal									
	141	142	143	144	145	146	147	148	149	150
Day										
1	30.0	27.0	28.0	30.0	30.0	29.0	33.0	28.0	25.0	31.0
2	29.0	27.0	30.0	38.0	41.0	41.0	39.0	37.0	30.0	36.0
3	30.0	25.0	26.0	44.0	34.0	38.0	38.0	30.0	27.0	35.0
4	32.0	31.0	33.0	36.0	29.0	35.0	39.0	33.0	27.0	37.0
5	16.0	43.0	24.0	53.0	27.0	47.0	37.0	33.0	22.0	42.0
6	45.0	12.0	25.0	40.0	35.0	36.0	42.0	34.0	20.0	32.0
7	33.0	31.0	35.0	62.0	41.0	43.0	42.0	45.0	24.0	53.0

APPENDIX 4

(Water consumption - continued)

Group 2♀: 62.5 mg/kg/day

Week 12	Animal									
	51	52	53	54	55	56	57	58	59	60
Day										
1	30.0	27.0	29.0	33.0	28.0	29.0	24.0	25.0	30.0	37.0
2	32.0	34.0	35.0	39.0	44.0	28.0	27.0	32.0	26.0	41.0
3	31.0	24.0	38.0	38.0	42.0	23.0	25.0	37.0	29.0	29.0
4	30.0	48.0	28.0	25.0	34.0	37.0	26.0	20.0	31.0	35.0
5	34.0	30.0	36.0	36.0	31.0	28.0	29.0	20.0	33.0	41.0
6	30.0	24.0	30.0	33.0	36.0	29.0	25.0	31.0	32.0	35.0
7	39.0	26.0	40.0	45.0	39.0	33.0	31.0	32.0	24.0	35.0

Group 3♀: 250 mg/kg/day

Week 12	Animal									
	61	62	63	64	65	66	67	68	69	70
Day										
1	23.0	26.0	23.0	32.0	30.0	21.0	21.0	27.0	30.0	28.0
2	26.0	35.0	28.0	43.0	40.0	20.0	31.0	30.0	30.0	34.0
3	24.0	29.0	25.0	28.0	32.0	18.0	26.0	31.0	32.0	29.0
4	27.0	26.0	27.0	37.0	29.0	24.0	27.0	30.0	36.0	37.0
5	29.0	33.0	25.0	35.0	38.0	19.0	22.0	29.0	40.0	40.0
6	27.0	25.0	26.0	34.0	37.0	25.0	28.0	30.0	27.0	39.0
7	36.0	37.0	28.0	38.0	34.0	21.0	28.0	28.0	38.0	39.0

APPENDIX 4

(Water consumption - continued)

Group 4♀: 1000 mg/kg/day

Week 12	Animal									
	71	72	73	74	75	76	77	78	79	80
1	37.0	28.0	27.0	36.0	33.0	26.0	34.0	23.0	28.0	30.0
2	42.0	29.0	32.0	32.0	36.0	28.0	37.0	31.0	23.0	33.0
3	41.0	26.0	30.0	36.0	39.0	25.0	33.0	28.0	23.0	29.0
4	34.0	23.0	26.0	34.0	39.0	29.0	31.0	24.0	25.0	35.0
5	43.0	28.0	27.0	53.0	42.0	27.0	29.0	26.0	23.0	34.0
6	42.0	36.0	23.0	33.0	31.0	33.0	37.0	29.0	31.0	35.0
7	48.0	31.0	35.0	44.0	38.0	36.0	34.0	26.0	29.0	36.0

Group 4♀: 1000 mg/kg/day

Week 12	Animal									
	151	152	153	154	155	156	157	158	159	160
1	24.0	37.0	29.0	31.0	28.0	55.0	30.0	27.0	29.0	29.0
2	30.0	48.0	32.0	42.0	41.0	31.0	38.0	31.0	34.0	34.0
3	29.0	42.0	30.0	32.0	43.0	27.0	40.0	28.0	29.0	29.0
4	36.0	46.0	32.0	42.0	45.0	33.0	32.0	28.0	26.0	31.0
5	30.0	51.0	26.0	31.0	31.0	46.0	31.0	26.0	44.0	32.0
6	30.0	45.0	33.0	35.0	52.0	28.0	39.0	33.0	33.0	33.0
7	35.0	49.0	36.0	43.0	46.0	46.0	42.0	31.0	35.0	39.0

APPENDIX 4

(Water consumption - continued)

Group 1♂: Control

Week R3	Animal									
	121	122	123	124	125	126	127	128	129	130
Day										
1	51.0	31.0	43.0	43.0	37.0	28.0	35.0	26.0	30.0	31.0
2	43.0	27.0	37.0	42.0	33.0	34.0	36.0	32.0	37.0	33.0
3	49.0	30.0	37.0	42.0	28.0	40.0	37.0	34.0	36.0	37.0
4	48.0	32.0	35.0	44.0	34.0	33.0	38.0	31.0	37.0	35.0
5	44.0	25.0	40.0	43.0	33.0	33.0	39.0	31.0	34.0	38.0
6	40.0	28.0	37.0	44.0	28.0	27.0	43.0	33.0	35.0	34.0
7	51.0	33.0	33.0	39.0	29.0	36.0	34.0	30.0	34.0	37.0

Group 4♂: 1000 mg/kg/day

Week R3	Animal									
	131	132	133	134	135	136	137	138	139	140
Day										
1	35.0	42.0	39.0	31.0	33.0	39.0	36.0	33.0	56.0	47.0
2	47.0	36.0	39.0	30.0	37.0	48.0	38.0	33.0	54.0	42.0
3	42.0	38.0	41.0	31.0	33.0	50.0	41.0	35.0	63.0	47.0
4	44.0	38.0	39.0	30.0	33.0	48.0	40.0	27.0	54.0	49.0
5	43.0	36.0	41.0	30.0	36.0	43.0	34.0	31.0	54.0	46.0
6	34.0	37.0	35.0	35.0	37.0	45.0	38.0	31.0	54.0	42.0
7	49.0	39.0	36.0	32.0	34.0	41.0	41.0	27.0	50.0	30.0

APPENDIX 4

(Water consumption - continued)

Group 1♀: Control

Week R3	Animal									
	141	142	143	144	145	146	147	148	149	150
Day										
1	26.0	24.0	18.0	36.0	40.0	31.0	41.0	32.0	23.0	35.0
2	28.0	24.0	26.0	49.0	34.0	32.0	40.0	30.0	25.0	40.0
3	28.0	32.0	21.0	46.0	37.0	33.0	45.0	40.0	27.0	34.0
4	25.0	27.0	16.0	35.0	34.0	35.0	38.0	55.0	30.0	35.0
5	26.0	29.0	16.0	36.0	36.0	33.0	44.0	38.0	30.0	36.0
6	28.0	23.0	33.0	42.0	35.0	31.0	38.0	33.0	22.0	32.0
7	28.0	28.0	30.0	40.0	31.0	42.0	38.0	43.0	26.0	38.0

Group 4♀: 1000 mg/kg/day

Week R3	Animal									
	151	152	153	154	155	156	157	158	159	160
Day										
1	27.0	48.0	25.0	24.0	34.0	35.0	35.0	25.0	30.0	39.0
2	26.0	43.0	31.0	25.0	40.0	37.0	47.0	32.0	28.0	33.0
3	36.0	49.0	33.0	31.0	44.0	40.0	40.0	33.0	33.0	43.0
4	35.0	42.0	27.0	31.0	40.0	37.0	40.0	29.0	22.0	42.0
5	34.0	52.0	31.0	29.0	32.0	41.0	40.0	30.0	28.0	45.0
6	24.0	41.0	31.0	25.0	32.0	33.0	36.0	28.0	27.0	41.0
7	35.0	40.0	32.0	28.0	43.0	43.0	40.0	25.0	31.0	41.0

APPENDIX 5

Ophthalmoscopy - individual findings

(Main and Recovery groups)

Pre-dose

Group/dosage (mg/kg/day)	Animal no.	Eye#	Findings*
1 ♂ Control	24	L	No abnormalities detected
2 ♂ 62.5			No abnormalities detected
3 ♂ 250			Hyaloid remnants
4 ♂ 1000			No abnormalities detected
1 ♀ Control			No abnormalities detected
2 ♀ 62.5			No abnormalities detected
3 ♀ 250			No abnormalities detected
4 ♀ 1000			No abnormalities detected

L Left

* Only animals with findings listed

APPENDIX 5

(Ophthalmoscopy - continued)

Week 13

Group/dosage (mg/kg/day)	Animal no.	Eye	Findings
1♂ Control			No abnormalities detected
2♂ 62.5			No abnormalities detected
3♂ 250			No abnormalities detected
4♂ 1000			No abnormalities detected
1♀ Control			No abnormalities detected
2♀ 62.5			No abnormalities detected
3♀ 250			No abnormalities detected
4♀ 1000			No abnormalities detected

APPENDIX 6

Haematology - individual values

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	PCV %	Hb g/dl	RBC $10^{12}/l$	MCHC g/dl	MCV fl	MCH pg	Plt $10^9/l$	TT s	
1♂ Control	1	47.9	16.1	8.75	33.5	54.7	18.4	1163	27	
	2	49.5	16.3	8.57	32.9	57.7	19.0	1034	25	
	3	50.2	16.4	8.68	32.7	57.8	18.9	864	24	
	4	49.2	16.0	8.94	32.6	55.0	18.0	1264	23	
	5	49.2	16.4	8.82	33.4	55.8	18.6	1031	24	
	121	50.3	16.2	8.97	32.2	56.1	18.1	958	23	
	122	50.5	16.1	9.22	31.9	54.7	17.5	1160	23	
	123	45.7	15.0	7.85	32.8	58.2	19.1	1213	21	
	124	49.3	16.4	8.50	33.2	58.0	19.3	1141	22	
	125	48.5	15.7	9.09	32.4	53.4	17.3	1268	24	
	Mean		49.0	16.1	8.74	32.8	56.1	18.4	1110	24
	sd		1.42	0.43	0.385	0.51	1.70	0.68	133.8	1.4
	2♂ 62.5	11	46.2	15.5	8.49	33.6	54.5	18.3	1231	22
12		48.3	16.0	8.55	33.2	56.5	18.8	1139	26	
13		46.7	15.5	8.33	33.3	56.0	18.7	1168	22	
14		49.1	16.3	9.12	33.2	53.9	17.9	1023	24	
15		50.1	17.0	9.32	33.9	53.8	18.2	928	23	
1016		49.5	16.3	9.07	32.9	54.6	18.0	1001	27	
17		47.7	15.8	8.25	33.0	57.8	19.1	1170	24	
18		50.0	17.0	8.79	34.0	56.9	19.4	1109	24	
19		45.8	15.3	8.38	33.3	54.6	18.2	1269	25	
20		49.0	16.1	8.78	32.8	55.8	18.3	1056	24	
Mean			48.2	16.1	8.71	33.3	55.4	18.5	1109	24
sd		1.57	0.59	0.368	0.40	1.36	0.49	107.1	1.5	

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	MCH	Plt	TT	
		%	g/dl	$10^{12}/l$	g/dl	fl	pg	$10^9/l$	s	
3♂ 250	21	47.8	15.7	8.28	32.9	57.7	19.0	1152	25	
	22	50.7	16.9	9.15	33.3	55.4	18.5	1113	27	
	23	48.1	15.7	8.41	32.7	57.1	18.7	1002	23	
	24	47.1	15.8	8.20	33.5	57.5	19.2	1377	23	
	25	50.7	16.8	9.03	33.1	56.1	18.6	1055	24	
	26	50.6	17.0	9.65	33.5	52.5	17.6	1445	26	
	27	51.3	17.0	8.85	33.2	57.9	19.2	1137	23	
	28	48.3	16.2	8.69	33.5	55.6	18.6	649	23	
	29	46.8	15.5	8.18	33.2	57.3	19.0	1225	24	
	30	44.9	15.0	8.05	33.4	55.8	18.6	1187	22	
	Mean		48.6	16.2	8.65	33.2	56.3	18.7	1134	24
	sd		2.12	0.72	0.518	0.27	1.62	0.47	217.7	1.6
	4♂ 1000	31	48.4	15.7	8.30	32.4	58.3	18.9	1297	23
32		46.3	15.6	8.12	33.6	57.1	19.2	1107	20	
33		46.2	14.9	8.02	32.2	57.6	18.5	1252	23	
34		50.6	16.5	9.05	32.7	55.9	18.2	1226	30	
35		46.0	14.7	8.02	32.0	57.4	18.4	1193	24	
131		47.8	15.5	8.01	32.4	59.7	19.4	1168	24	
132		47.3	15.7	8.81	33.1	53.7	17.8	1211	24	
133		49.3	16.1	8.41	32.8	58.6	19.2	1096	23	
134		50.1	16.2	8.60	32.4	58.3	18.9	1083	26	
135		47.6	15.6	8.38	32.8	56.8	18.6	1141	21	
Mean			48.0	15.7	8.37	32.6	57.3	18.7	1177	24
sd			1.63	0.55	0.358	0.47	1.66	0.50	71.1	3.0

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	MCH	Plt	TT
		%	g/dl	$10^{12}/l$	g/dl	fl	pg	$10^9/l$	s
1♀ Control	41	47.2	16.4	8.53	34.7	55.4	19.2	1148	19
	42	47.3	16.0	8.18	33.8	57.8	19.5	980	21
	43	46.5	15.9	8.37	34.1	55.6	19.0	1392	20
	44	49.0	16.3	8.98	33.3	54.5	18.1	1097	19
	45	47.3	16.2	8.62	34.1	54.9	18.7	1169	22
	141	47.2	16.4	8.73	34.6	54.1	18.7	1179	23
	142	47.3	16.2	8.30	34.2	57.0	19.5	1181	21
	143	46.3	16.0	8.62	34.6	53.7	18.6	1478	24
	144	48.4	16.1	8.14	33.3	59.4	19.8	1202	19
	145	47.6	16.3	8.68	34.2	54.9	18.8	1280	20
		Mean	47.4	16.2	8.52	34.1	55.7	19.0	1211
	sd	0.80	0.18	0.265	0.50	1.80	0.51	142.6	1.7
2♀ 62.5	51	47.3	15.6	8.46	33.0	55.9	18.5	1016	20
	52	47.6	16.2	8.64	34.0	55.1	18.7	933	20
	53	45.3	15.5	7.97	34.1	56.8	19.4	1102	19
	54	46.8	15.8	8.23	33.8	56.8	19.2	1241	21
	55	49.0	16.3	8.61	33.3	57.0	19.0	1104	23
	56	48.7	16.5	8.43	33.8	57.8	19.6	1280	20
	57	46.4	15.8	7.91	34.1	58.6	20.0	1117	23
	58	44.1	15.5	7.95	35.2	55.4	19.5	1016	21
	59	47.6	16.3	8.74	34.3	54.4	18.7	964	23
	60	49.4	16.7	8.76	33.8	56.4	19.0	1013	20
		Mean	47.2	16.0	8.37	33.9	56.4	19.2	1079
	sd	1.66	0.43	0.333	0.59	1.27	0.47	113.6	1.5

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	MCH	Plt	TT
		%	g/dl	$10^{12}/l$	g/dl	fl	pg	$10^9/l$	s
3♀ 250	61	43.5	14.7	7.46	33.7	58.3	19.7	1148	20
	62	48.8	16.5	8.83	33.7	55.2	18.6	1121	20
	63	44.6	15.2	8.07	34.0	55.3	18.8	1104	22
	64	45.6	15.5	8.15	33.9	55.9	19.0	1026	21
	65	47.0	16.4	8.47	34.9	55.5	19.4	1227	20
	66	48.5	16.7	9.05	34.3	53.6	18.4	1144	22
	67	50.1	17.0	8.98	34.0	55.8	19.0	1057	21
	68	45.3	15.5	8.04	34.3	56.3	19.3	992	20
	69	45.0	15.4	8.31	34.3	54.1	18.6	1188	20
	70	43.8	15.1	7.90	34.5	55.4	19.1	1426	20
		Mean	46.2	15.8	8.33	34.2	55.5	19.0	1143
	sd	2.26	0.78	0.510	0.37	1.27	0.40	122.5	0.9
4♀ 1000	71	49.4	16.6	8.87	33.5	55.7	18.7	1134	20
	72	44.6	15.2	8.28	34.0	53.8	18.3	1119	19
	73	47.2	15.5	8.03	32.9	58.7	19.3	1100	20
	74	48.1	16.4	8.28	34.1	58.1	19.8	1009	21
	75	49.4	16.7	8.97	33.8	55.1	18.6	1407	21
	151	46.3	16.2	8.49	35.0	54.5	19.1	1126	19
	152	48.5	16.0	8.52	33.1	56.9	18.8	1273	21
	153	46.1	15.3	8.11	33.2	56.9	18.9	1160	20
	154	50.3	16.6	8.78	33.1	57.2	18.9	1141	22
	155	43.5	14.8	7.77	34.0	56.0	19.1	1242	19
		Mean	47.3	15.9	8.41	33.7	56.3	19.0	1171
	sd	2.21	0.68	0.389	0.64	1.56	0.41	110.3	1.1

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l	
1♂ Control	1	15.71	1.45	13.49	0.15	0.06	0.18	0.38	
	2	20.62	5.30	12.57	0.10	0.09	0.46	2.11	
	3	15.24	0.83	13.54	0.08	0.05	0.24	0.51	
	4	13.18	1.74	10.65	0.15	0.03	0.16	0.45	
	5	12.84	0.77	11.27	0.08	0.04	0.22	0.47	
	121	10.69	1.68	8.47	0.08	0.02	0.16	0.28	
	122	15.76	1.02	13.96	0.06	0.04	0.12	0.57	
	123	9.84	0.98	8.43	0.07	0.02	0.10	0.23	
	124	8.87	0.96	7.48	0.06	0.01	0.13	0.23	
	125	17.01	2.76	13.27	0.16	0.07	0.22	0.53	
	Mean sd		13.98 3.606	1.75 1.385	11.31 2.441	0.10 0.039	0.04 0.025	0.20 0.103	0.58 0.553
	2♂ 62.5	11	12.32	1.31	10.30	0.05	0.04	0.22	0.39
12		11.83	1.18	9.81	0.08	0.04	0.21	0.51	
13		11.86	1.65	9.47	0.10	0.04	0.20	0.41	
14		10.22	1.68	7.66	0.11	0.03	0.29	0.45	
15		10.20	0.96	8.61	0.12	0.04	0.21	0.27	
1016		12.41	1.13	10.59	0.07	0.05	0.22	0.34	
17		11.70	1.17	9.92	0.08	0.04	0.17	0.32	
18		9.48	1.10	7.55	0.07	0.02	0.30	0.43	
19		11.94	1.42	9.84	0.05	0.02	0.23	0.39	
20		15.43	1.64	12.86	0.08	0.06	0.23	0.57	
Mean sd			11.74 1.642	1.32 0.260	9.66 1.536	0.08 0.023	0.04 0.012	0.23 0.039	0.41 0.089

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
3♂ 250	21	12.97	2.02	10.14	0.09	0.05	0.19	0.48
	22	14.98	1.52	12.85	0.04	0.05	0.09	0.44
	23	12.95	1.98	9.99	0.11	0.04	0.20	0.63
	24	10.39	1.56	8.17	0.08	0.02	0.18	0.37
	25	8.08	0.99	6.55	0.06	0.02	0.19	0.28
	26	14.85	1.66	12.40	0.10	0.05	0.20	0.44
	27	14.22	1.57	11.46	0.14	0.05	0.37	0.62
	28	11.06	1.19	9.12	0.03	0.03	0.29	0.39
	29	13.98	1.64	11.63	0.07	0.05	0.16	0.44
	30	11.50	1.55	9.23	0.05	0.03	0.22	0.41
	Mean sd		12.50 2.219	1.57 0.310	10.15 1.974	0.08 0.034	0.04 0.013	0.21 0.075
4♂ 1000	31	7.91	1.06	6.35	0.10	0.02	0.11	0.27
	32	12.34	1.74	9.81	0.10	0.04	0.23	0.42
	33	11.54	1.52	9.24	0.08	0.03	0.24	0.43
	34	10.84	1.17	9.08	0.15	0.03	0.09	0.32
	35	11.26	1.78	8.52	0.13	0.03	0.24	0.55
	131	13.54	1.92	10.65	0.11	0.05	0.30	0.52
	132	8.72	1.52	6.86	0.04	0.02	0.09	0.20
	133	8.00	1.00	6.26	0.13	0.02	0.19	0.40
	134	7.38	1.54	5.41	0.07	0.02	0.12	0.22
	135	11.64	1.49	9.49	0.08	0.04	0.23	0.32
	Mean sd		10.32 2.140	1.47 0.309	8.17 1.794	0.10 0.033	0.03 0.011	0.18 0.075

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
1♀ Control	41	7.19	1.10	5.67	0.07	0.01	0.15	0.18
	42	5.92	0.82	4.71	0.06	0.02	0.10	0.21
	43	12.54	1.33	10.46	0.09	0.04	0.23	0.39
	44	10.12	1.32	8.09	0.07	0.02	0.26	0.36
	45	11.84	0.63	10.73	0.09	0.03	0.11	0.25
	141	6.83	1.00	5.53	0.09	0.02	0.06	0.13
	142	15.10	0.77	13.68	0.11	0.04	0.15	0.35
	143	11.29	0.53	10.19	0.13	0.02	0.13	0.28
	144	14.52	1.45	12.25	0.13	0.05	0.15	0.49
	145	10.89	0.89	9.60	0.07	0.04	0.06	0.24
		Mean sd	10.62 3.153	0.98 0.312	9.09 3.012	0.09 0.025	0.03 0.013	0.14 0.065
2♀ 62.5	51	10.50	0.85	9.03	0.06	0.02	0.15	0.39
	52	9.21	0.95	7.63	0.12	0.02	0.14	0.34
	53	10.63	0.96	8.98	0.10	0.03	0.19	0.37
	54	11.08	1.01	9.24	0.17	0.04	0.20	0.41
	55	11.56	0.82	10.07	0.07	0.05	0.17	0.39
	56	7.75	0.94	6.40	0.06	0.03	0.16	0.17
	57	12.92	1.20	10.99	0.04	0.04	0.19	0.46
	58	9.28	0.95	7.81	0.12	0.02	0.13	0.24
	59	5.08	0.64	4.26	0.04	0.01	0.06	0.07
	60	6.03	0.65	5.11	0.05	0.02	0.08	0.13
		Mean sd	9.40 2.481	0.90 0.167	7.95 2.156	0.08 0.043	0.03 0.012	0.15 0.047

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
3♀ 250	61	10.70	0.81	9.46	0.04	0.05	0.08	0.26
	62	7.91	0.98	6.40	0.09	0.02	0.17	0.25
	63	7.85	1.06	6.29	0.12	0.01	0.15	0.22
	64	10.86	1.39	8.75	0.11	0.03	0.19	0.39
	65	6.15	1.09	4.88	0.05	0.01	0.04	0.09
	66	6.67	0.77	5.58	0.05	0.02	0.09	0.16
	67	6.71	1.16	5.30	0.06	0.02	0.02	0.15
	68	8.02	0.94	6.72	0.06	0.02	0.10	0.19
	69	7.71	0.99	6.33	0.09	0.03	0.13	0.15
	70	7.15	0.88	6.01	0.06	0.01	0.07	0.12
		Mean sd	7.97 1.604	1.01 0.181	6.57 1.455	0.07 0.028	0.02 0.012	0.10 0.055
4♀ 1000	71	5.07	0.75	4.09	0.02	0.01	0.07	0.14
	72	10.21	1.53	7.85	0.21	0.04	0.27	0.32
	73	10.59	1.19	8.89	0.08	0.04	0.13	0.25
	74	10.38	0.66	9.15	0.12	0.03	0.15	0.27
	75	5.51	0.76	4.46	0.08	0.01	0.07	0.13
	151	11.64	1.48	9.61	0.08	0.03	0.18	0.26
	152	10.35	1.23	8.50	0.11	0.02	0.18	0.31
	153	11.37	1.25	9.48	0.09	0.03	0.18	0.34
	154	10.26	0.96	8.59	0.12	0.03	0.21	0.34
	155	8.34	1.17	6.69	0.13	0.02	0.14	0.19
		Mean sd	9.37 2.323	1.10 0.304	7.73 2.009	0.10 0.049	0.03 0.011	0.16 0.061

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
1♂ Control	1	-	-	-	+	-	+	-	-	-
	2	-	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-	-	-
	4	-	-	-	+	-	-	-	-	-
	5	-	-	-	-	-	-	-	-	-
	121	-	-	-	+	-	-	-	-	-
	122	-	-	-	+	-	-	-	-	-
	123	-	-	-	-	-	-	-	-	-
	124	-	-	-	-	-	-	-	-	-
	125	-	+	-	-	-	-	-	-	-
2♂ 62.5	11	-	-	-	+	-	-	-	-	-
	12	-	-	-	-	-	-	-	-	-
	13	-	-	-	-	-	-	-	-	-
	14	-	-	-	+	-	-	-	-	-
	15	-	-	-	+	-	+	-	-	-
	1016	-	-	-	+	-	-	-	-	-
	17	-	-	-	-	-	-	-	-	-
	18	-	-	-	-	-	-	-	-	-
	19	-	-	-	-	-	-	-	-	-
	20	-	-	-	-	-	-	-	-	-

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
3♂ 250	21	-	-	-	+	-	-	-	-	-
	22	-	-	-	-	-	-	-	-	-
	23	-	-	-	-	-	-	-	-	-
	24	-	-	-	-	-	-	-	-	-
	25	-	-	-	-	-	-	-	-	-
	26	-	+	-	+	-	+	-	-	-
	27	-	-	-	+	-	-	-	-	-
	28	-	-	-	+	-	+	-	-	-
	29	-	-	-	-	-	-	-	-	-
	30	-	-	-	+	-	+	-	-	-
4♂ 1000	31	-	-	-	-	-	-	-	-	-
	32	-	-	-	+	-	-	-	-	-
	33	-	-	-	+	-	-	-	-	-
	34	-	-	-	+	-	-	-	-	-
	35	-	-	-	+	-	-	-	-	-
	131	-	-	-	-	-	-	-	-	-
	132	-	+	-	+	-	-	-	-	-
	133	-	-	-	+	-	-	-	-	-
	134	-	-	-	-	-	-	-	-	-
	135	-	-	-	+	-	+	-	-	-

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
1♀ Control	41	-	-	-	-	-	+	-	-	-
	42	-	-	-	-	-	-	-	-	-
	43	-	-	-	-	-	-	-	-	-
	44	-	-	-	-	-	-	-	-	-
	45	-	-	-	-	-	+	-	-	-
	141	-	-	-	-	-	+	-	-	-
	142	-	-	-	-	-	+	-	-	-
	143	-	-	-	-	-	+	-	-	-
	144	-	-	-	-	-	-	-	-	-
	145	-	-	-	-	-	-	+	-	-
2♀ 62.5	51	-	-	-	-	-	-	-	-	-
	52	-	-	-	-	-	+	-	-	-
	53	-	-	-	-	-	-	-	-	-
	54	-	-	-	-	-	-	-	-	-
	55	-	-	-	-	-	-	-	-	-
	56	-	-	-	-	-	-	-	-	-
	57	-	-	-	-	-	-	-	-	-
	58	-	-	-	-	-	-	+	-	-
	59	-	-	-	-	-	-	+	-	-
	60	-	-	-	-	-	-	-	-	-

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
3♀ 250	61	-	-	-	-	-	+	-	-	-
	62	-	-	-	-	-	-	-	-	-
	63	-	-	-	-	-	-	-	-	-
	64	-	-	-	-	-	-	-	-	-
	65	-	-	-	-	-	+	-	-	-
	66	-	-	-	-	-	-	-	-	-
	67	-	-	-	-	-	-	-	-	-
	68	-	-	-	-	-	+	-	-	-
	69	-	-	-	-	-	-	+	-	-
	70	-	-	-	-	-	-	+	-	-
4♀ 1000	71	-	-	-	-	-	-	-	-	-
	72	-	-	-	-	-	-	-	-	-
	73	-	-	-	-	-	-	-	-	-
	74	-	-	-	-	-	-	-	-	-
	75	-	-	-	-	-	-	-	-	-
	151	-	-	-	-	-	+	-	-	-
	152	-	-	-	-	-	-	-	-	-
	153	-	-	-	-	-	-	-	-	-
	154	-	-	-	-	-	-	-	-	-
	155	-	-	-	-	-	+	-	-	-

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	MCH	Plt	TT	
		%	g/dl	$10^{12}/l$	g/dl	fl	pg	$10^9/l$	s	
1♂ Control	1	46.9	16.3	9.70	34.7	48.3	16.8	995	26	
	2	48.5	16.6	9.19	34.2	52.8	18.1	1021	21	
	3	47.7	16.9	9.21	35.3	51.8	18.3	793	22	
	4	46.0	15.9	9.27	34.7	49.6	17.2	1151	23	
	5	47.0	16.5	9.31	35.1	50.5	17.7	722	23	
	121	44.9	15.8	8.81	35.1	50.9	17.9	910	25	
	122	ctd	ctd	ctd	ctd	ctd	ctd	ctd	ctd	
	123	43.8	15.5	8.69	35.4	50.4	17.8	1170	24	
	124	46.6	16.6	9.15	35.7	50.9	18.2	1081	24	
	125	46.9	16.1	10.06	34.3	46.6	16.0	1166	21	
	Mean		46.5	16.2	9.27	34.9	50.2	17.6	1001	23
	sd		1.42	0.45	0.416	0.51	1.85	0.76	163.7	1.7
	2♂ 62.5	11	46.1	16.3	9.35	35.4	49.3	17.5	1223	21
12		46.9	16.5	9.21	35.2	50.9	17.9	980	24	
13		45.9	16.2	9.22	35.4	49.8	17.6	1072	24	
14		47.0	16.4	9.83	34.9	47.8	16.7	949	23	
15		47.2	16.5	9.45	34.9	49.9	17.4	1151	23	
1016		45.7	15.6	9.05	34.2	50.5	17.2	1089	22	
17		47.8	16.6	9.32	34.8	51.3	17.8	996	24	
18		48.4	17.1	9.13	35.4	53.0	18.8	1084	23	
19		43.8	15.5	8.90	35.4	49.2	17.4	1137	24	
20		48.6	17.2	9.67	35.4	50.3	17.8	996	23	
Mean			46.7	16.4	9.31	35.1	50.2	17.6	1068	23
sd		1.43	0.55	0.280	0.40	1.39	0.54	87.3	1.1	

sd Standard deviation

ctd Clotted Sample

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	PCV %	Hb g/dl	RBC 10 ¹² /l	MCHC g/dl	MCV fl	MCH pg	Plt 10 ⁹ /l	TT s	
3♂ 250	21	45.9	16.2	9.02	35.4	50.9	18.0	1081	22	
	22	47.7	16.7	9.37	35.0	50.9	17.8	973	23	
	23	45.0	15.8	8.69	35.1	51.8	18.2	1014	21	
	24	43.8	15.8	8.65	36.1	50.6	18.3	1448	23	
	25	48.6	17.4	9.70	35.9	50.1	18.0	713	25	
	26	45.7	16.4	9.54	35.8	47.9	17.2	1342	24	
	27	48.4	16.7	9.28	34.5	52.2	18.0	1100	23	
	28	44.0	15.5	8.46	35.2	52.0	18.3	990	24	
	29	44.5	15.8	8.57	35.5	52.0	18.5	1127	22	
	30	40.9	14.3	8.10	35.1	50.4	17.7	1144	22	
	Mean		45.5	16.1	8.94	35.4	50.9	18.0	1093	23
	sd		2.37	0.84	0.523	0.48	1.29	0.37	202.1	1.0
	4♂ 1000	31	46.3	16.2	8.79	35.0	52.7	18.4	1162	21
32		46.0	15.9	8.70	34.7	52.8	18.3	1161	23	
33		43.6	15.4	8.66	35.3	50.4	17.8	1243	21	
34		47.0	16.6	9.30	35.4	50.5	17.9	1040	23	
35		44.1	15.2	8.60	34.5	51.3	17.7	1035	22	
131		43.9	15.2	8.23	34.5	53.4	18.4	1167	21	
132		44.6	15.6	9.26	35.0	48.2	16.9	1314	23	
133		42.3	15.2	8.03	36.1	52.6	19.0	1114	22	
134		45.4	16.3	8.78	35.9	51.7	18.6	1169	24	
135		44.5	15.7	8.84	35.3	50.3	17.7	1164	21	
Mean			44.8	15.7	8.72	35.2	51.4	18.1	1157	22
sd			1.41	0.51	0.392	0.54	1.58	0.59	83.5	1.0

sd Standard deviation

APPENDIX 6
(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	MCH	Plt	TT	
		%	g/dl	10 ¹² /l	g/dl	fl	pg	10 ⁹ /l	s	
1♀ Control	41	44.6	16.1	8.47	36.1	52.6	19.0	1054	19	
	42	45.3	16.0	8.21	35.3	55.2	19.5	926	18	
	43	44.5	16.2	8.57	36.3	52.0	18.9	1246	19	
	44	44.4	15.8	8.65	35.5	51.4	18.2	946	19	
	45	44.2	15.4	8.47	34.8	52.2	18.2	987	21	
	141	45.1	16.5	8.73	36.5	51.7	18.9	1110	22	
	142	42.5	15.6	8.09	36.7	52.6	19.3	1172	23	
	143	43.3	15.5	8.39	35.8	51.6	18.5	1126	23	
	144	44.1	15.7	7.98	35.7	55.2	19.7	1058	20	
	145	45.1	16.5	8.86	36.6	50.9	18.6	1235	20	
	Mean		44.3	15.9	8.44	35.9	52.5	18.9	1086	20
	sd		0.86	0.39	0.281	0.62	1.50	0.52	112.6	1.9
	2♀ 62.5	51	42.0	15.1	8.15	36.1	51.5	18.6	1012	19
52		45.3	16.4	8.52	36.2	53.2	19.3	650	19	
53		43.1	15.3	7.90	35.6	54.5	19.4	1126	19	
54		45.4	16.3	8.66	36.0	52.4	18.9	1141	ctd	
55		44.6	16.1	8.43	36.1	52.8	19.1	1019	20	
56		43.8	15.7	7.93	35.7	55.3	19.8	1109	20	
57		43.1	15.1	7.76	35.2	55.5	19.5	1045	21	
58		42.5	15.3	7.89	35.9	53.9	19.3	947	19	
59		45.3	16.8	8.78	37.0	51.6	19.1	953	20	
60		45.7	16.0	8.24	34.9	55.5	19.4	956	18	
Mean			44.1	15.8	8.23	35.9	53.6	19.2	996	19
sd		1.35	0.60	0.358	0.58	1.55	0.33	141.2	0.9	

sd Standard deviation

ctd Clotted Sample

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	PCV %	Hb g/dl	RBC $10^{12}/l$	MCHC g/dl	MCV fl	MCH pg	Plt $10^9/l$	TT s
3♀ 250	61	39.2	14.1	7.31	35.9	53.7	19.3	985	19
	62	46.7	16.3	8.81	35.0	53.0	18.5	795	18
	63	43.7	15.9	8.48	36.3	51.6	18.7	1075	21
	64	44.4	16.0	8.47	36.0	52.4	18.9	1056	19
	65	44.0	15.9	8.28	36.2	53.2	19.2	1130	19
	66	46.5	16.6	8.91	35.6	52.3	18.6	1048	20
	67	45.2	15.8	8.35	35.0	54.2	19.0	938	19
	68	43.3	15.3	8.07	35.4	53.6	19.0	1039	20
	69	43.6	15.7	8.34	36.1	52.3	18.9	1218	20
	70	39.6	14.5	7.52	36.6	52.7	19.3	1283	19
	Mean sd		43.6 2.51	15.6 0.78	8.25 0.508	35.8 0.54	52.9 0.79	18.9 0.28	1057 137.9
4♀ 1000	71	46.1	16.0	8.64	34.8	53.4	18.6	864	17
	72	45.4	16.1	9.05	35.5	50.2	17.8	1134	19
	73	43.9	15.5	7.86	35.3	55.9	19.7	1076	19
	74	46.5	16.3	8.33	35.0	55.8	19.5	851	20
	75	44.7	15.9	8.47	35.6	52.8	18.8	1242	20
	151	41.8	15.5	8.22	37.0	50.8	18.8	964	ctd
	152	45.4	16.0	8.58	35.3	53.0	18.7	1159	21
	153	42.2	15.2	8.19	36.0	51.5	18.5	1082	18
	154	45.6	16.2	8.42	35.5	54.2	19.2	1129	20
	155	40.3	14.9	7.66	36.9	52.7	19.4	1077	19
	Mean sd		44.2 2.08	15.8 0.46	8.34 0.395	35.7 0.74	53.0 1.91	18.9 0.56	1058 127.1

sd Standard deviation

ctd Clotted Sample

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
1♂ Control	1	13.02	2.14	10.19	0.12	0.04	0.27	0.28
	2	20.77	8.41	10.21	0.14	0.07	0.74	1.20
	3	12.29	0.98	10.56	0.16	0.02	0.30	0.28
	4	13.84	1.55	11.35	0.29	0.04	0.30	0.32
	5	9.75	1.23	7.69	0.08	0.03	0.28	0.45
	121	12.14	2.21	9.24	0.16	0.02	0.30	0.21
	122	ctd	ctd	ctd	ctd	ctd	ctd	ctd
	123	11.39	1.40	9.50	0.13	0.02	0.18	0.15
	124	10.17	1.25	8.45	0.09	0.01	0.20	0.16
	125	16.64	3.01	12.20	0.37	0.06	0.44	0.56
	Mean	13.33	2.46	9.93	0.17	0.03	0.33	0.40
	sd	3.459	2.318	1.396	0.096	0.020	0.169	0.328
	2♂ 62.5	11	11.77	1.20	10.12	0.05	0.04	0.17
12		14.57	1.77	11.81	0.19	0.05	0.34	0.41
13		12.38	1.25	10.41	0.17	0.02	0.24	0.30
14		10.77	1.51	8.64	0.09	0.03	0.28	0.22
15		11.24	1.79	8.70	0.19	0.03	0.23	0.30
1016		14.07	2.02	11.28	0.11	0.05	0.31	0.31
17		10.83	1.02	9.24	0.06	0.03	0.26	0.22
18		10.07	1.54	7.76	0.14	0.01	0.37	0.25
19		10.40	0.95	8.81	0.12	0.02	0.23	0.26
20		15.52	1.55	13.38	0.11	0.04	0.21	0.23
Mean		12.16	1.46	10.02	0.12	0.03	0.26	0.27
sd	1.914	0.350	1.734	0.050	0.013	0.061	0.062	

sd Standard deviation

ctd Clotted Sample

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
3♂ 250	21	14.64	2.17	11.80	0.15	0.04	0.20	0.27
	22	14.74	2.46	11.79	0.11	0.04	0.14	0.20
	23	12.12	2.02	9.52	0.10	0.01	0.21	0.26
	24	16.67	4.59	11.14	0.16	0.04	0.38	0.36
	25	10.14	2.00	7.34	0.28	0.03	0.34	0.14
	26	12.03	1.31	10.22	0.13	0.03	0.13	0.22
	27	14.30	2.90	10.33	0.21	0.04	0.47	0.36
	28	8.75	1.01	7.50	0.05	0.02	0.11	0.07
	29	13.17	2.16	10.42	0.12	0.03	0.20	0.25
	30	8.65	1.52	6.70	0.06	0.02	0.16	0.19
	Mean sd		12.52 2.698	2.21 1.001	9.68 1.870	0.14 0.069	0.03 0.011	0.23 0.121
4♂ 1000	31	8.86	0.95	7.48	0.12	0.02	0.16	0.12
	32	12.79	2.41	9.77	0.09	0.02	0.26	0.25
	33	12.49	1.61	10.34	0.14	0.03	0.19	0.19
	34	11.65	1.80	9.32	0.16	0.03	0.12	0.21
	35	10.85	1.84	8.31	0.21	0.03	0.23	0.23
	131	15.77	2.40	12.38	0.12	0.04	0.35	0.48
	132	10.85	3.46	6.84	0.12	0.02	0.22	0.20
	133	11.52	1.91	8.69	0.18	0.01	0.31	0.42
	134	10.96	1.70	8.74	0.16	0.02	0.18	0.16
	135	11.89	2.72	8.52	0.12	0.03	0.30	0.20
	Mean sd		11.76 1.778	2.08 0.694	9.04 1.554	0.14 0.036	0.03 0.008	0.23 0.073

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
1♀ Control	41	6.58	0.77	5.43	0.02	0.02	0.18	0.16
	42	5.17	0.82	4.18	0.04	0.01	0.07	0.06
	43	7.70	0.82	6.59	0.09	0.01	0.11	0.08
	44	8.48	1.56	6.41	0.09	0.01	0.26	0.14
	45	9.94	1.02	8.38	0.21	0.02	0.14	0.17
	141	7.57	1.13	6.14	0.10	0.02	0.11	0.08
	142	12.40	0.91	10.98	0.10	0.04	0.19	0.19
	143	12.65	1.26	10.87	0.13	0.04	0.18	0.17
	144	10.46	1.24	8.60	0.16	0.01	0.23	0.22
	145	9.00	0.63	8.00	0.07	0.02	0.13	0.15
	Mean	9.00	1.02	7.56	0.10	0.02	0.16	0.14
	sd	2.414	0.282	2.232	0.055	0.012	0.059	0.052
2♀ 62.5	51	7.41	0.54	6.47	0.17	0.02	0.12	0.10
	52	10.12	0.76	8.77	0.15	0.02	0.21	0.20
	53	7.46	0.74	6.35	0.05	0.01	0.22	0.09
	54	10.22	1.28	8.36	0.20	0.03	0.17	0.18
	55	12.49	0.94	10.93	0.14	0.04	0.22	0.21
	56	7.51	1.24	5.90	0.06	0.02	0.18	0.11
	57	9.70	1.11	8.20	0.05	0.02	0.19	0.14
	58	10.02	0.98	8.50	0.15	0.02	0.18	0.18
	59	6.00	1.05	4.72	0.07	0.00	0.09	0.07
	60	4.98	0.66	4.06	0.03	0.01	0.11	0.11
	Mean	8.59	0.93	7.23	0.11	0.02	0.17	0.14
	sd	2.287	0.249	2.091	0.061	0.011	0.047	0.050

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l
3♀ 250	61	9.29	0.76	8.24	0.05	0.02	0.10	0.12
	62	6.93	0.86	5.67	0.11	0.01	0.17	0.11
	63	5.90	0.81	4.87	0.07	0.02	0.08	0.05
	64	7.30	1.10	5.79	0.08	0.01	0.18	0.14
	65	7.02	1.27	5.52	0.07	0.01	0.09	0.06
	66	6.00	0.59	5.17	0.05	0.01	0.12	0.07
	67	5.23	0.63	4.39	0.08	0.01	0.06	0.07
	68	5.88	0.70	4.95	0.04	0.01	0.10	0.07
	69	4.84	0.91	3.73	0.07	0.00	0.10	0.02
	70	6.42	0.58	5.59	0.09	0.01	0.11	0.04
	Mean sd	6.48 1.258	0.82 0.225	5.39 1.187	0.07 0.021	0.01 0.006	0.11 0.038	0.08 0.037
4♀ 1000	71	5.60	0.48	4.88	0.04	0.01	0.11	0.08
	72	7.70	1.02	5.98	0.15	0.02	0.31	0.21
	73	8.11	1.10	6.71	0.10	0.01	0.09	0.09
	74	7.72	0.50	6.83	0.07	0.03	0.15	0.14
	75	5.78	0.72	4.81	0.07	0.00	0.09	0.09
	151	8.16	1.03	6.76	0.09	0.02	0.14	0.11
	152	9.00	1.04	7.61	0.11	0.02	0.13	0.10
	153	8.20	1.15	6.64	0.07	0.01	0.19	0.14
	154	8.81	0.73	7.64	0.09	0.02	0.20	0.13
	155	7.60	0.80	6.42	0.10	0.01	0.18	0.10
	Mean sd	7.67 1.138	0.86 0.246	6.43 0.971	0.09 0.030	0.02 0.008	0.16 0.066	0.12 0.038

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
1♂ Control	1	-	+	-	+++	-	+	-	-	-
	2	-	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-	-	-
	4	-	+	-	+	-	-	-	-	-
	5	-	-	-	-	-	-	-	-	-
	121	-	-	-	+++	-	-	-	-	-
	122	ctd	ctd	ctd	ctd	ctd	ctd	ctd	ctd	ctd
	123	-	+	-	+++	-	-	-	-	-
	124	-	-	-	+++	-	+	-	-	-
	125	-	+	-	+	-	-	-	-	-
2♂ 62.5	11	-	+	-	+++	-	-	-	-	-
	12	-	+	-	+++	-	-	-	-	-
	13	-	+	-	-	-	-	-	-	-
	14	-	+	-	+	-	-	-	-	-
	15	-	+	-	+++	-	-	-	-	-
	1016	-	+	-	+	-	-	-	-	-
	17	-	-	-	-	-	-	-	-	-
	18	-	-	-	+	-	-	-	-	-
	19	-	+	-	+	-	-	-	-	-
	20	-	-	-	-	-	-	-	-	-

ctd Clotted Sample

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
3♂ 250	21	+	+	-	+++	-	+	-	-	-
	22	-	-	-	+	-	-	-	-	-
	23	-	-	-	+++	-	-	-	-	-
	24	-	+	-	+++	-	-	-	-	-
	25	-	-	-	-	-	-	-	-	-
	26	+	++	-	+++	-	+	-	-	-
	27	-	-	-	+	-	-	-	-	-
	28	-	-	-	+	-	-	-	-	-
	29	-	-	-	+	-	-	-	-	-
	30	+	+	-	+++	-	-	-	-	-
4♂ 1000	31	-	-	-	+	-	-	-	-	-
	32	-	-	-	+	-	-	-	-	-
	33	+	+	-	+++	-	+	-	-	-
	34	-	-	-	+++	-	-	-	-	-
	35	-	-	-	+	-	-	-	-	-
	131	-	-	-	+++	-	-	-	-	-
	132	++	++	-	+++	-	+	-	-	-
	133	+	+	-	+++	-	+	-	-	-
	134	-	-	-	-	-	-	-	-	-
	135	+	+	-	+++	-	+	-	-	-

sd Standard deviation

APPENDIX 6
(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
1♀ Control	41	-	-	-	-	-	-	-	-	-
	42	-	-	-	-	-	-	-	-	-
	43	-	-	-	-	-	-	-	-	-
	44	-	-	-	-	-	-	-	-	-
	45	-	-	-	+	-	-	-	-	-
	141	-	-	-	-	-	-	-	-	-
	142	-	-	-	+	-	+	-	-	-
	143	-	-	-	-	-	-	-	-	-
	144	-	-	-	-	-	-	-	-	-
	145	-	-	-	-	-	-	-	-	-
2♀ 62.5	51	-	-	-	-	-	-	-	-	-
	52	-	-	-	-	-	-	-	-	-
	53	-	-	-	-	-	-	-	-	-
	54	-	-	-	-	-	-	-	-	-
	55	-	-	-	-	-	-	-	-	-
	56	-	-	-	-	-	-	-	-	-
	57	-	-	-	-	-	-	-	-	-
	58	-	-	-	-	-	-	-	-	-
	59	-	-	-	-	-	-	-	-	-
	60	-	-	-	-	-	-	-	-	-

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
3♀ 250	61	-	-	-	+	-	-	-	-	-
	62	-	-	-	-	-	-	-	-	-
	63	-	-	-	+	-	-	-	-	-
	64	-	-	-	-	-	-	-	-	-
	65	-	-	-	+	-	-	-	-	-
	66	-	-	-	-	-	-	-	-	-
	67	-	-	-	-	-	-	-	-	-
	68	-	-	-	-	-	-	-	-	-
	69	-	-	-	-	-	-	-	-	-
	70	-	-	-	-	-	+	-	-	-
4♀ 1000	71	-	-	-	-	-	-	-	-	-
	72	-	-	-	-	-	-	-	-	-
	73	-	-	-	-	-	-	-	-	-
	74	-	-	-	-	-	-	-	-	-
	75	-	-	-	-	-	-	-	-	-
	151	-	-	-	-	-	-	-	-	-
	152	-	-	-	-	-	-	-	-	-
	153	-	-	-	+	-	-	-	-	-
	154	-	-	-	-	-	-	-	-	-
	155	-	-	-	+	-	+	-	-	-

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week R4 (15 May 1996)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	MCH	Plt	TT	
		%	g/dl	$10^{12}/l$	g/dl	fl	pg	$10^9/l$	s	
1♂ Control	121	47.4	16.5	9.12	34.8	52.0	18.1	845	24	
	122	49.9	16.8	9.66	33.7	51.6	17.4	934	24	
	123	46.9	16.4	9.10	34.9	51.5	18.0	1133	24	
	124	48.6	17.0	9.03	35.0	53.7	18.8	1003	23	
	125	47.3	15.6	9.82	33.1	48.1	15.9	1093	22	
	126	48.0	16.8	8.99	35.1	53.4	18.7	885	24	
	127	49.6	17.1	9.42	34.4	52.7	18.1	948	23	
	128	47.5	16.2	8.76	34.0	54.2	18.4	898	24	
	129	47.9	16.7	9.32	34.9	51.4	17.9	992	23	
	130	45.8	16.1	8.99	35.1	50.9	17.9	1028	ctd	
	Mean		47.9	16.5	9.22	34.5	52.0	17.9	976	24
	sd		1.23	0.46	0.330	0.69	1.74	0.82	92.0	0.7
	4♂ 1000	131	46.6	15.9	8.67	34.2	53.7	18.3	984	21
132		45.1	15.4	9.04	34.1	49.9	17.0	1056	23	
133		43.9	15.2	8.10	34.7	54.2	18.8	1060	24	
134		48.4	16.5	8.81	34.0	54.9	18.7	953	25	
135		47.0	16.4	9.25	34.9	50.9	17.7	896	23	
136		43.8	15.4	8.48	35.1	51.7	18.1	1146	21	
137		46.4	15.9	9.47	34.3	49.0	16.8	925	24	
138		48.0	16.6	8.75	34.5	54.9	19.0	854	22	
139		47.6	16.4	8.87	34.4	53.6	18.4	1017	22	
140		45.4	15.3	8.95	33.7	50.8	17.1	812	23	
Mean			46.2	15.9	8.84	34.4	52.4	18.0	970	23
sd		1.63	0.55	0.385	0.43	2.16	0.80	102.8	1.3	

sd Standard deviation

ctd Clotted Sample

APPENDIX 6

(Haematology - continued)

Week R4 (15/16 May 1996)

Group/ dosage mg/kg/day	Animal no.	PCV %	Hb g/dl	RBC 10 ¹² /l	MCHC g/dl	MCV fl	MCH pg	Plt 10 ⁹ /l	TT s	TT# s
1♀ Control	141	46.1	15.8	8.06	34.3	57.2	19.6	986	21	19
	142	46.5	15.9	8.14	34.2	57.2	19.6	951	ctd	22
	143	44.0	15.4	7.91	34.9	55.7	19.4	1348	ctd	19
	144	46.2	16.1	7.99	34.7	57.8	20.1	1020	ctd	17
	145	46.9	16.8	8.62	35.7	54.5	19.5	1088	20	21
	146	46.8	16.8	8.90	35.9	52.6	18.9	1142	22	19
	147	43.8	15.0	7.93	34.4	55.2	19.0	1108	ctd	16
	148	45.8	16.0	8.46	35.0	54.1	18.9	953	18	20
	149	46.0	16.3	8.43	35.3	54.6	19.3	965	ctd	20
	150	44.7	15.6	8.26	35.0	54.1	18.9	881	19	19
	Mean sd		45.7 1.12	16.0 0.57	8.27 0.328	34.9 0.57	55.3 1.66	19.3 0.40	1044 134.1	20 1.5
4♀ 1000	151	45.8	16.3	8.46	35.7	54.1	19.3	1109	19	21
	152	46.7	15.9	8.32	34.0	56.1	19.1	1046	22	20
	153	44.5	15.5	8.20	34.9	54.2	18.9	1076	20	19
	154	47.8	16.6	8.37	34.7	57.0	19.8	986	18	21
	155	43.5	15.2	7.73	34.9	56.2	19.6	925	20	ctd
	156	42.0	14.6	7.69	34.9	54.5	19.0	1208	20	21
	157	43.4	15.4	8.19	35.5	53.0	18.8	1007	21	21
	158	45.8	16.0	8.85	34.9	51.7	18.1	926	21	19
	159	45.0	15.7	8.36	34.8	53.8	18.7	921	20	ctd
	160	46.4	16.2	8.62	35.0	53.8	18.8	1090	19	19
	Mean sd		45.1 1.76	15.7 0.59	8.28 0.358	34.9 0.45	54.4 1.60	19.0 0.48	1029 94.3	20 1.2

sd Standard deviation

ctd Clotted Sample

TT analysis repeated 1 day later due to 5/10 control samples being clotted

APPENDIX 6

(Haematology - continued)

Week R4 (15 May 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 10 ⁹ /l	N 10 ⁹ /l	L 10 ⁹ /l	E 10 ⁹ /l	B 10 ⁹ /l	M 10 ⁹ /l	LUC 10 ⁹ /l	
1♂ Control	121	13.26	1.82	10.64	0.16	0.03	0.30	0.31	
	122	12.80	1.40	10.58	0.13	0.03	0.24	0.43	
	123	14.56	1.44	12.45	0.22	0.03	0.20	0.22	
	124	10.49	1.16	8.70	0.11	0.03	0.29	0.20	
	125	15.98	2.66	12.04	0.21	0.07	0.56	0.45	
	126	10.71	1.40	8.58	0.11	0.04	0.34	0.23	
	127	6.93	1.03	5.44	0.06	0.01	0.24	0.15	
	128	17.23	2.31	13.94	0.21	0.05	0.33	0.37	
	129	10.24	1.20	8.27	0.05	0.03	0.42	0.27	
	130	8.98	1.56	6.54	0.12	0.02	0.47	0.27	
	Mean		12.12	1.60	9.72	0.14	0.03	0.34	0.29
	sd		3.227	0.523	2.690	0.061	0.016	0.113	0.099
	4♂ 1000	131	14.57	1.82	11.86	0.11	0.05	0.38	0.34
132		10.11	1.62	7.81	0.13	0.01	0.31	0.23	
133		11.70	1.70	8.85	0.15	0.03	0.53	0.44	
134		8.91	1.92	6.32	0.13	0.03	0.30	0.21	
135		11.32	2.15	8.05	0.18	0.02	0.53	0.38	
136		16.04	1.91	13.24	0.11	0.04	0.42	0.32	
137		12.55	1.55	10.00	0.22	0.04	0.38	0.37	
138		13.14	1.04	11.52	0.09	0.03	0.21	0.26	
139		11.63	1.30	9.58	0.14	0.03	0.29	0.28	
140		14.90	2.30	11.51	0.30	0.05	0.40	0.35	
Mean			12.49	1.73	9.87	0.16	0.03	0.38	0.32
sd		2.221	0.378	2.161	0.063	0.013	0.103	0.072	

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week R4 (15 May 1996)

Group/ dosage mg/kg/day	Animal no.	WBC Total 109/l	N 109/l	L 109/l	E 109/l	B 109/l	M 109/l	LUC 109/l
1♀ Control	141	6.95	1.04	5.46	0.12	0.01	0.22	0.10
	142	10.32	0.80	8.94	0.17	0.03	0.21	0.16
	143	4.86	0.63	3.88	0.05	0.01	0.18	0.11
	144	9.90	1.18	7.90	0.21	0.02	0.39	0.20
	145	8.20	0.81	6.92	0.13	0.02	0.17	0.14
	146	7.33	0.66	6.15	0.13	0.01	0.24	0.13
	147	10.40	1.45	8.09	0.15	0.02	0.42	0.27
	148	7.54	1.08	6.09	0.10	0.01	0.17	0.09
	149	8.53	1.09	7.05	0.08	0.01	0.22	0.08
	150	11.19	1.62	8.63	0.20	0.02	0.50	0.22
	Mean sd		8.52 1.948	1.04 0.325	6.91 1.564	0.13 0.051	0.02 0.007	0.27 0.119
4♀ 1000	151	6.45	0.68	5.43	0.05	0.01	0.18	0.10
	152	10.17	1.53	8.12	0.11	0.03	0.27	0.11
	153	8.58	0.96	7.04	0.12	0.01	0.30	0.15
	154	8.66	0.80	7.20	0.19	0.03	0.30	0.15
	155	6.72	1.05	5.22	0.16	0.01	0.20	0.08
	156	12.20	1.22	10.24	0.09	0.02	0.42	0.21
	157	12.50	1.45	10.40	0.13	0.03	0.27	0.20
	158	5.72	1.20	4.00	0.10	0.02	0.26	0.15
	159	9.13	1.14	7.33	0.13	0.02	0.31	0.21
	160	6.89	0.71	5.75	0.10	0.01	0.19	0.12
	Mean sd		8.70 2.362	1.07 0.292	7.07 2.098	0.12 0.039	0.02 0.009	0.27 0.071

sd Standard deviation

APPENDIX 6

(Haematology - continued)

Week R4 (15 May 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
1♂ Control	121	-	-	-	+	-	-	-	-	-
	122	-	-	-	-	-	-	-	-	-
	123	-	-	-	-	-	-	-	-	-
	124	-	-	-	-	-	-	-	-	-
	125	-	-	-	-	+	-	-	-	-
	126	-	-	-	+	-	-	-	-	-
	127	-	-	-	+	-	-	-	-	-
	128	-	-	-	-	-	-	-	-	-
	129	-	-	-	-	-	-	-	-	-
	130	-	-	-	+	-	-	-	-	-
4♂ 1000	131	-	-	-	-	-	-	-	-	-
	132	+	-	-	+++	-	-	-	-	-
	133	+	-	-	+++	-	-	-	-	-
	134	-	-	-	-	-	-	-	-	-
	135	-	-	-	+	-	-	-	-	-
	136	-	-	-	+++	-	-	-	-	-
	137	-	-	-	+	-	-	-	-	-
	138	-	-	-	-	-	-	-	-	-
	139	-	-	-	+	-	-	-	-	-
	140	-	-	-	+	-	-	-	-	-

APPENDIX 6

(Haematology - continued)

Week 17 (15 May 1996)

Group/ dosage mg/kg/day	Animal no.	Anis	Micro	Macro	Var	Hypo	Hyper	LS	Atyp	Blast
1♀ Control	141	-	-	-	-	-	-	-	-	-
	142	-	-	-	-	-	-	-	-	-
	143	-	-	-	-	-	-	-	-	-
	144	-	-	-	-	-	-	-	-	-
	145	-	-	-	-	-	-	-	-	-
	146	-	-	-	-	-	-	-	-	-
	147	-	-	-	-	-	-	-	-	-
	148	-	-	-	-	-	-	-	-	-
	149	-	-	-	-	-	-	-	-	-
	150	-	-	-	-	-	-	-	-	-
4♀ 1000	151	-	-	-	-	-	-	-	-	-
	152	-	-	-	-	-	-	-	-	-
	153	-	-	-	-	-	-	-	-	-
	154	-	-	-	-	-	-	-	-	-
	155	-	-	-	-	-	-	-	-	-
	156	-	-	-	-	-	-	-	-	-
	157	-	-	-	-	-	-	-	-	-
	158	-	-	-	-	-	-	-	-	-
	159	-	-	-	-	-	-	-	-	-
	160	-	-	-	-	-	-	-	-	-

APPENDIX 7

Biochemistry - individual values

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γ GT mU/ ml	OCT mU/ ml	
			Total	Alb	Glob								
1♂ Control	1	98	6.7	3.1	3.6	14	0.5	302	20	48	1	2.7	
	2	88	6.4	2.8	3.6	15	0.5	345	25	57	1	0.5	
	3	104	6.7	3.1	3.6	11	0.6	296	20	64	1	2.1	
	4	108	6.4	3.0	3.4	12	0.5	446	29	57	1	2.2	
	5	92	6.5	3.1	3.4	15	0.5	282	23	70	1	1.0	
	121	100	6.7	3.3	3.4	15	0.5	424	26	60	2	1.7	
	122	110	6.8	3.3	3.5	17	0.6	412	25	69	1	1.7	
	123	101	6.2	2.9	3.3	15	0.5	463	34	69	1	2.3	
	124	106	6.8	3.2	3.6	12	0.5	369	25	67	1	1.7	
	125	116	6.9	3.1	3.8	16	0.5	357	29	74	1	1.7	
	Mean		102	6.6	3.1	3.5	14	0.5	370	26	64	1	1.8
	sd		8.4	0.22	0.16	0.15	1.9	0.04	64.8	4.3	7.9	0.3	0.64
	2♂ 62.5	11	130	6.3	3.0	3.3	13	0.5	290	25	69	1	1.6
12		109	6.5	3.0	3.5	13	0.5	362	18	53	1	0.6	
13		118	6.1	2.8	3.3	12	0.4	300	20	45	1	1.4	
14		97	6.0	2.8	3.2	12	0.6	363	24	66	1	2.5	
15		138	6.8	3.2	3.6	14	0.5	430	22	48	1	0.8	
1016		126	6.8	3.2	3.6	15	0.6	362	25	54	1	2.1	
17		132	6.4	3.0	3.4	12	0.6	266	23	65	1	2.0	
18		134	6.5	3.0	3.5	16	0.6	365	27	62	1	3.4	
19		105	6.6	3.1	3.5	12	0.5	287	23	59	1	1.6	
20		116	6.3	3.0	3.3	14	0.5	248	23	56	2	1.7	
Mean			121	6.4	3.0	3.4	13	0.5	327	23	58	1	1.8
sd		13.7	0.27	0.14	0.14	1.4	0.07	57.2	2.6	7.9	0.3	0.81	

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γGT mU/ ml	OCT mU/ ml	
			Total	Alb	Glob								
3♂ 250	21	96	6.5	3.0	3.5	15	0.6	315	26	83	1	1.6	
	22	88	6.7	3.1	3.6	14	0.6	347	22	60	1	3.3	
	23	92	6.3	3.0	3.3	11	0.5	319	21	54	1	1.3	
	24	94	6.9	3.0	3.9	13	0.5	174	19	46	1	2.4	
	25	91	6.4	3.0	3.4	15	0.5	387	23	66	1	4.8	
	26	126	6.3	3.0	3.3	14	0.5	282	20	53	1	0.9	
	27	100	6.9	3.2	3.7	15	0.5	428	30	77	1	1.8	
	28	100	6.9	3.2	3.7	14	0.6	235	25	63	1	3.1	
	29	97	6.5	3.0	3.5	13	0.5	299	27	50	2	3.5	
	30	103	6.6	3.0	3.6	15	0.5	210	25	63	1	1.7	
	Mean		99	6.6	3.1	3.6	14	0.5	300	24	62	1	2.4
	sd		10.6	0.24	0.08	0.19	1.3	0.05	78.4	3.4	11.7	0.3	1.21
	4♂ 1000	31	87	6.9	3.2	3.7	11	0.5	283	22	54	1	0.7
32		107	6.9	3.2	3.7	16	0.6	272	26	73	1	2.9	
33		73	6.5	3.0	3.5	11	0.6	280	18	49	1	1.8	
34		102	6.7	3.1	3.6	10	0.6	321	23	59	1	0.4	
35		92	6.9	3.2	3.7	14	0.6	274	23	59	1	2.7	
131		97	7.1	3.3	3.8	13	0.5	460	31	58	1	1.7	
132		73	6.8	3.2	3.6	16	0.6	299	22	64	1	2.6	
133		84	7.2	3.4	3.8	13	0.5	315	27	55	1	4.1	
134		76	6.7	3.2	3.5	11	0.5	362	23	53	1	1.4	
135		105	7.0	3.2	3.8	17	0.5	346	22	47	1	1.1	
Mean			90	6.9	3.2	3.7	13	0.6	321	24	57	1	2.4
sd		13.0	0.21	0.11	0.12	2.5	0.05	57.6	3.5	7.5	0.0	1.4	

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γGT mU/ ml	OCT mU/ ml	
			Total	Alb	Glob								
1♀ Control	41	101	6.8	3.4	3.4	18	0.6	196	21	50	1	1.1	
	42	102	6.6	3.3	3.3	16	0.5	204	22	50	<1	1.5	
	43	87	6.4	3.2	3.2	15	0.4	311	18	50	2	2.2	
	44	101	7.2	3.7	3.5	14	0.5	198	29	59	<1	7.6	
	45	92	6.7	3.3	3.4	13	0.5	193	24	50	<1	1.3	
	141	112	6.9	3.3	3.6	13	0.5	165	24	52	1	1.3	
	142	118	6.3	3.2	3.1	15	0.5	227	18	50	<1	1.3	
	143	114	6.0	3.0	3.0	15	0.4	211	16	57	<1	2.0	
	144	118	6.8	3.2	3.6	12	0.5	253	23	62	1	1.6	
	145	119	6.5	3.2	3.3	14	0.5	254	20	61	<1	1.1	
		Mean	106	6.6	3.3	3.3	15	0.5	221	22	54	<1	2.1
		sd	11.4	0.34	0.18	0.20	1.7	0.06	41.8	3.8	5.1		1.97
	2♀ 62.5	51	104	7.0	3.5	3.5	15	0.6	151	25	68	1	17.7
		52	98	6.7	3.2	3.5	14	0.5	244	20	50	1	1.7
53		98	6.7	3.4	3.3	13	0.5	156	20	48	1	1.8	
54		94	6.4	3.1	3.3	13	0.6	195	20	56	<1	0.5	
55		110	6.5	3.3	3.2	12	0.5	221	28	57	1	3.2	
56		115	7.1	3.4	3.7	15	0.5	196	19	47	1	1.3	
57		105	6.8	3.1	3.7	20	0.6	278	21	47	1	1.8	
58		92	6.3	3.1	3.2	11	0.5	170	20	59	<1	1.6	
59		101	6.8	3.2	3.6	16	0.6	177	20	51	<1	0.7	
60		105	7.5	3.7	3.8	13	0.4	159	18	55	1	4.9	
		Mean	102	6.8	3.3	3.5	14	0.5	195	21	54	<1	3.6
		sd	7.1	0.36	0.20	0.22	2.5	0.07	41.7	3.0	6.6		5.12

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γGT mU/ ml	OCT mU/ ml
			Total	Alb	Glob							
3♀ 250	61	131	6.6	3.3	3.3	16	0.6	204	15	43	1	1.2
	62	97	7.2	3.6	3.6	14	0.5	245	17	51	1	2.2
	63	97	6.5	3.2	3.3	14	0.5	244	27	51	<1	1.3
	64	98	6.7	3.3	3.4	17	0.6	183	20	47	<1	1.7
	65	105	7.0	3.5	3.5	18	0.6	261	27	51	<1	1.1
	66	119	7.4	3.7	3.7	17	0.6	180	16	54	1	9.2
	67	114	7.1	3.4	3.7	15	0.6	252	15	49	<1	1.6
	68	104	7.1	3.3	3.8	16	0.6	201	20	51	1	3.8
	69	112	6.9	3.3	3.6	16	0.5	205	22	57	1	2.1
	70	118	7.0	3.4	3.6	15	0.5	157	16	46	1	3.0
	Mean sd	110 11.3	7.0 0.28	3.4 0.16	3.6 0.17	16 1.3	0.6 0.05	213 35.3	20 4.6	50 4.0	<1	2.7 2.43
4♀ 1000	71	90	7.3	3.5	3.8	13	0.5	114	22	48	<1	1.1
	72	90	7.2	3.6	3.6	15	0.5	160	20	50	1	3.6
	73	101	6.9	3.3	3.6	14	0.5	148	21	45	3	2.0
	74	112	7.6	3.7	3.9	19	0.5	166	20	48	2	2.7
	75	101	7.5	3.6	3.9	14	0.6	175	24	51	<1	1.8
	151	120	6.5	3.2	3.3	13	0.5	203	19	42	1	2.1
	152	97	7.1	3.4	3.7	14	0.6	271	29	45	<1	1.9
	153	97	7.0	3.3	3.7	11	0.6	271	18	46	<1	2.5
	154	108	7.5	3.7	3.8	17	0.5	185	22	47	<1	2.5
	155	106	6.9	3.2	3.7	12	0.5	160	21	57	1	2.3
	Mean sd	102 9.5	7.2 0.34	3.5 0.20	3.7 0.18	14 2.3	0.5 0.05	185 50.8	22 3.1	48 4.1	<2	2.3 0.66

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl	
1♂ Control	1	0.1	146	3.5	5.8	5.0	102	71	
	2	0.1	147	4.3	5.8	6.3	101	64	
	3	0.1	146	3.8	5.6	5.0	100	83	
	4	0.1	145	3.9	5.7	5.1	103	63	
	5	0.1	147	3.7	5.6	5.0	103	64	
	121	0.1	146	4.0	5.7	5.1	102	55	
	122	0.1	147	3.8	5.7	5.0	103	67	
	123	0.1	146	3.6	5.6	4.9	101	68	
	124	0.1	146	3.8	5.7	4.8	102	95	
	125	0.1	147	3.5	5.6	5.0	101	80	
		Mean	0.1	146	3.8	5.7	5.1	102	71
		sd	0.00	0.7	0.24	0.08	0.42	1.0	11.8
	2♂ 62.5	11	0.1	145	3.6	5.7	5.1	101	113
12		0.1	145	3.7	5.7	4.8	101	92	
13		0.1	146	3.7	5.4	4.9	103	59	
14		0.1	145	4.3	5.6	5.3	103	79	
15		0.1	145	3.8	5.5	4.2	101	70	
1016		0.1	145	3.5	5.6	5.0	99	59	
17		0.1	145	3.3	5.7	4.8	99	63	
18		0.1	145	3.4	5.5	4.6	101	67	
19		0.1	145	3.6	5.4	4.4	103	72	
20		0.1	145	3.7	5.6	4.9	102	69	
		Mean	0.1	145	3.7	5.6	4.8	101	74
	sd	0.00	0.3	0.27	0.12	0.33	1.5	16.8	

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
3♂ 250	21	0.1	147	3.8	5.8	5.3	102	75
	22	0.1	146	3.4	5.6	4.6	102	59
	23	0.1	146	3.7	5.7	5.0	103	73
	24	0.1	145	3.4	5.8	4.4	99	97
	25	0.1	146	4.0	5.7	5.1	102	74
	26	0.1	145	3.8	5.6	4.5	100	66
	27	0.1	145	4.2	5.6	4.5	101	100
	28	0.1	144	3.6	5.7	4.6	99	80
	29	0.1	146	3.8	5.5	5.3	102	66
	30	0.1	143	3.9	5.6	4.5	99	84
	Mean	0.1	145	3.8	5.7	4.8	101	77
	sd	0.00	1.2	0.25	0.10	0.36	1.5	13.3
	4♂ 1000	31	0.1	147	3.9	5.7	4.9	100
32		0.1	144	4.8	5.5	5.4	97	76
33		0.1	148	4.0	5.8	5.8	101	100
34		0.1	149	4.0	5.7	5.8	100	64
35		0.1	148	3.4	5.8	5.1	100	57
131		0.1	146	3.6	6.0	5.0	97	95
132		0.1	148	3.6	5.6	4.8	101	54
133		0.1	146	3.5	5.9	5.1	98	66
134		0.1	148	4.0	5.5	5.0	101	61
135		0.1	145	3.4	5.9	4.6	98	113
Mean		0.1	147	3.8	5.7	5.2	99	74
sd	0.00	1.6	0.42	0.17	0.40	1.6	21.0	

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
1♀ Control	41	0.1	145	3.3	5.6	4.3	104	108
	42	0.1	146	3.9	5.9	4.4	106	78
	43	0.1	144	3.5	5.8	4.4	101	112
	44	0.1	146	4.7	5.7	4.8	102	86
	45	0.1	146	3.7	5.8	4.0	104	77
	141	0.1	146	3.4	5.6	4.1	106	72
	142	0.1	144	3.6	5.7	4.5	102	102
	143	0.1	143	4.6	5.3	4.5	103	59
	144	0.1	145	3.7	5.8	4.4	103	132
	145	0.1	144	4.8	5.5	4.2	103	105
		Mean sd	0.1 0.00	145 1.1	3.9 0.57	5.7 0.18	4.4 0.23	103 1.6
2♀ 62.5	51	0.1	147	4.1	5.6	4.6	104	109
	52	0.1	145	3.6	5.7	4.4	104	123
	53	<0.1	145	4.3	5.6	4.7	104	78
	54	0.2	146	4.9	5.5	4.9	105	91
	55	<0.1	146	3.8	5.7	4.3	105	92
	56	<0.1	145	3.8	5.7	3.7	104	109
	57	0.1	145	4.1	5.9	4.5	105	79
	58	<0.1	145	4.0	5.4	3.8	104	106
	59	0.1	144	3.4	5.5	3.9	104	80
	60	<0.1	145	3.7	5.7	4.4	103	132
		Mean sd	<0.1 0.8	145 0.8	4.0 0.42	5.6 0.14	4.3 0.40	104 0.6

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 5 (20 February 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
3♀ 250	61	0.1	143	4.1	5.6	4.1	102	97
	62	<0.1	145	3.4	5.7	4.5	102	98
	63	0.1	146	3.6	5.4	4.3	104	98
	64	0.1	144	3.2	5.6	3.9	103	118
	65	<0.1	144	2.9	5.4	3.5	101	94
	66	0.1	146	4.0	5.7	3.8	103	133
	67	0.1	145	3.4	5.6	3.7	102	90
	68	<0.1	146	3.7	5.6	3.9	104	101
	69	0.1	144	3.5	5.6	3.6	104	103
	70	<0.1	145	3.0	5.5	3.8	103	105
		Mean sd	<0.1 1.0	145 1.0	3.5 0.39	5.6 0.11	3.9 0.31	103 1.0
4♀ 1000	71	0.1	147	3.0	5.7	3.8	103	90
	72	<0.1	146	3.2	5.8	4.0	100	76
	73	0.1	146	3.8	5.9	4.3	103	103
	74	<0.1	146	3.4	5.9	3.9	101	133
	75	0.1	148	3.2	5.8	4.0	103	79
	151	<0.1	144	4.3	5.6	4.6	101	95
	152	0.1	145	3.6	5.7	4.1	103	103
	153	<0.1	148	3.7	5.9	4.9	102	94
	154	0.1	145	3.9	5.9	4.2	103	68
	155	<0.1	145	4.2	5.6	4.1	104	95
		Mean sd	<0.1 1.3	146 1.3	3.6 0.43	5.8 0.12	4.2 0.33	102 1.3

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γ GT mU/ ml	OCT mU/ ml	
			Total	Alb	Glob								
1 δ Control	1	104	7.2	3.2	4.0	17	0.5	174	20	50	1	5.6	
	2	93	7.0	3.0	4.0	14	0.5	159	31	64	1	2.4	
	3	130	6.8	3.2	3.6	13	0.5	132	21	64	1	16.4	
	4	127	6.6	3.0	3.6	15	0.5	230	26	54	2	3.4	
	5	110	6.8	3.1	3.7	13	0.5	171	30	62	2	5.9	
	121	124	6.3	3.0	3.3	13	0.5	168	18	48	1	2.6	
	122	130	6.6	3.2	3.4	15	0.5	233	28	74	1	3.8	
	123	144	6.6	2.9	3.7	16	0.6	247	31	86	1	5.1	
	124	141	6.9	3.2	3.7	13	0.5	153	23	49	1	4.3	
	125	137	7.1	3.0	4.1	16	0.7	211	29	89	1	3.1	
	Mean		124	6.8	3.1	3.7	15	0.5	188	26	64	1	5.3
	sd		16.7	0.27	0.11	0.26	1.5	0.07	39.3	4.9	14.9	0.4	4.10
	2 δ 62.5	11	159	7.0	3.1	3.9	13	0.5	158	22	60	1	9.2
12		141	6.8	3.1	3.7	14	0.5	192	29	53	1	8.6	
13		127	7.0	3.0	4.0	12	0.5	185	21	47	2	4.4	
14		104	6.6	2.9	3.7	15	0.6	201	25	60	1	4.8	
15		153	6.8	3.2	3.6	17	0.5	226	22	47	1	2.0	
1016		125	7.0	3.0	4.0	16	0.6	164	21	63	1	4.3	
17		137	6.7	3.0	3.7	17	0.6	144	18	50	1	3.1	
18		129	6.7	3.1	3.6	18	0.6	200	39	77	1	2.0	
19		125	6.8	3.0	3.8	14	0.5	151	22	50	1	5.5	
20		123	6.8	3.1	3.7	15	0.6	160	24	52	2	5.9	
Mean			132	6.8	3.1	3.8	15	0.6	178	24	56	1	5.0
sd		15.9	0.14	0.08	0.15	1.9	0.05	26.6	5.9	9.3	0.4	2.45	

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γGT mU/ ml	OCT mU/ ml	
			Total	Alb	Glob								
3♂ 250	21	117	7.0	3.2	3.8	16	0.7	191	25	62	1	2.9	
	22	93	7.1	3.1	4.0	15	0.7	161	26	68	1	2.9	
	23	121	6.6	3.0	3.6	14	0.6	190	18	49	1	2.1	
	24	102	7.2	2.9	4.3	14	0.5	93	23	52	1	5.0	
	25	80	6.7	3.1	3.6	18	0.5	174	19	50	1	3.6	
	26	120	6.8	3.0	3.8	15	0.5	179	18	46	1	2.5	
	27	122	7.1	3.2	3.9	15	0.6	211	27	56	1	4.4	
	28	116	7.0	3.2	3.8	17	0.6	133	20	55	1	2.9	
	29	114	7.2	3.2	4.0	16	0.6	147	22	47	1	6.0	
	30	135	6.8	2.9	3.9	17	0.7	113	26	59	3	6.0	
	Mean sd		112 16.0	7.0 0.21	3.1 0.12	3.9 0.21	16 1.3	0.6 0.08	159 37.4	22 3.5	54 7.0	1 0.6	3.8 1.43
	4♂ 1000	31	93	7.4	3.3	4.1	13	0.5	163	23	49	1	4.5
32		106	7.7	3.2	4.5	18	0.6	178	179	276	3	132.5	
33		88	7.5	3.3	4.2	12	0.5	176	20	60	1	4.8	
34		109	7.1	3.2	3.9	12	0.6	193	20	50	1	4.8	
35		102	7.5	3.4	4.1	15	0.7	179	17	48	2	4.1	
131		144	7.8	3.5	4.3	14	0.5	278	17	57	1	3.9	
132		83	7.6	3.3	4.3	14	0.6	131	16	53	1	4.4	
133		92	7.5	3.5	4.0	14	0.5	207	24	64	1	2.8	
134		103	7.3	3.3	4.0	12	0.5	193	21	50	1	2.4	
135		106	7.6	3.4	4.2	17	0.6	197	22	52	1	8.6	
Mean sd			103 16.9	7.5 0.20	3.3 0.11	4.2 0.18	14 2.1	0.6 0.07	190 37.7	36 50.4	76 70.5	1 0.7	17.3 40.52

sd Standard deviation

APPENDIX 7
(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γGT mU/ ml	OCT mU ml
			Total	Alb	Glob							
1♀ Control	41	115	7.0	3.5	3.5	19	0.5	85	31	55	1	15.5
	42	116	6.8	3.4	3.4	13	0.5	97	18	46	1	2.3
	43	133	7.1	3.4	3.7	14	0.5	122	20	48	<1	7.9
	44	118	7.8	3.8	4.0	16	0.5	116	111	187	1	99.6
	45	115	6.6	3.1	3.5	12	0.6	99	19	53	1	2.9
	141	109	7.2	3.4	3.8	14	0.5	93	29	57	1	4.9
	142	133	6.2	3.0	3.2	13	0.5	106	15	48	<1	4.3
	143	113	6.8	3.0	3.8	14	0.5	146	17	58	1	5.1
	144	128	7.2	3.3	3.9	13	0.5	114	28	65	2	4.5
	145	113	7.5	3.5	4.0	17	0.6	93	52	151	<1	97.1
		Mean sd	119 8.7	7.0 0.45	3.3 0.25	3.7 0.27	15 2.2	0.5 0.04	107 18.0	34 29.2	77 49.6	<1
2♀ 62.5	51	116	7.6	3.7	3.9	16	0.5	75	36	85	<1	37.0
	52	107	7.3	3.4	3.9	15	0.5	129	22	59	<1	3.2
	53	116	7.3	3.6	3.7	16	0.5	82	59	105	<1	24.4
	54	120	6.9	3.4	3.5	17	0.6	82	25	52	<1	5.7
	55	118	6.4	3.2	3.2	14	0.5	109	21	61	3	2.4
	56	128	7.1	3.4	3.7	12	0.5	76	23	45	1	4.5
	57	116	7.1	3.3	3.8	19	0.6	119	22	48	<1	6.0
	58	117	6.3	3.1	3.2	12	0.5	83	17	42	1	2.7
	59	101	6.8	3.2	3.6	15	0.5	79	19	55	2	6.3
	60	98	7.8	3.9	3.9	14	0.5	84	20	57	1	13.8
		Mean sd	114 9.1	7.1 0.48	3.4 0.25	3.6 0.27	15 2.2	0.5 0.04	92 19.6	26 12.6	61 19.5	<2

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	γGT mU/ ml	OCT mU/ ml
			Total	Alb	Glob							
3♀ 250	61	130	6.9	3.3	3.6	15	0.5	81	13	39	<1	6.6
	62	88	7.6	3.8	3.8	16	0.5	113	17	48	<1	2.3
	63	116	7.0	3.3	3.7	12	0.5	115	23	58	1	4.4
	64	98	7.3	3.6	3.7	16	0.5	72	26	56	<1	12.4
	65	122	7.0	3.3	3.7	15	0.5	86	28	53	1	3.2
	66	107	7.6	3.7	3.9	16	0.6	98	18	72	1	13.8
	67	119	7.2	3.6	3.6	14	0.6	109	21	50	<1	4.2
	68	113	7.6	3.6	4.0	19	0.6	92	19	43	<1	4.1
	69	114	7.4	3.4	4.0	17	0.6	111	29	67	<1	4.6
	70	119	7.7	3.8	3.9	19	0.5	58	16	37	<1	5.8
	Mean sd	113 12.2	7.3 0.29	3.5 0.20	3.8 0.15	16 2.1	0.5 0.05	94 19.3	21 5.4	52 11.4	<1	6.1 3.87
4♀ 1000	71	141	7.6	3.6	4.0	12	0.7	45	36	56	<1	5.6
	72	83	7.8	3.8	4.0	16	0.5	89	23	52	1	10.7
	73	112	7.5	3.3	4.2	15	0.7	97	24	48	1	5.6
	74	114	8.3	3.9	4.4	18	0.6	70	21	48	1	2.7
	75	91	7.8	3.7	4.1	13	0.6	89	21	51	<1	3.0
	151	113	7.0	3.4	3.6	18	0.5	108	22	45	1	3.5
	152	97	7.3	3.4	3.9	14	0.6	87	17	44	1	2.1
	153	103	7.5	3.5	4.0	14	0.6	131	15	39	<1	5.9
	154	89	8.0	3.9	4.1	15	0.5	100	18	42	<1	2.4
	155	126	7.7	3.5	4.2	10	0.5	70	16	45	<1	2.9
	Mean sd	107 17.9	7.7 0.36	3.6 0.22	4.1 0.21	15 2.5	0.6 0.08	89 23.5	21 6.0	47 5.1	<1	4.4 2.62

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl	
1♂ Control	1	0.2	146	3.3	5.7	4.3	104	64	
	2	0.1	147	4.2	5.9	5.2	103	64	
	3	0.2	146	4.2	5.7	4.2	102	97	
	4	0.1	146	3.7	5.7	4.6	103	62	
	5	0.2	146	4.4	5.7	4.3	103	69	
	121	0.2	147	4.0	5.5	4.9	105	44	
	122	0.1	146	4.8	5.4	4.5	105	58	
	123	0.1	145	3.7	5.6	4.3	103	59	
	124	0.2	146	3.5	5.7	4.1	102	79	
	125	0.2	145	4.1	5.6	4.0	102	77	
	Mean		0.2	146	4.0	5.7	4.4	103	67
	sd		0.05	0.7	0.45	0.14	0.37	1.1	14.4
	2♂ 62.5	11	0.2	146	3.3	5.8	4.0	102	127
		12	0.2	145	3.5	5.8	3.9	102	104
13		0.2	145	3.8	5.7	4.1	102	73	
14		0.1	145	3.8	5.4	4.0	104	74	
15		0.2	146	3.6	5.6	3.5	102	76	
1016		0.1	148	3.8	5.7	4.4	102	59	
17		0.1	146	3.2	5.6	4.1	101	69	
18		0.1	145	3.4	5.6	4.0	101	66	
19		0.1	146	3.5	5.5	4.2	104	63	
20		0.2	146	3.7	5.5	3.8	104	62	
Mean			0.2	146	3.6	5.6	4.0	102	77
sd		0.05	0.9	0.22	0.13	0.24	1.2	21.6	

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
3♂ 250	21	0.1	147	3.1	5.8	4.0	101	86
	22	0.1	147	3.2	5.5	3.5	104	65
	23	0.1	146	3.4	5.8	3.9	102	77
	24	0.1	146	3.2	5.7	3.5	101	116
	25	0.1	146	4.0	5.6	4.0	103	76
	26	0.2	146	3.4	5.6	3.9	102	72
	27	0.1	147	4.1	5.8	4.5	101	104
	28	0.1	146	3.7	5.6	3.4	102	88
	29	0.2	146	3.6	5.4	4.1	103	75
	30	0.1	146	3.3	5.5	3.7	101	98
		Mean	0.1	146	3.5	5.6	3.9	102
	sd	0.04	0.5	0.34	0.14	0.33	1.1	16.0
4♂ 1000	31	0.1	146	3.7	5.9	3.8	101	92
	32	0.1	146	3.8	5.9	4.3	96	109
	33	0.2	146	3.5	5.8	4.0	101	136
	34	0.1	146	4.6	5.6	4.1	101	81
	35	0.1	147	3.6	5.7	4.1	100	75
	131	0.1	146	3.6	6.1	3.9	98	139
	132	0.1	147	3.9	6.0	4.0	101	72
	133	0.1	146	3.6	6.1	4.3	100	99
	134	0.1	146	3.4	5.6	3.5	101	73
	135	0.1	145	3.9	5.9	3.5	100	141
		Mean	0.1	146	3.8	5.9	4.0	100
	sd	0.03	0.6	0.34	0.18	0.28	1.7	28.1

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
1♀ Control	41	0.1	146	3.5	5.9	3.9	104	96
	42	0.2	145	3.9	5.7	3.5	107	80
	43	0.1	144	3.2	5.9	3.9	101	114
	44	0.2	146	3.9	5.7	3.2	105	95
	45	0.1	146	3.7	5.7	3.8	104	76
	141	0.2	145	3.3	5.6	3.7	105	79
	142	0.1	145	3.8	5.7	3.6	105	97
	143	0.2	145	3.7	5.4	3.5	107	83
	144	0.2	144	3.3	5.9	3.3	103	130
	145	0.2	146	3.5	5.8	3.4	103	104
	Mean sd		0.2 0.05	145 0.8	3.6 0.26	5.7 0.16	3.6 0.24	104 1.8
2♀ 62.5	51	0.2	145	4.3	5.6	2.9	106	120
	52	0.2	144	4.5	5.9	3.7	105	113
	53	0.2	145	3.5	5.5	3.4	105	87
	54	0.2	145	3.1	5.7	3.9	104	100
	55	0.1	144	4.0	5.6	3.6	106	100
	56	0.2	146	3.9	5.6	3.3	106	109
	57	0.2	144	3.2	5.6	3.3	105	89
	58	0.2	145	3.8	5.3	3.9	104	94
	59	0.2	145	4.2	5.5	3.9	104	78
	60	0.2	145	3.3	5.9	3.8	104	150
	Mean sd		0.2 0.03	145 0.6	3.8 0.49	5.6 0.18	3.6 0.34	105 0.9

sd Standard deviation

APPENDIX 7

(Biochemistry - continued)

Week 13 (17 April 1996)

Group/ dosage mg/kg/day	Animal no.	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl	
3♀ 250	61	0.1	144	4.5	5.7	3.7	106	109	
	62	0.2	146	3.6	5.7	3.7	104	108	
	63	0.1	147	3.6	5.5	3.2	107	105	
	64	0.1	144	4.1	5.9	3.9	104	142	
	65	0.2	146	4.1	5.4	3.1	106	105	
	66	0.1	147	3.3	5.6	3.0	106	145	
	67	0.2	146	3.8	5.7	3.5	104	99	
	68	0.2	146	3.5	5.8	3.6	104	111	
	69	0.1	145	3.3	5.7	2.7	104	102	
	70	0.1	143	3.0	5.7	2.8	102	132	
	Mean		0.1	145	3.7	5.7	3.3	105	116
	sd		0.05	1.3	0.45	0.14	0.42	1.5	17.1
	4♀ 1000	71	0.1	146	3.9	5.9	4.0	105	100
72		0.1	145	3.4	6.1	3.8	100	100	
73		0.1	146	3.4	5.8	3.0	105	135	
74		0.1	152	3.4	6.1	3.4	105	144	
75		0.1	148	3.3	5.8	3.0	104	91	
151		0.1	143	3.7	5.7	3.5	101	97	
152		0.1	146	3.4	5.7	3.2	104	113	
153		0.2	146	3.2	5.9	3.6	101	121	
154		0.2	143	3.7	6.0	4.0	100	80	
155		0.1	146	3.3	5.8	3.3	103	120	
Mean			0.1	146	3.5	5.9	3.5	103	110
sd			0.04	2.6	0.22	0.15	0.37	2.1	20.1

sd Standard deviation

APPENDIX 8

Organ weights - individual values

Terminal kill

Group/ dosage mg/kg/day	Animal no.	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
1♂ Control	1	451	1.88	12.3	22.8	1.59	19.5
	2	529	2.06	13.9	20.1	1.55	23.4
	3	532	1.97	12.8	24.2	1.61	18.6
	4	594	2.13	12.0	21.5	1.97	24.1
	5	416	1.98	10.6	13.1	1.34	16.2
	6	569	2.03	19.2	25.4	1.56	27.2
	7	507	2.04	15.0	32.3	1.69	24.3
	8	644	2.08	18.9	23.9	1.96	28.6
	9	602	2.00	13.5	28.5	1.69	21.9
	10	649	2.25	16.8	28.1	2.02	30.6
	Mean sd	549 77.5	2.04 0.099	14.5 2.94	24.0 5.27	1.70 0.219	23.4 4.55
2♂ 62.5	11	516	2.07	12.4	16.5	1.82	24.5
	12	610	2.02	11.6	26.0	1.95	29.0
	13	611	2.21	17.0	20.7	2.15	32.1
	14	489	1.96	11.0	20.0	1.53	15.0
	15	543	2.19	9.5	22.6	1.66	20.4
	1016	530	1.90	12.3	18.3	1.70	19.8
	17	576	2.08	13.9	24.9	1.54	22.7
	18	519	2.02	11.9	29.6	1.42	19.0
	19	506	2.00	12.0	21.0	1.66	18.3
	20	557	1.91	16.1	23.2	2.16	22.1
	Mean sd	546 42.3	2.04 0.105	12.8 2.29	22.3 3.86	1.76 0.255	22.3 5.11

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Animal no.	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g	
3♂ 250	21	504	2.06	13.2	24.5	1.53	22.3	
	22	468	1.91	#5.0	19.9	1.57	17.0	
	23	537	2.09	12.7	21.0	1.89	23.6	
	24	557	1.93	14.3	24.7	1.81	21.9	
	25	494	2.08	13.2	19.9	1.56	19.3	
	26	559	2.24	15.6	23.4	1.93	26.4	
	27	518	2.17	13.0	36.3	1.72	23.3	
	28	573	2.11	15.7	17.9	1.99	24.2	
	29	537	2.01	12.8	29.1	1.68	23.8	
	30	536	1.98	12.5	22.0	1.65	23.9	
	Mean		528	2.06	13.7	23.9	1.73	22.6
	sd		32.3	0.102	1.23	5.40	0.164	2.69
	4♂ 1000	31	469	1.99	11.7	28.6	1.43	22.5
32		449	2.09	11.7	15.3	1.55	22.7	
33		533	2.05	14.0	24.5	1.60	29.8	
34		431	1.92	10.2	21.0	1.52	25.9	
35		486	2.08	17.2	23.1	1.69	31.6	
36		512	1.98	14.6	25.2	1.61	28.7	
37		565	2.16	13.4	25.9	2.07	39.3	
38		568	1.99	17.4	23.7	1.97	28.3	
39		508	1.99	12.0	30.3	1.93	29.5	
40		633	2.09	18.1	26.5	1.82	38.8	
Mean			515	2.03	14.0	24.4	1.72	29.7
sd		61.5	0.072	2.76	4.17	0.218	5.73	

sd Standard deviation

Value excluded from calculation of mean and statistical analysis - organ damaged at *post mortem*

APPENDIX 8

(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Animal no.	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
1♀ Control	41	240	1.90	13.6	9.4	0.92	8.3
	42	266	1.83	11.9	11.0	0.95	9.2
	43	291	1.88	15.0	13.2	1.09	10.1
	44	266	1.86	17.2	14.6	1.19	10.6
	45	281	1.93	13.5	12.1	0.97	12.5
	46	295	2.06	9.9	19.6	1.11	12.0
	47	259	1.95	12.3	14.2	1.04	9.5
	48	265	1.78	21.0	17.0	1.00	10.3
	49	333	2.06	17.5	20.5	1.23	14.0
	50	308	1.75	15.5	17.5	1.16	10.0
	Mean		280	1.90	14.7	14.9	1.07
sd		27.0	0.106	3.23	3.67	0.106	1.71
2♀ 62.5	51	241	1.75	14.4	10.7	0.95	10.2
	52	237	1.74	10.5	12.7	1.01	8.8
	53	284	1.87	19.9	15.8	1.11	10.7
	54	305	1.85	14.0	13.2	1.06	11.1
	55	288	1.84	14.8	18.6	1.09	12.9
	56	304	1.87	14.0	16.7	1.06	10.1
	57	268	1.82	13.7	16.3	1.06	9.0
	58	253	1.84	13.2	16.3	0.96	11.2
	59	288	1.87	16.6	18.0	1.10	11.1
	60	279	1.89	12.6	15.0	1.08	11.6
	Mean		275	1.84	14.4	15.3	1.05
sd		24.3	0.051	2.49	2.47	0.058	1.21

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Terminal kill

Group/ Dosage mg/kg/day	Animal no.	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
3♀ 250	61	267	1.76	13.7	14.3	1.06	10.9
	62	248	1.80	11.3	12.3	1.02	9.2
	63	264	1.90	15.1	12.7	1.07	10.4
	64	298	1.91	15.7	14.2	1.04	11.9
	65	265	1.84	16.1	15.1	1.05	11.6
	66	273	1.87	13.4	15.7	1.00	10.5
	67	276	1.95	16.5	13.8	1.07	11.0
	68	280	1.86	14.4	16.3	1.11	11.2
	69	261	1.85	13.0	30.4	1.05	11.2
	70	310	1.91	18.0	16.6	1.22	14.7
	Mean sd		274 18.1	1.86 0.055	14.7 1.96	16.1 5.21	1.07 0.059
4♀ 1000	71	260	1.91	17.6	13.8	1.10	13.2
	72	266	1.77	14.8	11.8	1.10	13.7
	73	254	1.92	12.3	15.9	1.01	11.9
	74	329	1.90	17.2	21.3	1.18	18.0
	75	269	1.90	14.3	13.9	1.12	14.6
	76	263	1.83	12.2	16.3	1.00	11.5
	77	272	1.75	9.8	17.3	1.11	13.9
	78	270	1.80	15.2	18.7	1.08	14.6
	79	284	1.85	17.5	20.9	1.10	14.7
	80	261	1.85	16.1	13.8	0.95	15.3
Mean sd		273 21.5	1.85 0.061	14.7 2.60	16.4 3.19	1.08 0.066	14.2 1.82

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Animal no.	Spleen	Kidneys	Adrenals	Prostate	Testes		Seminal Vesicles	Epididymides	
		g	g	mg	g	L g.	R g.	g	Left g	Right g
1♂ Control	1	0.78	2.77	68.1	0.987	1.56	1.53	1.38	0.575	0.587
	2	0.78	3.31	46.8	0.963	1.75	1.79	1.16	0.616	0.696
	3	0.63	3.68	61.1	0.623	0.94	1.09	1.14	0.302	0.294
	4	0.97	4.24	68.7	1.007	1.88	1.92	1.17	0.653	0.698
	5	0.62	2.79	57.2	0.816	1.66	1.55	0.67	0.576	0.551
	6	0.95	3.83	76.2	1.264	2.05	2.01	2.23	0.767	0.835
	7	0.85	3.83	57.2	0.888	2.00	2.02	2.01	0.695	0.730
	8	0.84	3.81	71.9	1.331	1.78	1.75	1.92	0.687	0.763
	9	1.89	4.28	55.4	0.717	1.82	1.77	1.70	0.724	0.693
	10	1.17	4.58	87.0	0.991	1.58	1.62	2.20	0.582	0.565
	Mean	0.95	3.71	65.0	0.959	1.70	1.71	1.56	0.618	0.641
	sd	0.368	0.605	11.74	0.2192	0.313	0.278	0.531	0.1292	0.1515
2♂ 62.5	11	0.83	3.37	59.4	0.775	1.89	1.83	1.21	0.671	0.646
	12	0.92	4.43	67.6	0.969	1.99	2.06	1.82	0.814	0.769
	13	0.94	5.09	79.9	0.926	1.47	1.45	1.44	0.599	0.610
	14	0.64	3.00	58.9	1.005	1.85	1.15	1.03	0.747	0.561
	15	0.85	3.71	80.7	0.961	1.66	1.71	0.99	0.629	0.610
	1016	0.96	3.69	78.7	1.025	1.79	1.76	1.73	0.609	0.631
	17	0.84	4.72	72.1	1.079	1.74	1.79	1.95	0.645	0.628
	18	0.68	3.64	72.0	1.034	1.80	1.83	1.33	0.707	0.729
	19	0.68	3.72	52.9	1.100	2.11	2.06	1.75	0.727	0.729
	20	0.71	3.35	48.5	1.064	2.09	2.00	1.76	0.683	0.654
	Mean	0.80	3.87	67.1	0.994	1.84	1.77	1.50	0.683	0.663
	sd	0.119	0.661	11.58	0.0945	0.197	0.283	0.346	0.0673	0.0644

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Animal no.	Spleen	Kidneys	Adrenals	Prostate	Testes		Seminal	Epididymides	
		g	g	mg	g	L g	R g	Vesicles g	Left g	Right g
3♂ 250	21	0.82	4.34	71.8	1.240	1.82	1.85	1.04	0.709	0.676
	22	0.61	3.37	62.1	1.300	1.87	1.83	1.45	0.589	0.605
	23	0.86	5.60	74.9	1.068	1.86	1.91	1.31	0.744	0.698
	24	0.89	4.37	83.3	0.935	4.09	1.62	1.90	0.699	0.426
	25	0.82	4.07	55.1	1.015	1.69	1.74	1.42	0.659	0.624
	26	0.94	4.78	83.6	0.820	1.78	1.68	1.49	0.666	0.637
	27	0.90	4.21	66.4	1.418	1.69	1.74	1.19	0.633	0.644
	28	0.81	4.34	85.6	0.748	1.58	1.57	1.93	0.539	0.537
	29	0.73	4.14	83.4	1.096	1.97	2.10	1.89	0.661	0.672
	30	0.95	4.13	69.2	1.402	1.94	1.88	1.24	0.620	0.654
		Mean sd	0.83 0.101	4.33 0.567	73.5 10.46	1.104 0.2332	2.03 0.734	1.79 0.158	1.49 0.320	0.652 0.0600
4♂ 1000	31	0.66	3.63	55.9	0.603	1.82	1.84	1.13	0.646	0.706
	32	0.84	3.47	64.1	0.788	1.68	1.71	0.73	0.604	0.600
	33	0.92	4.37	72.0	1.199	1.51	1.50	1.55	0.652	0.654
	34	0.56	3.56	70.6	1.143	1.86	1.81	0.94	0.636	0.662
	35	0.74	4.49	94.1	0.957	1.72	1.76	1.95	0.621	0.664
	36	0.73	4.55	87.4	1.022	1.90	1.87	1.30	0.758	0.703
	37	1.04	5.77	87.4	0.835	1.49	1.48	1.87	0.594	0.599
	38	0.83	3.96	80.3	0.728	1.89	1.98	1.53	0.726	0.786
	39	0.91	3.69	62.0	1.159	1.98	1.90	1.67	0.661	0.654
	40	0.89	5.05	84.7	1.096	1.67	1.78	1.72	0.633	0.705
		Mean sd	0.81 0.141	4.25 0.743	75.9 12.77	0.953 0.2051	1.75 0.168	1.76 0.163	1.44 0.403	0.653 0.0517

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Terminal kill

Group/ dosage mg/kg/day	Animal no.	Spleen	Kidneys	Adrenals	Uterus	Ovaries
		g	g	mg	g	mg
1♀ Control	41	0.39	1.70	58.1	0.76	67.6
	42	0.50	1.84	77.3	0.47	78.6
	43	0.43	2.18	74.1	0.88	95.8
	44	0.52	1.95	62.0	1.07	67.5
	45	0.55	2.27	93.8	0.43	120.9
	46	0.54	2.28	71.8	0.70	123.6
	47	0.50	1.99	55.9	1.07	65.0
	48	0.42	1.95	74.5	0.61	80.7
	49	0.81	2.80	101.5	0.55	124.0
	50	0.54	2.12	63.5	0.58	78.4
	Mean	0.52	2.11	73.3	0.71	90.2
	sd	0.117	0.307	14.88	0.231	24.17
2♀ 62.5	51	0.46	2.05	64.5	0.50	53.8
	52	0.47	1.80	58.3	1.04	62.4
	53	0.59	2.21	70.4	0.51	96.3
	54	0.61	2.15	93.6	0.45	102.5
	55	0.65	2.56	93.7	0.45	105.9
	56	0.80	2.12	65.2	0.50	148.6
	57	0.54	1.95	78.4	0.58	111.6
	58	0.52	2.19	73.5	0.46	69.3
	59	0.45	2.10	100.2	1.25	81.9
	60	0.52	1.85	66.9	0.80	75.4
	Mean	0.56	2.10	76.5	0.65	90.8
	sd	0.107	0.214	14.51	0.283	28.13

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Terminal kill

Group/ Dosage mg/kg/day	Animal no.	Spleen	Kidneys	Adrenals	Uterus	Ovaries
		g	g	mg	g	mg
3♀ 250	61	0.66	1.97	63.9	0.49	73.7
	62	0.47	1.83	59.6	0.42	81.7
	63	0.52	2.03	69.6	0.78	88.6
	64	0.63	2.10	77.1	0.50	82.1
	65	0.49	2.10	81.9	1.23	88.0
	66	0.52	2.06	65.7	0.65	71.9
	67	0.60	2.25	75.7	0.48	100.2
	68	0.59	2.00	99.6	1.03	102.8
	69	0.68	2.16	99.3	0.62	79.0
	70	0.55	2.35	86.3	0.60	62.3
	Mean sd		0.57 0.073	2.09 0.147	77.9 14.02	0.68 0.263
4♀ 1000	71	0.40	2.14	87.0	0.70	77.6
	72	0.56	2.26	95.4	0.40	81.5
	73	0.53	2.08	76.7	0.61	80.8
	74	0.73	3.19	112.6	0.75	108.7
	75	0.50	2.79	94.3	0.62	84.0
	76	0.52	2.09	92.1	0.54	93.2
	77	0.49	2.18	78.5	0.82	92.9
	78	0.60	2.52	103.4	1.05	120.4
	79	0.65	2.16	75.5	0.72	100.2
	80	0.48	2.09	102.4	0.36	103.5
	Mean sd		0.55 0.093	2.35 0.375	91.8 12.44	0.66 0.203

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Recovery kill

Group/ dosage mg/kg/day	Animal no.	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g	
1♂ Control	121	470	2.13	12.2	16.1	1.43	18.9	
	122	411	1.84	8.3	11.7	1.52	17.7	
	123	619	2.08	10.8	20.3	1.78	29.2	
	124	490	1.94	11.3	20.7	1.80	21.1	
	125	534	2.07	13.0	24.0	1.68	25.8	
	126	522	1.97	10.6	17.5	1.74	19.9	
	127	443	1.97	9.7	25.8	1.25	15.6	
	128	630	2.13	10.2	24.0	1.79	27.9	
	129	503	1.87	11.0	31.4	1.43	20.4	
	130	641	2.08	13.9	28.4	1.84	28.7	
	Mean		526	2.01	11.1	22.0	1.63	22.5
	sd		80.0	0.105	1.62	5.94	0.203	4.95
	4♂ 1000	131	584	1.96	10.9	25.9	2.00	30.7
132		536	2.04	10.5	19.2	1.54	23.0	
133		572	2.05	13.2	31.0	1.74	25.3	
134		474	1.97	11.7	21.1	1.44	18.7	
135		590	2.20	15.0	31.9	1.91	28.9	
136		555	1.96	12.7	21.0	1.63	25.0	
137		560	2.13	10.4	28.0	1.91	29.9	
138		510	1.91	11.3	22.8	1.61	22.2	
139		578	1.90	11.3	28.5	1.63	26.6	
140		544	2.12	10.8	23.4	1.97	29.4	
Mean			550	2.02	11.8	25.3	1.74	26.0
sd		36.1	0.102	1.45	4.44	0.197	3.90	

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Recovery kill

Group/ dosage mg/kg/day	Animal no.	Body wt g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g
1♀ Control	141	238	1.70	8.7	14.5	0.92	10.0
	142	306	1.90	11.5	17.7	0.96	12.8
	143	208	1.83	10.2	16.0	0.86	9.6
	144	334	1.81	14.3	25.7	1.30	13.3
	145	335	1.88	13.5	20.3	1.27	13.8
	146	274	1.89	14.7	23.6	1.01	9.5
	147	345	1.90	19.4	21.6	1.33	14.3
	148	297	1.78	13.8	16.6	1.02	11.7
	150	343	1.86	17.3	24.2	1.18	14.4
	Mean	298	1.84	13.7	20.0	1.09	12.2
	sd	49.1	0.067	3.33	4.01	0.179	2.04
4♀ 1000	151	251	1.83	14.9	16.0	0.80	9.5
	152	294	1.88	12.8	24.1	0.95	10.9
	153	290	1.93	17.1	16.4	1.06	10.9
	154	265	1.84	11.6	14.7	1.26	9.2
	155	296	1.82	13.1	22.0	1.18	13.7
	156	308	1.87	12.8	22.7	0.98	13.0
	157	316	1.97	11.7	21.4	1.07	12.5
	158	288	1.99	11.6	16.9	1.03	12.1
	159	353	1.93	16.5	20.7	1.22	14.1
	160	307	1.94	13.8	22.3	1.03	13.9
	Mean	297	1.90	13.6	19.7	1.06	12.0
sd	28.0	0.061	1.99	3.36	0.136	1.79	

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Recovery kill

Group/ dosage mg/kg/day	Animal no.	Spleen	Kidneys	Adrenals	Prostate	Testes		Seminal Vesicles g	Epididymides		
		g	g	mg	g	L g	R g		Left g	Right g	
1♂ Control	121	0.63	3.26	65.4	1.065	1.909	1.943	0.99	0.700	0.734	
	122	0.59	2.72	49.5	0.828	1.877	1.772	1.64	0.661	0.676	
	123	0.94	3.87	77.9	0.879	1.715	1.662	0.96	0.652	0.633	
	124	0.57	3.30	82.1	0.957	1.816	1.830	1.27	0.647	0.658	
	125	1.03	3.87	68.2	1.389	1.756	1.715	1.44	0.778	0.736	
	126	0.62	3.52	46.3	1.279	2.204	2.181	1.77	0.706	0.764	
	127	0.65	2.76	51.3	1.090	1.799	1.859	1.06	0.724	0.722	
	128	0.79	3.85	59.9	1.080	1.857	1.835	1.92	0.788	0.689	
	129	0.71	3.34	58.5	1.062	1.781	1.783	1.00	0.662	0.621	
	130	0.88	4.43	69.4	1.101	1.872	1.792	1.11	0.628	0.693	
	Mean		0.74	3.49	62.9	1.073	1.859	1.837	1.31	0.695	0.693
	sd		0.160	0.533	11.96	0.1682	0.1354	0.1433	0.355	0.0552	0.0468
	4♂ 1000	131	1.01	4.88	56.2	1.124	1.781	1.794	0.98	0.644	0.689
132		0.73	3.43	53.9	1.311	1.671	1.716	1.14	0.604	0.721	
133		0.79	4.81	67.2	1.541	1.935	1.931	1.56	0.806	0.775	
134		0.57	3.73	52.5	1.115	1.764	1.783	1.81	0.599	0.668	
135		0.98	4.19	78.8	1.199	2.287	1.947	0.80	0.777	0.790	
136		0.61	4.03	64.3	1.014	1.899	1.901	1.49	0.723	0.686	
137		0.87	4.81	59.6	0.898	1.992	1.973	0.83	0.725	0.746	
138		0.63	3.49	85.5	0.866	1.708	1.682	1.31	0.646	0.641	
139		0.71	4.01	54.4	1.218	2.075	1.776	1.01	0.528	0.700	
140		0.95	4.88	70.4	0.877	1.972	2.048	1.84	0.720	0.733	
Mean			0.78	4.23	64.3	1.116	1.908	1.855	1.28	0.677	0.720
sd		0.161	0.583	11.25	0.2144	0.1875	0.1211	0.385	0.0873	0.0517	

sd Standard deviation

APPENDIX 8

(Organ weights - continued)

Recovery kill

Group/ dosage mg/kg/day	Animal no.	Spleen	Kidneys	Adrenals	Uterus	Ovaries
		g	g	mg	g	mg
1♀ Control	141	0.37	1.92	71.6	0.44	82.4
	142	0.44	1.96	83.8	0.56	96.2
	143	0.36	1.69	50.8	0.50	59.0
	144	0.56	2.27	92.9	0.58	118.6
	145	0.46	2.19	71.4	0.60	93.4
	146	0.44	2.22	66.1	0.62	68.9
	147	0.68	3.04	126.4	0.77	58.5
	148	0.56	2.30	88.7	0.61	97.7
	150	0.55	2.83	91.9	0.58	42.9
		Mean sd	0.49 0.105	2.27 0.428	82.6 21.45	0.59 0.091
4♀ 1000	151	0.47	2.04	73.0	0.61	58.5
	152	0.49	2.00	92.3	0.85	102.0
	153	0.45	2.15	85.8	0.60	85.4
	154	0.51	2.01	75.3	0.64	117.3
	155	0.55	2.50	91.0	0.62	80.8
	156	0.59	2.49	93.1	0.47	110.0
	157	0.66	2.38	85.4	0.69	89.9
	158	0.54	2.32	91.9	0.56	76.7
	159	0.78	3.18	82.6	0.57	130.1
	160	0.53	2.35	84.2	0.65	62.4
	Mean sd	0.56 0.097	2.34 0.350	85.5 7.04	0.63 0.098	91.3 23.37

sd Standard deviation

APPENDIX 9

Individual clinical and pathological findings

In this appendix the clinical, macroscopic and microscopic findings relating to each animal are listed.

The microscopic pathology was carried out by two pathologists. The initial examination was undertaken by the study pathologist, the results of which were then subjected to a routine peer review by a second pathologist. The diagnoses reported here represent the consensus opinions of both pathologists.

Study Pathologist: John M Offer, Ph.D., C.Biol., M.I.Biol.,
Consultant Pathologist
Department of Pathology

Peer Review: Chirukandath Gopinath, B.V.Sc., M.V.Sc., Ph.D., F.R.C.Path.,
Director of Pathology

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 1♂ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and poor grooming were noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Tail

Brown stained

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Trace)
Haemosiderosis: (Minimal)

Liver

Extramedullary haemopoiesis: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 1♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver (ORO stain); Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach (W N L); Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain. Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 2♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of hair loss was noted.

MACROSCOPIC FINDINGS

Skin Alopecia
Forelimb/s

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Trace)
Haemosiderosis: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric
Liver; Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum
Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 3♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Testes

Small
Blue: (Minimal)

Epididymides

Small

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Urinary Bladder

Intra-luminal plug of refluxed seminal colloid

Prostate

Focal interstitial lymphoid aggregations: (Minimal)

Epididymides

Reduced numbers of spermatozoa: (Marked , Bilateral)
Abnormal spermatogenic cells in ducts

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 3♂ - continued

MICROSCOPIC FINDINGS - continued

Testes

Seminiferous tubular atrophy: (Marked , Bilateral)

Rectum

Nematodes in lumen

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver; Liver (ORO stain); Pancreas; Kidneys; Seminal Vesicles; Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum. Colon; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 4♂ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Tail

Brown stained: (Minimal)

Lymph Nodes - Cervical

Enlarged: 6mm

Skeletal Muscle

Mass/es: (One) right thoracic region, A: 13x7x5mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Trace)

Pituitary

Focal vacuolation - pars distalis: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 4♂ - continued

MICROSCOPIC FINDINGS - continued

Skeletal Muscle

Fibroma: (NEOPLASTIC , BENIGN , PRIMARY) (with hypercellular areas)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical : (W.N.L.); Lymph Nodes - Mesenteric; Liver; Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids; Parathyroids; Adrenals; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 5♂ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges, prominent vertebrae and red genital discharge were noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)

Haemosiderosis: (Trace)

Liver

Hepatocyte necrosis - focal: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 6♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of hair loss was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Skin Alopecia

Forelimb/s: (Right , Minimal , Diffuse)

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Trace)

Kidneys

Interstitial inflammatory cell infiltration: (Minimal , Focal)

Prostate

Focal interstitial lymphoid aggregations: (Minimal)

Adrenals

Diffuse cellular vacuolation - zona fasciculata: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 6♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver : (W.N.L.); Liver (ORO stain); Pancreas; Urinary Bladder; Seminal Vesicles;
Epididymides; Testes; Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach;
Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone
Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 7♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lungs

Congested: (Minimal , Patchy)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Trace)

Haemosiderosis: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

Adrenals

Diffuse cellular vacuolation - zona fasciculata: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 7♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver;
Liver (ORO stain); Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes;
Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum;
Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 8♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Adrenals

Diffuse cellular vacuolation - zona fasciculata: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Prostate; Seminal Vesicles;
Epididymides; Testes; Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach;
Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone
Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 9♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of brown fur staining was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Brown)
Coarse - dorsum

Tail

Brown stained: (Minimal)

Spleen

Enlarged: (Minimal) 1.890g
Pale subcapsular area/s: (A few , Punctate)

Stomach Corpus Mucosa

A white nodule, near to limiting ridge: (Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)
Congestion: (Minimal)

Liver

Extramedullary haemopoiesis: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 9♂ - continued

MICROSCOPIC FINDINGS - continued

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

Urinary Bladder

Intra-luminal plug of refluxed seminal colloid

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric. Liver (ORO stain); Pancreas; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach : (W.N.L.); Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 10♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Liver

Enlarged: 30.575g

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Trace)
Haemosiderosis: (Minimal)

Liver

Sinusoidal dilatation/congestion: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 10♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Pancreas; Kidneys; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes. Thyroids;
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum;
Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 11♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur
Coarse - dorsum: (Minimal)

Liver
Median cleft, pale subcapsular area/s: (One , Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Increased numbers of alveolar macrophages: (Minimal , Focal)

Kidneys
Cortical tubules with eosinophilic inclusions: (Minimal)

The following tissues were considered normal:

Liver : (W.N.L.); Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 12♂ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and poor grooming were noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Lungs

Petechiae: (A few)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal , Focal)

Liver

Sinusoidal dilatation/congestion: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

The following tissues were considered normal:

Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 13♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur
Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Liver
Enlarged: 32.116g

Kidneys
Enlarged: 5.088g

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)

Liver
Sinusoidal dilatation/congestion: (Minimal)

Kidneys
Cortical tubules with eosinophilic inclusions: (Moderate)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 13♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 14♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum

Testes

Small: (Right)

Blue: (Right)

Epididymides

Small: (Right)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

Epididymides

Reduced numbers of spermatozoa: (Moderate , Unilateral)

Testes

Seminiferous tubular atrophy: (Marked , Unilateral)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 14♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 15♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum: (Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Extramedullary haemopoiesis: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)

The following tissues were considered normal:

Lungs; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 1016♂ (Terminal)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 17♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lungs

Petechiae: (A few)

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Hepatocyte vacuolation - median cleft: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

The following tissues were considered normal:

Lungs : (W.N.L.); Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 18♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: (Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals; Stomach : (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 19♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 20♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur
Coarse - dorsum

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys
Cortical tubules with eosinophilic inclusions: (Minimal)
Dilatation of the renal pelvis: (Minimal , Unilateral)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 21♂ (Terminal)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

MACROSCOPIC FINDINGS

Fur
Coarse - dorsum: (Minimal)

Liver
Median cleft, pale subcapsular area/s. (One) 2mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver
Extramedullary haemopoiesis: (Minimal)
Hepatocyte vacuolation - median cleft: (Minimal , Focal)

Kidneys
Cortical tubules with eosinophilic inclusions: (Moderate)

The following tissues were considered normal:

Lungs: Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 22♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 23♂ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and hair loss were noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Skin Alopecia

Forelimb/s: (Minimal)

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

Kidneys

Enlarged: 5.603g
Pale

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules - basophilic: (Minimal)
Cortical tubules - dilated: (Minimal , Focal)
Interstitial inflammatory cell infiltration: (Minimal)
Cortical tubules with eosinophilic inclusions: (Moderate)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 23♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Lungs; Liver : (W.N.L.); Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 24♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum: (Minimal)

Liver

Lobe/s missing: anterior caudate

Adhesions: left lobe to adipose tissue

Testes

Enlarged: (Left) 4.089g

Blue: (Right)

White subtunical striae: (Left)

Epididymides

Small: (Right)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Capsular adhesion

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)

Cortical tubules - basophilic: (Minimal)

Epididymides

Spermatozoa absent: (Unilateral)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 24♂ - continued

MICROSCOPIC FINDINGS - continued

Testes

Seminiferous tubular atrophy: (Marked , Bilateral)

Spermatocele in rete testis

Interstitial oedema: (Moderate , Unilateral)

The following tissues were considered normal:

Lungs; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 25♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur
Coarse - dorsum: (Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys
Cortical tubules with eosinophilic inclusions: (Moderate)
Cortical tubules - basophilic: (Minimal)
Cortical tubules with cellular debris casts: (Trace)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 26♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Liver

Median cleft, pale subcapsular area/s: (One , Punctate)

Stomach Antrum Mucosa

White nodules, near to limiting ridge: (Two) 1mm and punctate

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Lungs; Liver : (W.N.L.); Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 27♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Liver

Subcapsular cyst/s: (One) median lobe, 5mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Subcapsular cyst

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)

Cortical tubules - basophilic: (Minimal)

The following tissues were considered normal:

Lungs; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 28♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum: (Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 29♂ (Terminal)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 30♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)
Cortical tubules - basophilic: (Minimal)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 31♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.
Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Trace)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Marked)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver (ORO stain); Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides;
Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum;
Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 32♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.
Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum: (Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Hepatocyte necrosis - focal: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 32♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids;
Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum;
Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Tissues not available for examination were:

Parathyroids : (Not seen)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 33♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Tail

Brown stained: (Minimal)

Liver

Enlarged: 29.765g

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Trace)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)
Extramedullary haemopoiesis: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)
Cortical tubules - basophilic: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 33♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver (ORO stain); Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 34♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver;
Liver (ORO stain); Pancreas; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids;
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Duodenum; Jejunum; Ileum;
Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 35♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1, persisting for up to one hour after dosing on one occasion during Week 13.

Incidental findings of tail ridges, right eye damaged, hair loss and red periorbital staining right eye were noted.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum: (Minimal)
Encrusted - periorbital region/s: (Right . Black)

Eyes

Damaged: (Right)

Liver

Enlarged: 31.593g
Median cleft, pale subcapsular area/s: (One) 1mm

Adrenals

Enlarged: 94.1mg

Skeletal Muscle

Haemorrhage - periorbital region/s: (Right)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Pneumonitis: (Minimal , Focal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 35♂ - continued

MICROSCOPIC FINDINGS - continued

Heart

Myocarditis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Cortical tubules with eosinophilic inclusions: (Marked)
Cortical tubules - basophilic: (Minimal)
Cortical tubules with cellular debris casts (Trace)

Urinary Bladder

Intra-luminal plug of refluxed seminal colloid

Adrenals

Increased width of zona fasciculata: (Minimal)

Skeletal Muscle

Haemorrhage: (Moderate) (periorbital region)

Eyes

Keratitis: (Moderate , Unilateral)
Uveitis: (Moderate , Unilateral)

The following tissues were considered normal:

Trachea; Aorta; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric (W.N.L.); Pancreas; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids (One node); Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 36♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Cortical tubules with eosinophilic inclusions: (Marked)
Cortical tubules - basophilic: (Minimal)
Cortical tubules with cellular debris casts: (Minimal)

Adrenals

Diffuse cellular vacuolation - zona fasciculata: (Minimal)

Rectum

Nematodes in lumen

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 36♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric.
Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids.
Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum. Ileum.
Caecum; Colon; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 37♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Brown perioral staining immediately after dosing was noted on one occasion during Week 12. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 13.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS**Fur**

Coarse - dorsum: (Minimal)

Lymph Nodes - Cervical

Enlarged: 7mm

Liver

Enlarged: 39.278g

Median cleft, pale subcapsular area/s: (One) 1mm

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

Kidneys

Enlarged: 5.768g

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical

Increased cellularity - generalised: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 37♂ - continued

MICROSCOPIC FINDINGS - continued

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)
Hepatocyte vacuolation - median cleft: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Marked)
Cortical tubules - basophilic: (Minimal)

Prostate

Focal interstitial lymphoid aggregations: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Mesenteric; Liver (ORO stain);
Pancreas; Urinary Bladder; Seminal Vesicles; Epididymides; Testes; Thyroids; Adrenals;
Pituitary; Salivary Glands; Oesophagus; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum;
Sciatic Nerve; Brain; Bone Marrow/sternum

Tissues not available for examination were:

Parathyroids : (Not seen)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 38♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.

MACROSCOPIC FINDINGS

Fur

Coarse - dorsum: (Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Trace)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Marked)
Cortical tubules - basophilic: (Minimal)

Rectum

Nematodes in lumen

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 38♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver (ORO stain); Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes;
Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum;
Jejunum; Ileum; Caecum; Colon; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 39♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Noisy respiration one hour after dosing was noted on one occasion during Week 1.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Lungs

Petechiae: (A few)

Liver

Enlarged: 29.463g

Kidneys

Increased pelvic dilatation: (Right , Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 39♂ - continued

MICROSCOPIC FINDINGS - continued

Kidneys

Cortical tubules with eosinophilic inclusions: (Moderate)

Cortical tubules - basophilic: (Minimal)

Dilatation of the renal pelvis: (Minimal , Unilateral)

Adrenals

Diffuse cellular vacuolation - zona fasciculata: (Minimal)

The following tissues were considered normal:

Trachea; Lungs : (W.N.L.); Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver (ORO stain); Pancreas; Urinary Bladder; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
 Dosage Level: 1000 mg/kg/day
 Rat No/Sex: 40♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Brown perioral staining and half closed eyelids immediately after dosing were noted on one occasion during Weeks 12 and 13. Body jerks immediately after dosing were noted on one occasion during Week 13.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lymph Nodes - Cervical
 Enlarged: 9mm

Liver
 Enlarged: 38.769g

Stomach Antrum Mucosa
 A white nodule, near to limiting ridge: 1mm

Kidneys
 Enlarged: 5.046g

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical
 Increased cellularity - generalised: (Minimal)

Spleen
 Extramedullary haemopoiesis: (Minimal)
 Haemosiderosis: (Trace)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 40♂ - continued

MICROSCOPIC FINDINGS - continued

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Cortical tubules with eosinophilic inclusions: (Marked)

Cortical tubules - basophilic: (Minimal)

Urinary Bladder

Intra-luminal plug of refluxed seminal colloid

Adrenals

Diffuse cellular vacuolation - zona fasciculata: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Mesenteric; Pancreas; Prostate; Seminal Vesicles; Epididymides; Testes; Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach : (W.N.L.); Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 41 ♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

Uterus

Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Trace)
Haemosiderosis: (Trace)

Uterus

Luminal dilatation: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 41♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric.
Liver; Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Cervix; Ovaries; Thyroids.
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Duodenum; Jejunum. Ileum.
Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 42♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and hair loss were noted.

MACROSCOPIC FINDINGS

Skin Alopecia

Forelimb/s: (Minimal , Diffuse)
Left ventral cervical region: (Minimal , Diffuse)

Lungs

Petechiae: (A few)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Pneumonitis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

The following tissues were considered normal:

Trachea; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver.
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids.
Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum. Ileum.
Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 42♀ - continued

MICROSCOPIC FINDINGS - continued

Tissues not available for examination were:

Parathyroids : (Not seen)

Pathologist: J.M.Offer

APPENDIX 9
(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 43♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Uterus

Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Extramedullary haemopoiesis: (Minimal)

Uterus

Luminal dilatation: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Cervix; Ovaries; Thyroids
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum
Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 44♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and hair loss were noted.

MACROSCOPIC FINDINGS

Skin Alopecia
Forelimb/s: (Minimal , Diffuse)

Liver
Median cleft, pale subcapsular area/s: (One , Punctate)

Uterus
Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen
Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Uterus
Luminal dilatation: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 44♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver : (W.N.L.); Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Cervix; Ovaries;
Thyroids; Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum;
Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 45♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS

Fur
Stained - cranial region: (Minimal , Brown)

Lymph Nodes - Cervical
Enlarged: 6mm

Adrenals
Enlarged: 93.8mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical
Increased cellularity - generalised: (Minimal)

Spleen
Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver
Hepatocyte vacuolation - periportal: (Minimal)

Liver (ORO stain)
Periportal fat deposition: (Minimal)

Adrenals
Sinusoidal congestion: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 45♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Mesenteric; Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 46♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge. (Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical

Increased cellularity - generalised: (Minimal)

Spleen

Extramedullary haemopoiesis: (Minimal)

Haemosiderosis: (Trace)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 46♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Mesenteric; Liver; Pancreas; Kidneys;
Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Parathyroids; Adrenals; Pituitary; Salivary
Glands; Oesophagus; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain;
Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 47♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

Uterus

Fluid distension: 4mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)

Haemosiderosis: (Trace)

Uterus

Luminal dilatation: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver; Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Cervix; Ovaries;
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach;
Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain;
Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 48♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Trace)

Liver

Extramedullary haemopoiesis: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric.
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids.
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum.
Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 49♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Adrenals

Enlarged: 101.5mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Extramedullary haemopoiesis: (Minimal)

Adrenals

Increased width of zona fasciculata: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids;
Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum;
Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 50♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Trace)

Liver

Hepatocyte vacuolation - periportal: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 50♀ - continued

MICROSCOPIC FINDINGS - continued

Tissues not available for examination were:

Parathyroids : (Not seen)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 51♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 52♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Uterus

Fluid distension: 4mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Pneumonitis: (Minimal , Focal)

Liver

Extramedullary haemopoiesis: (Minimal)

Uterus

Luminal dilatation: (Minimal)

The following tissues were considered normal:

Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 53♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges, hair loss and brown fur staining were noted.

MACROSCOPIC FINDINGS

Skin Alopecia

Forelimb/s: (Minimal , Diffuse)
Right thoracic region: (Minimal , Diffuse)

Liver

Median cleft, pale subcapsular area/s: (One , Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs; Liver : (W.N.L.); Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 54♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lungs

Congested: (Minimal , Patchy)

Adrenals

Enlarged: 93.6mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal , Focal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Adrenals

Sinusoidal dilatation: (Minimal , Unilateral)

The following tissues were considered normal:

Liver; Kidneys

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 55♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

White nodules, near to limiting ridge (Two) 1mm

Adrenals

Enlarged: 93.7mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Adrenals

Sinusoidal dilatation: (Minimal , Unilateral)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 56♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and hair loss were noted.

MACROSCOPIC FINDINGS

Skin Alopecia

Forelimb/s: (Right)

Ovaries

Clear fluid distension - periovarian sac: (Left) 5mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Ovaries : (W.N.L.); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 57♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and hair loss were noted.

MACROSCOPIC FINDINGS

Skin Alopecia

Forelimb/s: (Minimal , Diffuse)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 58♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges, hair loss and brown fur staining were noted.

MACROSCOPIC FINDINGS

Fur
Stained - cranial region: (Minimal , Brown)

Skin Alopecia
Forelimb/s

Liver
Median cleft, pale subcapsular area/s: (One , Punctate)

Uterus
Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)

Uterus
Luminal dilatation: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 58♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver : (W.N.L.); Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 59♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Adrenals
Enlarged: 100.2mg

Uterus
Fluid distension: 4mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Uterus
Luminal dilatation: (Minimal)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals : (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 60♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Uterus

Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Uterus

Luminal dilatation: (Minimal)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 61 ♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS

Fur

Stained - cranial region: (Minimal , Brown)
Stained - cervical region/s: (Dorsal , Minimal , Brown)

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 62♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

MACROSCOPIC FINDINGS

Liver

Adhesions: median cleft, and median cleft to adipose tissue

Stomach Antrum Mucosa

White nodules, near to limiting ridge: (Two) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Extramedullary haemopoiesis: (Minimal)
Capsular adhesion

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa:
(Multiple)

The following tissues were considered normal:

Lungs; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 63♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

MACROSCOPIC FINDINGS

Liver

Median cleft, pale subcapsular area/s: (One , Punctate)

Uterus

Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Uterus

Luminal dilatation: (Minimal)

The following tissues were considered normal:

Lungs; Liver : (W.N.L.); Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 64♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

White nodules, near to limiting ridge: (Two) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver (ORO stain)

Periportal fat deposition: (Trace)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa:
(Multiple)

The following tissues were considered normal:

Lungs; Liver; Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 65♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

MACROSCOPIC FINDINGS

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

Uterus

Fluid distension: 4mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Uterus

Luminal dilatation: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Lungs; Liver : (W.N.L.); Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 66♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 67♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 68♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lungs

Pale subpleural focus/i: (A few , Punctate)

Adrenals

Enlarged: 99.6mg

Uterus

Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Uterus

Luminal dilatation: (Minimal)

Adrenals

Sinusoidal dilatation: (Minimal)

The following tissues were considered normal:

Lungs : (W.N.L.); Liver; Liver (ORO stain); Kidneys

Pathologist: J.M.Offer

APPENDIX 9
(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 69♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS

Fur
Stained - cranial region: (Minimal , Brown)

Adrenals
Enlarged: 99.3mg

Kidneys
Increased pelvic dilatation: (Right , Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys
Dilatation of the renal pelvis: (Minimal , Unilateral)

Adrenals
Sinusoidal congestion: (Minimal)

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 70♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs; Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 71♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Trace)

Haemosiderosis: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric.
Liver; Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Parathyroids.
Adrenals; Pituitary; Salivary Glands; Oesophagus; Duodenum; Jejunum; Ileum; Caecum. Colon.
Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 72♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 2.

MACROSCOPIC FINDINGS

Adrenals

Enlarged: 95.4mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Trace)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

Kidneys

Interstitial inflammatory cell infiltration: (Minimal , Focal)

Adrenals

Increased width of zona fasciculata: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 72♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver (ORO stain); Pancreas; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Parathyroids;
Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon;
Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
 Dosage Level: 1000 mg/kg/day
 Rat No/Sex: 73♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Noisy respiration immediately after dosing was noted on one occasion during Week 1. Half closed eyelids immediately after dosing was noted on one occasion during Week 12.

MACROSCOPIC FINDINGS

Lungs

Congested: (Patchy)

Liver

Median cleft, pale subcapsular area/s: (One . Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
 Haemosiderosis: (Trace)

The following tissues were considered normal:

Trachea; Lungs : (W.N.L.); Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver : (W.N.L.); Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 73♀ - continued

MICROSCOPIC FINDINGS - continued

Tissues not available for examination were:

Parathyroids : (Not seen)

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 74♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.
Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS**Stomach Antrum Mucosa**

A white nodule, near to limiting ridge: 1mm

Adrenals

Enlarged: 112.6mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)

Haemosiderosis: (Trace)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

Uterus

Luminal dilatation: (Minimal)

Adrenals

Increased width of zona fasciculata: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 74♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Cervix; Ovaries; Thyroids;
Parathyroids; Pituitary; Salivary Glands; Oesophagus; Duodenum; Jejunum; Ileum; Caecum;
Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
 Dosage Level: 1000 mg/kg/day
 Rat No/Sex: 75♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 13.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

White nodules, near to limiting ridge (Three) 1mm

Adrenals

Enlarged: 94.3mg

Kidneys

Increased pelvic dilatation: (Right , Moderate)

Ureters

Distended: (Right) 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Trace)

Haemosiderosis: (Trace)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 75♀ - continued

MICROSCOPIC FINDINGS - continued

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Dilatation of the renal pelvis: (Moderate , Unilateral)

Free blood in renal pelvis: (Unilateral)

Ureters

(One only)

Luminal dilatation: (Minimal)

Adrenals

Increased width of zona fasciculata: (Minimal)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Pancreas; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 76♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.
Incidental finding of brown fur staining was noted.

MACROSCOPIC FINDINGS

Fur

Stained - cranial region: (Minimal , Brown)

Lungs

Pale subpleural focus/i: (A few , Punctate)

Adrenals

Enlarged: 92.1mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Pneumonitis: (Minimal , Focal)

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Trace)

Liver

Extramedullary haemopoiesis: (Minimal)

Adrenals

Increased width of zona fasciculata: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 76♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric; Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids; Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 77♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Unsteady gait immediately after dosing was noted on one occasion during Week 9.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lymph Nodes - Cervical
Enlarged: 6mm

Uterus
Fluid distension: 3mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical
Increased cellularity - generalised: (Minimal)

Spleen
Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver
Hepatocyte hypertrophy - centrilobular: (Minimal)

Uterus
Luminal dilatation: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 77[♀] - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Mesenteric; Liver (ORO stain);
Pancreas; Kidneys; Urinary Bladder; Cervix; Ovaries; Thyroids; Parathyroids; Adrenals;
Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon;
Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 78♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1.

MACROSCOPIC FINDINGS

Adrenals

Enlarged: 103.4mg

Uterus

Fluid distension: 4mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Pyelitis: (Minimal , Unilateral)

Uterus

Luminal dilatation: (Minimal)

Adrenals

Increased width of zona fasciculata: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 78♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Pancreas; Urinary Bladder; Cervix; Ovaries; Thyroids; Parathyroids; Pituitary; Salivary Glands;
Oesophagus; Stomach; Duodenum; Jejunum; Ileum; Caecum; Colon; Rectum; Sciatic Nerve;
Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 79♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 2.
Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids
Parathyroids; Adrenals; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum
Ileum; Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 80♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs and half closed eyelids immediately after dosing were noted on one occasion during Week 12

MACROSCOPIC FINDINGS

Liver

Median cleft, pale subcapsular area/s: (One , Punctate)

Adrenals

Enlarged: 102.4mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Spleen

Extramedullary haemopoiesis: (Minimal)
Haemosiderosis: (Minimal)

Liver

Hepatocyte hypertrophy - centrilobular: (Minimal)
Sinusoidal dilatation/congestion: (Minimal)

Adrenals

Increased width of zona fasciculata: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 80♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Trachea; Lungs; Aorta; Heart; Thymus; Lymph Nodes - Cervical; Lymph Nodes - Mesenteric;
Liver (ORO stain); Pancreas; Kidneys; Urinary Bladder; Uterus; Cervix; Ovaries; Thyroids;
Parathyroids; Pituitary; Salivary Glands; Oesophagus; Stomach; Duodenum; Jejunum; Ileum;
Caecum; Colon; Rectum; Sciatic Nerve; Brain; Bone Marrow/sternum

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 81♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 82♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 83♂ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and scab formation were noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 84♂ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 85♂ (Terminal)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Fibres (C); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Tissues not available for examination were:

Dorsal Root Ganglion (L) : (Not seen)
Dorsal Root Fibres (L) : (Not seen)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 86♂

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 87♂

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 88♂

CLINICAL FINDINGS

Incidental findings of tail ridges and red urogenital discharge were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 89♂

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 90♂

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 91♂

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 92♂

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 93♂

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 94♂

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 95♂

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 96♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Half closed eyelids immediately after dosing was noted on one occasion during Week 11. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 13.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6).
Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L).
Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres
(L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 97♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Half closed eyelids and collapsed posture immediately after dosing were noted on one occasion during Week 13. Paddling of the forelimbs and body jerks immediately after dosing were noted on more than one occasion during Week 13.

Incidental finding of tail ridges was noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 98♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1, persisting for up to one hour after dosing on one occasion during Week 13. Unsteady gait immediately after dosing was noted on one occasion each in Weeks 9 - 11. Collapsed posture immediately after dosing was noted on one occasion during Week 10. Paddling of the forelimbs and body jerks immediately after dosing were noted on more than one occasion during Week 13.

Incidental findings of tail ridges and hair loss were noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M. Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 99♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on more than one occasion during Week 13.

Incidental finding of tail ridges was noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 100♂ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 11. Collapsed posture immediately after dosing was noted on one occasion during Week 12.

MICROSCOPIC FINDINGS

The following tissues were considered normal

Forebrain/cerebrum; Midbrain: Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia. Dorsal Root Ganglion (C); Dorsal Root Ganglion (L). Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 101 ♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 102♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and ulceration were noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 103♀ (Terminal)

CLINICAL FINDINGS

Incidental findings of tail ridges and brown fur staining were noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6).
Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L).
Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres
(L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 104♀ (Terminal)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 105♀ (Terminal)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 106♀

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 107♀

CLINICAL FINDINGS

Incidental finding of tail ridges was noted

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 108♀

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 109♀

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 62.5 mg/kg/day
Rat No/Sex: 110♀

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 111♀

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 112♀

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment were noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 113♀

CLINICAL FINDINGS

Salivation immediately after dosing was noted on one occasion during Week 1.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 114♀

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 250 mg/kg/day
Rat No/Sex: 115♀

CLINICAL FINDINGS

Salivation immediately after dosing was noted on one occasion during Week 1.

Incidental finding of tail ridges was noted.

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 116♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 11.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 117[♀] (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted occasionally from Week 11.

MICROSCOPIC FINDINGS

The following tissues were considered normal

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 118♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on two occasions, in Weeks 11 and 13. Half closed eyelids immediately after dosing was noted on two occasions in Week 12. Collapsed posture immediately after dosing was noted on one occasion during Week 12.

Incidental finding of tail ridges was noted.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C1-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M. Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 119♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Collapsed posture immediately after dosing was noted on one occasion during Week 11. Paddling of the forelimbs immediately after dosing was noted on two occasions, in Weeks 11 and 13.

Incidental findings of base of tail firm and malaligned, and lower incisors pale were noted

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Forebrain/cerebrum; Midbrain; Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9
(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 120♀ (Terminal)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 13.

Incidental finding of hair loss was noted

MICROSCOPIC FINDINGS

The following tissues were considered normal.

Forebrain/cerebrum; Midbrain. Cerebellum And Pons; Medulla Oblongata; Spinal Cord (C3-6); Spinal Cord (L1-4); Gasserian Ganglia; Dorsal Root Ganglion (C); Dorsal Root Ganglion (L); Dorsal Root Fibres (C); Dorsal Root Fibres (L); Ventral Root Fibres (C); Ventral Root Fibres (L); Sciatic Nerve (Sciatic Notch); Sciatic Nerve (Mid-thigh); Sural Nerve; Tibial Nerve

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 121 ♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

The following tissues were considered normal:

Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 122♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Liver

Median cleft, pale subcapsular area/s: (One) 2mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

The following tissues were considered normal:

Liver : (W.N.L.); Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 123♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Liver

Median cleft, pale subcapsular area/s: (One , Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

The following tissues were considered normal:

Liver : (W.N.L.); Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 124♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lungs

Congested: (Minimal , Patchy)

Kidneys

Increased pelvic dilatation: (Left , Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal , Focal)

Kidneys

Dilatation of the renal pelvis: (Minimal , Unilateral)

The following tissues were considered normal:

Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 125♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

The following tissues were considered normal:

Liver: Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 126♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

The following tissues were considered normal:

Liver: Liver (ORO stain): Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 1273 (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted

MACROSCOPIC FINDINGS

Liver

Median cleft, pale subcapsular areas (One, Punctate)

All the other organs and tissues appeared normal

MICROSCOPIC FINDINGS

The following observations were noted

Liver

Extramedullary haemopoiesis: (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

The following tissues were considered normal:

Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
 Dosage Level: Control
 Rat No/Sex: 128♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
 Coarse - dorsum

Lungs

Petechiae: (A few)

Adipose Tissue

Torsioned nodule/s: (One) right epididymal, 32x23x11mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal , Focal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

Adipose Tissue

Fat necrosis: (Area) (Right epididymal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 128♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver; Adrenals : (One only)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 129♂ (Recovery)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted.

Liver (ORO stain)
Periportal fat deposition: (Trace)

The following tissues were considered normal:

Liver; Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 130♂ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)
Cortical tubules - basophilic: (Minimal)

The following tissues were considered normal:

Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
 Dosage Level: 1000 mg/kg/day
 Rat No/Sex: 131♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Unsteady gait immediately after dosing was noted on one occasion during Week 9. Body jerks, collapsed posture and half closed eyelids immediately after dosing were noted on one occasion during Week 12.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Fur
 Coarse - dorsum: (Minimal)

Lungs
 Petechiae: (A few)

Liver
 Enlarged: 30.729g

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
 Vascular congestion: (Minimal , Focal)

Liver
 Extramedullary haemopoiesis: (Minimal)

Kidneys
 Cortical tubules with eosinophilic inclusions: (Trace)
 Cortical tubules - basophilic: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 131♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
 Dosage Level: 1000 mg/kg/day
 Rat No/Sex: 132♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Collapsed posture immediately after dosing was noted on one occasion during Weeks 5 and 12. Body jerks immediately after dosing were noted on one occasion during Week 5. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 13.

MACROSCOPIC FINDINGS

Fur
 Coarse - dorsum: (Minimal)

Lungs
 Petechiae: (A few)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
 Vascular congestion: (Minimal , Focal)

Liver
 Extramedullary haemopoiesis: (Minimal)

Kidneys
 Cortical tubules with eosinophilic inclusions: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 132♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver (ORO stain); Adrenals

Pathologist: J.M. Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 133♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 12.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)
Cortical tubules - basophilic: (Minimal)

The following tissues were considered normal:

Liver; Liver (ORO stain); Adrenals

Pathologist: J.M. Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 134♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on two occasions, in Weeks 11 and 13.

MACROSCOPIC FINDINGS**Fur**

Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

Lymph Nodes - Cervical

Enlarged: 9mm

Liver

Median cleft, pale subcapsular area/s (One) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical

Increased cellularity - generalised: (Minimal)

Liver

Hepatocyte vacuolation - median cleft (Minimal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 134♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 135♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Collapsed posture and half closed eyelids immediately after dosing were noted on one occasion during Week 12.

MACROSCOPIC FINDINGS

Fur

Stained - dorsum: (Minimal , Brown)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys

Cortical tubules with eosinophilic inclusions: (Trace)
Cortical tubules - basophilic: (Minimal)

The following tissues were considered normal:

Liver: Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 136♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Unsteady gait immediately after dosing was noted on one occasion during Week 9. Half closed eyelids immediately after dosing was noted occasionally from Week 11. Collapsed posture immediately after dosing was noted on two occasions, in Weeks 11 and 13. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 12. Body jerks immediately after dosing was noted on one occasion during Week 13.

Incidental findings of tail ridges and hair loss were noted.

MACROSCOPIC FINDINGS

Skin Alopecia
Forelimb/s: (Left)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal.

Liver; Liver (ORO stain); Kidneys. Adrenals

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 137♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Unsteady gait immediately after dosing was noted on two occasions, in Weeks 8 and 9. Collapsed posture and half closed eyelids immediately after dosing were noted on more than one occasion during Week 11. Brown perioral staining and body jerks immediately after dosing were noted on two occasions, in Weeks 12 and 13.

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS**Lungs**

Petechiae: (A few)

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal, Focal)

Kidneys

Cortical tubules with eosinophilic inclusions: (Minimal)

Cortical tubules - basophilic: (Minimal)

Cortical tubules with cellular debris casts: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 137♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver : (W.N.L.); Liver (ORO stain); Adrenals

Pathologist: J.M. Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 138♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Collapsed posture immediately after dosing was noted on one occasion during Week 11. Half closed eyelids immediately after dosing was noted on more than one occasion during Week 11. Body jerks immediately after dosing were noted on more than one occasion in Week 13.

MACROSCOPIC FINDINGS

Fur
Stained - dorsum: (Minimal , Brown)
Coarse - dorsum

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Kidneys
Cortical tubules with eosinophilic inclusions: (Trace)
Cortical tubules - basophilic: (Minimal)

The following tissues were considered normal:

Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 139♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Unsteady gait immediately after dosing was noted on one occasion during Week 8. Collapsed posture immediately after dosing was noted on one occasion during Week 12.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

White nodules, near to limiting ridge: (Two) 1mm

Testes

Asymmetrical

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Testes

Seminiferous tubular atrophy: (Minimal , Bilateral)

Interstitial oedema: (Minimal , Unilateral)

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa:
(Multiple)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 139♂ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 140♂ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Unsteady gait immediately after dosing was noted on one occasion during Week 8. Half closed eyelids immediately after dosing was noted on two occasions, in Weeks 12 and 13. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 11. Collapsed posture and body jerks immediately after dosing were noted on one occasion during Week 13.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lymph Nodes - Cervical
Enlarged: 8mm

Lungs
Petechiae: (A few)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical
Increased cellularity - generalised: (Minimal)

The following tissues were considered normal:

Lungs : (W.N.L.); Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 141 ♀ (Recovery)

CLINICAL FINDINGS

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS

Fur

Stained - lumbar region: (Minimal . Brown)

Lungs

Pale subpleural focus/i: (A few . Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs : (W.N.L.); Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 142♀ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge: (Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Extramedullary haemopoiesis: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

Kidneys

Cortical tubules - basophilic: (Trace)

The following tissues were considered normal:

Adrenals; Stomach : (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 143♀ (Recovery)

CLINICAL FINDINGS

Emaciated appearance, lower incisors maloccluded, upper incisors missing, hunched posture. piloerection and hypersensitive behaviour were noted from Week 16.

MACROSCOPIC FINDINGS

Incisors

Broken: (Left , Upper)
Missing: (Right , Upper)
Overgrown: (Lower)

Adipose Tissue

Minimal

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Liver: Liver (ORO stain); Kidneys: Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 144♀ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Adrenals

Enlarged: 92.9mg

All the other organs and tissues appeared normal

MICROSCOPIC FINDINGS

The following observations were noted

Liver

Extramedullary haemopoiesis: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Trace)

The following tissues were considered normal:

Kidneys; Adrenals : (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 145♀ (Recovery)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MACROSCOPIC FINDINGS

Fur
Stained - lumbar region: (Minimal . Brown)

Liver
Median cleft, pale subcapsular area/s: (One) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver
Hepatocyte vacuolation - median cleft: (Minimal)

The following tissues were considered normal:

Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 146♀ (Recovery)

CLINICAL FINDINGS

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Eyes
Congested: (Left , Minimal)

Lungs
Pale subpleural focus/i: (A few , Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Vascular congestion: (Minimal , Focal)

Liver
Extramedullary haemopoiesis: (Minimal)

Eyes
Conjunctival haemorrhage, inflammation and oedema: (Moderate , Unilateral)

The following tissues were considered normal:

Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 147♀ (Recovery)

CLINICAL FINDINGS

Incidental findings of tail ridges and left eye damaged were noted.

MACROSCOPIC FINDINGS

Eyes

Damaged: (Left)

Adrenals

Enlarged: 126.4mg

Ovaries

No corpora lutea visible

Skeletal Muscle

Haemorrhage - periorbital region/s: (Left)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Hepatocyte vacuolation - periportal: (Minimal)

Liver (ORO stain)

Periportal fat deposition: (Minimal)

Ovaries

Absence of corpora lutea

Skeletal Muscle

Haemorrhage: (Moderate) (Periorbital)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 147♀ - continued

MICROSCOPIC FINDINGS - continued

Eyes

Conjunctival haemorrhage, inflammation and oedema: (Moderate , Unilateral)

The following tissues were considered normal:

Kidneys; Adrenals : (W.N.L.)

Pathologist: J.M. Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 148♀ (Recovery)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 149♀ (Intercurrent)

CLINICAL FINDINGS

Week of death 18

No signs of ill health or behavioural change were noted.

Died during routine blood sampling procedures.

MACROSCOPIC FINDINGS

Died during routine bleed

Thoracic Cavity
Smelt of ether

Lungs
Congested: (Minimal)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Vascular congestion: (Minimal)

Factors Contributory To Death
Accident

The following tissues were considered normal:

Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9
(Pathology - continued)

Compound: DPTB
Dosage Level: Control
Rat No/Sex: 150♀ (Recovery)

CLINICAL FINDINGS

No signs of ill health or behavioural change were noted.

MACROSCOPIC FINDINGS

Stomach Antrum Mucosa

A white nodule, near to limiting ridge 1mm

Adrenals

Enlarged: 91.9mg

Kidneys

Increased pelvic dilatation: (Right . Minimal)

Ovaries

No corpora lutea visible

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver (ORO stain)

Periportal fat deposition: (Trace)

Ovaries

Absence of corpora lutea

Stomach

Focus of ectopic non-glandular epithelium within the glandular mucosa

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 150♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver; Kidneys : (W.N.L.); Adrenals : (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 151 ♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on two occasions, in Weeks 12 and 13. Body jerks immediately after dosing was noted on one occasion during Week 13.

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS

Lungs

Pale subpleural focus/i: (A few , Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs : (W.N.L.); Liver: Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 152♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 2. Paddling of the forelimbs immediately after dosing was noted on more than one occasion in Week 13.

MACROSCOPIC FINDINGS

Adrenals

Enlarged: 92.3mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Extramedullary haemopoiesis: (Minimal)

The following tissues were considered normal:

Liver (ORO stain); Kidneys; Adrenals (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
 Dosage Level: 1000 mg/kg/day
 Rat No/Sex: 153♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Half closed eyelids immediately after dosing was noted on one occasion during Week 12. Paddling of the forelimbs immediately after dosing was noted occasionally from Week 12. Body jerks immediately after dosing was noted on one occasion during Week 13.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lungs

Pale subpleural focus/i: (A few , Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Increased numbers of alveolar macrophages: (Minimal , Focal)

Vascular congestion: (Minimal , Focal)

Liver

Extramedullary haemopoiesis: (Minimal)

Kidneys

Mineralisation of pelvic/papillary epithelium: (Trace)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 153♀ - continued

MICROSCOPIC FINDINGS - continued

The following tissues were considered normal:

Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 154♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on one occasion in Week 13.

Incidental finding of tail ridges was noted.

MACROSCOPIC FINDINGS

Lymph Nodes - Cervical
Enlarged: 7mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lymph Nodes - Cervical
Increased cellularity - generalised: (Minimal)

Kidneys
Dystrophic mineralisation: (Trace)

The following tissues were considered normal:

Liver: Liver (ORO stain); Adrenals

Pathologist: J.M. Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 155♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Half closed eyelids immediately after dosing was noted on one occasion in Week 12.

MACROSCOPIC FINDINGS

Adrenals

Enlarged: 91.0mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Liver

Extramedullary haemopoiesis: (Minimal)

The following tissues were considered normal:

Liver (ORO stain); Kidneys; Adrenals : (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 156♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on two occasions, in Weeks 11 and 13.

Incidental findings of tail ridges and brown fur staining were noted.

MACROSCOPIC FINDINGS

Adrenals

Enlarged: 93.1mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Liver; Liver (ORO stain); Kidneys; Adrenals : (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 157♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Half closed eyelids immediately after dosing was noted on one occasion during Week 12. Paddling of the forelimbs immediately after dosing was noted on more than one occasion in Week 13. Body jerks immediately after dosing was noted on one occasion during Week 13.

Incidental findings of yellow urogenital staining and hair loss were noted.

MACROSCOPIC FINDINGS

Skin Alopecia

Forelimb/s: (Left , Minimal)

Liver

Median cleft, pale subcapsular area/s: (One) 1mm

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Liver : (W.N.L.); Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 158♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted on two occasions, in Weeks 9 and 11. Half closed eyelids and body jerks immediately after dosing were noted on one occasion during Week 13.

MACROSCOPIC FINDINGS

Lungs

Pale subpleural focus/i: (A few , Punctate)
Pale: (Left)

Adrenals

Enlarged: 91.9mg

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal , Focal)

The following tissues were considered normal

Liver; Liver (ORO stain); Kidneys; Adrenals (W.N.L.)

Pathologist: J.M.Offer

APPENDIX 9**(Pathology - continued)**

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 159♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Paddling of the forelimbs immediately after dosing was noted occasionally from Week 11. Half closed eyelids immediately after dosing was noted on one occasion during Week 12.

Incidental finding of left eye damaged was noted.

MACROSCOPIC FINDINGS**Eyes**

Damaged: (Left)

Lymph Nodes - Cervical

Enlarged: 6mm

Lungs

Pale subpleural focus/i: (A few , Punctate)

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs

Vascular congestion: (Minimal , Focal)

Lymph Nodes - Cervical

Increased cellularity - generalised: (Minimal)

Kidneys

Dystrophic mineralisation: (Minimal)

APPENDIX 9

(Pathology - continued)

Rat No/Sex: 159♀ - continued

MICROSCOPIC FINDINGS - continued

Eyes

Conjunctival haemorrhage, inflammation and oedema: (Moderate , Unilateral)

The following tissues were considered normal:

Liver; Liver (ORO stain); Adrenals

Pathologist: J.M.Offer

APPENDIX 9

(Pathology - continued)

Compound: DPTB
Dosage Level: 1000 mg/kg/day
Rat No/Sex: 160♀ (Recovery)

CLINICAL FINDINGS

Salivation immediately after dosing was noted occasionally from Week 1. Half closed eyelids immediately after dosing was noted on two occasions, in Weeks 11 and 12. Paddling of the forelimbs immediately after dosing was noted on one occasion during Week 13.

Incidental findings of tail ridges, brown fur staining and urogenital wetness were noted.

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Liver; Liver (ORO stain); Kidneys; Adrenals

Pathologist: J.M.Offer

Huntingdon

DIPROPYLENE GLYCOL T-BUTYL ETHER (DPTB)

**TOXICITY TO RATS BY REPEATED ORAL ADMINISTRATION FOR 13 WEEKS
INCORPORATING A NEUROTOXICITY SCREEN AND FOLLOWED BY A 4-WEEK
RECOVERY PERIOD**

Volume 2



DIPROPYLENE GLYCOL T-BUTYL ETHER (DPTB)
TOXICITY TO RATS BY REPEATED ORAL ADMINISTRATION FOR 13
WEEKS INCORPORATING A NEUROTOXICITY SCREEN AND FOLLOWED BY
A 4-WEEK RECOVERY PERIOD

Volume 2

Sponsor

ARCO Chemical Company,
3801 West Chester Pike,
Newtown Square,
Pennsylvania,
PA 19073 - 2387,
U.S.A.

Testing facility

Huntingdon Life Sciences Ltd
P.O. Box 2,
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Report issued 17 December 1996

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CERTIFICATE OF ANALYSIS

ARCO CHEMICAL COMPANY
 3801 West Chester Pike
 Newtown Square, Pennsylvania 19703



Contact: Frank Liotta
 Phone: 610-359-2308

 CERTIFICATE OF ANALYSIS

DIPROPYLENE GLYCOL t-BUTYL ETHER

Lot No.: HRC-1095
 Date: 11/08/95

Property	Analysis
Assay as Dipropylene Glycol t-Butyl Ether <i>(by GC, copy attached)</i>	>98%
Impurities <i>(by GC)</i>	
Dipropylene Glycol	0.47 wt. %
Dipropylene Glycol Di-t-butyl Ether	1.02 wt. %
Water Content <i>(by Karl Fisher)</i>	0.14%
APHA Color	5
Specific Gravity (@ 20°C)	0.912
Acidity	<0.001 meq/l
Distillation (@ 760 mm-Hg)	
IBP	205 °C
50% Point	213 °C
DP	218 °C

DPTB
FORMULATION ANALYSIS

Authors:

I Suzanne Dawe,
Wai-Han Cheung,
B Shenaz Nunhuck.

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INTRODUCTION

This report details the analytical procedure used and the results obtained for the concentrations of DPTB in test formulations analysed during the toxicity study.

The formulations for this study were prepared as solutions of DPTB in distilled water by Pharmacy personnel at Huntingdon Life Sciences Limited.

The analytical procedure validation and the homogeneity and stability of DPTB in aqueous formulations were determined for concentrations of 0.1 mg/ml and 100 mg/ml during an earlier study. The experimental details and the results obtained were presented in Huntingdon Life Sciences report ARO 25/960403 and are also included in this report for completeness.

EXPERIMENTAL PROCEDURE**ANALYTICAL PROCEDURE****Apparatus and instrumentation**

Gas liquid chromatograph (GLC): As detailed in the chromatographic section.

Balance: Mettler AT261, fitted with an LC-P45 printer.

General laboratory glassware.

Reagents

Test substance: DPTB.
 Supplier: Arco Chemical Company.
 Batch no: HRC 1095.
 Stated purity: >97%.

Water: Elgastat UHP-4, deionised reverse osmosis

Sample extraction

A representative sample of test formulation was appropriately diluted using water to provide a solution containing DPTB at an expected concentration of 100 µg/ml.

The concentration of DPTB in the final solution was quantified by gas liquid chromatography using flame ionisation detection as detailed in the following section.

Typical chromatographic conditions

Gas liquid chromatograph (GLC):
 Instrument: Hewlett Packard 5890.
 Autosampler: Hewlett Packard 6890.
 Detector: Flame ionisation.
 Data handling: Perkin-Elmer Nelson Access*Chrom.

Analytical column: Fused silica.
 Configuration: 30 m × 0.53 mm id.
 Liquid phase: DB-wax.
 Film thickness: 1 µm.

Temperatures:
 Injection port: 200°C.
 Oven: 75°C (1 minute),
 ramped at 20°C/minute to 135°C (5 minutes);
 ramped at 30°C/minute to 225°C (2 minutes);
 275°C.

Detector:

Gases:	
Carrier:	Helium, 10 ml/minute.
Detector:	Air, 450 ml/minute.
	Hydrogen, 40 ml/minute.
Injection volume:	1 μ l.
Injection mode:	Splitless for 1 minute then purged at a split ratio of 1 : 10.
Retention times:	Peak 1 6.0 minutes,
	Peak 2 6.2 minutes,
	Peak 3 6.7 minutes.
Integration sensitivity:	80 mV.

Calibration

A primary standard solution was prepared for each analytical occasion by dissolving an accurately weighed quantity (50 mg) of DPTB in water. A solution for instrument calibration at a concentration of 100 μ g/ml was prepared by appropriate dilution of the primary standard using water.

The calibration standard was injected onto the GLC, at regular intervals, alternating with every two samples throughout the injection sequence

At each analytical occasion, a duplicate calibration standard was prepared to confirm the accuracy of preparation.

Linearity solutions, containing DPTB at concentrations in the range 40 μ g/ml - 200 μ g/ml, were injected onto the GLC to confirm the linearity of detector response.

Calculation

The peak area response of the 3 major peaks at the characteristic retention times for DPTB in each calibration and sample chromatogram were measured. Since the response of each peak was consistent the concentration of DPTB was determined with respect to peak 1 using the following equation

$$\text{Concentration, mg/ml} = \frac{R_s}{R_c} \times C \times V \times 10^{-3}$$

Where R_s = Mean peak area response for DPTB (peak 1) in test chromatogram
 R_c = Mean peak area response for DPTB (peak 1) in the calibration standard
 C = Concentration of calibration standard (μ g/ml)
 V = Dilution factor of sample

Limit of detection

The limit of detection, defined as the concentration of DPTB in aqueous solution producing a peak response equivalent to $3 \times$ baseline noise, was determined by preparing solutions containing DPTB at decreasing concentrations to provide a peak of suitable size.

VALIDATION OF THE METHOD OF ANALYSIS

Prior to the start of the study, specimen aqueous formulations of DPTB were prepared at nominal concentrations of 0.1 mg/ml and 100 mg/ml by Analytical Chemistry personnel. The analytical procedure was validated at the low and high inclusion levels by determining the accuracy and precision of analytical results generated for the analysis of six replicate samples from the prepared formulations.

CHEMICAL STABILITY IN AQUEOUS FORMULATIONS

Specimen formulations (2000 ml), containing DPTB at nominal concentrations of 0.1 mg/ml and 100 mg/ml, were prepared and sub-divided ($250 \text{ ml} \times 8$) by Pharmacy personnel to simulate the anticipated preparation, distribution and sampling of doses for analysis during the toxicity study.

A bottle of each formulation was thoroughly mixed by inversion and magnetically stirred. After magnetic stirring for 5 minutes (0 hour), 2 hours and 4 hours, samples (1 ml) were removed for analysis from points at approximately one-quarter, one-half and three-quarters the depth (representing the top, middle and bottom) of the formulation.

The remaining bottles were refrigerated (nominally $+4^\circ\text{C}$) in the dark. At time-points representing 2 days, 8 days and 15 days storage, a fresh bottle of each formulation was equilibrated to room temperature for 1 hour, mixed by inversion, magnetically stirred (5 minutes) and sampled as detailed above.

On each occasion, the three samples from each formulation were analysed in accordance with the analytical procedure. The samples removed after stirring for 2 hours were retained frozen for contingency.

CONCENTRATIONS IN TEST FORMULATIONS

At specified intervals (Weeks 1 and 11) during treatment, freshly-prepared formulations were sampled by Pharmacy personnel and submitted for analysis. On receipt, each formulation was sampled in duplicate and analysed in accordance with the analytical procedure.

RESULTS AND DISCUSSION

The concentrations of DPTB in test formulations analysed during the study and the deviation of mean results from nominal values are summarised in Table 1. Mean results were within 4% of nominal concentrations.

The chemical stability of DPTB in aqueous solution, containing DPTB at nominal concentrations of 0.1 mg/ml and 100 mg/ml, was confirmed during ambient temperature storage for 4 hours and refrigerated storage for 15 days. However, the mean results obtained for the 0.1 mg/ml formulation were approximately 13% above nominal. Since this formulation had been serially diluted from the 100 mg/ml formulation, a second formulation was prepared at 0.1 mg/ml by direct weighing and dilution which was evaluated for stability. Mean results were within 4% of nominal concentrations, confirming accuracy of formulation and remained constant throughout the storage period. The results obtained are presented in Table 2.

Procedural recovery data obtained during method validation confirm the accuracy of the analytical procedure: a mean procedural recovery value of 96.7% (CV=0.47, n=6) was obtained at 0.1 mg/ml and 100.1% (CV=0.40, n=6) was obtained at 100 mg/ml. The results obtained are presented in Table 3.

The limit of detection was determined as 0.004 mg/ml using the operating parameters defined in the analytical procedure.

A typical calibration standard graph confirming the linearity of detector response for DPTB over the concentration range 40 - 200 µg/ml is presented in Figure 1.

Typical analytical chromatograms are presented in Figure 2. In Figure 2, the absence of a peak at the characteristic retention volumes for DPTB in the control sample chromatogram demonstrates the specificity of the GLC assay.

CONCLUSION

The mean concentrations of DPTB in test formulations analysed during the study were within 4% of nominal concentrations confirming the accuracy of formulation.

The results also confirm that formulations were chemically stable during ambient temperature storage for 4 hours and refrigerated storage for 15 days, a period of time exceeding the time from preparation to completion of dosing.

TABLE 1

Concentrations of DPTB in test formulations

Week of dosing	Group	Nominal inclusion (mg/ml)	Analysed concentration (mg/ml)			RME (%)
			Analysis 1	Analysis 2	Mean	
1	Control	0	ND	ND	ND	-
	2	6.25	6.59	6.39	6.49	-3.8
	3	25	25.9	24.8	25.3	-1.2
	4	100	101	103	102	-2.0
11	Control	0	ND	ND	ND	-
	2	6.25	6.08	6.10	6.09	-2.5
	3	25	24.7	24.9	24.8	-0.8
	4	100	99.7	100.5	100	0.0

ND None detected (<0.004 mg/ml)

RME Relative mean error, representing the deviation from nominal

TABLE 2
Chemical stability of DPTB in aqueous formulations

Nominal inclusion (mg/ml)	Trial	Storage conditions			Analysed concentration (mg/ml)				RME (%)
		Days	Hours	Temp, °C	Top	Middle	Bottom	Mean	
0.1	1	0	0	+21	0.112	0.114	0.112	0.113	0.0
			4	+21	0.114	0.112	0.112	0.113	
		2	0	+4	0.111	0.113	0.113	0.112	-0.9
			8	+4	0.113	0.113	0.113	0.113	0.0
			15	+4	0.113	0.113	0.113	0.113	0.0
0.1	2	0	0	+21	0.100	0.0997	0.101	0.100	-2
			4	+21	0.0997	0.103	0.103	0.102	
		2	0	+4	0.104	0.103	0.101	0.103	+3
			8	+4	0.0999	0.0991	0.0979	0.0990	-1
			15	+4	0.101	0.102	0.0996	0.101	-
100	1	0	0	+21	101	100	101	101	-
			4	+21	102	103	102	102	
		2	0	+4	102	101	101	101	-
			8	+4	102	102	102	102	-
			15	+4	104	104	103	103	-1

RME Relative mean error, representing the deviation from time zero.

Trial 1 Formulations prepared by serial dilution from the 100 mg/ml formulation

Trial 2 Formulation prepared by direct weighing and dilution

Results were calculated using unrounded figures.

TABLE 3

Procedural recovery data for DPTB in aqueous formulation

Analytical phase	Nominal fortification (mg/ml)	
	0.1	100
Validation	96.9	99.8
	97.0	100.6
	97.1	100.0
	96.6	100.5
	96.4	99.7
	95.9	99.7
Mean	96.7	100.1
CV (%)	0.47	0.40
Range	95.9 - 97.1	99.7 - 100.6
n	6	6

CV Coefficient of variation

n Number of determinations

Results are expressed as percent recovery and calculated using the following equation:

$$\% \text{ Recovery} = \frac{\text{Analysed concentration (mg/ml)}}{\text{Fortified concentration (mg/ml)}} \times 100$$

FIGURE 1

Typical calibration standard graph
(Week 11)

Method: DXB200: [D1.FORM.ARO.ARO26.AC4131]DPTB_LIQ_B.MET;7
 Component: PEAK 1
 Date: 19-AUG-1996 14:36:59.11
 Linear fit, Origin Treatment....Ignore.
 K0: -5.7875E+02 K1: 1.0033E+02
 Coeff. of determination: 0.9992

Standard Sample	Component Area	Component Mass	% Rel. St. Dev.
STD 1	3624	40.328	
STD 2	7477	80.656	
STD 3	11388	120.98	
STD 4	15429	161.31	
STD 5	19878	201.64	

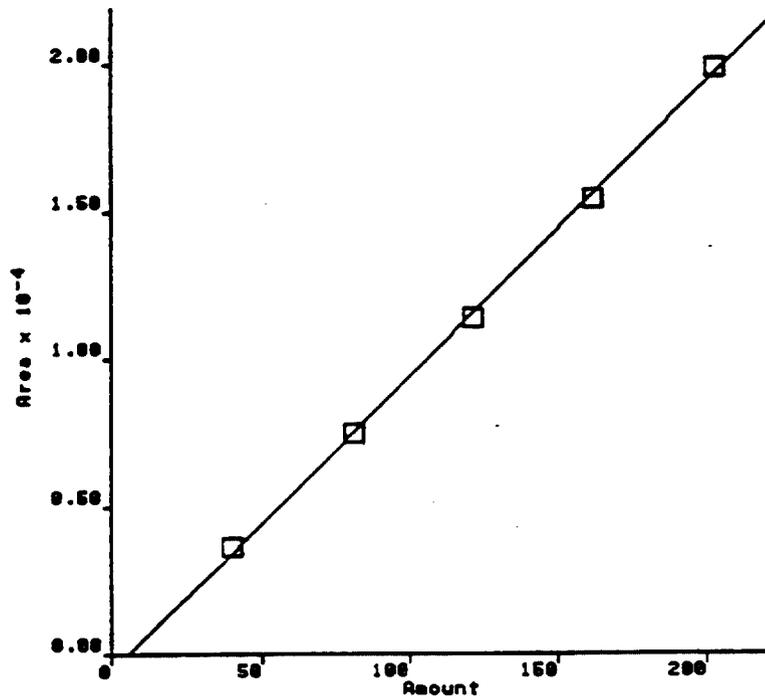
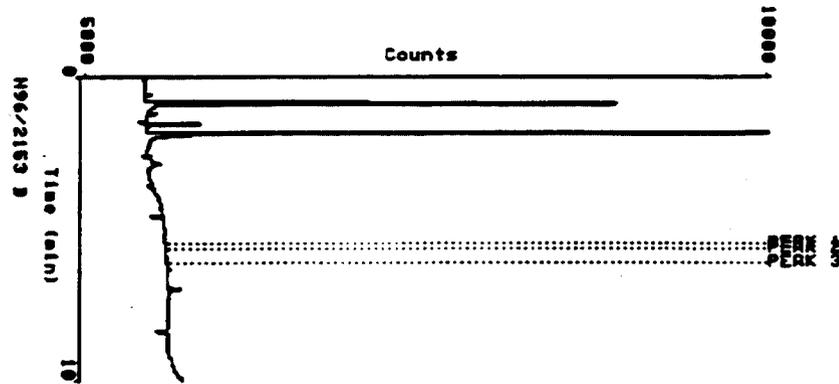


FIGURE 2

Typical sample chromatograms
(Week 11)

Group 1, Control (dilution factor 1 : 1)



Group 2, 6.25 mg/ml (dilution factor 1 : 62.5)

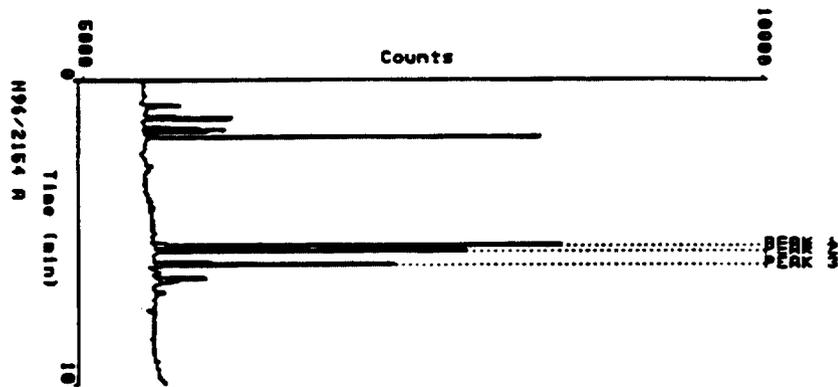
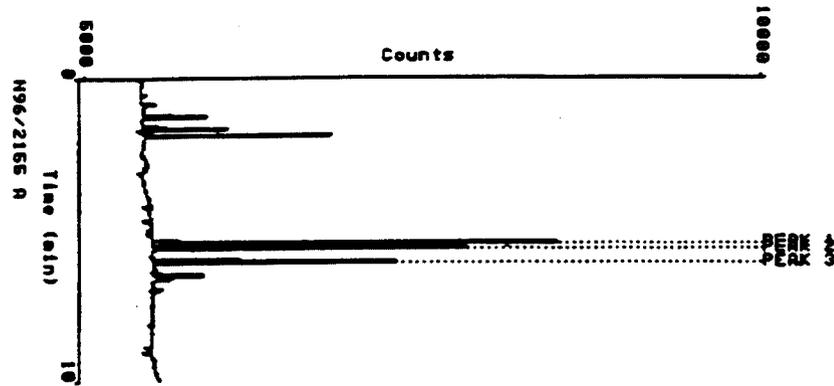


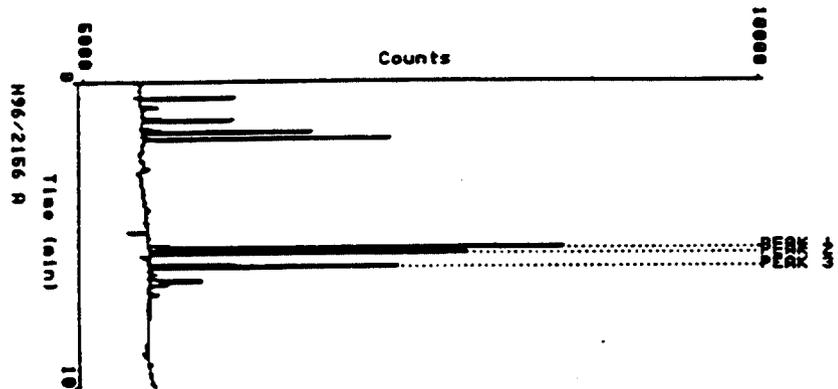
FIGURE 2

(continued)

Group 3, 25 mg/ml (dilution factor 1 : 250)



Group 4, 100 mg/ml (dilution factor 1 : 1000)



DPTB
BEHAVIOURAL SCREENING

Author

E W Hughes

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EXPERIMENTAL PROCEDURE

NEUROBEHAVIOURAL SCREENING

During the study, a functional observational battery and motor activity were performed at approximately the same time of day. Not all rats were tested in one day, but time of testing was balanced across the groups. Observations made during the treatment period were made prior to dosing. In addition observations in Week 13 were performed prior to any laboratory investigations.

The functional observational battery is detailed below:

The battery comprised 4 sets of observations. The first set of observations was performed while the animal was in its home cage. The second set was performed when initially handling the animal. The third set of observations was performed in the test arena and the fourth set comprised handling/specific testing of the animal. All these observations were made with the observer blind to the treatment condition of the animal.

Home cage observations:

- Posture in the cage
- Presence of convulsions, tremors, twitches
- Presence of spontaneous vocalisations
- Palpebral closure

Observations in the hand:

- Occurrence of convulsions, tremors, twitches
- Ease of removing the animal from the cage
- Ease of handling the animal
- Salivation/lacrimation
- Palpebral closure
- Exophthalmus
- Piloerection
- Vocalisation on handling

Observation in the arena:

- Occurrence of convulsions, tremors, twitches
- Level of activity in the arena (number of squares entered counted)
- Level of arousal
- Rearing count
- Grooming
- Piloerection
- Assessment of gait
- Record presence of faecal boluses, urine

Manipulations:

Approach response
 Touch response
 Startle response
 Righting reflex
 Tail pinch response
 Pupil reflex
 Grip strength (fore and hindlimb)
 Landing foot splay
 Body temperature ($^{\circ}$ C)
 Bodyweight (g)

At any point during the observations, additional comments were made as free text where considered appropriate. For the purposes of reporting, where all animals failed to exhibit a sign such as convulsions, this negative recording has not been presented in the report.

Motor activity was performed was monitored using a Coulbourn Infra-Red Activity Monitoring System. (System supplied by Coulbourn Instruments, Lehigh Valley, PA, U.S.A.).

This system uses an infra-red detector to monitor activity. The following categories of activity are recorded: the time spent in no movement, locomotor and non-locomotor activity. The number of occurrences (events) of each category is also recorded. For reporting this data only the locomotor activity is presented.

For testing, designated animals were placed singly into observation cages. Once all animals had been placed into the cages, the test session programme was started. The test session for each animal was 1 hour. Data was collected every 2 minutes and written onto a floppy disk.

The functional observational battery was performed in Room 17 and the motor activity monitoring was performed in Room 16.

ANALYSIS AND PRESENTATION OF THE BEHAVIOURAL SCREENING DATA

The following data were routinely subjected to statistical analysis: rearing and activity counts, grip strength, hindlimb splay, bodyweight and temperature. These data were analysed using a one-way analysis of variance followed by Williams' test (Williams 1971/2) for a dose-related response. Pre-dose data was analysed by analysis of variance followed by Student's *t* test.

The reporting of the categorical data for the observational battery has been handled in the following manner. The observational endpoints such as ease of handling, arousal, *etc* have been tabulated for frequency of occurrence for each group. Although during recording, some responses were classified in terms of the degree or type of response (*ie* startle: no reaction, an ear twitch, a flinch *etc*) for the purposes of reporting, as there were no remarkable differences between the groups, for a given endpoint the response has been reported as being either present or absent.

The categorical data were analysed in the following manner:

Where the recorded observations suggested a possible difference between controls and treated groups, the data were analysed using the Linear by Linear Association test (Agresti, 1990; Agresti, Mehta and Patel, 1990). All the recorded categories were used in the analysis. A two tailed test was generally reported except where the responses were considered directional in nature.

The Coulbourn activity data were analysed using a one-way analysis of variance followed by Williams' test (Williams 1971/2) for a dose-related response. Pre-dose data were analysed by analysis of variance followed by Student's *t* test.

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AGRESTI, A., MEHTA, C.R., PATEL, N.R. (1990) Exact inference for contingency tables with ordered categories. *J. Amer. Stat. Ass.* **85**: 453 - 458.

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RESULTS

OBSERVATIONAL ENDPOINTS (Table 1)

With respect to the incidence of routine observations, during Week 4 and Week 8 there was a tendency for more females treated at 1000 mg/kg/day to vocalise during the handling on removal from the cage compared with controls. This apparent difference from controls attained statistical significance in Week 8. There was no such difference observed in behaviour during Week 13.

The incidence of the observation of walking on toes was higher among treated females in Week 4 compared with controls. Differences did not attain statistical significance.

There were no other obvious differences in behaviour during the treatment period.

ACTIVITY COUNTS (Table 2)

There were no statistically significant differences between treated and control groups for activity counts.

REARING COUNTS (Table 3)

There were no statistically significant differences between treated and control groups.

GRIP STRENGTH (Tables 4, 5)

There were no statistically significant differences between treated and control groups for forelimb or hindlimb grip strength.

HINDLIMB SPLAY (Table 6)

During the treatment period, there were no statistically significant differences in hindlimb foot splay.

TEMPERATURE (Table 7)

Mean rectal temperature values were essentially similar among the groups.

BODYWEIGHT (Table 8)

Group mean bodyweights for treated males and females was considered comparable with their respective controls.

COULBOURN ACTIVITY MONITORING (Table 9)

There were no statistically significant differences in locomotor activity between treated and control groups.

DISCUSSION

Treatment with DPTB for thirteen weeks was not associated with any behavioural changes which were considered indicative of neurotoxicity. An increased incidence of vocalising among females treated at 1000 mg/kg/day was only observed during Weeks 4 and 8; this was not considered indicative of neurotoxicity.

CONCLUSION

Treatment with DPTB for thirteen weeks was not associated with any behavioural changes which were considered indicative of neurotoxicity.

TABLE 1

Group summary of observations

Group No. of animals	Pre-dose							
	Males				Females			
	1	2	3	4	1	2	3	4
	10	10	10	10	10	10	10	10
OBSERVATIONS:								
HOME CAGE								
posture = s/r	10	10	10	9	10	10	9	10
palpebral closure	0	1	0	0	0	0	0	0
REMOVAL FROM CAGE								
removing, easy	10	10	10	9	10	9	9	9
handling, easy	9	9	9	10	8	8	8	9
vocalising	2	0	1	1	2	2	1	1
IN THE ARENA								
grooming	3	1	4	3	0	3	1	1
arousal, alert	9	9	10	9	8	10	10	10
defecation	2	2	2	3	0	0	0	1
urine	2	1	1	2	3	2	0	1
GAIT								
walking on toes:	0	0	1	0	1	1	0	2
swaying/lurching	0	0	0	0	0	0	1	0
unable to assess	1	1	1	1	4	2	1	1
MANIPULATIONS								
approach, a reaction	10	10	10	10	10	10	10	10
touch, a reaction	10	9	10	10	10	8	10	10
startle (present)	10	10	10	10	10	10	10	10
righting, immediately	10	10	10	10	10	10	10	10
tail pinch, a reaction	10	10	10	10	10	10	10	10
pupil reflex (present)	10	9	9	9	9	9	10	10

Numbers reflect the number of animals showing the response
 S - sitting/standing in cage; r - rearing in cage

TABLE 1

(Group summary of observations - continued)

Group No. of animals	Week 4							
	Males				Females			
	1	2	3	4	1	2	3	4
	10	10	10	10	10	10	10	10
OBSERVATIONS:								
HOME CAGE								
posture = s/r	10	10	10	10	9	10	10	9
palpebral closure	0	0	0	0	1	0	0	0
REMOVAL FROM CAGE								
removing, easy	10	9	9	10	9	10	9	10
handling, easy	10	10	10	10	7	9	10	9
salivation	1	3	3	0	1	0	1	1
vocalising	1	0	3	1	1	1	1	3
IN THE ARENA								
grooming	2	1	0	2	4	3	2	1
arousal, alert	8	9	9	9	10	10	10	10
defecation	0	1	0	1	0	0	0	0
urine	3	2	3	1	2	0	0	0
GAIT								
walking on toes:	0	0	2	0	2	5	5	4
swaying/lurching	1	0	1	0	0	0	0	0
unable to assess	2	2	1	2	0	1	0	0
MANIPULATIONS								
approach, a reaction	10	9	10	10	10	10	10	10
touch, a reaction	6	9	7	7	10	10	10	8
startle (present)	10	9	10	10	10	10	9	10
righting, immediately	10	9	9	9	10	9	9	10
tail pinch, a reaction	10	10	10	10	10	10	10	10
pupil reflex (present)	10	9	9	9	10	8	9	10

Numbers reflect the number of animals showing the response
 S - sitting/standing in cage; r - rearing in cage

TABLE 1

(Group summary of observations - continued)

Group No. of animals	Week 8							
	Males				Females			
	1	2	3	4	1	2	3	4
OBSERVATIONS:	10	10	10	10	10	10	10	10
HOME CAGE								
posture = s/r	9	10	10	10	10	10	10	10
REMOVAL FROM CAGE								
removing, easy	10	10	8	10	10	10	10	10
handling, easy	9	10	7	9	9	9	9	8
salivation	3	2	3	0	1	0	1	0
vocalising	2	0	4	2	0	2	0	4a
IN THE ARENA								
tremors	1	0	1	1	1	0	0	0
grooming	2	1	0	3	3	4	5	1
arousal, alert	8	6	8	6	10	10	10	9
defecation	1	0	0	0	1	0	0	0
urine	7	6	3	4	2	1	1	0
GAIT								
walking on toes:	0	0	1	1	3	7	4	4
swaying/lurching	1	1	3	0	0	0	0	1
hunched	0	0	0	0	0	0	1	0
unable to assess	1	2	2	3	0	0	0	1
MANIPULATIONS								
approach, a reaction	10	9	9	8	10	10	10	10
touch, a reaction	6	7	6	7	7	8	8	9
startle (present)	10	10	10	10	10	10	10	10
righting, immediately	9	9	9	8	10	8	8	9
tail pinch, a reaction	10	10	10	10	10	10	10	10
pupil reflex (present)	9	10	9	10	9	9	9	10

Numbers reflect the number of animals showing the response
 S - sitting/standing in cage; r - rearing in cage
 a p=0.0179

TABLE 1

(Group summary of observations - continued)

Group No. of animals	Week 13							
	Males				Females			
	1	2	3	4	1	2	3	4
OBSERVATIONS:								
HOME CAGE								
posture = s/r	10	10	10	10	10	10	10	10
REMOVAL FROM CAGE								
removing, easy	9	10	10	10	10	10	9	9
handling, easy	10	10	10	10	10	9	9	9
salivation	2	3	1	0	2	0	0	0
vocalising	2	2	3	2	0	0	0	1
IN THE ARENA								
tremors	4	2	1	2	0	0	0	0
grooming	2	4	2	3	3	5	5	2
arousal, alert	9	7	9	6	9	10	10	1
defecation	2	0	0	1	0	0	0	0
urine	5	3	2	2	0	1	0	0
GAIT								
walking on toes:								
swaying/lurching	0	0	2	2	2	3	4	1
unable to assess	0	1	1	0	0	0	0	0
4	2	1	4	0	0	0	0	0
MANIPULATIONS								
approach, a reaction	9	9	8	8	10	10	10	10
touch, a reaction	6	7	8	9	9	10	10	9
startle (present)	10	10	10	10	10	10	10	10
righting, immediately	8	9	9	9	10	10	10	10
tail pinch, a reaction	9	10	10	10	10	10	10	10
pupil reflex (present)	10	10	10	9	9	9	9	10

Numbers reflect the number of animals showing the response
 S - sitting/standing in cage; r - rearing in cage

TABLE 2
Activity counts

Pre-dose

Group	Mean activity counts	
	Males	Females
1	9	7
2	12	10
3	11	13 ⁺
4	10	11

Week 4

Group	Mean activity counts	
	Males	Females
1	9	14
2	10	17
3	14	13
4	11	16

Week 8

Group	Mean activity counts	
	Males	Females
1	8	19
2	9	20
3	14	20
4	9	17

Week 13

Group	Mean activity counts	
	Males	Females
1	6	21
2	9	20
3	16	18
4	11	17

+ $p < 0.05$

TABLE 3
Rearing counts

Pre-dose

Group	Mean activity counts	
	Males	Females
1	10	8
2	12	9
3	14 ⁺	12
4	10	10

Week 4

Group	Mean activity counts	
	Males	Females
1	13	15
2	10	19
3	15	16
4	12	19

Week 8

Group	Mean activity counts	
	Males	Females
1	9	16
2	8	18
3	14	16
4	11	17

Week 13

Group	Mean activity counts	
	Males	Females
1	6	19
2	8	19
3	13	16
4	12	15

+ $p < 0.05$

TABLE 4
Grip strength forelimb

Pre-dose

Group	Mean forelimb grip strength (kg)	
	Males	Females
1	0.50	0.54
2	0.50	0.47
3	0.49	0.58
4	0.50	0.47

Week 4

Group	Mean forelimb grip strength (kg)	
	Males	Females
1	1.12	1.09
2	1.08	1.03
3	1.11	1.12
4	1.09	0.92

Week 8

Group	Mean forelimb grip strength (kg)	
	Males	Females
1	1.25	1.26
2	1.27	1.15
3	1.25	1.31
4	1.31	1.04

Week 13

Group	Mean forelimb grip strength (kg)	
	Males	Females
1	1.59	1.18
2	1.52	1.03
3	1.74	1.24
4	1.53	1.20

$p > 0.05$

TABLE 5
Grip strength hindlimb

Pre-dose

Group	Mean hindlimb grip strength (kg)	
	Males	Females
1	0.44	0.47
2	0.52	0.49
3	0.48	0.54
4	0.44	0.51

Week 4

Group	Mean hindlimb grip strength (kg)	
	Males	Females
1	0.86	0.81
2	0.96	0.80
3	0.92	0.86
4	1.02	0.76

Week 8

Group	Mean hindlimb grip strength (kg)	
	Males	Females
1	1.05	0.94
2	1.16	0.89
3	1.17	1.08
4	1.03	1.03

Week 13

Group	Mean hindlimb grip strength (kg)	
	Males	Females
1	1.17	1.00
2	1.30	0.96
3	1.24	0.98
4	1.28	1.24

$p > 0.05$

TABLE 6

Hindlimb splay

Pre-dose

Group	Mean splay values (cm)	
	Males	Females
1	8.2	6.7
2	7.4	6.0
3	8.0	7.7
4	7.0	6.3

Week 4

Group	Mean splay values (cm)	
	Males	Females
1	11.2	8.3
2	10.4	7.6
3	10.9	9.5
4	10.1	7.8

Week 8

Group	Mean splay values (cm)	
	Males	Females
1	11.5	7.8
2	11.3	7.4
3	11.4	9.2
4	10.7	8.2

Week 13

Group	Mean splay values (cm)	
	Males	Females
1	12.0	8.4
2	11.1	8.1
3	11.2	9.2
4	12.3	8.7

$p > 0.05$

TABLE 7

Rectal temperature

Pre-dose

Group	Mean temperature (°C)	
	Males	Females
1	38.0	38.4
2	38.0	38.3
3	38.1	38.5
4	38.1	38.2

Week 4

Group	Mean temperature (°C)	
	Males	Females
1	38.6	39.0
2	38.5	39.1
3	38.6	39.0
4	38.6	39.1

Week 8

Group	Mean temperature (°C)	
	Males	Females
1	38.6	39.0
2	38.4	39.0
3	38.5	39.1
4	38.7	38.9

Week 13

Group	Mean temperature (°C)	
	Males	Females
1	38.3	39.0
2	37.8	38.9
3	38.3	38.9
4	38.4	38.9

p > 0.05

TABLE 8

Bodyweights recorded during the functional observational battery

Pre-dose

Group	Mean bodyweights (g)	
	Males	Females
1	123	134
2	137	129
3	137	129
4	139	127

Week 4

Group	Mean bodyweights (g)	
	Males	Females
1	344	227
2	338	216
3	343	208
4	338	220

Week 8

Group	Mean bodyweights (g)	
	Males	Females
1	461	268
2	438	258
3	450	246
4	455	258

Week 13

Group	Mean bodyweights (g)	
	Males	Females
1	553	291
2	526	285
3	540	272
4	542	280

 $p > 0.05$

TABLE 9

Coulbourn activity monitoring

Pre-dose

Group	Mean large movements (in secs) during 1 hour observation period	
	Males	Females
1	692	646
2	647	611
3	677	598
4	679	544

Week 4

Group	Mean large movements (in secs) during 1 hour observation period	
	Males	Females
1	923	937
2	793	1094
3	844	1015
4	952	961

Week 8

Group	Mean large movements (in secs) during 1 hour observation period	
	Males	Females
1	1084	933
2	788	1134
3	1001	1046
4	1130	1069

Week 13

Group	Mean large movements (in secs) during 1 hour observation period	
	Males	Females
1	973	905
2	862	952
3	1025	1011
4	1047	1035

$p > 0.05$

APPENDIX 1

Functional observational battery - pre-dose, Weeks 4, 8 and 13

KEY

Tremors

B Body
 blank no tremor observed

the numbers associated with tremors indicate the degree of effect
 1,2,3 increasing degree of effect

Posture

S Sitting/standing in cage
 R Rearing in cage
 Cl Climbing in cage
 L Lying on side or curled up

Ease of removal from cage

2 easy (little resistance)
 3 moderately easy

Ease of handling

2 easy (little resistance)
 3 slightly awkward

Salivation (only scored if present)

Y sign observed with 1 being slight
 N sign not observed

Arousal

2,3,4,5 increasing levels of arousal with 4 being alert

Gait

T Walking on toes
 Hu Hunched
 A Swaying/lurching gait
 O Unusal gait - see additional comments
 U Unable to assess - see additional comments
 blank normal gait

the numbers associated with gait indicate the degree of effect
 1,2,3 increasing degree of effect

APPENDIX 1

(Functional observational battery - continued)

Approach

- 1 No reaction
- 2 Sniffs only
- 3 Approaches and sniffs
- 4 Freezes
- 5 Back/turns away
- O Other reaction - see additional comments

Touch

- 1 No reaction
- 2 Turns
- 3 Walks away
- 4 Freezes
- 5 Turns to opposite side
- O Other reaction - see additional comments

Startle

- 1 No reaction
- 2 Ear twitch only
- 3 Noticeable flinch
- 4 Noticeable jump
- O Other reaction - see additional comments

Tail pinch

- 1 no reaction
 - 2 turns
 - 2 turns immediately
 - 3 violent turn
 - 3 walks away
 - 4 freezes
 - 5 jumps forward
 - O Other reaction - see additional comments
- A 1 with a response that is not a turn indicates that the response included a turn such as walks away with a turn

Righting reflex

- 1 immediate reaction
- 2 reaction slow

Vocalising, grooming

- Y sign observed
- N sign not observed

the numbers associated with vocalising indicate the degree of effect
 1,2,3 increasing loudness of vocalising

APPENDIX 1

(Functional observational battery - continued)

Pupil reflex

- B reflex observed both eyes
- L/R reflex observed in left/right eye only
- N no reflex both eyes

Urine

- N none observed
- S small amount observed
- M moderate amount observed
- L large amount observed

Rearing and activity counts

Counts were made of rearing and activity when the animals were in the arena. A count for rearing was counted every time the animal lifted both fore feet clear of a supporting surface. The floor of the arena was marked off into 4 equal areas ("squares"). A count for activity was made whenever the animal moved all four feet into one of these squares.

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 1 males				
Animal no	6	7	8	9	10
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
Palprebal closure degree	N	N	N	N	N
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	3	2
Vocalising degree	N	N	Y	Y	N
IN THE ARENA					
Grooming	Y	N	N	Y	N
Activity count	6	10	13	8	5
Arousal	4	4	4	4	4
Rearing count	5	13	12	8	8
Bolus count	0	0	0	3	0
Urine present	N	N	S	S	N
Gait					
MANIPULATIONS					
Approach	3	3	5	3	5
Touch	3	3	2	3	3
Startle	3	3	3	3	2
Righting reflex	1	1	1	1	1
Tail pinch	3	2	3	3	3
turns		2			
vocalises degree	Y	Y	Y	Y	Y
Pupil reflex	2	2	2	1	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39	38.1	37.8	37.5	38.1
Bodyweight (g)	134	140	137	143	144
GRIP STRENGTH (kg)*					
Forelimb	0.52	0.52	0.56	0.50	0.54
Hindlimb	0.36	0.30	0.50	0.48	0.37
FOOTSPRAY (cm) *					
	7.4	7.4	9.5	10.2	9.8

* values represent the mean of two trials

Additional comments

Animal no.

- 6 Lower teeth pale
In the arena: eyes partially to half closed occas
- 7 Slight brown nasal staining
- 8 Lower teeth pale
- 9 Lower teeth pale, patchy hairloss back
In the arena: initial slipping of hindlimbs
- 10 Slight brown nasal staining, lower teeth pale
hairloss back

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 1 males					
	Animal no	81	82	83	84	85
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	S
Palprebal closure degree		N	N	N	N	N
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Vocalising degree		N	N	N	N	N
IN THE ARENA						
Grooming		N	Y	N	N	N
Activity count		18	6	9	11	1
Arousal		4	4	4	4	3
Rearing count		15	8	8	16	5
Bolus count		0	0	1	0	0
Urine present		N	N	N	N	N
Gait						U
MANIPULATIONS						
Approach		3	3	3	3	3
Touch		3	3	3	3	3
Startle		3	3	2	4	3
Righting reflex		1	1	1	1	1
Tail pinch		3	3	3	3	3
turns				1		1
vocalises degree		Y	Y	Y	Y	Y
Pupil reflex		2	2	2	1	2
Temperature (°C)		B	B	B	R	B
Bodyweight (g)		38.5	38.2	38.3	37.3	37.6
GRIP STRENGTH (kg) *		120	132	138	NR	146
Forelimb		0.53	0.42	0.37	0.50	0.55
Hindlimb		0.57	0.45	0.47	0.47	0.45
FOOTSPRAY (cm) *		9.5	7.5	6.1	7.1	8.1

* values represent the mean of two trials
NR not recorded in error

Additional comments

Animal no.

- 81 Patchy hair loss back
- 83 Lower teeth pale, general yellow staining of fur
During temperature: vocalising softly
- 84 Lower teeth pale patchy hair loss back
In the arena: initial slipping of hind feet
- 85 Lower teeth pale
In the arena: sitting on edge of arena
During temperature: head shake

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 2 males					
	Animal no	16	17	18	19	20
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	S
Palprebal closure degree		N	N	N	N	N
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	3	2	2
Vocalising degree		N	N	N	N	N
IN THE ARENA						
Grooming		N	N	N	N	N
Activity count		14	18	19	14	14
Arousal		4	4	4	4	4
Rearing count		11	11	19	15	13
Bolus count		1	0	0	4	0
Urine present		N	N	N	S	N
Gait						
MANIPULATIONS						
Approach		3	3	3	3	3
Touch		3	1	3	3	2
Startle		3	4	3	3	3
Righting reflex		1	1	1	1	1
Tail pinch		3	3	5	3	3
turns		1		1	1	
vocalises degree		Y	Y	Y	Y	Y
Pupil reflex		2	2	2	1	1
Temperature (°C)		N	B	B	B	B
Bodyweight (g)		38.1	38.4	38.2	37.6	38
GRIP STRENGTH (kg) *		133	139	136	141	139
Forelimb		0.54	0.51	0.56	0.48	0.46
Hindlimb		0.58	0.41	0.63	0.54	0.54
FOOTSPRAY (cm) *		6.7	7.2	4.4	9.3	7.8

* values represent the mean of two trials

Additional comments

Animal no.

- 16 Patchy hairloss back
- Pupil reflex: both pupils constricted
- 17 Lower teeth pale; patchy hairloss back
- 18 During manipulations: head shake occasionally
- 19 Lower teeth pale
- 20 Lower teeth pale; patchy hairloss back

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 2 males				
Animal no	86	87	88	89	90
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
Palprebal closure degree	N	Y	N	N	N
IN THE HAND					
Removing	2	1	2	2	2
Handling	2	2	2	2	2
Vocalising degree	N	N	N	N	N
IN THE ARENA					
Grooming	N	N	Y	N	N
Activity count	5	13	2	14	9
Arousal	3	4	4	4	4
Rearing count	6	10	8	15	11
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait			U		
MANIPULATIONS					
Approach	2	3	3	3	5
Touch	3	2	3	3	5
Startle	3	2	2	3	3
Righting reflex	1	1	1	1	1
Tail pinch	3	3	0	0	3
turns					
vocalises degree	Y	Y	Y	Y	Y
Pupil reflex	1	2	2	1	1
Temperature (°C)	B	B	B	B	B
Bodyweight (g)	38.6	38.1	37.5	37.7	38
GRIP STRENGTH (kg) *	124	127	141	145	146
Forelimb	0.36	0.58	0.51	0.55	0.46
Hindlimb	0.46	0.50	0.54	0.58	0.48
FOOTSPRAY (cm) *	6.2	10.1	7.6	7.7	6.9

* values represent the mean of two trials

Additional comments

Animal no.

86 Patchy hairloss rump
 87 Hair loss shoulders
 88 Patchy hair loss back
 In the arena: initial slipping of all limbs, limited walking
 Tail pinch: runs away
 89 Tail pinch: runs away
 90 General yellow staining fur; lower teeth pale
 Pupil reflex: left pupil very slow response

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 3 males					
	Animal no	26	27	28	29	30
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	S
Palprebal closure degree		N	N	N	N	N
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	3
Vocalising degree		N	N	N	N	N
IN THE ARENA						
Grooming		Y	Y	N	N	N
Activity count		7	10	13	14	1
Arousal		4	4	4	4	4
Rearing count		12	17	9	18	13
Bolus count		0	0	1	0	3
Urine present		N	N	N	N	M
Gait						U
MANIPULATIONS						
Approach		5	3	3	3	3
Touch		2	2	3	2	3
Startle		3	3	3	3	3
Righting reflex		1	1	1	1	1
Tail pinch turns		3	3	3	3	3
vocalises degree		Y	Y	Y	Y	Y
Pupil reflex		2	1	2	2	1
Temperature (°C)		B	B	B	B	B
Bodyweight (g)		38.5	38.6	37.9	37.8	37.4
GRIP STRENGTH (kg)*		137	135	136	138	136
Forelimb		0.53	0.54	0.35	0.46	0.57
Hindlimb		0.51	0.56	0.27	0.64	0.50
FOOTSPRAY (cm) *		6.9	7.4	4.8	8.1	7.8

* values represent the mean of two trials

Additional comments

Animal no.

- 26 Lower teeth pale
- 27 Patchy hairloss back, lower teeth pale
- 28 Lower teeth pale
- 29 In the arena: initial slipping of hindlimbs
During grip strength: head shake
- 30 In the arena: sat in corner

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 3 males					
Animal no	91	92	93	94	95	
OBSERVATIONS						
IN THE CAGE						
Posture	S	R	R	S	S	
Palprebal closure degree	N	N	N	N	N	
IN THE HAND						
Removing	2	2	2	2	2	
Handling	2	2	2	2	2	
Vocalising degree	N	Y	N	N	N	
IN THE ARENA						
Grooming	N	Y	N	N	Y	
Activity count	14	13	13	11	12	
Arousal	4	4	4	4	4	
Rearing count	19	13	8	14	14	
Bolus count	0	0	0	0	0	
Urine present	N	N	N	N	N	
Gait						T1
MANIPULATIONS						
Approach	3	3	5	3	3	
Touch	2	4	2	5	3	
Startle	3	3	3	2	3	
Righting reflex	1	1	1	1	1	
Tail pinch	0	2	2	3	3	
turns		2	2			
vocalises degree	Y	Y	Y		Y	
Pupil reflex	2	2	2		1	
Pupil reflex	B	B	B	B	B	
Temperature (°C)	39.1	37.1	38.5	38.1	37.9	
Bodyweight (g)	126	132	137	147	143	
GRIP STRENGTH (kg)*						
Forelimb	0.49	0.53	0.52	0.53	0.36	
Hindlimb	0.42	0.58	0.48	0.36	0.48	
FOOTSPRAY (cm) *						
	6.9	8.5	9.8	10.8	9.4	

* values represent the mean of two trials

Additional comments

Animal no.

- 91 Patchy hairloss rump
- 92 Tail pinch: runs away
- 92 Lower teeth pale
- 92 During grip strength: awkward to handle, vocalising moderately
- 92 During temperature: vocalising moderately
- 95 Lower teeth pale; patchy hairloss rump

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 4 males				
Animal no	36	37	38	39	40
OBSERVATIONS					
IN THE CAGE					
Posture	S	CL	S	S	S
Palprebal closure degree	N	N	N	N	N
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Vocalising degree	N	N	N	N	Y
IN THE ARENA					
Grooming	N	Y	N	N	N
Activity count	6	12	7	3	13
Arousal	4	4	4	3	4
Rearing count	12	8	9	3	13
Bolus count	3	0	0	0	0
Urine present	S	N	N	M	N
Gait				U	
MANIPULATIONS					
Approach	3	3	3	5	3
Touch	2	2	2	3	3
Startle	3	3	2	3	4
Righting reflex	1	1	1	1	1
Tail pinch	3	3	3	3	3
turns				1	
vocalises degree	Y	Y	Y	Y	Y
Pupil reflex	2	2	2	2	1
Pupil reflex	B	B	B	B	B
Temperature (°C)	37.9	38.7	37.9	38	38.1
Bodyweight (g)	136	139	140	137	142
GRIP STRENGTH (kg)*					
Forelimb	0.66	0.51	0.60	0.58	0.41
Hindlimb	0.60	0.43	0.41	0.51	0.41
FOOTSPRAY (cm) *					
	8.2	5.4	5.9	7.7	4.4

* values represent the mean of two trials

Additional comments

Animal no.

- 37 Lower teeth pale
During manipulations: head shake occasionally
- 38 Slight brown nasal staining, lower teeth pale
In the arena: initial slipping of hindlimbs
- 39 Lower teeth pale, patchy hairloss back
In the arena: limited walking
- 40 Slight brown nasal staining, patchy hairloss back
teeth pale

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 4 males				
Animal no	96	97	98	99	100
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
Palprebal closure degree	N	N	N	N	N
IN THE HAND					
Removing	2	3	2	2	2
Handling	2	2	2	2	2
Vocalising degree	N	N	N	N	N
IN THE ARENA					
Grooming	Y	N	N	Y	N
Activity count	9	15	8	8	17
Arousal	4	4	4	4	4
Rearing count	6	12	12	8	21
Bolus count	3	3	0	0	0
Urine present	N	N	N	N	N
Gait					
MANIPULATIONS					
Approach	3	5	3	3	3
Touch	3	3	3	5	3
Startle	3	3	2	3	2
Righting reflex	1	1	1	1	1
Tail pinch turns	3	3	0	3	3
vocalises degree	Y	Y	Y	Y	Y
Pupil reflex	1	2	2	1	2
Temperature (°C)	B	B	B	B	B
Bodyweight (g)	38.2	38.8	37.5	37.4	38.5
GRIP STRENGTH (kg)*	125	131	151	145	147
Forelimb	0.50	0.65	0.29	0.52	0.30
Hindlimb	0.48	0.56	0.37	0.43	0.25
FOOTSPRAY (cm) *	10.2	10.0	5.0	7.4	6.0

* values represent the mean of two trials

Additional comments

Animal no.

- 96 Lower teeth pale, slight brown nasal staining . .
hair loss back
- 97 Lower teeth pale
- 98 Slight hairloss back, lower teeth pale
Tail pinch: runs away
- 100 General yellow staining fur, patchy hair loss . . .
lower teeth pale

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 1 females				
Animal no	46	47	48	49	50
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
Palprebal closure degree	N	N	N	N	N
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	3	2	2	2
Vocalising degree	N	N	N	Y	N
IN THE ARENA					
Grooming	N	N	N	N	N
Activity count	7	9	2	5	2
Arousal	4	4	3	4	4
Rearing count	4	9	2	3	1
Bolus count	0	0	0	0	0
Urine present	M	N	N	N	S
Gait			U	U	U
MANIPULATIONS					
Approach	3	3	3	3	5
Touch	2	3	3	3	3
Startle	3	3	3	3	2
Righting reflex	1	1	1	1	1
Tail pinch turns	3	3	3	2	3
vocalises degree	Y	Y	Y	Y	Y
Pupil reflex	3	1	1	1	1
Temperature (°C)	B	B	B	B	B
Bodyweight (g)	39.1	38.8	38	38.7	37.8
	130	124	136	140	137
GRIP STRENGTH (kg)*					
Forelimb	0.49	0.52	0.63	0.44	0.56
Hindlimb	0.44	0.52	0.48	0.59	0.39
FOOTSPLAY (cm) *					
	8.0	5.0	7.7	8.1	5.8

* values represent the mean of two trials

Additional comments

Animal no.

- 46 In the arena: sat on edge of arena
- 47 Lower teeth pale; slight brown nasal staining
- 48 Slight brown nasal staining patchy hairloss base
In the arena: sat on edge of arena
Foot splay: on landing right hindfoot toe curled
- 49 Generalised yellow staining of fur lower teeth pale
In the arena: sitting on edge of arena, limited
During manipulations: head shake
- 50 Slight brown nasal staining, generalised yellow staining
of fur, ridged tail
In the arena: sitting on edge

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 1 females					
	Animal no	101	102	103	104	105
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	R	S	S
Palprebal closure		N	N	N	N	N
degree						
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	3	2	2
Vocalising		N	N	Y	N	N
degree				1		
IN THE ARENA						
Grooming		N	N	N	N	N
Activity count		3	8	15	11	10
Arousal		3	4	4	4	4
Rearing count		6	9	15	21	10
Bolus count		0	0	0	0	0
Urine present		S	N	N	N	N
Gait		U			T1	
MANIPULATIONS						
Approach		3	3	3	3	3
Touch		2	3	3	2	3
Startle		3	3	3	3	3
Righting reflex		1	1	1	1	1
Tail pinch		3	3	2	3	3
turns				2	1	
vocalises		Y	Y	Y	Y	Y
degree		2	2	2	2	2
Pupil reflex		B	B	B	B	B
Temperature (°C)		38.5	38.3	38.7	38.2	38.3
Bodyweight (g)		125	135	141	135	140
GRIP STRENGTH (kg) *						
Forelimb		0.58	0.44	0.59	0.61	0.51
Hindlimb		0.37	0.34	0.54	0.55	0.53
FOOTSPLAY (cm) *						
		6.5	6.9	7.5	7.5	4.5

* values represent the mean of two trials

Additional comments

Animal no.

- 101 Lower teeth pale
In the arena: sitting on edge of arena, limited walking
During grip strength: head shake
- 102 Lower teeth pale, tail ridged
During grip strength: head shake
- 104 Patchy hairloss back
During manipulations: head shake
- 105 Tail ridged
In the arena: walking on edge of arena
During grip strength: head shake

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 2 females				
Animal no	56	57	58	59	60
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
Palprebal closure degree	N	N	N	N	N
IN THE HAND					
Removing	2	2	2	2	3
Handling	2	2	2	2	3
Vocalising degree	N	N	N	N	N
IN THE ARENA					
Grooming	N	Y	Y	Y	N
Activity count	14	12	13	15	8
Arousal	4	4	4	4	4
Rearing count	10	13	13	7	11
Bolus count	0	0	0	0	0
Urine present	N	N	N	S	N
Gait					
MANIPULATIONS					
Approach	3	5	3	3	3
Touch	3	2	5	1	2
Startle	3	4	3	3	2
Righting reflex	1	1	1	1	1
Tail pinch	3	3	3	3	2
turns		1	1		2
vocalises degree	Y	Y	Y	Y	
Pupil reflex	1	2	1	1	
Temperature (°C)	B	B	B	B	B
Bodyweight (g)	38.3	38.5	38.6	38.7	38
GRIP STRENGTH (kg)*	123	125	122	132	127
Forelimb	0.52	0.67	0.41	0.57	0.57
Hindlimb	0.48	0.65	0.42	0.60	0.59
FOOTSPLAY (cm) *	6.0	7.1	5.1	6.4	6.0

* values represent the mean of two trials

Additional comments

Animal no.

- 56 During temperature: vocalising softly
- 57 Slight general yellow staining of fur
- 58 Lower teeth pale, general yellow staining of fur
Pupil reflex: vocalising softly
- 60 Slight brown nasal staining, patchy hairloss : 4
In the arena: sitting on edge of arena

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 2 females					110
	Animal no	106	107	108	109	
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	S
Palprebal closure degree		N	N	N	N	N
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	3	2
Vocalising degree		Y	N	Y	N	N
		1		1		
IN THE ARENA						
Grooming		N	N	N	N	N
Activity count		13	9	5	4	2
Arousal		4	4	4	4	4
Rearing count		18	5	2	10	2
Bolus count		0	0	0	0	0
Urine present		S	N	N	N	N
Gait		T1		U		U
MANIPULATIONS						
Approach		3	3	3	3	3
Touch		1	3	3	3	3
Startle		3	3	3	3	2
Righting reflex		1	1	1	1	1
Tail pinch		3	3	3	0	3
turns		1				
vocalises degree		Y	Y	Y	Y	Y
		1	1	2	1	1
Pupil reflex		B	B	B	B	N
Temperature (°C)		38.6	38.5	37.9	37.8	38.1
Bodyweight (g)		128	134	126	134	140
GRIP STRENGTH (kg) *						
Forelimb		0.32	0.34	0.41	0.41	0.53
Hindlimb		0.33	0.44	0.33	0.59	0.51
FOOTSPRAY (cm) *						
		5.3	7.6	5.3	5.3	5.6

* values represent the mean of two trials

Additional comments

Animal no.

- 106 Righting reflex: vocalising softly
During grip strength: head shake
- 107 Patchy hairloss back
In the arena: walking along edge of arena
During grip strength: head shake
- 108 In the arena: sitting/walking along edge of arena
- 109 Slight brown nasal staining
In the arena: sitting on edge of arena
Tail pinch: runs away
- 110 In the arena: sitting on edge of arena
Pupil reflex: both pupils constricted

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 3 females				
Animal no	66	67	68	69	70
OBSERVATIONS					
IN THE CAGE					
Posture	R	R	CL	S	S
Palprebal closure degree	N	N	N	N	N
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Vocalising degree	N	Y	N	N	N
IN THE ARENA					
Grooming	N	N	N	N	N
Activity count	12	15	11	14	5
Arousal	4	4	4	4	4
Rearing count	11	8	13	17	5
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait					
MANIPULATIONS					
Approach	3	3	5	3	3
Touch	2	2	5	2	3
Startle	3	3	3	3	3
Righting reflex	1	1	1	1	1
Tail pinch	2	5	3	3	3
turns	3			1	
vocalises degree	Y	Y	Y	Y	Y
Pupil reflex	1	1	2	2	2
Temperature (°C)	N	B	B	B	B
Bodyweight (g)	38.3	38.7	38.6	38.4	38.5
GRIP STRENGTH (kg) *	123	126	133	133	136
Forelimb	0.74	0.57	0.44	0.54	0.57
Hindlimb	0.61	0.52	0.37	0.50	0.56
FOOTSPRAY (cm) *	6.3	6.2	5.1	8.4	8.5

* values represent the mean of two trials

Additional comments

Animal no.

- 66 Lower teeth pale, patchy hair loss back
Pupil reflex: both pupils constricted
- 68 Slight brown nasal staining, end of tail ridged
generalised yellow staining of fur
In the arena: sitting on edge of arena
- 69 Slight brown nasal staining, lower teeth pale
During grip strength: head shake
- 70 Generalised yellow staining of fur
In the arena: sitting on edge of arena

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 3 females					
	Animal no	111	112	113	114	115
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	S
Palprebal closure		N	N	N	N	N
degree						
IN THE HAND						
Removing		2	3	2	2	2
Handling		2	3	3	2	2
Vocalising		N	N	N	N	N
degree						
IN THE ARENA						
Grooming		N	Y	N	N	N
Activity count		23	14	7	14	14
Arousal		4	4	4	4	4
Rearing count		19	20	3	8	14
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	N
Gait				U	A1	
MANIPULATIONS						
Approach		5	3	2	5	3
Touch		3	3	3	3	3
Startle		3	3	3	3	2
Righting reflex		1	1	1	1	1
Tail pinch		3	0	3	3	3
turns		1				
vocalises		Y	Y	Y	Y	Y
degree		1	2	2	1	2
Pupil reflex		B	B	B	B	B
Temperature (°C)		38.7	38.4	38.7	38.5	38.1
Bodyweight (g)		127	126	124	120	146
GRIP STRENGTH (kg) *						
Forelimb		0.56	0.70	0.60	0.62	0.50
Hindlimb		0.66	0.85	0.55	0.43	0.34
FOOTSPLAY (cm) *						
		10.1	10.2	7.3	8.2	6.9

* values represent the mean of two trials

Additional comments

Animal no.

- 111 Slight brown nasal staining, lower teeth pale
 112 Lower teeth pale
 Tail pinch: runs away
 113 Slight brown nasal staining, generalised yellow staining
 of fur
 In the arena: walking/sitting along edge of arena
 During manipulations: head shake
 114 Lower teeth pale
 115 Patchy hairloss rump, lower teeth pale
 In the arena: initial slipping of all limbs

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 4 females					
	Animal no	76	77	78	79	80
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	R
Palprebal closure degree		N	N	N	N	N
IN THE HAND						
Removing		2	2	2	3	2
Handling		2	2	3	2	2
Vocalising degree		N	N	N	N	N
IN THE ARENA						
Grooming		N	N	N	N	N
Activity count		25	11	3	7	8
Arousal		4	4	4	4	4
Rearing count		18	13	2	9	12
Bolus count		0	0	0	0	1
Urine present		N	N	N	N	S
Gait		T1		U		
MANIPULATIONS						
Approach		3	3	3	5	3
Touch		3	3	2	3	3
Startle		3	3	3	3	3
Righting reflex		1	1	1	1	1
Tail pinch		3	3	3	3	3
turns						
vocalises degree		Y	Y	Y	Y	Y
Pupil reflex		2	1	2	2	2
Temperature (°C)		B	B	B	B	B
Bodyweight (g)		38.2	38.2	37.8	38.4	37.9
GRIP STRENGTH (kg) *		121	123	114	135	132
Forelimb		0.36	0.49	0.54	0.58	0.28
Hindlimb		0.42	0.57	0.46	0.58	0.61
FOOTSPRAY (cm) *		4.4	5.8	6.4	6.8	9.2

* values represent the mean of two trials

Additional comments

Animal no.

- 76 Lower teeth pale, patchy hair loss back
- 77 Slight yellow staining of fur, tail ridged
Pupil reflex: head shake
- 78 Patchy hair loss back, brown staining lower jaw
In the arena: walking on edge of arena, limited walking
- 79 Slight brown nasal staining, patchy hairloss neck
- 80 Slight brown nasal staining, lower teeth pale
In the arena: head shake
During manipulations: faeces soft pale

APPENDIX 1

(Functional observational battery - continued)

Pre-dose	Group 4 females					
	Animal no	116	117	118	119	120
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	S
Palprebal closure degree		N	N	N	N	N
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Vocalising degree		N	Y 1	N	N	N
IN THE ARENA						
Grooming		N	N	Y	N	N
Activity count		14	6	4	15	12
Arousal		4	4	4	4	4
Rearing count		11	6	3	18	10
Bolus count		0	0	0	0	0
Urine present		N	S	N	N	N
Gait				U	T1	
MANIPULATIONS						
Approach		0	3	3	3	3
Touch		2	3	3	2	5
Startle		3	3	2	3	3
Righting reflex		1	1	1	1	1
Tail pinch		3	2	3	2	3
turns			2	1	2	
vocalises degree		Y	Y	Y	Y	Y
Pupil reflex		2	1	1	2	2
B		B	L	B	B	B
Temperature (°C)		39.2	38.2	38.1	38.7	37.7
Bodyweight (g)		134	117	134	119	145
GRIP STRENGTH (kg)*						
Forelimb		0.45	0.42	0.60	0.43	0.54
Hindlimb		0.38	0.53	0.56	0.37	0.61
FOOTSPRAY (cm) *						
		6.8	5.4	4.9	8.2	5.7

* values represent the mean of two trials

Additional comments

Animal no.

- 116 Patchy hairloss back
Approach response: walks past probe
- 117 In the arena: walking along edge of arena
Pupil reflex: right pupil constricted
- 118 Generalised yellow staining of fur
In the arena: sitting/walking along edge of arena
- 119 Lower teeth pale
- 120 In the arena: walking along edge of arena

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 1 male					
	Animal no	6	7	8	9	10
OBSERVATIONS						
IN THE CAGE						
Posture	S	S	R	S	S	
IN THE HAND						
Removing	2	2	2	2	2	
Handling	2	2	2	2	2	
Salivation	Y	N	N	N	N	
degree	1					
Vocalising	N	N	Y	N	N	
degree			2			
IN THE ARENA						
Grooming	N	Y	N	N	N	
Activity count	7	3	3	5	7	
Arousal	3	3	4	4	4	
Rearing count	8	7	7	13	11	
Bolus count	0	0	0	0	0	
Urine present	N	S	N	N	N	
Gait		U	U			
MANIPULATIONS						
Approach	3	5	5	3	3	
Touch	1	3	1	3	1	
Startle	3	3	3	2	3	
Righting reflex	1	1	1	1	1	
Tail pinch	3	3	5	3	3	
turns	1	2				
vocalises	Y	Y	Y	Y	Y	
degree	2	2	2	2	3	
Pupil reflex	B	B	B	B	B	
Temperature (°C)	39.4	38.6	38.2	37.9	38.2	
Bodyweight (g)	354	341	384	369	397	
GRIP STRENGTH (kg)*						
Forelimb	1.15	1.31	1.20	1.29	1.26	
Hindlimb	0.79	0.57	0.97	0.82	1.08	
FOOTSPRAY (cm)*						
	8.7	10.1	14.5	14.0	12.2	

* values represent the mean of two trials

Additional comments

Animal no.

- 7 Slight brown nasal staining
In the arena: limited walking
- 8 In the arena: partial to half closed eyes occasionally
limited walking
During manipulations: vocalising moderately
During tail pinch and pupil reflex: moderately alert to handle
Pupil reflex: small cloudy area left eye
- 9 Slight lack of grooming

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 1 male				
Animal no	81	82	83	84	85
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	R	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Grooming	N	N	N	Y	N
Activity count	17	10	12	17	6
Arousal	4	4	4	4	4
Rearing count	17	16	14	26	7
Bolus count	0	0	0	0	0
Urine present	M	N	N	N	M
Gait				T1	
MANIPULATIONS					
Approach	3	3	3	3	5
Touch	2	2	1	3	3
Startle	2	2	2	3	2
Righting reflex	1	1	1	1	1
Tail pinch	5	2	0	3	3
turns		3		1	
vocalises	Y	Y	Y	Y	Y
degree	2	2	3	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.0	38.8	38.8	38.3	38.5
Bodyweight (g)	283	310	363	290	351
GRIP STRENGTH (kg)*					
Forelimb	1.25	1.00	1.08	0.84	0.82
Hindlimb	0.88	0.88	0.93	0.94	0.73
FOOTSPRAY (cm)*	11.1	11.5	11.4	8.0	11.3

* values represent the mean of two trials

Additional comments

Animal no.

- 82 Moderate lack of grooming on rump
Pupil reflex: both pupils slow to repond
- 83 Slight brown nasal staining
Tail pinch: runs away
- 84 Slight brown nasal staining
- 85 Slight brown nasal staining, slight lack of : :
back

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 2 male				
Animal no	16	17	18	19	20
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	R	R
IN THE HAND					
Removing	2	2	3	2	2
Handling	2	2	2	2	2
Salivation	Y	Y	N	N	N
degree	1	1			
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Grooming	N	N	N	N	Y
Activity count	8	14	8	6	13
Arousal	4	4	4	4	4
Rearing count	6	12	7	13	12
Bolus count	0	0	3	0	0
Urine present	N	N	N	N	N
Gait					
MANIPULATIONS					
Approach	3	5	3	5	3
Touch	2	3	3	3	3
Startle	4	1	3	3	3
Righting reflex	1	3	1	1	1
Tail pinch	2	2	3	3	2
turns	2				3
vocalises	Y	Y	Y	Y	Y
degree	2	1	2	2	1
Pupil reflex	L	B	B	B	B
Temperature (°C)	39.0	38.8	39.0	37.9	38.6
Bodyweight (g)	333	376	362	326	352
GRIP STRENGTH (kg)*					
Forelimb	1.10	1.19	1.00	0.78	1.08
Hindlimb	1.07	0.65	0.96	0.64	1.10
FOOTSPRAY (cm)*	9.7	12.0	7.5	8.0	13.0

* values represent the mean of two trials

Additional comments

Animal no.

- 16 Pupil reflex: right pupil constricted
- 17 Moderate brown nasal staining
- 18 Slight brown nasal staining
- Pupil reflex: head shake
- 19 Slight lack of grooming
- 20 In the arena: whole body grooming

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 2 male				
Animal no	86	87	88	89	90
OBSERVATIONS					
IN THE CAGE					
Posture	R	R	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	Y	N	N	N	N
degree	1				
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Grooming	N	N	N	N	N
Activity count	11	18	1	13	3
Arousal	4	4	3	4	4
Rearing count	16	15	2	12	5
Bolus count	0	0	0	0	0
Urine present	N	S	N	S	N
Gait			U		U
MANIPULATIONS					
Approach	1	3	2	5	3
Touch	1	3	3	3	3
Startle	3	3	2	3	3
Righting reflex	1	1	1	1	1
Tail pinch	2	3	0	3	4
turns	2			1	
vocalises	Y	Y	Y	Y	Y
degree	2	2	2	2	1
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.5	38.6	38.3	38.1	37.4
Bodyweight (g)	298	306	345	337	348
GRIP STRENGTH (kg) *					
Forelimb	1.07	1.01	1.41	1.48	0.73
Hindlimb	0.95	1.00	1.23	1.38	0.65
FOOTSPLAY (cm) *					
	7.9	11.6	12.6	13.6	8.5

* values represent the mean of two trials

Additional comments

Animal no.

- 86 Slight lack of grooming back
 87 Moderate lack of grooming back
 88 Slight brown nasal staining
 In the arena: sitting in corner
 Tail pinch: runs away
 During manipulations: toe nail right hindfoot missing
 90 Lower teeth pale, slight brown nasal staining
 In the arena: limited walking
 Pupil reflex: head shake

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 3 male				
Animal no	26	27	28	29	30
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	S	S	S
IN THE HAND					
Removing	2	2	2	2	3
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	Y
degree					2
IN THE ARENA					
Grooming	N	N	N	N	N
Activity count	8	15	15	11	1
Arousal	4	4	4	4	3
Rearing count	10	14	15	12	3
Bolus count	0	0	0	0	0
Urine present	N	M	N	N	N
Gait			T1		U
MANIPULATIONS					
Approach	3	3	3	3	2
Touch	1	2	2	1	3
Startle	3	3	3	2	2
Righting reflex	2	1	1	1	1
Tail pinch	3	5	2	3	0
turns			2		2
vocalises	Y	Y	Y	Y	Y
degree	2	2	1	2	3
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.6	38.8	38.2	37.9	38.0
Bodyweight (g)	359	338	395	313	354
GRIP STRENGTH (kg)*					
Forelimb	1.34	1.19	0.82	1.32	1.26
Hindlimb	1.07	1.14	0.59	1.09	0.80
FOOTSPRAY (cm)*					
	11.2	11.1	8.3	11.5	8.2

* values represent the mean of two trials

Additional comments

Animal no.

- 26 During manipulations: faeces soft, pale
- 27 Slight brown nasal staining
- 28 Pale lower teeth
- 30 In the arena: rearing in corner
Tail pinch: runs away

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 3 male				
Animal no	91	92	93	94	95
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	R	R	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	Y	Y	Y	N
degree		1	1	1	
Vocalising	N	Y	N	N	Y
degree		1			1
IN THE ARENA					
Grooming	N	N	N	N	N
Activity count	25	20	13	19	11
Arousal	4	4	4	4	4
Rearing count	29	19	10	20	16
Bolus count	0	0	0	0	0
Urine present	S	S	N	N	N
Gait				A1	T1
MANIPULATIONS					
Approach	3	2	3	3	3
Touch	2	4	1	2	3
Startle	2	3	3	2	3
Righting reflex	1	1	1	1	1
Tail pinch	3	2	3	3	2
turns		3	1		3
vocalises	Y	Y	Y	Y	Y
degree	2	3	2	2	3
Pupil reflex	B	B	B	R	B
Temperature (°C)	39.2	39.1	38.4	38.9	38.8
Bodyweight (g)	284	344	353	364	330
GRIP STRENGTH (kg)*					
Forelimb	0.98	1.28	0.96	0.82	1.20
Hindlimb	0.46	1.24	0.96	0.94	0.97
FOOTSPRAY (cm)*					
	7.1	14.4	10.8	12.4	14.4

* values represent the mean of two trials

Additional comments

Animal no.

- 91 Slight brown nasal staining
- 92 Slight lack of grooming back, lower teeth pale
- 93 During manipulations: vocalising moderately
- 93 Slight lack of grooming back, slight brown nasal staining
- 94 Moderate lack of grooming back and rump
- 94 Pupil reflex: left pupil initially dilated, right pupil remained dilated, inside of eye visible
- 95 Slight lack of grooming back

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 4 male				
Animal no	36	37	38	39	40
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	S	R	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Grooming	N	N	N	N	N
Activity count	1	11	7	13	17
Arousal	2	4	4	4	4
Rearing count	3	9	6	16	14
Bolus count	3	0	0	0	0
Urine present	N	N	N	N	N
Gait	U				
MANIPULATIONS					
Approach	2	3	3	3	5
Touch	4	3	2	1	1
Startle	3	2	3	4	3
Righting reflex	1	1	2	1	1
Tail pinch	0	3	5	3	3
turns					1
vocalises	Y		Y	Y	Y
degree	3		1	2	1
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.9	39.0	38.9	38.6	37.8
Bodyweight (g)	305	356	339	322	366
GRIP STRENGTH (kg)*					
Forelimb	1.32	0.99	1.18	0.89	0.97
Hindlimb	0.80	1.78	0.90	0.96	0.89
FOOTSPRAY (cm)*					
	10.4	10.9	7.4	10.2	9.5

* values represent the mean of two trials

Additional comments

Animal no.

- 36 In the arena: sat in corner
Tail pinch runs away
- 38 Slight brown nasal staining, lack of grooming
Pupil reflex: pupils slow to respond
- 39 Slight brown nasal staining
Pupil reflex: pupils slow to respond
- During manipulations: faeces soft
- 40 Lower teeth pale

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 1 female				
Animal no	46	47	48	49	50
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	R	CL
IN THE HAND					
Removing	2	3	2	2	2
Handling	2	3	3	3	2
Salivation degree	N	N	N	N	N
Vocalising degree	N	N	Y	N	N
IN THE ARENA					
Grooming	Y	N	Y	N	N
Activity count	15	19	13	14	8
Arousal	4	4	4	4	4
Rearing count	17	21	11	10	7
Bolus count	0	0	0	0	0
Urine present	M	N	N	S	N
Gait				T1	
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	2	2	3	5	2
Startle	2	3	3	3	2
Righting reflex	1	1	1	1	1
Tail pinch	3	5	2	3	3
turns			3		
vocalises degree	Y	Y	Y		Y
Pupil reflex	2	2	3		2
Temperature (°C)	B	B	B	B	B
Bodyweight (g)	38.8	39.1	39.1	39.2	38.3
GRIP STRENGTH (kg)*	220	214	202	258	227
Forelimb	1.08	1.09	1.30	1.42	1.14
Hindlimb	0.84	0.30	1.14	1.16	0.67
FOOTSPRAY (cm)*	8.7	7.7	10.3	10.3	6.8

* values represent the mean of two trials

Additional comments

Animal no.

- 47 Slight brown nasal staining
In the arena: tail curling continuously
- 48 During manipulations: moderately awkward to handle
vocalising moderately; toenail right hindlimb stained
- 49 Following righting: froze and head shake
Positioning for tail pinch: head shake
- 50 Slight brown staining head/muzzle, slight brown nasal staining
In the arena: walking along edge of arena

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 1 female				
Animal no	101	102	103	104	105
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	R	S	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	Y	N	N	N	N
degree	1				
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Grooming	Y	N	N	Y	N
Activity count	14	8	16	12	16
Arousal	4	4	4	4	4
Rearing count	18	17	18	13	19
Bolus count	0	0	0	0	0
Urine present	N	N	S	N	N
Gait					T1
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	3	3	3	3	2
Startle	3	4	3	3	3
Righting reflex	1	1	1	1	1
Tail pinch	2	2	3	5	5
turns	2	2	1		
vocalises	Y	Y	Y	Y	Y
degree	1	2	2	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.3	39.0	39.2	39.0	39.1
Bodyweight (g)	207	240	248	210	248
GRIP STRENGTH (kg) *					
Forelimb	1.13	1.07	0.97	1.19	0.50
Hindlimb	0.43	0.94	0.83	0.92	0.91
FOOTSPRAY (cm) *					
	6.8	8.2	9.3	8.1	6.8

* values represent the mean of two trials

Additional comments

Animal no.

- 101 In the arena: whole body grooming
- 102 During manipulations: moderate brown staining
- 105 In the cage: very active, chasing tail and jumping

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 2 female				
Animal no	56	57	58	59	60
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	R	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Grooming	N	Y	N	Y	N
Activity count	25	19	17	22	21
Arousal	4	4	4	4	4
Rearing count	21	25	14	18	19
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait	T1			T1	T2
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	2	2	2	3	2
Startle	2	3	4	3	3
Righting reflex	1	1	1	1	1
Tail pinch	3	0	2	3	2
turns			2	1	3
vocalises	Y	Y	Y	Y	Y
degree	2	2	2	1	1
Pupil reflex	R	B	B	B	B
Temperature (°C)	38.9	39.1	38.8	39.5	39.3
Bodyweight (g)	240	214	201	219	214
GRIP STRENGTH (kg)*					
Forelimb	1.39	1.24	0.93	0.97	0.90
Hindlimb	1.09	0.70	0.63	1.01	0.85
FOOTSPRAY (cm)*	8.1	9.0	6.5	7.2	6.5

* values represent the mean of two trials

Additional comments

Animal no.

- 56 Pupil reflex: left pupil constricted
 57 Tail pinch: runs away
 58 Lower teeth pale, slight brown nasal staining
 60 Slight brown nasal staining, slight brown staining muzzle

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 2 female				
	Animal no	106	107	108	109
OBSERVATIONS					
IN THE CAGE					
Posture	R	S	R	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	3	2
Salivation	N	N	N	N	N
degree					
Vocalising	Y	N	N	N	N
degree	1				
IN THE ARENA					
Grooming	Y	N	N	N	N
Activity count	16	17	18	16	2
Arousal	4	4	4	4	4
Rearing count	24	19	19	19	7
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait	T1	T1			U
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	2	3	2	3	3
Startle	3	3	3	3	2
Righting reflex	1	1	1	1	2
Tail pinch	3	3	2	0	3
turns	1		2	1	
vocalises	Y	Y	Y	Y	Y
degree	1	2	2	2	2
Pupil reflex	B	L	B	B	B
Temperature (°C)	39.1	39.3	39.0	38.9	39.4
Bodyweight (g)	205	231	204	215	219
GRIP STRENGTH (kg) *					
Forelimb	0.93	1.09	0.99	1.01	0.86
Hindlimb	0.78	0.99	0.43	1.11	0.44
FOOTSPRAY (cm) *					
	9.0	9.4	6.9	7.3	6.2

* values represent the mean of two trials

Additional comments

Animal no.

- 106 In the arena: scratching
- 107 Pale lower teeth
In the arena: sitting on edge
Pupil reflex: right pupil constricted
- 108 Slight brown nasal staining
During manipulations: awkward to handle
- 109 Slight brown nasal staining
In the arena: head shake
Tail pinch: runs away
Pupil reflex: head shake
- 110 In the arena: walking/sitting on edge of arena

APPENDIX 1

(Functional observational battery - continued)

Week 4	Animal no	66	67	68	69	70
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	R
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Salivation		N	N	N	N	N
degree						
Vocalising		N	N	N	N	N
degree						
IN THE ARENA						
Grooming		Y	N	Y	N	N
Activity count		11	19	5	20	11
Arousal		4	4	4	4	4
Rearing count		14	21	9	19	12
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	N
Gait			T1		T1	
MANIPULATIONS						
Approach		3	3	3	3	5
Touch		2	0	5	5	2
Startle		3	3	3	3	3
Righting reflex		1	1	2	1	1
Tail pinch		0	5	3	3	3
turns						
vocalises			Y	Y	Y	Y
degree			2	1	2	1
Pupil reflex		L	B	B	B	B
Temperature (°C)		39.5	39.2	38.7	39.2	38.8
Bodyweight (g)		213	224	216	192	218
GRIP STRENGTH (kg)*						
Forelimb		1.35	1.08	0.88	1.09	1.16
Hindlimb		1.01	0.82	0.55	0.87	0.97
FOOTSPRAY (cm)*						
		9.1	8.3	5.7	9.0	10.5

* values represent the mean of two trials

Additional comments

Animal no.

- 66 Tail pinch: jumped forward froze followed by head ...
- Pupil reflex: right pupil constricted
- 67 Touch response: walks backwards
- 68 Slight brown nasal staining
- 69 Slight brown nasal staining, lower teeth pale
- 70 Slight brown nasal staining, left lower tooth ...

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 4 female					
	Animal no	76	77	78	79	80
OBSERVATIONS						
IN THE CAGE						
Posture		S	R	S	S	R
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Salivation		N	N	N	N	N
degree						
Vocalising		Y	N	N	N	N
degree		2				
IN THE ARENA						
Grooming		N	N	N	N	Y
Activity count		19	13	4	7	12
Arousal		4	4	4	4	4
Rearing count		19	17	9	13	14
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	N
Gait			T1			
MANIPULATIONS						
Approach		3	3	3	3	3
Touch		5	2	1	3	3
Startle		3	3	3	3	3
Righting reflex		1	1	1	1	1
Tail pinch		2	3	3	5	3
turns		3	1			
vocalises		Y	Y	Y	Y	Y
degree		3	1	2	2	2
Pupil reflex		B	B	B	B	B
Temperature (°C)		38.9	39.7	38.3	39.2	38.8
Bodyweight (g)		209	215	196	223	205
GRIP STRENGTH (kg)*						
Forelimb		0.36	0.96	1.17	0.93	0.97
Hindlimb		0.56	0.89	0.54	0.81	0.92
FOOTSPRAY (cm)*						
		4.1	6.3	7.0	8.2	13.1

* values represent the mean of two trials

Additional comments

Animal no.

- 76 Lower teeth pale
Tail pinch: turn was a jump
- 77 Lower teeth pale, slight brown nasal staining
In the arena: tail curling occasionally
Righting reflex: slow to complete
- 79 Slight brown nasal staining
- 80 Slight brown nasal staining, lower teeth pale
hairloss rump, slight brown staining head
Pupil reflex: both pupils slow to respond

APPENDIX 1

(Functional observational battery - continued)

Week 4	Group 4 female				
	Animal no	116	117	118	119
OBSERVATIONS					
IN THE CAGE					
Posture	S	CL	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	3	2
Salivation	N	N	N	Y	N
degree				1	
Vocalising	N	Y	N	N	Y
degree		1			2
IN THE ARENA					
Grooming	N	N	N	N	N
Activity count	24	24	15	30	16
Arousal	4	4	4	4	4
Rearing count	30	21	16	27	22
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait		T1		T2	T1
MANIPULATIONS					
Approach	3	5	3	3	3
Touch	2	3	1	2	3
Startle	4	3	2	3	3
Righting reflex	1	1	1	1	1
Tail pinch	2	0	3	3	5
turns	2		1		
vocalises	Y	Y	Y	Y	Y
degree	2	2	2	2	3
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.4	39.3	38.9	39.7	38.9
Bodyweight (g)	228	218	230	207	268
GRIP STRENGTH (kg)*					
Forelimb	1.05	1.22	0.94	0.54	1.09
Hindlimb	0.60	0.91	0.82	0.37	1.16
FOOTSPLAY (cm)*					
	11.2	6.2	7.5	6.6	7.9

* values represent the mean of two trials

Additional comments

Animal no.

- 117 During manipulations: brown nasal staining, vocalises moderately
- 119 Tail pinch: runs away
- 119 Lower teeth pale, kink base of tail
- 120 Slight brown nasal staining
- 120 In the arena: scratching

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 1 male				
Animal no	6	7	8	9	10
OBSERVATIONS					
IN THE CAGE					
Posture	R	S	S	L	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	3	2	2
Salivation	Y	N	Y	N	N
degree	1		1		
Vocalising	N	N	Y	N	N
degree			2		
IN THE ARENA					
Tremors					
Grooming	N	N	N	N	N
Activity count	12	6	1	4	6
Arousal	4	4	3	3	4
Rearing count	10	7	0	8	10
Bolus count	0	0	6	0	0
Urine present	S	M	M	N	S
Gait	A1		U		
MANIPULATIONS					
Approach	3	3	5	3	3
Touch	4	2	1	5	1
Startle	3	3	4	3	3
Righting reflex	1	1	1	1	2
Tail pinch	2	2	5	5	2
turns	3	2			3
vocalises	Y	Y	Y	Y	Y
degree	3	2	2	2	3
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.2	38.6	38.6	38.1	38.5
Bodyweight (g)	470	438	529	493	532
GRIP STRENGTH (kg)*					
Forelimb	1.28	1.62	2.08	1.21	1.45
Hindlimb	0.86	0.84	1.61	0.90	0.92
FOOTSPRAY (cm)*	10.0	9.5	13.2	13.5	12.0

* values represent the mean of two trials

Additional comments

Animal no.

- 6 Slight brown nasal staining, slight lack of grooming back
- 7 Slight brown nasal staining, slight hairloss on forepaws slight lack of grooming back
- 8 Moderate lack of grooming back
In the arena: sitting in corner
During manipulations: damaged claw right forelimb
During grip strength and foot splay: vocalising moderately
- 9 Slight lack of grooming back
In the arena: eyes partially closed occasionally
During temperature: slight body tremors
- 10 Moderate lack of grooming back
Righting reflex: very slow to complete

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 1 male				
Animal no	81	82	83	84	85
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	R	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	Y	N	N
degree			1		
Vocalising	N	N	Y	N	N
degree			1		
IN THE ARENA					
Tremors		B1			
Grooming	Y	N	N	Y	N
Activity count	9	9	12	12	8
Arousal	4	4	4	4	4
Rearing count	9	9	7	12	13
Bolus count	0	0	0	0	0
Urine present	S	S	N	N	M
Gait					
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	2	1	3	3	1
Startle	2	3	4	4	3
Righting reflex	1	1	1	1	1
Tail pinch	5	2	2	2	2
turns		3	3	2	2
vocalises	Y	Y	Y	Y	Y
degree	2	3	3	1	2
Pupil reflex	B	B	B	R	B
Temperature (°C)	38.9	38.6	38.7	38.6	38.3
Bodyweight (g)	405	404	481	404	457
GRIP STRENGTH (kg) *					
Forelimb	0.82	0.56	1.59	0.57	1.30
Hindlimb	1.12	0.96	1.27	1.20	0.83
FOOTSPLAY (cm) *	12.7	10.6	14.3	8.0	11.3

* values represent the mean of two trials

Additional comments

Animal no.

- 81 Slight lack of grooming back slight brown nasal staining
- 82 Moderate lack of grooming back, slight brown nasal staining
Pupil reflex: right pupil slow to respond
During temperature: slight body tremors
- 83 Slight lack of grooming back
In the arena: right eye slightly closed occasionally
Pupil reflex: head shake
- 84 Slight lack of grooming back, slight brown nasal staining
Pupil reflex: left pupil constricted
During pupil reflex: moderately awkward to handle
- 85 During manipulations: respiration rattling sound, slight brown nasal staining

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 2 male				
Animal no	16	17	18	19	20
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	R	R	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	Y	N	N	N	N
degree	1				
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	N	N	N	N	N
Activity count	7	14	6	10	11
Arousal	4	4	3	4	4
Rearing count	13	6	1	7	14
Bolus count	0	0	0	0	0
Urine present	S	N	N	S	S
Gait					A1
MANIPULATIONS					
Approach	3	3	3	5	3
Touch	1	3	3	2	1
Startle	2	3	3	2	2
Righting reflex	1	1	1	1	1
Tail pinch	2	5	5	3	2
turns	2				3
vocalises	Y	Y	Y	Y	Y
degree	2	1	2	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.0	38.8	38.0	38.0	38.4
Bodyweight (g)	420	477	453	423	466
GRIP STRENGTH (kg) *					
Forelimb	1.54	1.41	0.91	1.10	1.22
Hindlimb	1.50	1.05	1.14	1.07	1.32
FOOTSPRAY (cm) *					
	10.8	13.9	8.2	14.0	13.7

* values represent the mean of two trials

Additional comments

Animal no.

- 16 During manipulations: slight brown nasal staining
 17 Slight brown nasal staining, slight lack of grooming on back
 During temperature: slight body tremors
 18 Slight lack of grooming back
 In the arena: irregular breathing
 During temperature: slight body tremors
 19 Moderate hairloss both forelimbs, small scab left urogenital region
 20 Slight lack of grooming back

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 2 male				
Animal no	86	87	88	89	90
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	R	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	Y	N	N	N	N
degree	1				
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	N	Y	N	N	N
Activity count	19	12	1	5	1
Arousal	4	4	2	3	3
Rearing count	19	14	0	3	0
Bolus count	0	0	0	0	0
Urine present	N	S	N	S	S
Gait			U		U
MANIPULATIONS					
Approach	3	3	1	3	3
Touch	4	3	1	3	2
Startle	3	3	3	2	3
Righting reflex	2	1	1	1	1
Tail pinch	2	3	0	3	2
turns	3		1		2
vocalises	Y	Y	Y	Y	
degree	2	2	3	2	
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.6	38.5	38.4	38.1	37.3
Bodyweight (g)	403	406	451	417	460
GRIP STRENGTH (kg) *					
Forelimb	0.42	1.16	1.76	1.92	1.26
Hindlimb	1.11	0.86	1.33	1.64	0.64
FOOTSPRAY (cm) *					
	5.6	13.4	11.1	12.6	9.5

* values represent the mean of two trials

Additional comments

Animal no.

- 87 Slight lack of grooming back
During manipulations: slight salivation
- 88 In the arena: sat facing into corner
Tail pinch: runs away
During grip strength: vocalising moderately
During temperature: head shake
- 89 Slight lack of grooming back, slight brown nasal staining
- 90 Slight lack of grooming back, slight brown nasal staining
In the arena: initial slipping of hindlimbs, sat facing into corner

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 3 male				
Animal no	26	27	28	29	30
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	3
Salivation	Y	N	N	N	N
degree	1				
Vocalising	N	N	N	Y	Y
degree				2	2
IN THE ARENA					
Tremors					B1
Grooming	N	N	N	N	N
Activity count	15	15	19	7	1
Arousal	4	4	4	4	2
Rearing count	13	18	17	7	1
Bolus count	0	0	0	0	0
Urine present	N	M	N	S	N
Gait				A1	U
MANIPULATIONS					
Approach	3	3	3	3	5
Touch	1	4	3	3	3
Startle	3	2	4	3	2
Righting reflex	1	1	1	2	1
Tail pinch	3	3	2	3	2
turns		1	3		2
vocalises	Y	Y	Y	Y	Y
degree	3	2	2	2	3
Pupil reflex	N	B	B	B	B
Temperature (°C)	38.7	38.3	39.1	38.1	37.3
Bodyweight (g)	475	423	494	438	448
GRIP STRENGTH (kg)*					
Forelimb	1.64	1.35	1.37	1.21	1.54
Hindlimb	1.15	1.47	0.77	1.25	1.14
FOOTSPRAY (cm)*	11.3	11.2	12.0	10.6	9.6

* values represent the mean of two trials

Additional comments

Animal no.

- 26 Slight lack of grooming on back
Pupil reflex: both pupils constricted
- 27 Slight lack of grooming back
- 28 Slight lack of grooming back
- 29 Slight lack of grooming back
- 30 Slight lack of grooming back
In the arena: sitting in corner
During pupil reflex and grip strength: vocalises moderately

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 3 male				
Animal no	91	92	93	94	95
OBSERVATIONS					
IN THE CAGE					
Posture	R	R	S	S	R
IN THE HAND					
Removing	2	3	2	2	3
Handling	2	2	2	3	3
Salivation	N	N	Y	Y	N
degree			1	1	
Vocalising	N	Y	N	N	Y
degree		2			2
IN THE ARENA					
Tremors					
Grooming	N	N	N	N	N
Activity count	34	19	10	21	1
Arousal	4	4	4	4	2
Rearing count	40	12	6	20	1
Bolus count	0	0	0	0	0
Urine present	M	N	N	N	N
Gait		T1	A1	A1	U
MANIPULATIONS					
Approach	3	0	3	3	1
Touch	2	1	1	0	1
Startle	3	3	3	3	4
Righting reflex	1	1	1	1	1
Tail pinch	3	2	3	3	2
turns	1	3	1	1	3
vocalises	Y	Y		Y	Y
degree	2	3		2	3
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.9	39.0	38.3	38.5	38.4
Bodyweight (g)	381	438	481	465	455
GRIP STRENGTH (kg)*					
Forelimb	0.86	1.03	1.09	0.84	1.59
Hindlimb	0.73	1.68	1.16	1.18	1.23
FOOTSPRAY (cm)*					
	9.4	12.0	11.1	13.8	13.6

* values represent the mean of two trials

Additional comments

Animal no.

- 91 Slight lack of grooming back
Righting reflex: slow to complete
- 92 Moderate lack of grooming back, slight brown staining, lower teeth pale
Approach response: tail tremble
Tail pinch: turn was a jump
During grip strength and foot splay: vocalised loudly
- 93 Slight lack of grooming back
Righting reflex: slow to complete
- 94 Moderate lack of grooming back
Touch response: walks backwards
- 95 Slight lack of grooming back
In the arena: sitting in corner

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 4 male				
Animal no	36	37	38	39	40
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	Y	N	N	N	N
degree	1				
IN THE ARENA					
Tremors	B1				
Grooming	N	N	Y	N	Y
Activity count	1	18	12	15	7
Arousal	2	4	4	4	4
Rearing count	0	18	17	18	6
Bolus count	0	0	0	0	0
Urine present	N	S	N	N	S
Gait	U	T1			
MANIPULATIONS					
Approach	1	3	3	3	5
Touch	4	2	5	3	3
Startle	3	3	2	5	4
Righting reflex	1	2	1	1	1
Tail pinch	0	5	5	3	0
turns				1	
vocalises	Y	Y	Y	Y	Y
degree	3	2	2	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.5	38.8	38.7	38.9	38.8
Bodyweight (g)	406	473	473	428	509
GRIP STRENGTH (kg) *					
Forelimb	1.42	1.42	1.46	1.83	0.67
Hindlimb	0.74	0.88	0.96	1.29	0.81
FOOTSPRAY (cm) *	10.8	11.9	9.1	10.9	7.7

* values represent the mean of two trials

Additional comments

Animal no.

- 36 Damaged claw left forepaw
In the arena: standing facing into corner, fore- hindlimbs splayed so that not supporting body, thorax touching floor of arena
Tail pinch: runs away
During manipulations: faeces pale
- 37 Slight brown staining head, slight lack of grooming back
- 38 Slight lack of grooming back
During pupil reflex: head shake and slightly splayed hindlimbs
- 39 Slight lack of grooming back
- 40 Slight lack of grooming back
Tail pinch: runs away

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 4 male				
Animal no	96	97	98	99	100
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	R	R	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	3	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	Y	N	N	N
degree		1			
IN THE ARENA					
Tremors					
Grooming	N	N	N	N	Y
Activity count	4	2	17	1	1-
Arousal	3	3	4	3	4
Rearing count	7	2	19	4	14
Bolus count	0	0	0	0	0
Urine present	S	N	M	N	N
Gait		U		U	
MANIPULATIONS					
Approach	1	2	3	2	3
Touch	1	1	1	3	5
Startle	4	3	3	3	3
Righting reflex	1	1	1	1	2
Tail pinch	2	0	3	0	0
turns	3			1	
vocalises	Y	Y	Y	Y	Y
degree	2	3	2	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.1	38.8	38.4	38.8	38.6
Bodyweight (g)	401	509	427	458	468
GRIP STRENGTH (kg) *					
Forelimb	0.90	1.21	1.50	1.64	1.06
Hindlimb	1.12	1.26	1.13	1.00	1.11
FOOTSPLAY (cm) *					
	11.9	11.3	10.0	11.1	12.3

* values represent the mean of two trials

Additional comments

Animal no.

- 96 Slight lack of grooming back
- 97 Slight lack of grooming back
In the arena: sitting in corner
Righting reflex: slow to complete
Tail pinch: runs away
- 98 Moderate hairloss both forelimbs, tip of tail
slight lack of grooming back
During manipulations: faeces soft
- 99 Slight lack of grooming back
In the arena: sitting in corner
Tail pinch: runs away
- 100 In the arena: tail curling occasionally
Tail pinch: runs away
During manipulations: faeces soft, pale

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 1 female				
Animal no	46	47	48	49	50
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	3	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors	B1				
Grooming	N	N	N	Y	Y
Activity count	10	22	17	23	19
Arousal	4	4	4	4	4
Rearing count	8	21	14	6	14
Bolus count	2	0	0	0	0
Urine present	M	N	N	S	N
Gait		T1		T1	
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	3	5	3	0	1
Startle	3	2	3	2	3
Righting reflex	1	1	1	1	1
Tail pinch	0	3	3	3	3
turns		1	1		1
vocalises	Y	Y	Y	Y	Y
degree	2	1	2	1	2
Pupil reflex	B	L	B	B	B
Temperature (°C)	38.9	39.3	39.1	39.2	38.9
Bodyweight (g)	272	243	245	304	276
GRIP STRENGTH (kg) *					
Forelimb	1.34	1.09	1.31	1.67	1.23
Hindlimb	1.25	0.18	1.16	1.50	0.86
FOOTSPRAY (cm) *					
	6.5	7.2	6.5	8.7	6.5

* values represent the mean of two trials

Additional comments

Animal no.

- 46 Tail pinch: runs away
- 47 In the arena: tail curling
Pupil reflex: right pupil constricted
During pupil reflex: head shake
Grip strength: not gripping bar with hindfeet
- 48 Slight brown staining neck, claw on left forepaw
- 49 Tip of tail missing
In the hand: head shake
In the arena: whole body grooming
Touch response: walks backwards then froze
Righting reflex and tail pinch: response followed by freezing
During manipulations: head shake, slight salivation
- 50 Slight brown nasal staining, slight brown staining on
slight lack of grooming back, left top tooth
left bottom tooth broken

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group1 female					
	Animal no	101	102	103	104	105
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	R	S
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Salivation		N	Y	N	N	N
degree			1			
Vocalising		N	N	N	N	N
degree						
IN THE ARENA						
Tremors						
Grooming		Y	N	N	N	N
Activity count		19	18	22	18	21
Arousal		4	4	4	4	4
Rearing count		18	21	18	19	23
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	N
Gait						T1
MANIPULATIONS						
Approach		3	3	5	3	3
Touch		3	3	2	1	1
Startle		3	4	2	4	3
Righting reflex		1	1	1	1	1
Tail pinch		2	2	2	2	0
turns		2	2	2	3	
vocalises		Y	Y	Y	Y	Y
degree		2	1	2	2	2
Pupil reflex		B	B	B	B	B
Temperature (°C)		38.7	39.4	39.3	38.5	38.9
Bodyweight (g)		244	274	283	241	297
GRIP STRENGTH (kg)*						
Forelimb		1.24	1.27	1.04	1.41	1.02
Hindlimb		0.23	1.13	0.88	1.14	1.09
FOOTSPRAY (cm)*						
		8.6	9.4	6.8	9.2	8.5

* values represent the mean of two trials

Additional comments

Animal no.

- 101 Slight hairloss forepaws
Grip strength: not gripping bar with hindlimbs
- 102 Scab left side of muzzle
- 104 Slight brown nasal staining, slight brown stain
- 105 Slight brown nasal staining, slight brown stain
head
Tail pinch: runs away

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 2 female				
Animal no	56	57	58	59	60
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	Y	Y	N	Y	Y
Activity count	31	20	12	16	22
Arousal	4	4	4	4	4
Rearing count	22	21	15	12	21
Bolus count	0	0	0	0	0
Urine present	S	N	N	N	N
Gait	T1	T1			T2
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	5	3	1	3	1
Startle	3	2	3	2	3
Righting reflex	2	1	1	1	1
Tail pinch	2	3	3	0	2
turns	2				3
vocalises	Y	Y	Y	Y	Y
degree	2	2	2	2	2
Pupil reflex	L	B	B	B	B
Temperature (°C)	38.8	38.7	38.8	39.6	39.1
Bodyweight (g)	288	251	232	268	253
GRIP STRENGTH (kg)*					
Forelimb	0.98	1.20	1.31	1.32	1.07
Hindlimb	0.49	0.98	0.92	1.29	0.90
FOOTSPRAY (cm)*	6.6	8.5	7.2	7.1	7.0

* values represent the mean of two trials

Additional comments

Animal no.

- 56 Slight brown staining muzzle
Pupil reflex: right pupil constricted
- 57 Slight brown staining head, ears, and muzzle
- 59 In the arena: tail curling occasionally
During manipulations: moderate salivation
Tail pinch: runs away
- 60 Slight brown staining head and forepaws

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 2 female				
Animal no	106	107	108	109	110
OBSERVATIONS					
IN THE CAGE					
Posture	R	S	S	R	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	3	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	Y	Y	N
degree			1	2	
IN THE ARENA					
Tremors					
Grooming	N	N	N	N	N
Activity count	20	24	15	20	21
Arousal	4	4	4	4	4
Rearing count	17	23	16	15	20
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait	T1	T1		T2	T1
MANIPULATIONS					
Approach	5	3	3	3	3
Touch	2	3	2	5	5
Startle	3	3	3	4	3
Righting reflex	2	1	1	1	1
Tail pinch	2	3	3	2	3
turns	3		1		
vocalises	Y	Y	Y		Y
degree	2	1	2		1
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.4	39.3	38.6	38.4	39.1
Bodyweight (g)	240	279	249	263	260
GRIP STRENGTH (kg)*					
Forelimb	0.92	1.14	1.31	1.35	0.91
Hindlimb	1.07	1.14	0.28	1.02	0.84
FOOTSPLAY (cm)*	7.3	9.3	8.0	7.3	5.6

* values represent the mean of two trials

Additional comments

Animal no.

- 108 Patchy hairloss rump
Grip strength: not gripping bar with hindlimbs and slightly awkward to handle
- 109 In the arena: sitting on edge of arena
- 110 In the arena: sitting on edge of arena
During pupil reflex: head shake

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 3 female				
Animal no	66	67	68	69	70
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	Y	N	Y	Y	N
Activity count	10	26	14	37	14
Arousal	4	4	4	4	4
Rearing count	7	18	13	27	10
Bolus count	0	0	0	0	0
Urine present	N	N	N	M	N
Gait					
		T2		T2	
		HU1			
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	2	1	3	2	3
Startle	3	3	3	2	3
Righting reflex	2	2	1	1	1
Tail pinch	2	3	3	3	3
turns	2	1		1	
vocalises	Y	Y	Y	Y	Y
degree	1	2	2	2	2
Pupil reflex	B	B	B	L	B
Temperature (°C)	39.1	39.0	39.3	39.5	38.8
Bodyweight (g)	255	260	253	230	278
GRIP STRENGTH (kg)*					
Forelimb	1.67	1.13	1.30	1.18	1.27
Hindlimb	1.31	1.15	0.90	0.80	1.07
FOOTSPRAY (cm)*					
	6.6	7.7	6.7	6.4	9.5

* values represent the mean of two trials

Additional comments

Animal no.

66 Slight hairloss left forepaw
 68 In the arena: tail curling occasionally
 69 Slight brown nasal staining, slight lack of grooming
 back
 Pupil reflex: right pupil dilated
 Holding for tail pinch: head shake

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 3 female				
Animal no	111	112	113	114	115
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	3	2	2
Salivation	N	N	N	Y	N
degree				1	
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	N	Y	N	Y	N
Activity count	19	19	20	21	18
Arousal	4	4	4	4	4
Rearing count	17	16	21	16	16
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait			T1	T1	
MANIPULATIONS					
Approach	2	3	3	3	3
Touch	1	3	2	2	5
Startle	2	2	3	2	2
Righting reflex	1	1	1	1	1
Tail pinch	2	3	3	3	3
turns	2		1		
vocalises	Y	Y	Y		Y
degree	2	2	2		2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.2	39.2	39.2	38.8	38.7
Bodyweight (g)	234	215	223	217	297
GRIP STRENGTH (kg)*					
Forelimb	1.58	1.43	1.15	1.18	1.26
Hindlimb	1.54	1.22	1.00	0.87	1.00
FOOTSPRAY (cm)*					
	12.6	9.6	10.5	10.6	11.7

* values represent the mean of two trials

Additional comments

Animal no.

- 112 Slight lack of grooming rump
Grip strength: vocalising moderately
- 114 Slight lack of grooming rump
- 115 Slight bend in middle of tail

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 4 female				
Animal no	76	77	78	79	80
OBSERVATIONS					
IN THE CAGE					
Posture	R	R	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	Y	N	Y	N	N
degree	1		1		
IN THE ARENA					
Tremors					
Grooming	N	N	N	Y	N
Activity count	27	9	12	16	14
Arousal	4	4	4	4	4
Rearing count	21	8	14	16	8
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait	A1		T1		
	T2				
MANIPULATIONS					
Approach	3	3	5	3	3
Touch	5	3	3	3	3
Startle	3	4	3	3	3
Righting reflex	1	2	1	1	1
Tail pinch	2	2	2	0	3
turns	3	3	2		
vocalises	Y	Y	Y	Y	Y
degree	2	2	1	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.2	39.3	38.2	39.3	39.1
Bodyweight (g)	245	251	243	261	235
GRIP STRENGTH (kg)*					
Forelimb	0.16	1.20	1.22	1.03	1.02
Hindlimb	1.03	0.97	0.98	0.76	0.86
FOOTSPREAD (cm)*					
	5.7	6.6	6.2	6.2	12.5

* values represent the mean of two trials

Additional comments

Animal no.

- 76 Slight lack of grooming back
Grip strength: not gripping bar with forepaws
During temperature: vocalising softly
- 77 Moderate hairloss forepaws, scabs base of tail
In the arena: tail curling occasionally
- 78 Slight lack of grooming back
In the arena: head shake, occasional slight sway
- 79 During pupil reflex: slightly awkward to handle
Tail pinch: runs away
- 80 Slight lack of grooming back

APPENDIX 1

(Functional observational battery - continued)

Week 8	Group 4 female				
Animal no	116	117	118	119	120
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	S	R	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	3	2	3	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	Y	N	N	Y
degree		1			1
IN THE ARENA					
Tremors					
Grooming	N	N	N	N	N
Activity count	21	21	1	29	17
Arousal	4	4	3	4	4
Rearing count	23	26	0	28	22
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait			U	T1	T1
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	2	3	1	0	3
Startle	3	2	4	3	3
Righting reflex	1	1	1	1	1
Tail pinch	2	0	3	2	0
turns	2		1	2	
vocalises	Y	Y	Y	Y	Y
degree	2	2	2	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.9	39.4	38.4	39.1	38.5
Bodyweight (g)	270	255	264	250	305
GRIP STRENGTH (kg)*					
Forelimb	1.48	1.14	1.35	0.37	1.43
Hindlimb	1.31	1.28	1.27	0.41	1.46
FOOTSPLAY (cm)*					
	10.5	8.0	8.8	8.5	9.5

* values represent the mean of two trials

Additional comments

Animal no.

116	Slight brown nasal staining
117	In the arena: walked backwards occasionally Tail pinch: runs away
118	In the arena: sitting in corner
119	Slight brown staining head, base of tail kinked Touch response: walks backwards Grip strength: not gripping bars with either fore- hind limbs
120	Slight hairloss forelimbs Tail pinch: runs away

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 1 male				
Animal no	6	7	8	9	10
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	3	2	2
Salivation	Y	N	N	N	N
degree	1				
Vocalising	Y	N	Y	N	N
degree	1		2		
IN THE ARENA					
Tremors	B1-2				B1
Grooming	N	N	N	N	N
Activity count	1	1	2	4	1
Arousal	2	2	2	4	2
Rearing count	1	3	1	9	1
Bolus count	0	2	0	0	0
Urine present	S	S	N	N	N
Gait	U	U	U		U
MANIPULATIONS					
Approach	5	3	2	3	1
Touch	3	4	1	1	4
vocalises					
degree					
Startle	3	3	4	3	3
Righting reflex	1	1	1	1	2
Tail pinch	2	4	3	3	2
turns	2				3
vocalises	Y		Y	Y	Y
degree	2		2	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.1	38.4	38.3	37.1	38.1
Bodyweight (g)	561	499	637	598	652
GRIP STRENGTH (kg)*					
Forelimb	1.74	1.63	1.79	1.71	2.06
Hindlimb	1.08	0.89	1.53	0.84	1.59
FOOTSPRAY (cm)*					
	10.6	12.8	13.9	13.4	12.1

* values represent the mean of two trials

APPENDIX 1

(Functional observational battery - continued)

Additional comments

Animal no.

- 6 Moderate lack of grooming; back slight hairloss
forepaws/forelimbs
In the arena: eyes-partially closed occasionally sat
along edge of arena, tremors progressed from slight
to moderate
- 7 Slight brown nasal staining; slight lack of grooming on
back; slight hairloss left forepaw
In the arena: sitting in corner; faeces soft
Holding for tail pinch: stationary position
- 8 Moderate lack of grooming back; abdomen slightly firm
to touch
In the arena: sitting in corner
Holding for tail pinch: stationary position
- 9 Moderate lack of grooming back; slight brown nasal
staining
In the arena: eyes-partially to half closed occasionally
During manipulations: toenail left forepaw damaged
During temperate: slight body tremors
- 10 Moderate lack of grooming back
In the arena: sitting in corner
Righting reflex: slow to complete

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 1 male				
Animal no	81	82	83	84	85
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	Y	N	N
degree			1		
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors		B1	B1		
Grooming	N	N	N	Y	Y
Activity count	8	7	9	12	10
Arousal	4	4	4	4	4
Rearing count	6	7	8	10	13
Bolus count	0	2	0	0	0
Urine present	S	S	N	N	S
Gait					
MANIPULATIONS					
Approach	3	5	5	3	3
Touch	3	1	3	3	1
vocalises					
degree					
Startle	2	3	3	3	3
Righting reflex	1	1	2	1	1
Tail pinch	5	2	5	2	1
turns	1	2		2	
vocalises	Y	Y	Y	Y	
degree	2	3	2	2	
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.3	38.4	38.5	38.7	37.8
Bodyweight (g)	498	468	569	512	537
GRIP STRENGTH (kg)*					
Forelimb	1.36	1.55	1.59	0.98	1.44
Hindlimb	1.34	0.94	1.29	1.18	1.04
FOOTSPRAY (cm)*					
	12.3	11.8	13.4	12.7	7.2

* values represent the mean of two trials

Additional comments

Animal no.

- 81 Slight lack of grooming back
- 82 Slight lack of grooming back
In the arena: eyes-partially closed occasionally
Pupil reflex: pupils slow to respond
- 83 Slight lack of grooming back
- 84 Slight brown staining neck; slight lack of grooming back
- 85 Slight brown nasal staining; slight lack of grooming back
During manipulations: slight red nasal discharge
Holding for tail pinch: stationary position

APPENDIX 1

(Functional observational battery - continued)

Week 13	Animal no	Group 2 male				
		16	17	18	19	20
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	S
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Salivation		Y	Y	N	N	N
degree		1	1			
Vocalising		N	N	N	N	N
degree						
IN THE ARENA						
Tremors			B1			
Grooming		Y	N			
Activity count		15	3	13	11	5
Arousal		4	3	4	4	3
Rearing count		18	3	11	11	3
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	S
Gait		A1	U			
MANIPULATIONS						
Approach		3	3	3	5	3
Touch		1	3	3	1	5
vocalises						
degree						
Startle		3	3	3	3	3
Righting reflex		1	1	2	1	1
Tail pinch		2	3	3	3	2
turns		2				2
vocalises		Y	Y	Y	Y	Y
degree		3	2	2	2	2
Pupil reflex		B	B	B	B	B
Temperature (°C)		38.5	38.5	38.2	37.1	37.1
Bodyweight (g)		538	589	541	508	553
GRIP STRENGTH (kg) *						
Forelimb		1.47	1.51	1.09	1.74	1.53
Hindlimb		1.57	1.00	1.22	0.95	1.45
FOOTSPRAY (cm) *						
		9.2	11.1	7.8	13.3	13.3

* values represent the mean of two trials

Additional comments

Animal no.

- 16 Slight lack of grooming back
- 17 Slight lack of grooming back
In the arena: limited walking
- 18 Moderate lack of grooming back
- 19 Slight lack of grooming back; moderate hair loss on forelimbs
- 20 Moderate lack of grooming back

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 2 male				
Animal no	86	87	88	89	90
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	R	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	Y	N	N	N	N
degree	1				
Vocalising	Y	N	Y	N	N
degree	1		2		
IN THE ARENA					
Tremors			B1		
Grooming	N	N	N	Y	Y
Activity count	7	14	1	13	5
Arousal	4	4	2	4	4
Rearing count	4	10	1	13	4
Bolus count	0	0	0	0	0
Urine present	N	S	N	S	N
Gait			U		
MANIPULATIONS					
Approach	2	3	1	3	3
Touch	1	4	4	3	3
vocalises					
degree					
Startle	3	3	3	3	3
Righting reflex	1	1	1	1	1
Tail pinch	2	3	3	3	2
turns	2	1	1	1	2
vocalises	Y	Y	Y	Y	Y
degree	2	2	2	2	1
Pupil reflex	B	B	B	B	B
Temperature (°C)	37.1	38.5	38.0	38.1	37.2
Bodyweight (g)	469	503	548	474	533
GRIP STRENGTH (kg)*					
Forelimb	1.11	1.56	1.99	1.92	1.25
Hindlimb	1.23	1.27	1.57	1.54	1.26
FOOTSPRAY (cm)*					
	8.3	10.8	10.5	14.1	13.2

* values represent the mean of two trials

Additional comments

Animal no.

- 86 Slight lack of grooming back
- 87 Moderate lack of grooming back
- 88 Slight brown nasal staining; slight brown staining; moderate lack of grooming back
In the arena: sat along edge of arena
- 89 Holding for tail pinch: position stationary
Moderate lack of grooming back; tip of tail missing; of tail bent
During manipulations: slight red nasal discharge
- 90 Slight lack of grooming back
Holding for tail pinch: stationary position
During temperature: slight body tremors

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 3 male				
Animal no	26	27	28	29	30
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	R	S	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	Y	N	N	N	Y
degree	2				3
IN THE ARENA					
Tremors					
Grooming	N	N	N	Y	N
Activity count	19	18	15	11	4
Arousal	4	4	4	4	4
Rearing count	16	16	15	11	3
Bolus count	0	0	0	0	0
Urine present	N	M	N	N	N
Gait	T2				
MANIPULATIONS					
Approach	3	3	3	3	5
Touch	4	1	3	4	3
vocalises					Y
degree					1
Startle	3	2	2	2	2
Righting reflex	1	1	1	1	1
Tail pinch	3	3	3	3	3
turns					1
vocalises	Y	Y	Y	Y	Y
degree	2	2	1	1	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.7	38.7	37.9	37.8	38.0
Bodyweight (g)	570	511	576	533	525
GRIP STRENGTH (kg)*					
Forelimb	2.06	1.60	1.36	1.76	1.92
Hindlimb	1.48	1.24	0.87	1.47	1.08
FOOTSPRAY (cm)*					
	12.5	11.7	11.5	11.9	9.1

* values represent the mean of two trials

Additional comments

Animal no.

- 26 Slight lack of grooming back
In the arena: tail curling occasionally
Pupil reflex: pupils very slow to respond
- 27 Moderate lack of grooming on back
- 28 Slight lack of grooming back
- 29 Slight lack of grooming back
- 30 Moderate lack of grooming back

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 3 male				
Animal no	91	92	93	94	95
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	R	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	Y	N	N
degree			1		
Vocalising	N	Y	N	N	N
degree		2			
IN THE ARENA					
Tremors					B1
Grooming	N	N	N	Y	N
Activity count	28	22	15	28	1
Arousal	4	4	4	4	2
Rearing count	26	11	10	22	0
Bolus count	0	0	0	0	0
Urine present	M	N	N	N	N
Gait			T1	A1	U
MANIPULATIONS					
Approach	3	1	3	3	1
Touch	3	1	3	3	4
vocalises					
degree					
Startle	2	3	3	3	3
Righting reflex	2	1	1	1	1
Tail pinch	3	5	3	3	5
turns	1	1		1	
vocalises	Y	Y	Y	Y	Y
degree	1	2	1	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	37.0	38.7	38.8	38.9	38.4
Bodyweight (g)	463	535	567	554	565
GRIP STRENGTH (kg)*					
Forelimb	1.63	1.93	1.91	1.16	2.05
Hindlimb	0.67	1.62	1.61	1.39	1.03
FOOTSPRAY (cm)*					
	9.4	14.9	8.5	12.7	10.2

* values represent the mean of two trials

Additional comments

Animal no.

- 91 Slight lack of grooming back
- 92 Moderate lack of grooming back
- 93 Slight lack of grooming back
- 93 During manipulations: moderate brown nasal staining
- 94 Slight lack of grooming back
- 95 Slight hairloss right forepaw; slight lack of grooming rump
- In the arena: sat near edge of arena
- Righting reflex: slow to complete
- Holding for tail pinch: stationary position

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 4 male				
Animal no	36	37	38	39	40
OBSERVATIONS					
IN THE CAGE					
Posture	S	S	S	R	S
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors	B1				
Grooming	N	Y	Y	N	N
Activity count	2	23	9	11	16
Arousal	3	4	4	4	4
Rearing count	7	22	20	15	17
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait	U				T1
MANIPULATIONS					
Approach	1	3	3	3	3
Touch	2	2	3	3	5
vocalises					
degree					
Startle	3	2	2	3	3
Righting reflex	1	2	1	1	1
Tail pinch	3	3	3	3	3
turns			1	1	1
vocalises	Y	Y	Y	Y	
degree	3	2	2	2	
Pupil reflex	B	B	B	B	B
Temperature (°C)	38.3	39.2	38.4	38.7	38.8
Bodyweight (g)	499*	550	556	508	620
GRIP STRENGTH (kg)*					
Forelimb	1.80	1.18	1.53	1.89	0.85
Hindlimb	1.00	1.51	1.23	1.56	1.26
FOOTSPLAY (cm)*					
	13.0	11.6	9.5	11.3	10.8

* values represent the mean of two trials

Additional comments

Animal no.

- 36 Toenail right forepaw damaged; slight lack of grooming back
In the arena: limited walking
- 37 Moderate lack of grooming back; matted fur lower back
- 38 Slight lack of grooming back
Pupil reflex: right pupil slow to respond
- 39 Slight hairloss left forepaw; moderate lack of grooming back
Pupil reflex: pupils slow to respond
- 40 Slight lack of grooming back
Grip strength: second trial not gripping bars with forelimbs

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 4 male				
Animal no	96	97	98	99	100
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	S	S	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	Y	N	Y	N
degree		2		2	
IN THE ARENA					
Tremors		B1			
Grooming	N	N	N	N	Y
Activity count	1	1	16	3	23
Arousal	2	2	4	3	4
Rearing count	0	0	12	5	17
Bolus count	1	0	0	0	0
Urine present	N	N	S	N	S
Gait	U	U		U	T1
MANIPULATIONS					
Approach	1	5	3	3	3
Touch	4	1	4	2	5
vocalises					
degree					
Startle	3	3	2	3	3
Righting reflex	1	1	1	1	1
Tail pinch	2	5	3	2	3
turns	3	1		3	
vocalises	Y	Y	Y	Y	Y
degree	3	3	2	2	2
Pupil reflex	N	B	B	B	B
Temperature (°C)	37.5	39.0	38.4	37.9	38.1
Bodyweight (g)	476	599	496	558	560
GRIP STRENGTH (kg)*					
Forelimb	1.13	2.35	1.43	2.04	1.13
Hindlimb	1.36	1.34	1.16	1.03	1.32
FOOTSPLAY (cm)*	13.2	12.1	13.9	14.1	13.1

* values represent the mean of two trials

APPENDIX 1

(Functional observational battery - continued)

Additional comments

Animal no.

- 96 Slight lack of grooming back; slight brown nasal staining
In the arena: faeces soft; sitting in corner
Pupil reflex: both pupils constricted
Holding for tail pinch: stationary position
- 97 Moderate lack of grooming back; slightly yellow stained urogenital region
In the arena: sitting in corner
Pupil reflex: both pupils slow to respond
- 98 Moderate hairloss forelimbs; moderate lack of grooming back
- 99 Moderate brown staining neck; slight lack of grooming back
In the arena: limited walking
Pupil reflex: left pupil slow to respond
- 100 Slight lack of grooming back
In the arena: tail curling occasionally

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 1 female				
Animal no	46	47	48	49	50
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	S	R	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	N	N	N	Y	Y
Activity count	9	17	12	14	36
Arousal	4	4	4	4	5
Rearing count	3	18	6	7	28
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	S
Gait		T1			
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	3	1	3	3	3
vocalises					
degree					
Startle	3	3	3	2	2
Righting reflex	1	1	1	1	1
Tail pinch	3	3	2	3	3
turns			3		1
vocalises	Y	Y	Y	Y	Y
degree	2	1	3	2	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.6	38.6	38.9	38.8	39.0
Bodyweight (g)	303	255	265	333	310
GRIP STRENGTH (kg)*					
Forelimb	1.20	1.50	0.77	1.73	1.16
Hindlimb	1.14	0.31	1.53	1.15	1.00
FOOTSPRAY (cm)*	7.2	7.4	6.3	10.6	7.9

* values represent the mean of two trials

Additional comments

Animal no.

- 46 Slight brown nasal staining, slight lack of grooming; rump; slight matted fur lower back
During manipulations: faeces soft
- 47 In the arena: tail curled; scratching
During pupil reflex: slightly awkward to handle
During grip strength: not gripping bar with hindlimbs
- 48 Slight brown staining head and neck, slight lack of grooming back
- 49 Slight brown staining head; tip of tail missing
During manipulations: faeces soft and pale
- 50 Slight brown staining forelimbs; slight lack of grooming back
In the arena: walking along edge of arena

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 1 female					
	Animal no	101	102	103	104	105
OBSERVATIONS						
IN THE CAGE						
Posture	S	S	R	R	R	
IN THE HAND						
Removing	2	2	2	2	2	
Handling	2	2	2	2	2	
Salivation	Y	Y	N	N	N	
degree	1	1				
Vocalising	N	N	N	N	N	
degree						
IN THE ARENA						
Tremors						
Grooming	N	N	Y	N	N	
Activity count	23	13	24	24	34	
Arousal	4	4	4	4	4	
Rearing count	26	14	25	28	33	
Bolus count	0	0	0	0	0	
Urine present	N	N	N	N	N	
Gait						T2
MANIPULATIONS						
Approach	5	3	3	3	3	
Touch	5	3	3	5	2	
vocalises						
degree						
Startle	3	3	3	3	3	
Righting reflex	1	1	1	1	1	
Tail pinch	3	3	2	5	3	
turns	1	1	3			
vocalises	Y	Y	Y	Y	Y	
degree	2	2	2	2	2	
Pupil reflex	B	L	B	B	B	
Temperature (°C)	38.9	38.9	39.0	38.9	39.0	
Bodyweight (g)	271	296	308	259	305	
GRIP STRENGTH (kg)*						
Forelimb	1.01	1.39	1.10	0.90	1.11	
Hindlimb	0.45	1.23	0.70	1.16	1.36	
FOOTSPRAY (cm)*						
	8.1	8.2	9.4	8.5	10.2	

* values represent the mean of two trials

Additional comments

Animal no.

- 101 Slight lack of grooming back
During manipulations: slight red nasal discharge
- 102 During grip strength: not gripping bar with muzzle
Slight lack of grooming back, small scab left muzzle
- 103 Pupil reflex: right pupil constricted
During manipulations: slight red nasal discharge
- 105 During pupil reflex and grip strength: slight red nasal discharge to handle
Slight brown staining head and neck

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 2 female				
Animal no	56	57	58	59	60
OBSERVATIONS					
IN THE CAGE					
Posture	R	S	S	S	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	3
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	N	N	Y	Y	Y
Activity count	26	26	14	23	25
Arousal	4	4	4	4	4
Rearing count	37	23	8	15	21
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait	T1				T1
MANIPULATIONS					
Approach	3	3	3	3	3
Touch	5	3	3	3	0
vocalises					
degree					
Startle	3	3	3	2	3
Righting reflex	1	1	1	1	1
Tail pinch	3	0	2	3	2
turns			3	1	2
vocalises	Y	Y	Y	Y	Y
degree	2	2	2	2	2
Pupil reflex	B	B	B	B	L
Temperature (°C)	38.8	39.3	39.1	39.2	38.7
Bodyweight (g)	312	274	254	293	281
GRIP STRENGTH (kg) *					
Forelimb	1.53	1.23	0.43	1.51	0.75
Hindlimb	0.89	1.20	1.32	1.27	0.82
FOOTSPRAY (cm) *					
	6.4	11.8	8.2	6.9	7.0

* values represent the mean of two trials

APPENDIX 1

(Functional observational battery - continued)

Additional comments

Animal no.

- 56 Slight brown nasal staining
During manipulations: slight red nasal discharge
- 57 Slight brown staining head, slight lack of grooming back
Pupil reflex: right eye slow to respond
Tail pinch: runs away
- 58 Moderate hairloss forelimbs, slight lack of grooming back
In the arena: scratching
During grip strength: not gripping bar with right forelimbs, moderately awkward to handle
During manipulations: faeces soft and pale
- 59 In the arena: tail curling occasionally
- 60 Slight brown nasal staining, slight brown staining head, neck, muzzle: slightly wet urogenital region
Touch response: walks backwards
Pupil reflex: right pupil constricted
During pupil reflex: slightly awkward to handle
During manipulations: moderate red nasal discharge, head shake

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 2 female				
	Animal no	106	107	108	109
OBSERVATIONS					
IN THE CAGE					
Posture	S	R	S	S	R
IN THE HAND					
Removing	2	2	2	2	2
Handling	2	2	2	2	2
Salivation	N	N	N	N	N
degree					
Vocalising	N	N	N	N	N
degree					
IN THE ARENA					
Tremors					
Grooming	N	Y	N	N	Y
Activity count	21	23	6	16	23
Arousal	4	4	4	4	4
Rearing count	17	24	9	15	25
Bolus count	0	0	0	0	0
Urine present	N	N	N	N	N
Gait	T1				
MANIPULATIONS					
Approach	3	3	3	3	5
Touch	4	3	2	5	5
vocalises					
degree					
Startle	3	2	2	2	3
Righting reflex	1	1	1	1	1
Tail pinch	2	3	3	5	3
turns	2			1	
vocalises	Y	Y	Y	Y	Y
degree	1	1	2	3	2
Pupil reflex	B	B	B	B	B
Temperature (°C)	39.0	38.9	38.4	38.3	38.9
Bodyweight (g)	259	307	281	301	288
GRIP STRENGTH (kg)*					
Forelimb	1.41	0.79	1.10	1.04	0.55
Hindlimb	0.78	1.09	0.65	1.11	0.50
FOOTSPRAY (cm)*					
	8.3	10.4	7.5	8.5	5.9

* values represent the mean of two trials

Additional comments

Animal no.

- 106 Slight lack of grooming back
- 107 Slight brown staining head, slight lack of grooming back
- 108 Slight brown nasal staining, slight lack of grooming back
- 109 During righting reflex: vocalising moderately
Slight brown nasal staining
- 110 During grip strength: slightly awkward to handle
Slight brown staining head, neck; slight brown staining
Grip strength: not gripping bars with fore and hind limbs

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 3 female					
	Animal no	66	67	68	69	70
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	R	R
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Salivation		N	N	N	N	N
degree						
Vocalising		N	N	N	N	N
degree						
IN THE ARENA						
Tremors						
Grooming		Y	N	Y	Y	N
Activity count		16	28	9	34	16
Arousal		4	4	4	4	4
Rearing count		17	21	2	27	13
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	N
Gait		T1	T1		T1	
MANIPULATIONS						
Approach		3	3	3	3	3
Touch		2	2	3	2	5
vocalises						
degree						
Startle		2	3	2	3	3
Righting reflex		1	1	1	1	1
Tail pinch		3	5	3	4	3
turns		1				1
vocalises		Y	Y	Y	Y	Y
degree		1	2	1	1	2
Pupil reflex		B	B	B	B	N
Temperature (°C)		38.6	39.3	38.5	39.1	38.6
Bodyweight (g)		276	277	282	253	301
GRIP STRENGTH (kg)*						
Forelimb		1.55	1.03	1.33	1.32	1.45
Hindlimb		1.15	0.62	0.79	0.95	1.04
FOOTSPRAY (cm)*						
		6.3	7.9	6.9	9.7	10.4

* values represent the mean of two trials

Additional comments

Animal no.

- 66 Slight hairloss left forepaw; slight lack of grooming rump
During manipulations: faeces-soft
During pupil reflex: head shake
- 68 Slight lack of grooming back
- 69 Slight brown staining head, neck; slight lack of grooming back
In the arena: bunny hops occasionally
Pupil reflex: right pupil very slow to respond
- 70 Slight lack of grooming back
Pupil reflex: both pupils constricted

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 3 female					
	Animal no	111	112	113	114	115
OBSERVATIONS						
IN THE CAGE						
Posture		S	S	S	S	R
IN THE HAND						
Removing		2	2	3	2	2
Handling		3	2	2	2	2
Salivation		N	N	N	N	N
degree						
Vocalising		N	N	N	N	N
degree						
IN THE ARENA						
Tremors						
Grooming		N	Y	N	Y	N
Activity count		10	13	13	25	16
Arousal		4	4	4	4	4
Rearing count		12	13	16	21	15
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	N
Gait				T1		
MANIPULATIONS						
Approach		5	3	2	3	3
Touch		3	5	2	5	5
vocalises						
degree						
Startle		2	3	2	2	2
Righting reflex		1	1	1	1	1
Tail pinch		2	3	0	3	3
turns		2				
vocalises		Y	Y	Y	Y	Y
degree		1	2	2	1	2
Pupil reflex		B	B	B	B	B
Temperature (°C)		39.3	39.1	39.1	39.1	38.6
Bodyweight (g)		256	231	253	251	341
GRIP STRENGTH (kg) *						
Forelimb		1.73	0.76	0.72	1.07	1.45
Hindlimb		1.44	1.18	1.22	0.62	0.79
FOOTSPRAY (cm) *						
		11.5	8.8	10.2	8.8	11.4

* values represent the mean of two trials

Additional comments

Animal no.

- 111 Slight lack of grooming back; slight brown staining head, neck
- 112 Slight lack of grooming back; slight brown nasal staining; slight brown staining head, neck
- 113 In the arena: scratching; upper body shakes
Tail pinch: runs away
Grip strength: second forelimb trial not gripping
During temperature: vocalising softly
- 114 Slight brown nasal staining; slight lack of grooming rump
- 115 Slight brown staining, neck; slight lack of grooming back

APPENDIX 1

(Functional observational battery - continued)

Week 13	Group 4 female					
	Animal no	116	117	118	119	120
OBSERVATIONS						
IN THE CAGE						
Posture		S	R	R	S	S
IN THE HAND						
Removing		2	2	2	2	2
Handling		2	2	2	2	2
Salivation		N	N	N	N	N
degree						
Vocalising		N	Y	N	N	N
degree			2			
IN THE ARENA						
Tremors						
Grooming		N	Y	N	N	N
Activity count		17	17	18	27	18
Arousal		4	4	4	4	4
Rearing count		19	17	11	29	16
Bolus count		0	0	0	0	0
Urine present		N	N	N	N	N
Gait					T1	
MANIPULATIONS						
Approach		3	3	3	3	3
Touch		2	3	5	3	2
vocalises						
degree						
Startle		2	2	3	3	3
Righting reflex		1	1	1	1	1
Tail pinch		3	2	0	2	3
turns			2		3	
vocalises		Y	Y		Y	Y
degree		2	3		3	2
Pupil reflex		B	B	B	B	B
Temperature (°C)		39.2	39.3	38.9	37.9	38.7
Bodyweight (g)		293	280	282	272	324
GRIP STRENGTH (kg)*						
Forelimb		1.62	1.05	1.23	1.02	1.51
Hindlimb		1.54	1.74	1.29	0.78	1.37
FOOTSPRAY (cm)*						
		11.5	8.4	7.6	8.6	8.4

* values represent the mean of two trials

Additional comments

Animal no.

- 116 Slight lack of grooming rump
- 117 Slight brown staining head, neck
During grip strength and foot splay: vocalising moderately
- 118 Slight brown staining head
Holding for tail pinch: head shake
Tail pinch: walks away, freezes followed by head shake
- 119 Slight brown staining head, neck; slight brown nasa.
staining; slight lack of grooming back
- 120 Moderate hairloss forelimbs; slight brown nasa.
staining; slight lack of grooming back

APPENDIX 2

Locomotor activity

Animal no.	Total time spent in locomotor activity (secs) when tested during:			
	Predose	Week 4	Week 8	Week 13
Group 1 Sex Male				
6	981	595	889	1127
7	762	836	955	604
8	505	1124	889	1026
9	356	369	308	138
10	920	841	1426	1603
81	487	768	875	700
82	689	1089	1587	1118
83	782	1595	1620	1262
84	798	878	924	1174
85	639	1139	1364	981
Group 2 Sex Male				
16	616	1103	706	609
17	930	476	642	706
18	712	926	1020	1160
19	773	657	930	762
20	649	699	663	357
86	384	771	1168	929
87	376	643	599	1167
88	632	1187	1167	1082
89	972	957	524	586
90	427	514	463	1260
Group 3 Sex Male				
26	880	1053	643	1211
27	224	410	654	642
28	867	1105	1117	1161
29	781	467	881	721
30	599	520	694	1039
91	691	1093	1225	1277
92	700	865	1050	1004
93	658	1016	1084	933
94	522	913	1003	999
95	845	996	1659	1267
Group 4 Sex Male				
36	613	622	971	1285
37	833	720	704	782
38	569	1433	1161	602
39	686	743	612	428
40	542	866	1024	900
96	344	617	914	1107
97	1016	1393	1464	1711
98	794	1507	1493	1390
99	816	799	1730	1511
100	575	823	1227	754

APPENDIX 2

(Locomotor activity - continued)

Animal no.	Total time spent in locomotor activity (secs) when tested during:			
	Pre-dose	Week 4	Week 8	Week 13
Group 1 Sex Female				
46	443	810	851	842
47	414	633	724	1177
48	548	874	934	775
49	410	852	401	552
50	606	1306	1100	1085
101	388	460	675	473
102	729	929	1102	1182
103	911	1223	1063	960
104	1064	1164	1352	1163
105	951	1115	1126	843
Group 2 Sex Female				
56	505	934	919	1031
57	474	787	685	558
58	475	1110	1104	884
59	352	839	748	603
60	671	1220	1025	961
106	296	747	929	988
107	431	1020	1207	1139
108	830	1442	1607	1188
109	863	1304	1302	820
110	1220	1539	1810	1349
Group 3 Sex Female				
66	238	749	513	426
67	624	892	1010	1187
68	506	758	953	986
69	601	1009	1409	937
70	399	1266	1311	734
111	371	669	1041	982
112	847	1078	1310	1585
113	440	1213	1025	1571
114	777	1026	626	623
115	1180	1495	1262	1077
Group 4 Sex Female				
76	246	1075	778	500
77	347	612	486	470
78	714	793	1274	1023
79	310	586	858	862
80	420	733	573	710
116	482	758	840	1139
117	966	1399	2047	1761
118	368	1004	1055	1219
119	883	1169	1476	1340
120	707	1478	1302	1327