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RE: Notification of Substantial Risk

8803000020475

Dear Sir or Madam:

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), Rhodia Inc. (Rhodia) is submitting the following information:

"RP 74: 28-Day Oral Toxicity (Gavage) Study in the Wistar Rat"[2]

Although Rhodia Inc. does not believe that this substance would present an unreasonable hazard to workers, or to the public, when properly used in its intended applications, the study nonetheless appears to meet the EPA's reporting criteria for TSCA Section 8(e).

In this study, this compound was administered by daily oral gavage to SPF-bred Wistar rats of both sexes at dose levels of 50, 200 and 800 mg/kg/day for a period of 28 days. A control group was treated similarly with the vehicle, corn oil, only.

Fatty changes along with centrilobular to diffuse hepatocellular hypertrophy, accompanied by increased organ weights, were recorded in the liver of males and females at 800 mg/kg/day. In the kidneys of males at 800 mg/kg/day, hyaline droplets were present in tubular cells (and also present at 200 mg/kg/day), together with tubular basophilia and interstitial edema. In females at 800 mg/kg/day, minimal to slight tubular casts were seen. Tubular dilation was recorded in high-dosed animals of both sexes. The pattern of changes noted in the kidneys of males closely resembles the early stages of $\alpha 2\mu$-globulin nephropathy. It is generally accepted as a phenomenon exclusively found in male rats, and therefore, it is not relevant to human risk assessment. Hemosiderin was increased in severity and/or incidence in the spleen of animals of both sexes at 800 mg/kg/day, which is thought to be related to macrocytic anemia. Increased granulopoiesis and erythropoiesis was noted in the spleen of these animals.

Other effects that were noted: Slightly lower body weights (-4.3%, -5.6%, -7.7% and -6.5%) were noted in females at 800 mg/kg/day (during treatment weeks 1,2,3 and 4, respectively). Significantly reduced body weight gain (-25.5% and -20.3%) were noted in females treated at 800 mg/kg/day during treatment weeks 3 and 4. Treatment-related effects on absolute organ weights at 800 mg/kg/day in males included increased mean weights of liver (17.2%), kidneys (22.1%) and spleen (65.4%), but decreased thymus weights (-30%). Females at 800 mg/kg/day showed increased relative weights of liver (30.6%), kidneys (7.9%) and spleen (17.6%), but decreased thymus weights (-19.2%). Mean carcass weights at 800 mg/kg/day were reduced in males by 8.5% and significantly reduced in females by 9.5%. Test-related effects on relative organ weights (organ weight to body weight ratios) in males at 800 mg/kg/day were confined by increased weights of liver, kidneys and spleen, but increased weights of thymus. Relative organ weight effects in females at 800 mg/kg/day were increased weights of brain, heart, liver, kidneys,

[2] [The test substance had been assigned the Premanufacture Notice Number of P-03-152 by the Agency. The chemical is identified by CAS# [ ], with a CAS name of "[ ].

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spleen and ovaries. Organ to brain weight ratios of liver, kidneys and spleen at 800 mg/kg/day were significantly increased in males and females.

Clinical laboratory investigations revealed a normochrome, slightly macrocytic anemia associated with thrombophilia (in males), neutrophilia (which did not reach significance in females) and monocytosis. The higher reticulocyte counts and the shift in the reticulocyte maturation index to immature cells recorded for males and females at 800 me/kg/day points to a stimulated erythropoietic activity. Treatment related changes in blood chemistry parameters in males occurred at 800 mg/kg/day and included a lower mean value for glucose, but higher creatinin, total bilirubin and glutamate dehydrogenase levels together with higher plasma sodium, calcium, phosphate, protein and albumin levels. Treatment related changes in females were equally confined to the high dose group and comprised higher total bilirubin and lactate dehydrogenase levels and lower glutamate dehydrogenase and alkaline phosphatase levels together with higher values for sodium and calcium, protein, albumin and globulin.

In males and females at 800 mg/kg/day, inflammatory lesions were recorded in the stomach, which may have been caused by an irritative potential of the test item, or could have been induced mechanically, since the incidence occurred also in a male of the control group.

This study was communicated to Rhodia on August 8, 2003.

Rhodia asserts that the specific chemical identity information contained within this notice constitutes confidential business information, and has included the appropriate sanitized copy.

Should you have any questions, or require any further information, please call (215) 369-9734. Thank you.

Very truly yours,
RHODIA INC.

Judith L. Kranetz
Manager, Product Safety

JLK/
Atts
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RCC Study Number 845763

RP 74:

28-Day Oral Toxicity (Gavage) Study in the Wistar Rat

Final Report (PART I OF II)

Authors: Dr. E.W. Sommer, Dr. D. Schroeder, Dr. P. Gretener, Dr. K. Weber

Sponsor: Rhodia Services DPS
190, avenue Thiers
F-69457 Lyon Cedex 06 / France

RCC

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1 PREFACE

1.1 GENERAL

Title	**RP 74:** 28-Day Oral Toxicity (Gavage) Study in Rats
Sponsor	Rhodia Services DPS 190, avenue Thiers F-69457 Lyon Cedex 06 / France
Study Monitor	B. Hendrickx Rhodia Services DPS 190, avenue Thiers F-69457 Lyon Cedex 06 / France
Test Facility	a) RCC Ltd Toxicology Division CH – 4452 Itingen / Switzerland
	b) RCC Ltd Toxicology Division CH – 4332 Stein / Switzerland
Test Site	c) RCC Ltd Environmental Chemistry & Pharmanalytics Division CH – 4452 Itingen / Switzerland

1.2 RESPONSIBILITIES

Study Director	Dr. E. Sommer (b)
Deputy Study Director	Dr. B. Damme (a)
Technical Coordinator	P. Althaus Ravenstijn (a)
Clinical Laboratory Investigations	Dr. P. Gretener (a)
Necropsy/Histotechnique	Dr. K. Weber (a)
Study Pathologist	Dr. K. Weber (a)
Head of Lead Quality Assurance	I. Wüthrich

1.2.1 PRINCIPAL INVESTIGATORS

Analytical Chemistry	Dr. D. Schroeder (c)

1.3 SCHEDULE

Experimental Starting Date	18 December 2002
Experimental Completion Date	22 January 2003
Delivery of Animals	18 December 2002
Acclimatization/Pretest	18 December 2002 to 24 December 2002
Administration/Treatment	25 December 2002 to 21 January 2003
Termination (Necropsy)	22 January 2003
Study completion date	16 April 2003

1.4 ARCHIVING

RCC Ltd (CH-4452 Itingen / Switzerland) will retain the study plan, raw data, sample of test item(s), specimens (as long as the quality permits evaluation) and the final report of the present study for at least ten years. Wet tissue samples will be archived at RCC Ltd for a minimum of five years. Thereafter, in agreement with the Sponsor, these samples may be further archived at RCC Ltd or transferred to another GLP archive facility for the remainder of the prescribed period. No data will be discarded without the Sponsor's consent.

1.5 ACCREDITATION

The test facility "RCC Ltd, Toxicology Division" is accredited according to ISO/IEC 17025 under accreditation number STS 085 by the Swiss Accreditation Service.

1.6 TEST GUIDELINES

The study procedures described in this report conform with the following guidelines:

Directive 96 / 54 / EC, B. 7. "Repeated dose (28 days) toxicity (oral)", September 30, 1996.

"Repeated Dose Oral Toxicity - Rodent: 28-day or 14-day Study", OECD Guidelines for the Testing of Chemicals, Section 4, Health Effects, Number 407, July 27,1995.

1.7 ANIMAL WELFARE

This study will be performed in an AAALAC-approved laboratory in accordance with the Swiss Animal Protection law under license no. 35.

1.8 SIGNATURES

Study Director: E.W. Sommer, Dr. phil. II

.....
date: 16 - APRIL - 2003

Management: H. Fankhauser, Dr. phil. nat.

.....
date: 16-April - 2003

The signatures of Dr. D. Schroeder (Analytical Chemistry) and Dr. K. Weber (Pathology) are included in the relevant attached reports.

1.9 STATEMENT OF COMPLIANCE / GLP GUIDELINES

RCC STUDY NUMBER:	845763
TEST ITEM:	RP 74
STUDY DIRECTOR:	E.W. Sommer, Dr. phil. II
TITLE:	RP 74: 28-Day Oral Toxicity (Gavage) Study in the Wistar Rat

This study has been performed in compliance with the:

Swiss Ordinance relating to Good Laboratory Practice, adopted February 2nd, 2000 [RS 813.016.5] This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C (97)186/Final].

There were no circumstances that may have affected the quality or integrity of the data.

Study Director: E.W. Sommer, Dr. phil. II

E.W. Sommer

date: 16 - APRIL - 2003

1.10 QUALITY ASSURANCE STATEMENT

RCC Ltd, Toxicology Division, CH-4452 Itingen / Switzerland

STATEMENT

RCC STUDY NUMBER: 845763
TEST ITEM: RP 74
STUDY DIRECTOR: E.W. Sommer, Dr. phil. II
TITLE: RP 74: 28-Day Oral Toxicity (Gavage) Study in the Wistar Rat

The general facilities and activities are inspected periodically and the results are reported to the responsible person and the management.

Study procedures were periodically inspected. The study plan and this report were audited by the Quality Assurance Unit. The dates are given below.

Dates and Types of QAU Inspections		Dates of Reports to the Study Director and to Management
29.10.02	Study Plan	29.10.02
25.12.02	Test System, Test Item, Treatment, Dose Prep.	25.12.02
22.01.03	Necropsy	22.01.03
20.01.03	Process-based (blood sampling)	20.01.03
21.01.03	Process-based (Clin. Lab. Investigations)	21.01.03
28.01.03	Process-based (Histotechnique)	28.01.03
05. - 07./11. - 13.03.03	Report	13.03.03

This statement also confirms that this final report reflects the raw data. In addition, this final report includes a QAU-Statement issued by the Test Site Quality Assurance Unit.

Quality Assurance: S. Reinhardt

S. Reinhardt

date: 16-APR-2003

2 SUMMARY

GENERAL

In this subacute toxicity study, RP 74 (batch no. ASS 685: 94.4% purity) was administered by daily oral gavage to SPF-bred Wistar rats (HanBrl: WIST) of both sexes at dose levels of 50, 200 and 800 mg/kg body weight/day for a period of 28 days. A control group (0 mg/kg body weight/day) was treated similarly with the vehicle, corn oil, only.

The groups comprised 5 animals per sex which were sacrificed after 4 weeks of treatment. General clinical signs (daily cage-side observations) and detailed clinical signs (weekly outside cage observations), food consumption and body weights were recorded periodically during the pretest and the treatment periods. Functional observational battery and locomotor activity were performed during week 4.

At the end of the treatment period, blood samples were withdrawn for hematology and plasma chemistry analyses. Urine samples were collected for urinalysis. All animals were killed, necropsied and examined post mortem. Histological examinations were performed on organs and tissues from all control and high dose animals, and all gross lesions from all animals. In addition, adrenals (males only), stomach, liver, kidneys, spleen, thymus, and bone marrow were examined from all animals of low and medium dose groups.

MORTALITY / VIABILITY

One male of the control group was sacrificed on day 24 of treatment due to poor health condition.

All other animals survived until scheduled necropsy.

CLINICAL SIGNS

GENERAL CLINICAL SIGNS

Two males and all females of the high dose group presented with transient salivation on individual days within the period from day 16 through 28.

All other animals revealed no clinical signs during the daily general clinical observation periods.

FUNCTIONAL OBSERVATIONAL BATTERY

One male of the high dose group exhibited salivation in week 4.

Grip Strength

Grip strength was not affected by treatment with the test item. The seemingly significance in the lower value seen in the forelimbs in females at 50 mg/kg/day has been derived from the rather low standard deviation but stayed within the normal reference range.

LOCOMOTOR ACTIVITY

Locomotor activity was not affected by the test item.

FOOD CONSUMPTION

Food consumption and relative food consumption were not affected by the test item.

BODY WEIGHT DEVELOPMENT

Slightly lower body weights (-4.3%, -5,6%, -7.7% and -6.5%) were noted in females at 800 mg/kg/day during treatment weeks 1, 2, 3 and 4, respectively). Significantly reduced body weight gain (-25.5% and -20.3%) were noted in females treated at 800 mg/kg/day during treatment weeks 3 and 4.

CLINICAL LABORATORY INVESTIGATIONS

Hematology

At the end of the treatment period, males and females of group 4 (800 mg/kg/day) had a normochrome, slightly macrocytic anemia associated with thrombophilia (in males), neutrophilia (which did not reach significance in females), and monocytosis. The higher reticulocyte counts and the shift in the reticulocyte maturation index to immature cells (lower value for L-Reti and higher value for H-Reti) recorded for males and females of group 4 points to a stimulated erythropoietic activity.

Clinical chemistry

Some differences in the effects of the test item on blood chemistry parameters were seen between males and females. Treatment-related changes in males were confined to the high dose group treated at 800 mg/kg/day and included a lower mean value for glucose, higher creatinin, total bilirubin and glutamate dehydrogenase levels together with higher plasma sodium, calcium, phosphate, protein and albumin levels. Treatment-related changes in females were equally confined to the high dose group and comprised higher total bilirubin and lactate dehydrogenase levels and lower glutamate dehydrogenase and alkaline phosphatase levels together with higher values for sodium and calcium, protein, albumin and globulin.

ORGAN WEIGHTS

Treatment-related effects on absolute organ weights at 800 mg/kg/day in males included increased mean weights of liver (17.2%), kidneys (22.1%) and spleen (65.4%) but decreased thymus weights (-30%), and in females increased mean weights of liver (30.6%), kidneys (7.9%) and spleen (17.6%) but decreased thymus weights (-19.2%). Mean carcass weights at 800 mg/kg/day were reduced in males by 8.5% and significantly reduced in females by 9.5%. Test item-related effects on relative organ weights (organ weight to body weight ratios) in males at 800 mg/kg/day were confined to increased weights of liver, kidneys, and spleen but decreased weights of thymus. Relative organ weight effects in females at 800 mg/kg/day comprised increased weights of brain, heart, liver, kidneys, spleen and ovaries. Organ to brain weight ratios of liver, kidneys and spleen at 800 mg/kg/day were significantly increased in males and females.

PATHOLOGY

MACROSCOPIC FINDINGS

The kidneys of one high dose male (no. 16) were enlarged. This finding was considered as treatment-related. All other findings were within the range of background lesions that may be recorded in rats of this strain and age. They comprised thickened duodenum, thymus enlargement or size reduction, uterine dilatation and splenic discoloration.

MICROSCOPIC FINDINGS

Fatty change along with centrilobular to diffuse hepatocellular hypertrophy, accompanied by increased organ weights were recorded in the liver of males and females at 800 mg/kg/day.

In the kidneys of males at 800 mg/kg/day hyaline droplets were present in tubular cells (and also present at 200 mg/kg/day), together with tubular basophilia and interstitial edema, and, in a single case, tubular epithelial necrosis was noted along with tubular epithelial swelling. In females at 800 mg/kg/day minimal to slight tubular casts were seen. In animals of both sexes at 800 mg/kg/day tubular dilation was recorded.

Hemosiderin, megakaryocytosis, granulopoiesis and erythropoiesis were increased in severity and/or incidence in the spleen of animals of both sexes at 800 mg/kg/day.

In males and females at 800 mg/kg/day inflammatory lesions were recorded in the stomach mainly forestomach) and consisted of inflammation, epithelial and basal cell hyperplasia and ulceration. Similar findings occurred in a male of the control group that had to be sacrificed on day 24 due to poor health condition. An irritative potential of the test item or mechanically induced lesions might have caused this inflammatory reaction in the stomach.

The findings of increased thymic atrophy in males and females at 800 mg/kg/day and the diffuse hypertrophy in the adrenal cortex of one male at 800 mg/kg/day and increased vacuolation in the zona fasciculate in males at 200 and 800 mg/kg/day were considered as to be secondary caused by stress.

3 ASSESSMENT

Oral administration of RP 74 to Wistar rats at doses of 50, 200 and 800 mg/kg/day for 28 days revealed no test item-related effects on food consumption, on grip strength or on locomotor activity, and no clinical signs besides of salivation in two males and all females of the high dose group on individual days towards the end of the treatment period. A slight reduction in body weights and body weight gain was noted in females treated at 800 mg/kg/day from weeks 2 through 4. One male of the control group had to be sacrificed on day 24 of treatment due to poor health condition.

Clinical laboratory investigations revealed a normochrome, slightly macrocytic anemia associated with thrombophilia (in males), neutrophilia (which did not reach significance in females), and monocytosis. The higher reticulocyte counts and the shift in the reticulocyte maturation index to immature cells recorded for males and females at 800 mg/kg/day points to a stimulated erythropoietic activity. Treatment related changes on blood chemistry parameters in males occurred at 800 mg/kg/day and included a lower mean value for glucose, but higher creatinin, total bilirubin and glutamate dehydrogenase levels together with higher plasma sodium, calcium, phosphate, protein and albumin levels. Treatment-related changes in females were equally confined to the high dose group and comprised higher total bilirubin and lactate dehydrogenase levels and lower glutamate dehydrogenase and alkaline phosphatase levels together with higher values for sodium and calcium, protein, albumin and globulin.

Treatment-related effects on absolute organ weights at 800 mg/kg/day in males and females included increased mean weights of liver, kidneys and spleen but decreased thymus weights. The mean carcass weights at 800 mg/kg/day were decreased in males and females. Test item-related effects on relative organ weights in males and females at 800 mg/kg/day were confined to increased weights of liver, kidneys, and spleen but decreased weights of thymus. In addition, females at 800 mg/kg/day showed also increased relative weights of brain, heart, and ovaries. Carcass weights were equally reduced in males and females.

Fatty change along with centrilobular to diffuse hepatocellular hypertrophy, accompanied by increased organ weights, were recorded in the liver of males and females at 800 mg/kg/day. In the kidneys of males at 800 mg/kg/day hyaline droplets were present in tubular cells (and also present at 200 mg/kg/day), together with tubular basophilia and interstitial edema. In females at 800 mg/kg/day minimal to slight tubular casts were seen. Tubular dilation was recorded in high dosed animals of both sexes. The pattern of changes noted in the kidneys of males closely resembles the early stages of α2μ-globulin nephropathy. It is generally accepted as a phenomenon exclusively found in male rats, and therefore, it is not relevant to human risk assessment. Hemosiderin was increased in severity and/or incidence in the spleen of animals of both sexes at 800 mg/kg/day which is thought to be related to macrocytic anemia. Increased granulopoiesis and erythropoiesis was noted in the spleen of these animals.

In males and females at 800 mg/kg/day inflammatory lesions were recorded in the stomach may have been caused by an irritative potential of the test item or could have been induced mechanically since the incidence occurred also in a male of the control group.

Based on the results obtained in this study, 50 and 200 mg/kg b.w./day of RP 74 were established as the no-observed-effect-level (NOEL) in males and females, respectively. For both sexes 200 mg/kg b.w./day was determined as the no-observed-adverse-effect-level (NOAEL).

4 OBJECTIVE

4.1 PURPOSE AND RATIONALE

The purpose of this oral toxicity study was to assess the cumulative toxicity of RP 74 when administered daily to rats by gavage for a period of 28 days.

This study should provide a rational basis for toxicological risk assessment in man. The results of this study should indicate potential target organs and should identify chemicals with neurotoxic potential.

5 MATERIALS AND METHODS

5.1 TEST SYSTEM

Test system	Rat, HanBrl:WIST (SPF)
Rationale	Recognized by the international guidelines as the recommended test system.
Source	RCC Ltd Biotechnology & Animal Breeding Division CH-4414 Fuellinsdorf / Switzerland
Total number of animals per group	Groups 1 - 4: 5 males and 5 females each
Total number of animals	20 males and 20 females
Age at delivery	Approximately 6 weeks
Body weight range at acclimatization	Males: 132.6 – 153.5 grams (means 144.1 grams) Females:115.1 – 125.3 grams (means 121.4 grams)
Identification	Cage card and individual ear tattoo
Randomization	Computer-generated random algorithm
Acclimatization	Under test conditions after health examination. Only animals without any visible signs of illness were used for the study.

5.2 ALLOCATION

Allocation And Dose Levels	Group 1* 0 mg/kg/day	Group 2 50 mg/kg/day	Group 3 200 mg/kg/day	Group 4 800 mg/kg/day
Males	1 - 5	6 - 10	11 - 15	16 - 20
Females	21 - 25	26 - 30	31 - 35	36 - 40

* - Control animals were treated with the vehicle only

5.3 HUSBANDRY

Room number	E 15 at RCC Ltd, Itingen
Conditions	Standard Laboratory Conditions. Air-conditioned with 10-15 air changes per hour, and continuously monitored environment with a target range for temperature of 22 ± 3 °C and for relative humidity between 30 and 70 %. 12 hours fluorescent light / 12 hours dark, music during the light period.
Accommodation	In groups of five in Makrolon® type-4 cages with wire mesh tops and standardized softwood bedding ('Lignocel' Schill AG,CH-4132 Muttenz / Switzerland).
Diet	Pelleted standard Provimi Kliba 3433 (batch no. 67/02, 75/02) rat maintenance diet (Provimi Kliba AG, CH-4303 Kaiseraugst/ Switzerland) was available *ad libitum*. The feed batches were analyzed for contaminants (see Appendix III, pp. 173 – 177).
Water	Community tap-water from Itingen was available *ad libitum* in water bottles. Results of bacteriological assay, chemical and contaminant analyses of representative samples are attached to this report (see Appendix II, pp. 169 – 172). None of the contaminants analyzed in the water and diet is considered to have been present at a concentration which would have affected the validity of the results.

5.4 TEST ITEM

Identity	RP 74
Description	clear brown liquid
Batch number	ASS 685
Purity	94.4%
Stability of test item	Stable under storage conditions
Expiry date	30 September 2003
Storage conditions	at room temperature (17-23°C) in the original container away from direct sunlight under nitrogen headspace
Safety precautions	Routine hygienic procedures (gloves, goggles, face mask)

The data were provided by the sponsor.

5.5 DOSE FORMULATION

The test item formulations were prepared daily. The formulations were stored at room temperature until use.

The test item was weighed (without correction of purity) into a glass beaker on a tared precision balance and the vehicle added. The mixtures were prepared using a magnetic stirrer.

Homogeneity of the test item in the vehicle was maintained during the daily administration period using a magnetic stirrer.

The dose formulations were mixed and administered at room temperature (17-23°C) in glass beakers, and thereafter were disposed of.

5.5.1 ANALYSIS OF DOSE FORMULATIONS

Concentration, homogeneity and stability (after 2 hours at room temperature) of the dose formulations were determined in samples taken after experimental start. Concentration and homogeneity of the dose formulations were determined in samples taken during week 3 of the treatment. The analyses was performed by RCC Ltd, according to a HPLC analytical method supplied by the sponsor. The results are presented in Appendix V (p. 221-236).

5.6 VEHICLE AND CONTROL ITEM

Identity	corn oil
Description	yellow liquid
Art.no.	6212.1
Supplier	Carl Roth GmbH + Co. 76185 Karlsruhe
Batch number	13253525
Expiry date	09 July 2005
Stability of test item	Stable under storage conditions
Storage conditions	at room temperature (17-23°C) in the original container away from direct sunlight
Safety precautions	Routine hygienic procedures (gloves, goggles, face mask)

5.7 TREATMENT

Method	Oral, by gavage.
Rationale	Accidental oral ingestion is a possible route of human exposure.
Daily dose levels	Group 1: 0 mg/kg body weight Group 2: 50 mg/kg body weight Group 3: 200 mg/kg body weight Group 4: 800 mg/kg body weight
Rationale for dose level selection	Based upon the results of a non-GLP 5-day dose-range-finding study (RCC Project 845762) in which RP 74 was administered by gavage to 2 rats per group and sex. In this study food consumption and body weight were dose-dependently reduced.
Frequency of administration	Daily
Dose volume	5 ml/kg body weight
Duration of acclimatization period	7 days
Duration of treatment	28 days

5.8 OBSERVATIONS

5.8.1 MORTALITY / VIABILITY

Observations for mortality/viability were performed twice daily.

5.8.2 GENERAL CLINICAL OBSERVATIONS (DAILY)

To detect changes in the state of health or behavior, or any reaction to treatment, general clinical observations (cage side observations) were performed once during pretest and twice daily thereafter on treatment days 1 to 3, and then once daily on days 4 to 28.

5.8.3 DETAILED CLINICAL OBSERVATIONS (WEEKLY)

Detailed clinical observations were performed during pretest and once weekly thereafter at about the same time each day. Detailed clinical observations were conducted in a structured way with animals being observed in a standard arena. Observations were conducted identically to those performed as part of the FOB during week 4 and included tests for sensorimotor functions.

5.8.4 FUNCTIONAL OBSERVATIONAL BATTERY (FOB)

At week 4, relevant parameters from a modified Irwin screen test were performed on all rats. A description of all test parameters is listed in the report. Any abnormal findings was recorded and graded in severity.

Hind-forelimb grip strength measurement was performed using a push-pull strain gauge (Mecmesin, AFG 25N).

Locomotor activity was measured quantitatively. Decreased or increased activity was recorded. Activity was measured with Activity Monitor AM 1052 (Benwick Electronic Equipment Design Manufacture, England). Activity of the animals (low-beams count) was recorded for 15-minute intervals over a period of 60 minutes. These data and the total activity over 60 minutes are reported.

5.8.5 FOOD CONSUMPTION

The food consumption was recorded once during the pretest period and weekly thereafter, using an on-line electronic recording system consisting of a Mettler balance connected to the RCC computer.

5.8.6 BODY WEIGHTS

Body weights were recorded weekly during pretest and treatment and before necropsy, using an on-line electronic recording system consisting of a Mettler balance connected to the RCC computer.

5.9 CLINICAL LABORATORY INVESTIGATIONS

Blood sampling: After 4 weeks: 22 January 2003

Blood samples for hematology and clinical chemistry were collected from all animals under light isoflurane anesthesia. The animals were fasted for approximately 18 hours before blood sampling but allowed access to water ad libitum. Blood samples were collected early in the working day to reduce biological variation caused by circadian rhythms. Blood samples were drawn from the retro-orbital plexus using micro-hematocrit glass capillary tubes.

The assays were performed at RCC Ltd (Stein) under internal laboratory quality control conditions to assure reliable test results.

In the summary and individual tables the names of some parameters have been abbreviated. Any abbreviation has been defined in this section. Clinical laboratory data are expressed, with a few exceptions, in general accordance with the International System of Units (SI).

Key to abbreviations of units:

l	liter	g	gram	m	milli (10^{-3})
mol	mole	kg	kilogram	µ	micro (10^{-6})
sec	second	T	tera (10^{12})	n	nano (10^{-9})
		G	giga (10^{9})	p	pico (10^{-12})
				f	femto (10^{-15})

General remarks:

n.d. = not determined, no value measured for this parameter
Reference values generally depend on the method used for analysis. The assignment is given by a method code.

5.9.1 HEMATOLOGY

The following anticoagulants were used during blood collection:

Complete blood cell count	Di-potassium-EDTA
Methemoglobin	Lithium heparin
Coagulation	Sodium citrate, 3.8% (1 part anticoagulant to 9 parts blood)

Complete blood cell count

Parameter	Abbreviation	Unit		Method code	Instrumentation
Erythrocyte count	RBC	T/l		M01	Advia 120[1]
Hemoglobin	Hb	mmol/l		M01	Advia 120
Hematocrit	Hct	rel.1		M01	Advia 120
Mean corpuscular volume	MCV	fl		M01	Advia 120
Red cell volume distribution width	RDW	rel.1		M01	Advia 120
Mean corpuscular hemoglobin	MCH	fmol		M01	Advia 120
Mean corpuscular hemoglobin concentration	MCHC	mmol/l		M01	Advia 120
Hemoglobin concentration distribution width	HDW	mmol/l		M01	Advia 120
		relative	absolute		
Reticulocyte count	Reti	rel.1	G/l	M02	Advia 120
Reticulocyte maturity index	L Reti	rel.1		M01	Advia 120
(low, medium, high fluorescence)	M Reti	rel.1		M01	Advia 120
	H Reti	rel.1		M01	Advia 120
Leukocyte count, total	WBC	G/l		M01	Advia 120
Differential leukocyte count		relative	absolute		Advia 120
Neutrophils	Neut	rel.1	G/l	M01	Advia 120
Eosinophils	Eos	rel.1	G/l	M01	Advia 120
Basophils	Baso	rel.1	G/l	M01	Advia 120
Lymphocytes	Lympho	rel.1	G/l	M01	Advia 120
Monocytes	Mono	rel.1	G/l	M01	Advia 120
Large unstained cells	Luc	rel.1	G/l	M01	Advia 120
Platelet count	Plt	G/l		M01	Advia 120

[1] ADVIA 120 hematology system (Bayer)

Hemoglobin derivatives

Parameter	Abbreviation	Unit	Method	Method code	Instru-mentation
Methemoglobin	MetHb	rel. 1	Spectrometry, results given as ratio of total hemoglobin	M01	OSM3[2]

Coagulation

Parameter	Abbreviation	Unit	Method	Method code	Instru-mentation
Prothrombin time (=Thromboplastin time)	PT	rel. 1	Clotting assay, recombinant thromboplastin reagent Results as ratio of normal activity	M01	STA[3]
Activated partial thromboplastin time	PTT	sec	Clotting assay, synthetic phospholipid reagent, colloidal silica activator	M01	STA

5.9.2 CLINICAL CHEMISTRY

Lithium heparin (12-30 I.U./ml) was used as anticoagulant during blood collection.

Parameter	Abbre-viation	Unit	Method	Method code	Instru-mentation
Glucose	Gluc	mmol/l	Hexokinase/G6P-DH	M01	Hitachi 917[4]
Urea	Urea	mmol/l	Urease/GLDH	M01	Hitachi 917
Creatinine	Creat	µmol/l	Enzymatic colorimetric test	M01	Hitachi 917
Bilirubin, total	Bili-tot	µmol/l	Reaction with 2,5-Dichloro-phenyl-diazonium salt	M01	Hitachi 917
Cholesterol, total	Chol	mmol/l	Enzymatic, CHOD/PAP	M01	Hitachi 917
Triglycerides	Trigly	mmol/l	Glycerol-Kinase GPO/PAP method	M01	Hitachi 917
Phospholipids	Phos-Lip	mmol/l	Phospholipase-Cholinoxidase-Peroxidase-reaction	M01	Hitachi 917
Aspartate aminotransferase EC 2.6.1.1	ASAT	U/l 37°C	MDH/NADH coupled reaction	M01	Hitachi 917

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[2] Hemoximeter OSM3

[3] STA-compact analyzer (Roche Diagnostics)

[4] Hitachi 917 analyzer, Roche Diagnostics

Parameter	Abbre-viation	Unit	Method	Method code	Instru-mentation
Alanine aminotransferase EC 2.6.1.2	ALAT	U/l 37°C	LDH/NADH coupled reaction	M01	Hitachi 917
Lactate dehydrogenase EC 1.1.1.27	LDH	U/l 37°C	NADH/LDH coupled reaction using pyruvate as substrate	M01	Hitachi 917
Glutamate dehydrogenase EC 1.4.1.3	GLDH	U/l 37°C	Standard method, optimized (DGKC)	M01	Hitachi 917
Alkaline phosphatase EC 3.1.3.1	AlP	U/l 37°C	p-Nitrophenyl-phosphate as substrate	M01	Hitachi 917
Gamma-glutamyl transferase EC 2.3.2.2	GGT	U/l 37°C	Substrate: L-gamma-glutamyl-3-carboxy-4-nitroanilide	M01	Hitachi 917
Creatine kinase EC 2.7.3.2	CK	U/l 37°C	HK/ATP and G6P-DH/NADPH coupled reaction method	M01	Hitachi 917
Sodium	Na+	mmol/l	Ion selective electrode	M01	Hitachi 917
Potassium	K+	mmol/l	Ion selective electrode	M01	Hitachi 917
Chloride	Cl-	mmol/l	Ion selective electrode	M01	Hitachi 917
Calcium	Ca++	mmol/l	o-Cresolphthalein complexone method	M01	Hitachi 917
Phosphorus inorganic	PO4-in	mmol/l	Phosphomolybdate reaction	M01	Hitachi 917
Protein, total	Prot	g/l	Biuret reaction	M01	Hitachi 917
Albumin	Alb	g/l	Bromocresol green method	M02	Hitachi 917
Globulin	Glob	g/l	Calculated value (Total protein minus Albumin)	M02	
Albumin/Globulin Ratio	A/G	rel.1	Calculated value (Albumin/Globulin)	M02	

5.10 PATHOLOGY

5.10.1 NECROPSY

All animals were weighed and necropsied. Descriptions of all macroscopic abnormalities were recorded. All animals surviving to the end of the observation period and all moribund animals were anesthetized by intraperitoneal injection of pentobarbitone and killed by exsanguination.

Sacrifice:
after 4 weeks 22 January 2003

Samples of the following tissues and organs were collected from all animals at necropsy and, unless otherwise indicated, fixed in neutral phosphate buffered 4% formaldehyde solution. Additional tissues (such as ear tattoo) were retained in accordance with standard procedures but were not be processed or examined further.

Adrenal glands
Aorta
Bone (sternum, femur including joint)
Bone marrow (femur)
Brain (cerebrum, cerebellum, brain stem)
Cecum
Colon
Duodenum
Epididymides (fixed in Bouin's solution)
Esophagus
Eyes w/optic nerve (fixed in Davidson's solution)
Harderian gland (fixed in Davidson's solution)
Heart
Ileum, with Peyer's patches
Jejunum with Peyer's patches
Kidneys
Larynx
Lacrimal gland, exorbital
Liver
Lungs, filled w/formalin at necropsy
Lymph nodes - mesenteric, mandibular
Mammary gland area
Nasal cavity
Ovaries
Pancreas
Pituitary gland
Prostate gland
Rectum
Salivary glands - mandibular, sublingual
Sciatic nerve
Seminal vesicles
Skeletal muscle
Skin
Spinal cord - cervical, midthoracic, lumbar
Spleen
Stomach
Testes (fixed in Bouin's solution)
Thymus
Thyroid (incl. parathyroid gland, if possible)
Tongue
Trachea
Urinary bladder, filled w/formalin at necropsy
Uterus
Vagina
Gross lesions

5.10.2 ORGAN WEIGHTS

The following organ weights were recorded on the scheduled dates of necropsy listed and their organ to terminal body weight ratios as well as organ to brain weight ratios determined:

Brain	Thymus	Spleen	Ovaries
Heart	Kidneys	Testes	
Liver	Adrenals	Epididymides	

5.10.3 HISTOTECHNIQUE

All organ and tissue samples to be examined by the study pathologist (see Histopathology, below) were processed, embedded and cut at an approximate thickness of 2-4 micrometers and stained with hematoxylin and eosin.

5.10.4 HISTOPATHOLOGY

Slides of all organs and tissues listed in boldface type (see Necropsy, above) which were collected at terminal sacrifices from the animals of the control and high-dose groups were examined by the study pathologist. The same applied to all occurring gross lesions and to all animals which had to be terminated in extremis. Because of possible test item-related morphologic changes noted in animals treated with RP 74, adrenals (males only), stomach, liver, kidneys, spleen, thymus, and bone marrow were examined also in the animals from the mid- and low-dose groups. All abnormalities were described and included in the report. The histopathological evaluation was completed on March 18, 2003.

5.11 DATA COMPILATION

5.11.1 GENERAL

The following data were recorded on-line: Food consumption, body weights, clinical laboratory data, organ weights and macroscopic findings at necropsy and histopathology. Clinical observations, data from the functional observations, locomotor activity and grip strength were recorded manually on paper sheets. The computer-generated values which appear in the tables represent the rounded-off results of the raw data values or of calculations which used the exact raw data values. Group means were calculated according to the definition of any mean value using the individual values per animal and the number of animals.

5.12 DATA CALCULATION

5.12.1 FOOD CONSUMPTION

The food consumption was calculated per rat and per food consumption interval. It expresses the average food consumed per animal and per day over the food consumption interval.

$$FC = \frac{C}{AD}$$

FC is Food consumption in grams of food per animal and day;

C is measured food consumption in grams per cage over the consumption interval and

AD is total consumption days over all animals in the cage during the consumption interval.

5.12.2 RELATIVE FOOD CONSUMPTION

The relative food consumption was calculated according to the following formula:

$$RFC = \left[\frac{FC}{BW(i)} \right] \times 1000$$

BW(i) is the most ideal body weight in grams.

RFC is relative food consumption in grams of food per kg body weight and day, and

FC is food consumption in grams of food per animal and day.

5.13 STATISTICAL ANALYSIS

The following statistical methods were used to analyze the grip strength, locomotor activity, body weight, organ weights and ratios:

- The Dunnett-test[5](many to one t-test) based on a pooled variance estimate was applied if the variables can be assumed to follow a normal distribution for the comparison of the treated groups and the control groups for each sex.
- The Steel-test[6] (many-one rank test) was applied instead of the Dunnett-test when the data can not be assumed to follow a normal distribution.
- Fisher's exact-test[7] was applied to the macroscopic and microscopic findings.
- Armitage/Cochran Trend Test[8] for non-neoplastic lesions ($p \leq 0.05$).

Analyses of clinical laboratory data were carried out using the statistical routines contained in the NOVATOX system. Quantitative data were analyzed either using parametric or non-parametric statistical tests following a pre-test for uniformity of the within group variances based upon the Bartlett's test of homogeneity of variances[9]. In the case of a non-significant Bartlett's test ($p>0.05$) a one-way analysis of variance (ANOVA)[10] was carried out. If the overall test of differences between the groups was significant ($p \leq 0.05$), comparisons were made between the control group and each of the treatment groups using Dunnett's multiple comparison test. In cases where Bartlett's test was significant ($p \leq 0.05$) the Kruskal-Wallis[11] non-parametric test of the differences between the groups was carried out. If this test was significant ($p \leq 0.05$), comparisons were made between the control group and each of the treatment groups using Dunn's multiple comparison test [12].

Ordinal data were analyzed using the non-parametric Kruskal-Wallis test. If this test was significant ($p \leq 0.05$), comparisons were made between the control group and each of the treatment groups using Dunn's multiple comparison test (Dunn, 1964).

All statistical tests are two-sided: testing for an overall difference rather than a difference in only one direction. Flags for significant differences between control and treated groups (* for $p \leq 0.05$ and ** for $p \leq 0.01$) are given in the tables. Statistical tests performed and flags used are indicated in the footnote of each table.

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[5] Dunnett, C.W., A Multiple Comparison Procedure for Comparing Several Treatment with a Control, J. Amer. Stat. Assoc. 50, 1096-1121 (1955).

[6] Miller, R.G., Simultaneous Statistical Inference, Springer Verlag, New York (1981).

[7] Fisher, R.A., Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).

[8] Armitage, P., Test for linear trends in proportions and frequencies, Biometrics 11, 375-386 (1955).

[9] Gad, S.C. and Weil, C.S., Statistics and Experimental design for Toxicologists. The Telford Press, Caldwell, New Jersey, 43 – 45, 1986.

[10] Gad, S.C. and Weil, C.S., Statistics and Experimental design for Toxicologists. The Telford Press, Caldwell, New Jersey, 75 – 78, 1986.

[11] Kruskal, W.H. and Wallis, W.A.., Use of ranks in one-criterion variance analysis. Journal of the American Statistical Association, 47, 583 – 621, 1952.

[12] Dunn, O.J., Multiple comparisons using rank sums, Technometrics, 6, 241 – 252, 1964.

6 RESULTS

6.1 VIABILITY/MORTALITY

One male (no. 5) of the control group was sacrificed on day 24 of treatment due to poor health condition.

All other animals survived until scheduled necropsy.

See pp. 78 – 85

6.2 OBSERVATIONS

6.2.1 GENERAL CLINICAL SIGNS (DAILY)

One male (no. 5) of the control group exhibited hunched posture, ruffled fur, soft feces and was emaciated on day 24. These signs were not considered to be treatment-related.

Two males (nos. 17 and 20) and all females (nos. 36 to 40) of the high dose group presented with salivation on individual days within the period from day 16 through 28.

All other animals revealed no clinical signs during the daily general clinical observation periods.

See pp. 40 – 47, 86 – 125

6.2.2 DETAILED CLINICAL OBSERVATIONS (WEEKLY)

Two females (nos. 36 and 39) showed salivation in week 3.

One male (no. 5) and one female (no. 22) of the control groups showed soft feces in week 3 or had a bent tail in week 1, respectively, that were considered not to be treatment-related effects.

See pp. 48 – 49, 126 – 133

6.2.3 FUNCTIONAL OBSERVATIONAL BATTERY

One male (no. 17) of the high dose group exhibited transient salivation in week 4.

Grip strength was not affected by treatment. The seemingly significance in the value obtained for the grip strength of the forelimb in females at 50 mg/kg/day has been derived from the rather low standard deviation but stayed within the normal reference range.

See pp. 48-50, 134-136

6.2.4 LOCOMOTOR ACTIVITY

Locomotor activity revealed significantly higher values after 45 minutes and in total counts in males at 50 mg/kg/day, but lower values after 15 and 30 minutes in males at 800 mg/kg/day. There was a significantly higher locomotor activity after 15, 30 (not significant), 45, and 60 minutes and in total counts in females at 200 mg/kg/day. However, these activities were not regarded as treatment-related effects as they did lack any dose response-relationship.

See pp. 51 – 52, 137 – 138

6.3 FOOD CONSUMPTION

Food consumption and relative food consumption were not affected by the test item. A minimal reduction in food intake occurred in males of the control group during the third and forth treatment weeks which is considered as normal biological variation.

See pp. 31 – 34, 53 – 60, 139 – 142

6.4 BODY WEIGHT DEVELOPMENT

Slightly lower body weights (-4.3%, -5.6%, -7.7% and -6.5%) were noted in females at 800 mg/kg/day during treatment weeks 1 to 4, respectively. Significantly reduced body weight gain (-25.5% and -20.3%) were noted in females treated at 800 mg/kg/day during treatment weeks three and four. These findings were considered treatment-related.

See pp. 35 – 38, 61 – 68, 143 – 146

6.5 CLINICAL LABORATORY INVESTIGATIONS

6.5.1 HEMATOLOGY

At the end of the treatment period, males and females of group 4 (800 mg/kg/day) had a normochrome, slightly macrocytic anemia associated with thrombophilia (in males), neutrophilia (which did not reach significance in females), and monocytosis. The higher reticulocyte counts and the shift in the reticulocyte maturation index to immature cells (lower value for L-Reti and higher value for H-Reti) recorded for males and females of group 4 points to a stimulated erythropoietic activity.

See pp. 178 – 220

6.5.2 CLINICAL CHEMISTRY

Some differences in the effects of the test item on blood chemistry parameters were seen between males and females. Treatment-related changes in males were confined to the high dose group treated at 800 mg/kg/day and included a lower mean value for glucose, higher creatinin, total bilirubin and glutamate dehydrogenase levels together with higher plasma sodium, calcium, phosphate, protein and albumin levels. Treatment-related changes in females were equally confined to the high dose group and comprised higher total bilirubin and lactate dehydrogenase levels and lower glutamate dehydrogenase and alkaline phosphatase levels (all of which did not reach statistical significance) together with higher values for sodium and calcium, protein, albumin and globulin.

See pp. 178 – 220

6.6 PATHOLOGY

6.6.1 ORGAN WEIGHTS

Treatment-related effects on absolute organ weights at 800 mg/kg/day in males included increased mean weights of liver (17.2%), kidneys (22.1%) and spleen (65.4%) but decreased thymus weights (-30%), and in females increased mean weights of liver (30.6%), kidneys (7.9%) and spleen (17.6%) but decreased thymus weights (-19.2%). Mean carcass weights at 800 mg/kg/day were reduced in males by 8.5% and significantly reduced in females by 9.5%.Test item-related effects on relative organ weights in males at 800 mg/kg/day were confined to increased weights of liver, kidneys, and spleen but decreased weights of thymus (-23.5%). Relative organ weight effects in females at 800 mg/kg/day comprised increased weights of brain, heart, liver, kidneys, spleen and ovaries. Organ to brain weight ratios of liver, kidneys and spleen at 800 mg/kg/day were significantly increased in males and females. These findings were considered to be test item-related.

See pp. 71 – 76, 155 – 165

6.6.2 MACROSCOPIC FINDINGS

The kidneys of one high dose male (no. 16) were enlarged. This finding was considered as treatment-related. All other findings were within the range of background lesions that may be recorded in rats of this strain and age. They comprised thickened duodenum, thymus enlargement or size reduction, uterine dilatation and splenic discoloration.

See pp. 69 – 70, 147 – 154

6.6.3 MICROSCOPIC FINDINGS

6.6.3.1 Treatment-related microscopic findings:

Liver

Fatty change along with centrilobular to diffuse hepatocellular hypertrophy, accompanied by increased organ weights were recorded in the liver of males and females at 800 mg/kg/day.

Kidneys

In the kidneys of males at 800 mg/kg/day hyaline droplets were present in tubular cells (and also present at 200 mg/kg/day), together with tubular basophilia and interstitial edema, and, in a single case, tubular epithelial necrosis was noted along with tubular epithelial swelling. In females at 800 mg/kg/day minimal to slight tubular casts were seen. In animals of both sexes at 800 mg/kg/day tubular dilation was recorded.

Spleen

Hemosiderin, megakaryocytosis, granulopoiesis and erythropoiesis were increased in severity and/or incidence in the spleen of animals of both sexes at 800 mg/kg/day.

Stomach

In males and females at 800 mg/kg/day inflammatory lesions were recorded in the stomach (mainly in the forestomach) and consisted of inflammation, epithelial and basal cell hyperplasia and ulceration. Similar findings occurred in a male of the control group that had to be sacrificed on day 24 due to poor health condition. An irritative potential of the test item or mechanically induced lesions might have caused this inflammatory reaction in the stomach.

6.6.3.2 Incidental microscopic findings

The findings of increased thymic atrophy in males and females at 800 mg/kg/day and the diffuse hypertrophy in the adrenal cortex of one male at 800 mg/kg/day and increased vacuolation in the zona fasciculate in males at 200 and 800 mg/kg/day were considered as to be secondary caused by stress.

Additionally, a variety of other changes was found in this study. They commonly occur in laboratory rats of this strain and age, and, neither their incidences nor their distribution or morphologic appearance gave any indication of a treatment-related association.

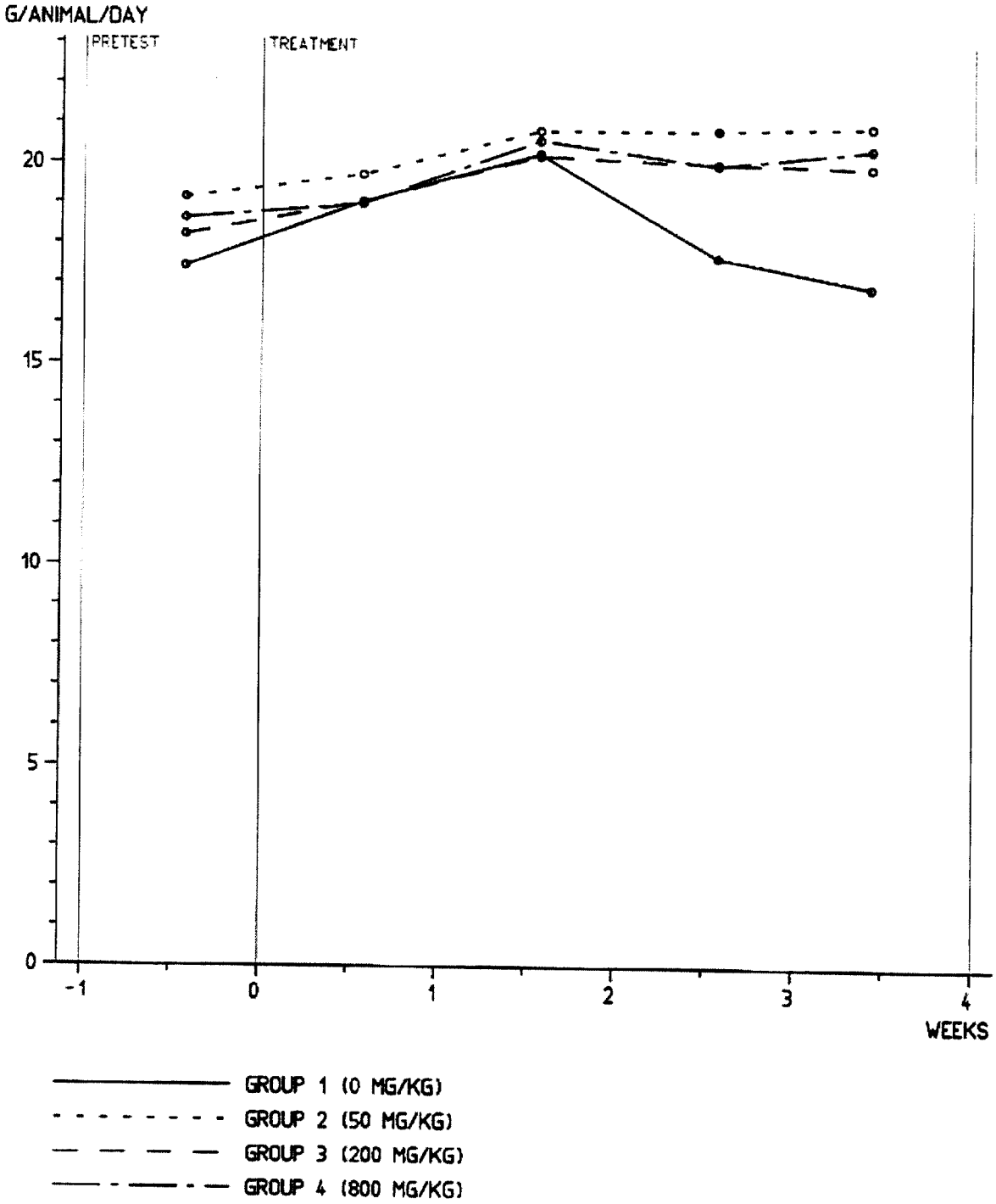
6.6.3.3 Animals found dead during the test period

One male (no. 5) of the control group was sacrificed on day 24 of treatment due to poor health condition.

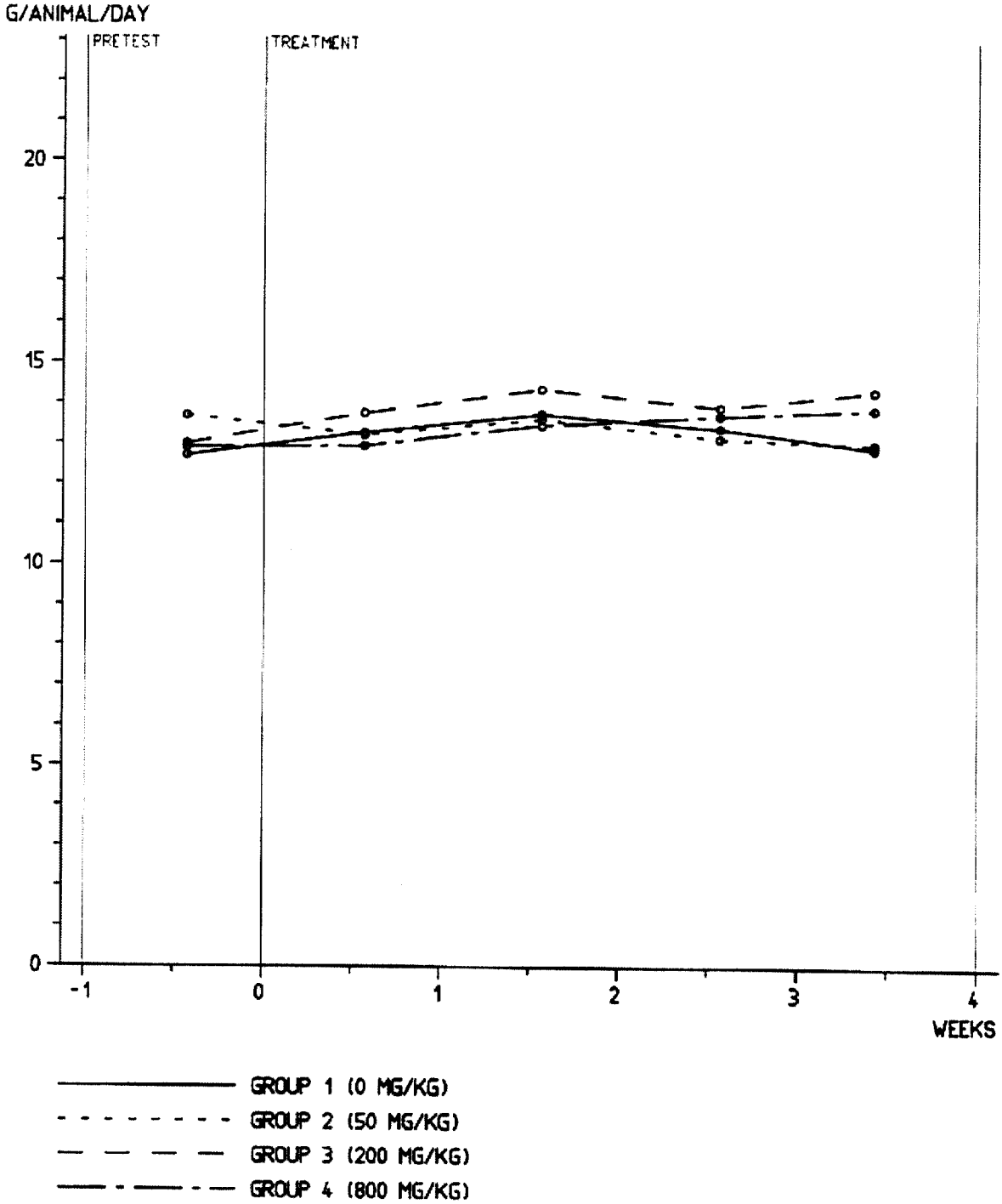
See pp. 237 – 318

7 FIGURES

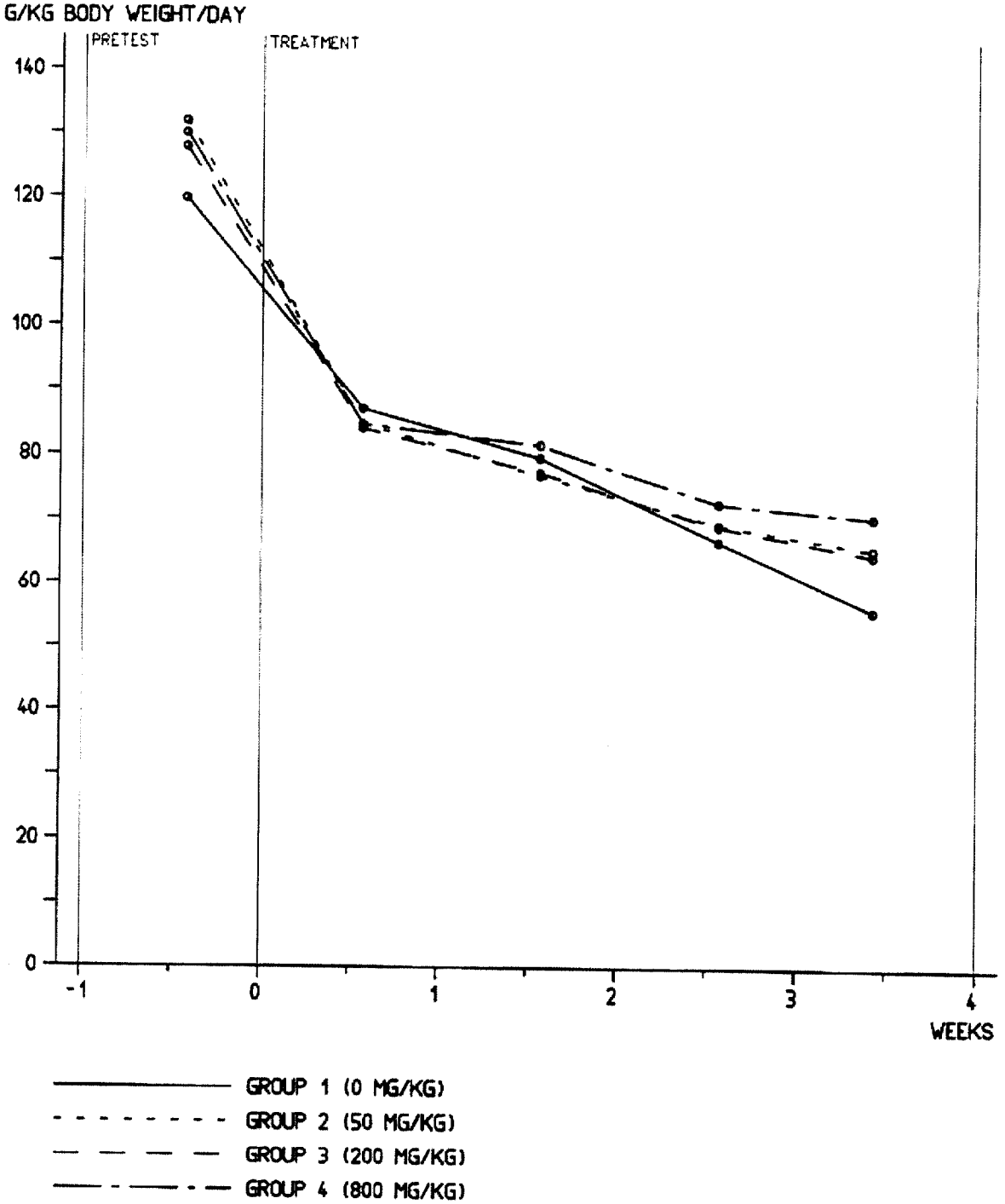
FOOD CONSUMPTION
MALES



FOOD CONSUMPTION
FEMALES



RELATIVE FOOD CONSUMPTION
MALES



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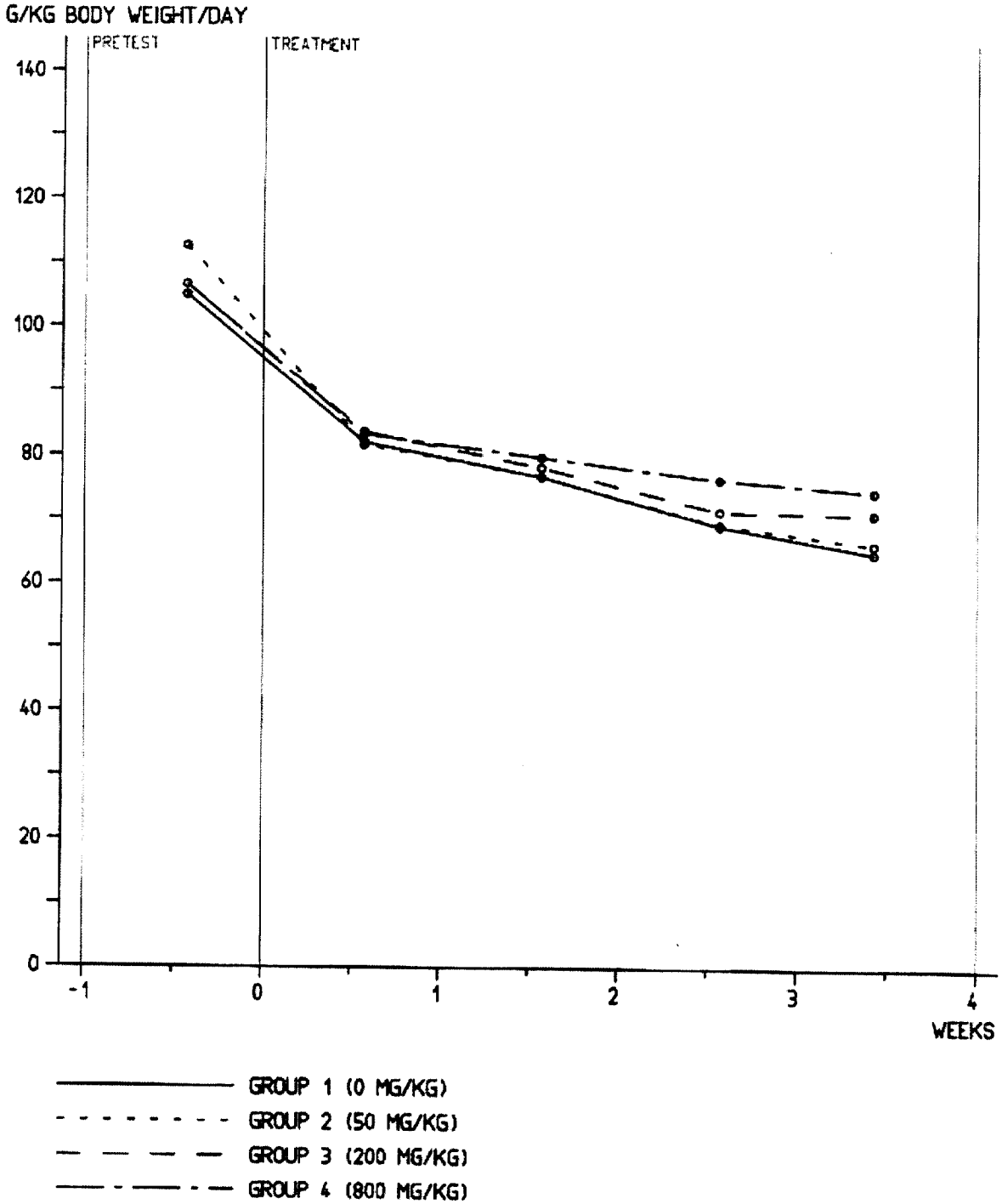
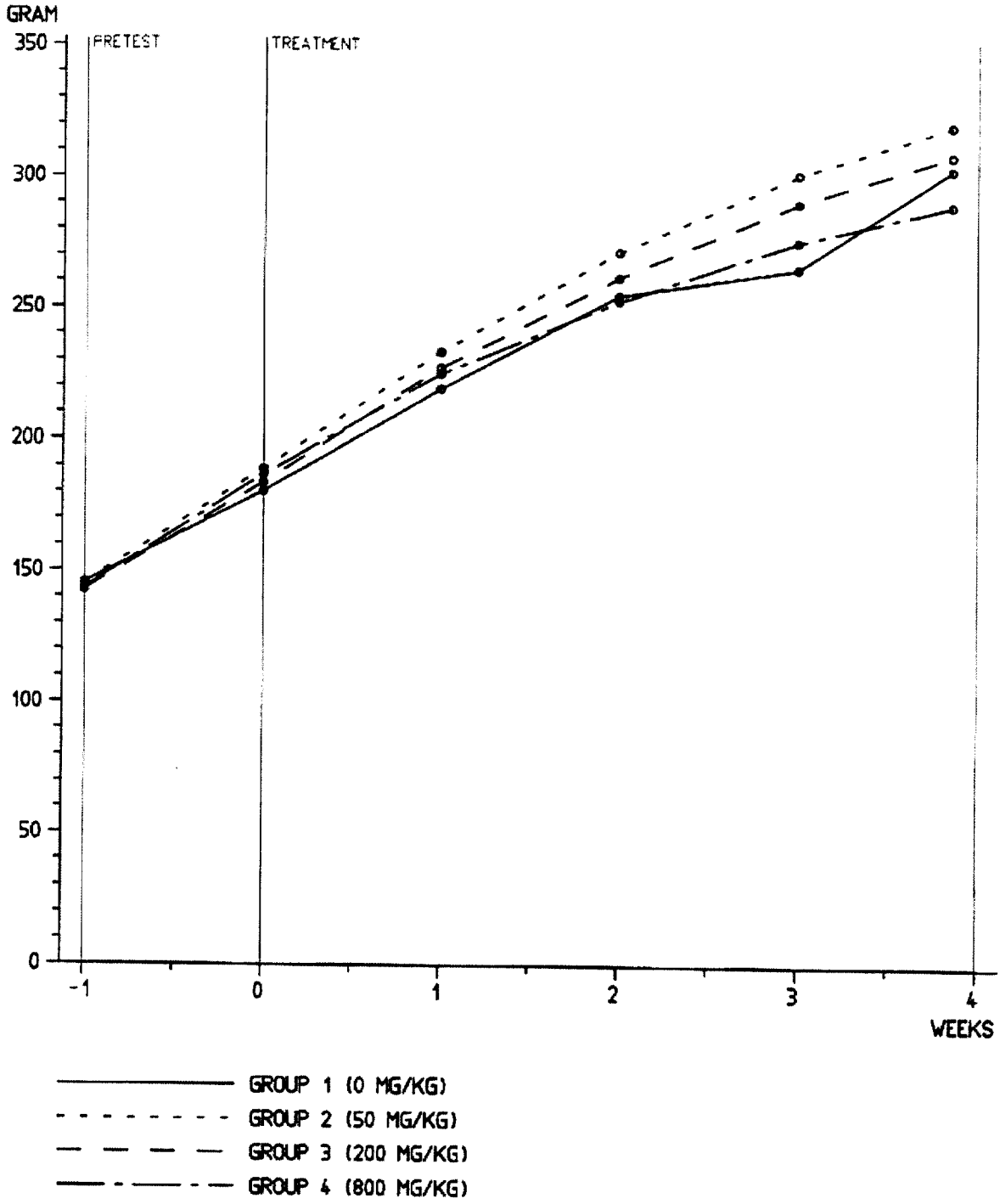
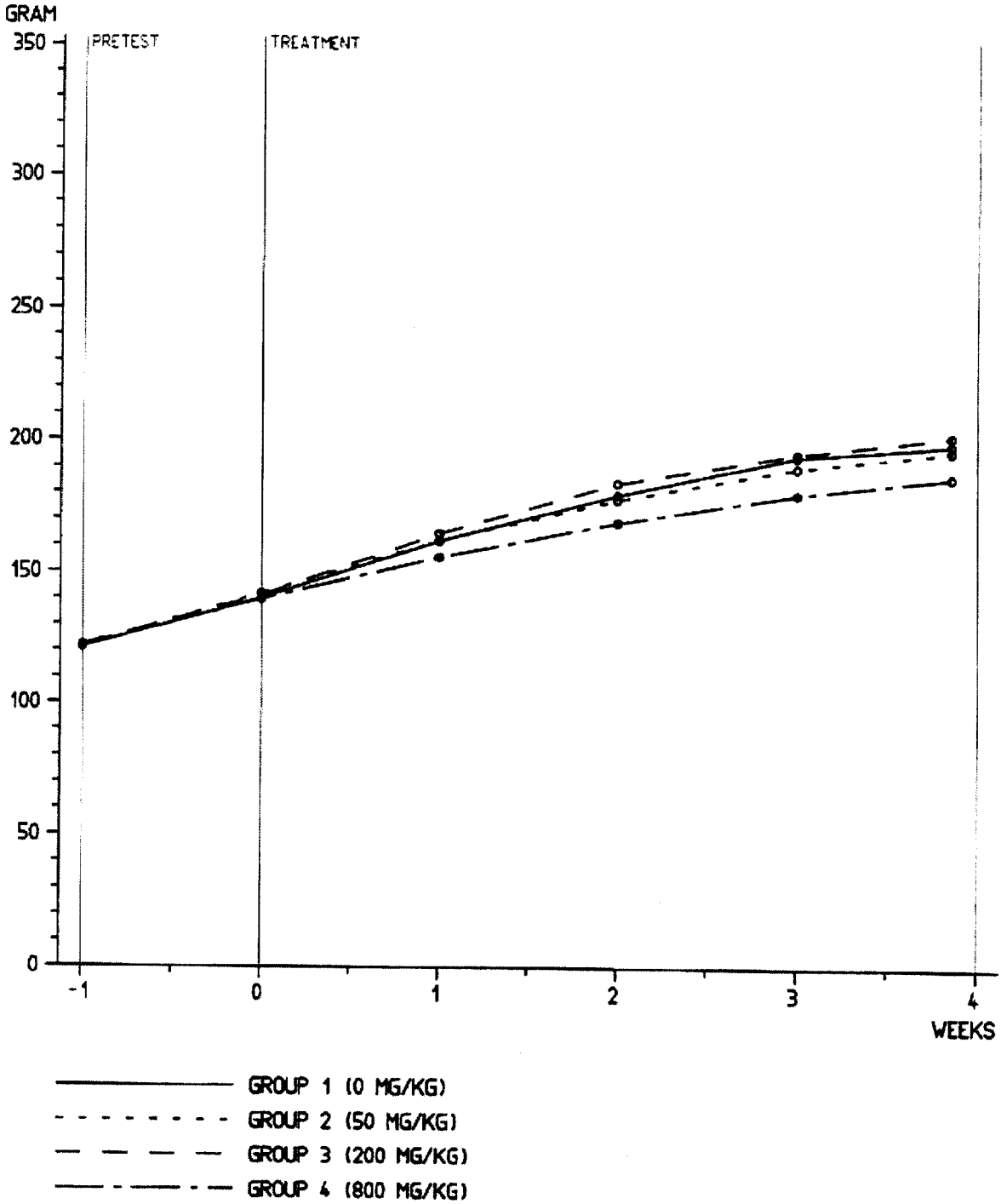
RELATIVE FOOD CONSUMPTION
FEMALES



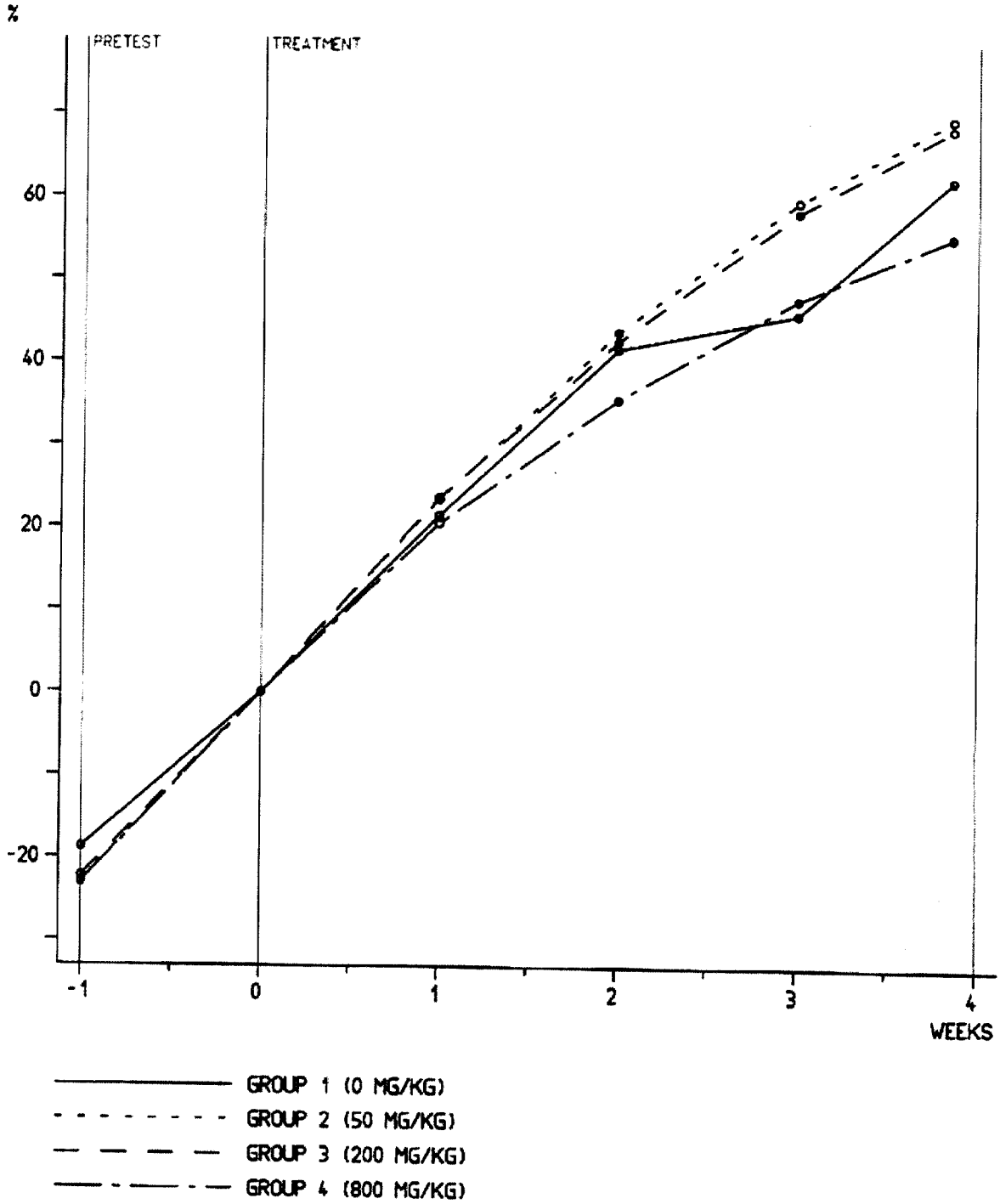
BODY WEIGHTS
MALES



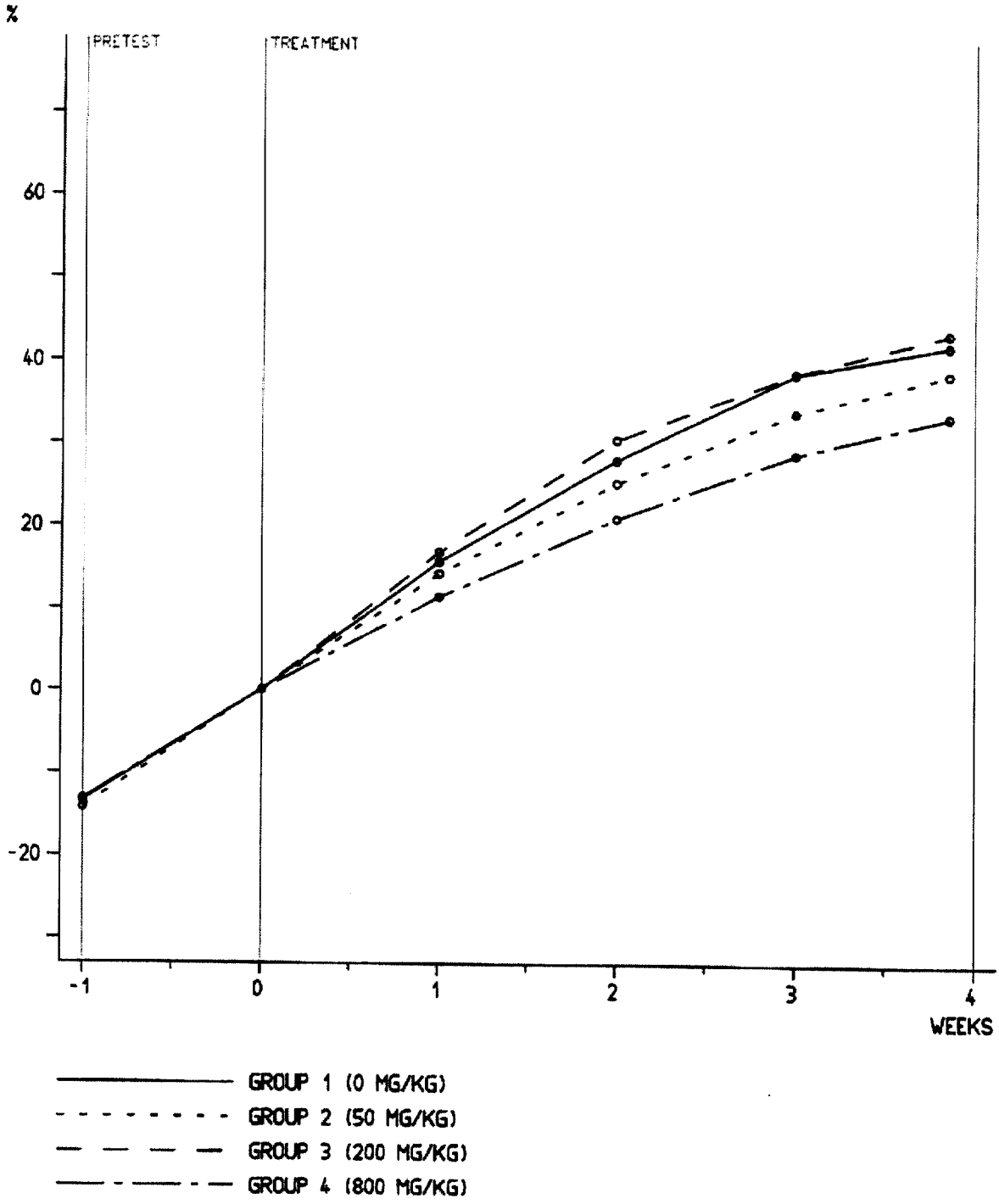
BODY WEIGHTS
FEMALES



BODY WEIGHT GAIN
MALES



BODY WEIGHT GAIN
FEMALES



8 SUMMARY TABLES

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DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 1 (CONTROL), MALES

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
	Ruffled Fur	1-3																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS	Soft Feces	1																						1-
	Emaciated	1-3																						1-

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1			1-				
	Ruffled Fur	1-3			1-				
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS	Soft Feces	1	1-	1-	1-				
	Emaciated	1-3	1+	1-	1+				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No animals affected

n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
n+ = Mean severity between 1.68 and 2.33
n! = Mean severity between 2.34 and 3.00

DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 1 (CONTROL), FEMALES

				Study day / treatment																				
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
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P = Pretest examination (during acclimatization)

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n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
n+ = Mean severity between 1.68 and 2.33
n! = Mean severity between 2.34 and 3.00

RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 2 (LOW DOSE), MALES

				Study day / treatment																			
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

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n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
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n! = Mean severity between 2.34 and 3.00

DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 2 (LOW DOSE), FEMALES

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No animals affected

n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
n+ = Mean severity between 1.68 and 2.33
n! = Mean severity between 2.34 and 3.00

RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 3 (MID DOSE), MALES

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

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MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No animals affected

n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
n+ = Mean severity between 1.68 and 2.33
n! = Mean severity between 2.34 and 3.00

RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 3 (MID DOSE), FEMALES

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

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BEH = Behavioral
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P = Pretest examination (during acclimatization)

[ ] = No animals affected

n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
n+ = Mean severity between 1.68 and 2.33
n! = Mean severity between 2.34 and 3.00

DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 4 (HIGH DOSE), MALES

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																	1-	1-	1-	1-	1-	
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3	1-	1-	1-	1-			1-
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
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BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No animals affected

n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
n+ = Mean severity between 1.68 and 2.33
n' = Mean severity between 2.34 and 3.00

DAILY CAGE-SIDE OBSERVATIONS, SUMMARY

GROUP 4 (HIGH DOSE), FEMALES

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	No of animals in gr.		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																	2-	3-	3-	3-	3-	3-
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
	No of animals in gr.		5	5	5	5	5	5	5
APP	Piloerection	1-3							
	Salivation	1-3	3-	3-	1-	1-	1-	3-	2-
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
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BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
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n! = Mean severity between 2.34 and 3.00

WEEKLY OUTSIDE CAGE OBSERVATIONS, SUMMARY DATA

MALES

			GROUP 1					GROUP 2					GROUP 3					GROUP 4				
NUMBER OF ANIMALS IN GR.			5	5	5	5	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
FINDINGS / STUDY WEEK		SCORE	P	1	2	3	4	P	1	2	3	4	P	1	2	3	4	P	1	2	3	4
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				1-
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Indic light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle - hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1				1-																

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
REF = Reflexes
P = Pretest examination (during acclimatization)

[ ] = No animals affected

n = Number of affected animals
n- = Mean severity between 1.00 and 1.67
n– = Mean severity between 1.68 and 2.33
n' = Mean severity between 2.34 and 3.00

WEEKLY OUTSIDE CAGE OBSERVATIONS, SUMMARY DATA

FEMALES

			GROUP 1					GROUP 2					GROUP 3					GROUP 4				
NUMBER OF ANIMALS IN GR.			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
FINDING / STUDY WEEK		SCORE	P	1	2	3	4	P	1	2	3	4	P	1	2	3	4	P	1	2	3	4
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																			2-	
	Tail bent								1-													
MOT	Ataxia	1-3																				
	Tremor twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Indirect light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle - hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

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GRIP STRENGTH AT WEEK 4, SUMMARY

	MALES	Mean (g)	FEMALES	Mean (g)
GROUP 1				
(0 mg/kg/day)	Forelimb	Hindlimb	Forelimb	Hindlimb
Mean	1096	813	1000	749
St.dev.	165	85	37	37
N	4	4	5	5
GROUP 2				
(50 mg/kg/day)	Forelimb	Hindlimb	Forelimb	Hindlimb
Mean	1177	855	951 *	714
St.dev.	86	80	18	26
N	5	5	5	5
GROUP 3				
(200 mg/kg/day)	Forelimb	Hindlimb	Forelimb	Hindlimb
Mean	1143	825	931	755
St.dev.	157	77	70	25
N	5	5	5	5
GROUP 4				
(800 mg/kg/day)	Forelimb	Hindlimb	Forelimb	Hindlimb
Mean	1111	829	911	697
St.dev.	66	27	51	47
N	5	5	5	5

F-Test sig. at 5% or 1% level

LOCOMOTOR ACTIVITY, SUMMARY

LOW BEAMS COUNT MALES AT WEEK 4

Group 1	15 min.	30 Min.	45 min.	60 min.	Total
Mean	862	534	236	79	1711
St.dev.	122	70	180	70	240
N	4	4	4	4	4

Group 2	15 min.	30 Min.	45 min.	60 min.	Total
Mean	1068	700	595 *	239	2602 **
St.dev.	179	165	38	168	233
N	5	5	5	5	5

Group 3	15 min.	30 Min.	45 min.	60 min.	Total
Mean	695	450	417	181	1743
St.dev.	150	281	130	168	478
N	5	5	5	5	5

Group 4	15 min.	30 Min.	45 min.	60 min.	Total
Mean	571 *	269 *	200	317	1357
St.dev.	225	185	201	249	368
N	5	5	5	5	5

F Test sig. at 5% or 1% level

LOCOMOTOR ACTIVITY, SUMMARY

LOW BEAMS COUNT FEMALES AT WEEK 4

Group 1	15 min.	30 Min.	45 min.	60 min.	Total
Mean	820	411	69	253	1553
St.dev.	142	174	88	137	459
N	5	5	5	5	5

Group 2	15 min.	30 Min.	45 min.	60 min.	Total
Mean	960	546	196	436	2139
St.dev.	216	141	158	201	486
N	5	5	5	5	5

Group 3	15 min.	30 Min.	45 min.	60 min.	Total
Mean	1093 *	666	356 **	425 *	2540 *
St.dev.	196	217	159	86	530
N	5	5	5	5	5

Group 4	15 min.	30 Min.	45 min.	60 min.	Total
Mean	877	456	225	303	1861
St.dev.	200	166	170	194	597
N	5	5	5	5	5

* T Test sig. at 5% or 1% level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	17.4	19.1	18.2	18.6
WEEKS 1-2	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8 WEEKS 1-2	MEAN	19.9	19.[illegible]	19.[illegible]	19.0
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15 WEEKS 2-3	MEAN	20.3	20.8	20.2	20.6
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22 WEEKS 3-4	MEAN	17.7	20.9	20.0	20.[illegible]
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-29 WEEK 4	MEAN	17.0	21.0	20.0	20.4
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT		18.5	20.6	19.8	20.0

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	11.7	13.7	13.0	11.9
WEEKS 1-2	ST.DEV.	---	---	---	---
	N/CAGE	1	1	1	1

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-6 WEEKS 1-2	MEAN	13.3	12.1	13.7	12.9
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15 WEEKS 2-3	MEAN	13.7	13.6	14.3	13.4
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22 WEEKS 3-4	MEAN	13.4	13.1	13.9	13.[illegible]
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-29 WEEK 4	MEAN	12.9	13.0	14.3	13.9
	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT		13.3	13.2	14.1	13.5

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

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-9	MEAN	120	131	128	130
WEEKS 1-2	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-6	MEAN	87	86	94	85
WEEKS 1-2	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15	MEAN	79	77	77	81
WEEKS 2-3	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22	MEAN	67	69	69	73
WEEKS 3-4	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-28	MEAN	56	65	65	71
WEEK 4	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT		72	74	74	77

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

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	105	112	108	106
WEEKS 1/2	ST DEV.	---	---	---	---
	N (CAGE)	1	1	1	1

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	82	82	84	83
WEEKS 1-2	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15	MEAN	77	77	78	80
WEEKS 2-3	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22	MEAN	69	69	71	76
WEEKS 3-4	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-28	MEAN	65	66	71	74
WEEK 4	ST.DEV.	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT		73	73	76	78

BODY WEIGHTS (GRAM) SUMMARY
MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	145	145	141	143
WEEK 1	ST.DEV.	6.9	3.6	8.8	5.[illegible]
	N	5	5	5	5

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

BODY WEIGHTS (GRAM) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 500 MG/KG
DAY 1 WEEK 1	MEAN	180	189	183	186
	ST.DEV.	17.3	8.2	11.5	8.1
	N	5	5	5	5
DAY 8 WEEK 2	MEAN	219	233	227	226
	ST.DEV.	21.3	15.0	17.3	11.1
	N	5	5	5	5
DAY 15 WEEK 3	MEAN	255	271	262	253
	ST.DEV.	25.9	18.1	19.4	20.4
	N	5	5	5	5
DAY 22 WEEK 4	MEAN	265	301	290	275
	ST.DEV.	54.5	23.3	20.8	24.2
	N	5	5	5	5
DAY 28 WEEK 4	MEAN	304	320	309	290
	ST.DEV.	31.1	28.2	23.3	26.8
	N	4	5	5	5

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

BODY WEIGHTS (GRAM) SUMMARY
FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	101	102	102	101
WEEK 1	ST.DEV.	3.6	2.6	[illegible]	[illegible]
	N	5	5	5	5

* , ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHTS (GRAM) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAY 1 WEEK 1	MEAN	140	140	141	147
	ST.DEV.	3.4	1.6	1.2	[illegible]
	N	5	5	5	5
DAY 8 WEEK 2	MEAN	162	162	164	155 *
	ST.DEV.	3.9	3.2	3.5	4.3
	N	5	5	5	5
DAY 15 WEEK 3	MEAN	179	177	183	169 *
	ST.DEV.	6.2	5.7	5.2	6.4
	N	5	5	5	5
DAY 22 WEEK 4	MEAN	194	189	195	179 **
	ST.DEV.	8.3	6.6	2.0	[illegible]
	N	5	5	5	5
DAY 28 WEEK 4	MEAN	199	196	202	186 **
	ST.DEV.	[illegible]	4.8	4.8	[illegible]
	N	5	5	5	5

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

BODY WEIGHT GAIN (%) SUMMARY
MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	-18.6	-23.0	[illegible]	-23.1
WEEK 1	ST.DEV.	6.6	2.5	[illegible]	[illegible]
	N	5	5	5	5

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

BODY WEIGHT GAIN (%) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAY 1 WEEK 1	MEAN	0.0	0.0	0.0	0.0
	ST.DEV	0.0	0.0	0.0	0.0
	N	5	5	5	5
DAY 8 WEEK 2	MEAN	21.6	23.5	23.7	22.5
	ST.DEV.	3.2	2.7	4.0	3.0
	N	5	5	5	5
DAY 15 WEEK 3	MEAN	41.7	43.7	42.6	39.8
	ST.DEV.	6.2	3.5	3.6	6.2
	N	5	5	5	5
DAY 22 WEEK 4	MEAN	45.9	59.6	58.2	47.2
	ST.DEV	15.0	5.7	2.9	8.9
	N	5	5	5	5
DAY 28 WEEK 4	MEAN	62.4	69.8	66.6	55.5
	ST.DEV.	10.1	3.3	5.1	10.2
	N	4	5	5	5

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

BODY WEIGHT GAIN (%) SUMMARY
FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	-13.5	-14.2	-11.4	-13.5
WEEK 1	ST.DEV.	2.7	1.3	4.6	1.2
	N	5	5	5	5

* , ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHT GAIN (%) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
DAY 1 WEEK 1	MEAN	0.0	0.0	0.0	0.0
	ST.DEV.	0.0	0.0	0.0	0.0
	N	5	5	5	5
DAY 8 WEEK 2	MEAN	15.5	14.1	16.7	11.4
	ST.DEV.	2.1	3.0	1.8	2.1
	N	5	5	5	5
DAY 15 WEEK 3	MEAN	28.0	25.2	30.4	20.9
	ST.DEV.	4.7	4.0	4.9	5.7
	N	5	5	5	5
DAY 22 WEEK 4	MEAN	38.5	33.7	38.5	28.7 *
	ST.DEV.	4.7	4.6	4.9	6.4
	N	5	5	5	5
DAY 28 WEEK 4	MEAN	41.9	38.5	43.4	33.4 *
	ST.DEV.	4.8	4.0	6.0	3.8
	N	5	5	5	5

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

MACROSCOPICAL FINDINGS SUMMARY
MALES

	GROUP 1 0 MG/KG		GROUP 2 50 MG/KG		GROUP 3 200 MG/KG		GROUP 4 800 MG/KG	
ANIMALS EXAMINED	5		5		5		5	
ANIMALS WITHOUT FINDINGS	4		4		5		4	
ANIMALS AFFECTED:								
DUODENUM.....								
THICKENED	1	20%	0	0%	0	0%	0	0%
KIDNEYS.....								
ENLARGED	0	0%	0	0%	0	0%	1	20%
EPIDIDYMIDES.....								
NODULE(S)	1	20%	0	0%	0	0%	0	0%
SPLEEN.....								
DISCOLORATION	1	20%	0	0%	0	0%	0	0%
THYMUS.....								
ENLARGED	0	0%	1	20%	0	0%	0	0%
REDUCED IN SIZE	1	20%	0	0%	0	0%	0	0%

* , ** : Fisher's Exact Test based on counts significant at 5% (*) or 1% (**) level

MACROSCOPICAL FINDINGS SUMMARY
FEMALES

	GROUP 1 0 MG/KG		GROUP 2 50 MG/KG		GROUP 3 200 MG/KG		GROUP 4 800 MG/KG	
ANIMALS EXAMINED	5		5		5		5	
ANIMALS WITHOUT FINDINGS	5		5		4		5	
ANIMALS AFFECTED:								
UTERUS								
DILATION	0	0%	0	0%	1	20%	0	0%

: Fisher's Exact Test based on counts significant at 5% (#) or 1% (##) level

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 4 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	287.055	300.286	286.206	262.590
	ST.DEV.	27.905	25.321	20.523	23.507
	N	4	5	5	5
BRAIN	MEAN	1.89	1.99	1.96	1.89
	ST.DEV.	0.06	0.04	0.08	0.06
	N	4	5	5	5
HEART	MEAN	0.969	0.994	1.004	0.962
	ST.DEV.	0.083	0.101	0.047	0.032
	N	4	5	5	5
LIVER	MEAN	8.51	8.74	9.02	9.97
	ST.DEV	1.30	0.65	0.72	0.72
	N	4	5	5	5
THYMUS	MEAN	0.50	0.54	0.48	0.35
	ST.DEV	0.09	0.19	0.13	0.06
	N	4	5	5	5
KIDNEYS	MEAN	1.90	1.80	1.97	2.32 *
	ST.DEV	0.15	0.08	0.13	0.39
	N	4	5	5	5
ADRENALS	MEAN	0.058	0.064	0.062	0.056
	ST.DEV.	0.003	0.007	0.007	0.008
	N	4	5	5	5
SPLEEN	MEAN	0.578	0.639	0.601	0.956 **
	ST.DEV	0.071	0.036	0.092	0.133
	N	4	5	5	5
TESTES	MEAN	3.41	3.39	3.44	3.33
	ST.DEV.	0.28	0.31	0.24	0.04
	N	4	5	5	5
EPIDIDYMIDES	MEAN	1.122	1.034	1.030	0.912
	ST.DEV.	0.117	0.180	0.184	0.096
	N	4	5	5	5

* ** Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 4 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
BODY W (GRAM)	MEAN ST.DEV N	287.055 27.905 4	300.286 25.321 5	286.206 20.523 5	262.590 23.507 5
BRAIN (%)	MEAN ST.DEV N	0.66 0.04 4	0.67 0.05 5	0.69 0.03 5	0.73 0.06 5
HEART (%)	MEAN ST.DEV. N	0.338 0.018 4	0.331 0.024 5	0.352 0.025 5	0.368 0.024 5
LIVER (%)	MEAN ST.DEV. N	2.97 0.38 4	2.91 0.10 5	3.15 0.13 5	3.91 ** 0.19 5
THYMUS (%)	MEAN ST.DEV N	0.17 0.02 4	0.18 0.06 5	0.17 0.04 5	0.13 0.02 5
KIDNEYS (%)	MEAN ST.DEV N	0.66 0.04 4	0.60 0.06 5	0.69 0.03 5	0.88 ** 0.10 5
ADRENALS (%)	MEAN ST.DEV N	0.020 0.002 4	0.021 0.002 5	0.022 0.003 5	0.021 0.003 5
SPLEEN (%)	MEAN ST.DEV. N	0.202 0.016 4	0.214 0.020 5	0.210 0.027 5	0.364 ** 0.039 5
TESTES (%)	MEAN ST.DEV N	1.19 0.02 4	1.13 0.06 5	1.21 0.11 5	1.28 0.11 5
EPIDIDYMIDES (%)	MEAN ST.DEV. N	0.391 0.023 4	0.343 0.041 5	0.358 0.049 5	0.350 0.051 5

*,**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 4 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
BRAIN (GRAM)	MEAN ST.DEV N	1.89 0.06 4	1.99 0.04 5	1.96 0.05 5	1.89 0.06 5
HEART (%)	MEAN ST.DEV. N	51.138 3.076 4	49.839 4.717 5	51.375 3.153 5	50.885 1.916 5
LIVER (%)	MEAN ST.DEV. N	448.56 61.87 4	438.34 27.70 5	460.91 27.88 5	526.98 * 40.21 5
THYMUS (%)	MEAN ST.DEV. N	26.18 4.37 4	27.12 9.32 5	24.74 6.01 5	18.50 3.18 5
KIDNEYS (%)	MEAN ST.DEV. N	100.16 5.75 4	90.21 2.80 5	100.52 4.17 5	122.15 * 19.11 5
ADRENALS (%)	MEAN ST.DEV. N	3.087 0.133 4	3.204 0.344 5	3.175 0.318 5	2.957 0.385 5
SPLEEN (%)	MEAN ST.DEV N	30.508 3.161 4	32.047 1.427 5	30.645 3.736 5	50.471 ** 6.725 5
TESTES (%)	MEAN ST.DEV N	179.74 9.65 4	170.10 14.07 5	175.88 12.39 5	176.19 4.50 5
EPIDIDYMIDES (%)	MEAN ST.DEV N	59.143 4.755 4	51.746 7.958 5	52.466 7.972 5	48.203 5.496 5

* **: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 4 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	183.416	182.968	186.300	165.966 **
	ST.DEV.	8.049	4.868	2.686	3.331
	N	5	5	5	5
BRAIN	MEAN	1.85	1.81	1.82	1.78
	ST.DEV.	0.05	0.04	0.10	0.02
	N	5	5	5	5
HEART	MEAN	0.685	0.734	0.744	0.719
	ST.DEV.	0.044	0.025	0.059	0.[illegible]
	N	5	5	5	5
LIVER	MEAN	5.53	5.18	6.17	7.22 **
	ST.DEV.	0.63	0.40	0.49	0.97
	N	5	5	5	5
THYMUS	MEAN	0.47	0.45	0.48	0.38 *
	ST.DEV.	0.04	0.05	0.06	0.05
	N	5	5	5	5
KIDNEYS	MEAN	1.26	1.24	1.30	1.36
	ST.DEV.	0.08	0.10	0.09	0.09
	N	5	5	5	5
ADRENALS	MEAN	0.075	0.072	0.074	0.073
	ST.DEV.	0.004	0.006	0.009	0.006
	N	5	5	5	5
SPLEEN	MEAN	0.506	0.441	0.509	0.595 *
	ST.DEV.	0.034	0.049	0.046	0.079
	N	5	5	5	5
OVARIES	MEAN	0.104	0.097	0.096	0.126
	ST.DEV.	0.024	0.014	0.013	0.027
	N	5	5	5	5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 4 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
BODY W. (GRAM)	MEAN	183.416	182.968	180.300	165.966 **
	ST.DEV.	8.049	4.868	2.686	3.321
	N	5	5	5	5
BRAIN (%)	MEAN	1.01	0.99	0.98	1.08 *
	ST.DEV.	0.04	0.04	0.05	0.02
	N	5	5	5	5
HEART (%)	MEAN	0.374	0.401	0.389	0.432 *
	ST.DEV.	0.035	0.010	0.030	0.037
	N	5	5	5	5
LIVER (%)	MEAN	3.02	2.84	3.31	4.34 **
	ST.DEV.	0.34	0.29	0.26	0.54
	N	5	5	5	5
THYMUS (%)	MEAN	0.26	0.25	0.26	0.23
	ST.DEV.	0.02	0.03	0.03	0.03
	N	5	5	5	5
KIDNEYS (%)	MEAN	0.68	0.68	0.70	0.82 **
	ST.DEV.	0.04	0.07	0.05	0.05
	N	5	5	5	5
ADRENALS (%)	MEAN	0.041	0.038	0.039	0.044
	ST.DEV.	0.001	0.002	0.005	0.003
	N	5	5	5	5
SPLEEN (%)	MEAN	0.276	0.241	0.273	0.358 **
	ST.DEV.	0.015	0.028	0.021	0.042
	N	5	5	5	5
OVARIES (%)	MEAN	0.057	0.053	0.051	0.075 *
	ST.DEV.	0.013	0.007	0.005	0.015
	N	5	5	5	5

*,**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 4 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 50 MG/KG	GROUP 3 200 MG/KG	GROUP 4 800 MG/KG
BRAIN (GRAM)	MEAN	1.85	1.81	1.82	1.76
	ST.DEV.	0.05	0.04	0.10	0.02
	N	5	5	5	5
HEART (%)	MEAN	37.002	40.532	43.670	40.254
	ST.DEV.	1.281	1.950	3.359	3.855
	N	5	5	5	5
LIVER (%)	MEAN	298.73	285.87	339.30	404.52 **
	ST.DEV.	38.50	19.41	26.32	54.52
	N	5	5	5	5
THYMUS (%)	MEAN	25.58	25.07	26.24	21.05
	ST.DEV.	1.21	2.45	4.08	1.68
	N	5	5	5	5
KIDNEYS (%)	MEAN	67.72	68.31	71.14	76.51 *
	ST.DEV.	5.02	5.90	4.23	5.48
	N	5	5	5	5
ADRENALS (%)	MEAN	4.040	3.865	4.030	4.087
	ST.DEV.	0.226	0.293	0.373	0.297
	N	5	5	5	5
SPLEEN (%)	MEAN	27.265	24.279	27.924	33.353 **
	ST.DEV.	1.773	2.161	2.139	4.319
	N	5	5	5	5
OVARIES (%)	MEAN	5.641	5.350	5.253	7.028
	ST.DEV.	1.344	0.777	0.431	1.497
	N	5	5	5	5

*,**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

9 INDIVIDUAL TABLES

MORTALITY DATA
MALES
GROUP 1 (0 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
1	22-JAN-03		25-DEC-02	21-JAN-03
2	22-JAN-03		25-DEC-02	21-JAN-03
3	22-JAN-03		25-DEC-02	21-JAN-03
4	22-JAN-03		25-DEC-02	21-JAN-03
5		17-JAN-03	25-DEC-02	17-JAN-03

MORTALITY DATA
MALES
GROUP 2 (50 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
6	22-JAN-03		25-DEC-02	21-JAN-03
7	22-JAN-03		25-DEC-02	21-JAN-03
8	22-JAN-03		25-DEC-02	21-JAN-03
9	22-JAN-03		25-DEC-02	21-JAN-03
10	22-JAN-03		25-DEC-02	21-JAN-03

MORTALITY DATA
MALES
GROUP 3 (200 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
11	22-JAN-03		25-DEC-02	21-JAN-03
12	22-JAN-03		25-DEC-02	21-JAN-03
13	22-JAN-03		25-DEC-02	21-JAN-03
14	22-JAN-03		25-DEC-02	21-JAN-03
15	22-JAN-03		25-DEC-02	21 JAN-03

MORTALITY DATA
MALES
GROUP 4 (800 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
16	21-JAN-03		25-DEC-02	21-JAN-03
17	21-JAN-03		25-DEC-02	21-JAN-03
18	21-JAN-03		25-DEC-02	21-JAN-03
19	21-JAN-03		25-DEC-02	21-JAN-03
20	21-JAN-03		25-DEC-02	21-JAN-03

MORTALITY DATA
FEMALES
GROUP 1 (0 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
21	22-JAN-03		25-DEC-02	21-JAN-03
22	22-JAN-03		25-DEC-02	21-JAN-03
23	22-JAN-03		25-DEC-02	21-JAN-03
24	22-JAN-03		25-DEC-02	21-JAN-03
25	22-JAN-03		25-DEC-02	21-JAN-03

MORTALITY DATA
FEMALES
GROUP 2 (50 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
26	22-JAN-03		25-DEC-02	21-JAN-03
27	22-JAN-03		25-DEC-02	21-JAN-03
28	22-JAN-03		25-DEC-02	21-JAN-03
29	22-JAN-03		25-DEC-02	21-JAN-03
30	22-JAN-03		25-DEC-02	21-JAN-03

MORTALITY DATA
FEMALES
GROUP 3 (200 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
31	22-JAN-03		25-DEC-02	21-JAN-03
32	22-JAN-03		25-DEC-02	21-JAN-03
33	22-JAN-03		25-DEC-02	21-JAN-03
34	22-JAN-03		25-DEC-02	21-JAN-03
35	22-JAN-03		25-DEC-02	21-JAN-03

MORTALITY DATA
FEMALES
GROUP 4 (800 MG/KG)

ANIMAL	SCHEDULED NECROPSY	KILLED IN EXTREMIS	TREATMENT FROM	TO
36	22-JAN-03		25-DEC-02	21-JAN-03
37	22-JAN-03		25-DEC-02	21-JAN-03
38	22-JAN-03		25-DEC-02	21-JAN-03
39	22-JAN-03		25-DEC-02	21-JAN-03
40	22-JAN-03		25-DEC-02	21-JAN-03

RCC STUDY NUMBER 845763
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), MALES

ANIMAL No. 1

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1-3							
MOT	Ataxia	1-2							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), MALES

ANIMAL No. 2

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), MALES

ANIMAL No. 3

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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RCC STUDY NUMBER 845763
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), MALES

ANIMAL No. 4

				Study day / treatment																				
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

RCC STUDY NUMBER 845763
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), MALES

ANIMAL No. 5

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
	Ruffled Fur	1-3																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS	Soft Feces	1																						1
	Emaciated	1-3																						1

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3				x	x	x	x
	Salivation	1-3				x	x	x	x
	Hunched posture	1			1	x	x	x	x
	Ruffled Fur	1-3			1	x	x	x	x
MOT	Ataxia	1-3				x	x	x	x
	Tremor/twitching	1-3				x	x	x	x
	Prostration	1				x	x	x	x
BEH	Hyperactivity	1-3				x	x	x	x
	Somnolence	1-3				x	x	x	x
RES	Dyspnea	1				x	x	x	x
	Tachypnea	1				x	x	x	x
	Bradypnea	1				x	x	x	x
MIS	Soft Feces	1	1	1	1	x	x	x	x
	Emaciated	1-3	2	1	2	x	x	x	x

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted
n = Severity of findings
x = Animal sacrificed for ethical reason

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), MALES

ANIMAL No. 6

				Study day / treatment																			
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), MALES

ANIMAL No. 7

				Study day / treatment																				
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), MALES

ANIMAL No. 8

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), MALES

ANIMAL No. 9

				Study day / treatment																			
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), MALES

ANIMAL No. 10

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), MALES

ANIMAL No. 11

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), MALES

ANIMAL No. 12

				Study day / treatment																			
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), MALES

ANIMAL No. 13

	PARAMETER	SCORE	P	Study day / treatment																			
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), MALES

ANIMAL No. 14

				Study day / treatment																				
	PARAMETER	SCORE	P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

			Treatment						
	PARAMETER	SCORE	22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), MALES

ANIMAL No. 15

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[.....] = No abnormal findings noted

n = Severity of findings

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), MALES

ANIMAL No. 16

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), MALES

ANIMAL No. 17

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3	1	1	1	1			1
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), MALES

ANIMAL No. 18

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), MALES

ANIMAL No. 19

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), MALES

ANIMAL No. 20

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																	1	1	1	1	1	
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), FEMALES

ANIMAL No. 21

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), FEMALES

ANIMAL No. 22

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), FEMALES

ANIMAL No. 23

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), FEMALES

ANIMAL No. 24

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 1 (CONTROL), FEMALES

ANIMAL No. 25

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), FEMALES

ANIMAL No. 26

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), FEMALES

ANIMAL No. 27

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), FEMALES

ANIMAL No. 28

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), FEMALES

ANIMAL No. 29

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

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MOT = Motor
BEH = Behavioral
RES = Respiration
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P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 2 (LOW DOSE), FEMALES

ANIMAL No. 30

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), FEMALES

ANIMAL No. 31

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), FEMALES

ANIMAL No. 32

	PARAMETER	SCORE	P	Study day / treatment																				
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), FEMALES

ANIMAL No. 33

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), FEMALES

ANIMAL No. 34

	PARAMETER	SCORE	P	Study day / treatment																			
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
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RES = Respiration
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P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

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DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 3 (MID DOSE), FEMALES

ANIMAL No. 35

	PARAMETER	SCORE	Study day / treatment																					
			P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment						
			22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3							
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), FEMALES

ANIMAL No. 36

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						1
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3	1					1	
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), FEMALES

ANIMAL No. 37

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																		1	1	1	1	
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3						1	1
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

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RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), FEMALES

ANIMAL No. 38

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																	1	1	1	1	1	
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3		1			1	1	
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), FEMALES

ANIMAL No. 39

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																						1
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3	1	1	1				
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

RCC STUDY NUMBER 845763
RP 74

DAILY CAGE-SIDE OBSERVATIONS, INDIVIDUAL DATA

GROUP 4 (HIGH DOSE), FEMALES

ANIMAL No. 40

	PARAMETER	SCORE	P	Study day / treatment 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
APP	Piloerection	1-3																						
	Salivation	1-3																						
	Hunched posture	1																	1	1	1	1	1	1
MOT	Ataxia	1-3																						
	Tremor/twitching	1-3																						
	Prostration	1																						
BEH	Hyperactivity	1-3																						
	Somnolence	1-3																						
RES	Dyspnea	1																						
	Tachypnea	1																						
	Bradypnea	1																						
MIS																								

	PARAMETER	SCORE	Treatment 22	23	24	25	26	27	28
APP	Piloerection	1-3							
	Salivation	1-3	1	1		1			1
	Hunched posture	1							
MOT	Ataxia	1-3							
	Tremor/twitching	1-3							
	Prostration	1							
BEH	Hyperactivity	1-3							
	Somnolence	1-3							
RES	Dyspnea	1							
	Tachypnea	1							
	Bradypnea	1							
MIS									

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
MIS = Miscellaneous
P = Pretest examination (during acclimatization)

[ ] = No abnormal findings noted

n = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

PRETEST

			GROUP 1 (CONTROL)										GROUP 2 (LOW DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	1	2	3	4	5	21	22	23	24	25	6	7	8	9	10	26	27	28	29	30
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. Exploration																					
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Indic. light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle - hearing	1																				
MIS	Lachrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

[ ] = No abnormal findings noted

n = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

PRETEST

			GROUP 3 (MID DOSE)										GROUP 4 (HIGH DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	11	12	13	14	15	31	32	33	34	35	16	17	18	19	20	36	37	38	39	40
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Photic light reflex	1																				
	Push off (hind legs)	1																				
	Pain response	1																				
	Startle - hearing	1																				
MIS	Lachrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

| | = No abnormal findings noted

n = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 1

			GROUP 1 (CONTROL)										GROUP 2 (LOW DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	1	2	3	4	5	21	22	23	24	25	6	7	8	9	10	26	27	28	29	30
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				
	Tail bent	1							1													
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Iridic light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

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n = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 1

GROUP 3 (MID DOSE) GROUP 4 (HIGH DOSE)

FINDINGS / ANIMAL NO		SCORE	MALES					FEMALES					MALES					FEMALES				
			11	12	13	14	15	31	32	33	34	35	16	17	18	19	20	36	37	38	39	40
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Iridic light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle / hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
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| | = No abnormal findings noted

r = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 2

			GROUP 1 (CONTROL)										GROUP 2 (LOW DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	1	2	3	4	5	21	22	23	24	25	6	7	8	9	10	26	27	28	29	30
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Iridic light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle/hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
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RES = Respiration
REF = Reflexes
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[ ] = No abnormal findings noted

n = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 2

			GROUP 3 (MID DOSE)										GROUP 4 (HIGH DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	11	12	13	14	15	31	32	33	34	35	16	17	18	19	20	36	37	38	39	40
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Incr. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Indir. light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle - hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

| | = No abnormal findings noted

1 = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 3

			GROUP 1 (CONTROL)										GROUP 2 (LOW DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	1	2	3	4	5	21	22	23	24	25	6	7	8	9	10	26	27	28	29	30
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																				
MOT	Ataxia	1-3																				
	Tremor/twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Hen. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Indir. light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle - hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

[ ] = No abnormal findings noted

n = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 3

			GROUP 3 (MID DOSE)										GROUP 4 (HIGH DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	11	12	13	14	15	31	32	33	34	35	16	17	18	19	20	36	37	38	39	40
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	1																1			1	
MOT	Ataxia	1-3																				
	Hemochromatosis	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	1																				
	Bradypnea	1																				
REF	Blink	1																				
	Pinna	1																				
	Pupil light reflex	1																				
	Push off (hind legs)	1																				
	Pain response	1																				
	Startle / hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

[ ] = No abnormal findings noted

n = Severity of findings

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 4

			GROUP 1 (CONTROL)										GROUP 2 (LOW DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	1	2	3	4	5	21	22	23	24	25	6	7	8	9	10	26	27	28	29	30
APP	Piloerection	1-3					x															
	Salivation	1-3					x															
	Hunched posture	1					x															
							x															
MOT	Ataxia	1-3					x															
	Tremor/twitching	1-3					x															
	Prostration	1					x															
	Circling	1					x															
	Spasm	1-3					x															
BEH	Hyperactivity	1-3					x															
	Somnolence	1-3					x															
	Inc. exploration	1-3					x															
	Red. grooming	1-3					x															
	Vocalization	1-3					x															
RES	Dyspnea	1					x															
	Tachypnea	1					x															
	Bradypnea	1					x															
REF	Blink	1					x															
	Pinna	1					x															
	Indir. light reflex	1					x															
	Push-off (hind legs)	1					x															
	Pain response	1					x															
	Startle / hearing	1					x															
MIS	Lacrimation	1-3					x															
	Limbs cyanotic	1					x															
	Mydriasis	1					x															
	Miosis	1					x															
	Exophthalmos	1					x															
	Red. muscle tone	1-3					x															
	Feces soft	1					x															

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

[ ] = No abnormal findings noted

n = Severity of findings

x = Animal sacrificed for ethical reason

WEEKLY OUTSIDE CAGE OBSERVATIONS, INDIVIDUAL DATA

WEEK 4

			GROUP 3 (MID DOSE)										GROUP 4 (HIGH DOSE)									
			MALES					FEMALES					MALES					FEMALES				
FINDINGS / ANIMAL NO		SCORE	11	12	13	14	15	31	32	33	34	35	16	17	18	19	20	36	37	38	39	40
APP	Piloerection	1-3																				
	Salivation	1-3																				
	Hunched posture	+												1								
MOT	Ataxia	1-3																				
	Tremor twitching	1-3																				
	Prostration	1																				
	Circling	1																				
	Spasm	1-3																				
BEH	Hyperactivity	1-3																				
	Somnolence	1-3																				
	Inc. exploration	1-3																				
	Red. grooming	1-3																				
	Vocalization	1-3																				
RES	Dyspnea	1																				
	Tachypnea	+																				
	Bradypnea	+																				
REF	Blink	1																				
	Pinna	1																				
	Pupil light reflex	1																				
	Push-off (hind legs)	1																				
	Pain response	1																				
	Startle / hearing	1																				
MIS	Lacrimation	1-3																				
	Limbs cyanotic	1																				
	Mydriasis	1																				
	Miosis	1																				
	Exophthalmos	1																				
	Red. muscle tone	1-3																				
	Feces soft	1																				

Abbreviations:

APP = Appearance
MOT = Motor
BEH = Behavioral
RES = Respiration
REF = Reflexes
MIS = Miscellaneous

[ ] - No abnormal findings noted

n = Severity of findings

GRIP STRENGTH AT WEEK 4. INDIVIDUAL DATA

MALES Mean (g)

GROUP 1 (0 mg/kg/day)

Animal No.	Forelimb	Hindlimb
1	907	723
2	1280	923
3	1177	777
4	1020	830
5 #		

GROUP 2 (50 mg/kg/day)

Animal No.	Forelimb	Hindlimb
6	1153	757
7	1050	817
8	1263	940
9	1183	827
10	1217	933

GROUP 3 (200 mg/kg/day)

Animal No.	Forelimb	Hindlimb
11	883	693
12	1243	887
13	1167	863
14	1287	860
15	1133	820

GROUP 4 (800 mg/kg/day)

Animal No.	Forelimb	Hindlimb
16	1207	867
17	1113	833
18	1093	830
19	1023	827
20	1120	790

FEMALES Mean (g)

GROUP 1 (0 mg/kg/day)

Animal No.	Forelimb	Hindlimb
21	997	727
22	1057	767
23	997	697
24	953	790
25	997	763

GROUP 2 (50 mg/kg/day)

Animal No.	Forelimb	Hindlimb
26	967	707
27	940	677
28	970	710
29	927	743
30	950	733

GROUP 3 (200 mg/kg/day)

Animal No.	Forelimb	Hindlimb
31	907	720
32	1050	757
33	867	777
34	920	780
35	913	740

GROUP 4 (800 mg/kg/day)

Animal No.	Forelimb	Hindlimb
36	970	710
37	930	760
38	880	650
39	840	650
40	937	717

Animal had to be sacrificed for humane reasons

RCC STUDY NUMBER 845763
RP 74

LOCOMOTOR ACTIVITY. INDIVIDUAL DATA

LOW BEAMS COUNT — MALES

Animal No	15 min.	30 Min.	45 min.	60 min.	Total
Group 1 — 0 mg/kg					
1	853	636	446	69	2004
2	692	513	212	23	1440
3	947	477	11	181	1616
4	954	509	275	44	1782
5 #					
Group 2 — 50 mg/kg					
6	785	630	570	373	2358
7	1018	609	629	99	2355
8	1169	524	643	435	2771
9	1121	932	572	46	2671
10	1248	805	560	242	2855
Group 3 — 200 mg/kg					
11	508	427	475	19	1429
12	850	731	447	237	2265
13	718	717	312	412	2159
14	576	71	264	224	1135
15	825	304	586	11	1726
Group 4 — 1000 mg/kg					
16	858	151	96	220	1325
17	341	236	2	631	1210
18	725	512	533	228	1998
19	570	393	162	5	1130
20	363	51	206	502	1122

Animal had to be sacrificed for humane reasons

LOCOMOTOR ACTIVITY, INDIVIDUAL DATA

LOW BEAMS COUNT

FEMALES

Animal No		15 min.	30 Min.	45 min.	60 min.	Total
Group 1	0 mg/kg					
21		811	557	0	347	1715
22		1056	524	221	340	2141
23		784	488	51	366	1689
24		779	354	15	133	1281
25		672	131	58	77	938
Group 4	50 mg/kg					
26		776	713	117	409	2015
27		869	552	248	371	2040
28		954	344	29	163	1490
29		872	489	442	529	2332
30		1330	634	145	708	2817
Group 4	200 mg/kg					
31		906	429	164	358	1857
32		1020	630	331	341	2322
33		1199	929	548	550	3226
34		1382	847	255	406	2890
35		957	496	484	468	2405
Group 4	1000 mg/kg					
36		743	543	416	366	2068
37		1145	553	146	282	2126
38		630	161	0	6	797
39		893	522	372	320	2107
40		973	499	193	542	2207

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

	PRETEST	TREATMENT			
DAYS	1-8	1-8	8-15	16-22	22-29
WEEKS	1-2	1-2	2/3	3/4	4
CAGE					
GROUP 1 (0 MG/KG)					
1	17.4	19.0	20.2	17.7	17.0
GROUP 2 (50 MG/KG)					
2	19.1	19.7	20.8	20.9	21.0
GROUP 3 (200 MG/KG)					
3	18.2	19.0	20.2	20.0	20.0
GROUP 4 (800 MG/KG)					
4	18.6	19.0	20.6	20.0	20.4

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

	PRETEST	TREATMENT			
DAYS	1-8	1-8	9-15	15-22	22-28
WEEKS	1-2	1-2	2-3	3-4	4
DAGE					
GROUP 1 (0 MG/KG)					
5	12.7	12.2	13.7	13.4	12.9
GROUP 2 (50 MG/KG)					
6	12.7	13.2	13.6	13.1	13.0
GROUP 3 (200 MG/KG)					
7	13.0	13.7	14.5	13.9	14.3
GROUP 4 (800 MG/KG)					
8	13.9	12.9	13.4	13.7	13.6

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

	PRETEST	TREATMENT			
DAYS	1-8	1-8	8-16	16-22	22-26
WEEKS	1-2	1-2	2-3	3-4	4
DAGE					
GROUP 1 (0 MG/KG)					
1	120	87	79	67	56
GROUP 2 (50 MG/KG)					
2	132	85	77	69	65
GROUP 3 (200 MG/KG)					
3	138	84	---	69	65
GROUP 4 (800 MG/KG)					
4	130	95	81	73	70

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

	PRETEST	TREATMENT			
DAYS	1-8	1-8	8-15	15-22	22-28
WEEKS	1-2	1-2	2-3	3-4	4
SAME					
GROUP 1 (0 MG/KG)					
5	105	82	[illegible]	69	65
GROUP 2 (50 MG/KG)					
6	113	82	[illegible]	69	66
GROUP 3 (200 MG/KG)					
7	106	84	78	71	71
GROUP 4 (800 MG/KG)					
8	106	83	80	76	74

BODY WEIGHTS (GRAM)
MALES

	PRETEST	TREATMENT				
DAYS	1	1	8	15	22	29
WEEKS	1	1	2	3	4	4
ANIMAL						
GROUP 1 (0 MG/KG)						
1	146	176	206	234	251	266
2	153	197	246	288	323	340
3	149	193	235	270	293	320
4	137	180	221	257	279	330
5	141	153	187	235	179	---
GROUP 2 (50 MG/KG)						
6	144	180	221	256	281	297
7	147	199	252	297	335	360
8	150	195	242	280	303	320
9	142	182	218	254	278	291
10	141	187	226	270	309	334
GROUP 3 (200 MG/KG)						
11	141	196	240	279	307	330
12	136	176	221	253	278	297
13	150	194	244	273	301	319
14	152	188	240	271	306	326
15	143	169	199	232	260	274
GROUP 4 (800 MG/KG)						
16	145	184	227	262	278	297
17	134	176	212	238	254	263
18	146	185	206	225	247	260
19	142	190	234	266	298	316
20	149	198	242	272	300	315

BODY WEIGHTS (GRAM)
FEMALES

	PRETEST	TREATMENT				
DAYS	1	1	8	15	22	28
WEEKS	1	1	2	3	4	4
ANIMAL						
GROUP 1 (0 MG/KG)						
21	124	141	166	177	199	204
22	115	137	161	183	199	205
23	120	142	167	188	200	202
24	122	139	156	173	180	187
25	125	143	161	176	192	197
GROUP 2 (50 MG/KG)						
26	121	142	164	193	195	200
27	123	142	158	172	189	198
28	123	141	159	170	178	189
29	117	140	166	181	193	200
30	124	144	161	180	192	194
GROUP 3 (200 MG/KG)						
31	118	135	160	183	194	199
32	125	149	168	187	197	199
33	130	137	164	181	194	204
34	125	146	168	183	197	209
35	121	138	163	184	193	198
GROUP 4 (800 MG/KG)						
36	122	139	159	177	187	194
37	125	144	156	171	180	191
38	118	136	151	170	186	184
39	119	140	160	166	171	184
40	122	139	151	163	174	176

BODY WEIGHT GAIN (%)
MALES

	PRETEST	TREATMENT				
DAYS	1	1	8	15	22	28
WEEKS	1	1	2	3	4	4
ANIMAL						
GROUP 1 (0 MG/KG)						
1	17.6	0.0	16.1	31.7	41.5	49.0
2	-22.1	0.0	24.5	46.3	63.8	72.6
3	-22.5	0.0	32.0	40.3	52.5	61.1
4	-23.8	0.0	22.7	42.9	55.1	60.5
5	[illegible]	0.0	21.6	47.1	57.0	---
GROUP 2 (50 MG/KG)						
6	-19.8	0.0	22.7	41.9	56.1	64.7
7	-26.3	0.0	26.3	49.0	66.2	80.6
8	-22.8	0.0	26.1	43.8	55.6	64.2
9	-21.7	0.0	20.0	39.5	52.9	60.3
10	-24.2	0.0	22.2	44.4	65.2	79.2
GROUP 3 (200 MG/KG)						
11	-25.7	0.0	26.4	47.1	61.7	73.8
12	-23.1	0.0	25.1	43.3	57.6	68.6
13	-21.8	0.0	30.7	40.6	55.3	64.3
14	-19.4	0.0	27.8	44.2	62.7	73.5
15	-21.3	0.0	18.3	37.5	53.9	62.6
GROUP 4 (800 MG/KG)						
16	-21.1	0.0	23.6	42.5	51.3	61.6
17	-23.7	0.0	20.9	35.3	44.7	49.8
18	-21.0	0.0	11.7	21.7	33.7	40.8
19	-25.0	0.0	23.2	40.4	57.0	66.6
20	-24.5	0.0	23.1	37.9	51.7	58.5

BODY WEIGHT GAIN (%)
FEMALES

	PRETEST	TREATMENT				
DAYS	1	1	8	15	22	29
WEEKS	1	1	2	3	4	4
ANIMAL						
GROUP 1 (0 MG/KG)						
21	-17.5	0.0	15.1	25.2	41.0	44.4
22	-16.2	0.0	17.3	33.2	43.7	49.1
23	-15.8	0.0	17.6	31.9	40.6	40.7
24	-9.8	0.0	15.5	27.6	33.0	38.1
25	-12.9	0.0	12.3	22.0	34.1	37.5
GROUP 2 (50 MG/KG)						
26	-14.8	0.0	15.5	29.1	37.4	41.2
27	-13.4	0.0	11.4	21.3	32.5	39.6
28	-12.8	0.0	13.1	20.8	26.5	34.1
29	-16.3	0.0	18.7	29.2	38.2	43.2
30	-12.7	0.0	11.8	25.4	31.0	34.5
GROUP 3 (200 MG/KG)						
31	-12.0	0.0	15.6	36.0	44.5	48.2
32	-15.7	0.0	12.8	25.6	32.6	33.6
33	-12.4	0.0	19.2	31.9	41.2	48.4
34	-14.5	0.0	14.8	25.0	34.6	43.2
35	-12.2	0.0	15.3	32.7	39.9	43.8
GROUP 4 (400 MG/KG)						
36	-11.9	0.0	14.6	27.4	34.8	38.8
37	-13.6	0.0	7.8	18.7	24.8	32.1
38	-13.5	0.0	10.7	24.8	36.3	35.3
39	-14.8	0.0	14.4	17.9	22.4	31.8
40	-12.1	0.0	9.2	15.5	25.1	28.8

MACROSCOPICAL FINDINGS
MALES
GROUP 1 (0 MG/KG)

ANIMAL 1

(SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 2

(SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 3

(SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 4

(SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 5

(KILLED IN EXTREMIS, 17-JAN-2003)

DUODENUM.....	MUCOSA: THICKENED.
EPIDIDYMIDES	TAIL, LEFT SIDE: NODULE(S), D=5 MM, YELLOWISH, SOFT.
SPLEEN.....	DISCOLORATION, LIGHT BROWN.
THYMUS	REDUCED IN SIZE.

MACROSCOPICAL FINDINGS
MALES
GROUP 2 (50 MG/KG)

ANIMAL 6

(SCHEDULED NECROPSY 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 7

(SCHEDULED NECROPSY 22-JAN-2003)

THYMUS.. .. .. ENLARGED.

ANIMAL 8

(SCHEDULED NECROPSY 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 9

(SCHEDULED NECROPSY 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 10

(SCHEDULED NECROPSY 22-JAN-2003)

NO FINDINGS NOTED

MACROSCOPICAL FINDINGS
MALES
GROUP 3 (200 MG/KG)

ANIMAL 11 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 12 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 13 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 14 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 15 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

MACROSCOPICAL FINDINGS
MALES
GROUP 4 (800 MG/KG)

ANIMAL 16 (SCHEDULED NECROPSY 22-JAN-2003)

KIDNEYS BOTH SIDES ENLARGED

ANIMAL 17 (SCHEDULED NECROPSY 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 18 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 19 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 20 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

MACROSCOPICAL FINDINGS
FEMALES
GROUP 1 (0 MG/KG)

ANIMAL 21 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 22 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 23 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 24 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 25 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

MACROSCOPICAL FINDINGS
FEMALES
GROUP 2 (50 MG/KG)

ANIMAL 26 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 27 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 28 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 29 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 30 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

MACROSCOPICAL FINDINGS
FEMALES
GROUP 3 (200 MG/KG)

ANIMAL 31 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 32 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 33 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 34 (SCHEDULED NECROPSY, 22-JAN-2003)

UTERUS ..... BOTH HORNS: DILATION, D=5 MM, CONTAINS FLUID.

ANIMAL 35 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

MACROSCOPICAL FINDINGS
FEMALES
GROUP 4 (800 MG/KG)

ANIMAL 36 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 37 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 38 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 39 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ANIMAL 40 (SCHEDULED NECROPSY, 22-JAN-2003)

NO FINDINGS NOTED

ORGAN WEIGHTS (GRAM)
AFTER 4 WEEKS
MALES

GROUP 1 (0 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
1	253.000	1.82	0.866	6.74	0.47	1.68	0.055	0.497
2	320.820	1.95	1.014	8.35	0.63	1.96	0.057	0.646
3	291.450	1.92	1.061	9.68	0.41	1.97	0.060	0.541
4	282.950	1.89	0.942	9.25	0.48	1.99	0.061	0.630
5	---	---	---	---	---	---	---	---

ANIMAL NUMBER	TESTES	EPIDIDYMIS
1	3.09	1.048
2	3.77	1.179
3	3.39	1.200
4	3.29	1.159
5	---	---

GROUP 2 (50 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
6	276.140	2.00	0.993	8.33	0.52	1.88	0.070	0.684
7	335.940	2.05	1.064	9.39	0.82	1.88	0.069	0.669
8	299.790	2.00	0.917	8.96	0.27	1.79	0.058	0.623
9	276.760	1.94	0.873	7.93	0.55	1.74	0.054	0.595
10	313.800	1.97	1.104	9.21	0.55	1.70	0.066	0.624

ANIMAL NUMBER	TESTES	EPIDIDYMIS
6	3.30	0.998
7	3.79	1.291
8	3.07	1.217
9	3.16	0.814
10	3.64	0.951

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
11	307.090	1.99	1.051	9.65	0.44	2.03	0.054	0.557
12	273.290	1.86	1.045	8.32	0.51	1.80	0.056	0.540
13	292.340	2.04	1.015	8.81	0.69	2.00	0.071	0.731
14	300.890	2.00	0.956	9.91	0.37	2.14	0.068	0.664
15	257.420	1.89	0.954	8.43	0.41	1.87	0.062	0.515

ORGAN WEIGHTS (GRAM)
AFTER 4 WEEKS
MALES

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	TESTES	EPIDIDYMID
11	3.23	1.143
12	3.59	0.990
13	3.76	1.258
14	3.42	0.985
15	3.19	0.772

GROUP 4 (800 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
16	268.090	1.87	1.003	10.09	3.41	2.67	0.055	1.330
17	240.730	1.95	0.941	8.94	0.27	2.11	0.060	0.877
18	235.600	1.80	0.933	9.74	0.33	1.85	0.050	0.882
19	288.400	1.94	0.980	10.91	0.34	2.76	0.069	1.155
20	280.130	1.91	0.976	10.16	0.40	2.19	0.048	0.836

ANIMAL NUMBER	TESTES	EPIDIDYMID
16	3.30	1.050
17	3.35	0.931
18	3.30	0.893
19	3.39	0.905
20	3.33	0.781

ORGAN/BODY WEIGHT RATIOS (%)
AFTER 4 WEEKS
MALES

GROUP 1 (0 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
1	253.000	0.72	0.341	2.67	0.18	0.66	0.022	0.197
2	320.920	0.61	0.318	2.60	0.19	0.61	0.016	0.201
3	291.450	0.66	0.361	3.12	0.14	0.68	0.021	0.186
4	382.950	0.67	0.333	3.27	0.17	0.70	0.022	0.223
5	---	---	---	---	---	---	---	---

ANIMAL NUMBER	TESTES	EPIDIDYMIS
1	1.22	0.275
2	1.17	0.367
3	1.16	0.412
4	1.20	0.420
5	---	---

GROUP 2 (50 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
6	276.140	0.72	0.359	3.02	0.19	0.69	0.025	0.248
7	335.940	0.61	0.323	2.80	0.24	0.56	0.021	0.199
8	299.790	0.67	0.306	2.99	0.09	0.60	0.019	0.208
9	276.760	0.70	0.215	2.83	0.20	0.63	0.019	0.215
10	312.800	0.62	0.353	2.94	0.18	0.54	0.022	0.200

ANIMAL NUMBER	TESTES	EPIDIDYMIS
6	1.20	0.361
7	1.12	0.384
8	1.03	0.373
9	1.14	0.294
10	1.16	0.304

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
11	307.090	0.65	0.342	3.14	0.14	0.66	0.018	0.181
12	273.290	0.68	0.383	3.04	0.19	0.66	0.020	0.198
13	292.340	0.70	0.347	3.01	0.24	0.68	0.024	0.250
14	300.890	0.66	0.318	3.29	0.12	0.71	0.023	0.221
15	297.420	0.73	0.370	3.27	0.16	0.73	0.024	0.300

ORGAN/BODY WEIGHT RATIOS (%)
AFTER 4 WEEKS
MALES

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	TESTES	EPIDIDYMIS
11	1.05	0.372
12	1.31	0.362
13	1.29	0.430
14	1.14	0.327
15	1.24	0.308

GROUP 4 (800 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
16	268.090	0.70	0.373	3.76	0.15	0.99	0.020	0.384
17	248.730	0.81	0.391	3.72	0.11	0.88	0.025	0.364
18	235.600	0.76	0.391	4.14	0.14	0.79	0.021	0.374
19	268.400	0.67	0.340	3.78	0.12	0.96	0.024	0.400
20	280.130	0.68	0.348	3.63	0.14	0.78	0.017	0.298

ANIMAL NUMBER	TESTES	EPIDIDYMIS
16	1.23	0.392
17	1.39	0.387
18	1.40	0.379
19	1.17	0.314
20	1.19	0.279

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER 4 WEEKS
MALES

GROUP 1 (0 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	TESTES
1	1.82	47.624	370.94	35.67	92.14	3.083	27.197	169.53
2	1.95	52.128	427.13	32.09	100.17	2.942	33.035	192.75
3	1.92	54.859	505.40	21.39	107.94	3.152	28.204	177.04
4	1.89	49.986	490.67	25.67	108.39	3.285	33.415	178.88
5	---	---	---	---	---	---	---	---

ANIMAL NUMBER	EPIDIDYMIS
1	52.156
2	60.294
3	62.643
4	61.478
5	---

GROUP 2 (50 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	TESTES
6	2.00	49.645	416.74	25.83	94.19	3.502	34.236	165.19
7	2.05	52.823	457.44	39.82	91.43	3.381	32.572	184.44
8	2.00	45.781	447.38	13.61	89.36	2.901	31.104	153.43
9	1.94	44.873	402.44	28.24	89.67	3.767	30.603	162.30
10	1.97	56.082	467.82	28.11	86.54	3.470	31.719	185.07

ANIMAL NUMBER	EPIDIDYMIS
6	49.905
7	62.883
8	55.781
9	41.860
10	46.103

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	TESTES
11	1.95	52.749	484.54	21.94	101.91	3.721	27.941	162.19
12	1.86	56.075	446.11	27.61	96.53	3.977	28.955	192.64
13	2.04	49.738	431.86	33.79	98.05	3.475	25.838	184.45
14	2.00	47.880	496.37	18.58	107.11	3.413	22.278	171.47
15	1.89	50.431	445.69	21.78	99.01	3.289	27.215	168.64

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER 4 WEEKS
MALES

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	EPIDIDYMIS
11	57.489
12	53.082
13	61.656
14	49.379
15	45.822

GROUP 4 (800 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	TESTES
16	1.87	53.518	549.97	21.78	142.64	2.927	55.107	176.30
17	1.95	49.149	457.81	13.71	108.09	3.056	44.878	171.61
18	1.80	51.142	541.51	18.50	102.93	2.751	49.008	183.64
19	1.94	50.503	562.61	17.58	142.53	3.542	59.525	174.70
20	1.91	51.114	532.91	20.95	114.53	2.512	43.836	174.70

ANIMAL NUMBER	EPIDIDYMIS
16	56.155
17	47.648
18	49.025
19	46.657
20	40.931

ORGAN WEIGHTS (GRAM)
AFTER 4 WEEKS
FEMALES

GROUP 1 (0 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
22	197.900	1.87	0.667	5.18	0.47	1.32	0.074	0.501
23	184.690	1.83	0.687	6.30	0.52	1.32	0.081	0.492
24	186.860	1.88	0.716	5.87	0.52	1.30	0.077	0.511
25	170.070	1.78	0.775	5.24	0.43	1.22	0.069	0.480
26	181.560	1.91	0.621	4.67	0.43	1.17	0.074	0.481

ANIMAL NUMBER	OVARIES
22	0.133
23	0.091
24	0.118
25	0.110
26	0.173

GROUP 2 (50 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
27	186.770	1.87	0.752	5.39	0.49	1.20	0.081	0.514
28	182.050	1.80	0.710	4.81	0.51	1.20	0.064	0.437
29	175.110	1.85	0.709	5.66	0.47	1.34	0.069	0.459
30	187.140	1.80	0.736	5.10	0.40	1.12	0.068	0.392
31	183.820	1.76	0.765	5.06	0.41	1.34	0.068	0.402

ANIMAL NUMBER	OVARIES
27	0.116
28	0.089
29	0.086
30	0.385
31	0.108

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
32	184.920	1.73	0.800	6.04	0.45	1.31	0.068	0.510
33	186.780	1.92	0.781	6.94	0.53	1.43	0.090	0.534
34	184.460	1.71	0.660	6.25	0.55	1.20	0.068	0.461
35	190.800	1.88	0.775	6.06	0.42	1.22	0.072	0.571
36	184.540	1.87	0.703	5.58	0.43	1.22	0.071	0.467

ORGAN WEIGHTS (GRAM)
AFTER 4 WEEKS
FEMALES

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	OVARIES
31	0.092
32	0.113
33	0.092
34	0.093
35	0.089

GROUP 4 (800 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
36	170.060	1.79	0.819	7.70	0.34	1.36	0.078	0.714
37	167.210	1.78	0.666	8.66	0.42	1.50	0.067	0.582
38	167.380	1.80	0.757	6.84	0.38	1.32	0.077	0.616
39	163.390	1.79	0.642	6.26	0.43	1.26	0.078	0.498
40	161.790	1.75	0.704	6.61	0.32	1.39	0.066	0.565

ANIMAL NUMBER	OVARIES
36	0.164
37	0.139
38	0.119
39	0.090
40	0.118

ORGAN/BODY WEIGHT RATIOS (%)
AFTER 4 WEEKS
FEMALES

GROUP 1 (0 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
21	187.900	0.99	0.355	[illegible]	0.25	0.69	0.039	0.299
22	188.650	0.97	0.364	3.34	0.27	[illegible]	0.043	0.263
23	188.860	1.00	0.379	3.11	0.27	0.69	0.041	[illegible]
24	170.070	1.05	0.432	3.31	0.26	[illegible]	0.040	0.282
25	181.560	1.05	0.343	2.57	0.24	0.62	0.041	0.265

ANIMAL NUMBER	OVARIES
21	0.071
22	0.048
23	0.063
24	0.065
25	0.039

GROUP 2 (50 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
26	186.720	1.00	0.403	2.72	0.26	0.64	0.043	0.275
27	182.050	0.99	0.390	2.64	0.28	0.66	0.035	0.240
28	175.110	1.05	0.405	3.35	0.27	0.76	0.040	0.262
29	187.140	0.96	0.393	2.73	0.21	0.60	0.036	0.209
30	183.820	0.95	0.416	2.75	0.22	0.73	0.037	0.219

ANIMAL NUMBER	OVARIES
26	0.062
27	0.049
28	0.049
29	0.046
30	0.059

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	BODY W (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
31	184.920	0.93	0.432	3.27	0.24	0.71	0.037	0.276
32	186.780	1.03	0.418	3.71	0.28	0.76	0.048	0.286
33	184.460	0.93	0.358	3.39	0.30	0.65	0.037	0.250
34	190.800	0.98	0.406	3.17	0.22	0.69	0.037	0.299
35	184.540	1.01	0.381	3.02	0.23	0.66	0.038	0.253

ORGAN/BODY WEIGHT RATIOS (%)
AFTER 4 WEEKS
FEMALES

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	OVARIES
31	0.050
32	0.060
33	0.050
34	0.049
35	0.048

GROUP 4 (800 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN
36	170.060	1.05	0.482	4.53	0.20	0.80	0.046	0.420
37	167.210	1.06	0.400	5.19	0.25	0.90	0.040	0.348
38	167.380	1.08	0.452	4.09	0.23	0.79	0.048	0.368
39	163.390	1.10	0.393	3.83	0.26	0.77	0.046	0.305
40	161.790	1.08	0.435	4.06	0.20	0.86	0.041	0.349

ANIMAL NUMBER	OVARIES
36	0.096
37	0.082
38	0.071
39	0.055
40	0.073

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER 4 WEEKS
FEMALES

GROUP 1 (0 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	OVARIES
21	1.87	35.741	277.47	25.64	70.01	3.976	30.064	[illegible]
22	1.83	37.456	343.83	28.12	72.13	4.407	[illegible]	4.868
23	1.88	38.014	311.82	27.43	69.02	4.095	27.148	[illegible]
24	1.78	41.237	316.27	24.63	68.33	3.850	26.909	[illegible]
25	1.91	32.560	244.28	22.66	59.12	3.873	25.160	3.664

GROUP 2 (50 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	OVARIES
26	1.87	40.283	272.40	25.97	64.12	4.347	27.498	6.221
27	1.80	39.483	267.72	28.42	66.49	3.566	24.317	4.957
28	1.85	38.394	317.26	25.49	72.29	3.748	24.959	4.662
29	1.80	40.913	283.75	22.12	62.21	3.793	21.800	4.745
30	1.76	43.587	288.24	23.33	76.34	3.880	22.922	6.165

GROUP 3 (200 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	OVARIES
31	1.73	46.254	349.30	26.12	75.80	3.905	29.525	5.333
32	1.82	40.639	361.17	27.62	74.30	4.686	27.783	5.863
33	1.71	38.591	365.24	32.37	70.17	4.357	26.955	5.383
34	1.68	41.271	322.32	22.35	70.49	3.806	30.397	4.934
35	1.87	37.593	298.46	22.77	64.93	3.796	24.980	4.753

GROUP 4 (800 MG/KG)

ANIMAL NUMBER	BRAIN (GRAM)	HEART	LIVER	THYMUS	KIDNEYS	ADRENALS	SPLEEN	OVARIES
36	1.79	45.682	429.02	18.79	75.56	4.321	39.810	9.070
37	1.78	37.560	487.41	23.59	84.25	3.774	32.686	7.733
38	1.80	42.039	379.91	20.98	73.29	4.247	34.194	6.557
39	1.79	35.835	349.29	23.87	70.18	4.336	27.828	5.836
40	1.75	40.262	376.90	18.01	79.36	3.753	32.246	6.777

RCC Study Number 845763

RP 74:

28-Day Oral Toxicity (Gavage) Study in the Wistar Rat

Final Report (PART II OF II)

Authors: Dr. E.W. Sommer, Dr. D. Schroeder, Dr. P. Gretener, Dr. K. Weber

Sponsor: Rhodia Services DPS
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RCC

APPENDIX I:

OBSERVATIONS

SUMMARY OF PARAMETERS (MINIMUM REQUIREMENT FOR EACH ANIMAL)									
OBSERVATIONS: DAILY CAGE-SIDE (D), PRETEST (P), WEEKLY (W) AND FOB (F)									
	SCORE	PARAMETER	D	P	W 1	W 2	W 3	F 4	Comments
APPEARANCE	1-3	Piloerection	X	X	X	X	X	X	None
	1-3	Salivation	X	X	X	X	X	X	None
	1	Hunched posture	X	X	X	X	X	X	None
MOTOR	1-3	Ataxia	X	X	X	X	X	X	None
	1-3	Tremor/twitching	X	X	X	X	X	X	None
	1	Prostration	X	X	X	X	X	X	None
	1	Circling		X	X	X	X	X	None
	1-3	Spasm		X	X	X	X	X	None
BEHAVIOR	1-3	Hyperactivity	X	X	X	X	X	X	None
	1-3	Somnolence	X	X	X	X	X	X	None
	1-3	Increased exploration		X	X	X	X	X	None
	1-3	Reduced grooming		X	X	X	X	X	None
	1-3	Vocalisation		X	X	X	X	X	None
RESPIRATION	1	Dyspnea	X	X	X	X	X	X	None
	1	Tachypnea	X	X	X	X	X	X	None
	1	Bradypnea	X	X	X	X	X	X	None
REFLEXES	1	Blink		X	X	X	X	X	None
	1	Pinna		X	X	X	X	X	None
	1	Iridic light reflex		X	X	X	X	X	None
	1	Push-off (hind leg)		X	X	X	X	X	None
	1	Pain response		X	X	X	X	X	None
	1	Startle/hearing		X	X	X	X	X	None
Miscellaneous	1-3	Lacrimation		X	X	X	X	X	None
	1	Limbs cyanotic		X	X	X	X	X	None
	1	Mydriasis		X	X	X	X	X	None
	1	Miosis		X	X	X	X	X	None
	1	Exophthalmos		X	X	X	X	X	None
	1-3	Reduced muscle tone		X	X	X	X	X	None
	1-3	Scab on neck	X		X	X	X		Study specific
	1	Soft feces	X						Cage specific
	1-3	Pale feces	X						Cage specific
	1-3	Alopecia	X			X			Study specific

NB Findings described as 'Study-specific' include abnormal findings which were detected during daily observation of the standard parameters and subsequently tracked throughout the study for onset in other animals and progression/regression in the affected animals. Parameters marked with 'X' were specifically observed for presence or absence. 'Study specific' findings marked with 'X' were observed in the week noted, and no longer evident if 'X' did not appear in subsequent weeks. Cage-specific findings (if present) refer to observations which could not be ascribed to a single animal in the cage and were therefore ascribed to all individuals in the cage.

X observed

APPENDIX II:

DRINKING WATER ANALYSES

BACTERIOLOGICAL ASSAY OF DRINKING WATER, ITINGEN

Official Laboratory	Liestal, 02.07.2002
Basel-Landschaft	Ref.no. 200019518
Sampling point	59.99.N Net water RCC Ltd. Itingen, Room No. 10
Sampled on.	02.07.2002
Sample	
Time of sampling	7.50-8.20
Water temperature (°C)	14.5

BACTERIOLOGICAL TEST:

Aerobic mesophilic bacteria / ml	1
E.coli / 100 ml	0
Enterococci / 100 ml	0

ASSESSMENT.

At the time of sampling the tested bacteriological parameters met the requirements for drinking water according to article 275 of the "Eidg. Lebensmittelverordnung"

Official Laboratory
The Official Chemist

(signed Dr. N. Jaggi)

CHEMICAL WATER ANALYSIS, ITINGEN

Official Laboratory Basel-Landschaft	Liestal, 02.07.2002 Ref.no. 200019519
Sampling point	59.99.N. Net water RCC Ltd, Itingen, Room no. 10
Sampled on	02.07.2002
Time of sampling	7.50-8.20
Water temperature (°C)	14.5

CHEMICAL TEST:

Appearance			clear, colourless
Odor			not remarkable
Taste			not remarkable
UV-absorption at 254 nm/100 cm			1.61
Conductivity		µS/cm	691.0
Oxygen demand	($KMnO_4$ cons.)	mg/l	2.2
Turbidity	FNU		1.12
Chloride	Cl^-	mg/l	17.2
Nitrate	NO_3^-	mg/l	17.8
Sulphate	SO_4^{--}	mg/l	106.6
Nitrite	NO_2^-	mg/l	<0.005
Total hardness		fr.H°	38.4
Alkaline hardness		fr.H°	26.5
Non carbonate hardness		fr.H°	11.9
Calcium	Ca^{++}	mg/l	134.4
Magnesium	Mg^{++}	mg/l	11.8

ASSESSMENT:

At the time of sampling, the tested chemical parameters met the requirements for drinking water according to article 275 of the "Eidg. Lebensmittelverordnung".

Official Laboratory
The Official Chemist

(signed Dr. N. Jaggi)

CONTAMINANT ASSAY OF DRINKING WATER, ITINGEN

RCC Study No.: 904994

Date of Sampling: 02.07.2002

Sample: H_2O, RCC Ltd, Itingen, Room No 10

PARAMETER	ASSAY LEVEL µg/l	LIMIT * µg/l
Lindane	< 0.05	0.1
Heptachlor	< 0.05	0.1
Malathion	< 0.05	0.1
DDT, total	< 0.05	0.1
Dieldrin	< 0.05	0.1
Cadmium	< 0.5	5
Arsenic	< 3	50
Lead	< 3	50
Mercury	< 1	1
Selenium	< 3	10
Copper	23	1500
PCBs (28, 52, 101, 138, 153, 180)	< 0.05	0.1
Nitrosamines, total (DMN, DEN, NPIP, NMORPH)	< 0.002	-----

< 0.05 = less than 0.05 microgram per liter

* Schweizer Lebensmittelbuch

July 22, 2002

signed K Biedermann

APPENDIX III:

CHEMICAL ANALYSIS OF FEED

ANALYTICAL TEST REPORT

RCC Study 842160
17.09.02

Prepared for	PROVIMI KLIBA AG 4303 Kaiseraugst
Attention of	Dr. Isler
Materials tested	KLIBA-NAFAG 3433, Batch 67/02 vom 10.09.02
Test performed	AAS GC, GC-MS, HPLC
Test results	See attached Table 1
Submitted	E. Dettwiler
Issued by	K. Biedermann

September 27, 2002/bon

ATTACHMENT

RCC Study 842160
17.09.02

Table 1 - Test Results

KLIBA-NAFAG 3433,
Batch 67/02 vom 10.09.02

PARAMETER	ASSAY LEVEL mg/kg	LIMIT* mg/kg
Aflatoxins (B1, B2, G1, G2), total	< 0.001	0.005
Estrogens (DES, Hexestrol, Dienestrol), total	< 0.001	0.001
Lindane	< 0.005	0.02
Heptachlor	< 0.005	0.02
Malathion	< 0.5	2.5
DDT, total	< 0.025	0.100
Dieldrin	< 0.005	0.02
Cadmium	0.03	0.160
Arsenic	< 0.15	1.0
Lead	0.43	1.5
Mercury	< 0.05	0.1
Selenium	< 0.15	0.6
Copper	19	....
PCBs	< 0.025	0.05
Nitrosamines (DMN, DEN, NPIP, NMORPH), total	< 0.002	0.010

< 0.001 = less than 0.001 milligram per kilogram
* = USP EPA, Federal Register, Vol. 44, No. 91, May 9, 1979

FINAL REPORT

ANALYTICAL TEST REPORT

RCC Study 842160
07 11 02

Prepared for	PROVIMI KLIBA AG 4303 Kaiseraugst
Attention of	Dr. Isler
Materials tested	KLIBA-NAFAG 3433, Batch 75/02 vom 25.10 02
Test performed	AAS, GC, GC-MS, HPLC
Test results	See attached Table 1
Submitted	E. Dettwiler
Issued by	K. Biedermann

November 19, 2002/bon

ATTACHMENT

RCC Study 842160
07.11.02

Table 1 - Test Results

KLIBA-NAFAG 3433,
Batch 75/02 vom 25.10.02

PARAMETER	ASSAY LEVEL mg/kg	LIMIT* mg/kg
Aflatoxins (B1, B2, G1, G2), total	< 0.001	0.005
Estrogens (DES, Hexestrol, Dienestrol), total	< 0.001	0.001
Lindane	< 0.005	0.02
Heptachlor	< 0.005	0.02
Malathion	< 0.5	2.5
DDT, total	< 0.025	0.100
Dieldrin	< 0.005	0.02
Cadmium	0.04	0.160
Arsenic	< 0.15	1.0
Lead	0.39	1.5
Mercury	< 0.05	0.1
Selenium	< 0.15	0.6
Copper	17	---
PCBs	< 0.025	0.05
Nitrosamines (DMN, DEN, NPIP, NMORPH), total	< 0.002	0.010

< 0.001 = less than 0.001 milligram per kilogram
* = USP EPA Federal Register, Vol. 44, No. 91, May 9, 1979

APPENDIX IV:

CLINICAL LABORATORY DATA

RCC Study Number 845763

RP 74:

28-Day Oral Toxicity (Gavage) Study
in the Wistar Rat

Author: Peter Gretener
Dr. med. vet. FVH

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1.1 CLINICAL LABORATORY INVESTIGATIONS

Blood sampling: After 4 weeks: 22 January 2003

Blood samples for hematology and clinical chemistry were collected from all animals under light isoflurane anesthesia. The animals were fasted for approximately 18 hours before blood sampling but allowed access to water ad libitum. Blood samples were collected early in the working day to reduce biological variation caused by circadian rhythms. Blood samples were drawn from the retro-orbital plexus using micro-hematocrit glass capillary tubes.

The assays were performed at RCC Ltd (Stein) under internal laboratory quality control conditions to assure reliable test results.

In the summary and individual tables the names of some parameters have been abbreviated. Any abbreviation has been defined in this section. Clinical laboratory data are expressed, with a few exceptions, in general accordance with the International System of Units (SI).

Key to abbreviations of units:

l	liter	g	gram	m	milli (10^{-3})
mol	mole	kg	kilogram	µ	micro (10^{-6})
sec	second	T	tera (10^{12})	n	nano (10^{-9})
		G	giga (10^{9})	p	pico (10^{-12})
				f	femto (10^{-15})

General remarks:

n.d. = not determined, no value measured for this parameter
Reference values generally depend on the method used for analysis. The assignment is given by a method code.

1.1.1 HEMATOLOGY

The following anticoagulants were used during blood collection:

Complete blood cell count	Di-potassium-EDTA
Methemoglobin	Lithium heparin
Coagulation	Sodium citrate, 3.8% (1 part anticoagulant to 9 parts blood)

Complete blood cell count

Parameter	Abbreviation	Unit	Method code	Instrumentation
Erythrocyte count	RBC	T/l	M01	Advia 120[1]
Hemoglobin	Hb	mmol/l	M01	Advia 120
Hematocrit	Hct	rel.1	M01	Advia 120
Mean corpuscular volume	MCV	fl	M01	Advia 120
Red cell volume distribution width	RDW	rel.1	M01	Advia 120
Mean corpuscular hemoglobin	MCH	fmol	M01	Advia 120

[1] ADVIA 120 hematology system (Bayer)

Complete blood cell count

Parameter	Abbreviation	Unit		Method code	Instrumentation
Mean corpuscular hemoglobin concentration	MCHC	mmol/l		M01	Advia 120
Hemoglobin concentration distribution width	HDW	mmol/l		M01	Advia 120
		relative	absolute		
Reticulocyte count	Reti	rel.1	G/l	M02	Advia 120
Reticulocyte maturity index	L Reti	rel.1		M01	Advia 120
(low, medium, high fluorescence)	M Reti	rel.1		M01	Advia 120
	H Reti	rel.1		M01	Advia 120
Leukocyte count, total	WBC	G/l		M01	Advia 120
Differential leukocyte count		relative	absolute		Advia 120
Neutrophils	Neut	rel.1	G/l	M01	Advia 120
Eosinophils	Eos	rel.1	G/l	M01	Advia 120
Basophils	Baso	rel.1	G/l	M01	Advia 120
Lymphocytes	Lympho	rel.1	G/l	M01	Advia 120
Monocytes	Mono	rel.1	G/l	M01	Advia 120
Large unstained cells	Luc	rel.1	G/l	M01	Advia 120
Platelet count	Plt	G/l		M01	Advia 120

Hemoglobin derivatives

Parameter	Abbreviation	Unit	Method	Method code	Instru-mentation
Methemoglobin	MetHb	rel. 1	Spectrometry, results given as ratio of total hemoglobin	M01	OSM3[2]

[2] Hemoximeter OSM3

Coagulation

Parameter	Abbreviation	Unit	Method	Method code	Instru-mentation
Prothrombin time (=Thromboplastin time)	PT	rel. 1	Clotting assay, recombinant thromboplastin reagent Results as ratio of normal activity	M01	STA[3]
Activated partial thromboplastin time	PTT	sec	Clotting assay, synthetic phospholipid reagent, colloidal silica activator	M01	STA

1.1.2 CLINICAL CHEMISTRY

Lithium heparin was used as anticoagulant during blood collection.

Parameter	Abbre-viation	Unit	Method	Method code	Instru-mentation
Glucose	Gluc	mmol/l	Hexokinase/G6P-DH	M01	Hitachi 917[4]
Urea	Urea	mmol/l	Urease/GLDH	M01	Hitachi 917
Creatinine	Creat	µmol/l	Enzymatic colorimetric test	M01	Hitachi 917
Bilirubin, total	Bili-tot	µmol/l	Reaction with 2,5-Dichloro-phenyl-diazonium salt	M01	Hitachi 917
Cholesterol, total	Chol	mmol/l	Enzymatic, CHOD/PAP	M01	Hitachi 917
Triglycerides	Trigly	mmol/l	Glycerol-Kinase GPO/PAP method	M01	Hitachi 917
Phospholipids	Phos-Lip	mmol/l	Phospholipase-Cholinoxidase-Peroxidase-reaction	M01	Hitachi 917
Aspartate aminotransferase EC 2.6.1.1	ASAT	U/l 37°C	MDH/NADH coupled reaction	M01	Hitachi 917
Alanine aminotransferase EC 2.6.1.2	ALAT	U/l 37°C	LDH/NADH coupled reaction	M01	Hitachi 917
Lactate dehydrogenase EC 1.1.1.27	LDH	U/l 37°C	NADH/LDH coupled reaction using pyruvate as substrate	M01	Hitachi 917

[3] STA-compact analyzer (Roche Diagnostics)

[4] Hitachi 917 analyzer, Roche Diagnostics

Parameter	Abbre-viation	Unit	Method	Method code	Instru-mentation
Glutamate dehydrogenase EC 1.4.1.3	GLDH	U/l 37°C	Standard method, optimized (DGKC)	M01	Hitachi 917
Alkaline phosphatase EC 3.1.3.1	AlP	U/l 37°C	p-Nitrophenyl-phosphate as substrate	M01	Hitachi 917
Gamma-glutamyl transferase EC 2.3.2.2	GGT	U/l 37°C	Substrate: L-gamma-glutamyl-3-carboxy-4-nitroanilide	M01	Hitachi 917
Creatine kinase EC 2.7.3.2	CK	U/l 37°C	HK/ATP and G6P-DH/NADPH coupled reaction method	M01	Hitachi 917
Sodium	Na+	mmol/l	Ion selective electrode	M01	Hitachi 917
Potassium	K+	mmol/l	Ion selective electrode	M01	Hitachi 917
Chloride	Cl^-	mmol/l	Ion selective electrode	M01	Hitachi 917
Calcium	Ca++	mmol/l	o-Cresolphthalein complexone method	M01	Hitachi 917
Phosphorus inorganic	PO4-in	mmol/l	Phosphomolybdate reaction	M01	Hitachi 917
Protein, total	Prot	g/l	Biuret reaction	M01	Hitachi 917
Albumin	Alb	g/l	Bromocresol green method	M02	Hitachi 917
Globulin	Glob	g/l	Calculated value (Total protein minus Albumin)	M02	
Albumin/Globulin Ratio	A/G	rel.1	Calculated value (Albumin/Globulin)	M02	

1.2 HEMATOLOGY (MEANS)

MALES

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 500 mg/kg
RBC	10^12				
WEEK 5	MEAN	8.573ad	8.508	8.690	7.779*
	S.D.	0.526	0.508	1.211	0.303
	N	4	5	5	5
Hb	mmol/l				
WEEK 5	MEAN	9.65 a	9.85	10.10	9.46
	S.D.	0.53	0.44	0.21	0.26
	N	4	5	5	5
Hct	rel. 1				
WEEK 5	MEAN	0.4475 a	0.4500	0.4620	0.4440
	S.D.	0.0016	0.0159	0.0084	0.0114
	N	4	5	5	5
MCV	fL				
WEEK 5	MEAN	52.97ad	52.90	51.96	57.02*
	S.D.	2.85	2.39	0.69	3.64
	N	4	5	5	5
RDW	rel. 1				
WEEK 5	MEAN	0.1152 a	0.1120	0.1181	0.1246
	S.D.	0.0048	0.0022	0.0059	0.0105
	N	4	5	5	5
MCH	fmol				
WEEK 5	MEAN	1.148 a	1.162	1.132	1.220
	S.D.	0.066	0.060	0.019	0.081
	N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett * = p<0.05

MALES

Hematology (means)

	Group Group Name Dose Level		Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 800 mg/kg
MCH	rel. 1					
WEEK 5		MEAN	22.065ad	21.950	21.768	21.324**
		S.D.	0.103	0.307	0.233	0.176
		N	4	5	5	5
MCV	rel. 1					
WEEK 5		MEAN	1.602 a	1.452	1.558	1.459
		S.D.	0.067	0.077	0.113	0.199
		N	4	5	5	5
Retic	rel. 1					
WEEK 5		MEAN	0.0258ad	0.0246	0.0302	0.0648**
		S.D.	0.0217	0.0048	0.0033	0.0084
		N	4	5	5	5
Retic	G 1					
WEEK 5		MEAN	221.3ad	207.4	266.2	502.0*
		S.D.	10.6	35.4	25.1	62.2
		N	4	5	5	5
L Retic	rel. 1					
WEEK 5		MEAN	0.4397ad	0.4089	0.3770	0.3326**
		S.D.	0.0520	0.0457	0.0509	0.0200
		N	4	5	5	5
M Retic	rel. 1					
WEEK 5		MEAN	0.3508ad	0.3460	0.3395	0.2902**
		S.D.	0.0227	0.0061	0.0317	0.0174
		N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA - Dunnett kd=Kruskal-Wallis - Dunn * = p<0.05 ** = p<0.01

Hematology (means)

MALES

	Group Group Name Dose level		Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 800 mg/kg
H Neut	rel. 1					
WEEK 5		MEAN	0.3110ad	0.2452	0.2834	0.4176**
		S.D.	0.0726	0.0405	0.0751	0.0279
		N	4	5	5	5
WBC	3:1					
WEEK 5		MEAN	9.047 a	9.440	9.642	10.762
		S.D.	1.695	1.526	0.734	1.918
		N	4	5	5	5
Neut	rel. 1					
WEEK 5		MEAN	0.1242ad	0.1360	0.1648*	0.1724*
		S.D	0.0323	0.0087	0.0274	0.0211
		N	4	5	5	5
Eos	rel. 1					
WEEK 5		MEAN	0.0083 a	0.0104	0.0118	0.0070
		S.D	0.0015	0.0065	0.0051	0.0021
		N	4	5	5	5
Baso	rel. 1					
WEEK 5		MEAN	0.0035 a	0.0039	0.0036	0.0042
		S.D.	0.0006	0.0011	0.0005	0.0011
		N	4	5	5	5
Lymph	rel. 1					
WEEK 5		MEAN	0.8378ad	0.8234	0.7962*	0.7864**
		S.D	0.0242	0.0126	0.0251	0.0176
		N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett * = p<0.05 ** = p<0.01

MALES

Hematology means

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 800 mg/kg
Mono	rel. 1				
WEEK 5	MEAN	0.0168ad	0.0174	0.0178	0.0230*
	S.D.	0.0010	0.0036	0.0033	0.0040
	N	4	5	5	5
Lac	rel. 1				
WEEK 5	MEAN	0.0070 a	0.0094	0.0088	0.0078
	S.D.	0.0029	0.0048	0.0027	0.0024
	N	4	5	5	5
Nat	G/1				
WEEK 5	MEAN	1.133ad	1.278	1.596	1.852**
	S.D.	0.274	0.232	0.375	0.317
	N	4	5	5	5
Eos	G/1				
WEEK 5	MEAN	0.078 k	0.102	0.112	0.076
	S.D.	0.005	0.076	0.043	0.027
	N	4	5	5	5
Baso	G/1				
WEEK 5	MEAN	0.030 a	0.036	0.034	0.042
	S.D.	0.012	0.015	0.005	0.013
	N	4	5	5	5
Lymphc	G/1				
WEEK 5	MEAN	7.552 a	7.770	7.666	8.454
	S.D.	1.502	1.504	0.492	1.083
	N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis * = p<0.05 ** = p<0.01

MALES

Hematology (means)

	Group Group Name Dose Level		Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 500 mg/kg
Mono	G/l					
WEEK 5		MEAN	0.153ad	0.162	0.170	0.250*
		S.D.	0.033	0.037	0.042	0.055
		N	4	5	5	5
Lux	G/l					
WEEK 5		MEAN	0.065 a	0.086	0.062	0.078
		S.D.	0.024	0.053	0.023	0.022
		N	4	5	5	5
Plt	G/l					
WEEK 5		MEAN	997.0ad	960.6	1052.4	1359.6**
		S.D.	41.0	101.9	122.4	54.6
		N	4	5	5	5
MetHb	rel 1					
WEEK 5		MEAN	0.0080 a	0.0082	0.0084	0.0094
		S.D.	0.0000	0.0011	0.0005	0.0009
		N	4	5	5	5
PT	rel 1					
WEEK 5		MEAN	0.877 a	0.926	0.954	0.874
		S.D.	0.033	0.092	0.034	0.034
		N	4	5	5	5
PTT	sec					
WEEK 5		MEAN	16.65 a	17.28	16.96	16.54
		S.D.	0.98	1.69	3.34	1.92
		N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett * = p<0.05 ** = p<0.01

FEMALES — Hematology (mean)

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 800 mg/kg
RBC	T/L				
WEEK 5	MEAN	7.984ad	8.001	7.902	6.789**
	S.D.	0.342	0.337	0.253	0.377
	N	5	5	5	5
Hb	mmol/L				
WEEK 5	MEAN	9.46ad	9.28	8.92*	8.49**
	S.D.	0.21	0.22	0.26	0.36
	N	5	5	5	5
Hct	rel. 1				
WEEK 5	MEAN	0.4280ad	0.4240	0.4200	0.3940**
	S.D.	0.0164	0.0114	0.0100	0.0180
	N	5	5	5	5
MCV	fl				
WEEK 5	MEAN	53.46ad	53.02	52.76	58.36**
	S.D.	1.13	1.63	1.51	2.12
	N	5	5	5	5
RDW	rel. 1				
WEEK 5	MEAN	0.1042ad	0.1040	0.1120	0.1190*
	S.D.	0.0030	0.0016	0.0085	0.0039
	N	5	5	5	5
MSH	fmol				
WEEK 5	MEAN	1.188ad	1.162	1.122	1.246
	S.D.	0.035	0.031	0.042	0.051
	N	5	5	5	5

Statistical key: ad=ANOVA - Dunnett kd=Kruskal-Wallis - Dunn * = p<0.05 ** = p<0.01

FEMALES

Hematology means

	Group Group Name Dose Level		Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose [illegible] mg/kg
MCHC	mmol/l					
WEEK 5		MEAN	22.216ad	21.912	21.846	21.350**
		S.D.	0.344	0.196	0.301	0.342
		N	5	5	5	5
MCV	mmol/l					
WEEK 5		MEAN	1.366 a	1.350	1.366	1.360
		S.D.	0.048	0.035	0.049	0.101
		N	5	5	5	5
Retic	rel. 1					
WEEK 5		MEAN	0.0284ad	0.0308	0.0356	0.0722**
		S.D.	0.0046	0.0044	0.0086	0.0091
		N	5	5	5	5
Retic	G 1					
WEEK 5		MEAN	227.8ad	245.8	260.4	481.4**
		S.D.	44.4	32.4	64.7	57.0
		N	5	5	5	5
L Retic	rel 1					
WEEK 5		MEAN	0.4246ad	0.4004	0.3936	0.2874**
		S.D.	0.0469	0.0566	0.0843	0.0416
		N	5	5	5	5
M Retic	rel. 1					
WEEK 5		MEAN	0.3264ad	0.3314	0.3082	0.2714**
		S.D.	0.0176	0.0197	0.0130	0.0315
		N	5	5	5	5

Statistical Key: a=ANOVA ad=ANOVA + Dunnett ** = p<0.01

FEMALES

Hematology (means)

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose [illegible] mg/kg
H Rett	rel. 1				
WEEK 5	MEAN	0.2490ad	0.2686	0.2982	0.4413**
	S.D.	0.0536	0.0626	0.0843	0.0676
	N	5	5	5	5
WBC	G/l				
WEEK 5	MEAN	6.798ad	7.022	5.396	8.122
	S.D.	0.613	1.537	0.511	0.873
	N	5	5	5	5
Neut	rel. 1				
WEEK 5	MEAN	0.1280 a	0.1350	0.1366	0.1822
	S.D.	0.0314	0.0687	0.0453	0.0723
	N	5	5	5	5
Eos	rel. 1				
WEEK 5	MEAN	0.0104 a	0.0114	0.0118	0.0104
	S.D.	0.0025	0.0055	0.0048	0.0051
	N	5	5	5	5
Baso	rel. 1				
WEEK [illegible]	MEAN	0.0028ad	0.0024	0.0020	0.0035
	S.D.	0.0008	0.0025	0.0027	0.0008
	N	5	5	5	5
Lympho	rel. 1				
WEEK 5	MEAN	0.8394 a	0.8292	0.8276	0.7724
	S.D.	0.0337	0.0727	0.0499	0.0786
	N	5	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett ** = p<0.01

FEMALES

Hematology (means)

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 800 mg/kg
Mono	rel. 1				
WEEK 5	MEAN	0.0134ad	0.0146	0.0162	0.0230*
	S.D.	0.0056	0.0032	0.0049	0.0060
	N	5	5	5	5
Lux	rel. 1				
WEEK 5	MEAN	0.0062 a	0.0074	0.0056	0.0090
	S.D.	0.0011	0.0023	0.0021	0.0023
	N	5	5	5	5
Neut	G/l				
WEEK 5	MEAN	0.854ad	0.680	0.752	1.465
	S.D.	0.160	0.360	0.306	0.557
	N	5	5	5	5
Eos	G/l				
WEEK 5	MEAN	0.070 a	0.078	0.062	0.082
	S.D.	0.016	0.037	0.028	0.039
	N	5	5	5	5
Baso	G/l				
WEEK 5	MEAN	0.018ad	0.016	0.012	0.032
	S.D.	0.008	0.009	0.004	0.007
	N	5	5	5	5
Lympho	G/l				
WEEK 5	MEAN	5.718kd	5.834	4.454	6.294
	S.D.	0.743	1.736	0.289	1.077
	N	5	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett kd=Kruskal-Wallis + Dunn * = p<0.05

FEMALES

Hematology means:

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose [illegible] mg/kg
Mono	G/1				
WEEK 5	MEAN	0.090ad	0.100	0.09[illegible]	0.134**
	S.D.	0.035	0.023	0.02[illegible]	0.054
	N	5	5	5	5
Lur	G/1				
WEEK [illegible]	MEAN	0.042ad	0.054	0.03[illegible]	0.074*
	S.D	0.011	0.025	0.005	[illegible]
	N	5	5	5	5
Plt	G/1				
WEEK 5	MEAN	1079.4 a	1113.6	1084.4	1050.2
	S.D	75.7	71.5	69.5	210.1
	N	5	5	5	5
MetHb	rel. 1				
WEEK 5	MEAN	0.0076 a	0.0074	0.0074	0.0084
	S.D.	0.0005	0.0005	0.0005	0.0009
	N	5	5	5	5
FT	rel. 1				
WEEK 5	MEAN	0.982 a	0.986	0.974	1.014
	S.D.	0.061	0.047	0.079	0.094
	N	5	5	5	5
PTT	sec				
WEEK 5	MEAN	16.86 a	16.78	18.08	17.38
	S.D.	1.08	1.60	0.83	1.45
	N	5	5	5	5

Statistical key: a=ANOVA ad=ANOVA - Dunnett * = p<0.05 ** = p<0.01

1.3 BLOOD CHEMISTRY (MEANS)

MALES

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 800 mg/kg
Glur	mmol/l				
WEEK 5	MEAN	4.963ad	5.552	4.790	3.176**
	S.D.	0.675	0.426	0.418	0.618
	N	4	5	5	5
Crea	mmol/l				
WEEK 5	MEAN	6.080 a	6.248	6.750	6.744
	S.D.	1.035	1.653	0.778	0.849
	N	4	5	5	5
Creat	mmol/l				
WEEK 5	MEAN	23.33ad	25.82	24.62	28.84**
	S.D.	1.19	2.15	1.95	0.97
	N	4	5	5	5
Bili-tot	mmol/l				
WEEK 5	MEAN	1.452ad	1.750	1.920	2.778**
	S.D.	0.381	0.258	0.357	0.459
	N	4	5	5	5
Chol	mmol/l				
WEEK 5	MEAN	1.742 a	2.010	1.872	1.670
	S.D.	0.150	0.268	0.167	0.227
	N	4	5	5	5
Trigly	mmol/l				
WEEK 5	MEAN	0.978 a	1.528	1.516	1.418
	S.D.	0.212	0.553	0.505	0.661
	N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett ** = p<0.01

MALES

Blood chemistry (means)

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 800 mg/kg
Phos-Lip	mmol/l				
WEEK 5	MEAN	1.692 k	2.008	1.978	1.946
	S.D.	0.083	0.266	0.028	0.164
	N	4	5	5	5
ASAT	U/l				
WEEK 5	MEAN	70.28ad	67.22	66.12	60.72
	S.D.	4.10	6.51	8.37	9.20
	N	4	5	5	5
ALAT	U/l				
WEEK 5	MEAN	64.15ad	48.04	60.74	83.42
	S.D	9.99	9.47	15.29	19.14
	N	4	5	5	5
LDH	U/l				
WEEK 5	MEAN	155.77 k	140.32	210.55	188.96
	S.D.	32.06	4.65	100.65	39.17
	N	4	5	5	5
GLDH	U/l				
WEEK 5	MEAN	4.55kd	5.35	5.68	8.04*
	S.D.	0.79	1.42	0.24	1.92
	N	4	5	5	5
ALP	U/l				
WEEK 5	MEAN	151.55 a	133.40	141.70	148.82
	S.D.	31.43	23.91	31.47	12.74
	N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis kd=Kruskal-Wallis - Dunn * = p<0.05

MALES

Blood chemistry (mean)

	Group Group Name Dose Level		Group 1 Control 0 mg/kg	Group 2 Low Dose [illegible] mg/kg	Group 3 Mid Dose [illegible] mg/kg	Group 4 High Dose [illegible] mg/kg
GGT	U/l					
WEEK 5		MEAN	0.00 a	0.00	0.00	0.00
		S.D.	0.00	0.00	0.00	0.00
		N	4	5	5	5
CK	U/l					
WEEK 5		MEAN	181.52 a	184.58	239.62	234.38
		S.D.	22.48	21.90	62.42	21.66
		N	4	5	5	5
Na+	mmol/l					
WEEK 5		MEAN	141.90ad	142.99	142.30	144.26**
		S.D.	0.36	0.80	0.67	0.80
		N	4	5	5	5
K+	mmol/l					
WEEK 5		MEAN	3.620ad	3.729	3.654	3.368
		S.D.	0.223	0.261	0.221	0.230
		N	4	5	5	5
Cl-	mmol/l					
WEEK 5		MEAN	99.65 a	99.52	99.26	97.36
		S.D.	1.15	1.22	1.30	2.19
		N	4	5	5	5
Ca++	mmol/l					
WEEK 5		MEAN	2.825ad	2.834	2.880	3.032**
		S.D.	0.090	0.039	0.046	0.024
		N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett ** = p<0.01

MALES

Blood chemistry (means)

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 200 mg/kg	Group 4 High Dose 500 mg/kg
BUN-in	mmol/l				
WEEK 5	MEAN	2.063ad	2.000	2.042	2.624**
	S.D.	0.216	0.121	0.206	0.241
	N	4	5	5	5
Prot	g/l				
WEEK 5	MEAN	67.747ad	68.622	68.424	73.072*
	S.D.	2.274	1.818	1.305	3.492
	N	4	5	5	5
Alb	g/l				
WEEK 5	MEAN	43.080ad	44.454	44.854	48.028**
	S.D.	2.131	1.593	0.998	2.443
	N	4	5	5	5
Glob	g/l				
WEEK 5	MEAN	24.667 a	24.168	23.550	25.046
	S.D.	1.213	0.683	1.232	1.481
	N	4	5	5	5
A/G	ml/l				
WEEK 5	MEAN	1.750 a	1.839	1.910	1.922
	S.D.	0.133	0.076	0.115	0.097
	N	4	5	5	5

Statistical key: a=ANOVA ad=ANOVA + Dunnett * = p<0.05 ** = p<0.01

FEMALES — Blood Chemistry Means

	Group Group Name Dose Level		Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose 250 mg/kg	Group 4 High Dose 500 mg/kg
Glu	mmol/l					
WEEK 5		MEAN	4.222 a	4.562	4.558	3.996
		S.D.	0.581	0.359	0.357	0.472
		N	5	5	5	5
Urea	mmol/l					
WEEK 5		MEAN	5.406ad	5.554	5.837	6.936
		S.D.	0.483	0.533	0.677	0.783
		N	5	5	5	5
Creat	umol/l					
WEEK 5		MEAN	27.36 a	26.64	27.00	26.20
		S.D.	2.63	2.93	2.43	2.53
		N	5	5	5	5
Bili-tot	umol/l					
WEEK 5		MEAN	1.458ad	1.112	1.556	1.216
		S.D.	0.327	0.253	0.411	0.635
		N	5	5	5	5
Chol	mmol/l					
WEEK 5		MEAN	1.382 a	1.436	1.654	1.644
		S.D.	0.196	0.478	0.365	0.183
		N	5	5	5	5
Trigly	mmol/l					
WEEK 5		MEAN	0.532 a	0.406	0.379	0.482
		S.D.	0.198	0.123	0.072	0.107
		N	5	5	5	5

Statistical key: a=ANOVA ad=ANOVA - Dunnett

FEMALES

Blood chemistry means

	Group Group Name Dose Level	Group 1 Control 0 mg/kg	Group 2 Low Dose 50 mg/kg	Group 3 Mid Dose [illegible] mg/kg	Group 4 High Dose [illegible] mg/kg
Phos-Lip	mmol/l				
WEEK 5	MEAN	1.560 a	1.564	1.524	1.656
	S.D.	0.163	0.428	0.215	0.145
	N	5	5	5	5
AST	U/l				
WEEK 5	MEAN	48.56 a	58.44	64.31	65.66
	S.D.	8.90	6.97	8.79	9.35
	N	5	5	5	5
ALT	U/l				
WEEK 5	MEAN	38.24 a	34.28	34.60	43.30
	S.D.	10.69	3.26	5.60	9.23
	N	5	5	5	5
LDH	U/l				
WEEK 5	MEAN	140.32ab	123.58	134.30	245.40
	S.D.	22.38	21.33	37.61	106.17
	N	5	5	5	5
GLDH	U/l				
WEEK 5	MEAN	5.34ab	3.62	4.67	3.79*
	S.D.	1.25	0.29	1.00	0.29
	N	5	5	5	5
ALP	U/l				
WEEK 5	MEAN	63.54ab	57.92	54.26	48.76**
	S.D.	3.71	8.78	6.67	3.07
	N	5	5	5	5

Statistical key: a=ANOVA ab=ANOVA + Dunnett KW=Kruskal-Wallis + Dunn * = p<0.05 ** = p<0.01