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Report

Laboratory Code:	LU 55686
INN:	Ademetionine
Report No.:	MPF/WT 9344E
Date of Report:	1 September 1995
Title:	52-week oral toxicity (capsule) study with SAMe SD_4 in the dog
Reported by:	S J Corney, T R Allen, H Luetkemeier, J Wilson
Study Facility:	RCC Research and Consulting Company Ltd. CH-4452 Itingen/Switzerland
Language:	English
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Pages total:	
Report:	584
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Dossier Part:	III A b
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Knoll AG
Research and Development
P.O. Box 21 08 05
D-67008 Ludwigshafen
Germany

knoll

NAME OF COMPANY: Knoll AG, Ludwigshafen/Germany NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT: SAMe SD_4 (LU 55686)	TABULATED STUDY REPORT ref. to III.B.210 _____ / _____ Page Number	

REPEATED DOSE TOXICITY: Chronic toxicity (beyond 3 months)

Ref. to document: Volume: **Page:** **to** **Addendum No.:**
Report date: 1 September 1995 **Number:** MPF/WT 9344E **Study period (years):** 1993 - 1994

Species/Strain: Beagle dog

Number of animals: 56 | **Duration of treatment:** 52 weeks

Observation period after the end of dosing: -

Administration route: Oral, by capsule (the tablets were enclosed directly in "TORPAC" gelatine capsules to facilitate application)

Treatment of controls: 18 tablets/animal/day; the tablets contain only the excipients with microcellulose as main compound (= placebo)

Age: 7 to 9 ½ months **at study initiation**
Body weight: m: 7.9 - 11.8 kg, f: 6.1 - 10.9 kg

Treatment days per week: 7 days

Study group	(1) Contr.		(2)		(3)		(4)	
Dosage <mg/kg bwt/d>	0		200* (388)		400* (776)		800* (1552)	
Sex (m/f)	m	f	m	f	m	f	m	f
Number of test animals#	8	8	6	6	6	6	8	8
Number of animals died or sacrificed in extremis	0	0	0	0	0	0	0	0

Clinical observations:	yes <X>	no < >	**Clin. chemistry:**	yes <X> no < >
Food consumption:	yes <X>	no < >	**Urinalysis:**	yes <X> no < >
Water consumption:	yes < >	no <X>	**Organ weights:**	yes <X> no < >
Body weight:	yes <X>	no < >	**Necropsy:**	yes <X> no < >
Haematology:	yes <X>	no < >	**Histology:**	yes <X> no < >

Additional examinations: Ophthalmoscopic examinations, electrocardiograms, blood pressure

Additional information: * Doses relate to the active ingredient S-adenosyl-L-methionine (= SAMe ion). The required quantity of SAMe SD_4 was attained by applying a correction factor of 1.94 to the nominal dose levels (= total dose); values indicated in brackets. # After 26 weeks of treatment 2 males and 2 females of each group were sacrificed and full histopathological evaluation was performed (interim report after 26 weeks available).

Histology performed according to EEC Notes for Guidance: yes <X> no < >
Study conduct by the applicant: yes < > no <X>
If "no", indicate the name and address of the institute that conducted the study:
RCC Research and Consulting Company Ltd., CH-4452 Itingen/Basle
Study in compliance with GLP: yes <X> no < > not required < >

NAME OF COMPANY: Knoll AG, Ludwigshafen/Germany NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT: SAMe SD_4 (LU 55686)	TABULATED STUDY REPORT ref. to III.B.211 SUPPLEMENTARY SHEET _____ / _____ Page Number	

REPEATED DOSE TOXICITY: Chronic toxicity (beyond to 3 months)

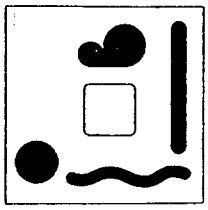
Ref. to document: Volume: **Page:** to **Addendum No.:**
Report date: 1 September 1995 **Number:** MPF/WT 9344E **Study period (years):** 1993 - 1994

Important findings:	Group 2		Group 3		Group 4	
	M	F	M	F	M	F
Clinical signs						
• Loose/watery faeces (mean number of days affected)	I (166)		I (226)		I,r (288) affected almost daily	I,r (249)
	(The mean number of days in controls was 90 in males and 97 in females)					
• Body weight gain	D*		D*		D*,r	
Haematology (weeks 13, 25, 51)						
• Erythrocyte count					[D*]	
• Haemoglobin concentration					[D*]	
• Haematocrit					[D*]	
Clinical biochemistry						
• Cholesterol			D		D, r	
• Phospholipid					D, r	
• Glutamate dehydrogenase				I	I, r	I, r
• Alanine aminotransferase				I		I, r
• γ-glutamyltransferase				I		I, r

Treatment was withdrawn from one female at 800 mg SAMe/kg/day between days 303 and 330 due to persistent, complete inappetence and severe weight loss. Blood investigations before withdrawal of treatment revealed decreased glucose, cholesterol, chlorine and phospholipid concentrations, moderately to markedly increased alanine aminotransferase and glutamate dehydrogenase activities and magnesium, protein and albumin concentrations with an increased albumin/globulin ratio. After the withdrawal of treatment, a further deterioration in the condition of the dog was first evident, despite the provision of tinned meat. Thereafter, the dog gradually improved, although slight anemia was evident at a blood investigation on day 323 (week 47). Treatment was resumed on day 331 and the dog completed the treatment period. Nevertheless, the ratio of tinned meat was continued until the end of the study.

Explanations:

D = decrease I = increase p = permanent t = transitory ns = not significant * = $p < 0.05$
**** = $p < 0.01$ + = mild ++ = moderate +++ = severe n = no. of animals**
[ ] within the laboratory historical control r = reversible within the 8-week recovery period



RCC PROJECT 344856

KNOLL PROJECT MPF/WT 9344 E

52-WEEK ORAL TOXICITY (CAPSULE) STUDY WITH

SAMe SD_4

IN THE DOG

REPORT: VOLUME 1 OF 2

Authors: S.J. Corney, T.R. Allen, H. Luetkemeier, Dr. J. Wilson

Sponsor: KNOLL AG
Postfach 21 08 05
D-67008 Ludwigshafen/Rhein

Study Completion: 01 September 1995

RCC

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TABLES - INDIVIDUAL DATA

ATTACHMENTS

PREFACE

GENERAL

Title	52-week Oral Toxicity (Capsule) Study with SAMe SD_4 in the Dog
Sponsor	KNOLL AG Postfach 21 08 05 D-67008 Ludwigshafen/Rhein
Study Monitors	Dr. V. Bühler Mr. R. Neidhardt
Testing Facilities	RCC RESEARCH AND CONSULTING COMPANY LTD. CH-4452 Itingen / Switzerland BRL BIOLOGICAL RESEARCH LABORATORIES LTD. Wölferstrasse 4, CH-4414 Füllinsdorf / Switzerland
RCC Project Number	344856
KNOLL Project Number	MPF/WT 9344 E
Test Article	SAMe SD_4
Test System	Beagle dog

PROJECT STAFF

Study Director	S.J. Corney
Nominated Deputy for Study Director	T.R. Allen
Study Veterinarian	Dr. J. Zimmerli
Technical Coordinator	L. Braun
Clinical Laboratory Investigations	H. Luetkemeier
Necropsy / Histotechnique	Dr. J. Wilson / Dr. K. Weber
Histopathology, Reporting	Dr. J. Wilson

SCHEDULE

Acclimatization	22 June 1993 - 21 July 1993	
Pretest	14 July 1993 - 21 July 1993	
Administration	22 July 1993 - 20/21 July 1994	
Recovery	21 July 1994 - 14 September 1994	
Termination (Necropsy)	After 26 weeks administration:	20 January 1994
	After 52 weeks administration:	21/22 July 1994
	After 8 weeks recovery:	15 September 1994
Interim Report after 26 weeks	01 June 1995*	

ARCHIVING

RCC, CH-4452 Itingen / Switzerland

All raw data, protocol, interim and final reports, specimens and raw data of laboratory investigations and pathology and test article reference sample will be archived at the above facility for at least ten years. At the end of this period, the archived material will not be destroyed without the prior consent of the Sponsor.

* The results and conclusion in the interim report were based on the available information at the time and, therefore, may not reflect the present results and conclusion of the final report.

PROJECT STAFF SIGNATURES

Study Director: S.J. Corney

S. Corney
date: 01- September - 1995

Nominated Deputy for Study Director: T.R. Allen

T.R. Allen
date: 2 August 1995

Technical Coordinator: L. Braun

L. Braun
date: 22. August 1995

Clinical Laboratory Investigations: H. Luetkemeier

H. Luetkemeier
date: 03-AUG-1995

Necropsy / Histotechnique: Dr. J. Wilson

J. Wilson
date: 23 Aug. 95

Dr. K. Weber

K. Weber
date: 23 Aug. 95

The signature of Dr. J. Wilson (Histopathology) is included in the relevant attachment.

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE

RCC PROJECT NUMBER : 344856

TEST ARTICLE : SAMe SD_4

TITLE : 52-week Oral Toxicity (Capsule) Study with SAMe SD_4 in the Dog

STUDY DIRECTOR : S.J. Corney

This study was conducted in compliance with the following Good Laboratory Practice Regulations:

Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986.

The OECD Principles of Good Laboratory Practice, Environment Monograph Nr. 45. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring - Nr. 1. Environment Directorate, Organisation of Economic Co-operation and Development, Paris 1992.

US Food and Drug Administration: Non-clinical Laboratory Studies - Good Laboratory Practice Regulations. US Federal Register Vol. 43, No. 247 (Part 58), December 22, 1978. Last revision July 03, 1991.

Grundsätze der Guten Laborpraxis (GLP), Chemikaliengesetz (Anhang 1) Bundesgesetzblatt Nr. 47, 29. Juli, 1994.

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

Study Director: S.J. Corney

S. Corney

date: 01-September 1995

QUALITY ASSURANCE STATEMENT

R C C RESEARCH AND CONSULTING COMPANY LTD.
CH-4452 ITINGEN / SWITZERLAND

PROJECT NUMBER	:	344856
TEST ARTICLE	:	SAMe SD_4
TITLE	:	52-week Oral Toxicity (Capsule) Study with SAMe SD_4 in the Dog
STUDY DIRECTOR	:	S.J. Corney

The conduct of this study was subjected to periodic inspections and the report audited by the RCC Quality Assurance Unit. The dates are given below:

Dates of QAU Inspections/ Audits	Dates of Reports to the Study Director and to Management
20 July 1993	22 July 1993
26 July 1993	26 July 1993
29 July 1993	29 July 1993
13 August 1993	13 August 1993
15 October 1993	15 October 1993
18 October 1993	18 October 1993
06 January 1994	06 January 1994
10 January 1994	10 January 1994
11 January 1994	11 January 1994
20 January 1994	21 January 1994
10 March 1994	10 March 1994
24 March 1994	24 March 1994
25 May 1994	25 May 1994
21 July 1994	21 July 1994
26/27/28/29/30 June, 03/04/05/06/07/10/11/12/ 13/14/17/18/19/20/21/24/25 July 1995	25 July 1995

Manager, Quality Assurance Unit: Dr. G. Menne

date: September 01, 1995

GLP GUIDELINES

This study was conducted in compliance with:

Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986.

The OECD Principles of Good Laboratory Practice, Environment Monograph Nr. 45. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring - Nr. 1. Environment Directorate, Organisation of Economic Co-operation and Development, Paris 1992.

US Food and Drug Administration: Non-clinical Laboratory Studies - Good Laboratory Practice Regulations. US Federal Register Vol. 43, No. 247 (Part 58), December 22, 1978. Last revision July 03, 1991.

Grundsätze der Guten Laborpraxis (GLP), Chemikaliengesetz (Anhang 1) Bundesgesetzblatt Nr. 47, 29. Juli, 1994.

TEST GUIDELINES

This study was conducted in compliance with:

Official Journal of the European Communities, No. L 147 (75/318/EEC), June 9, 1975. Council Directive of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect to the testing of proprietary medicinal products.

Official Journal of the European Communities, No. L 332 (83/571/EEC), November 28, 1983. Council recommendation of 26 October 1983, concerning tests relating to the placing on the market of proprietary medicinal products.

Gesetz zum Schutz vor gefährlichen Stoffen (Chemikaliengesetz), Bundesgesetzblatt Nr. 13, Bonn, 22. März, 1990.

Guidelines for Testing of Chemicals, Organisation for Economic Cooperation and Development (OECD), Chronic Toxicity Studies" No. 452, 1981.

SUMMARY

GENERAL

In this toxicity study, S-ADENOSYL-L-METHIONINE-1,4-BUTANEDISULFONATE (SAMe SD_4) was administered orally, by capsule, to pure-bred beagle dogs for a period of at least 52 weeks, followed by an 8-week treatment-free recovery period for two males and two females of Groups 1 and 4. In addition, two males and two females of each group were sacrificed after 26 weeks of treatment. The study consisted of four groups; Groups 1 and 4 contained eight male and eight female dogs and Groups 2 and 3 contained six male and six female dogs. The following doses were administered once daily:

Group	SAMe (active dose)	SAMe SD_4 (total dose)
1	0 mg/kg body weight	0 mg/kg body weight
2	200 mg/kg body weight	388 mg/kg body weight
3	400 mg/kg body weight	776 mg/kg body weight
4	800 mg/kg body weight	1552 mg/kg body weight

For the purposes of reporting, the doses of SAMe are used in the text and the tables.

The results of the study are summarized as follows:

MORTALITY

There were no unscheduled deaths.

Treatment was withdrawn from one female at 800 mg/kg/day (in terms of the active dose, SAMe) between Days 303 and 330 due to persistent, complete inappetence and severe weight loss. Blood investigations before withdrawal of treatment revealed decreased glucose, cholesterol, chlorine and phospholipid concentrations, moderately to markedly increased alanine aminotransferase and glutamate dehydrogenase activities and magnesium, protein and albumin concentrations with an increased albumin/globulin ratio. After the withdrawal of treatment, a further deterioration in the condition of the dog was first evident, despite the provision of tinned meat. Thereafter, the dog gradually improved, although slight anemia was evident at a blood investigation on Day 323 (Week 47). Treatment was resumed on Day 331 and the dog completed the treatment period. Nevertheless, the ration of tinned meat was continued until the end of the study.

CLINICAL SIGNS

Treatment with SAMe SD_4 was associated with an increased mean incidence of loose/watery faeces in the males at 200, 400 or 800 mg SAMe/kg/day and the females of the high dose group. The severity of this sign showed a relationship to dose and was such that some animals of the high dose group were affected almost daily throughout the treatment phase of the study.

CLINICAL SIGNS (continued)

Loose/watery faeces predominantly occurred once daily and was observed at the first daily observation indicating that it occurred between 6 and 22 hours after dosing.

In general, only sporadic incidences of loose/watery faeces occurred in the dogs of the high dose group during the recovery period.

There were no other clinical signs that could be related to treatment with SAMe SD_4.

FOOD CONSUMPTION

Food intake was unaffected by treatment with SAMe SD_4.

BODY WEIGHTS

Treatment with SAMe SD_4 resulted in reduced group mean body weight gain in the males of all treated groups when compared with the controls. The differences from the controls were statistically significant for each group and most marked in the first 26 weeks of treatment. The reduction was most pronounced in the dogs of the high dose group. Improved weight gain was noted in the male dogs of the high dose group during the 8-week recovery period.

Body weight gain in the females was unaffected by treatment with SAMe SD_4.

OPHTHALMOSCOPIC EXAMINATIONS

Ophthalmoscopic parameters were unaffected by treatment with SAMe SD_4.

ELECTROCARDIOGRAMS

Electrocardiographic parameters were unaffected by treatment with SAMe SD_4.

BLOOD PRESSURE

There was no effect on blood pressure that could be related to treatment with SAMe SD_4.

HEMATOLOGY

Slightly decreased erythrocyte count, hemoglobin concentration and hematocrit were evident in the males at 800 mg SAMe/kg/day in Weeks 13, 25 and 51 when compared with the controls. The differences from the controls for these parameters were statistically significant. These findings were still apparent at the end of the recovery period.

Hematology parameters in the dogs at 200 or 400 mg SAMe/kg/day were unaffected by treatment.

CLINICAL BIOCHEMISTRY

The administration of SAMe SD_4 was associated with decreased cholesterol levels in the males at 400 mg SAMe/kg/day and decreased cholesterol and phospholipid levels in the males at 800 mg SAMe/kg/day.

In addition, increased mean glutamate dehydrogenase activity was recorded in the females at 400 mg SAMe/kg/day and both sexes at 800 mg SAMe/kg/day in Week 51 and in individual dogs of these groups at other investigations. The severity of these increases was unrelated to dose. Slightly to moderately increased alanine aminotransferase and/or gamma glutamyltransferase activities were also recorded on occasions in dogs of these groups. These findings were not apparent at the end of the recovery period. Clinical biochemistry parameters of the dogs at 200 mg SAMe/kg/day were unaffected by treatment.

Slight to marked changes in the above parameters were also recorded in a female of the high dose group before withdrawal of treatment (see Viability/Mortality).

URINALYSIS

Urinary pH was lower in the females at 800 mg SAMe/kg/day than the controls.

There were no other changes to the urinalysis parameters that could be related to the administration of SAMe SD_4.

ORGAN WEIGHTS

Organ weights were unaffected by treatment with SAMe SD_4.

MACROSCOPIC AND MICROSCOPIC FINDINGS

There were no treatment-related macroscopic or microscopic findings.

ASSESSMENT

Treatment with the salt SAMe SD_4, at doses equivalent to 200, 400 or 800 mg SAMe/kg/day, was associated with a dose-dependent increase in the incidence of loose/watery faeces in the males. An increased incidence of loose/watery faeces was also recorded in the females of the high dose group only. This finding was thought to be due to an osmotic effect of the test article (a salt) within the gut. A relationship between this loose/watery faeces and the low weight gain recorded in the male treated dogs cannot be excluded, although examination of the individual data revealed no clear correlation between these two factors. With the exception of one animal, body weight gain in the females was unaffected by treatment. In addition, there was no evidence of plasma electrolyte imbalance in any animal.

Clinical biochemistry changes, notably decreased cholesterol and/or phospholipid levels and increased glutamate dehydrogenase and, to a lesser extent, alanine aminotransferase and/or gamma-glutamyltransferase activities were evident in dogs at 400 or 800 mg SAMe/kg/day. Marked changes in these parameters were also evident in a female of the high dose group before withdrawal from treatment between Days 303 and 330. The increase of liver enzymes noted after approximately 52 weeks on test were associated with treatment. However, no remarkable histopathologic findings were seen in this organ at the end of the study.

At 800 mg SAMe/kg/day a slight, but significant, decrease was seen in the red blood cell values in the males only. At the same dose level, a decrease in urinary pH was measured in the females at Weeks 13, 25 and 51. The values for both of these parameters were within the normal physiologic range (laboratory historical control data) and were not considered to be of toxicologic relevance.

There were no histopathological evidence of toxicity at any of the dose levels investigated.

Under the conditions of this study, the remarkable changes of body weight depression, loose stool, elevated liver enzymes, equivocal red blood cell values and urinary pH findings were considered to represent physiologic rather than toxicologic findings in the absence of electrolyte imbalance and histopathologic changes. Therefore, the no-toxic-effect-level (NOTEL) was considered to be $\geq$ 800 mg SAMe/kg/day.

OBJECTIVE

The purpose of this study was to assess the cumulative toxicity of SAMe SD_4 when administered to beagle dogs by oral ingestion (capsule) for a period of at least 52 weeks. The reversibility of any treatment-related findings was investigated during a treatment-free recovery period of 8 weeks for some dogs. In addition, the time-course of any pathological lesions were investigated by an interim sacrifice after 26 weeks in some dogs.

This study was designed to provide a rational basis for the assessment of the toxicologic risk to man and to indicate potential target organs.

MATERIALS AND METHODS

Experimental Design

TEST SYSTEM

Animals	Pure-bred beagle dogs, dewormed and vaccinated against distemper, leptospirosis, parainfluenza, contagious hepatitis, rabies and parvovirus.
Rationale	Recognized by international guidelines as a recommended non-rodent test system.
Breeder	BRL BIOLOGICAL RESEARCH LABORATORIES LTD. Wölferstrasse 4 CH-4414 Füllinsdorf / Switzerland
Total number of Animals	29 males and 29 females, of which 28 males and 28 females were selected for the study (see allocation).
Age (at allocation to study)	7 to 9½ months.
Body weight range (at allocation to study)	Males: 7.9 - 11.8 kg Females: 6.1 - 10.9 kg
Identification	Provisional identification before treatment start: Individual kennel number 1 - 58. Permanent identification at start of treatment: Individual kennel number 1 - 56. Ear tattoo (performed by the breeder).
Acclimatization	30 days under test conditions, after veterinary examination.

ALLOCATION

Shortly after arrival the dogs were temporarily allocated to groups by a computer generated random algorithm; the spare animals were allocated to Group 5 and assigned numbers 57-58. Thereafter, pretreatment investigations were carried out on all dogs. Shortly before start of the treatment, the data obtained were reviewed and the allocation was adjusted: male dog tattoo 3627, allocated as no. 12 was replaced with dog tattoo 3643, allocated as no. 57; female dog tattoo 3524, allocated as no. 55 was replaced with dog tattoo 3518, allocated as no. 58 and male dog tattoo 3621, allocated as no. 23 was exchanged with dog tattoo 3607, allocated as no. 7 due to some biochemistry values. The rejected animals took no further part in the study after commencement of treatment. Only data from dogs assigned to the study are included in the report. The permanent group identification and animal numbers assigned to treatment are given below:

	Group 1	Group 2	Group 3	Group 4
SAMe (active dose)	0 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
SAMe SD_4 (total dose)	0 mg/kg	388 mg/kg	776 mg/kg	1552 mg/kg
Males - after 52 weeks	1- 6*	9-12	15-18	21-26*
- after 26 weeks	7- 8	13-14	19-20	27-28
Females - after 52 weeks	29-34*	37-40	43-46	49-54*
- after 26 weeks	35-36	41-42	47-48	55-56

*) At the end of the 52-week treatment period two male and two female animals from Groups 1 (Nos. 5, 6, 33, 34) and 4 (Nos. 25, 26, 51, 53) were selected for an 8-week treatment-free recovery period.

The animals in each treatment group were housed in adjacent kennels.

HUSBANDRY

Room Numbers	1U01 and 1U03, Itingen
Conditions	Standard Laboratory Conditions. Air-conditioned with target ranges for room temperature 20 ±3°C, relative humidity 40-70% (with transient extremes notably during kennel cleaning) and 20 air changes per hour. Room temperature and humidity were monitored continually. Kennel floor temperature was maintained at approximately 21°C. There was a 12 hour fluorescent light/12 hour dark cycle and at least 8 hours music during the light period.
Accommodation	Individual kennel with minimum of 2.0 square meters floor space.

HUSBANDRY (continued)

Diet

350 (accuracy ±1) g pelleted standard Kliba 335 dog maintenance diet (KLIBA Klingentalmühle AG, CH-4303 Kaiseraugst / Switzerland) presented at approximately 11^{00} daily. Any remaining diet was withdrawn between 06^{00} and 07^{30} the following morning.

The following dogs were given wetted diet (350 g pelleted standard diet with 350 g tap water) due to erratic food intake.

No. 34 - Days 59 - 61
No. 45 - Days 92 onwards
No. 51 - Days 47 - 50, 92 - 295 and 313 onwards
No. 56 - Days 57 - 61 and 64 - 75

Dog No. 54 was offered wetted pelleted diet from Days 26 - 27 and wetted granular diet from Days 28 - 32, due to difficulty in swallowing (see Medication).

In addition, dog No. 51 was offered wetted granular diet on Days 310-312 in an attempt to stimulate appetite. Dog No. 45 and No. 51 were offered between 100 and 350 g of meat during the following intervals due to poor food intake: No. 45 - Days 307 to 366 and No. 51 - Days 229 to 294 and 307 onwards. The quantity of meat offered and consumed daily is presented in the individual food consumption data.

The diet was withdrawn at approximately 15^{00} the day before clinical laboratory investigations. On the days when ECG determinations and clinical laboratory investigations were performed, the feeding time was delayed in relation to the time of dose application.

Results of the analyses for contaminants in the pelleted diet are included in this report (see Attachment 1, pp. 369-401).

Water

Tap water was supplied ad libitum by an automatic watering system. Results of bacteriological, chemical and contaminant analyses scheduled to be conducted at least once yearly by RCC (contaminants analyses only) and the Official Chemist of the Kanton Baselland (bacteriological and chemical analyses) are included in this report (see Attachment 2, pp. 402-410).

TEST ARTICLE

Identification	S-Adenosyl-L-Methionine-1,4-butanedisulfonate = SAMe SD_4 = LU 55686 (Code) = Transmetil (Trade name employed in Italy) = Ademetionine (INN) Active ingredient is S-Adenosyl-L-Methionine (= SAMe ion)
Description	White tablets (enteric coated)

Tablets used for dosing

Batch Number	SAMe ion (mg/tablet)	Expiry Date
P189/2	50	April 1995
9305003	300	April 1995
P110/35	400	March 1995
9302001	500	January 1995
9304003	500	March 1995
P177/13	Placebo*	February 1996

*) The placebo tablets contained only the excipients with microcellulose as main compound.

Storage instructions	Test article: At 2 - 8°C, in the dark, protected from humidity. Placebo : At room temperature, not above 25°C.
Safety precautions	Routine hygienic precautions were employed to assure personnel health and safety.

TREATMENT

Method	Oral, by capsule.
Rationale for method	The oral route is an anticipated route of human exposure to the test article.
Frequency	Daily, commencing at approximately 09^{00}. On the days of blood and urine sampling, plasma sampling and ECG recordings animals were not dosed until after the samples or recordings had been obtained.

Dose levels

	SAMe ion (Active Dose)	SAMe SD_4** (Total Dose)
Group 1	0* mg/kg/day	0 mg/kg/day
Group 2	200 mg/kg/day	388 mg/kg/day
Group 3	400 mg/kg/day	776 mg/kg/day
Group 4	800 mg/kg/day	1552 mg/kg/day

*) Placebo = 18 tablets/animal/day
**) Total dose attained by applying a correction factor of 1.94 to the active dose.

TREATMENT (continued)

Doses relate to the active ingredient S-Adenosyl-L-Methionine (= SAMe ion). The number of tablets per dog was calculated based on the declared weight specified below.

Batch number	Declared weight	Active ingredient
P189/2	50 mg	51.3 mg
9305003	300 mg	313 mg
P110/35	400 mg	394 mg
9302001	500 mg	509 mg
9304003	500 mg	521 mg

Rationale for dose levels: The dose levels were selected by the Sponsor.

Preparation of capsules: The tablets were enclosed directly in "TORPAC" gelatine capsules to facilitate application. The "TORPAC" capsules containing the placebo tablets were color-coded and prepared at a different time from those of the test article.

The dose levels were adjusted to individual body weights once weekly.

Duration of pretest period: 8 days.

Duration of interim treatment period: 26 weeks.

Duration of main treatment period: 52 weeks - males, 52 weeks and 1 day - females.

Duration of recovery period: 8 weeks.

Observations

VIABILITY/MORTALITY

Observations for viability were recorded from commencement of the pretest period at least twice daily, in the morning and in the afternoon.

CLINICAL SIGNS

Each animal was examined at least twice daily from commencement of the pretest period for any change in behaviour or appearance. A description of any abnormality was recorded.

SAMe SD_4

FOOD CONSUMPTION

Food consumption was recorded daily from commencement of the pretest period. The daily ration was weighed before and after feeding. The individual food consumption over each week for each animal and the weekly group mean of these values are reported.

BODY WEIGHTS

The body weight of each animal was recorded at least once weekly from commencement of the pretest period and before necropsy.

OPHTHALMOSCOPIC EXAMINATIONS

Each animal was examined for abnormalities of the eyes at least 20 minutes after the instillation of 0.5% tropicamide solution (Mydriaticum, Dispersa AG, Hettlingen / Switzerland) using a binocular indirect ophthalmoscope (all pupil model, Keeler Instruments, Inc. / USA) and the results were recorded. The observation area included the cornea, conjunctiva, sclera, iris, lens and fundus. Photographs were taken at the discretion of the ophthalmologist and are retained in the raw data.

Pretest	14 July 1993
13 weeks	18 October 1993
25 weeks	10 January 1994
51 weeks	11 July 1994
8 weeks recovery	12 September 1994

ELECTROCARDIOGRAMS

Electrocardiograms of each animal were recorded using standard ECG methods and the Multiscriptor EK 36 recorder (Hellige GmbH). Electrocardiograms were obtained using Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF) leads. The heart rate, P wave duration and amplitude and P-Q, QRS and Q-T intervals were measured using a representative section of the electrocardiogram from lead II.

During the treatment period records were made shortly before administration (i.e. 24 hours following the preceding dose) and 3 hours after administration on the dates listed below.

Pretest	15 July 1993
13 weeks	19/20 October 1993
25 weeks	06/07 January 1994
51 weeks	07/08 July 1994
8 weeks recovery	12 September 1994

BLOOD PRESSURE

The systolic arterial blood pressure was recorded indirectly (tail-cuff method) for each animal using equipment produced by Rhema-Labortechnik GmbH, Germany, (Model No. 208002). During the treatment period records were made shortly before administration (i.e. 24 hours following the preceding dose) and 3 hours after administration on the dates listed below.

Pretest	15 July 1993
13 weeks	19/20 October 1993
25 weeks	06/07 January 1994
51 weeks	07/08 July 1994
8 weeks recovery	12 September 1994

Clinical Laboratory Investigations

GENERAL

Blood and urine samples were collected from all animals. The animals were fasted overnight but allowed access to water ad libitum. Blood samples were collected between the hours of 06^{05} and 08^{30} to reduce biological variation caused by circadian rhythms. Blood samples were drawn from the jugular vein into evacuated blood collection tubes. Urine was collected into a specimen vial using a catheter.

Blood and urine sampling:

Pretest	14 July 1993
4 weeks	13 August 1993
13 weeks	15 October 1993
25 weeks	10 January 1994
51 weeks	11 July 1994
8 weeks recovery	12 September 1994

Additional blood sampling for hematology and clinical biochemistry to monitor the general health status of animal No. 51 was performed on the following dates:

42 weeks	10 May 1994
43 weeks	17 May 1994
44 weeks	25 May 1994
45 weeks	31 May 1994
47 weeks	09 June 1994
48 weeks	20 June 1994

The assays of blood and urine parameters were performed, at BRL Biological Research Laboratories Ltd., under internal laboratory quality control conditions to assure reliable test results.

Manufacture of the reagents supplied by Bio Merieux s.a. Geneva/Switzerland, for the analysis of ornithine carbamyltransferase (OCT) was discontinued. Therefore only the scheduled investigation at pretest could be undertaken. The results of this analysis at pretest are not reported and are retained in the raw data.

GENERAL (continued)

The summary and individual tables were generated by a computer. The program limits the width of each column to 10 characters. Therefore, the names of some parameters have been abbreviated. Any abbreviation has been defined in this section under "Parameter" in upper-case letters enclosed by parentheses.

Clinical laboratory data are expressed in general accordance with the International System of Units (SI), which in structure comprises base units, derived units and supplementary units. It also includes a series of prefixes by means of which decimal multiples and submultiples of these units can be formed. In some cases non-SI units or conventional units may be used.

Remark code identification:
INH = in oestrus

General remarks:
Historical reference values for untreated beagle dogs, see pp. 411-429.

Key to abbreviations of Units of Measure:

L	: liter	T	: tera (10^{12})
MOL	: mole	G	: giga (10^{9})
SEC	: second	M	: milli (10^{-3})
g	: gram	µ	: micro (10^{-6})
KG	: kilogram	N	: nano (10^{-9})
KAT	: katal	F	: femto (10^{-15})

HEMATOLOGY

The following anticoagulants were used during blood collection:
EDTA-K3 (hematology)
Sodium citrate, 3.8% (coagulation; 1 part anticoagulant to 9 parts blood)

The following commercial reference controls were used to monitor the performance of the method:

Hematology:
Eightcheck-3WP (normal range)
Eightcheck-L-3WP (low abnormal range)
Ret-check (reticulocyte control)
(TOA Medical Electronics Co., Ltd. Kobe/Japan)

Coagulation:
IL Calibration Plasma - At pretest, 4, 13, 25, 42, 43, 44, and 45 weeks
(Instrumentation Laboratory, Lexington, Ma/U.S.A)

Ci-Trol-1 (normal range) and Ci-Trol-2 (high abnormal range) - At pretest, 4, 13, 25, 42, 43, 44, and 45 weeks
(Baxter Dade AG, Duedingen/Switzerland)

IL Control Plasma (normal range) and IL Control Plasma (abnormal range) - At 47, 48 and 51 weeks, and at 8 weeks recovery
(Instrumentation Laboratory, SpA, Milano/Italy)

HEMATOLOGY

The following methods were used to determine the values of the parameters listed:

Parameter	Method / Instrumentation	Unit
Erythrocyte count (RBC)	Hydrodynamic focusing electric resistance detection - Sysmex (TOA)E-4000 Multi-Parameter Automated Hematology Analyzer	T/l
Hemoglobin (HB)	Cyanmethemoglobin - Sysmex (TOA) E-4000 Multi-Parameter Automated Hematology Analyzer	mmol/l
Hematocrit (HCT)	Cumulative pulse height detection - Sysmex (TOA) E-4000 Multi-Parameter Automated Hematology Analyzer	l/l
Mean corpuscular volume (MCV)	Calculated value: HCT/RBC - Sysmex (TOA) E-4000 Multi-Parameter Automated Hematology Analyzer	fl
Mean corpuscular hemoglobin (MCH)	Calculated value: HB/RBC - Sysmex (TOA) E-4000 Multi-Parameter Automated Hematology Analyzer	fmol
Mean corpuscular hemoglobin concentration (MCHC)	Calculated value: HB/HCT - Sysmex (TOA) E-4000 Multi-Parameter Automated Hematology Analyzer	mmol/l
Platelet count (PLATELETS)	Hydrodynamic focusing electric resistance detection - Sysmex (TOA) E-4000 Multi-Parameter Automated Hematology Analyzer	G/l
Reticulocyte count (RETIC.)	Flow cytometric analysis based on RNA fluorescently labelled cells using Auramine-O and an argon laser - Sysmex (TOA) R-1000 Automated Reticulocyte Analyzer	% (rel.) T/l (abs.)
Reticulocyte fluorescence ratios (HFR = high MFR = middle LFR = low)	Flow cytometric analysis based on RNA fluorescently labelled cells using Auramine-O and an argon laser - Sysmex (TOA) R-1000 Automated Reticulocyte Analyzer	%
Nucleated erythrocytes (normoblasts) (NEN)	Reported as number of nucleated erythrocytes per 100 leukocytes in the differential leukocyte count (see next page)	NEN/100 WBC

Parameter	Method / Instrumentation	Unit
Total leukocyte count (WBC)	Electric resistance detection - Sysmex (TOA) E-4000 Multi-Parameter Automated Hematology Analyzer	G/l
Differential leukocyte count (Diff. WBC Count)	Monocellular layer blood smears produced with an Omron Microx Centrifugal Spinner	
	Blood smear stained with a modified Wright's Eosin Methylene Blue solution (OMRON) using an Omron Microx Auto-Stainer	
	Manual count of 100 leukocytes using a Leitz Laborlux 12 or Dialux 22 light microscope	1 (rel.) G/l (abs.)
	Cell classification: BAND. = Band Neutrophil SEG. = Segmented Neutrophil EO. = Eosinophil BASO. = Basophil LYMPH. = Lymphocyte MONO. = Monocyte PLAS. = Plasma Cell OTHER = Blast Cell (undifferentiated)	
Red cell morphology	By microscopic examination of stained blood smear. Erythrocytes that vary from the normal in size, shape and hemoglobin content, or contain greater amounts of nuclear remnants are indicated as abnormal erythrocytes, and are characterized as such.	normal/ abnormal
Coagulation:		
Thromboplastin time (PT)	Automated laser-nephelometric centrifugal analyzer method, using an IL™ calcium thromboplastin reagent (a lyophilized extract from rabbit brain, certified according to ICSH/ ICTH(*) recommendations) - Instrumentation Laboratory (IL) ACL 300 Coagulation System	sec

(*) ICSH = International Committee for Standardization in Hematology
ICTH = International Committee on Thrombosis and Hemostasis

Parameter	Method / Instrumentation	Unit
Activated partial thromboplastin time (APTT)	Automated laser-nephelometric centrifugal analyzer method, using an IL™ bovine brain cephalin, ellagic acid activated reagent - Instrumentation Laboratory (IL) ACL 300 Coagulation System.	sec

CLINICAL BIOCHEMISTRY

The following anticoagulant was used during blood collection:
Lithium heparin (143 U.S.P. Units).

The following commercial reference controls were used to monitor the performance of the method:

Clinical Biochemistry:
Qualitrol HS-N (normal range)
Qualitrol HS-P (high range)
(E. Merck, Darmstadt/Germany)

Lyotrol N (normal range - for the assay control of total lipids and phospholipids)
(bio Mérieux, Charbonnières-les Bains/France)

Protein Electrophoresis:
Qualitrol® Protein - Reference control used at pretest and 4 weeks
(E. Merck, Darmstadt/Germany)

Seronorm™ Protein - Reference control used at 13, 25, 42, 43, 44, 45, 47, 48 and 51 weeks, and at 8 weeks recovery
(Nycomed Pharma AS, Oslo/Norway)

The following methods were used to determine the values of the parameters listed:

Parameter	Method / Instrumentation	Unit
Glucose	GLUC-DH - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Urea	Urease-GLDH - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l

Parameter	Method / Instrumentation	Unit
Creatinine	Jaffé-reaction without deproteinization, kinetic - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µmol/l
Bilirubin, total (BILI. T.)	DPD - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µmol/l
Lipids, total (LIPIDS T.)	Enzymatic, PAP - Epos Selective Analyzer 5060 (Eppendorf)	g/l
Cholesterol, total (CHOLEST. T.)	CHOD-PAP - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Triglycerides (TRIGL.)	GPO-PAP - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Phospholipids (PHOS. LIPID)	Phospholipase D/Choline oxidase/PAP - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Aspartate aminotransferase (ASAT/GOT)	Kinetic measurement of the rate of decrease in NADH (NADH/MDH coupled reaction). Method based on German Soc. of Clin. Chem. (DGKC) recommendations - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µkat/l (37°C)
Alanine aminotransferase (ALAT/GPT)	Kinetic measurement of the rate of decrease in NADH (NADH/LDH coupled reaction). Method based on German Soc. of Clin. Chem. (DGKC) recommendations - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µkat/l (37°C)
Lactate dehydrogenase (LDH)	Kinetic measurement of the rate of decrease in NADH (direct NADH/LDH coupled reaction using pyruvate as substrate PYR --> LAC reaction). Method based on German Soc. of Clin. Chem. (DGKC) recommendations - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µkat/l (37°C)

Parameter	Method / Instrumentation	Unit
Glutamate dehydrogenase (GLDH)	Kinetic measurement of the rate of decrease in NADH (reductive amination of 2-oxoglutarate with NADH in the presence of ammonium acetate). Method based on German Soc. of Clin. Chem. (DGKC) recommendations - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	nkat/l (37°C)
Creatine kinase (CK)	Kinetic measurement of the rate of increase in NADPH (CK-NAC activated). Method based on German Soc. of Clin. Chem. (DGKC) recommendations - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µkat/l (37°C)
Alkaline phosphatase (ALP)	Kinetic chromogenic method measuring the formation of p-nitrophenylate (hydrolysis of p-nitrophenylphosphate, diethanolamine buffer pH 9.8). Method based on German Soc. of Clin. Chem. (DGKC) recommendations - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µkat/l (37°C)
Gamma-glutamyl-transferase (G-GT)	Kinetic colorimetric method based on the procedure of Szasz, using L-gamma-glutamyl-3-carboxy-4-nitroanilide as substrate - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	nkat/l (37°C)
Iron	Ferrozin (disassociation of Fe(III) from transferrin by guanidine hydrochloride. Reduction of the Fe(III) form to Fe (II) by ascorbic acid and the formation of an iron-chromagen complex with ferrozin) - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µmol/l
Calcium	Reaction with o-cresolphthalein complexone - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Phosphorus	Direct phosphomolybdate reaction (340/380 nm) - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l

Parameter	Method / Instrumentation	Unit
Magnesium	Xylidyl blue - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Sodium	ISE (Ion-Selective Electrode/ Indirect potentiometry) - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Potassium	ISE (Ion-Selective Electrode/ Indirect potentiometry) - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Chloride	ISE (Ion-Selective Electrode/ Indirect potentiometry) - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	mmol/l
Protein, total	Biuret reaction - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	g/l
Protein electrophoresis (PROT. ELECTROPH.)	Horizontal agarose gel electrophoresis, using a Beckman Paragon Electrophoretic System. Quantitative evaluation of protein patterns by densitometry, using a Beckman Appraise computerised densitometer. Electrophoretic fractions: ALBUMIN = Albumin A1-GLOB. = Alpha 1-globulin A2-GLOB. = Alpha 2-globulin B1-GLOB. = Beta 1-globulin B2-GLOB. = Beta 2-globulin SB-GLOB. = Sum of beta globulins G-GLOB. = Gamma globulin Calculated value based on peak area: A/G RATIO = Albumin to Globulin ratio	1 (rel.) g/l (abs.)

URINALYSIS

The following commercial reference control was used to monitor the performance of the method:

Urinalysis:
Chek-Stix Urinalysis Control Strips
(Ames Division, Miles Laboratories, Inc., Elkhart, Indiana/USA)

Lyphochek Quantitative Urine Control - Normal I and Abnormal II-(for the assay control of Osmolality)
(Bio-Rad, ECS Division, Anaheim, California/USA)

The following methods were used to determine the values of the parameters listed:

Parameter	Method / Instrumentation	Unit
Specific gravity (SPEC. GRAV.)	Atago Uricon Refractometer	1
Osmolality	Wescor Vapor Pressure Osmometer, Model 5500 (Osmometer used at pretest, 4 and 13 weeks)	mmol/kg
	Freezing-point depression-Fiske 2400 Multi-Sample Osmometer (Osmometer used at 25 and 51 weeks, and at 8 weeks recovery)	mmol/kg
Color	Visual observation	-
Appearance	Visual observation	-
pH	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames)	-
		score:
Protein	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames)	0=negative/trace 1=0.3 g/l 2=1.0 g/l 3=≥3.0 g/l
	Questionable results are confirmed with Albustix Reagent-Test-Strip (Ames)	

Parameter	Method / Instrumentation	Unit
Glucose	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames)	0=negative 1=5.5 mmol/l 1=14 mmol/l 2=28 mmol/l 3=≥55 mmol/l
Ketone	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames)	0=negative 0=0.5 mmol/l 1=1.5 mmol/l 2=4.0 mmol/l 3=≥8.0 mmol/l
Bilirubin	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames) Positive results are confirmed with Ictotest Reagent Tablets (Ames)	0=negative 1=small 2=moderate 3=large
Blood	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames) Questionable results are confirmed with Hemastix Reagent-Test-Strip (Ames)	0=negative 1=trace/small 2=moderate 3=large
Urobilinogen (UROBILI.)	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames)	0= 3.2 µmol/l 0=16 µmol/l 1=33 µmol/l 2=66 µmol/l 3=≥131 µmol/l
Urine Sediment (SED. MICRO.)	Specimen centrifugation at 3000 r.p.m. for 10 minutes. Microscopic examination of 10 high power fields (400x) in different parts of cover-slipped area for normal and abnormal constituents using a Leitz Laborlux 12 light microscope. normal - score = 0	

Parameter	Method / Instrumentation	Unit
Urine Sediment (SED. MICRO.) continued	Normal urine contains a minute amount of cellular and non-cellular constituents of the urinary tract including white cells, red cells, epithelial cells, hyaline or granular casts, mucous threads, and amorphous or crystalline forms of normal solids. abnormal - score = 1, 2, or 3 1 = small amount 2 = moderate amount 3 = large amount Presence of abnormal amounts of urinary constituents are reported. The evaluation is based on findings relative to the control group, on dose-related changes, the presence of a small amount of red blood cells, the presence of a moderate amount of white blood cells, epithelial cells, casts, mucous threads, amorphous or crystalline forms of solids. A combination of two or more of these findings in a smaller amount is also considered abnormal. Key for indicated amounts of urinary constituents: RBC = Red blood cells WBC = White blood cells SQUAM. = Squamous epithelial cells RENAL = Renal epithelial cells ROUND = Round epithelial cells TRIP.PHOS. = Triple phosphate crystals	

Plasma Level Determinations

Samples of blood were obtained for plasma level determination from all animals at pretest and from the dogs of Groups 2, 3 and 4 during the treatment period at the dates and intervals specified below. Samples of blood were also taken at 3, 6 and 24 hours after dosing from the animals of Group 1 on the specified dates.

On each occasion approximately 3 ml of blood was drawn from the jugular vein and collected in lithium heparin (25 i.u./ml blood) blood collecting tubes. The tubes were stored on ice and centrifuged for 10 minutes at 6000 g, at approximately 5°C, within one hour.

PLASMA LEVEL DETERMINATIONS (continued)

The supernatant plasma was deproteinized with an equal volume of perchloric acid (0.8M), re-centrifuged and the clear supernatant stored at approximately -20°C in plastic tubes in the dark prior to dispatch to Dr. P. Giulidori, BioResearch SpA., I-20060 Liscate Milan/Italy for analyses. The results of these analyses will be reported separately.

Pretest	16 July 1993	
Day 1	22/23 July 1993	(3, 6 and 24 hours after dosing)
5 weeks	24/25 August 1993	(3, 6 and 24 hours after dosing)
25 weeks	11/12 January 1994	(3, 6 and 24 hours after dosing)
51 weeks	12/13 July 1994	(3, 6 and 24 hours after dosing)

Tissue Level Determinations

Approximately 5-10 g of the residual tissue from the right kidney, lung and liver after histopathological sampling were collected from all animals on the scheduled necropsy dates. The tissue samples were shock-frozen in liquid nitrogen and subsequently stored in plastic bags at approximately -80°C in the dark. The deep-frozen tissue samples were sent to Dr. P. Giulidori, BioResearch SpA., I-20060 Liscate Milan/Italy for future investigation, if necessary.

Pathology

NECROPSY, ORGAN WEIGHTS AND HISTOPATHOLOGY

Dates of necropsy:

After 26 weeks treatment	20 January 1994
After 52 weeks treatment	21/22 July 1994
After 8 weeks recovery	15 September 1994

At the end of the assigned study periods all dogs were anesthetized by intravenous injection of sodium pentobarbital (Narcoren, Rhône Merieux) and then killed by exsanguination. Necropsies were performed by experienced prosectors supervised by a veterinary pathologist. At post-mortem examination, all organs were examined and all findings recorded.

The weights of the following organs of all animals were recorded before fixation. Paired organs were weighed separately.

Adrenal glands, brain (including brainstem), heart, kidneys, liver, pituitary gland, prostate gland, spleen, testes with epididymides, thyroid gland with parathyroid.

NECROPSY, ORGAN WEIGHTS AND HISTOPATHOLOGY (continued)

The tissues listed in the following paragraph were removed and fixed, whole or in part, in neutral phosphate-buffered 4% formaldehyde solution (10% formalin). The eyes with optic nerve were fixed in Heidenhain's Susa solution. Bone marrow smears from one sternebrum from all animals were taken for possible future investigation.

Adrenal glands, aorta, bone - femur including articular surface, bone marrow - femur and sternum, brain - including sections of medulla/pons, cerebral and cerebellar cortex, epididymides, esophagus, eyes with optic nerve, female mammary gland area, (male mammary gland area), gallbladder, heart, kidneys, large intestine - cecum, colon and rectum, larynx, liver, lungs infused with formalin, lymph nodes - retropharyngeal and mesenteric, ovaries, pancreas, pituitary gland, prostate gland, salivary glands - mandibular, parotid and (sublingual), sciatic nerve, skeletal muscle, skin, small intestine - duodenum, jejunum and ileum, spinal cord - cervical, midthoracic and lumbar segments, spleen, stomach, testes, thymus, thyroid gland including parathyroid gland, tongue, trachea, urinary bladder, uterus (with vagina) and all gross lesions.

All sampled tissues (except male mammary gland, sublingual salivary gland and vagina) of all animals were trimmed, processed and embedded in paraffin wax, sectioned at a nominal thickness of 4 micrometers and stained with haematoxylin and eosin. The stained sections were examined by a veterinary pathologist using a light microscope. Histotechnology and histopathology were performed at RCC Itingen.

Data Compilation

Digital VAX computers were used to sort, treat and present suitable data for inclusion in the report. All electronically recorded data are conserved on a magnetic medium.

Individual values were rounded before printing. All derived values which appear in the tables represent the rounded results of calculations which used the exact raw data values.

The weekly mean of the daily food consumption values was calculated for each animal and was used to calculate an unweighted group mean.

For those dogs offered wetted diet, the portion of dry diet consumed was calculated and is presented in the individual data.

Statistical Analysis

The following statistical methods were used to analyze the body weights, organ weights, clinical laboratory, blood pressure and electrocardiographic data:

Univariate one-way analysis of variance was used to assess the significance of intergroup differences.

If the variables could be assumed to follow a normal distribution, the Dunnett-test (many-one t-test) based on a pooled variance estimate was applied for the comparison between the treated groups and the control groups for each sex.

The Student's t-test was used as a further analysis for ECG data to compare post-dose values with pre-dose values from the same group.

The Steel-test (many-one rank test) was applied when the data could not be assumed to follow a normal distribution.

Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables.

Individual values, means, standard deviations and statistics were rounded before printing. For example, test statistics were calculated on the basis of exact values for means and pooled variances and then rounded to two decimal places. Therefore, two groups may display the same printed means for a given parameter, yet display different test statistic values.

References:

- C.W. Dunnett: A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Statist. Assoc. 50, 1096-1121 (1955).

- R.G. Miller: Simultaneous Statistical Inference, Springer Verlag, New York (1981).

RESULTS

Observations

VIABILITY/MORTALITY

There were no unscheduled deaths.

Female No. 51 at 800 mg/kg/day (in terms of the active dose, SAMe) was not dosed from Days 303 to 330 of treatment due to persistent, complete inappetence (although tinned meat had previously been offered to stimulate appetite) and severe weight loss. Blood investigations before withdrawal of treatment revealed decreased glucose, cholesterol, chlorine and phospholipid concentrations, moderately to markedly increased alanine aminotransferase and glutamate dehydrogenase activities and magnesium, protein and albumin concentrations with an increased albumin/globulin ratio. Despite the withdrawal of treatment and the provision of tinned meat, the dog continued to show poor appetite and its condition initially further deteriorated. Thereafter, the dog gradually recovered although a slight anemia, characterized by a decrease in the red cell parameters, increased mean cell volume, thrombocytosis, reticulocytosis and the presence of nucleated erythrocytes in the peripheral blood, was evident at a blood investigation on Day 323 (Week 47). Treatment was resumed on Day 331 and the satisfactory health status of the dog was confirmed at a blood investigation on Day 334 (Week 48). Nevertheless, the ration of tinned meat was continued until the end of the study.

CLINICAL SIGNS (see pp. 121-177)

Treatment with SAMe SD_4 was associated with an increased mean incidence of loose/watery faeces in the males at 200, 400 and 800 mg SAMe/kg/day and the females of the high dose group. The incidence and severity of this sign showed a relationship to dose and was such that some animals of the high dose group were affected almost daily throughout the treatment phase of the study.

The mean number of days loose/watery faeces was observed in each group (excluding the dogs killed after 26 weeks of treatment) was:

	Group 1 0 mg/kg	Group 2 200 mg/kg	Group 3 400 mg/kg	Group 4 800 mg/kg
Males	90	166	226	288
Females	97	67	87	249

Loose/watery faeces predominantly occurred once daily and was observed at the first daily observation, indicating that the sign had occurred between 6 and 22 hours after dosing. However, a second daily incidence of loose/watery faeces occasionally occurred in most dogs from all groups, usually from 4 to 6 hours after dosing.

During the recovery period, only sporadic incidences of loose/watery faeces occurred in the animals of the high dose group, with the exception of male No. 26 between Days 6 and 24.

CLINICAL SIGNS (continued)

The incidence of loose/watery faeces in the females at 200 or 400 mg SAMe/kg/day was similar to that of the controls.

There were no other clinical signs that could be related to treatment with SAMe SD_4.

FOOD CONSUMPTION (see pp. 41-42, 46-55, 179-197)

There was no effect on food intake that could be related to treatment with SAMe SD_4.

Low food intake was recorded in some female dogs of all groups, including controls, on occasions during the treatment period. These decreases were most marked in females No. 45 at 400 mg SAMe/kg/day and, particularly, No. 51 at 800 mg SAMe/kg/day. Treatment was withdrawn from dog No. 51 from Day 303 to 330 due to complete inappetence (see Viability/Mortality). These animals were given wetted diet and, towards the end of the treatment period, tinned meat to stimulate appetite. This resulted in improved food intake. A relationship of these individual findings to treatment is considered unlikely as mean food intake over the treatment period of the female groups was similar and in the absence of any effects in the males.

BODY WEIGHTS (see pp. 43-44, 56-67, 198-213)

Treatment with SAMe SD_4 resulted in reduced group mean body weight gain in the males of all treated groups when compared with the controls. These differences were most marked in the first 26 weeks of treatment. Body weight gain in the females was unaffected by treatment.

Mean body weight gain on Day 364, as a percentage of the weight recorded on Day 1 of treatment, is presented below:

	Group 1 0 mg/kg	Group 2 200 mg/kg	Group 3 400 mg/kg	Group 4 800 mg/kg
Males				
MEAN	23.3	8.4 *	11.2 *	7.2 **
ST.DEV.	8.1	3.3	4.5	11.1
N+	6	4	4	6
Females				
MEAN	17.0	14.1	8.4	15.9
ST.DEV.	12.0	5.0	7.0	10.2
N+	6	4	4	6

+: Excluding animals sacrificed after 26 weeks of treatment.
*/**: Dunnett-Test based on pooled variance significant at 5 % (*) or 1 % (**) level.

BODY WEIGHTS (continued)

The majority of males from all groups showed weight gains below that of any control male. Male No. 26 at 800 mg SAMe/kg/day, which lost 1.2 kg, was most markedly affected. This animal subsequently gained 1.7 kg during the 8 week recovery period.

OPHTHALMOSCOPIC EXAMINATIONS (see pp. 214-230)

There was no indication that treatment with SAMe SD_4 had any adverse effect upon the eyes.

ELECTROCARDIOGRAMS (see pp. 68-77, 231-245)

The electrocardiographic parameters were unaffected by treatment with SAMe SD_4.

The only finding of note was a single incidence of second degree atrioventricular block in female No. 50 at 800 mg SAMe/kg/day at the investigation three hours after dosing in Week 25. This finding is considered to be spontaneous in origin and unrelated to treatment with SAMe SD_4.

BLOOD PRESSURE (see pp. 78-82, 246-252)

Blood pressure was unaffected by treatment with SAMe SD_4.

Clinical Laboratory Investigations

HEMATOLOGY (see pp. 83-90, 253-282)

Assessment of the hematology data revealed the following changes in comparison with the controls:

- Slightly decreased erythrocyte, hemoglobin concentration and hematocrit in the males at 800 mg SAMe/kg/day in Weeks 13, 25 and 51. The difference from the controls for each of these parameters was statistically significant. These findings were still apparent at the end of the recovery period.

  A slight anemia was also apparent in female No. 51 of this group following withdrawal of treatment (see Viability/Mortality section) and is considered to reflect the poor condition of the animal rather than a direct effect of treatment.

HEMATOLOGY (continued)

- Slightly increased platelet count in the males and females at 800 mg SAMe/kg/day, particularly in Weeks 13 and 25, and in the females at 200 mg SAMe/kg/day, notably in Week 13. This finding is considered to be fortuitous in the absence of a clear dose-relationship.

  There were no other changes that could be associated with the administration of SAMe SD_4.

CLINICAL BIOCHEMISTRY (see pp. 91-98, 285-320)

Assessment of the clinical biochemistry data revealed the following changes in comparison with the control and pretest data:

- Slightly decreased group mean cholesterol levels in the males at 400 or 800 mg SAMe/kg/day at each investigation during the treatment period. The differences from the controls were statistically significant, except for the males at 400 mg SAMe/kg/day in Week 4, although the severity was unrelated to dose. At the end of the recovery period, cholesterol levels were similar in control and treated animals. Moderately decreased cholesterol levels were also recorded in female No. 51 at 800 mg SAMe/kg/day before withdrawal of treatment (see Viability/Mortality, p. 35).

- Slightly decreased group mean phospholipid levels in the males at 800 mg SAMe/kg/day in Week 51. At the end of the recovery period phospholipid levels were similar for control and treated animals.

- Slightly increased group mean glutamate dehydrogenase activity in the females at 400 mg SAMe/kg/day, notably No. 45, and the males and females at 800 mg SAMe/kg/day in Week 51. The differences from the controls were statistically significant for the males at 800 mg SAMe/kg/day and the females at 400 mg SAMe/kg/day.

  Similar increases were also evident in individual animals on other occasions, particularly male No. 25 at 800 mg SAMe/kg/day in Week 4. Markedly increased activity of this enzyme was also recorded in female No. 51 at 800 mg SAMe/kg/day before withdrawal of treatment (see Viability/Mortality, p. 35).

- Slightly to moderately increased alanine aminotransferase and/or gamma glutamyltransferase activities in individual animals, notably No. 45 at 400 mg SAMe/kg/day and No. 49 at 800 mg SAMe/kg/day in Week 51 and in female No. 51 of the high dose group before withdrawal of treatment (see Viability/Mortality, p. 35).

  An association of these findings with the administration of SAMe at 400 or 800 mg/kg/day is not excluded. However, increased alanine aminotransferase and/or glutamate-dehydrogenase activities were also evident on occasions in some control animals, notably male No. 7 in Week 25.

  At the end of the recovery period, glutamate dehydrogenase, alanine aminotransferase and gamma glutamyltransferase activities of the animals at 800 mg SAMe/kg/day were similar to those of the controls.

CLINICAL BIOCHEMISTRY (continued)

There were no other changes that could be associated with the administration of SAMe SD_4. An increase in protein and albumin levels were recorded from Week 13 in the treated females when compared with the controls. These differences, which frequently attained statistical significance, are considered to be attributable to low control values and unrelated to treatment.

URINALYSIS (see pp. 99-102, 321-338)

Urinary pH was lower in the females at 800 mg SAMe/kg/day than the controls. The differences attained statistical significance in Weeks 13, 25 and 51.

There were no other changes to the urinalysis parameters that could be related to the administration of SAMe SD_4.

Pathology

ORGAN WEIGHTS (see pp. 103-120, 339-368)

Organ weights were unaffected by treatment with SAMe SD_4.

MACROSCOPIC FINDINGS (see Attachment 4, pp. 430-584)

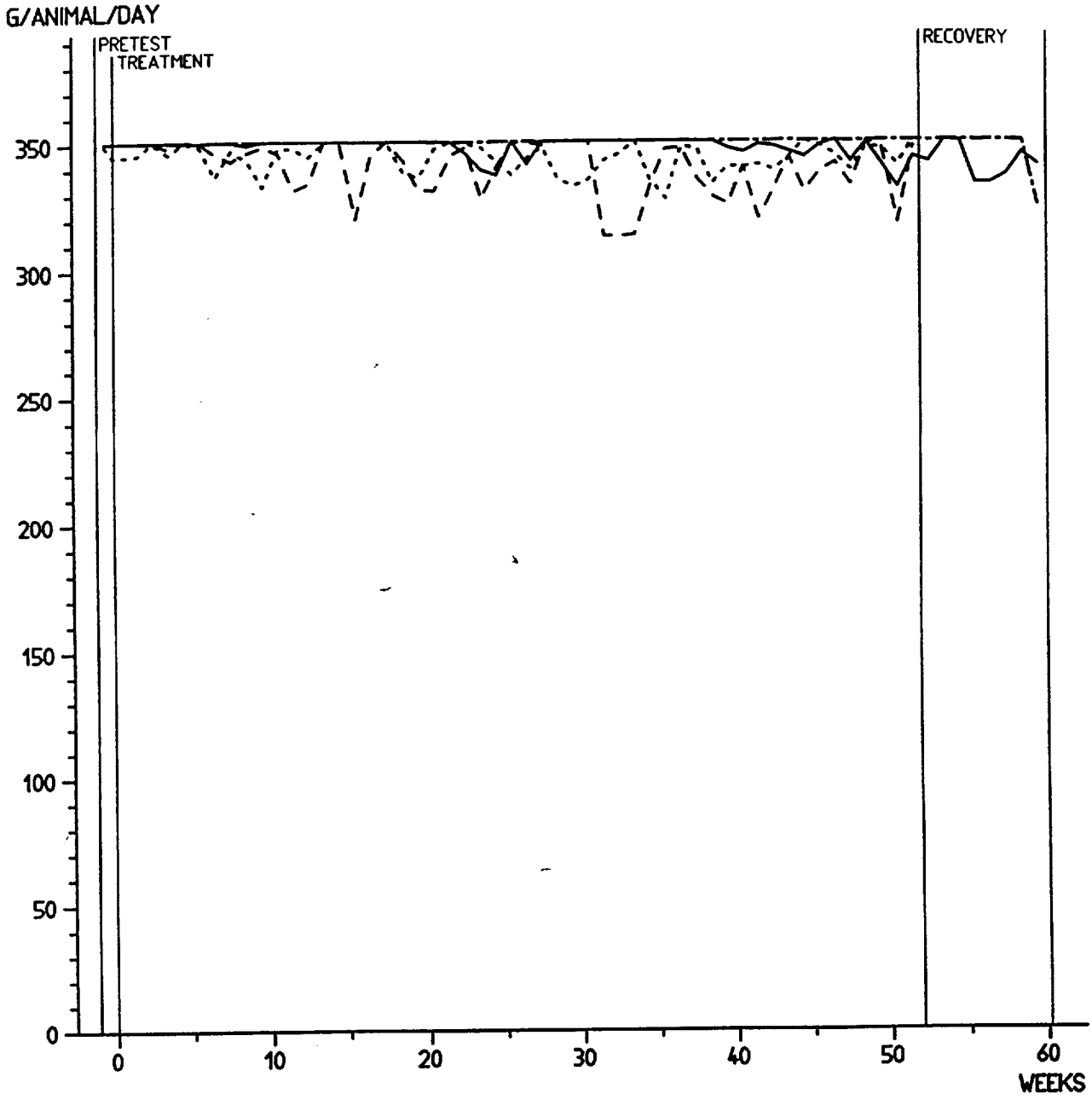
No treatment-related findings were detected at any of the necropsies. Reddish discoloration representing congestion was a common finding, particularly in the gastro-intestinal tract of most dogs, and is due to the method of euthanasia.

MICROSCOPIC FINDINGS (see Attachment 4, pp. 430-584)

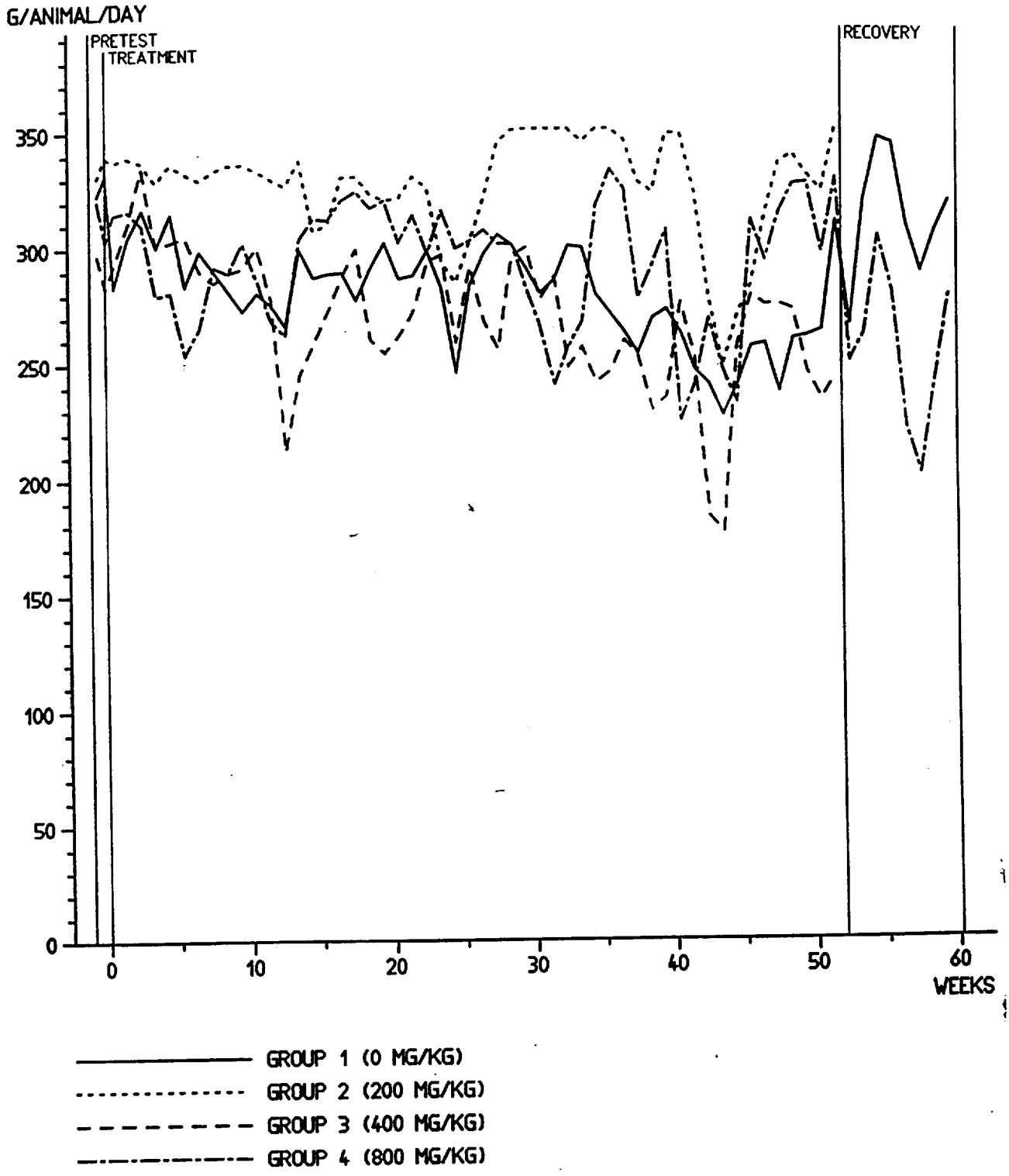
No treatment-related microscopic findings were noted in any of the sacrifice groups. All microscopic findings recorded were of a spontaneous nature and occurred at similar incidences in control and treated groups. These findings were within the normal range of background morphologic alterations which may be recorded in beagle dogs at these ages.

FIGURES

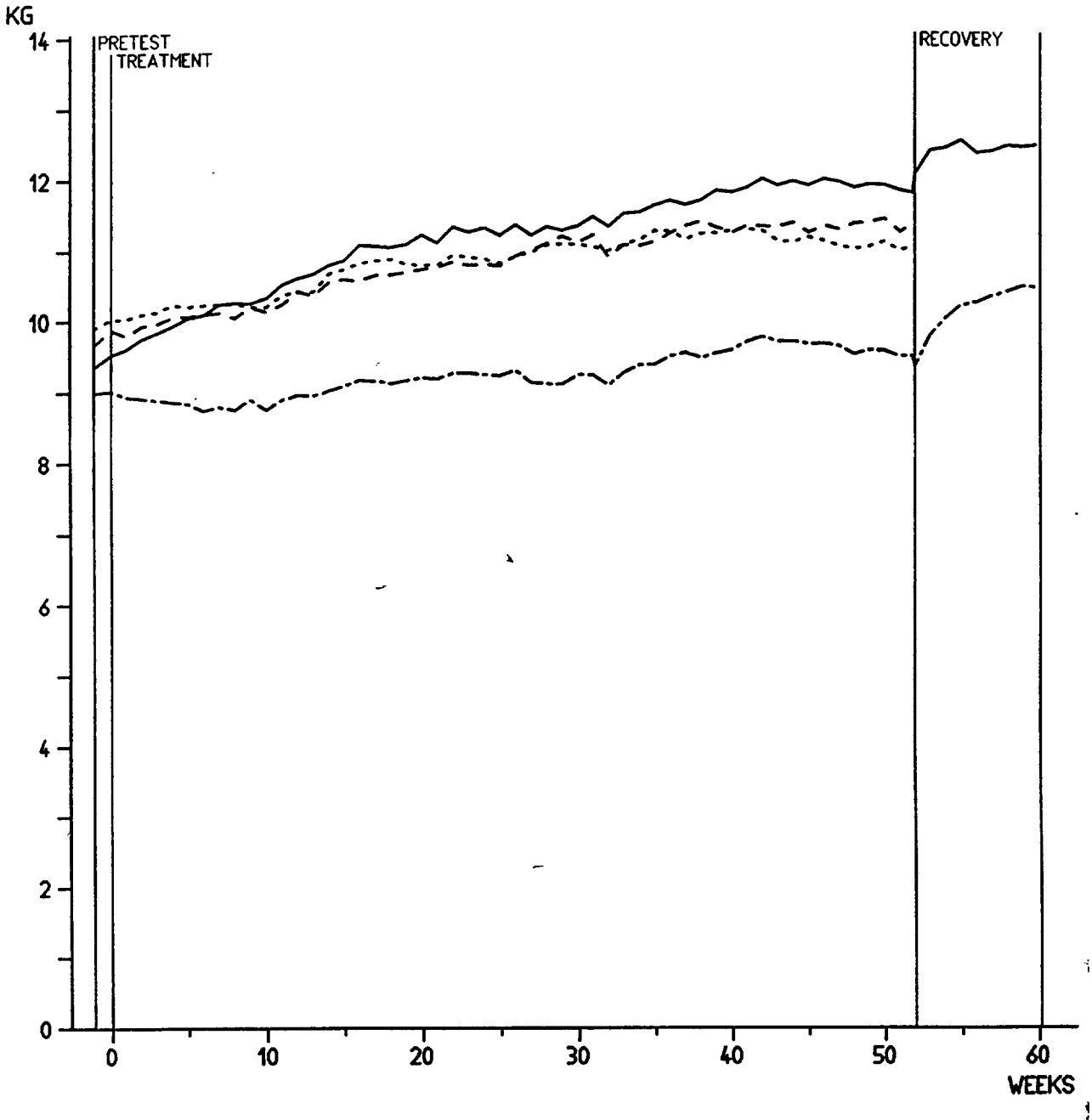
FOOD CONSUMPTION
MALES



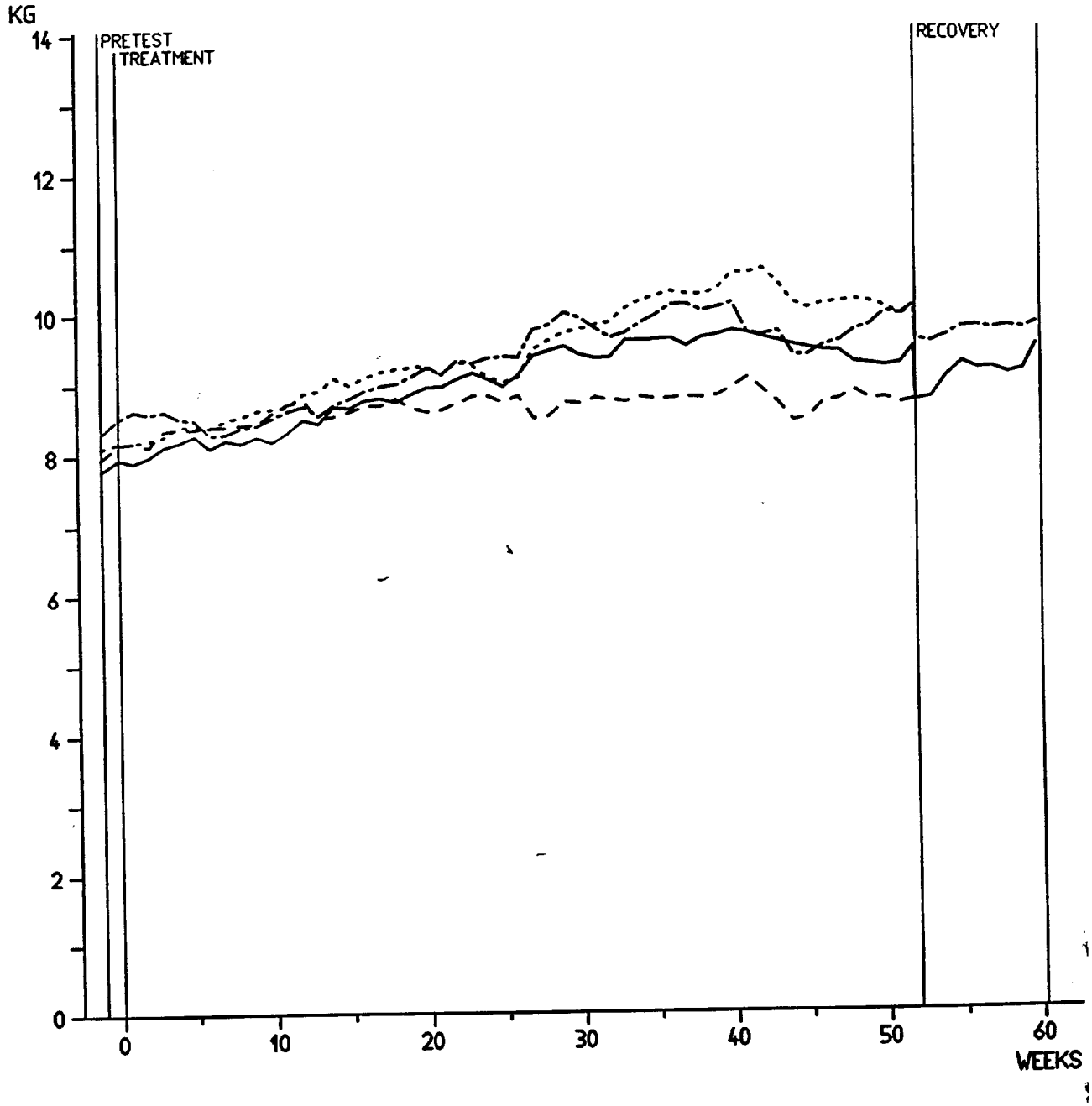
FOOD CONSUMPTION
FEMALES



BODY WEIGHTS
MALES



BODY WEIGHTS
FEMALES



TABLES

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	350	349	350	350
WEEKS 1/2	ST.DEV.	0.1	2.5	0.1	0.1
	N	8	6	6	8
DAYS 8-9	MEAN	350	345	350	350
WEEK 2	ST.DEV.	0.4	14.1	0.3	0.2
	N	8	6	6	8
MEAN OF MEANS OVER PRETEST		350	347	350	350

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	350	345	350	350
WEEKS 1/2	ST.DEV.	0.1	13.0	0.1	0.2
	N	8	6	6	8
DAYS 8-15	MEAN	350	345	350	350
WEEKS 2/3	ST.DEV.	0.1	12.3	0.2	0.1
	N	8	6	6	8
DAYS 15-22	MEAN	350	350	350	350
WEEKS 3/4	ST.DEV.	0.1	0.1	0.2	0.1
	N	8	6	6	8
DAYS 22-29	MEAN	350	346	348	350
WEEKS 4/5	ST.DEV.	0.1	11.2	5.8	0.1
	N	8	6	6	8
DAYS 29-36	MEAN	350	350	350	350
WEEKS 5/6	ST.DEV.	0.2	0.2	0.2	0.2
	N	8	6	6	8
DAYS 36-43	MEAN	350	348	350	350
WEEKS 6/7	ST.DEV.	0.2	4.2	0.3	0.1
	N	8	6	6	8
DAYS 43-50	MEAN	350	337	346	350
WEEKS 7/8	ST.DEV.	0.2	33.9	11.6	0.1
	N	8	6	6	8
DAYS 50-57	MEAN	350	347	343	350
WEEKS 8/9	ST.DEV.	0.1	5.5	18.7	0.1
	N	8	6	6	8
DAYS 57-64	MEAN	349	343	346	350
WEEKS 9/10	ST.DEV.	4.1	17.0	10.3	0.1
	N	8	6	6	8
DAYS 64-71	MEAN	350	333	348	350
WEEKS 10/11	ST.DEV.	0.1	31.2	4.8	0.1
	N	8	6	6	8
DAYS 71-78	MEAN	350	348	346	350
WEEKS 11/12	ST.DEV.	0.1	6.4	7.1	0.1
	N	8	6	6	8
DAYS 78-85	MEAN	350	348	332	350
WEEKS 12/13	ST.DEV.	0.2	5.9	45.6	0.1
	N	8	6	6	8
DAYS 85-92	MEAN	350	344	334	350
WEEKS 13/14	ST.DEV.	0.1	10.1	40.5	0.1
	N	8	6	6	8
DAYS 92-99	MEAN	350	350	350	350
WEEKS 14/15	ST.DEV.	0.1	0.1	0.1	0.1
	N	8	6	6	8
DAYS 99-106	MEAN	350	350	349	350
WEEKS 15/16	ST.DEV.	0.1	0.1	2.4	0.1
	N	8	6	6	8
DAYS 106-113	MEAN	350	350	320	350
WEEKS 16/17	ST.DEV.	0.1	0.1	50.4	0.1
	N	8	6	6	8
DAYS 113-120	MEAN	350	350	345	350
WEEKS 17/18	ST.DEV.	0.1	0.2	12.8	0.1
	N	8	6	6	8
DAYS 120-127	MEAN	350	350	350	350
WEEKS 18/19	ST.DEV.	0.1	1.1	0.0	0.1
	N	8	6	6	8

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 127-134	MEAN	350	339	343	350
WEEKS 19/20	ST.DEV.	0.2	28.1	12.0	0.0
	N	8	6	6	8
DAYS 134-141	MEAN	350	336	332	350
WEEKS 20/21	ST.DEV.	0.2	34.5	35.9	0.1
	N	8	6	6	8
DAYS 141-148	MEAN	350	347	331	350
WEEKS 21/22	ST.DEV.	0.2	7.0	31.4	0.2
	N	8	6	6	8
DAYS 148-155	MEAN	350	350	345	350
WEEKS 22/23	ST.DEV.	0.2	0.2	13.2	0.1
	N	8	6	6	8
DAYS 155-162	MEAN	346	350	348	350
WEEKS 23/24	ST.DEV.	12.1	2.1	5.0	0.1
	N	8	6	6	8
DAYS 162-169	MEAN	339	348	328	350
WEEKS 24/25	ST.DEV.	30.4	5.1	44.6	0.2
	N	8	6	6	8
DAYS 169-176	MEAN	337	343	341	350
WEEKS 25/26	ST.DEV.	29.1	13.8	13.3	0.1
	N	8	6	6	8
DAYS 176-183	MEAN	350	337	350	350
WEEKS 26/27	ST.DEV.	0.1	32.2	0.8	0.1
	N	8	6	6	8
DAYS 183-190	MEAN	341	344	350	350
WEEKS 27/28	ST.DEV.	22.0	12.8	1.0	0.1
	N	6	4	4	6
DAYS 190-197	MEAN	350	348	349	350
WEEKS 28/29	ST.DEV.	0.2	4.2	2.5	0.1
	N	6	4	4	6
DAYS 197-204	MEAN	350	336	350	350
WEEKS 29/30	ST.DEV.	0.1	29.2	0.1	0.1
	N	6	4	4	6
DAYS 204-211	MEAN	350	333	350	350
WEEKS 30/31	ST.DEV.	0.1	35.5	0.1	0.1
	N	6	4	4	6
DAYS 211-218	MEAN	350	335	350	350
WEEKS 31/32	ST.DEV.	0.1	30.1	0.1	0.1
	N	6	4	4	6
DAYS 218-225	MEAN	350	343	313	350
WEEKS 32/33	ST.DEV.	0.2	14.9	62.2	0.1
	N	6	4	4	6
DAYS 225-232	MEAN	350	345	313	350
WEEKS 33/34	ST.DEV.	0.1	10.1	69.3	0.1
	N	6	4	4	6
DAYS 232-239	MEAN	350	350	314	350
WEEKS 34/35	ST.DEV.	0.2	0.2	43.6	0.1
	N	6	4	4	6
DAYS 239-246	MEAN	350	335	333	350
WEEKS 35/36	ST.DEV.	0.2	29.7	35.2	0.1
	N	6	4	4	6
DAYS 246-253	MEAN	350	328	347	350
WEEKS 36/37	ST.DEV.	0.1	44.5	4.9	0.1
	N	6	4	4	6

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 253-260	MEAN	350	348	348	350
WEEKS 37/38	ST.DEV.	0.1	4.3	5.8	0.1
	N	6	4	4	6
DAYS 260-267	MEAN	350	347	336	350
WEEKS 38/39	ST.DEV.	0.1	5.8	28.8	0.1
	N	6	4	4	6
DAYS 267-274	MEAN	350	334	329	350
WEEKS 39/40	ST.DEV.	0.2	33.5	24.8	0.1
	N	6	4	4	6
DAYS 274-281	MEAN	347	340	326	350
WEEKS 40/41	ST.DEV.	7.0	20.3	28.4	0.2
	N	6	4	4	6
DAYS 281-288	MEAN	346	340	340	350
WEEKS 41/42	ST.DEV.	7.6	20.5	19.9	0.2
	N	6	4	4	6
DAYS 288-295	MEAN	349	341	320	350
WEEKS 42/43	ST.DEV.	3.8	18.3	39.0	0.1
	N	6	4	4	6
DAYS 295-302	MEAN	348	339	331	350
WEEKS 43/44	ST.DEV.	5.4	23.2	25.1	0.1
	N	6	4	4	6
DAYS 302-309	MEAN	346	344	344	350
WEEKS 44/45	ST.DEV.	10.6	13.2	12.6	0.2
	N	6	4	4	6
DAYS 309-316	MEAN	344	350	330	350
WEEKS 45/46	ST.DEV.	10.7	0.1	39.3	0.2
	N	6	4	4	6
DAYS 316-323	MEAN	349	348	338	350
WEEKS 46/47	ST.DEV.	3.6	3.5	13.8	0.2
	N	6	4	4	6
DAYS 323-330	MEAN	350	344	342	350
WEEKS 47/48	ST.DEV.	0.0	11.5	10.5	0.2
	N	6	4	4	6
DAYS 330-337	MEAN	342	339	333	350
WEEKS 48/49	ST.DEV.	13.3	22.7	34.2	0.0
	N	6	4	4	6
DAYS 337-344	MEAN	350	348	350	350
WEEKS 49/50	ST.DEV.	1.9	4.5	0.1	0.1
	N	6	4	4	6
DAYS 344-351	MEAN	341	347	348	350
WEEKS 50/51	ST.DEV.	14.7	6.4	5.3	0.1
	N	6	4	4	6
DAYS 351-358	MEAN	332	341	318	350
WEEKS 51/52	ST.DEV.	29.1	19.4	31.8	0.1
	N	6	4	4	6
DAYS 358-365	MEAN	344	350	348	350
WEEKS 52/53	ST.DEV.	15.4	0.2	5.0	0.1
	N	6	4	4	6
MEAN OF MEANS OVER TREATMENT		348	344	340	350

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8 WEEKS 1/2	MEAN ST.DEV. N	342 11.4 2	---	---	350 0.0 2
DAYS 8-15 WEEKS 2/3	MEAN ST.DEV. N	350 0.2 2	---	---	351 0.1 2
DAYS 15-22 WEEKS 3/4	MEAN ST.DEV. N	350 0.2 2	---	---	350 0.0 2
DAYS 22-29 WEEKS 4/5	MEAN ST.DEV. N	334 23.4 2	---	---	350 0.1 2
DAYS 29-36 WEEKS 5/6	MEAN ST.DEV. N	334 3.1 2	---	---	350 0.0 2
DAYS 36-43 WEEKS 6/7	MEAN ST.DEV. N	337 18.5 2	---	---	350 0.1 2
DAYS 43-50 WEEKS 7/8	MEAN ST.DEV. N	346 6.6 2	---	---	350 0.0 2
DAYS 50-57 WEEKS 8/9	MEAN ST.DEV. N	341 5.2 2	---	---	325 35.6 2
MEAN OF MEANS OVER RECOVERY		342	---	---	347

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	323	331	297	320
WEEKS 1/2	ST.DEV.	37.9	32.0	51.9	35.3
	N	8	6	6	8
DAYS 8-9	MEAN	331	339	283	303
WEEK 2	ST.DEV.	36.3	27.0	62.1	68.8
	N	8	6	6	8
MEAN OF MEANS OVER PRETEST		327	335	290	312

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8	MEAN	283	337	292	314
WEEKS 1/2	ST.DEV.	74.2	32.4	52.9	49.6
	N	8	6	6	8
DAYS 8-15	MEAN	304	339	309	316
WEEKS 2/3	ST.DEV.	65.7	28.2	63.4	42.9
	N	8	6	6	8
DAYS 15-22	MEAN	317	337	335	310
WEEKS 3/4	ST.DEV.	39.8	32.9	24.5	50.3
	N	8	6	6	8
DAYS 22-29	MEAN	300	328	300	279
WEEKS 4/5	ST.DEV.	46.1	50.5	31.3	62.7
	N	8	6	6	8
DAYS 29-36	MEAN	314	336	302	281
WEEKS 5/6	ST.DEV.	43.5	34.8	41.2	65.7
	N	8	6	6	8
DAYS 36-43	MEAN	283	332	305	254
WEEKS 6/7	ST.DEV.	44.0	29.8	36.6	102.9
	N	8	6	6	8
DAYS 43-50	MEAN	298	329	290	265
WEEKS 7/8	ST.DEV.	44.2	46.3	41.6	87.7
	N	8	6	6	8
DAYS 50-57	MEAN	290	333	285	291
WEEKS 8/9	ST.DEV.	53.5	42.4	43.7	88.6
	N	8	6	6	8
DAYS 57-64	MEAN	281	335	289	289
WEEKS 9/10	ST.DEV.	71.9	36.9	41.3	47.2
	N	8	6	6	8
DAYS 64-71	MEAN	273	336	291	302
WEEKS 10/11	ST.DEV.	74.1	35.9	55.9	58.2
	N	8	6	6	8
DAYS 71-78	MEAN	280	333	300	286
WEEKS 11/12	ST.DEV.	63.1	42.8	32.8	75.8
	N	8	6	6	8
DAYS 78-85	MEAN	275	329	277	268
WEEKS 12/13	ST.DEV.	65.0	51.6	56.0	90.0
	N	8	6	6	8
DAYS 85-92	MEAN	266	326	212	262
WEEKS 13/14	ST.DEV.	74.5	51.0	79.6	113.6
	N	8	6	6	8
DAYS 92-99	MEAN	299	337	245	303
WEEKS 14/15	ST.DEV.	45.6	32.5	54.1	48.1
	N	8	6	6	8
DAYS 99-106	MEAN	287	307	258	312
WEEKS 15/16	ST.DEV.	56.8	69.4	24.9	50.4
	N	8	6	6	8
DAYS 106-113	MEAN	288	310	272	311
WEEKS 16/17	ST.DEV.	58.2	63.3	39.3	50.5
	N	8	6	6	8
DAYS 113-120	MEAN	289	330	287	320
WEEKS 17/18	ST.DEV.	57.3	40.9	37.7	44.0
	N	8	6	6	8
DAYS 120-127	MEAN	277	331	299	324
WEEKS 18/19	ST.DEV.	70.1	44.2	46.1	47.2
	N	8	6	6	8

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 127-134	MEAN	291	323	260	317
WEEKS 19/20	ST.DEV.	66.6	41.8	88.2	52.0
	N	8	6	6	8
DAYS 134-141	MEAN	302	320	254	320
WEEKS 20/21	ST.DEV.	51.9	46.6	76.2	46.3
	N	8	6	6	8
DAYS 141-148	MEAN	286	321	261	302
WEEKS 21/22	ST.DEV.	53.9	42.4	69.4	53.7
	N	8	6	6	8
DAYS 148-155	MEAN	288	330	272	314
WEEKS 22/23	ST.DEV.	59.7	38.7	63.4	55.5
	N	8	6	6	8
DAYS 155-162	MEAN	298	326	293	297
WEEKS 23/24	ST.DEV.	56.3	60.3	67.4	69.2
	N	8	6	6	8
DAYS 162-169	MEAN	282	293	297	316
WEEKS 24/25	ST.DEV.	61.5	100.2	47.0	41.7
	N	8	6	6	8
DAYS 169-176	MEAN	245	284	259	299
WEEKS 25/26	ST.DEV.	59.0	93.8	53.3	48.4
	N	8	6	6	8
DAYS 176-183	MEAN	283	302	292	302
WEEKS 26/27	ST.DEV.	73.1	69.1	48.0	62.3
	N	8	6	6	8
DAYS 183-190	MEAN	297	321	268	307
WEEKS 27/28	ST.DEV.	57.8	59.2	27.6	67.9
	N	6	4	4	6
DAYS 190-197	MEAN	305	345	255	301
WEEKS 28/29	ST.DEV.	47.6	10.7	7.7	77.9
	N	6	4	4	6
DAYS 197-204	MEAN	301	350	296	301
WEEKS 29/30	ST.DEV.	47.9	1.2	33.4	49.4
	N	6	4	4	6
DAYS 204-211	MEAN	291	350	300	282
WEEKS 30/31	ST.DEV.	49.0	0.1	38.8	74.5
	N	6	4	4	6
DAYS 211-218	MEAN	280	350	277	265
WEEKS 31/32	ST.DEV.	56.3	0.1	44.2	80.5
	N	6	4	4	6
DAYS 218-225	MEAN	286	350	287	240
WEEKS 32/33	ST.DEV.	62.7	0.1	32.6	120.3
	N	6	4	4	6
DAYS 225-232	MEAN	300	350	248	256
WEEKS 33/34	ST.DEV.	57.6	0.0	22.2	104.2
	N	6	4	4	6
DAYS 232-239	MEAN	299	345	256	267
WEEKS 34/35	ST.DEV.	45.8	6.3	43.1	67.9
	N	6	4	4	6
DAYS 239-246	MEAN	279	350	241	317
WEEKS 35/36	ST.DEV.	62.6	0.1	69.3	38.5
	N	6	4	4	6
DAYS 246-253	MEAN	271	350	246	333
WEEKS 36/37	ST.DEV.	79.2	0.2	69.7	32.0
	N	6	4	4	6

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 253-260	MEAN	263	346	259	325
WEEKS 37/38	ST.DEV.	70.7	9.4	63.8	37.3
	N	6	4	4	6
DAYS 260-267	MEAN	253	328	252	277
WEEKS 38/39	ST.DEV.	80.3	45.1	59.5	103.6
	N	6	4	4	6
DAYS 267-274	MEAN	269	323	229	291
WEEKS 39/40	ST.DEV.	64.3	53.9	52.0	63.1
	N	6	4	4	6
DAYS 274-281	MEAN	272	348	235	307
WEEKS 40/41	ST.DEV.	55.4	4.8	48.9	56.5
	N	6	4	4	6
DAYS 281-288	MEAN	262	348	275	224
WEEKS 41/42	ST.DEV.	59.1	4.7	33.3	90.7
	N	6	4	4	6
DAYS 288-295	MEAN	246	323	252	240
WEEKS 42/43	ST.DEV.	71.2	36.2	44.4	112.3
	N	6	4	4	6
DAYS 295-302	MEAN	240	278	183	268
WEEKS 43/44	ST.DEV.	57.4	73.6	102.8	139.2
	N	6	4	4	6
DAYS 302-309	MEAN	227	248	176	246
WEEKS 44/45	ST.DEV.	38.4	109.0	84.8	137.8
	N	6	4	4	6
DAYS 309-316	MEAN	239	269	256	232
WEEKS 45/46	ST.DEV.	58.2	87.0	47.3	139.3
	N	6	4	4	6
DAYS 316-323	MEAN	256	283	279	311
WEEKS 46/47	ST.DEV.	68.8	61.6	48.0	49.7
	N	6	4	4	6
DAYS 323-330	MEAN	258	313	274	293
WEEKS 47/48	ST.DEV.	59.0	42.7	46.3	79.8
	N	6	4	4	6
DAYS 330-337	MEAN	237	336	275	314
WEEKS 48/49	ST.DEV.	44.8	13.5	50.3	47.6
	N	6	4	4	6
DAYS 337-344	MEAN	260	339	272	326
WEEKS 49/50	ST.DEV.	38.3	13.2	22.9	51.5
	N	6	4	4	6
DAYS 344-351	MEAN	261	330	245	327
WEEKS 50/51	ST.DEV.	47.5	25.6	74.6	49.0
	N	6	4	4	6
DAYS 351-358	MEAN	263	323	233	297
WEEKS 51/52	ST.DEV.	31.5	24.2	77.9	45.7
	N	6	4	4	6
DAYS 358-365	MEAN	310	350	244	329
WEEKS 52/53	ST.DEV.	42.1	0.1	91.3	39.4
	N	6	4	4	6
MEAN OF MEANS OVER TREATMENT		279	327	268	293

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAYS 1-8 WEEKS 1/2	MEAN ST.DEV. N	266 29.5 2	---	---	250 41.0 2
DAYS 8-15 WEEKS 2/3	MEAN ST.DEV. N	320 43.4 2	---	---	262 37.8 2
DAYS 15-22 WEEKS 3/4	MEAN ST.DEV. N	346 5.8 2	---	---	304 65.4 2
DAYS 22-29 WEEKS 4/5	MEAN ST.DEV. N	344 8.5 2	---	---	280 86.6 2
DAYS 29-36 WEEKS 5/6	MEAN ST.DEV. N	309 58.1 2	---	---	222 17.6 2
DAYS 36-43 WEEKS 6/7	MEAN ST.DEV. N	289 87.2 2	---	---	202 8.1 2
DAYS 43-50 WEEKS 7/8	MEAN ST.DEV. N	306 62.8 2	---	---	241 18.7 2
DAYS 50-57 WEEKS 8/9	MEAN ST.DEV. N	319 44.4 2	---	---	279 9.6 2
MEAN OF MEANS OVER RECOVERY		312	---	---	255

BODY WEIGHTS (KG) SUMMARY
MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	9.3	9.9	9.7	9.0
WEEK 1	ST.DEV.	1.0	1.1	0.8	0.9
	N	8	6	6	8

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

BODY WEIGHTS (KG) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	9.5	10.0	9.9	9.0
WEEK 1	ST.DEV.	1.1	1.0	0.7	0.9
	N	8	6	6	8
DAY 8	MEAN	9.6	10.0	9.8	8.9
WEEK 2	ST.DEV.	1.1	1.1	0.7	0.9
	N	8	6	6	8
DAY 15	MEAN	9.7	10.1	9.9	8.9
WEEK 3	ST.DEV.	1.1	1.1	0.7	0.9
	N	8	6	6	8
DAY 22	MEAN	9.8	10.1	10.0	8.9
WEEK 4	ST.DEV.	1.1	1.0	0.7	0.9
	N	8	6	6	8
DAY 29	MEAN	9.9	10.2	10.1	8.9
WEEK 5	ST.DEV.	1.1	1.0	0.7	0.9
	N	8	6	6	8
DAY 36	MEAN	10.0	10.2	10.1	8.8 *
WEEK 6	ST.DEV.	1.1	1.0	0.7	0.8
	N	8	6	6	8
DAY 43	MEAN	10.1	10.2	10.1	8.7 *
WEEK 7	ST.DEV.	1.1	1.0	0.7	0.8
	N	8	6	6	8
DAY 50	MEAN	10.2	10.2	10.1	8.8 *
WEEK 8	ST.DEV.	1.1	1.1	0.8	0.9
	N	8	6	6	8
DAY 57	MEAN	10.3	10.2	10.0	8.7 *
WEEK 9	ST.DEV.	1.1	1.1	0.9	0.8
	N	8	6	6	8
DAY 64	MEAN	10.2	10.2	10.2	8.9 *
WEEK 10	ST.DEV.	1.2	1.1	0.9	0.8
	N	8	6	6	8
DAY 71	MEAN	10.3	10.2	10.1	8.7 *
WEEK 11	ST.DEV.	1.2	1.2	0.9	0.8
	N	8	6	6	8
DAY 78	MEAN	10.5	10.4	10.2	8.9 **
WEEK 12	ST.DEV.	1.2	1.0	0.9	0.8
	N	8	6	6	8
DAY 85	MEAN	10.6	10.4	10.4	9.0 **
WEEK 13	ST.DEV.	1.2	1.0	0.9	0.8
	N	8	6	6	8
DAY 92	MEAN	10.7	10.4	10.4	8.9 **
WEEK 14	ST.DEV.	1.2	0.9	0.9	0.9
	N	8	6	6	8
DAY 99	MEAN	10.8	10.7	10.5	9.0 **
WEEK 15	ST.DEV.	1.1	0.9	0.8	0.9
	N	8	6	6	8
DAY 106	MEAN	10.9	10.7	10.6	9.1 **
WEEK 16	ST.DEV.	1.2	0.8	0.8	0.8
	N	8	6	6	8
DAY 113	MEAN	11.1	10.8	10.6	9.2 **
WEEK 17	ST.DEV.	1.2	0.8	0.9	0.9
	N	8	6	6	8

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

BODY WEIGHTS (KG) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 120	MEAN	11.1	10.9	10.6	9.1 **
WEEK 18	ST.DEV.	1.1	0.8	0.8	0.9
	N	8	6	6	8
DAY 127	MEAN	11.0	10.9	10.7	9.1 **
WEEK 19	ST.DEV.	1.2	0.8	0.8	0.9
	N	8	6	6	8
DAY 134	MEAN	11.1	10.8	10.7	9.2 **
WEEK 20	ST.DEV.	1.2	0.9	0.8	0.8
	N	8	6	6	8
DAY 141	MEAN	11.2	10.8	10.7	9.2 **
WEEK 21	ST.DEV.	1.2	1.0	0.8	0.8
	N	8	6	6	8
DAY 148	MEAN	11.1	10.8	10.8	9.2 **
WEEK 22	ST.DEV.	1.2	0.9	0.8	0.9
	N	8	6	6	8
DAY 155	MEAN	11.3	10.9	10.8	9.3 **
WEEK 23	ST.DEV.	1.2	0.9	0.7	0.8
	N	8	6	6	8
DAY 162	MEAN	11.3	10.9	10.8	9.3 **
WEEK 24	ST.DEV.	1.2	0.9	0.8	0.8
	N	8	6	6	8
DAY 169	MEAN	11.3	10.9	10.8	9.2 **
WEEK 25	ST.DEV.	1.2	0.9	0.8	0.8
	N	8	6	6	8
DAY 176	MEAN	11.2	10.8	10.8	9.2 **
WEEK 26	ST.DEV.	1.2	0.9	0.8	0.7
	N	8	6	6	8
DAY 183	MEAN	11.4	10.9	10.9	9.3 **
WEEK 27	ST.DEV.	1.2	1.0	0.9	0.8
	N	8	6	6	8
DAY 190	MEAN	11.2	11.0	11.0	9.1 **
WEEK 28	ST.DEV.	1.3	1.1	0.9	0.8
	N	6	4	4	6
DAY 197	MEAN	11.3	11.1	11.1	9.1 **
WEEK 29	ST.DEV.	1.4	1.0	0.9	0.8
	N	6	4	4	6
DAY 204	MEAN	11.3	11.1	11.2	9.1 *
WEEK 30	ST.DEV.	1.4	1.1	1.0	0.8
	N	6	4	4	6
DAY 211	MEAN	11.3	11.1	11.1	9.2 *
WEEK 31	ST.DEV.	1.4	1.2	0.9	0.8
	N	6	4	4	6
DAY 218	MEAN	11.5	11.0	11.2	9.2 **
WEEK 32	ST.DEV.	1.3	1.1	0.8	0.8
	N	6	4	4	6
DAY 225	MEAN	11.3	11.0	10.9	9.1 **
WEEK 33	ST.DEV.	1.3	1.1	1.0	0.9
	N	6	4	4	6
DAY 232	MEAN	11.5	11.1	11.1	9.3 **
WEEK 34	ST.DEV.	1.3	1.1	1.1	0.7
	N	6	4	4	6

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

BODY WEIGHTS (KG) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 239	MEAN	11.5	11.1	11.1	9.4 *
WEEK 35	ST.DEV.	1.4	1.1	1.0	0.8
	N	6	4	4	6
DAY 246	MEAN	11.6	11.3	11.1	9.4 *
WEEK 36	ST.DEV.	1.4	1.2	1.1	0.8
	N	6	4	4	6
DAY 253	MEAN	11.7	11.3	11.2	9.5 *
WEEK 37	ST.DEV.	1.4	1.2	1.0	0.8
	N	6	4	4	6
DAY 260	MEAN	11.6	11.1	11.3	9.5 *
WEEK 38	ST.DEV.	1.5	1.0	0.9	0.8
	N	6	4	4	6
DAY 267	MEAN	11.7	11.2	11.4	9.5 **
WEEK 39	ST.DEV.	1.5	1.0	1.0	0.8
	N	6	4	4	6
DAY 274	MEAN	11.8	11.2	11.3	9.5 **
WEEK 40	ST.DEV.	1.5	1.2	0.9	0.8
	N	6	4	4	6
DAY 281	MEAN	11.8	11.3	11.2	9.6 *
WEEK 41	ST.DEV.	1.5	1.2	1.0	0.8
	N	6	4	4	6
DAY 288	MEAN	11.9	11.3	11.3	9.7 *
WEEK 42	ST.DEV.	1.4	1.3	0.9	0.9
	N	6	4	4	6
DAY 295	MEAN	12.0	11.3	11.3	9.8 *
WEEK 43	ST.DEV.	1.5	1.3	0.9	0.8
	N	6	4	4	6
DAY 302	MEAN	11.9	11.1	11.3	9.7 *
WEEK 44	ST.DEV.	1.5	1.2	1.0	0.8
	N	6	4	4	6
DAY 309	MEAN	12.0	11.1	11.4	9.7 **
WEEK 45	ST.DEV.	1.5	1.2	0.9	0.7
	N	6	4	4	6
DAY 316	MEAN	11.9	11.2	11.2	9.7 **
WEEK 46	ST.DEV.	1.5	1.1	0.9	0.8
	N	6	4	4	6
DAY 323	MEAN	12.0	11.1	11.3	9.7 *
WEEK 47	ST.DEV.	1.6	1.1	1.0	0.9
	N	6	4	4	6
DAY 330	MEAN	12.0	11.0	11.3	9.6 **
WEEK 48	ST.DEV.	1.6	1.1	0.9	0.8
	N	6	4	4	6
DAY 337	MEAN	11.9	11.0	11.4	9.5 **
WEEK 49	ST.DEV.	1.6	1.0	0.9	0.8
	N	6	4	4	6
DAY 344	MEAN	11.9	11.0	11.4	9.6 *
WEEK 50	ST.DEV.	1.6	1.1	0.9	0.8
	N	6	4	4	6
DAY 351	MEAN	11.9	11.1	11.4	9.6 **
WEEK 51	ST.DEV.	1.7	1.0	0.9	0.8
	N	6	4	4	6

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

BODY WEIGHTS (KG) SUMMARY
MALES

TREATMENT			GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 358		MEAN	11.8	11.0	11.2	9.5 *
WEEK 52		ST.DEV.	1.8	0.8	0.8	0.8
		N	6	4	4	6
DAY 364		MEAN	11.8	11.0	11.4	9.5 *
WEEK 52		ST.DEV.	1.8	1.0	0.8	0.8
		N	6	4	4	6

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

BODY WEIGHTS (KG) SUMMARY
MALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 1 WEEK 1	MEAN	12.1	---	---	9.4
	ST.DEV.	2.7			1.5
	N	2			2
DAY 8 WEEK 2	MEAN	12.4	---	---	9.8
	ST.DEV.	2.4			1.2
	N	2			2
DAY 15 WEEK 3	MEAN	12.4	---	---	10.0
	ST.DEV.	2.3			1.1
	N	2			2
DAY 22 WEEK 4	MEAN	12.5	---	---	10.2
	ST.DEV.	2.2			1.0
	N	2			2
DAY 29 WEEK 5	MEAN	12.4	---	---	10.3
	ST.DEV.	2.3			0.9
	N	2			2
DAY 36 WEEK 6	MEAN	12.4	---	---	10.3
	ST.DEV.	2.4			0.8
	N	2			2
DAY 43 WEEK 7	MEAN	12.5	---	---	10.4
	ST.DEV.	2.2			0.8
	N	2			2
DAY 50 WEEK 8	MEAN	12.4	---	---	10.5
	ST.DEV.	2.3			0.8
	N	2			2
DAY 56 WEEK 8	MEAN	12.5	---	---	10.5
	ST.DEV.	2.2			0.6
	N	2			2

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

BODY WEIGHTS (KG) SUMMARY
FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	7.8	8.1	8.0	8.3
WEEK 1	ST.DEV.	1.2	1.4	0.5	0.9
	N	8	6	6	8

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

BODY WEIGHTS (KG) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	7.9	8.2	8.2	8.5
WEEK 1	ST.DEV.	1.2	1.2	0.6	0.9
	N	8	6	6	8
DAY 8	MEAN	7.9	8.2	8.2	8.6
WEEK 2	ST.DEV.	1.2	1.3	0.5	0.9
	N	8	6	6	8
DAY 15	MEAN	8.0	8.2	8.1	8.6
WEEK 3	ST.DEV.	1.2	1.2	0.6	0.9
	N	8	6	6	8
DAY 22	MEAN	8.1	8.3	8.3	8.6
WEEK 4	ST.DEV.	1.2	1.2	0.6	0.9
	N	8	6	6	8
DAY 29	MEAN	8.2	8.4	8.4	8.5
WEEK 5	ST.DEV.	1.2	1.3	0.5	0.8
	N	8	6	6	8
DAY 36	MEAN	8.3	8.4	8.4	8.5
WEEK 6	ST.DEV.	1.2	1.4	0.6	0.9
	N	8	6	6	8
DAY 43	MEAN	8.1	8.4	8.4	8.3
WEEK 7	ST.DEV.	1.2	1.2	0.5	0.8
	N	8	6	6	8
DAY 50	MEAN	8.2	8.5	8.4	8.3
WEEK 8	ST.DEV.	1.1	1.3	0.7	0.9
	N	8	6	6	8
DAY 57	MEAN	8.2	8.5	8.4	8.4
WEEK 9	ST.DEV.	1.1	1.3	0.7	0.9
	N	8	6	6	8
DAY 64	MEAN	8.3	8.6	8.4	8.4
WEEK 10	ST.DEV.	1.1	1.3	0.5	1.0
	N	8	6	6	8
DAY 71	MEAN	8.2	8.6	8.6	8.5
WEEK 11	ST.DEV.	1.2	1.2	0.6	1.0
	N	8	6	6	8
DAY 78	MEAN	8.3	8.7	8.7	8.6
WEEK 12	ST.DEV.	1.2	1.3	0.6	1.1
	N	8	6	6	8
DAY 85	MEAN	8.5	8.9	8.8	8.7
WEEK 13	ST.DEV.	1.2	1.3	0.6	1.2
	N	8	6	6	8
DAY 92	MEAN	8.4	8.9	8.5	8.5
WEEK 14	ST.DEV.	1.4	1.3	0.8	1.4
	N	8	6	6	8
DAY 99	MEAN	8.7	9.1	8.5	8.7
WEEK 15	ST.DEV.	1.3	1.3	0.5	1.3
	N	8	6	6	8
DAY 106	MEAN	8.7	9.0	8.6	8.8
WEEK 16	ST.DEV.	1.3	1.3	0.6	1.2
	N	8	6	6	8
DAY 113	MEAN	8.8	9.1	8.7	8.9
WEEK 17	ST.DEV.	1.3	1.3	0.7	1.2
	N	8	6	6	8

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

BODY WEIGHTS (KG) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 120	MEAN	8.8	9.2	8.7	9.0
WEEK 18	ST.DEV.	1.4	1.3	0.7	1.1
	N	8	6	6	8
DAY 127	MEAN	8.7	9.2	8.8	9.0
WEEK 19	ST.DEV.	1.4	1.4	0.6	1.0
	N	8	6	6	8
DAY 134	MEAN	8.8	9.2	8.6	9.1
WEEK 20	ST.DEV.	1.5	1.3	0.8	1.0
	N	8	6	6	8
DAY 141	MEAN	8.9	9.2	8.6	9.2
WEEK 21	ST.DEV.	1.5	1.2	0.8	0.9
	N	8	6	6	8
DAY 148	MEAN	8.9	9.1	8.6	9.1
WEEK 22	ST.DEV.	1.6	1.3	0.8	0.9
	N	8	6	6	8
DAY 155	MEAN	9.0	9.3	8.7	9.3
WEEK 23	ST.DEV.	1.6	1.3	0.9	0.9
	N	8	6	6	8
DAY 162	MEAN	9.1	9.2	8.8	9.3
WEEK 24	ST.DEV.	1.7	1.4	0.9	1.0
	N	8	6	6	8
DAY 169	MEAN	9.0	9.1	8.8	9.3
WEEK 25	ST.DEV.	1.7	1.5	0.8	1.0
	N	8	6	6	8
DAY 176	MEAN	8.9	9.0	8.7	9.4
WEEK 26	ST.DEV.	1.8	1.4	0.8	0.9
	N	8	6	6	8
DAY 183	MEAN	9.1	9.1	8.8	9.4
WEEK 27	ST.DEV.	1.9	1.3	0.9	1.0
	N	8	6	6	8
DAY 190	MEAN	9.4	9.5	8.5	9.8
WEEK 28	ST.DEV.	2.0	0.9	0.6	0.9
	N	6	4	4	6
DAY 197	MEAN	9.4	9.6	8.5	9.8
WEEK 29	ST.DEV.	2.0	0.9	0.5	0.9
	N	6	4	4	6
DAY 204	MEAN	9.5	9.7	8.7	10.0
WEEK 30	ST.DEV.	2.0	0.9	0.6	1.0
	N	6	4	4	6
DAY 211	MEAN	9.4	9.8	8.7	9.9
WEEK 31	ST.DEV.	1.9	1.0	0.7	1.0
	N	6	4	4	6
DAY 218	MEAN	9.3	9.8	8.8	9.8
WEEK 32	ST.DEV.	1.8	0.9	0.6	1.1
	N	6	4	4	6
DAY 225	MEAN	9.4	9.9	8.7	9.6
WEEK 33	ST.DEV.	1.8	1.0	0.6	1.3
	N	6	4	4	6
DAY 232	MEAN	9.6	10.0	8.7	9.7
WEEK 34	ST.DEV.	1.8	1.1	0.5	1.3
	N	6	4	4	6

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

BODY WEIGHTS (KG) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 239	MEAN	9.6	10.2	8.8	9.8
WEEK 35	ST.DEV.	1.9	1.1	0.6	1.2
	N	6	4	4	6
DAY 246	MEAN	9.6	10.2	8.8	9.9
WEEK 36	ST.DEV.	1.9	1.1	0.7	1.2
	N	6	4	4	6
DAY 253	MEAN	9.6	10.3	8.8	10.1
WEEK 37	ST.DEV.	2.0	1.1	0.7	1.0
	N	6	4	4	6
DAY 260	MEAN	9.5	10.3	8.8	10.1
WEEK 38	ST.DEV.	2.0	1.1	0.7	1.0
	N	6	4	4	6
DAY 267	MEAN	9.6	10.2	8.8	10.0
WEEK 39	ST.DEV.	2.0	1.0	0.7	1.2
	N	6	4	4	6
DAY 274	MEAN	9.7	10.3	8.8	10.1
WEEK 40	ST.DEV.	2.1	0.9	0.9	1.2
	N	6	4	4	6
DAY 281	MEAN	9.7	10.5	8.9	10.1
WEEK 41	ST.DEV.	2.1	1.1	0.8	1.2
	N	6	4	4	6
DAY 288	MEAN	9.7	10.5	9.1	9.7
WEEK 42	ST.DEV.	2.4	1.0	0.5	1.3
	N	6	4	4	6
DAY 295	MEAN	9.6	10.6	8.9	9.7
WEEK 43	ST.DEV.	2.2	1.0	0.3	1.6
	N	6	4	4	6
DAY 302	MEAN	9.6	10.4	8.7	9.7
WEEK 44	ST.DEV.	2.2	0.7	0.5	1.9
	N	6	4	4	6
DAY 309	MEAN	9.5	10.1	8.4	9.4
WEEK 45	ST.DEV.	2.3	0.7	0.6	2.1
	N	6	4	4	6
DAY 316	MEAN	9.5	10.0	8.5	9.4
WEEK 46	ST.DEV.	2.2	0.4	0.6	1.9
	N	6	4	4	6
DAY 323	MEAN	9.4	10.1	8.7	9.5
WEEK 47	ST.DEV.	2.3	0.5	0.6	1.6
	N	6	4	4	6
DAY 330	MEAN	9.4	10.1	8.7	9.6
WEEK 48	ST.DEV.	2.4	0.6	0.6	1.5
	N	6	4	4	6
DAY 337	MEAN	9.3	10.2	8.9	9.7
WEEK 49	ST.DEV.	2.3	0.7	0.7	1.3
	N	6	4	4	6
DAY 344	MEAN	9.2	10.1	8.7	9.8
WEEK 50	ST.DEV.	2.3	0.7	0.5	1.3
	N	6	4	4	6
DAY 351	MEAN	9.2	10.1	8.8	10.0
WEEK 51	ST.DEV.	2.5	0.7	0.7	1.4
	N	6	4	4	6

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

BODY WEIGHTS (KG) SUMMARY
FEMALES

TREATMENT			GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY	358	MEAN	9.2	9.9	8.7	9.9
WEEK	52	ST.DEV.	2.3	0.8	0.8	1.3
		N	6	4	4	6
DAY	364	MEAN	9.5	10.0	8.7	10.1
WEEK	52	ST.DEV.	2.3	0.5	0.8	1.3
		N	6	4	4	6

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

BODY WEIGHTS (KG) SUMMARY
FEMALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
DAY 1	MEAN	8.7	---	---	9.6
WEEK 1	ST.DEV.	2.1			0.4
	N	2			2
DAY 8	MEAN	8.8	---	---	9.6
WEEK 2	ST.DEV.	1.8			0.4
	N	2			2
DAY 15	MEAN	9.1	---	---	9.6
WEEK 3	ST.DEV.	1.6			0.2
	N	2			2
DAY 22	MEAN	9.3	---	---	9.8
WEEK 4	ST.DEV.	1.6			0.4
	N	2			2
DAY 29	MEAN	9.2	---	---	9.8
WEEK 5	ST.DEV.	1.5			1.0
	N	2			2
DAY 36	MEAN	9.2	---	---	9.8
WEEK 6	ST.DEV.	1.4			0.9
	N	2			2
DAY 43	MEAN	9.1	---	---	9.8
WEEK 7	ST.DEV.	1.3			1.0
	N	2			2
DAY 50	MEAN	9.2	---	---	9.8
WEEK 8	ST.DEV.	1.4			1.0
	N	2			2
DAY 56	MEAN	9.5	---	---	9.8
WEEK 8	ST.DEV.	1.2			1.1
	N	2			2

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

ELECTROCARDIOGRAMS SUMMARY
PRETEST
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Pretest	MEAN	130	123	137	125
	ST.DEV.	37	27	22	21
	N	8	6	6	8
P AMPLITUDE (msec)					
Pretest	MEAN	0.31	0.29	0.29	0.32
	ST.DEV.	0.05	0.06	0.02	0.09
	N	8	6	6	8
P DURATION (msec)					
Pretest	MEAN	35	33	34	36
	ST.DEV.	5	4	5	3
	N	8	6	6	8
P-Q INTERVAL (msec)					
Pretest	MEAN	84	89	81	89
	ST.DEV.	8	11	9	9
	N	8	6	6	8
QRS INTERVAL (msec)					
Pretest	MEAN	33	31	33	33
	ST.DEV.	4	2	3	4
	N	8	6	6	8
Q-T INTERVAL (msec)					
Pretest	MEAN	173	185	174	171
	ST.DEV.	18	9	6	11
	N	8	6	6	8

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

ELECTROCARDIOGRAMS SUMMARY
PRETEST
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Pretest	MEAN	139	115	152	148
	ST.DEV.	18	23	29	24
	N	8	6	6	8
P AMPLITUDE (msec)					
Pretest	MEAN	0.39	0.31	0.33	0.34
	ST.DEV.	0.08	0.08	0.09	0.07
	N	8	6	6	8
P DURATION (msec)					
Pretest	MEAN	34	32	36	33
	ST.DEV.	4	3	2	4
	N	8	6	6	8
P-Q INTERVAL (msec)					
Pretest	MEAN	89	88	83	83
	ST.DEV.	6	8	4	7
	N	8	6	6	8
QRS INTERVAL (msec)					
Pretest	MEAN	33	31	32	32
	ST.DEV.	4	2	3	3
	N	8	6	6	8
Q-T INTERVAL (msec)					
Pretest	MEAN	174	178	167	173
	ST.DEV.	12	8	8	14
	N	8	6	6	8

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

ELECTROCARDIOGRAMS SUMMARY
13 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Before dosing	MEAN	129	130	125	125
	ST.DEV.	33	24	36	21
	N	8	6	6	8
3 h after dosing	MEAN	144	130	130	124
	ST.DEV.	12	30	32	23
	N	8	6	6	8
P AMPLITUDE (msec)					
Before dosing	MEAN	0.31	0.28	0.29	0.32
	ST.DEV.	0.06	0.08	0.02	0.13
	N	8	6	6	8
3 h after dosing	MEAN	0.38	0.30	0.28	0.34
	ST.DEV.	0.08	0.07	0.07	0.13
	N	8	6	6	8
P DURATION (msec)					
Before dosing	MEAN	34	38	33	36
	ST.DEV.	4	3	4	4
	N	8	6	6	8
3 h after dosing	MEAN	34	35	35	35
	ST.DEV.	5	3	4	4
	N	8	6	6	8
P-Q INTERVAL (msec)					
Before dosing	MEAN	83	91	82	93
	ST.DEV.	8	8	10	14
	N	8	6	6	8
3 h after dosing	MEAN	80	89	81	90
	ST.DEV.	5	10	9	10
	N	8	6	6	8
QRS INTERVAL (msec)					
Before dosing	MEAN	31	30	33	32
	ST.DEV.	2	0	4	4
	N	8	6	6	8
3 h after dosing	MEAN	31	32	34	33
	ST.DEV.	2	3	5	5
	N	8	6	6	8
Q-T INTERVAL (msec)					
Before dosing	MEAN	176	178	179	171
	ST.DEV.	13	13	10	12
	N	8	6	6	8
3 h after dosing	MEAN	174	180	180	171
	ST.DEV.	10	13	8	11
	N	8	6	6	8

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

ELECTROCARDIOGRAMS SUMMARY
13 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Before dosing	MEAN	141	108	147	114
	ST.DEV.	26	28	27	29
	N	8	6	6	8
3 h after dosing	MEAN	153	102 **	128	111 **
	ST.DEV.	25	13	29	29
	N	8	6	6	8
P AMPLITUDE (msec)					
Before dosing	MEAN	0.36	0.25	0.29	0.31
	ST.DEV.	0.09	0.06	0.07	0.10
	N	8	6	6	8
3 h after dosing	MEAN	0.38	0.28	0.29	0.33
	ST.DEV.	0.10	0.07	0.09	0.08
	N	8	6	6	8
P DURATION (msec)					
Before dosing	MEAN	33	34	37	35
	ST.DEV.	5	4	4	5
	N	8	6	6	8
3 h after dosing	MEAN	34	35	37	34
	ST.DEV.	4	3	4	5
	N	8	6	6	8
P-Q INTERVAL (msec)					
Before dosing	MEAN	86	92	83	92
	ST.DEV.	6	8	5	11
	N	8	6	6	8
3 h after dosing	MEAN	84	90	84	91
	ST.DEV.	6	9	5	9
	N	8	6	6	8
QRS INTERVAL (msec)					
Before dosing	MEAN	32	30	33	34
	ST.DEV.	4	0	3	4
	N	8	6	6	8
3 h after dosing	MEAN	32	32	32	34
	ST.DEV.	4	3	3	4
	N	8	6	6	8
Q-T INTERVAL (msec)					
Before dosing	MEAN	164	180	166	183 *
	ST.DEV.	13	13	15	13
	N	8	6	6	8
3 h after dosing	MEAN	163	183 *	178	186 **
	ST.DEV.	11	10	14	13
	N	8	6	6	8

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

ELECTROCARDIOGRAMS SUMMARY
25 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Before dosing	MEAN	135	147	135	125
	ST.DEV.	23	18	23	26
	N	8	6	6	8
3 h after dosing	MEAN	145	142	103 *	124
	ST.DEV.	29	19	31	18
	N	8	6	6	8
P AMPLITUDE (msec)					
Before dosing	MEAN	0.38	0.33	0.28 *	0.33
	ST.DEV.	0.08	0.06	0.05	0.08
	N	8	6	6	8
3 h after dosing	MEAN	0.38	0.33	0.28	0.34
	ST.DEV.	0.09	0.05	0.04	0.11
	N	8	6	6	8
P DURATION (msec)					
Before dosing	MEAN	35	36	33	36
	ST.DEV.	5	5	4	5
	N	8	6	6	8
3 h after dosing	MEAN	35	37	33	36
	ST.DEV.	5	4	4	3
	N	8	6	6	8
P-Q INTERVAL (msec)					
Before dosing	MEAN	83	87	80	93
	ST.DEV.	8	9	8	13
	N	8	6	6	8
3 h after dosing	MEAN	84	88	83	93
	ST.DEV.	5	10	11	10
	N	8	6	6	8
QRS INTERVAL (msec)					
Before dosing	MEAN	32	30	32	31
	ST.DEV.	4	0	4	2
	N	8	6	6	8
3 h after dosing	MEAN	32	31	32	32
	ST.DEV.	4	2	4	4
	N	8	6	6	8
Q-T INTERVAL (msec)					
Before dosing	MEAN	178	175	178	176
	ST.DEV.	9	5	10	14
	N	8	6	6	8
3 h after dosing	MEAN	179	176	191 a	178
	ST.DEV.	12	9	10	18
	N	8	6	6	8

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

ELECTROCARDIOGRAMS SUMMARY
25 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Before dosing	MEAN	148	93 **	142	128
	ST.DEV.	24	27	15	28
	N	8	6	6	8
3 h after dosing	MEAN	158	100 **	123 *	125 *
	ST.DEV.	30	24	16	17
	N	8	6	6	8
P AMPLITUDE (msec)					
Before dosing	MEAN	0.35	0.26	0.30	0.29
	ST.DEV.	0.09	0.07	0.03	0.08
	N	8	6	6	8
3 h after dosing	MEAN	0.37	0.28 *	0.32	0.31
	ST.DEV.	0.08	0.04	0.04	0.09
	N	8	6	6	8
P DURATION (msec)					
Before dosing	MEAN	33	33	35	35
	ST.DEV.	4	4	3	4
	N	8	6	6	8
3 h after dosing	MEAN	35	33	35	34
	ST.DEV.	4	4	3	4
	N	8	6	6	8
P-Q INTERVAL (msec)					
Before dosing	MEAN	86	92	82	88
	ST.DEV.	8	7	7	9
	N	8	6	6	8
3 h after dosing	MEAN	86	89	85	94
	ST.DEV.	6	8	7	13
	N	8	6	6	8
QRS INTERVAL (msec)					
Before dosing	MEAN	32	31	32	32
	ST.DEV.	3	2	3	3
	N	8	6	6	8
3 h after dosing	MEAN	31	32	33	33
	ST.DEV.	2	3	3	3
	N	8	6	6	8
Q-T INTERVAL (msec)					
Before dosing	MEAN	167	186 *	171	181 *
	ST.DEV.	14	7	2	14
	N	8	6	6	8
3 h after dosing	MEAN	168	188 **	177	181
	ST.DEV.	13	9	9	11
	N	8	6	6	8

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

ELECTROCARDIOGRAMS SUMMARY
51 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Before dosing	MEAN	120	145	118	95
	ST.DEV.	28	21	29	27
	N	6	4	4	6
3 h after dosing	MEAN	122	140	125	110
	ST.DEV.	29	22	21	21
	N	6	4	4	6
P AMPLITUDE (msec)					
Before dosing	MEAN	0.38	0.36	0.33	0.30
	ST.DEV.	0.05	0.08	0.06	0.06
	N	6	4	4	6
3 h after dosing	MEAN	0.41	0.38	0.34	0.29 **
	ST.DEV.	0.06	0.05	0.08	0.04
	N	6	4	4	6
P DURATION (msec)					
Before dosing	MEAN	34	35	35	38
	ST.DEV.	5	4	4	3
	N	6	4	4	6
3 h after dosing	MEAN	35	35	36	35
	ST.DEV.	4	0	5	3
	N	6	4	4	6
P-Q INTERVAL (msec)					
Before dosing	MEAN	84	83	80	94
	ST.DEV.	5	10	14	9
	N	6	4	4	6
3 h after dosing	MEAN	87	89	80	93
	ST.DEV.	6	14	11	11
	N	6	4	4	6
QRS INTERVAL (msec)					
Before dosing	MEAN	31	33	31	33
	ST.DEV.	2	3	3	4
	N	6	4	4	6
3 h after dosing	MEAN	32	33	33	33
	ST.DEV.	3	3	3	4
	N	6	4	4	6
Q-T INTERVAL (msec)					
Before dosing	MEAN	182	178	185	187
	ST.DEV.	13	13	6	23
	N	6	4	4	6
3 h after dosing	MEAN	183	180	186	182
	ST.DEV.	16	14	15	18
	N	6	4	4	6

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

ELECTROCARDIOGRAMS SUMMARY
51 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)					
Before dosing	MEAN	145	108 *	135	128
	ST.DEV.	14	26	17	16
	N	6	4	4	6
3 h after dosing	MEAN	158	113 *	120	110 *
	ST.DEV.	32	29	22	14
	N	6	4	4	6
P AMPLITUDE (msec)					
Before dosing	MEAN	0.34	0.29	0.30	0.32
	ST.DEV.	0.08	0.09	0.07	0.05
	N	6	4	4	6
3 h after dosing	MEAN	0.39	0.31	0.29 *	0.30
	ST.DEV.	0.07	0.06	0.05	0.05
	N	6	4	4	6
P DURATION (msec)					
Before dosing	MEAN	31	30	36 *	33
	ST.DEV.	2	0	3	4
	N	6	4	4	6
3 h after dosing	MEAN	33	30	34	33
	ST.DEV.	4	0	5	4
	N	6	4	4	6
P-Q INTERVAL (msec)					
Before dosing	MEAN	90	86	81	92
	ST.DEV.	9	8	5	9
	N	6	4	4	6
3 h after dosing	MEAN	88	91	80	98
	ST.DEV.	11	9	4	12
	N	6	4	4	6
QRS INTERVAL (msec)					
Before dosing	MEAN	33	30	31	33
	ST.DEV.	3	0	3	3
	N	6	4	4	6
3 h after dosing	MEAN	35	33	33	31 *
	ST.DEV.	3	3	3	2
	N	6	4	4	6
Q-T INTERVAL (msec)					
Before dosing	MEAN	167	179	178	178
	ST.DEV.	14	6	5	4
	N	6	4	4	6
3 h after dosing	MEAN	168	181	175	179
	ST.DEV.	17	10	11	7
	N	6	4	4	6

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

ELECTROCARDIOGRAMS SUMMARY
8 WEEKS RECOVERY
MALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)			
Recovery	MEAN	130	120
	ST.DEV.	57	14
	N	2	2
P AMPLITUDE (msec)			
Recovery	MEAN	0.40	0.38
	ST.DEV.	0.14	0.11
	N	2	2
P DURATION (msec)			
Recovery	MEAN	35	33
	ST.DEV.	7	4
	N	2	2
P-Q INTERVAL (msec)			
Recovery	MEAN	85	85
	ST.DEV.	7	7
	N	2	2
QRS INTERVAL (msec)			
Recovery	MEAN	35	30
	ST.DEV.	0	0
	N	2	2
Q-T INTERVAL (msec)			
Recovery	MEAN	175	180
	ST.DEV.	21	0
	N	2	2

ELECTROCARDIOGRAMS SUMMARY
8 WEEKS RECOVERY
FEMALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
HEART RATE (bpm)			
Recovery	MEAN	135	120
	ST.DEV.	21	42
	N	2	2
P AMPLITUDE (msec)			
Recovery	MEAN	0.38	0.30
	ST.DEV.	0.04	0.07
	N	2	2
P DURATION (msec)			
Recovery	MEAN	35	35
	ST.DEV.	7	7
	N	2	2
P-Q INTERVAL (msec)			
Recovery	MEAN	93	90
	ST.DEV.	4	14
	N	2	2
QRS INTERVAL (msec)			
Recovery	MEAN	35	33
	ST.DEV.	7	4
	N	2	2
Q-T INTERVAL (msec)			
Recovery	MEAN	168	183
	ST.DEV.	4	18
	N	2	2

BLOOD PRESSURE SUMMARY
PRETEST
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)					
Pretest	MEAN	129	134	121	138
	ST.DEV.	19	16	16	18
	N	8	6	6	8

FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)					
Pretest	MEAN	130	133	137	137
	ST.DEV.	19	15	14	16
	N	8	6	6	8

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

BLOOD PRESSURE SUMMARY
25 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)					
Before dosing	MEAN	147	145	139	146
	ST.DEV.	19	18	19	26
	N	8	6	6	8
3 h after dosing	MEAN	155	141	158	162
	ST.DEV.	19	14	23	11
	N	8	6	6	8

FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)					
Before dosing	MEAN	130	132	149	115
	ST.DEV.	29	23	24	27
	N	8	6	6	8
3 h after dosing	MEAN	136	132	152	135
	ST.DEV.	31	31	10	22
	N	8	6	6	8

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

BLOOD PRESSURE SUMMARY
51 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)					
Before dosing	MEAN	141	143	143	136
	ST.DEV.	22	24	27	18
	N	6	4	4	6
3 h after dosing	MEAN	146	153	157	148
	ST.DEV.	8	14	25	34
	N	6	4	4	6

FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)					
Before dosing	MEAN	144	147	146	142
	ST.DEV.	15	24	12	26
	N	6	4	4	6
3 h after dosing	MEAN	143	151	147	133
	ST.DEV.	20	10	16	11
	N	6	4	4	6

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.
a/b: t-test significant at 5% or 1% level; before dosing vs. after dosing.

BLOOD PRESSURE SUMMARY
8 WEEKS RECOVERY
MALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)			
Recovery	MEAN	137	143
	ST.DEV.	39	34
	N	2	2

FEMALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BLOOD PRESSURE (mmHg)			
Recovery	MEAN	125	126
	ST.DEV.	35	7
	N	2	2

HEMATOLOGY SUMMARY
MALES

		RBC T/l	HB mmol/l	HCT l/l	MCV fl	MCH fmol	MCHC mmol/l	PLATELETS G/l
PRETEST								
1	0 MG/KG	6.69	9.5	0.44	66.0	1.42	21.5	336
2	200 MG/KG	6.31	8.8	0.41	65.2	1.40	21.4	319
3	400 MG/KG	6.89	9.8	0.45	65.9	1.42	21.6	290
4	800 MG/KG	6.43	9.1	0.43	66.1	1.42	21.5	329
4 WEEKS								
1	0 MG/KG	6.69	9.5	0.45	66.7	1.42	21.3	360
2	200 MG/KG	6.37	9.0	0.42	65.6	1.40	21.4	328
3	400 MG/KG	6.55	9.3	0.44	66.7	1.42	21.2	309
4	800 MG/KG	6.42	9.1	0.43	67.5	1.42	21.0	395
13 WEEKS								
1	0 MG/KG	7.02	10.2	0.47	67.3	1.45	21.5	391
2	200 MG/KG	6.74	9.5	0.45	66.2	1.42	21.4	378
3	400 MG/KG	6.65	9.6	0.45	67.4	1.45	21.5	333
4	800 MG/KG	6.13 **	8.8 **	0.42 +	68.4	1.44	21.0 +	519
25 WEEKS								
1	0 MG/KG	7.70	10.9	0.52	67.1	1.41	21.0	358
2	200 MG/KG	7.25	10.1	0.51	70.3	1.39	19.7	337
3	400 MG/KG	7.24	10.2	0.49	68.3	1.41	20.7	306
4	800 MG/KG	6.63 **	9.3 **	0.46 +	69.0	1.40	20.3	504 *
51 WEEKS								
1	0 MG/KG	7.72	11.0	0.53	69.4	1.43	20.6	403
2	200 MG/KG	7.61	10.6	0.52	68.1	1.39	20.4	364
3	400 MG/KG	7.39	10.4	0.51	68.9	1.40	20.4	370
4	800 MG/KG	6.69 **	9.5 **	0.47 +	70.3	1.41	20.1	476
8 WEEKS RECOVERY								
1	0 MG/KG	7.73	11.5	0.53	68.7	1.48	21.6	321
4	800 MG/KG	6.61	9.7	0.45	68.0	1.46	21.5	417

		RETICULOCYTE COUNT						
		RETIC. %	RETIC. T/l	HFR. %	MFR. %	LFR. %	NEN /100 WBC	WBC G/l
PRETEST								
1	0 MG/KG	1.01	0.0659	3.7	13.5	82.8	0.0	11.8
2	200 MG/KG	0.99	0.0606	4.3	14.6	81.2	0.0	11.2
3	400 MG/KG	0.77	0.0511	1.9	9.4	88.7 +	0.2	11.2
4	800 MG/KG	1.10	0.0691	3.3	12.6	84.2	0.1	10.0
4 WEEKS								
1	0 MG/KG	1.04	0.0685	2.1	12.7	85.2	0.0	13.0
2	200 MG/KG	0.96	0.0610	2.8	13.8	83.4	0.2	10.2
3	400 MG/KG	0.69 +	0.0444 *	2.7	9.2	88.1	0.2	10.9
4	800 MG/KG	0.88	0.0558	1.8	15.5	82.7	0.3	10.0
13 WEEKS								
1	0 MG/KG	1.31	0.0929	6.2	20.1	73.7	0.0	13.3
2	200 MG/KG	1.39	0.0940	6.2	21.0	72.9	0.0	11.9
3	400 MG/KG	0.85	0.0563 *	5.5	12.2 +	82.3	0.2	10.5
4	800 MG/KG	1.39	0.0847	6.3	19.8	73.9	0.0	10.7
25 WEEKS								
1	0 MG/KG	1.13	0.0835	7.6	18.6	73.9	0.0	11.7
2	200 MG/KG	0.91	0.0640	5.8	16.5	77.7	0.3	12.2
3	400 MG/KG	0.73 +	0.0509 *	5.7	12.6	81.7	0.3	9.7
4	800 MG/KG	1.11	0.0695	6.6	19.4	74.0	0.1	10.9

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

HEMATOLOGY SUMMARY
MALES

		RETICULOCYTE COUNT						
		RETIC. %	RETIC. T/l	HFR. %	MFR. %	LFR. %	MEN /100 WBC	WBC G/l
51 WEEKS								
1	0 MG/KG	1.23	0.0865	3.0	16.3	80.7	0.2	10.6
2	200 MG/KG	1.10	0.0782	2.7	18.6	78.7	0.0	11.1
3	400 MG/KG	0.86	0.0582	2.3	14.5	83.2	0.0	10.4
4	800 MG/KG	1.12	0.0688	3.0	19.8	77.3	0.2	11.6
8 WEEKS RECOVERY								
1	0 MG/KG	1.24	0.0919	2.8	15.0	82.3	0.0	9.1
4	800 MG/KG	0.65	0.0402	1.3	11.5	87.2	1.0	10.4

		DIFF.WBC COUNT (REL.)						
		BAND 1	SEG. 1	EO. 1	BASO. 1	LYMPH. 1	MONO. 1	PLAS. 1
PRETEST								
1	0 MG/KG	0.00	0.65	0.03	0.00	0.31	0.02	0.00
2	200 MG/KG	0.00	0.68	0.03	0.00	0.29	0.01	0.00
3	400 MG/KG	0.00	0.66	0.04	0.00	0.30	0.01	0.00
4	800 MG/KG	0.00	0.65	0.02	0.00	0.32	0.01	0.00
4 WEEKS								
1	0 MG/KG	0.00	0.70	0.02	0.00	0.26	0.01	0.00
2	200 MG/KG	0.00	0.68	0.02	0.00	0.29	0.01	0.00
3	400 MG/KG	0.00	0.72	0.03	0.00	0.24	0.01	0.00
4	800 MG/KG	0.00	0.67	0.03	0.00	0.29	0.01	0.00
13 WEEKS								
1	0 MG/KG	0.00	0.73	0.01	0.00	0.24	0.02	0.00
2	200 MG/KG	0.00	0.69	0.03	0.00	0.26	0.02	0.00
3	400 MG/KG	0.00	0.72	0.02	0.00	0.25	0.01	0.00
4	800 MG/KG	0.00	0.70	0.02	0.00	0.25	0.03	0.00
25 WEEKS								
1	0 MG/KG	0.00	0.62	0.02	0.00	0.34	0.01	0.00
2	200 MG/KG	0.00	0.66	0.02	0.00	0.30	0.02	0.00
3	400 MG/KG	0.00	0.56	0.06	0.00	0.36	0.02	0.00
4	800 MG/KG	0.00	0.60	0.02	0.00	0.37	0.01	0.00
51 WEEKS								
1	0 MG/KG	0.00	0.70	0.02	0.00	0.28	0.01	0.00
2	200 MG/KG	0.00	0.81	0.02	0.00	0.16	0.01	0.00
3	400 MG/KG	0.00	0.70	0.02	0.00	0.26	0.02	0.00
4	800 MG/KG	0.00	0.73	0.02	0.00	0.25	0.01	0.00
8 WEEKS RECOVERY								
1	0 MG/KG	0.00	0.68	0.04	0.00	0.27	0.02	0.00
4	800 MG/KG	0.00	0.70	0.02	0.00	0.28	0.01	0.00

		DIFF.WBC COUNT (REL.)	DIFF.WBC COUNT (ABS.)				
		OTHER 1	BAND G/l	SEG. G/l	EO. G/l	BASO. G/l	LYMPH. G/l
PRETEST							
1	0 MG/KG	0.00	0.0	7.7	0.4	0.0	3.5
2	200 MG/KG	0.00	0.0	7.6	0.3	0.0	3.2
3	400 MG/KG	0.00	0.0	7.3	0.4	0.0	3.4
4	800 MG/KG	0.00	0.0	6.4	0.2	0.0	3.2

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

HEMATOLOGY SUMMARY
MALES

	DIFF.WBC COUNT (REL.)	DIFF.WBC COUNT (ABS.)				
	OTHER 1	BAND G/l	SEG. G/l	EO. G/l	BASO. G/l	LYMPH. G/l
4 WEEKS						
1 0 MG/KG	0.00	0.0	9.3	0.3	0.0	3.2
2 200 MG/KG	0.00	0.0	7.0	0.2	0.0	2.9
3 400 MG/KG	0.00	0.0	7.9	0.3	0.0	2.6
4 800 MG/KG	0.00	0.0	6.7	0.3	0.0	2.9
13 WEEKS						
1 0 MG/KG	0.00	0.0	9.7	0.2	0.0	3.2
2 200 MG/KG	0.00	0.0	8.4	0.4	0.0	2.9
3 400 MG/KG	0.00	0.0	7.6	0.2	0.0	2.6
4 800 MG/KG	0.00	0.0	7.6	0.2	0.0	2.6
25 WEEKS						
1 0 MG/KG	0.00	0.0	7.5	0.3	0.0	3.8
2 200 MG/KG	0.00	0.0	8.2	0.2	0.0	3.6
3 400 MG/KG	0.00	0.0	5.4	0.5	0.0	3.5
4 800 MG/KG	0.00	0.0	6.6	0.2	0.0	4.0
51 WEEKS						
1 0 MG/KG	0.00	0.0	7.3	0.2	0.0	3.0
2 200 MG/KG	0.00	0.0	8.9	0.2	0.0	1.8
3 400 MG/KG	0.00	0.0	7.3	0.2	0.0	2.7
4 800 MG/KG	0.00	0.0	8.4	0.2	0.0	2.9
8 WEEKS RECOVERY						
1 0 MG/KG	0.00	0.0	6.2	0.3	0.0	2.4
4 800 MG/KG	0.00	0.0	7.2	0.2	0.0	2.9

	DIFF.WBC COUNT (ABS.)			COAGULATION		
	MONO. G/l	PLAS. G/l	OTHER G/l	PT SEC.	APTT SEC.	
PRETEST						
1 0 MG/KG	0.2	0.0	0.0	6.6	10.5	
2 200 MG/KG	0.1	0.0	0.0	6.4	10.7	
3 400 MG/KG	0.1	0.0	0.0	6.2	10.3	
4 800 MG/KG	0.1	0.0	0.0	6.6	10.6	
4 WEEKS						
1 0 MG/KG	0.2	0.0	0.0	6.6	10.3	
2 200 MG/KG	0.1	0.0	0.0	6.4	10.9	**
3 400 MG/KG	0.1	0.0	0.0	6.2	10.4	
4 800 MG/KG	0.1	0.0	0.0	6.5	10.6	
13 WEEKS						
1 0 MG/KG	0.2	0.0	0.0	6.6	10.4	
2 200 MG/KG	0.2	0.0	0.0	6.4	10.7	
3 400 MG/KG	0.1	0.0	0.0	6.2	10.6	
4 800 MG/KG	0.3	0.0	0.0	6.5	10.7	
25 WEEKS						
1 0 MG/KG	0.1	0.0	0.0	6.3	10.7	
2 200 MG/KG	0.2	0.0	0.0	6.3	10.7	
3 400 MG/KG	0.2	0.0	0.0	6.3	10.5	
4 800 MG/KG	0.1	0.0	0.0	6.3	11.1	
51 WEEKS						
1 0 MG/KG	0.1	0.0	0.0	6.4	10.3	
2 200 MG/KG	0.1	0.0	0.0	6.5	10.7	
3 400 MG/KG	0.2	0.0	0.0	6.3	10.6	
4 800 MG/KG	0.1	0.0	0.0	6.7	10.7	

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

HEMATOLOGY SUMMARY
MALES

	DIFF.WBC COUNT (ABS.)			COAGULATION	
	MONO. G/l	PLAS. G/l	OTHER G/l	PT SEC.	APTT SEC.
8 WEEKS RECOVERY					
1 0 MG/KG	0.1	0.0	0.0	6.4	10.0
4 800 MG/KG	0.1	0.0	0.0	6.3	10.4

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

HEMATOLOGY SUMMARY
FEMALES

	RBC T/l	HB mmol/l	HCT l/l	MCV fl	MCH fmol	MCHC mmol/l	PLATELETS G/l
PRETEST							
1 0 MG/KG	6.83	9.9	0.46	67.7	1.45	21.5	261
2 200 MG/KG	6.72	9.5	0.44	66.2	1.41	21.3	334
3 400 MG/KG	7.36	10.7	0.50	68.1	1.46	21.4	248
4 800 MG/KG	7.27	10.4	0.49	67.4	1.43	21.3	334
4 WEEKS							
1 0 MG/KG	7.14	10.0	0.48	67.7	1.40	20.8	305
2 200 MG/KG	6.73	9.5	0.45	66.5	1.41	21.3	369
3 400 MG/KG	7.24	10.4	0.49	68.4	1.44	21.1	308
4 800 MG/KG	7.09	10.1	0.48	67.9	1.43	21.0	361
13 WEEKS							
1 0 MG/KG	7.14	10.4	0.49	68.4	1.46	21.3	302
2 200 MG/KG	6.74	9.5	0.45	66.9	1.41	21.1	450 **
3 400 MG/KG	7.42	10.8	0.51	69.0	1.46	21.2	306
4 800 MG/KG	7.08	10.3	0.49	68.7	1.45	21.1	415 *
25 WEEKS							
1 0 MG/KG	7.53	10.7	0.52	69.4	1.43	20.6	303
2 200 MG/KG	7.29	10.3	0.50	68.2	1.41	20.7	390
3 400 MG/KG	7.74	11.1	0.53	68.9	1.44	20.8	304
4 800 MG/KG	7.33	10.3	0.50	68.6	1.40	20.5	420 **
51 WEEKS							
1 0 MG/KG	7.62	11.0	0.53	70.1	1.45	20.7	353
2 200 MG/KG	7.46	10.4	0.51	67.8	1.40	20.7	437
3 400 MG/KG	7.51	10.8	0.53	69.9	1.44	20.7	343
4 800 MG/KG	7.25	10.4	0.51	70.4	1.43	20.3	498
8 WEEKS RECOVERY							
1 0 MG/KG	6.31	9.9	0.46	72.4	1.56	21.6	257
4 800 MG/KG	7.80	11.1	0.51	65.7	1.42	21.7	373

	RETICULOCYTE COUNT						
	RETIC. %	RETIC. T/l	HFR. %	MFR. %	LFR. %	NEN /100 WBC	WBC G/l
PRETEST							
1 0 MG/KG	0.92	0.0628	3.3	13.3	83.5	0.0	11.0
2 200 MG/KG	0.91	0.0594	2.9	12.1	85.1	0.0	9.8
3 400 MG/KG	0.97	0.0694	3.2	10.8	86.0	0.0	9.1
4 800 MG/KG	1.12	0.0785	3.9	16.1	80.0	0.0	10.7
4 WEEKS							
1 0 MG/KG	1.04	0.0744	1.7	12.5	85.9	0.0	9.8
2 200 MG/KG	0.93	0.0619	1.9	13.2	84.9	0.3	11.1
3 400 MG/KG	0.77	0.0551	1.9	13.5	84.6	0.3	12.2
4 800 MG/KG	0.71	0.0498	1.4	13.5	85.1	0.1	11.0
13 WEEKS							
1 0 MG/KG	1.20	0.0865	4.7	16.5	78.9	0.1	11.6
2 200 MG/KG	0.79	0.0536	2.5 +	11.2	86.4 +	0.2	10.8
3 400 MG/KG	0.86	0.0628	3.9	15.8	80.3	0.0	8.8 *
4 800 MG/KG	1.14	0.0816	4.6	19.6	75.8	0.0	9.2
25 WEEKS							
1 0 MG/KG	0.71	0.0526	4.1	13.7	82.2	0.0	9.6
2 200 MG/KG	0.85	0.0596	3.8	12.7	83.5	0.0	8.4
3 400 MG/KG	0.75	0.0550	4.4	14.3	81.4	0.3	7.8
4 800 MG/KG	0.71	0.0504	3.1	15.3	81.7	0.1	9.0

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

HEMATOLOGY SUMMARY
FEMALES

		RETICULOCYTE COUNT						
		RETIC. %	RETIC. T/l	HFR. %	MFR. %	LFR. %	MEN /100 WBC	WBC G/l
51 WEEKS								
1	0 MG/KG	0.85	0.0620	2.2	12.7	85.2	0.0	9.3
2	200 MG/KG	0.71	0.0495	1.4	9.2	89.5	0.0	8.3
3	400 MG/KG	0.94	0.0653	1.8	13.8	84.4	0.3	8.8
4	800 MG/KG	0.74	0.0489	2.7	13.8	83.5	0.0	9.3
8 WEEKS RECOVERY								
1	0 MG/KG	0.91	0.0545	1.5	12.7	85.8	0.0	10.1
4	800 MG/KG	0.65	0.0493	1.9	8.2	90.0	0.0	7.7

		DIFF.WBC COUNT (REL.)						
		BAND 1	SEG. 1	EO. 1	BASO. 1	LYMPH. 1	MONO. 1	PLAS. 1
PRETEST								
1	0 MG/KG	0.00	0.70	0.03	0.00	0.26	0.02	0.00
2	200 MG/KG	0.00	0.67	0.02	0.00	0.30	0.01	0.00
3	400 MG/KG	0.00	0.73	0.01	0.00	0.25	0.01	0.00
4	800 MG/KG	0.00	0.65	0.02	0.00	0.32	0.01	0.00
4 WEEKS								
1	0 MG/KG	0.00	0.69	0.02	0.00	0.28	0.01	0.00
2	200 MG/KG	0.00	0.64	0.02	0.00	0.33	0.01	0.00
3	400 MG/KG	0.00	0.73	0.02	0.00	0.24	0.01	0.00
4	800 MG/KG	0.00	0.66	0.02	0.00	0.32	0.01	0.00
13 WEEKS								
1	0 MG/KG	0.00	0.73	0.02	0.00	0.23	0.02	0.00
2	200 MG/KG	0.00	0.70	0.02	0.00	0.24	0.04	0.00
3	400 MG/KG	0.00	0.65	0.04 +	0.00	0.29	0.02	0.00
4	800 MG/KG	0.00	0.62 +	0.03	0.00	0.31	0.04	0.00
25 WEEKS								
1	0 MG/KG	0.00	0.54	0.04	0.00	0.41	0.01	0.00
2	200 MG/KG	0.00	0.54	0.06	0.00	0.39	0.01	0.00
3	400 MG/KG	0.00	0.57	0.03	0.00	0.39	0.01	0.00
4	800 MG/KG	0.00	0.45	0.04	0.00	0.49	0.02	0.00
51 WEEKS								
1	0 MG/KG	0.00	0.71	0.02	0.00	0.26	0.02	0.00
2	200 MG/KG	0.00	0.69	0.03	0.00	0.27	0.01	0.00
3	400 MG/KG	0.00	0.70	0.02	0.00	0.29	0.01	0.00
4	800 MG/KG	0.00	0.68	0.01	0.00	0.30	0.01	0.00
8 WEEKS RECOVERY								
1	0 MG/KG	0.00	0.64	0.07	0.00	0.29	0.01	0.00
4	800 MG/KG	0.00	0.67	0.03	0.00	0.29	0.01	0.00

		DIFF.WBC COUNT (REL.)	DIFF.WBC COUNT (ABS.)				
		OTHER 1	BAND G/l	SEG. G/l	EO. G/l	BASO. G/l	LYMPH. G/l
PRETEST							
1	0 MG/KG	0.00	0.0	7.7	0.3	0.0	2.7
2	200 MG/KG	0.00	0.0	6.5	0.2	0.0	3.0
3	400 MG/KG	0.00	0.0	6.8	0.1	0.0	2.2
4	800 MG/KG	0.00	0.0	7.0	0.2	0.0	3.4

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

HEMATOLOGY SUMMARY
FEMALES

	DIFF.WBC COUNT (REL.)	DIFF.WBC COUNT (ABS.)				
	OTHER 1	BAND G/l	SEG. G/l	EO. G/l	BASO. G/l	LYMPH. G/l
4 WEEKS						
1 0 MG/KG	0.00	0.0	6.8	0.2	0.0	2.7
2 200 MG/KG	0.00	0.0	7.0	0.2	0.0	3.7
3 400 MG/KG	0.00	0.0	9.3	0.2	0.0	2.6
4 800 MG/KG	0.00	0.0	7.3	0.2	0.0	3.4
13 WEEKS						
1 0 MG/KG	0.00	0.0	8.5	0.2	0.0	2.6
2 200 MG/KG	0.00	0.0	7.7	0.2	0.0	2.5
3 400 MG/KG	0.00	0.0	5.7 *	0.3	0.0	2.6
4 800 MG/KG	0.00	0.0	5.8 *	0.2	0.0	2.9
25 WEEKS						
1 0 MG/KG	0.00	0.0	5.2	0.4	0.0	3.8
2 200 MG/KG	0.00	0.0	4.6	0.5	0.0	3.1
3 400 MG/KG	0.00	0.0	4.5	0.2	0.0	3.0
4 800 MG/KG	0.00	0.0	4.3	0.3	0.0	4.3
51 WEEKS						
1 0 MG/KG	0.00	0.0	6.6	0.2	0.0	2.3
2 200 MG/KG	0.00	0.0	5.8	0.2	0.0	2.2
3 400 MG/KG	0.00	0.0	6.1	0.1	0.0	2.5
4 800 MG/KG	0.00	0.0	6.7	0.1	0.0	2.4
8 WEEKS RECOVERY						
1 0 MG/KG	0.00	0.0	6.5	0.8	0.0	2.8
4 800 MG/KG	0.00	0.0	5.1	0.2	0.0	2.3

	DIFF.WBC COUNT (ABS.)			COAGULATION	
	MONO. G/l	PLAS. G/l	OTHER G/l	PT SEC.	APTT SEC.
PRETEST					
1 0 MG/KG	0.2	0.0	0.0	6.2	11.1
2 200 MG/KG	0.1	0.0	0.0	6.3	10.6
3 400 MG/KG	0.1	0.0	0.0	6.3	10.9
4 800 MG/KG	0.2	0.0	0.0	6.3	10.8
4 WEEKS					
1 0 MG/KG	0.1	0.0	0.0	6.2	11.2
2 200 MG/KG	0.1	0.0	0.0	6.3	10.9
3 400 MG/KG	0.2	0.0	0.0	6.2	10.8
4 800 MG/KG	0.1	0.0	0.0	6.3	11.0
13 WEEKS					
1 0 MG/KG	0.3	0.0	0.0	6.3	11.3
2 200 MG/KG	0.4	0.0	0.0	6.2	10.3
3 400 MG/KG	0.2	0.0	0.0	6.3	11.2
4 800 MG/KG	0.3	0.0	0.0	6.6	11.4
25 WEEKS					
1 0 MG/KG	0.1	0.0	0.0	6.2	11.7
2 200 MG/KG	0.1	0.0	0.0	6.3	11.0
3 400 MG/KG	0.1	0.0	0.0	6.3	11.3
4 800 MG/KG	0.1	0.0	0.0	6.3	11.0
51 WEEKS					
1 0 MG/KG	0.2	0.0	0.0	6.3	11.6
2 200 MG/KG	0.1	0.0	0.0	6.3	10.8
3 400 MG/KG	0.0	0.0	0.0	6.5	11.2
4 800 MG/KG	0.1	0.0	0.0	6.3	10.8

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

HEMATOLOGY SUMMARY
FEMALES

	DIFF.WBC COUNT (ABS.)			COAGULATION	
	MONO. G/l	PLAS. G/l	OTHER G/l	PT SEC.	APTT SEC.
8 WEEKS RECOVERY					
1 0 MG/KG	0.1	0.0	0.0	6.2	10.1
4 800 MG/KG	0.1	0.0	0.0	6.4	10.3

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

CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GLUCOSE mmol/l	UREA mmol/l	CREATININE umol/l	BILI. T. umol/l	LIPIDS T. g/l	CHOLEST.T. mmol/l	TRIGL. mmol/l
PRETEST								
1	0 MG/KG	5.63	4.25	62	3.6	3.1	3.46	0.46
2	200 MG/KG	5.68	4.06	66	3.9	2.9	3.37	0.36
3	400 MG/KG	5.59	4.36	64	4.0	2.8	3.21	0.37
4	800 MG/KG	5.60	4.42	59	4.0	2.8	3.11	0.36
4 WEEKS								
1	0 MG/KG	5.52	4.44	61	4.0	2.9	3.64	0.44
2	200 MG/KG	5.62	4.76	68	4.3	2.5	3.26	0.36
3	400 MG/KG	5.84	4.46	64	4.4	2.6	3.09	0.39
4	800 MG/KG	5.82	4.36	59	4.2	2.8	2.98 *	0.46
13 WEEKS								
1	0 MG/KG	5.72	5.10	69	3.9	3.7	3.73	0.51
2	200 MG/KG	5.49	4.79	70	4.7 *	3.1	3.35	0.41
3	400 MG/KG	5.70	5.33	70	4.3	3.3	2.95 *	0.47
4	800 MG/KG	5.39	5.43	61 *	3.9	3.8	3.15 *	0.57
25 WEEKS								
1	0 MG/KG	5.92	5.31	68	3.5	3.5	3.79	0.56
2	200 MG/KG	5.76	4.99	70	4.1	2.7	3.16	0.39
3	400 MG/KG	5.65	5.18	65	3.8	2.5	2.79 **	0.37
4	800 MG/KG	5.79	4.89	58	3.9	3.8	3.01 *	0.73
51 WEEKS								
1	0 MG/KG	5.64	4.88	74	3.6	2.7	2.97	0.56
2	200 MG/KG	5.42	4.29	71	4.5	2.3	2.68	0.46
3	400 MG/KG	5.46	5.73	79	4.1	1.9	2.25 *	0.35
4	800 MG/KG	5.53	4.89	60	4.1	2.6	2.23 *	0.73
8 WEEKS RECOVERY								
1	0 MG/KG	6.21	5.02	69	3.7	2.6	2.99	0.61
4	800 MG/KG	5.38	5.17	56	4.0	3.0	2.95	0.68

		PHOS.LIPID mmol/l	ASAT(GOT) ukat/l	ALAT(GPT) ukat/l	LDH ukat/l	GLDH nkat/l	CK ukat/l	ALP ukat/l
PRETEST								
1	0 MG/KG	3.92	0.51	0.52	1.15	93.3	3.41	4.63
2	200 MG/KG	3.89	0.52	0.50	1.11	44.9	3.51	4.38
3	400 MG/KG	3.68	0.49	0.45	0.96	59.6	2.91	4.85
4	800 MG/KG	3.56	0.55	0.52	1.14	54.8	3.42	4.56
4 WEEKS								
1	0 MG/KG	4.04	0.52	0.52	1.56	69.4	3.60	4.24
2	200 MG/KG	3.92	0.54	0.47	1.46	43.7	3.62	3.33
3	400 MG/KG	3.61	0.53	0.42	1.27	34.5	3.26	3.94
4	800 MG/KG	3.46	0.53	0.59	1.25	106.6	2.87	3.41
13 WEEKS								
1	0 MG/KG	4.23	0.37	0.44	1.18	53.2	2.96	3.37
2	200 MG/KG	4.02	0.49	0.49	1.40	36.7	2.71	3.09
3	400 MG/KG	3.59	0.45	0.46	1.16	38.3	2.28	3.04
4	800 MG/KG	3.77	0.35	0.46	1.52	55.6	2.26	2.79
25 WEEKS								
1	0 MG/KG	4.06	0.36	0.66	1.30	140.3	2.70	2.67
2	200 MG/KG	3.59	0.53 **	0.60	1.46	46.2	2.92	2.14
3	400 MG/KG	3.30 *	0.43	0.52	0.94	53.0	2.48	2.29
4	800 MG/KG	3.40	0.37	0.59	1.09	81.7	2.48	2.23

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

CLINICAL BIOCHEMISTRY SUMMARY
MALES

		PHOS.LIPID mmol/l	ASAT(GOT) ukat/l	ALAT(GPT) ukat/l	LDH ukat/l	GLDH nkat/l	CK ukat/l	ALP ukat/l
51 WEEKS								
1	0 MG/KG	3.42	0.43	0.48	1.71	44.3	2.67	1.91
2	200 MG/KG	3.15	0.62	0.75	1.58	44.0	2.17	1.97
3	400 MG/KG	2.85	0.54	0.70	1.10 *	63.0	2.07	1.75
4	800 MG/KG	2.60 *	0.58	0.71	1.28	132.7 **	2.40	2.07
8 WEEKS RECOVERY								
1	0 MG/KG	3.53	0.30	0.44	1.08	65.5	1.81	1.78
4	800 MG/KG	3.59	0.51	0.37	0.84	55.0	2.03	2.18

		G-GT nkat/l	IRON umol/l	CALCIUM mmol/l	PHOSPHORUS mmol/l	MAGNESIUM mmol/l	SODIUM mmol/l	POTASSIUM mmol/l
PRETEST								
1	0 MG/KG	31.33	32.66	2.73	1.99	0.77	141.9	4.33
2	200 MG/KG	35.97	28.28	2.79	2.04	0.77	142.4	4.38
3	400 MG/KG	35.26	32.08	2.80	2.01	0.82	141.3	4.36
4	800 MG/KG	34.49	38.59	2.74	1.90	0.80	142.1	4.35
4 WEEKS								
1	0 MG/KG	36.25	38.09	2.72	1.71	0.79	139.7	3.67
2	200 MG/KG	39.92	30.58	2.77	1.77	0.79	140.2	3.72
3	400 MG/KG	35.98	34.12	2.78	1.67	0.79	139.7	3.56
4	800 MG/KG	40.14	47.38 *	2.67	1.81	0.79	139.9	3.79
13 WEEKS								
1	0 MG/KG	37.93	43.19	2.72	1.58	0.77	144.7	4.28
2	200 MG/KG	39.53	31.88	2.73	1.60	0.77	143.3	4.07
3	400 MG/KG	32.67	28.43	2.72	1.55	0.81	145.3	4.07
4	800 MG/KG	32.89	43.56	2.62	1.68	0.79	143.2	4.08
25 WEEKS								
1	0 MG/KG	36.84	41.10	2.76	1.36	0.79	144.5	3.99
2	200 MG/KG	41.53	28.68 *	2.74	1.44	0.76	144.5	3.94
3	400 MG/KG	38.11	33.62	2.80	1.38	0.82	144.7	3.79
4	800 MG/KG	31.58	42.64	2.65 *	1.62 *	0.79	144.1	3.95
51 WEEKS								
1	0 MG/KG	31.29	36.76	2.50	1.16	0.78	152.9	4.08
2	200 MG/KG	43.03	31.17	2.60	1.30	0.76	154.6	3.90
3	400 MG/KG	40.45	26.42	2.64	1.14	0.83	154.5	3.87
4	800 MG/KG	33.59	35.62	2.49	1.46 **	0.79	150.0 *	3.97
8 WEEKS RECOVERY								
1	0 MG/KG	34.73	41.09	2.58	1.27	0.87	147.4	3.63
4	800 MG/KG	37.39	38.09	2.61	1.30	0.80	147.6	3.45

				PROT.ELECTROPH.(REL.)				
		CHLORIDE mmol/l	PROTEIN T. g/l	ALBUMIN 1	A1-GLOB. 1	A2-GLOB. 1	B1-GLOB. 1	B2-GLOB. 1
PRETEST								
1	0 MG/KG	119.1	56.0	0.448	0.151	0.091	0.127	0.136
2	200 MG/KG	118.0	55.9	0.442	0.151	0.086	0.121	0.144
3	400 MG/KG	116.8	57.6	0.439	0.149	0.089	0.121	0.140
4	800 MG/KG	119.0	56.6	0.484	0.146	0.071 +	0.118	0.132

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

CLINICAL BIOCHEMISTRY SUMMARY
MALES

		CHLORIDE mmol/l	PROTEIN T. g/l	PROT.ELECTROPH.(REL.) ALBUMIN 1	A1-GLOB. 1	A2-GLOB. 1	B1-GLOB. 1	B2-GLOB. 1
4 WEEKS								
1	0 MG/KG	116.3	58.0	0.459	0.140	0.098	0.123	0.132
2	200 MG/KG	117.4	57.7	0.471	0.137	0.086	0.110	0.138
3	400 MG/KG	118.0	59.5	0.475	0.132	0.095	0.112	0.127
4	800 MG/KG	120.6 **	58.2	0.481	0.131	0.082	0.113	0.139
13 WEEKS								
1	0 MG/KG	124.5	59.0	0.456	0.139	0.094	0.129	0.128
2	200 MG/KG	122.8	60.6	0.428	0.135	0.091	0.129	0.152 +
3	400 MG/KG	124.9	59.2	0.454	0.129	0.096	0.122	0.138
4	800 MG/KG	126.1	56.0	0.452	0.138	0.091	0.121	0.141
25 WEEKS								
1	0 MG/KG	123.4	57.6	0.458	0.141	0.104	0.114	0.130
2	200 MG/KG	122.0	58.9	0.444	0.127	0.096	0.110	0.157 +
3	400 MG/KG	122.2	58.7	0.453	0.128	0.099	0.111	0.144
4	800 MG/KG	124.6	55.5	0.433	0.136	0.099	0.118	0.153 +
51 WEEKS								
1	0 MG/KG	121.0	55.5	0.511	0.132	0.091	0.104	0.117
2	200 MG/KG	121.0	59.9	0.478	0.110	0.096	0.101	0.150
3	400 MG/KG	121.5	57.2	0.513	0.113	0.091	0.102	0.127
4	800 MG/KG	121.9	54.4	0.515	0.101 +	0.093	0.109	0.137
8 WEEKS RECOVERY								
1	0 MG/KG	127.5	54.9	0.503	0.131	0.102	0.104	0.116
4	800 MG/KG	124.2	56.7	0.486	0.133	0.090	0.110	0.127

		PROT.ELECTROPH.(REL.) SB-GLOB. 1	G-GLOB. 1	A/G RATIO	PROT.ELECTROPH.(ABS.) ALBUMIN g/l	A1-GLOB. g/l	A2-GLOB. g/l	B1-GLOB. g/l
PRETEST								
1	0 MG/KG	0.263	0.047	0.81	25.1	8.5	5.1	7.1
2	200 MG/KG	0.265	0.057	0.80	24.7	8.5	4.8	6.7
3	400 MG/KG	0.261	0.062 +	0.79	25.3	8.6	5.1	7.0
4	800 MG/KG	0.250	0.049	0.95	27.4	8.2	4.0 *	6.7
4 WEEKS								
1	0 MG/KG	0.254	0.048	0.85	26.6	8.1	5.7	7.1
2	200 MG/KG	0.247	0.058	0.90	27.2	7.9	5.0	6.3 *
3	400 MG/KG	0.238	0.061 +	0.91	28.3	7.8	5.6	6.6
4	800 MG/KG	0.253	0.055	0.93	27.9	7.6	4.8	6.6
13 WEEKS								
1	0 MG/KG	0.257	0.054	0.84	26.9	8.2	5.5	7.6
2	200 MG/KG	0.281	0.066	0.75	25.9	8.2	5.5	7.8
3	400 MG/KG	0.260	0.062	0.83	26.9	7.6	5.7	7.2
4	800 MG/KG	0.262	0.057	0.83	25.4	7.7	5.1	6.8
25 WEEKS								
1	0 MG/KG	0.244	0.054	0.85	26.4	8.1	6.0	6.6
2	200 MG/KG	0.267	0.067 +	0.80	26.2	7.5	5.7	6.4
3	400 MG/KG	0.255	0.064	0.84	26.6	7.6	5.8	6.5
4	800 MG/KG	0.270	0.062	0.77	24.1	7.6	5.5	6.5
51 WEEKS								
1	0 MG/KG	0.221	0.045	1.05	28.4	7.3	5.1	5.8
2	200 MG/KG	0.251	0.065	0.92	28.6	6.6	5.8	6.0
3	400 MG/KG	0.229	0.055	1.06	29.3	6.5	5.2	5.8
4	800 MG/KG	0.246	0.046	1.07	28.1	5.5 **	5.0	5.9

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

CLINICAL BIOCHEMISTRY SUMMARY
MALES

		PROT.ELECTROPH.(REL.)			PROT.ELECTROPH.(ABS.)			
		SB-GLOB. 1	G-GLOB. 1	A/G RATIO	ALBUMIN g/l	A1-GLOB. g/l	A2-GLOB. g/l	B1-GLOB. g/l
8 WEEKS RECOVERY								
1	0 MG/KG	0.220	0.046	1.01	27.6	7.2	5.6	5.7
4	800 MG/KG	0.237	0.055	0.95	27.5	7.5	5.1	6.2

		PROT.ELECTROPH.(ABS.)		
		B2-GLOB. g/l	SB-GLOB. g/l	G-GLOB. g/l
PRETEST				
1	0 MG/KG	7.6	14.7	2.7
2	200 MG/KG	8.1	14.8	3.2
3	400 MG/KG	8.0	15.0	3.6 **
4	800 MG/KG	7.5	14.2	2.8
4 WEEKS				
1	0 MG/KG	7.6	14.8	2.8
2	200 MG/KG	7.9	14.2	3.4
3	400 MG/KG	7.5	14.1	3.6 *
4	800 MG/KG	8.1	14.7	3.2
13 WEEKS				
1	0 MG/KG	7.5	15.1	3.2
2	200 MG/KG	9.2 **	17.0 *	4.0
3	400 MG/KG	8.1	15.4	3.7
4	800 MG/KG	7.9	14.7	3.2
25 WEEKS				
1	0 MG/KG	7.5	14.0	3.1
2	200 MG/KG	9.2 **	15.7	3.9 *
3	400 MG/KG	8.5	15.0	3.8 *
4	800 MG/KG	8.5	15.0	3.4
51 WEEKS				
1	0 MG/KG	6.5	12.3	2.5
2	200 MG/KG	9.0 **	15.0 **	3.9 **
3	400 MG/KG	7.3	13.1	3.2
4	800 MG/KG	7.4	13.3	2.5
8 WEEKS RECOVERY				
1	0 MG/KG	6.3	12.0	2.5
4	800 MG/KG	7.2	13.4	3.1

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

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

	GLUCOSE mmol/l	UREA mmol/l	CREATININE umol/l	BILI. T. umol/l	LIPIDS T. g/l	CHOLEST.T. mmol/l	TRIGL. mmol/l
PRETEST							
1 0 MG/KG	5.14	5.26	64	4.0	2.9	3.18	0.42
2 200 MG/KG	5.37	4.58	62	4.2	2.9	3.17	0.40
3 400 MG/KG	4.78	4.97	66	4.2	2.8	2.82	0.37
4 800 MG/KG	5.00	5.11	65	3.7	2.7	3.13	0.41
4 WEEKS							
1 0 MG/KG	5.36	5.13	64	3.9	2.8	3.43	0.46
2 200 MG/KG	5.56	4.93	62	4.6	2.3	3.04	0.34
3 400 MG/KG	4.94	5.25	61	4.6	2.4	2.95	0.34
4 800 MG/KG	5.18	5.86	64	4.9 **	2.9	3.54	0.47
13 WEEKS							
1 0 MG/KG	5.31	4.96	67	3.8	3.7	3.51	0.54
2 200 MG/KG	5.67	5.46	65	4.3	3.9	4.04	0.54
3 400 MG/KG	5.20	5.43	65	4.8 **	2.9	3.18	0.36
4 800 MG/KG	4.83	5.57	65	4.4	3.2	3.33	0.39
25 WEEKS							
1 0 MG/KG	5.33	5.04	63	3.3	3.1	3.43	0.52
2 200 MG/KG	5.49	5.05	64	4.0 *	2.7	3.54	0.38
3 400 MG/KG	5.04	5.49	65	4.1 **	2.3	2.74	0.33
4 800 MG/KG	5.06	5.53	59	4.0 **	3.5	3.86	0.60
51 WEEKS							
1 0 MG/KG	4.75	4.83	66	4.1	2.8	3.00	0.57
2 200 MG/KG	5.49	4.59	65	4.2	2.0	2.61	0.36
3 400 MG/KG	5.19	4.90	65	4.2	2.3	2.44	0.53
4 800 MG/KG	4.84	4.97	61	4.5	3.1	3.60	0.51
8 WEEKS RECOVERY							
1 0 MG/KG	4.54	4.93	60	4.3	3.8	4.24	0.55
4 800 MG/KG	5.24	5.84	57	4.0	3.2	3.91	0.53

	PHOS.LIPID mmol/l	ASAT(GOT) ukat/l	ALAT(GPT) ukat/l	LDH ukat/l	GLDH nkat/l	CK ukat/l	ALP ukat/l
PRETEST							
1 0 MG/KG	3.58	0.49	0.54	1.29	58.4	2.41	4.09
2 200 MG/KG	3.57	0.57	0.51	1.12	55.8	3.16	4.66
3 400 MG/KG	3.45	0.48	0.52	1.06	56.7	2.43	3.62
4 800 MG/KG	3.67	0.50	0.54	1.22	52.8	2.92	3.63
4 WEEKS							
1 0 MG/KG	3.88	0.47	0.41	1.66	27.2	2.85	3.62
2 200 MG/KG	3.44	0.52	0.49	1.29	35.3	2.75	4.10
3 400 MG/KG	3.50	0.49	0.43	1.29	42.9	2.50	3.58
4 800 MG/KG	3.96	0.46	0.48	1.35	50.9 *	2.37	3.46
13 WEEKS							
1 0 MG/KG	4.08	0.31	0.35	1.14	16.0	1.90	2.86
2 200 MG/KG	4.43	0.40	0.48	1.03	43.6	2.15	3.79
3 400 MG/KG	3.69	0.42	0.45	1.06	60.4	1.89	2.69
4 800 MG/KG	3.77	0.40	0.62	1.04	81.3	2.53	2.73
25 WEEKS							
1 0 MG/KG	3.83	0.35	0.39	1.20	51.6	2.57	2.16
2 200 MG/KG	3.88	0.41	0.59	1.11	61.0	2.57	2.99
3 400 MG/KG	3.21	0.41	0.46	0.96	59.4	2.24	2.14
4 800 MG/KG	4.18	0.35	0.60	1.04	91.4	2.18	2.40

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

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

	PHOS.LIPID mmol/l	ASAT(GOT) ukat/l	ALAT(GPT) ukat/l	LDH ukat/l	GLDH nkat/l	CK ukat/l	ALP ukat/l
51 WEEKS							
1 0 MG/KG	3.52	0.41	0.47	1.20	32.2	2.24	2.41
2 200 MG/KG	3.07	0.48	0.45	1.00	32.3	2.39	3.03
3 400 MG/KG	2.97	0.48	0.92	1.13	187.3 **	2.28	2.39
4 800 MG/KG	4.03	0.35	0.83	1.09	106.5	2.35	2.84
8 WEEKS RECOVERY							
1 0 MG/KG	4.40	0.50	0.30	0.97	20.3	2.03	3.19
4 800 MG/KG	4.43	0.35	0.53	0.91	55.0	1.71	1.76

	G-GT nkat/l	IRON umol/l	CALCIUM mmol/l	PHOSPHORUS mmol/l	MAGNESIUM mmol/l	SODIUM mmol/l	POTASSIUM mmol/l
PRETEST							
1 0 MG/KG	37.18	30.95	2.78	1.96	0.82	142.9	4.19
2 200 MG/KG	35.45	38.47	2.77	1.78	0.84	142.6	4.17
3 400 MG/KG	37.18	40.47	2.79	1.64 *	0.81	143.2	4.27
4 800 MG/KG	34.51	40.96	2.80	1.78	0.84	143.5	4.16
4 WEEKS							
1 0 MG/KG	45.45	38.00	2.77	1.73	0.83	142.0	3.62
2 200 MG/KG	41.12	35.38	2.73	1.51	0.84	141.7	3.57
3 400 MG/KG	44.47	26.17	2.84	1.56	0.83	142.5	3.54
4 800 MG/KG	41.05	37.21	2.82	1.72	0.85	143.8	3.42
13 WEEKS							
1 0 MG/KG	42.78	34.54	2.72	1.53	0.81	145.8	4.17
2 200 MG/KG	43.98	44.12	2.79	1.65	0.84	146.0	4.00
3 400 MG/KG	48.78	34.08	2.81	1.46	0.82	147.1	3.93
4 800 MG/KG	49.55	40.96	2.83	1.59	0.84	147.9 **	3.85 *
25 WEEKS							
1 0 MG/KG	44.47	40.24	2.70	1.40	0.83	146.3	3.79
2 200 MG/KG	55.25	40.38	2.78	1.30	0.83	147.4	3.82
3 400 MG/KG	57.36	34.67	2.79	1.28	0.84	147.6	3.79
4 800 MG/KG	41.43	43.70	2.79	1.57	0.84	147.8	3.76
51 WEEKS							
1 0 MG/KG	44.86	37.57	2.60	1.46	0.86	149.8	4.00
2 200 MG/KG	54.68	34.52	2.63	1.23	0.82	151.5	3.71
3 400 MG/KG	74.28	32.84	2.72	1.15	0.75 **	154.5	3.73
4 800 MG/KG	42.93	39.31	2.70	1.43	0.92	153.0	3.81
8 WEEKS RECOVERY							
1 0 MG/KG	50.96	43.39	2.57	1.26	0.81	145.3	3.83
4 800 MG/KG	43.50	46.54	2.75	1.29	0.88	147.8	3.56

			PROT.ELECTROPH.(REL.)				
	CHLORIDE mmol/l	PROTEIN T. g/l	ALBUMIN 1	A1-GLOB. 1	A2-GLOB. 1	B1-GLOB. 1	B2-GLOB. 1
PRETEST							
1 0 MG/KG	115.6	58.2	0.469	0.151	0.081	0.119	0.132
2 200 MG/KG	117.8	57.4	0.486	0.157	0.076	0.118	0.117
3 400 MG/KG	114.7	59.7	0.502	0.140	0.069	0.118	0.124
4 800 MG/KG	115.9	59.9	0.476	0.149	0.076	0.129	0.120

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

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		CHLORIDE mmol/l	PROTEIN T. g/l	PROT.ELECTROPH.(REL.) ALBUMIN 1	A1-GLOB. 1	A2-GLOB. 1	B1-GLOB. 1	B2-GLOB. 1
4 WEEKS								
1	0 MG/KG	116.1	58.9	0.439	0.154	0.085	0.120	0.142
2	200 MG/KG	117.1	57.8	0.465	0.153	0.078	0.119	0.130
3	400 MG/KG	116.3	60.8	0.471	0.139	0.086	0.117	0.136
4	800 MG/KG	117.5	62.6	0.452	0.146	0.088	0.113	0.144
13 WEEKS								
1	0 MG/KG	123.1	58.0	0.465	0.150	0.077	0.124	0.128
2	200 MG/KG	124.5	60.3	0.436	0.163	0.079	0.127	0.139
3	400 MG/KG	124.8	61.8	0.496	0.135	0.072	0.121	0.125
4	800 MG/KG	125.3	62.6 *	0.510	0.133	0.077	0.115	0.116
25 WEEKS								
1	0 MG/KG	121.7	55.6	0.466	0.152	0.079	0.111	0.131
2	200 MG/KG	123.9	60.1 *	0.465	0.152	0.080	0.111	0.132
3	400 MG/KG	122.0	60.3 *	0.489	0.131	0.078	0.107	0.140
4	800 MG/KG	122.8	60.6 **	0.450	0.153	0.088	0.110	0.143
51 WEEKS								
1	0 MG/KG	116.7	53.2	0.471	0.134	0.082	0.111	0.141
2	200 MG/KG	118.7	59.6	0.512	0.121	0.076	0.110	0.129
3	400 MG/KG	117.8	60.3 *	0.543	0.119	0.064	0.107	0.119
4	800 MG/KG	115.5	61.4 **	0.513	0.130	0.077	0.109	0.130
8 WEEKS RECOVERY								
1	0 MG/KG	123.3	54.1	0.456	0.166	0.079	0.101	0.146
4	800 MG/KG	121.2	60.7	0.527	0.140	0.073	0.106	0.109

		PROT.ELECTROPH.(REL.) SB-GLOB. 1	G-GLOB. 1	A/G RATIO	PROT.ELECTROPH.(ABS.) ALBUMIN g/l	A1-GLOB. g/l	A2-GLOB. g/l	B1-GLOB. g/l
PRETEST								
1	0 MG/KG	0.251	0.048	0.89	27.2	8.8	4.8	6.9
2	200 MG/KG	0.234	0.047	0.96	27.9	9.0	4.4	6.8
3	400 MG/KG	0.242	0.048	1.02	29.9	8.3	4.1	7.0
4	800 MG/KG	0.249	0.051	0.92	28.5	8.9	4.6	7.7
4 WEEKS								
1	0 MG/KG	0.263	0.059	0.79	25.8	9.1	5.0	7.1
2	200 MG/KG	0.249	0.055	0.88	26.8	8.8	4.5	6.9
3	400 MG/KG	0.253	0.053	0.90	28.6	8.4	5.2	7.1
4	800 MG/KG	0.257	0.057	0.83	28.3	9.2	5.5	7.1
13 WEEKS								
1	0 MG/KG	0.251	0.058	0.88	26.9	8.7	4.5	7.1
2	200 MG/KG	0.266	0.055	0.78	26.3	9.8	4.8	7.7
3	400 MG/KG	0.246	0.052	0.99	30.6 *	8.3	4.4	7.5
4	800 MG/KG	0.231	0.055	1.05	31.9 **	8.4	4.8	7.2
25 WEEKS								
1	0 MG/KG	0.242	0.061	0.88	25.9	8.5	4.4	6.2
2	200 MG/KG	0.243	0.060	0.87	27.9	9.1	4.9	6.7
3	400 MG/KG	0.246	0.055	0.96	29.5	7.9	4.7	6.4
4	800 MG/KG	0.253	0.057	0.84	27.2	9.3	5.3	6.7
51 WEEKS								
1	0 MG/KG	0.252	0.061	0.91	25.3	7.2	4.3	5.9
2	200 MG/KG	0.239	0.052	1.05	30.4	7.2	4.5	6.6
3	400 MG/KG	0.227	0.048	1.19	32.6 *	7.2	3.9	6.5
4	800 MG/KG	0.239	0.042 +	1.09	31.4 *	8.0	4.8	6.7

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

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

	PROT.ELECTROPH.(REL.)			PROT.ELECTROPH.(ABS.)			
	SB-GLOB. 1	G-GLOB. 1	A/G RATIO	ALBUMIN g/l	A1-GLOB. g/l	A2-GLOB. g/l	B1-GLOB. g/l
8 WEEKS RECOVERY							
1 0 MG/KG	0.247	0.054	0.84	24.8	9.1	4.2	5.4
4 800 MG/KG	0.215	0.046	1.15	31.9	8.5	4.4	6.4

	PROT.ELECTROPH.(ABS.)		
	B2-GLOB. g/l	SB-GLOB. g/l	G-GLOB. g/l
PRETEST			
1 0 MG/KG	7.7	14.6	2.8
2 200 MG/KG	6.7	13.5	2.7
3 400 MG/KG	7.4	14.5	2.8
4 800 MG/KG	7.2	14.9	3.1
4 WEEKS			
1 0 MG/KG	8.4	15.5	3.5
2 200 MG/KG	7.5	14.4	3.2
3 400 MG/KG	8.3	15.4	3.2
4 800 MG/KG	9.0	16.1	3.5
13 WEEKS			
1 0 MG/KG	7.4	14.5	3.4
2 200 MG/KG	8.4	16.1	3.3
3 400 MG/KG	7.7	15.2	3.2
4 800 MG/KG	7.3	14.5	3.5
25 WEEKS			
1 0 MG/KG	7.2	13.4	3.4
2 200 MG/KG	7.9	14.6	3.6
3 400 MG/KG	8.4	14.8	3.3
4 800 MG/KG	8.6 *	15.3 **	3.4
51 WEEKS			
1 0 MG/KG	7.4	13.3	3.2
2 200 MG/KG	7.7	14.2	3.1
3 400 MG/KG	7.2	13.7	2.9
4 800 MG/KG	8.0	14.7	2.6 +
8 WEEKS RECOVERY			
1 0 MG/KG	7.8	13.2	2.9
4 800 MG/KG	6.6	13.0	2.8

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

URINALYSIS SUMMARY
MALES

	SPEC.GRAV. 1	OSMOLALITY mmol/kg	pH	PROTEIN SCORE 0/3	GLUCOSE SCORE 0/3	KETONE SCORE 0/3	BILIRUBIN SCORE 0/3
PRETEST							
1 0 MG/KG	1.021	689	6	0	0	0	0
2 200 MG/KG	1.020	669	6	0	0	0	0
3 400 MG/KG	1.028	967	5	0	0	0	1
4 800 MG/KG	1.023	748	6	0	0	0	0
4 WEEKS							
1 0 MG/KG	1.022	744	6	1	0	0	1
2 200 MG/KG	1.022	689	6	1	0	0	1
3 400 MG/KG	1.030	1056	6	1	0	0	1
4 800 MG/KG	1.028	939	6	0	0	0	0
13 WEEKS							
1 0 MG/KG	1.016	568	6	0	0	0	0
2 200 MG/KG	1.023	802	6	0	0	0	1
3 400 MG/KG	1.033 **	1115 *	6	0	0	0	1
4 800 MG/KG	1.029 *	1050 *	6	0	0	0	0
25 WEEKS							
1 0 MG/KG	1.027	853	6	0	0	0	0
2 200 MG/KG	1.019	559	7	1	0	0	1
3 400 MG/KG	1.028	893	7	0	0	0	1
4 800 MG/KG	1.023	768	6	0	0	0	0
51 WEEKS							
1 0 MG/KG	1.026	865	6	1	0	0	1
2 200 MG/KG	1.022	639	6	1	0	0	1
3 400 MG/KG	1.030	1069	6	1	0	0	1
4 800 MG/KG	1.030	939	5	0	0	0	0
8 WEEKS RECOVERY							
1 0 MG/KG	1.022	708	7	1	0	0	1
4 800 MG/KG	1.031	1067	6	1	0	0	1

	BLOOD SCORE 0/3	UROBILI. SCORE 0/3	BLOOD CELLS RBC SCORE 0/3	BLOOD CELLS WBC SCORE 0/3	EPITHELIAL CELLS SQUAM. SCORE 0/3	EPITHELIAL CELLS RENAL SCORE 0/3	EPITHELIAL CELLS ROUND SCORE 0/3
PRETEST							
1 0 MG/KG	1	0	0	0	0	0	0
2 200 MG/KG	0	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0
4 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	1	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0
13 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0
25 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	1	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	1	0	0	0	0	0	0

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

URINALYSIS SUMMARY
MALES

			BLOOD CELLS		EPITHELIAL CELLS		
	BLOOD SCORE 0/3	UROBILI. SCORE 0/3	RBC SCORE 0/3	WBC SCORE 0/3	SQUAM. SCORE 0/3	RENAL SCORE 0/3	ROUND SCORE 0/3
51 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	1	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0
8 WEEKS RECOVERY							
1 0 MG/KG	1	0	1	1	0	0	0
4 800 MG/KG	1	0	1	0	1	0	0

	CRYSTALS
	TRIP.PHOS. SCORE 0/3
PRETEST	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
4 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
13 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
25 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
51 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
8 WEEKS RECOVERY	
1 0 MG/KG	0
4 800 MG/KG	1

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

URINALYSIS SUMMARY
FEMALES

	SPEC.GRAV. 1	OSMOLALITY mmol/kg	pH	PROTEIN SCORE 0/3	GLUCOSE SCORE 0/3	KETONE SCORE 0/3	BILIRUBIN SCORE 0/3
PRETEST							
1 0 MG/KG	1.031	1061	6	0	0	0	0
2 200 MG/KG	1.023	776	6	0	0	0	0
3 400 MG/KG	1.036	1202	7	0	0	0	0
4 800 MG/KG	1.032	1110	7	0	0	0	0
4 WEEKS							
1 0 MG/KG	1.023	767	7	0	0	0	0
2 200 MG/KG	1.027	930	6	0	0	0	0
3 400 MG/KG	1.033	1129	6	0	0	0	0
4 800 MG/KG	1.034	1207	5	0	0	0	0
13 WEEKS							
1 0 MG/KG	1.025	851	7	0	0	0	0
2 200 MG/KG	1.026	904	7	0	0	0	0
3 400 MG/KG	1.031	1050	6	0	0	0	0
4 800 MG/KG	1.035	1220	5 +	0	0	0	0
25 WEEKS							
1 0 MG/KG	1.026	923	7	0	0	0	0
2 200 MG/KG	1.036	1271	7	1	0	0	0
3 400 MG/KG	1.033	1209	6	0	0	0	0
4 800 MG/KG	1.032	1150	5 +	0	0	0	0
51 WEEKS							
1 0 MG/KG	1.025	815	7	0	0	0	0
2 200 MG/KG	1.032	998	7	0	0	0	1
3 400 MG/KG	1.029	918	6	0	0	0	1
4 800 MG/KG	1.025	825	5 +	0	0	0	0
8 WEEKS RECOVERY							
1 0 MG/KG	1.026	895	6	0	0	0	1
4 800 MG/KG	1.032	1115	5	0	0	0	1

			BLOOD CELLS		EPITHELIAL CELLS		
	BLOOD SCORE 0/3	UROBILI. SCORE 0/3	RBC SCORE 0/3	WBC SCORE 0/3	SQUAM. SCORE 0/3	RENAL SCORE 0/3	ROUND SCORE 0/3
PRETEST							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	1	0	1	0	0	0	0
4 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0
13 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0
25 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0

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

URINALYSIS SUMMARY
FEMALES

			BLOOD CELLS		EPITHELIAL CELLS		
	BLOOD SCORE 0/3	UROBILI. SCORE 0/3	RBC SCORE 0/3	WBC SCORE 0/3	SQUAM. SCORE 0/3	RENAL SCORE 0/3	ROUND SCORE 0/3
51 WEEKS							
1 0 MG/KG	0	0	0	0	0	0	0
2 200 MG/KG	0	0	0	0	0	0	0
3 400 MG/KG	0	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0
8 WEEKS RECOVERY							
1 0 MG/KG	1	0	0	0	0	0	0
4 800 MG/KG	0	0	0	0	0	0	0

	CRYSTALS
	TRIP.PHOS. SCORE 0/3
PRETEST	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
4 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
13 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
25 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
51 WEEKS	
1 0 MG/KG	0
2 200 MG/KG	0
3 400 MG/KG	0
4 800 MG/KG	0
8 WEEKS RECOVERY	
1 0 MG/KG	0
4 800 MG/KG	0

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

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 26 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	11463	10649	10577	9926
	ST.DEV.	272	571	129	347
	N	2	2	2	2
BRAIN	MEAN	70.5	79.7	75.2	79.2
	ST.DEV.	5.5	1.3	8.7	8.3
	N	2	2	2	2
PITUITARY	MEAN	0.058	0.072	0.047	0.050
	ST.DEV.	0.013	0.023	0.003	0.013
	N	2	2	2	2
HEART	MEAN	85.1	91.8	85.3	90.5
	ST.DEV.	2.0	7.1	0.4	3.3
	N	2	2	2	2
LIVER	MEAN	367.4	313.2	343.5	358.1
	ST.DEV.	5.8	16.9	4.3	16.8
	N	2	2	2	2
THYROID(L)	MEAN	0.428	0.375	0.359	0.372
	ST.DEV.	0.086	0.034	0.091	0.033
	N	2	2	2	2
THYROID(R)	MEAN	0.337	0.366	0.384	0.279
	ST.DEV.	0.006	0.011	0.063	0.001
	N	2	2	2	2
KIDNEY(L)	MEAN	23.85	25.84	23.49	25.95
	ST.DEV.	0.54	3.65	2.63	1.40
	N	2	2	2	2
KIDNEY(R)	MEAN	24.11	26.17	22.87	27.35
	ST.DEV.	1.64	1.55	1.97	2.15
	N	2	2	2	2
ADRENAL(R)	MEAN	0.667	0.669	0.619	0.685
	ST.DEV.	0.040	0.099	0.103	0.165
	N	2	2	2	2
ADRENAL(L)	MEAN	0.627	0.597	0.623	0.781
	ST.DEV.	0.075	0.150	0.086	0.133
	N	2	2	2	2
SPLEEN	MEAN	30.98	27.81	29.56	28.30
	ST.DEV.	4.75	13.14	5.94	1.65
	N	2	2	2	2
TESTIS(R)	MEAN	7.94	8.57	9.04	10.40
	ST.DEV.	0.11	1.13	0.06	1.01
	N	2	2	2	2
TESTIS(L)	MEAN	7.43	9.13	9.95	10.50
	ST.DEV.	0.45	0.29	1.63	0.10
	N	2	2	2	2
PROSTATE	MEAN	7.83	8.99	8.84	11.45
	ST.DEV.	2.45	0.10	0.41	3.57
	N	2	2	2	2

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 26 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	11463	10649	10577	9926
(GRAM)	ST.DEV.	272	571	129	347
	N	2	2	2	2
BRAIN	MEAN	0.6	0.8	0.7	0.8
(%)	ST.DEV.	0.1	0.1	0.1	0.1
	N	2	2	2	2
PITUITARY	MEAN	0.0005	0.0007	0.0004	0.0005
(%)	ST.DEV.	0.0001	0.0002	0.0000	0.0001
	N	2	2	2	2
HEART	MEAN	0.7	0.9	0.8	0.9
(%)	ST.DEV.	0.0	0.1	0.0	0.1
	N	2	2	2	2
LIVER	MEAN	3.2	2.9	3.2	3.6
(%)	ST.DEV.	0.0	0.3	0.0	0.0
	N	2	2	2	2
THYROID(L)	MEAN	0.0037	0.0035	0.0034	0.0037
(%)	ST.DEV.	0.0007	0.0001	0.0008	0.0002
	N	2	2	2	2
THYROID(R)	MEAN	0.0029	0.0034	0.0036	0.0028
(%)	ST.DEV.	0.0001	0.0001	0.0006	0.0001
	N	2	2	2	2
KIDNEY(L)	MEAN	0.21	0.24	0.22	0.26
(%)	ST.DEV.	0.00	0.05	0.03	0.00
	N	2	2	2	2
KIDNEY(R)	MEAN	0.21	0.25	0.22	0.28
(%)	ST.DEV.	0.01	0.03	0.02	0.01
	N	2	2	2	2
ADRENAL(R)	MEAN	0.0058	0.0063	0.0058	0.0069
(%)	ST.DEV.	0.0005	0.0006	0.0009	0.0019
	N	2	2	2	2
ADRENAL(L)	MEAN	0.0055	0.0056	0.0059	0.0079
(%)	ST.DEV.	0.0005	0.0011	0.0007	0.0016
	N	2	2	2	2
SPLEEN	MEAN	0.27	0.26	0.28	0.29
(%)	ST.DEV.	0.04	0.11	0.05	0.03
	N	2	2	2	2
TESTIS(R)	MEAN	0.07	0.08	0.09	0.10
(%)	ST.DEV.	0.00	0.01	0.00	0.01
	N	2	2	2	2
TESTIS(L)	MEAN	0.06	0.09	0.09	0.11
(%)	ST.DEV.	0.01	0.01	0.02	0.00
	N	2	2	2	2
PROSTATE	MEAN	0.07	0.08	0.08	0.11
(%)	ST.DEV.	0.02	0.00	0.00	0.03
	N	2	2	2	2

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 26 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BRAIN (GRAM)	MEAN	70.5	79.7	75.2	79.2
	ST.DEV.	5.5	1.3	8.7	8.3
	N	2	2	2	2
PITUITARY (%)	MEAN	0.0818	0.0905	0.0627	0.0626
	ST.DEV.	0.0117	0.0298	0.0035	0.0095
	N	2	2	2	2
HEART (%)	MEAN	121.2	115.1	114.3	115.2
	ST.DEV.	12.2	7.0	13.8	16.3
	N	2	2	2	2
LIVER (%)	MEAN	523.2	392.7	460.3	453.6
	ST.DEV.	49.0	15.0	59.0	26.3
	N	2	2	2	2
THYROID(L) (%)	MEAN	0.6132	0.4707	0.4872	0.4695
	ST.DEV.	0.1691	0.0500	0.1777	0.0072
	N	2	2	2	2
THYROID(R) (%)	MEAN	0.4794	0.4592	0.5184	0.3537
	ST.DEV.	0.0293	0.0215	0.1437	0.0379
	N	2	2	2	2
KIDNEY(L) (%)	MEAN	33.98	32.38	31.25	32.85
	ST.DEV.	3.41	4.07	0.11	1.67
	N	2	2	2	2
KIDNEY(R) (%)	MEAN	34.40	32.82	30.47	34.58
	ST.DEV.	5.01	1.42	0.91	0.90
	N	2	2	2	2
ADRENAL(R) (%)	MEAN	0.9472	0.8402	0.8369	0.8808
	ST.DEV.	0.0175	0.1375	0.2342	0.3011
	N	2	2	2	2
ADRENAL(L) (%)	MEAN	0.8966	0.7504	0.8402	1.0006
	ST.DEV.	0.1761	0.1999	0.2110	0.2726
	N	2	2	2	2
SPLEEN (%)	MEAN	44.35	35.02	40.04	36.04
	ST.DEV.	10.19	17.03	12.53	5.86
	N	2	2	2	2
TESTIS(R) (%)	MEAN	11.29	10.74	12.10	13.14
	ST.DEV.	0.72	1.25	1.32	0.10
	N	2	2	2	2
TESTIS(L) (%)	MEAN	10.55	11.45	13.19	13.32
	ST.DEV.	0.18	0.18	0.64	1.26
	N	2	2	2	2
PROSTATE (%)	MEAN	11.01	11.28	11.87	14.31
	ST.DEV.	2.62	0.31	1.92	3.02
	N	2	2	2	2

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 26 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	7938	8159	9344	8228
	ST.DEV.	693	1817	1416	794
	N	2	2	2	2
BRAIN	MEAN	77.0	73.9	76.8	63.4
	ST.DEV.	8.7	10.0	8.5	5.7
	N	2	2	2	2
PITUITARY	MEAN	0.065	0.080	0.061	0.070
	ST.DEV.	0.012	0.001	0.024	0.002
	N	2	2	2	2
HEART	MEAN	65.9	66.9	69.9	60.2
	ST.DEV.	5.0	5.2	15.3	6.7
	N	2	2	2	2
LIVER	MEAN	289.9	272.0	311.2	291.1
	ST.DEV.	6.6	70.0	122.9	7.8
	N	2	2	2	2
THYROID(L)	MEAN	0.351	0.349	0.333	0.219
	ST.DEV.	0.062	0.133	0.080	0.037
	N	2	2	2	2
THYROID(R)	MEAN	0.359	0.243	0.390	0.263
	ST.DEV.	0.006	0.114	0.004	0.018
	N	2	2	2	2
KIDNEY(L)	MEAN	21.48	19.91	25.24	20.20
	ST.DEV.	0.10	8.00	2.56	4.87
	N	2	2	2	2
KIDNEY(R)	MEAN	21.44	19.91	23.78	20.57
	ST.DEV.	0.28	7.23	3.19	2.33
	N	2	2	2	2
ADRENAL(R)	MEAN	0.658	0.664	0.658	0.704
	ST.DEV.	0.104	0.156	0.071	0.179
	N	2	2	2	2
ADRENAL(L)	MEAN	0.633	0.664	0.651	0.551
	ST.DEV.	0.103	0.066	0.106	0.077
	N	2	2	2	2
SPLEEN	MEAN	42.98	25.16	38.09	36.88
	ST.DEV.	10.53	4.15	9.63	18.10
	N	2	2	2	2

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 26 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	7938	8159	9344	8228
(GRAM)	ST.DEV.	693	1817	1416	794
	N	2	2	2	2
BRAIN	MEAN	1.0	0.9	0.8	0.8
(%)	ST.DEV.	0.2	0.1	0.0	0.1
	N	2	2	2	2
PITUITARY	MEAN	0.0008	0.0010	0.0006	0.0008
(%)	ST.DEV.	0.0001	0.0002	0.0002	0.0001
	N	2	2	2	2
HEART	MEAN	0.8	0.8	0.7	0.7
(%)	ST.DEV.	0.1	0.1	0.1	0.0
	N	2	2	2	2
LIVER	MEAN	3.7	3.3	3.3	3.5
(%)	ST.DEV.	0.2	0.1	0.8	0.2
	N	2	2	2	2
THYROID(L)	MEAN	0.0045	0.0042	0.0037	0.0027
(%)	ST.DEV.	0.0012	0.0007	0.0014	0.0002
	N	2	2	2	2
THYROID(R)	MEAN	0.0045	0.0029	0.0042	0.0032
(%)	ST.DEV.	0.0005	0.0008	0.0007	0.0001
	N	2	2	2	2
KIDNEY(L)	MEAN	0.27	0.24	0.27	0.24
(%)	ST.DEV.	0.02	0.04	0.01	0.04
	N	2	2	2	2
KIDNEY(R)	MEAN	0.27	0.24	0.25	0.25
(%)	ST.DEV.	0.03	0.04	0.00	0.00
	N	2	2	2	2
ADRENAL(R)	MEAN	0.0084	0.0081	0.0071	0.0085
(%)	ST.DEV.	0.0020	0.0001	0.0003	0.0014
	N	2	2	2	2
ADRENAL(L)	MEAN	0.0081	0.0083	0.0070	0.0067
(%)	ST.DEV.	0.0020	0.0010	0.0001	0.0003
	N	2	2	2	2
SPLEEN	MEAN	0.54	0.31	0.40	0.46
(%)	ST.DEV.	0.09	0.02	0.04	0.26
	N	2	2	2	2

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 26 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BRAIN (GRAM)	MEAN	77.0	73.9	76.8	63.4
	ST.DEV.	8.7	10.0	8.5	5.7
	N	2	2	2	2
PITUITARY (%)	MEAN	0.0852	0.1084	0.0782	0.1099
	ST.DEV.	0.0252	0.0138	0.0226	0.0065
	N	2	2	2	2
HEART (%)	MEAN	85.8	90.8	90.5	95.8
	ST.DEV.	3.1	5.3	9.9	19.2
	N	2	2	2	2
LIVER (%)	MEAN	379.5	364.7	399.0	461.4
	ST.DEV.	51.4	45.1	115.7	53.7
	N	2	2	2	2
THYROID(L) (%)	MEAN	0.4544	0.4641	0.4416	0.3493
	ST.DEV.	0.0297	0.1168	0.1532	0.0893
	N	2	2	2	2
THYROID(R) (%)	MEAN	0.4690	0.3205	0.5115	0.4177
	ST.DEV.	0.0455	0.1105	0.0624	0.0665
	N	2	2	2	2
KIDNEY(L) (%)	MEAN	28.08	26.44	32.90	32.33
	ST.DEV.	3.04	7.24	0.33	10.59
	N	2	2	2	2
KIDNEY(R) (%)	MEAN	28.01	26.51	30.94	32.73
	ST.DEV.	2.79	6.18	0.71	6.62
	N	2	2	2	2
ADRENAL(R) (%)	MEAN	0.8521	0.8912	0.8573	1.1265
	ST.DEV.	0.0391	0.0904	0.0033	0.3831
	N	2	2	2	2
ADRENAL(L) (%)	MEAN	0.8201	0.9002	0.8456	0.8770
	ST.DEV.	0.0418	0.0323	0.0441	0.2002
	N	2	2	2	2
SPLEEN (%)	MEAN	56.97	33.95	49.23	57.11
	ST.DEV.	20.10	1.01	7.07	23.42
	N	2	2	2	2

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 52 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	11317	10846	11114	9396
	ST.DEV.	1655	941	730	669
	N	4	4	4	4
BRAIN	MEAN	86.9	77.7 *	75.5 **	80.6
	ST.DEV.	4.7	3.0	4.0	5.1
	N	4	4	4	4
PITUITARY	MEAN	0.086	0.068	0.062 *	0.063 *
	ST.DEV.	0.006	0.013	0.012	0.008
	N	4	4	4	4
HEART	MEAN	91.9	102.3	95.1	90.8
	ST.DEV.	8.2	9.6	9.7	6.8
	N	4	4	4	4
LIVER	MEAN	369.0	372.3	367.4	377.0
	ST.DEV.	24.9	49.6	36.8	12.4
	N	4	4	4	4
THYROID(L)	MEAN	0.467	0.456	0.359	0.324
	ST.DEV.	0.081	0.175	0.130	0.067
	N	4	4	4	4
THYROID(R)	MEAN	0.422	0.383	0.290	0.251
	ST.DEV.	0.086	0.126	0.096	0.071
	N	4	4	4	4
KIDNEY(L)	MEAN	27.70	28.61	29.17	29.73
	ST.DEV.	5.25	1.97	6.80	2.46
	N	4	4	4	4
KIDNEY(R)	MEAN	29.08	29.09	28.88	30.70
	ST.DEV.	5.51	1.89	7.03	2.85
	N	4	4	4	4
ADRENAL(R)	MEAN	0.621	0.687	0.742	0.603
	ST.DEV.	0.080	0.093	0.140	0.087
	N	4	4	4	4
ADRENAL(L)	MEAN	0.628	0.703	0.773	0.647
	ST.DEV.	0.083	0.111	0.238	0.049
	N	4	4	4	4
SPLEEN	MEAN	35.24	33.61	51.05	27.28
	ST.DEV.	6.87	3.75	33.16	3.26
	N	4	4	4	4
TESTIS(R)	MEAN	8.99	10.93	10.26	8.30
	ST.DEV.	1.03	0.63	2.07	0.77
	N	4	4	4	4
TESTIS(L)	MEAN	10.25	10.36	10.22	8.64
	ST.DEV.	1.97	1.20	1.62	0.84
	N	4	4	4	4
PROSTATE	MEAN	13.06	13.30	11.29	9.97
	ST.DEV.	2.85	4.83	1.35	3.15
	N	4	4	4	4

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

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 52 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	11317	10846	11114	9396
(GRAM)	ST.DEV.	1655	941	730	669
	N	4	4	4	4
BRAIN	MEAN	0.8	0.7	0.7	0.9
(%)	ST.DEV.	0.1	0.0	0.1	0.1
	N	4	4	4	4
PITUITARY	MEAN	0.0008	0.0006	0.0006	0.0007
(%)	ST.DEV.	0.0001	0.0001	0.0001	0.0001
	N	4	4	4	4
HEART	MEAN	0.8	0.9	0.9	1.0
(%)	ST.DEV.	0.1	0.1	0.1	0.1
	N	4	4	4	4
LIVER	MEAN	3.3	3.5	3.3	4.0
(%)	ST.DEV.	0.5	0.6	0.4	0.3
	N	4	4	4	4
THYROID(L)	MEAN	0.0041	0.0042	0.0032	0.0035
(%)	ST.DEV.	0.0004	0.0015	0.0012	0.0007
	N	4	4	4	4
THYROID(R)	MEAN	0.0037	0.0035	0.0026	0.0027
(%)	ST.DEV.	0.0006	0.0010	0.0009	0.0007
	N	4	4	4	4
KIDNEY(L)	MEAN	0.25	0.26	0.26	0.32
(%)	ST.DEV.	0.06	0.02	0.06	0.03
	N	4	4	4	4
KIDNEY(R)	MEAN	0.26	0.27	0.26	0.33
(%)	ST.DEV.	0.05	0.03	0.06	0.03
	N	4	4	4	4
ADRENAL(R)	MEAN	0.0055	0.0064	0.0067	0.0064
(%)	ST.DEV.	0.0008	0.0009	0.0013	0.0008
	N	4	4	4	4
ADRENAL(L)	MEAN	0.0056	0.0066	0.0070	0.0069
(%)	ST.DEV.	0.0003	0.0015	0.0020	0.0008
	N	4	4	4	4
SPLEEN	MEAN	0.31	0.31	0.45	0.29
(%)	ST.DEV.	0.06	0.06	0.27	0.02
	N	4	4	4	4
TESTIS(R)	MEAN	0.08	0.10	0.09	0.09
(%)	ST.DEV.	0.01	0.00	0.02	0.01
	N	4	4	4	4
TESTIS(L)	MEAN	0.09	0.10	0.09	0.09
(%)	ST.DEV.	0.02	0.00	0.02	0.01
	N	4	4	4	4
PROSTATE	MEAN	0.12	0.12	0.10	0.11
(%)	ST.DEV.	0.04	0.04	0.02	0.04
	N	4	4	4	4

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

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 52 WEEKS
MALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BRAIN	MEAN	86.9	77.7 *	75.5 **	80.6
(GRAM)	ST.DEV.	4.7	3.0	4.0	5.1
	N	4	4	4	4
PITUITARY	MEAN	0.0990	0.0876	0.0815	0.0780
(%)	ST.DEV.	0.0106	0.0147	0.0127	0.0121
	N	4	4	4	4
HEART	MEAN	105.8	131.5 **	126.2 *	112.7
(%)	ST.DEV.	8.2	8.0	13.9	2.7
	N	4	4	4	4
LIVER	MEAN	424.8	479.4	485.6	469.2
(%)	ST.DEV.	22.4	64.8	26.4	29.7
	N	4	4	4	4
THYROID(L)	MEAN	0.5358	0.5890	0.4824	0.4050
(%)	ST.DEV.	0.0722	0.2387	0.1981	0.0972
	N	4	4	4	4
THYROID(R)	MEAN	0.4837	0.4917	0.3882	0.3131
(%)	ST.DEV.	0.0840	0.1598	0.1456	0.0936
	N	4	4	4	4
KIDNEY(L)	MEAN	31.77	36.85	38.60	36.88
(%)	ST.DEV.	5.00	2.46	8.52	1.14
	N	4	4	4	4
KIDNEY(R)	MEAN	33.32	37.49	38.27	38.10
(%)	ST.DEV.	4.90	2.87	9.05	2.33
	N	4	4	4	4
ADRENAL(R)	MEAN	0.7136	0.8832	0.9890 *	0.7459
(%)	ST.DEV.	0.0680	0.1025	0.2201	0.0719
	N	4	4	4	4
ADRENAL(L)	MEAN	0.7210	0.9065	1.0318	0.8069
(%)	ST.DEV.	0.0722	0.1529	0.3411	0.0913
	N	4	4	4	4
SPLEEN	MEAN	40.67	43.44	67.55	33.85
(%)	ST.DEV.	8.47	6.35	43.29	3.31
	N	4	4	4	4
TESTIS(R)	MEAN	10.36	14.06 **	13.52 *	10.29
(%)	ST.DEV.	1.13	0.49	2.16	0.45
	N	4	4	4	4
TESTIS(L)	MEAN	11.83	13.32	13.51	10.71
(%)	ST.DEV.	2.33	1.33	1.73	0.45
	N	4	4	4	4
PROSTATE	MEAN	15.15	17.13	14.97	12.27
(%)	ST.DEV.	3.87	6.04	1.82	3.33
	N	4	4	4	4

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

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 52 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	9735	9854	8643	10248
	ST.DEV.	2743	621	846	1480
	N	4	4	4	4
BRAIN	MEAN	75.7	73.0	66.7	75.3
	ST.DEV.	8.2	2.3	3.5	4.3
	N	4	4	4	4
PITUITARY	MEAN	0.066	0.072	0.059	0.078
	ST.DEV.	0.014	0.023	0.011	0.013
	N	4	4	4	4
HEART	MEAN	75.9	82.1	66.5	73.8
	ST.DEV.	8.9	2.5	9.2	10.0
	N	4	4	4	4
LIVER	MEAN	340.4	327.6	280.8	376.4
	ST.DEV.	62.2	39.6	73.6	71.9
	N	4	4	4	4
THYROID(L)	MEAN	0.321	0.319	0.381	0.383
	ST.DEV.	0.095	0.062	0.028	0.095
	N	4	4	4	4
THYROID(R)	MEAN	0.316	0.297	0.338	0.348
	ST.DEV.	0.091	0.027	0.073	0.029
	N	4	3	4	4
KIDNEY(L)	MEAN	22.38	25.04	22.40	27.40
	ST.DEV.	5.67	3.25	1.21	6.45
	N	4	4	4	4
KIDNEY(R)	MEAN	22.82	25.36	21.89	26.47
	ST.DEV.	5.63	2.68	1.58	5.89
	N	4	4	4	4
ADRENAL(R)	MEAN	0.834	0.857	0.744	0.838
	ST.DEV.	0.077	0.192	0.241	0.170
	N	4	4	4	4
ADRENAL(L)	MEAN	0.812	0.839	0.694	0.788
	ST.DEV.	0.081	0.196	0.155	0.088
	N	4	4	4	4
SPLEEN	MEAN	38.51	42.53	39.75	34.32
	ST.DEV.	11.42	29.51	16.02	12.11
	N	4	4	4	4

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

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 52 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BODY W. (GRAM)	MEAN	9735	9854	8643	10248
	ST.DEV.	2743	621	846	1480
	N	4	4	4	4
BRAIN (%)	MEAN	0.8	0.7	0.8	0.7
	ST.DEV.	0.2	0.1	0.1	0.1
	N	4	4	4	4
PITUITARY (%)	MEAN	0.0007	0.0007	0.0007	0.0008
	ST.DEV.	0.0002	0.0002	0.0001	0.0001
	N	4	4	4	4
HEART (%)	MEAN	0.8	0.8	0.8	0.7
	ST.DEV.	0.1	0.1	0.1	0.0
	N	4	4	4	4
LIVER (%)	MEAN	3.6	3.3	3.2	3.7
	ST.DEV.	0.5	0.3	0.7	0.4
	N	4	4	4	4
THYROID(L) (%)	MEAN	0.0033	0.0032	0.0044	0.0039
	ST.DEV.	0.0003	0.0005	0.0002	0.0014
	N	4	4	4	4
THYROID(R) (%)	MEAN	0.0032	0.0031	0.0039	0.0034
	ST.DEV.	0.0002	0.0004	0.0005	0.0003
	N	4	3	4	4
KIDNEY(L) (%)	MEAN	0.23	0.25	0.26	0.26
	ST.DEV.	0.02	0.03	0.03	0.03
	N	4	4	4	4
KIDNEY(R) (%)	MEAN	0.24	0.26	0.25	0.26
	ST.DEV.	0.01	0.02	0.03	0.02
	N	4	4	4	4
ADRENAL(R) (%)	MEAN	0.0090	0.0088	0.0087	0.0081
	ST.DEV.	0.0024	0.0022	0.0030	0.0006
	N	4	4	4	4
ADRENAL(L) (%)	MEAN	0.0090	0.0086	0.0081	0.0077
	ST.DEV.	0.0034	0.0021	0.0021	0.0003
	N	4	4	4	4
SPLEEN (%)	MEAN	0.41	0.42	0.48	0.33
	ST.DEV.	0.10	0.27	0.26	0.09
	N	4	4	4	4

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

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 52 WEEKS
FEMALES

		GROUP 1 0 MG/KG	GROUP 2 200 MG/KG	GROUP 3 400 MG/KG	GROUP 4 800 MG/KG
BRAIN	MEAN	75.7	73.0	66.7	75.3
(GRAM)	ST.DEV.	8.2	2.3	3.5	4.3
	N	4	4	4	4
PITUITARY	MEAN	0.0885	0.0988	0.0887	0.1035
(%)	ST.DEV.	0.0215	0.0330	0.0139	0.0174
	N	4	4	4	4
HEART	MEAN	100.5	112.6	99.5	98.5
(%)	ST.DEV.	8.7	6.1	9.7	15.3
	N	4	4	4	4
LIVER	MEAN	448.3	450.0	418.3	504.1
(%)	ST.DEV.	55.4	65.1	92.0	115.6
	N	4	4	4	4
THYROID(L)	MEAN	0.4171	0.4389	0.5724	0.5114
(%)	ST.DEV.	0.0793	0.0935	0.0536	0.1352
	N	4	4	4	4
THYROID(R)	MEAN	0.4111	0.4036	0.5045	0.4648
(%)	ST.DEV.	0.0735	0.0241	0.0906	0.0581
	N	4	3	4	4
KIDNEY(L)	MEAN	29.32	34.36	33.64	36.60
(%)	ST.DEV.	5.13	4.90	1.83	9.07
	N	4	4	4	4
KIDNEY(R)	MEAN	29.86	34.79	32.87	35.36
(%)	ST.DEV.	4.63	4.07	2.27	8.43
	N	4	4	4	4
ADRENAL(R)	MEAN	1.1104	1.1738	1.1144	1.1182
(%)	ST.DEV.	0.1472	0.2637	0.3524	0.2425
	N	4	4	4	4
ADRENAL(L)	MEAN	1.0906	1.1484	1.0394	1.0504
(%)	ST.DEV.	0.2245	0.2644	0.2217	0.1388
	N	4	4	4	4
SPLEEN	MEAN	50.99	58.66	59.94	46.19
(%)	ST.DEV.	14.43	41.60	25.30	17.76
	N	4	4	4	4

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

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 8 WEEKS RECOVERY
MALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	12189	10225
	ST.DEV.	2250	632
	N	2	2
BRAIN	MEAN	82.5	76.6
	ST.DEV.	3.5	6.0
	N	2	2
PITUITARY	MEAN	0.060	0.076
	ST.DEV.	0.023	0.014
	N	2	2
HEART	MEAN	99.3	92.3
	ST.DEV.	0.8	13.3
	N	2	2
LIVER	MEAN	386.4	374.5
	ST.DEV.	17.3	32.9
	N	2	2
THYROID(L)	MEAN	0.370	0.348
	ST.DEV.	0.000	0.069
	N	2	2
THYROID(R)	MEAN	0.386	0.283
	ST.DEV.	0.006	0.002
	N	2	2
KIDNEY(L)	MEAN	28.08	27.12
	ST.DEV.	0.62	0.89
	N	2	2
KIDNEY(R)	MEAN	27.42	27.53
	ST.DEV.	1.06	1.78
	N	2	2
ADRENAL(R)	MEAN	0.767	0.647
	ST.DEV.	0.058	0.025
	N	2	2
ADRENAL(L)	MEAN	0.738	0.577
	ST.DEV.	0.081	0.049
	N	2	2
SPLEEN	MEAN	41.43	25.86
	ST.DEV.	8.61	5.98
	N	2	2
TESTIS(R)	MEAN	9.71	9.74
	ST.DEV.	0.68	0.37
	N	2	2
TESTIS(L)	MEAN	9.55	10.53
	ST.DEV.	0.71	0.56
	N	2	2
PROSTATE	MEAN	9.81	10.89
	ST.DEV.	0.45	0.03
	N	2	2

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 8 WEEKS RECOVERY
MALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	12189	10225
(GRAM)	ST.DEV.	2250	632
	N	2	2
BRAIN	MEAN	0.7	0.8
(%)	ST.DEV.	0.2	0.1
	N	2	2
PITUITARY	MEAN	0.0005	0.0007
(%)	ST.DEV.	0.0003	0.0001
	N	2	2
HEART	MEAN	0.8	0.9
(%)	ST.DEV.	0.2	0.1
	N	2	2
LIVER	MEAN	3.2	3.7
(%)	ST.DEV.	0.7	0.5
	N	2	2
THYROID(L)	MEAN	0.0031	0.0034
(%)	ST.DEV.	0.0006	0.0009
	N	2	2
THYROID(R)	MEAN	0.0032	0.0028
(%)	ST.DEV.	0.0005	0.0002
	N	2	2
KIDNEY(L)	MEAN	0.23	0.27
(%)	ST.DEV.	0.05	0.03
	N	2	2
KIDNEY(R)	MEAN	0.23	0.27
(%)	ST.DEV.	0.05	0.00
	N	2	2
ADRENAL(R)	MEAN	0.0064	0.0063
(%)	ST.DEV.	0.0007	0.0006
	N	2	2
ADRENAL(L)	MEAN	0.0061	0.0056
(%)	ST.DEV.	0.0005	0.0001
	N	2	2
SPLEEN	MEAN	0.34	0.25
(%)	ST.DEV.	0.01	0.04
	N	2	2
TESTIS(R)	MEAN	0.08	0.10
(%)	ST.DEV.	0.02	0.00
	N	2	2
TESTIS(L)	MEAN	0.08	0.10
(%)	ST.DEV.	0.02	0.00
	N	2	2
PROSTATE	MEAN	0.08	0.11
(%)	ST.DEV.	0.01	0.01
	N	2	2

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 8 WEEKS RECOVERY
MALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BRAIN	MEAN	82.5	76.6
(GRAM)	ST.DEV.	3.5	6.0
	N	2	2
PITUITARY	MEAN	0.0716	0.1002
(%)	ST.DEV.	0.0252	0.0262
	N	2	2
HEART	MEAN	120.5	121.5
(%)	ST.DEV.	4.2	26.8
	N	2	2
LIVER	MEAN	468.4	488.4
(%)	ST.DEV.	0.8	5.0
	N	2	2
THYROID(L)	MEAN	0.4489	0.4513
(%)	ST.DEV.	0.0193	0.0544
	N	2	2
THYROID(R)	MEAN	0.4685	0.3698
(%)	ST.DEV.	0.0270	0.0315
	N	2	2
KIDNEY(L)	MEAN	34.05	35.44
(%)	ST.DEV.	0.72	1.60
	N	2	2
KIDNEY(R)	MEAN	33.24	36.12
(%)	ST.DEV.	0.15	5.13
	N	2	2
ADRENAL(R)	MEAN	0.9321	0.8454
(%)	ST.DEV.	0.1104	0.0325
	N	2	2
ADRENAL(L)	MEAN	0.8975	0.7576
(%)	ST.DEV.	0.1363	0.1234
	N	2	2
SPLEEN	MEAN	50.49	34.15
(%)	ST.DEV.	12.61	10.46
	N	2	2
TESTIS(R)	MEAN	11.76	12.76
(%)	ST.DEV.	0.32	1.48
	N	2	2
TESTIS(L)	MEAN	11.57	13.80
(%)	ST.DEV.	0.36	1.80
	N	2	2
PROSTATE	MEAN	11.91	14.25
(%)	ST.DEV.	1.06	1.07
	N	2	2

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 8 WEEKS RECOVERY
FEMALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	9179	9730
	ST.DEV.	1363	1438
	N	2	2
BRAIN	MEAN	76.3	68.7
	ST.DEV.	3.5	4.9
	N	2	2
PITUITARY	MEAN	0.068	0.066
	ST.DEV.	0.004	0.008
	N	2	2
HEART	MEAN	74.3	67.1
	ST.DEV.	13.6	4.0
	N	2	2
LIVER	MEAN	357.8	334.4
	ST.DEV.	59.1	29.2
	N	2	2
THYROID(L)	MEAN	0.431	0.421
	ST.DEV.	0.081	0.066
	N	2	2
THYROID(R)	MEAN	0.362	0.317
	ST.DEV.	0.075	0.070
	N	2	2
KIDNEY(L)	MEAN	25.25	26.16
	ST.DEV.	5.58	3.57
	N	2	2
KIDNEY(R)	MEAN	24.51	24.90
	ST.DEV.	2.35	1.76
	N	2	2
ADRENAL(R)	MEAN	0.910	0.658
	ST.DEV.	0.212	0.081
	N	2	2
ADRENAL(L)	MEAN	0.795	0.596
	ST.DEV.	0.247	0.030
	N	2	2
SPLEEN	MEAN	34.67	41.71
	ST.DEV.	1.32	13.05
	N	2	2

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 8 WEEKS RECOVERY
FEMALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BODY W.	MEAN	9179	9730
(GRAM)	ST.DEV.	1363	1438
	N	2	2
BRAIN	MEAN	0.8	0.7
(%)	ST.DEV.	0.2	0.2
	N	2	2
PITUITARY	MEAN	0.0007	0.0007
(%)	ST.DEV.	0.0001	0.0000
	N	2	2
HEART	MEAN	0.8	0.7
(%)	ST.DEV.	0.3	0.1
	N	2	2
LIVER	MEAN	3.9	3.5
(%)	ST.DEV.	0.1	0.2
	N	2	2
THYROID(L)	MEAN	0.0048	0.0043
(%)	ST.DEV.	0.0016	0.0000
	N	2	2
THYROID(R)	MEAN	0.0040	0.0032
(%)	ST.DEV.	0.0014	0.0002
	N	2	2
KIDNEY(L)	MEAN	0.28	0.27
(%)	ST.DEV.	0.10	0.08
	N	2	2
KIDNEY(R)	MEAN	0.27	0.26
(%)	ST.DEV.	0.07	0.06
	N	2	2
ADRENAL(R)	MEAN	0.0102	0.0069
(%)	ST.DEV.	0.0038	0.0019
	N	2	2
ADRENAL(L)	MEAN	0.0090	0.0062
(%)	ST.DEV.	0.0040	0.0012
	N	2	2
SPLEEN	MEAN	0.38	0.42
(%)	ST.DEV.	0.07	0.07
	N	2	2

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
AFTER 8 WEEKS RECOVERY
FEMALES

		GROUP 1 0 MG/KG	GROUP 4 800 MG/KG
BRAIN (GRAM)	MEAN ST.DEV. N	76.3 3.5 2	68.7 4.9 2
PITUITARY (%)	MEAN ST.DEV. N	0.0886 0.0087 2	0.0967 0.0192 2
HEART (%)	MEAN ST.DEV. N	97.0 13.3 2	97.6 1.1 2
LIVER (%)	MEAN ST.DEV. N	471.1 99.3 2	489.1 77.0 2
THYROID(L) (%)	MEAN ST.DEV. N	0.5629 0.0795 2	0.6173 0.1403 2
THYROID(R) (%)	MEAN ST.DEV. N	0.4725 0.0763 2	0.4651 0.1347 2
KIDNEY(L) (%)	MEAN ST.DEV. N	32.95 5.78 2	37.96 2.51 2
KIDNEY(R) (%)	MEAN ST.DEV. N	32.08 1.59 2	36.21 0.01 2
ADRENAL(R) (%)	MEAN ST.DEV. N	1.1872 0.2229 2	0.9546 0.0508 2
ADRENAL(L) (%)	MEAN ST.DEV. N	1.0353 0.2762 2	0.8668 0.0170 2
SPLEEN (%)	MEAN ST.DEV. N	45.43 0.37 2	61.50 23.33 2

CLINICAL SIGNS

All clinical signs observed during pretest and the scheduled treatment period and, where appropriate, the recovery period are reported.

The number in parentheses following each sign is the maximum grading. These are defined as (1), sign present, no severity designated; (2), where 1 = slight, 2 = marked and up to (3), where 1 = slight, 2 = moderate and 3 = marked. When a number of observations are recorded on the same day the maximum grading recorded is reported.

The animals were examined at regular intervals from the commencement of pretest for signs of oestrus. There was no evidence that the time of onset of oestrous cyclical activity nor the duration of these cycles were affected by treatment. Therefore, the data are not reported but are retained in the raw data.

Body temperature and, on occasions, pulse were recorded to monitor the general health status of animals showing inappetence and on occasion apathy. The data recorded were generally within the expected range and are therefore not reported, but are retained as raw data.

INDIVIDUAL DATA AVAILABLE ON REQUEST