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Report

Laboratory Code:	LU 55686
INN:	Ademetionine
Report No.:	MPF/WT 9215 E
Date of Report:	8 June 1995
Title:	S-Adenosyl-L-Methionine 1,4 Butane-disulfonate (SAMe SD_4) 52-week chronic toxicity (gavage) study in the rat
Reported by:	H Schmid, B Keller, H Luetkemeier, K Weber, J T Wilson, P Giulidori
Study Facility:	RCC, Research and Consulting Company Ltd, CH-4414 Füllingsdorf/Switzerland
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Pages Report:	1885
Annex:	
Dossier Part:	III B
Text File:	BfT/WT/WT 9215 E

Knoll AG
Research and Development
P.O. Box 21 08 05
D-67008 Ludwigshafen
Germany

REPEATED DOSE TOXICITY: Chronic toxicity (beyond 3 months)

Ref. to document: Volume: **Page:** **to** **Addendum No.:**
Report date: 8 June 1995 **Number:** MPF/WT 9215E **Study period (years):** 1992 - 1993

Species/Strain: rat, Sprague-Dawley, SPF-quality

Number of animals: 440 | **Duration of treatment:** 52 weeks

Observation period after the end of dosing: 8 weeks

Administration route: oral, by gavage

Treatment of controls: Distilled water

Age: approx. 4 weeks **at study initiation:**
Body weight: m: 52 - 106 g, f: 47 - 73 g

Treatment days per week: 7 days

Study group	**(1) Contr.**		**(2)**		**(3)**		**(4)**	
Dosage <mg/kg/day>	0		440 (869)*		1000 (1976)*		2 x 1000 (2 x 1976)*	
Sex (m/f)	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**
Number of test animals	55	55	55	55	55	55	55	55
Number of animals died or sacrificed in extremis	7	3	3	4	3	3	2	2

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 examination

Additional information:* Active dose levels relate to the SAMe ion, which represents 50.6 % of SAMe SD_4. Accordingly, the required quantity of SAMe SD_4 was attained by applying a correction factor of 1.976 to the nominal active (SAMe ion) dose levels (= total dose indicated in brackets)

Histology performed according to EEC Notes for Guidance: yes <X> no < >
Study conducted 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/Basel
Study in compliance with GLP: yes <X> no < > not required < >

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

Ref. to document: Volume: Page: to Addendum No.:
Report date: 8 June 1995 Number: MPF/WT 9215E Study period (years): 1992 - 1993

Important findings:	Group 2		Group 3		Group 4	
	M	F	M	F	M	F
Clinical signs						
Diarrhea (fluid/soft stool) [max. incidence]			I,r (>95 %)	I,r (35 %)	I,r (>95 %)	I,r (>95 %)
Food consumption (mean difference from controls)			D,r (7 %)	D,r (5 %)	D,r (12 %)	D,r (15 %)
Body weight (mean difference from controls)			D (12 %)	D (10 %)	D (18 %)	D (15 %)
Relative food consumption (mean difference from controls)						D,r (5 %)
Haematology						
Erythrocyte count (RBC)				D*,r,+ at week 16	D*,r,+ at week 16	D*,r,+ at week 8,16
Haemoglobin (HB) concentration				D*,r,+ at weeks 8,16	D*,r,+ at weeks 8,16	D*,r,+ at weeks 8,16
Mean corpuscular HB concentration (MCHC)				D*,r,+ at week 8	D*,r,+ at weeks 8,16, 52	D*,r,+ on day 2, at weeks 8,16,52
Haematocrit (HCT)					D*,r,+ at week 16	D*,r,+ at weeks 8,16
Reticulocyte count (rel./abs.)				D,r,+ at week 16		D*,r,+ at weeks 8,16
Thromboplastine time (PT)					I*,r,+ at weeks 16,26,52	I*,r,+ at week 52
Activated partial thromboplastin time (APTT)			D*,r,+ at weeks 8,26,52	D*,r,+ at week 52	D*,r,+ at weeks 8,26,52	D*,r,+ at week 52
Clinical biochemistry						
Glucose					D*,+ at weeks 8, 16, 26, 52, 60	D*,+ at weeks 8,16,52, 60
Urea			I*,r,+ at weeks 16,26,52		I*,r,+ at weeks 16,26,52	I*,r,+ at weeks 8,16,26,52
Creatinine					I*,r,+ at weeks 8,26	I*,r,+ at week 8
Total bilirubin					I*,r,+ at weeks 16,26	I*,r,+ at weeks 8,16,26,52
Total cholesterol				I*,r,+ at weeks 16, 26,52,60		I*,r,+ at week 26
Triglyceride						I*,r,+ at weeks 16,26
Aspartate aminotransferase (ASAT)					I*,r,+ on day 2	I*,r,+ on day 2

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, [ ] due to abnormal control values, r = reversible after 8 weeks recovery period

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

Ref. to document: Volume: Page: to Addendum No.:
Report date: 8 June 1995 Number: MPF/WT 9215E Study period (years): 1992 - 1993

Important findings:	Group 2		Group 3		Group 4	
	M	F	M	F	M	F
Clinical Biochemistry (cont'd.)						
Alanine aminotransferase (ALAT)			I*,r,+ at week 52		I*,r,+ at weeks 8,16,26,52	I*,r,+ at weeks 8,16,26,52
Lactate dehydrogenase (LDH)					I*,r,+ at weeks 16,26	I*,r,+ at weeks 8,52
Alkaline phosphatase (ALP)			I*,r,+ at week 26		I*,r,+ at weeks 16,26,52	I*,r,+ at weeks 26,52
Calcium				I*,r,+ at week 16	D*,r,+ at week 8	I*,r,+ at weeks 16,52
Phosphorus				I*,r,+ at weeks 26,52	I*,r,+ at weeks 26,52	I*,r,+ at weeks 16,26,52
Sodium					D*,r,+ at weeks 8,16	
Potassium					D*,r,+ at weeks 26,52	D*,r,+ at weeks 16,52
Chloride					I*,r,+ at weeks 8,16, 52	
α_2-globulin fraction (abs., rel.)		D*,r,+ at week 26		D*,r,+ on day 2, at weeks 8,16, 26,52	D*,r at weeks 8,60	D*,+ on day 2, at weeks 8,16, 26,52,60
γ-globulin fraction (abs., rel.)					D*,r,+ at week 16	D*,r,+ at week 16
Urinalysis						
Volume					D*,r,+ on day 2, at weeks 8,26,52	
Specific gravity	I*,r,+ on day 2, at week 52		I*,r,+ on day 2, at weeks 8,16,26,52	I*,r,+ at weeks 8,52	I*,r,+ on day 2, at weeks 8,16,26,52	I*,r,+ on day 2, at weeks 8,16, 26,52
pH	D*,r,+ at weeks 8,16,26,52	D*,r,+ at weeks 16,52	D*,r,+ at weeks 8,16,26,52	D*,r,+ at weeks 16,52	D*,r,+ at weeks 8,16,26,52	D*,r,+ at weeks 8,26
Protein score					I*,r,+-++ on day 2	I*,r,0,+-++ on day 2
Blood score					I+,r,+ on day 2	I*,r,+ on day 2, at weeks 16,52
γ-Glutamyltransferase (G-GT)	I*,r,+-++ at weeks 8,26,52	I*,r,++ at weeks 8,16,26,52	I*,r,+-++ at weeks 8,26,52	I*,r,+-++ at weeks 8,16,26, 52,60	D*,-,+ at weeks 26,52	
Lactate dehydrogenase (LDH)					I*,r,+-+++ on day 2, at weeks 8,16,26	I*,r,+++ on day 2, at weeks 16,26,52
Alkaline phosphatase (ALP)	I*,r,+ at weeks 8,16,52	I*,r,+-++ at weeks 8,16,26,52	I*,r,+ at week 8	I*,r,++ at weeks 16,26,52	I*,r,++ on day 2, D,r,+ at week 26	I*,r,+++ on day 2

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, [ ] due to abnormal control values, r = reversible after 8 weeks recovery period

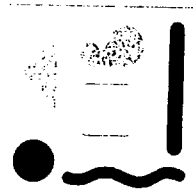
REPEATED DOSE TOXICITY: Chronic toxicity (beyond to 3 months)

Ref. to document: Volume: **Page:** **to** **Addendum No.:**
Report date: 8 June 1995 **Number:** MPF/WT 9215E **Study period (years):** 1992 - 1993

Important findings:	Group 2		Group 3		Group 4	
	M	F	M	F	M	F
Urinalysis (cont'd.)						
Leucine aminopeptidase (LAP)	I*,r,+ at weeks 8,52	I*,r,+ at weeks 16,26,52		I*,r,+ at weeks 8,52	I*,r,+-+++ on day 2, D*,r,+ at weeks 16,26,52	
β-N-acetyl-D-glucosaminidase (BNAG)					I*,r,+-++ on day 2, at week 16	I*,r,+-++ on day 2, at weeks 16,26,52
Sodium excretion	I*,r,++ at week 16	I*,r,+ at week 52	I*,r,+-+++ on day 2, at weeks 8,16 26,52	I*,r,+ on day 2, at week 26	I*,r,+-+++ on day 2, at weeks 8,16,26,52	I*,r,+-++ at weeks 8,16,26,52
Potassium excretion	D*,r,+ at week 26	D*,r,+ at week 8	D*,r,+ on day 2, at weeks 8,16	D*,r,+ at week 8	D*,r,+ on day 2, at weeks 8,16,26	D*,r,+ on day 2, at week 8
Total protein						I*,r,+ on day 2, at weeks 8,16
Creatinine excretion				D*,+ at week 60	D*,+ at weeks 8,16,26, 52,60	D*,r,+ on day 2, at weeks 16,26,52
Creatinine clearance				D*,+ on day 2 at week 60	D*,r,+ at weeks 8,16,26,52	D*,r,+ on day 2, at weeks 8, 16,26,52
Organ weight changes (rel.) Kidneys (mean differences from control)				I* (29 %)	I* (28 %),r	I* (58 %)
Macroscopical findings Dilated cecum/liquid contents			+,r	+,r	+,r	+,r
Microscopic findings (mean severity in brackets)						
Kidneys: tubular vacuolisation	n = 28,r (1.6)	n = 7,r (1.4)	n = 35,r (1.9)	n = 19,r (1.2)	n = 36,r (2.1)	n = 22,r (1.1)
tubular dilatation	n = 6,r (1.5)	n = 3,r (1.3)	n = 6,r (1.7)	n = 13,r (1.4)	n = 19,r (1.5)	n = 21,r (1.4)
Testes: focal interstitial cell hyperplasia	n = 1,r (1.0)		n = 2 (1.0)		n = 12 (1.6)	
Sciatic nerve: mineralisation	n = 7 (1.1)		n = 11 (1.1)	n = 1 (1.0)	n = 14 (1.5)	n = 3 (1.0)
	[4 control males and 1 control female were also affected (1.0)]					

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, [ ] due to abnormal control values, r = reversible after 8 weeks recovery period



S-ADENOSYL-L-METHIONINE 1,4-BUTANEDISULFONATE ($SAMe\ SD_4$)

52-WEEK CHRONIC TOXICITY (GAVAGE) STUDY IN THE RAT

REPORT

PART I

Data Requirements:	OECD Guideline 452 (1981)
Authors:	H. Schmid, B. Keller, H. Luetkemeier, K. Weber, J.T. Wilson, P. Giulidori
Performing Laboratories:	1) RCC, RESEARCH AND CONSULTING COMPANY LTD. P.O. Box, CH-4452 Itingen/Switzerland 2) BRL, BIOLOGICAL RESEARCH LABORATORIES LTD. CH-4414 Füllinsdorf / Switzerland 3) EPS, (U.K.) Willow Court Netherwood Road Hereford HR2 6JU, U.K. 4) BioResearch 20060 Liscate (Milan)/Italy
RCC Project:	311545
KNOLL Project:	MPF/WT 9215 E

RCC

Group

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE

KNOLL PROJECT NUMBER	:	MPF/WT 9215 E
RCC PROJECT NUMBER	:	311545
TEST ARTICLE	:	S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4)
STUDY DIRECTOR	:	Dr. H. Schmid
TITLE	:	52-week chronic toxicity (gavage) study with S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4) in the rat.

The conduct of this study at RCC was in compliance with the Good Laboratory Practice regulations listed on page 11.

Study Director — Dr. H. Schmid

H. Schmid

date: June 08, 1995

Managing Director — T.R. Allen

date: 11 May 1995

QUALITY ASSURANCE STATEMENT

RCC, RESEARCH AND CONSULTING COMPANY LTD,
4452 ITINGEN/SWITZERLAND

KNOLL PROJECT NUMBER	:	MPF/WT 9215 E
RCC PROJECT NUMBER	:	311545
TEST ARTICLE	:	S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4)
STUDY DIRECTOR	:	Dr. H. Schmid
TITLE	:	52-week chronic toxicity (gavage) study with S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4) in the rat.

The conduct of this study was subjected to periodic inspections and the report was 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
12.10.92	12.10.92
28.10.92	28.10.92
03.11.92	03.11.92
17.12.92	17.12.92
11.02.93	11.02.93
15.04.93	15.04.93
10.06.93	10.06.93
03.08.93	03.08.93
17.08.93	17.08.93
22.10.93	22.10.93
27.10.93	27.10.93
17.12.93	17.12.93
21.12.93	21.12.93
16.12.94	
19.-23.12.94	
27.-30.12.94	
03.01.95	03.01.95
01.06.95	01.06.95
02.06.95	02.06.95

Manager, Quality Assurance Unit Dr. G. Menne

CONTENTS

PART I

CONTENTS (CONT'D)

CONTENTS (CONT'D)

PREFACE

GENERAL

Title	52-week chronic toxicity (gavage) study with S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4) in the rat.
Sponsor	KNOLL AG Postfach 21 08 05 D-67008 Ludwigshafen/Rhein Germany
Study Monitor	Dr. V. Bühler
Testing Facilities	RCC, Research and Consulting Company Ltd. CH-4452 Itingen / Switzerland BRL, BIOLOGICAL RESEARCH LABORATORIES LTD. CH-4414 Füllinsdorf / Switzerland EPS, (U.K.) for histotechnique Willow Court Netherwood Road Hereford HR2 6JU, U.K. BioResearch 20060 Liscate (Milan)/Italy
RCC Project Number	311545
KNOLL Number	MPF/WT 9215 E
Test Article	S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4)
Test System	Rat

PROJECT STAFF

Study Director/ Study Veterinarian	Dr. H. Schmid
Nominated Deputy for Study Director	Dr. A. Dotti
Technical Coordinators	D. Probst (until Sept. 30, 1993) M. Cassidy B. Keller (for report finalization)

PROJECT STAFF (cont'd)

Clinical Laboratory Investigations	H. Luetkemeier (BRL)
Necropsy/Histotechnique	Dr. K. Weber
Histopathology	Dr. J.T. Wilson
EDP and Statistics	TEC Terrier EDV Consulting AG Schneckelerstrasse 9 CH-4414 Füllinsdorf/Switzerland
Analytical Chemistry	Dr. P. Giulidori (BioResearch) 20060 Liscate (Milan)/Italy

SCHEDULE

Delivery of animals	males: October 13, 1992 females: October 14, 1992
Pretest	males: October 13, - October 26, 1992 females: October 14, - October 27, 1992
Administration	males: October 27, 1992 - termination for Allocation A and up to October 25, 1993 for Allocation B females: October 28, 1992 - termination for Allocation A and up to October 26, 1993 for Allocation B
Recovery (Allocation B)	males: October 26, 1993 - termination females: October 27, 1993 - termination
Termination	Allocation A males: October 27, 1993 - November 04, 1993 females: October 28, 1993 - November 05, 1993 Allocation B males: December 21, 1993 - December 23, 1993 females: December 22, 1993 - December 23, 1993
Report	June, 1995

ARCHIVING

The Research and Consulting Company Ltd. (CH 4452 Itingen / Switzerland) will archive the following data for at least ten years: protocol, report, copy of report, all specimens, raw data and reference sample of test article.

PROJECT STAFF SIGNATURES

Study Director/Study Veterinarian — Dr. H. Schmid

H. Schmid
date: June 08, 1995

Nominated Deputy for Study Director — Dr. A. Dotti

date: 12-MAY-1995

Technical Coordinator — B. Keller

date: May 12, 1995

Clinical Laboratory Investigations — H. Luetkemeier

date: 12-MAY-1995

Necropsy/Histotechnique — Dr. K. Weber

K. Weber
date: May 12, 1995

Histopathology — Dr. J.T. Wilson

date: May 12, 1995

EDP and Statistics — W. Thüring

date: May 12, 1995

Managing Director — T.R. Allen

T.R. Allen
date:

GLP GUIDELINES

This study was conducted in compliance with:

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

"Non-clinical Laboratory Studies - Good Laboratory Practice Regulations", Food and Drug Administration, U.S.A. Federal Register, Vol. 52, no. 172, September 04, 1987.

OECD Principles of Good Laboratory Practice, OECD, Paris, 1981.

Good Laboratory Practice (GLP) Procedures according to "Gesetz zum Schutz vor gefährlichen Stoffen (Chemikaliengesetz)", Bundesrepublik Deutschland, Appendix 1, Bundesgesetzblatt Nr. 13, Bonn, March 22, 1990.

TEST GUIDELINE

"Chronic Toxicity Studies", OECD Guidelines for the Testing of Chemicals, Section 4, Health Effects, Number 452, May 12, 1981.

SUMMARY OF PROTOCOL AMENDMENTS

First Amendment

- Ophthalmoscopic examinations at 51 weeks were rescheduled for operational reasons.

Second Amendment

- The extent of histopathology was redefined.

SUMMARY

GENERAL

In this chronic toxicity study S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4) was administered to Sprague-Dawley rats by daily gavage for a period of 52 weeks. The dose levels used were 1 x 0, 1 x 440, 1 x 1000 and 2 x 1000 mg SAMe/kg/day. The study comprised four groups of 55 males and 55 females each. After 52 weeks of treatment each 15 animals per group and sex were allowed a 8-week treatment-free recovery period.

The following nomenclature is used in this report:

SAMe = active principle of the test article
SAMe SD_4 = salt of the active principle with 1,4-butanedisulfonic acid

RESULTS

Mortality

Survival was not affected by treatment with the test article.

Clinical Signs

Diarrhea (fluid/soft stool) was recorded for both sexes at 1000 and 2 x 1000 mg/kg with dose-related onset and/or incidence. This clinical sign reversed during the treatment-free recovery period, rapidly. No test article related clinical signs were noted in any other group.

Nodules and Masses

Treatment with the test article had no influence on the incidence or group distribution of palpable masses.

Ophthalmoscopic Examinations

There were no test article related findings.

Food Consumption

Mean food consumption over the treatment period was decreased in a dose-related manner in both sexes at 1000 and 2 x 1000 mg SAMe/kg but approached the control group level during the recovery period. No effects were seen in animals at 440 mg SAMe/kg.

Body Weight

Body weight was decreased in a dose-related manner for both sexes at 1000 and 2 x 1000 mg SAMe/kg by up to approximately 18% with the differences remaining during the recovery period. No effects were seen in animals at 440 mg SAMe/kg.

Relative Food Consumption

Average mean relative food consumption was marginally decreased by approximately 5 % in females at 2 x 1000 mg SAMe/kg during treatment. During the recovery period overall relative mean food consumption was increased in both sexes at 1000 and 2 x 1000 mg SAMe/kg thus reflecting the changes in food intake during that period. No effects on overall relative mean food consumption were seen in any other group.

Hematology

No effects were seen in animals at 440 mg SAMe/kg. The following slight effects on hematology parameters were noted in animals at 1000 and 2 x 1000 mg SAMe/kg during treatment:

- Decreased erythrocyte count (RBC), hemoglobin (HB) concentration and mean corpuscular hemoglobin concentration (MCHC) at 1000 and 2 x 1000 mg SAMe/kg, and decreased hematocrit (HCT) at 2 x 1000 mg SAMe/kg.

- Increased reticulocyte count (rel./abs.) at 1000 and 2 x 1000 mg SAMe/kg.

- Prolonged thromboplastin time (PT) at 2 x 1000 mg SAMe/kg and shortened activated partial thromboplastin time (APTT) at 1000 and 2 x 1000 mg SAMe/kg.

At termination of the treatment-free recovery period these findings were found to be reversed.

Clinical Biochemistry

Slight changes in clinical biochemistry parameters mostly affected animals at 2 x 1000 mg SAMe/kg with smaller effects seen in animals at 1000 mg SAMe/kg. The following changes were noted during treatment:

- Decreased glucose level at 2 x 1000 mg SAMe/kg.

- Increased urea level at 1000 and 2 x 1000 mg SAMe/kg, and increased creatinine level at 2 x 1000 mg SAMe/kg.

- Increased total bilirubin level at 2 x 1000 mg SAMe/kg.

- Increased total cholesterol level at 1000 and 2 x 1000 mg SAMe/kg, and increased triglyceride level at 2 x 1000 mg SAMe/kg.

- Increased aspartate aminotransferase (ASAT) activity at 2 x 1000 mg SAMe/kg and increased alanine aminotransferase (ALAT) activity at 1000 and 2 x 1000 mg SAMe/kg.

- Increased alkaline phosphatase (ALP) activity at 1000 and 2 x 1000 mg SAMe/kg and increased lactate dehydrogenase (LDH) activity at 2 x 1000 mg SAMe/kg.

- Increased calcium and increased phosphorus level at 1000 and 2 x 1000 mg SAMe/kg.

- Decreased sodium and potassium level, and increased chloride level at 2 x 1000 mg SAMe/kg.

- Decreased alpha 2-globulin fraction (abs./rel.) at 440, 1000 and 2 x 1000 mg SAMe/kg and decreased gammma-globulin fraction (abs./rel.) at 2 x 1000 mg SAMe/kg.

At the end of the treatment-free recovery period most of these findings were found to be reversed and comparable to those of the controls. The only changes to be noted were a decreased glucose level as well as a decreased alpha 2-globulin fraction at 2 x 1000 mg SAMe/kg. In addition, a decreased cholesterol level was observed at 1000 mg SAMe/kg. These findings may be attributed to the nutritional state of these animals.

Urinalysis

Changes observed in urinalysis parameters affected all treated groups with evidence of a dose- and time-relationship in most cases. The following effects were noted:

- Decreased volume at 2 x 1000 mg SAMe/kg and increased specific gravity at 440, 1000 and at 2 x 1000 mg SAMe/kg.

- Lower pH at 440, 1000 and 2 x 1000 mg SAMe/kg.

- Increased protein (score) and blood (score) at 2 x 1000 mg SAMe/kg.

- Increased gamma-glutamyltransferase (G-GT) activity at 440 and 1000 mg SAMe/kg but decreased at 2 x 1000 mg SAMe/kg.

- Increased lactate dehydrogenase (LDH) and beta-N-acetyl-D-glucosaminidase (B-N-AG) activity at 2 x 1000 mg SAMe/kg.

- Increased alkaline phosphatase (ALP) and leucine aminopeptidase (LAP) activity at 440, 1000 and 2 x 1000 mg SAMe/kg. At 2 x 1000 mg SAMe/kg, the initial increase was followed by a decrease in these enzymes.

- Increased urinary sodium and decreased urinary potassium excretion at 440, 1000 and 2 x 1000 mg SAMe/kg.

- Increased total protein at 2 x 1000 mg SAMe/kg.

- Decreased creatinine excretion and creatinine clearance at 1000 and 2 x 1000 mg SAMe/kg.

After the treatment-free recovery period the only notable changes were: a decreased creatinine excretion at 2 x 1000 mg/kg, a decreased creatinine excretion and creatinine clearance at 1000 mg SAMe/kg, and an increased gamma-glutamyltransferase (G-GT) activity at the latter dose. All other changes were found to be reversed.

Organ Weights

The relative kidney weight was increased in females at 1000 mg SAMe/kg (by 29%) and both sexes at 2 x 1000 mg SAMe/kg (in males by 28%, in females by 58%) at the end of treatment. In females, these changes were still persistent after the recovery period. No treatment-related changes were seen in any other group.

Macroscopical Findings

At terminal necropsy the finding of dilated cecum with liquid contents distinguished treated animals from controls mainly affecting rats at 1000 and 2 x 1000 mg SAMe/kg. This finding was not present following the recovery phase.

Microscopical Findings

Non-neoplastic Lesions:

A microscopic correlate to the above macroscopic observation was not in evidence. Microscopic findings with an increased incidence were present in the kidneys, sciatic nerve and testes.

A dose related increase in minimal to severe tubular vacuolation and minimal to slight tubular dilation was noted in the kidneys. All treated groups were affected. However, following the recovery period both findings were almost completely reversed. These findings were regarded as reversible adaptive responses.

Chiefly minor degrees of focal mineralization of the nutrient blood vessels of the sciatic nerve were recorded in all groups, almost exclusively in males and were increased in incidence with dose of the test article. This finding was not reversed after recovery. However, it was not found in a contemporary two year study at similar doses of SAMe SD_4, and therefore the relationship to the test article is regarded equivocal.

In the testes there was dose related increase in minimal to moderate degrees of interstitial cell hyperplasia, which was not present in controls. All treated groups were affected and the finding was still in evidence following the recovery period. In the aforementioned contemporary two year study this finding was present at a lower incidence and showed no relationship to treatment. Hence, it is considered, that the incidences recorded in this study may have been due to chance or may also have been transitory in nature.

Neoplastic Lesions:

There was no treatment-related increase in the incidence of neoplastic lesions. On the contrary, the incidence of neoplasms was slightly higher in controls than in treated groups.

ASSESSMENT

The daily administration of S-Adenosyl-L-Methionine 1,4 Butanedisulfonate (SAMe SD_4) to Sprague-Dawley rats by gavage at doses of 440, 1000 and 2 x 1000 mg SAMe/kg for a period of 52 weeks produced treatment-related effects in the kidneys at all doses. The kidney lesions consisted of tubular vacuolation and dilatation, and were found to be reversible after the treatment-free recovery period.

During the study decreased food consumption, decreased body weight and diarrhea (soft/fluid stool) were noted in animals at 1000 and 2 x 1000 mg SAMe/kg. The latter finding is thought to be due to an osmotic effect of the test article (a salt) within the gut. This is compatible with the necropsy finding of dilated cecum with liquid contents mainly recorded in animals at these doses.

Early in the study, increases in urinary enzymes pointed at the kidney as target organ. Generally, the effects were observed first at the high dose but with the progression of the study became also apparent at mid and low dose, the effects being slight at 440 mg SAMe/kg. Later in the study, similar or even lower urinary excretion of some enzymes (alkaline phosphatase, leucine aminopeptidase, gamma-glutamyltransferase) was noted for animals at the high dose when compared with the controls possibly indicating regeneration despite continued treatment. Other changes in urinary parameters of the high dose group like the decrease in creatinine excretion and clearance, the presence of blood and protein indicated an impaired renal function. This is further supported by the altered blood electrolytes levels.

The few other effects on clinical biochemistry parameters mostly noted in animals at mid and high dose may be attributed to metabolic adaptation and/or to the nutritional status of the animals.

Hematology data are pointing at a mild anemia in animals at mid and high dose as indicated by a decrease in erythrocyte count and an increase in reticulocytes. These changes were found to be reversed after the recovery period.

At the end of treatment, histopathology showed a dose-related increase of renal tubular vacuolation and dilatation. Both clinical laboratory and morphological kidney findings were almost completely reversed after the recovery period, and therefore are considered to be functional adaptive responses possibly due to an osmotic effect of the test article.

Minor degrees of focal mineralization of the nutrient blood vessels of the sciatic nerve were recorded in all groups, almost exclusively affecting males and were increased in incidence with dose of the test article. After recovery this finding was still present. However, it was not found in a contemporary two year study at similar doses of SAMe SD_4, and therefore the relationship to the test article is considered equivocal.

Minimal to moderate degrees of interstitial cell hyperplasia of the testes were seen in all treated groups at the end of treatment but not in controls, and was still in evidence after the recovery period. This finding was present at a lower incidence in the aforementioned two year study, and showed no relationship to treatment. Hence, it is considered, that in the present study it may have been due to chance or may also have been transitory in nature.

In this study the "no-toxic-effect level (NTEL)" is considered to be 440 mg SAMe/kg.

OBJECTIVE

PURPOSE / RATIONALE

The purpose of this 52-week study was to assess the chronic toxicity of SAMe SD_4 when administered to rats by gavage for one year, and to assess the reversibility of any treatment-related changes after a 8-week recovery period.

This study should provide a rational basis for toxicology risk assessment in man.

MATERIALS AND METHODS

Experimental Design

TEST SYSTEM

Test system	IcoIbm:OFA Sprague-Dawley Rat, SPF quality.
Rationale	Recognized by the international guidelines as the recommended test system.
Source	BRL Biological Research Laboratories Ltd. CH-4414 Füllinsdorf / Switzerland
Total number of animals	220 males, 220 females.
Age (at delivery from the breeder)	approximately 4 weeks.
Body weight and range (at delivery from the breeder)	males: 52-106 grams (mean: 81 grams) females: 47- 73 grams (mean: 59 grams)
Identification	Individual ear number (tattoo).
Randomization	Computer-generated random algorithm.
Acclimation	14 days under test conditions, with a veterinary examination.

ALLOCATION

Active Dose (mg SAMe ion/kg body weight/day)		Group 1 1 x 0	Group 2 1 x 440(869)*	Group 3 1 x 1000(1976)	Group 4 2 x 1000 (1976) interval between dosing: 6 hours
Males	A	1- 40	56- 95	111-150	166-205
	B	41- 55	96-110	151-165	206-220
Females	A	221-260	276-315	331-370	386-425
	B	261-275	316-330	371-385	426-440

A - Main study and Ophthalmoscopic Examinations
B - Clinical Laboratory Examination and Recovery Group (8 weeks)

* Values in brackets indicate total dose (mg SAMe SD_4/kg body weight/day)

HUSBANDRY

Room Number: E11/12 (RCC Itingen)

Conditions:
The study was conducted under Optimal Hygienic Conditions behind a barrier system. The animals were housed individually in Makrolon type-3 cages with wire mesh tops and granulated softwood bedding (Lignocel, Schill AG, Muttenz/ Switzerland). Before use, the bedding was autoclaved at 120°C for 50 minutes. The animal room was air-conditioned with 10-15 air changes per hour, the temperature was 22±3°C, the relative humidity was 40-70%, the light/dark cycle was 12 hours of artificial fluorescent light each day. Music was played during each light period for at least 8 hours.

Diet:
The diet was pelleted standard Kliba 343 rat/mouse maintenance diet ("Kliba", Klingentalmuehle AG, 4303 Kaiseraugst/Switzerland), and was available ad libitum. Results of contaminant analyses in the diet batches used are included in this report (see Attachment 1, page 863).

Water:
Tap water was available ad libitum via water bottles. Results of bacteriological, chemical and contaminant analyses conducted by RCC (contaminant analyses only) and the Official Chemist of the Kanton Basel-Landschaft (bacteriological and chemical analyses) are included in this report (see Attachment 2, page 886)

TEST ARTICLE

Identification	S-Adenosyl-L-Methionine 1,4-Butanedisulfonate (SAMe SD_4)
Description	White powder
Batch number	920700729
Purity	SAMe ion: 50.6% according to BioResearch Analytical Report of September 09, 1992.
Stability of test article	Expiration date: September, 1994 according to re-analysis of August 31, 1993 performed by BioResearch.
Instructions for test article storage	In well closed containers at a temperature not more than 4°C.

TREATMENT

Method	Oral, by gavage.
Rationale	Simulates the route of human exposure.
Frequency	Once daily, with the exception of group 4 animals, which were dosed twice daily with a time interval of 6 hours between dosing.

Dose levels*

	Active Daily Dose (SAMe ion)	Total Dose (SAMe SD_4)	
Group 1:	0	0	mg/kg body weight/day
Group 2:	440	869	mg/kg body weight/day
Group 3:	1000	1976	mg/kg body weight/day
Group 4:	2x1000	2x1976	mg/kg body weight/day

Active dose levels for groups 2, 3 and 4 relate to the SAMe ion, which represents 50.6 % of SAMe SD_4. Accordingly, the required quantity of SAMe SD_4 was attained by applying a correction factor of 1.976 to the nominal active (SAMe ion) dose levels (= total dose).

Rationale	Based upon the results of a multiple daily dosing (gavage) study with SAMe SD_4 in rats (RCC project 324415).
Vehicle (Solvent)	Distilled water. Control animals were treated with distilled water only, the pH of which was adjusted to 5.5 to 6.2, if necessary.

* During treatment days 82 to 85 (males) respectively 81 to 84 (females) inadvertently too low doses were administered based on body weights recorded

TREATMENT (cont'd)

Stability of Test Article Dosing Solutions	4 hours at room temperature (<25°C): groups 2 and 3 at maximum 6 hours at 3°C and subsequent 4 hours at room temperature (<25°C): group 4 4 days at -20°C
Dose volume	5 ml/kg body weight/day (groups 1-3) 2x5 ml/kg body weight/day (group 4)
Duration of acclimatization period	14 days.
Duration of treatment	52 weeks.
Duration of recovery period	8 weeks.
Safety precautions	Routine hygienic procedures were applied to assure personnel health and safety.

TEST ARTICLE PREPARATION

Solutions of SAMe SD_4 were prepared according to instructions of BioResearch Milan (see Attachment 4, page 904). The pH of dosing solutions (incl. control) was adjusted to 5.5-6.2.

Dosing Solutions were prepared once daily.

TEST ARTICLE ANALYSES IN DOSING SOLUTIONS

Ten ml of each dosing solution (incl. control) were sampled at week 1 and at month 3, 6, 9 and 12 prior to and after dosing and stored deep-frozen (-80°C) until shipment to BIORESEARCH (Dr. P. Giulidori) for analyses.

Observations

VIABILITY / MORTALITY

Each rat was checked for viability twice daily.

CLINICAL SIGNS/NODULES AND MASSES

The animals were examined for clinical signs of toxicity at least once daily. In addition to the daily observations, each rat had a weekly detailed clinical examination which included a palpation for tissue masses. A description of any lesion or mass observed at any examination was recorded and the subsequent progress monitored.

FOOD CONSUMPTION

The food consumption was recorded for a 7-day period. The data were recorded weekly until week 13 and twice monthly thereafter, using an on-line electronic recording system consisting of a Mettler balance connected to the RCC computer system.

BODY WEIGHTS

The body weight of each animal was recorded weekly until week 13 and twice monthly thereafter, using an on-line electronic recording system consisting of a Mettler balance connected to the RCC computer system.

OPHTHALMOSCOPIC EXAMINATIONS

Ophthalmoscopic examinations were performed on all allocation A animals at pretest (October 15/16, 1992) at week 25 (April 15/16, 1993) and at 52 weeks (October 19/20, 1993).

Ten minutes after the application of a mydriatic solution (Dispersa AG, Winterthur/Switzerland) the cornea, lens, anterior chamber, vitreous body and ocular fundus of both eyes were examined using a Heine Miroflex 2 Ophthalmoscope (Eisenhut Vet. AG, Allschwil/Switzerland).

A description of any abnormality was recorded.

Clinical Laboratory Investigations

GENERAL

Blood samples for hematology and clinical biochemistry were collected from all allocation B animals under light ether anesthesia. The animals were fasted for approximately 18 hours before blood sampling but allowed access to water ad libitum. Blood samples were collected from each animal between 06.00 and 09.10h to reduce biological variation caused by circadian rhythms. Blood samples were drawn from the retro-orbital plexus using a micro-hematocrit glass capillary tube.

Urine was collected on ice during the 18-hours fasting period into a specimen vial, using a metabolism cage. High dose group animals were placed in metabolism cages after the second application of the respective day.

Blood and urine sampling:

At day 2	28/29 - October - 1992
At 08 weeks	17/18 - December - 1992
At 16 weeks	11/12 - February - 1993
At 26 weeks	22/23 - April - 1993
At 52 weeks	21/22 - October - 1993
At 60 weeks	16/17 - December - 1993

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.

The summary and individual tables were generated by a computer. The program used 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:
NV = no value for one or more parameters
HEM = hemolytic sample

General remarks:
Explanatory notes for data not presented in the tables, see page 615.

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-K2 (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
(Instrumentation Laboratory, Lexington,Ma/U.S.A)

Ci-Trol-1 (normal range)
Ci-Trol-2 (high abnormal range)
(Baxter Dade AG, Duedingen/Switzerland)

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

Parameter	Method / Instrumentation	Unit
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
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	

Parameter	Method / Instrumentation	Unit
	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
	Normal red cell morphology key: score = 0	
	Abnormal red cell morphology key: score = 1, 2, or 3	1=slight 2=moderate 3=marked
	POLY. = Polychromatophilia	
Coagulation:		
Thromboplastin time (=Prothrombin 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 (*) recommendation) - Instrumentation Laboratory (IL) ACL 300 Coagulation System	sec
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

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

CLINICAL BIOCHEMISTRY

The following anticoagulant was used during blood collection:
Lithium heparin (63 U.S.P. Units).

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

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

Qualitrol® Protein (for the assay control of protein electrophoresis)
(E.Merck,Darmstadt/Germany)

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
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
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

* Reference controls used at day 2 and at 8, 16 and 26 weeks.
** Reference controls used at 52 and 60 weeks.

Parameter	Method / Instrumentation	Unit
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)
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)
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
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
Albumin	Bromocresol green (BCG) - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	g/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 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 standard method:

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

The following commercial reference controls were used to monitor the performance of the additional parameters measured in 18-hour urine samples:

- Lyphochek Quantitative Urine Control - Normal I and Abnormal II - (for the assay control of Sodium, Potassium, Protein T. and Creatinine)
  (Bio-Rad, ECS Division, Anaheim, California/USA)

- Qualitrol N / Qualitrol H* and Qualitrol HS-N / Qualitrol HS-P**
  (for the assay control of G-GT, LDH and ALP)
  (E. Merck, Darmstadt/Germany)

- Precinorm U/Precipath U
  (for the assay control of LAP)
  (Boehringer Mannheim GmbH, Mannheim/Germany)

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

Parameter	Method / Instrumentation	Unit
Volume (18-hour)	Metabolism cage (Model K. Ehret & Co., Emmendingen/Germany)	ml
Specific gravity (SPEC. GRAV.)	Atago Uricon Refractometer	1
pH	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames)	-
Protein	Reagent-Test-Strip (Ames Multistix 10 SG) - Clini-Tek 200 Semi-Automated Urine Chemistry Analyzer (Ames) Questionable results are confirmed with Albustix Reagent-Test-Strip (Ames)	score: 0=negative/trace 1=0.3 g/l 2=1.0 g/l 3=$\geq$3.0 g/l

* Reference controls used at day 2 and at 8, 16 and 26 weeks.
** Reference controls used at 52 and 60 weeks.

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=neg mmol/l 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

Parameter	Method / Instrumentation	Unit
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 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 TRIP.PHOS. = Triple phosphate crystals CA.PHOS. = Calcium phosphate	

Parameter	Method / Instrumentation	Unit
Additional parameters measured in 18-hour urine samples:		
Gamma-glutamyl-transferase (G-GT)	Kinetic colorimetric method based on the procedure of Szasz, using L-gamma-glutamyl-3-carboxy-4-nitro-anilide as substrate - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	nkat/18h (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)	nkat/18h (37°C)
Alkaline phosphatase (ALP)	Kinetic chromogenic method measuring the formation of p-nitrophenylate (hydrolysis of p-nitrophyl-phosphate, diethanolamine buffer pH 9.8). Method based on German Soc. of Clin.Chem. (DGKG) recommendations. - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	nkat/18h (37°C)
Leucine amino-peptidase (LAP)	Optimized kinetic method measuring the formation of p-nitroaniline at 405 nm (hydrolysis of L-leucine 4-nitroanilide at pH 7.5). Method based on German Soc. of Clin. Chem. (DGKC) recommendations - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	nkat/18h (37°C)
ß-N-Acetyl-D-glucosaminidase (ß-N-AG)	Colorimetric method based on the enzymatic hydrolysis of 3-Cresol-sulfonphthaleinyl-N-acetyl-ß-D-glucosaminide by ß-N-AG with the release of 3-cresolsulfonphthalein, sodium salt (3-cresol purple), which is measured at 580 nm - Epos Selective Analyzer 5060 (Eppendorf)	U/18h (37°C)

Parameter	Method / Instrumentation	Unit
Sodium	Flame emission photometry with internal lithium standard - Automated Flame Photometer System, AFM 5051 (Eppendorf)	mmol/18h
Potassium	Flame emission photometry with internal lithium standard - Automated Flame Photometer System, AFM 5051 (Eppendorf)	mmol/18h
Protein, total	Protein-dye binding method of Bradford using Coomassie Brilliant Blue (G-250) dye - Epos Selective Analyzer 5060 (Eppendorf)	g/18h
Creatinine	Jaffé-reaction without deproteinization, kinetic - Eris Selective Multi-Test Analyzer 6170 (Eppendorf/Olympus)	µmol/18h
Creatinine clearance (CREAT.Cr.)	Endogenous clearance test. Calculated value based on the creatinine concentration of the urine ($U_{Cr.}$) and plasma ($P_{Cr.}$) and the urine flow rate in ml/min (V)	ml/min

$$\text{Creat.Cr.} = \frac{U_{Cr.} \times V}{P_{Cr.}}$$

Plasma Level Determinations

At least 1.5 ml of blood was collected on ice under light ether anesthesia from the retro-orbital plexus of the 10 allocation A animals with the lowest identification numbers per group and sex 15 minutes after dosing on the day of necropsy. Group 4 animals were dosed once, only, on the day of necropsy. The blood samples were collected in heparinized tubes (25 i.U./ml blood). Blood was centrifuged for 10 minutes at 3'000 g within 1 hour after sampling and processed according to instructions provided by BioResearch Milan (see Attachment 5, page 909). Plasma was stored deep-frozen until shipment to BioResearch Milan. Analyses were performed by BioResearch Milan. The results will be reported separately.

Blood sampling:
October 27/28/29 and November 01/02/03/04/05, 1993

Pathology

NECROPSY

After 52 weeks (allocation A) October 27/28/29 and
November 01/02/03/04/05, 1993
After 60 weeks (allocation B) December 21/22/23, 1993

All animals were weighed and necropsied. Descriptions of all macroscopic abnormalities were recorded. Necropsies were performed by experienced prosectors supervised by a veterinary pathologist. All animals surviving to the end of the observation period and all moribund animals were anesthetized by intraperitoneal injection of sodium pentobarbital and killed by exsanguination.

Representative samples of the left kidney (cortex, medulla, and cortico-medullary junction) from 5 high dose animals per sex (allocation A and B) were used for eventual electronmicroscopic investigations. These samples were fixed in a sodium-cacodylate buffered solutions of 2.5 % glutaraldehyde and sent to KNOLL AG.

Samples of the following tissues and organs were collected from all animals at necropsy and fixed in 4% neutral phosphate buffered formaldehyde solution:

Adrenal glands
Aorta
Brain
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with optic nerve and Harderian gland
Femur - including articular surface and bone marrow
Heart
Ileum
Jejunum
Kidneys
Larynx
Liver
Lungs - infused with formalin
Lymph nodes - mandibular, mesenteric
Mammary gland area of both sexes
Nasopharynx
Ovaries
Pancreas
Pituitary gland
Prostate gland
Rectum
Salivary gland - mandibular, sublingual
Seminal vesicles
Sciatic nerve
Skeletal muscle
Skin
Spinal cord - cervical, lumbar, mid-thoracic
Spleen
Sternum with bone marrow
Stomach

NECROPSY (cont'd)

Testes
Thymus
Thyroid gland
Tongue
Trachea
Urinary bladder - infused with formalin
Uterus
Vagina
Gross lesions/tissue masses and tumors

ORGAN WEIGHTS

The following organ weights were recorded on the scheduled dates of necropsy:

Adrenal glands
Brain
Heart
Kidneys
Liver
Ovaries
Pituitary gland
Spleen
Testes
Thyroid gland

HISTOTECHNIQUE

All organ and tissue samples, as defined under Histopathology (see below) were processed, embedded and cut at a nominal thickness of 4 micrometers and stained with hematoxylin and eosin.

HISTOPATHOLOGY

Slides (one stained section unless otherwise stated in parentheses) of the following tissues collected at scheduled sacrifice from all animals of the control and high dose group as well as from all animals which died spontaneously or were terminated in extremis and all gross lesions from all animals were examined by a veterinary pathologist:

Adrenal glands (2), aorta, bone - femur and sternum, bone marrow - sternal and femoral, brain (4), epididymides (2), esophagus (2), eyes (2), Harderian glands (2), heart, kidneys (2), large intestine - cecum, colon, rectum; liver (2), lungs (2), lymphnodes - mesenteric and mandibular (2), mammary gland area, optic nerves (2), ovaries (2), pancreas, pituitary gland, prostate gland, salivary glands - submandibular (2) and sublingual (2), sciatic nerve (2), seminal vesicles (2), skeletal muscle (2), skin, small intestine - duodenum, jejunum and ileum; spinal cord - cervical, mid-thoracic and lumbar (3), spleen, stomach, testes (2), thymus, thyroid gland (2), tongue, trachea, urinary bladder, uterus (3), vagina and all gross lesions and tissue masses.

In addition, kidneys, sciatic nerve, spleen and testes from animals of the intermediate dose groups were also sectioned and examined.

Data Compilation

DATA RECORDING

The following data were recorded on-line:

clinical signs/nodules and masses,
food consumption,
body weights,
macroscopical findings,
organ weights,
histopathology,
clinical laboratory investigations (Sysmex E-4000, Eris 6170, Clini-Tek 200, Beckmann Appraise and ACL 300). [Except sampling day February 11,1993 (males group 3 and 4) and sampling day October 22, 1993 (females groups 1, 2, 3 and 4)]

The following data were recorded on data sheets and transcribed for compilation and analysis:

viability/mortality,
clinical laboratory investigations except those stated above.

The computer-generated values which appear in the tables represent the rounded-off results of calculations which used the exact raw data values.

CALCULATION OF FOOD CONSUMPTION

Mean food consumption values were calculated.

Group means were calculated using the individual values and the number of animals.

Individual Food Consumption:

The food consumption expresses the average food consumed per day over the food consumption interval.

$$\text{Formula: } FC = \frac{C}{AD} \quad \text{where}$$

FC = Food consumption (in g of food per day)

C = Measured food consumption over the consumption interval (in g of food).

AD = Total of consumption days for the animal during the consumption interval (death during the consumption interval is therefore taken into account)

SAMe SD_4

RELATIVE FOOD CONSUMPTION

The relative food consumption (RFC) was calculated weekly, according to the following formula:

$$RFC = \frac{\text{weekly food consumption (g)}}{\text{midweek body weight (g)}} \times \frac{1000}{7}$$

Unit: gram food per kg body weight per day.

SURVIVAL

The age-specific survival rate up to termination for each group and sex was calculated with Kaplan-Meier non-parametric estimates based on censored survival data, censorship being imposed on unnatural causes of death (e.g. death during blood sampling procedures).

Reference:

Kaplan, E.L. and Meier, P. (1958). Non-parametric estimation from incomplete observation. J. Am. Stat. Assoc. 53, 458-482.

Statistical Analysis

The following statistical methods were used to analyze the body weight, food consumption, organ weights and clinical laboratory data :

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

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

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

Fisher's exact test was applied to ophthalmoscopy data.

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

References :

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

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

- R.A. Fisher: Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).

RESULTS

Observations

MORTALITY (see pp. 59-62, 215-230)

Survival was not affected by treatment with the test article.

A total of 27 animals died during the study. The table below shows the distribution among the groups:

	Unscheduled Deaths							
Dose (mg SAMe/kg)	0		440		1000		2 x 1000	
Sex	M	F	M	F	M	F	M	F
Total Number	7	3	3	4	3	3	2	2
-Treatment Period								
Spontaneous Death	5	0	1	0	1	0	0	2
Killed in extremis	0	2	1	4	2	3	0	0
-Recovery Period								
Spontaneous Death	1	0	0	0	0	0	2	0
Killed in extremis	1	1	1	0	0	0	0	0

There were no significant differences in the total numbers, nor in the time pattern, of non-scheduled deaths in the treated groups compared with the control group. The commonest cause of non-survival was neoplasia.

CLINICAL SIGNS (see pp. 121-156, 423-481)

Diarrhea (fluid/soft stool) was recorded for both sexes at 1000 and 2 x 1000 mg/kg with dose-related onset and/or incidence. This clinical sign reversed during the treatment-free recovery period, rapidly. No test article related clinical signs were noted in any other group.

In males at 1000 respectively 2 x 1000 mg SAMe/kg more than 95% of the animals were affected by diarrhea (fluid/soft stool) as from week 21 respectively week 10 with the incidence subsisting up to the end of treatment. In females at 1000 mg SAMe/kg diarrhea (fluid/soft stool) was observed as from week 34 reaching a maximum incidence of 25 to 35% between weeks 43 to 49. At the end of treatment 15 to 25% were still affected. At the highest dose level of 2 x 1000 mg SAMe/kg, the maximum of more than 95% of females affected was reached by 37 and lasted until the end of treatment. As from week 3 of the treatment-free recovery period diarrhea (fluid/soft stool) was no longer seen in any male or female of the previously affected groups.

All other clinical signs observed were those commonly seen in rats of this strain and age housed under the conditions described above.

NODULES AND MASSES (see pp. 157-180, 482-511)

Treatment with the test article had no influence on the incidence or group distribution of palpable masses.

OPHTHALMOSCOPIC EXAMINATIONS (see pp. 181-182, 512-518)

There were no test article related findings.

All findings observed were considered to be incidental and unrelated to treatment, and are commonly seen in rats of this strain and age housed under the conditions described above.

FOOD CONSUMPTION (see pp. 63-66, 75-88, 231-294)

Mean food consumption over the treatment period was decreased in a dose-related manner in both sexes at 1000 and 2 x 1000 mg SAMe/kg. No effects were seen in animals at 440 mg SAMe/kg.

The average mean differences from controls were approximately 7 % respectively 5 % for males respectively females at 1000 mg SAMe/kg and approximately 12 % for both sexes at 2 x 1000 mg SAMe/kg. During the treatment-free recovery period average mean food consumption at 1000 and 2 x 1000 mg SAMe/kg approached or even reached the control group level.

BODY WEIGHT (see pp. 67-70, 89-102, 295-358)

Body weight was decreased in a dose-related manner for both sexes at 1000 and 2 x 1000 mg SAMe/ kg. No effects were seen in animals at 440 mg SAMe/kg.

At the end of treatment the differences from controls amounted to approximately 12 % respectively 10 % in males respectively females at 1000 mg SAMe/kg. At 2 x 1000 mg SAMe/kg the differences were approximately 18 % / 15 % in males / females. The lower body weights remained during the recovery period.

RELATIVE FOOD CONSUMPTION (see pp. 71-74, 103-120, 359-422)

Average mean relative food consumption was marginally decreased by approximately 5 % in females at 2 x 1000 mg SAMe/kg during treatment. During the recovery period overall relative mean food consumption was increased in both sexes at 1000 and 2 x 1000 mg SAMe/kg thus reflecting the changes in food intake during that period. No effects on overall relative mean food consumption were seen in any other group.

A decreased relative food consumption was noted for males at 1000 and 2 x 1000 mg SAMe/kg during the early part of the study which was followed by an increase during the second part of the study. The increase compensated for the initial decrease thus leading to an average mean relative food consumption similar to that in controls. The statistically significant decreases in relative food consumption were noted up to treatment week 19/20 whereas most of the increases were seen afterwards. The latter may be explained as an impaired food conversion caused by the diarrhea (soft/fluid stool) which was marked in these groups.

Clinical Laboratory Investigations

HEMATOLOGY (see pp. 183-190, 519-614)

Effects on hematology parameters were noted in animals at 1000 and 2 x 1000 mg SAMe/kg. No effects were seen in animals at 440 mg SAMe/kg.

The following statistically significant differences from control means are considered to be treatment-related:

- Slightly decreased erythrocyte count (RBC) in females at 1000 mg SAMe/kg at 16 weeks and in females at 2 x 1000 mg SAMe/kg at 8 and 16 weeks. Also decreased in males at 2 x 1000 mg SAMe/kg at 16 weeks.

- Slightly decreased hemoglobin (HB) concentration in both sexes at 2 x 1000 mg SAMe/kg at 8 and 16 weeks and in females at 1000 mg SAMe/kg at 8 and 16 weeks.

- Marginally decreased hematocrit (HCT) in females at 2 x 1000 mg SAMe/kg at 8 weeks and in males at the same dose at 16 weeks.

- Slightly decreased mean corpuscular hemoglobin concentration (MCHC) index in females at 2 x 1000 mg SAMe/kg at day 2 and in both sexes at the same dose at 8, 16 and 52 weeks. Also decreased in females at 1000 mg SAMe/kg at 8 weeks.

- Slightly increased reticulocyte count (rel. and abs.) in females at 1000 mg SAMe/kg at 16 weeks and in females at 2 x 1000 mg SAMe/kg at 8 and 16 weeks. The absolute increase noted in females at 1000 and 2 x 1000 mg SAMe/kg at 16 weeks did not achieve statistical significance, however is considered to be treatment-related.

HEMATOLOGY (cont'd)

- Slightly prolonged thromboplastin time (PT) in males at 2 x 1000 mg SAMe/kg at 16, 26 and 52 weeks and in females at the same dose at 52 weeks.

- Slightly shortened activated partial thromboplastin time (APTT) in males at 1000 and 2 x 1000 mg SAMe/kg at 8, 26 and 52 weeks, and in females at the same doses at 52 weeks.

At termination of the treatment-free recovery period these findings were found to be reversed.

All other differences in the results of the hematological parameters were considered to be incidental and unrelated to treatment, and of normal biological variation.

CLINICAL BIOCHEMISTRY (see pp. 191-196, 618-713)

Changes in clinical biochemistry parameters mostly affected animals at 2 x 1000 mg SAMe/kg with smaller effects seen in animals at 1000 mg SAMe/kg. Almost all changes observed were absent after the treatment-free recovery period.

The following statistically significant differences from control means are considered to be treatment-related:

- Slightly decreased glucose levels in both sexes at 2 x 1000 mg SAMe/kg at 8, 16, 26, 52 and 60 weeks.

- Slightly increased urea levels in females at 2 x 1000 mg SAMe/kg at 8 weeks and in both sexes at the same dose at 16, 26 and 52 weeks as well as in males at 1000 mg SAMe/kg at 16, 26 and 52 weeks.

- Slightly increased creatinine level in both sexes at 2 x 1000 mg SAMe/kg at 8 weeks and in males at the same dose at 26 weeks.

- Slightly increased total bilirubin level in females at 2 x 1000 mg SAMe/kg at 8, 16, 26 and 52 weeks, and in males at the same dose at 16 and 26 weeks.

- Slightly increased total cholesterol level in females at 2 x 1000 mg SAMe/kg at 26 weeks and in females at 1000 mg SAMe/kg at 16, 26, 52 and 60 weeks.

- Slightly increased triglyceride level in females at 2 x 1000 mg SAMe/kg at 16 and 26 weeks.

- Slightly increased aspartate aminotransferase (ASAT) activity in both sexes at 2 x 1000 mg SAMe/kg on day 2.

- Slightly increased alanine aminotransferase (ALAT) activity in both sexes at 2 x 1000 mg SAMe/kg at 8, 16, 26 and 52 weeks and in males at 1000 mg SAMe/kg at 52 weeks.

CLINICAL BIOCHEMISTRY (cont'd)

- Slightly increased **lactate dehydrogenase (LDH)** activity in males at 2 x 1000 mg SAMe/kg at 16 and 26 weeks and in females at the same dose level at 8 and 52 weeks.

- Slightly increased **alkaline phosphatase (ALP)** activity in males at 2 x 1000 mg SAMe/kg at 16 weeks and in both sexes at the same dose at 26 and 52 weeks. A slight increase was also noted in males at 1000 mg SAMe/kg at 26 weeks.

- Slightly decreased **calcium** level in males at 2 x 1000 mg SAMe/kg at 8 weeks. In females at 2 x 1000 mg SAMe/kg slightly increased at 16 and 52 weeks as well as in females at 1000 mg SAMe/kg at 16 weeks.

- Slightly increased **phosphorus** level in males at 2 x 1000 mg SAMe/kg at weeks 26 and 52 and in females at the same dose at weeks 16, 26 and 52 weeks. Also increased in females at 1000 mg SAMe/kg at weeks 26 and 52.

- Slightly decreased **sodium** level in males at 2 x 1000 mg SAMe/kg at weeks 8 and 16.

- Slightly decreased **potassium** level in males at 2 x 1000 mg SAMe/kg at 26 and 52 weeks and in females at the same dose at 16 and 52 weeks.

- Slightly increased **chloride** level in males at 2 x 1000 mg SAMe/kg at 8, 16, 26 and 52 weeks.

- Slightly decreased **alpha 2-globulin fraction (abs. and rel.)** in males at 2 x 1000 mg SAMe/kg at 8 and 60 weeks, and in females at 1000 and 2 x 1000 mg SAMe/kg on day 2, weeks 8, 16, 26 and 52 as well as in females at 2 x 1000 mg SAMe/kg at 60 weeks (abs.). Also slightly decreased in females at 440 mg SAMe/kg at 26 weeks.

- Slightly decreased **gammma-globulin fraction (abs. and rel.)** in both sexes at 2 x 1000 mg SAMe/kg at 16 weeks.

At the end of the treatment-free recovery period most of these findings were found to be reversed and comparable to those of the controls. The only changes to be noted were a slightly decreased **glucose** level as well as a slightly decreased **alpha 2-globulin fraction** in both sexes at 2 x 1000 mg SAMe/kg. In addition, a slightly decreased **cholesterol** level was observed in females at 1000 mg SAMe/kg. These findings may be attributed to the nutritional state of these animals.

All other differences in the results of the clinical biochemistry parameters were considered to be incidental and unrelated to treatment, and of normal biological variation.

URINALYSIS (see pp. 197-202, 714-809)

Changes observed in urinalysis parameters affected all treated groups with evidence of a dose- and time-relationship in most cases.

The following statistically significant differences from control means are considered to be treatment-related:

- Slightly decreased volume in males at 2 x 1000 mg SAMe/kg on day 2, at weeks 8, 26 and 52.

- Slightly increased specific gravity in both sexes at 2 x 1000 mg SAMe/kg on day 2, at weeks 8, 16, 26 and 52. Increased also in males at 1000 mg SAMe/kg on all occasions during treatment as well as in females at the same dose at 8 and 52 weeks. In addition, a slight increase was noted in males at 440 mg SAMe/kg on day 2 and at week 52.

- Slightly lower pH in males at 440, 1000 and 2 x 1000 mg SAMe/kg at 8, 16, 26 and 52 weeks and in females at the same doses at 8 and 26 weeks. In addition, a slightly lower pH was also noted for females at 440 and 1000 mg SAMe/kg at 16 and 52 weeks.

- Slightly to moderately increased protein (score) in both sexes at 2 x 1000 mg SAMe/kg on day 2.

- Moderate increase in blood (score) in both sexes at 2 x 1000 mg SAMe/kg on day 2 as well as a slight increase in females at the same dose at weeks 16 and 52.

- Slightly to moderately increased gamma-glutamyltransferase (G-GT) activity (see also pp. 46-47) in males at 440 and 1000 mg SAMe/kg at 8, 26 and 52 weeks, but slightly decreased in males at 2 x 1000 mg SAMe/kg at 26 and 52 weeks. Moderately increased in females at 440 and 1000 mg SAMe/kg at 8, 16, 26 and 52 weeks as well as slightly increased in females at 1000 mg SAMe/kg at 60 weeks.

- Slightly to markedly increased lactate dehydrogenase (LDH) activity (see also pp. 48-49) in males at 2 x 1000 mg SAMe/kg on day 2, at 8, 16 and 26 weeks. Markedly increased in females at 2 x 1000 mg SAMe/kg on day 2, at 16, 26 and 52 weeks.

- Moderately increased alkaline phosphatase (ALP) activity (see also pp. 50-51) in males at 2 x 1000 mg SAMe/kg on day 2, but slightly decreased at 26 weeks. Slightly increased in males at 1000 mg SAMe/kg at 8 weeks as well as in males at 440 mg SAMe/kg at 8, 16 and 52 weeks. Markedly increased in females at 2 x 1000 mg SAMe/kg on day 2 and moderately increased in females at 1000 mg SAMe/kg at 16, 26 and 52 weeks. Also slightly to moderately increased in females at 440 mg SAMe/kg at 8, 16, 26 and 52 weeks.

URINALYSIS (cont'd)

- Slightly to markedly increased **leucine aminopeptidase (LAP)** activity (see also pp. 52-53) in both sexes at 2 x 1000 mg SAMe/kg on day 2, but slightly decreased at this dose level in males at 16, 26 and 52 weeks. Slightly increased in females at 1000 mg SAMe/kg at 8 and 52 weeks. Slightly increased in males at 440 mg SAMe/kg at 8 and 26 weeks as well as in females at the same dose level at 16, 26 and 52 weeks.

- Slightly to moderately increased **beta-N-acetyl-D-glucosaminidase (B-N-AG)** activity (see also pp. 54-55) in males at 2 x 1000 mg SAMe/kg on day 2 and at 16 weeks as well as in females at 2 x 1000 mg SAMe/kg on day 2, at 16, 26 and 52 weeks.

- Slightly to markedly increased urinary **sodium** excretion in males at 1000 and 2 x 1000 mg SAMe/kg on day 2, at weeks 8, 16, 26 and 52. For males at 440 mg SAMe/kg also moderately increased at week 16. For females, sodium excretion was slightly to moderately increased at 2 x 1000 mg SAMe/kg on day 2, at weeks 8, 16, 26 and 52, and slightly increased in females at 1000 mg SAMe/kg on day 2 and at week 26. In addition, a slightly increased urinary sodium excretion was noted for females at 440 mg SAMe/kg at week 52.

- Slightly decreased urinary **potassium** excretion in males at 1000 and 2 x 1000 mg SAMe/kg on day 2, at 8 and 16 weeks as well as in males at 440 and 2 x 1000 mg/kg at 26 weeks. In females at 2 x 1000 mg SAMe/kg a slightly decreased potassium excretion was noted on day 2 and at week 8. In addition, a slight decrease was recorded in females at 440 and 1000 mg SAMe/kg at week 8.

- Slightly increased **total protein** in females at 2 x 1000 mg SAMe/kg on day 2, and at weeks 8 and 16.

- Slightly decreased **creatinine excretion** in males at 2 x 1000 mg SAMe/kg at 8, 16, 26, 52 and 60 as well as in females at the same dose on day 2, weeks 16, 26 and 52. Creatinine excretion was also slightly decreased in females at 1000 mg SAMe/kg at 60 weeks.

- Slightly decreased **creatinine clearance** in both sexes at 2 x 1000 mg SAMe/kg at 8, 16, 26 and 52 weeks, and in females at 1000 and 2 x 1000 mg SAMe/kg on day 2. Creatinine clearance was also slightly decreased in females at 1000 mg SAMe/kg at 60 weeks.

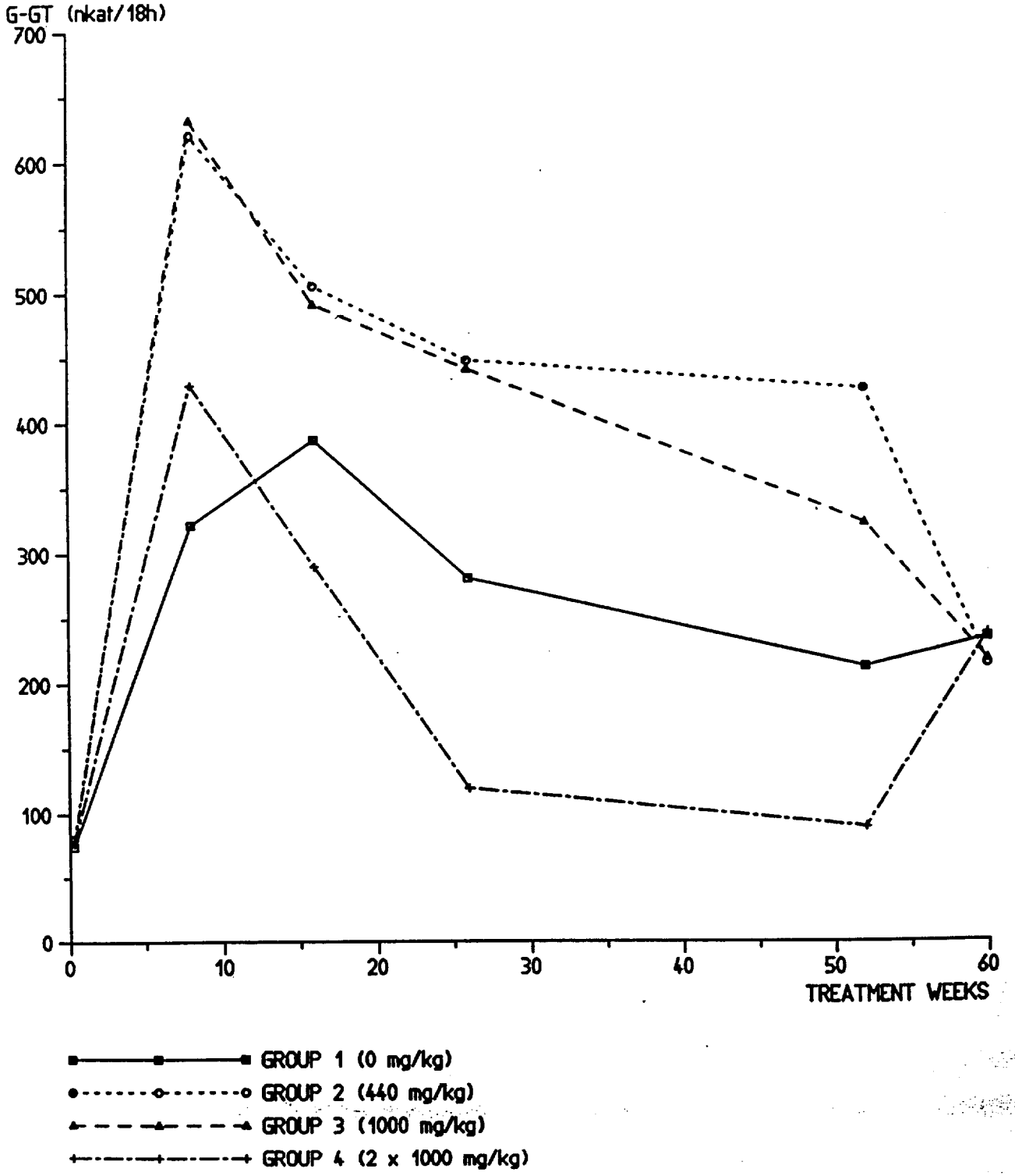
After the treatment-free recovery period the only notable changes were: a slightly decreased **creatinine excretion** in males at 2 x 1000 mg/kg and a slightly decreased **creatinine excretion** and **creatinine clearance** in females at 1000 mg SAMe/kg. Moreover, a slightly increased **gamma-glutamyltransferase (G-GT)** activity was observed in females at the latter dose. All other changes were found to be reversed.

All other differences in the results of the urinalysis parameters were considered to be incidental and unrelated to treatment, and of normal biological variation.

URINARY INDICATORS OF NEPHROTOXICITY

G-GT: BRUSH BORDER ENZYME

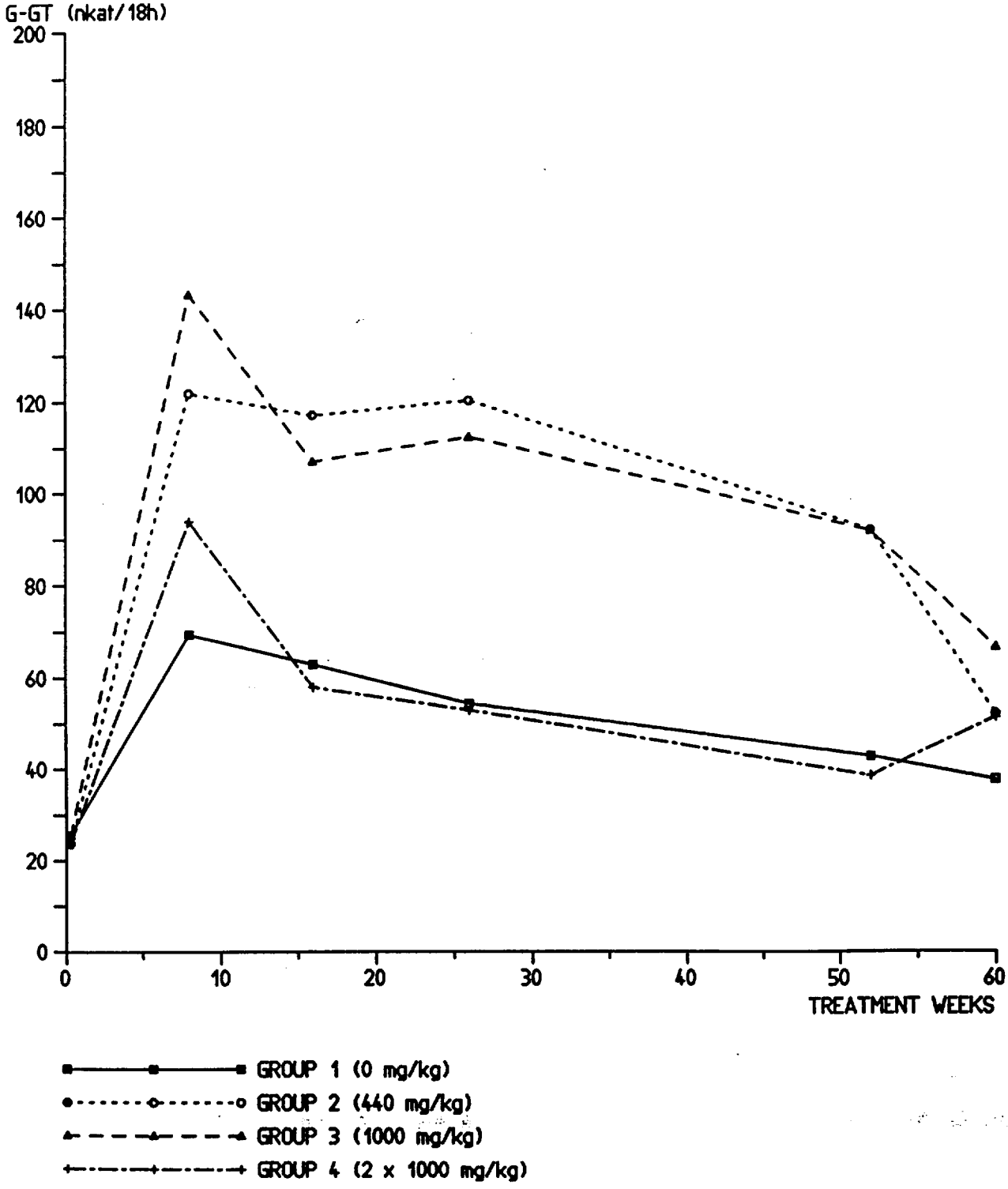
MALES



URINARY INDICATORS OF NEPHROTOXICITY

G-GT: BRUSH BORDER ENZYME

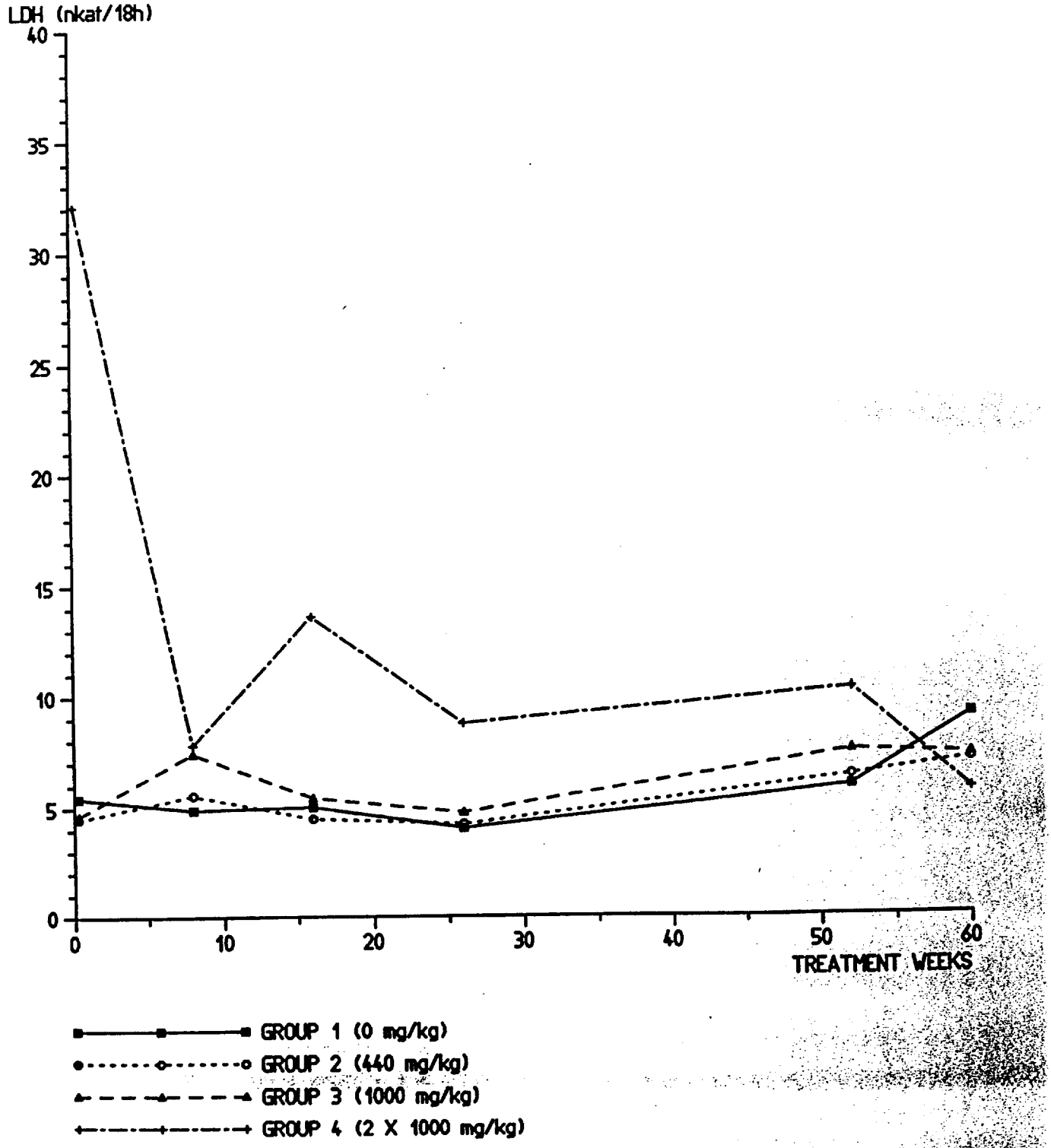
FEMALES



URINARY INDICATORS OF NEPHROTOXICITY

LDH: GENERAL TUBULAR ENZYME

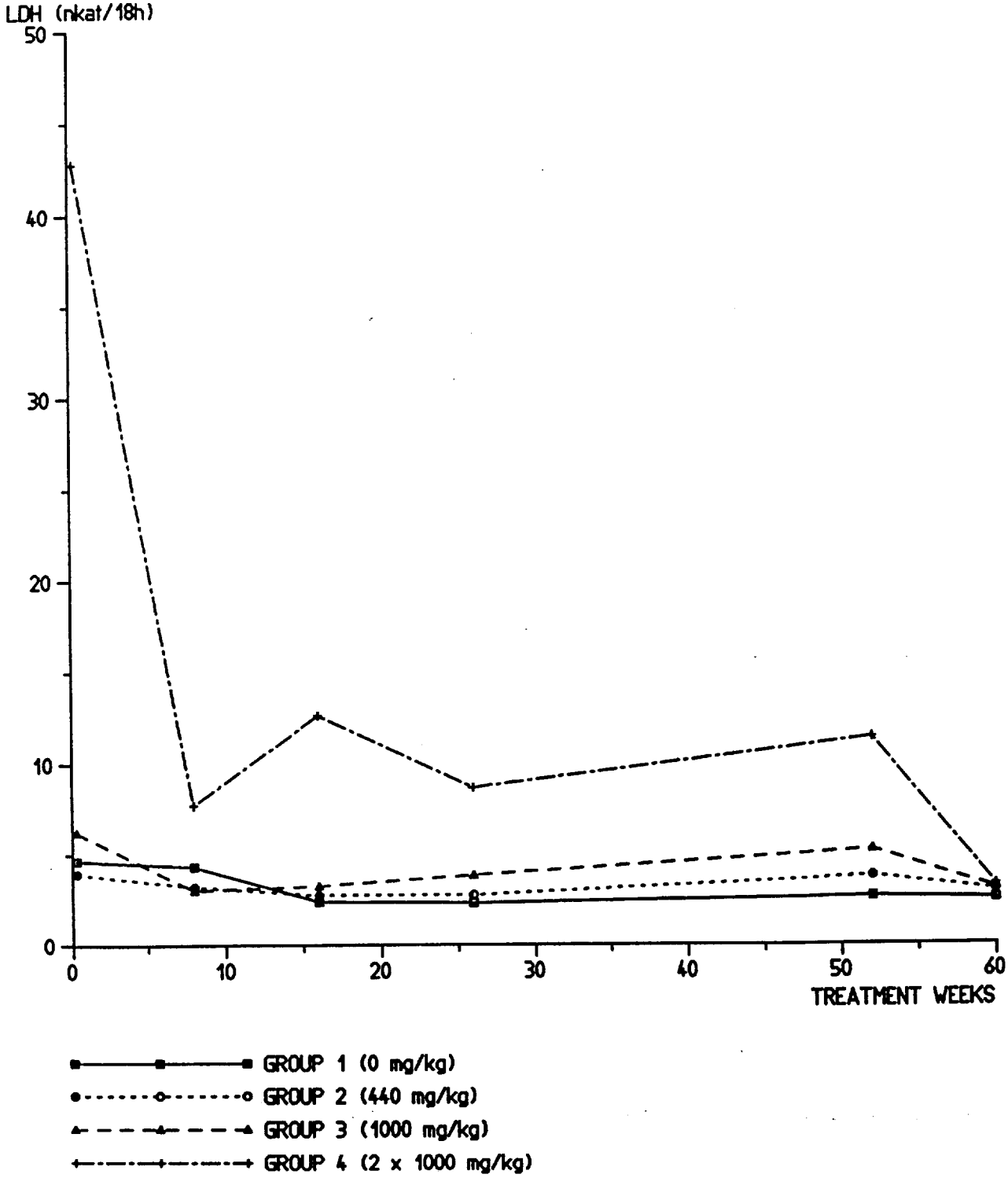
MALES



URINARY INDICATORS OF NEPHROTOXICITY

LDH: GENERAL TUBULAR ENZYME

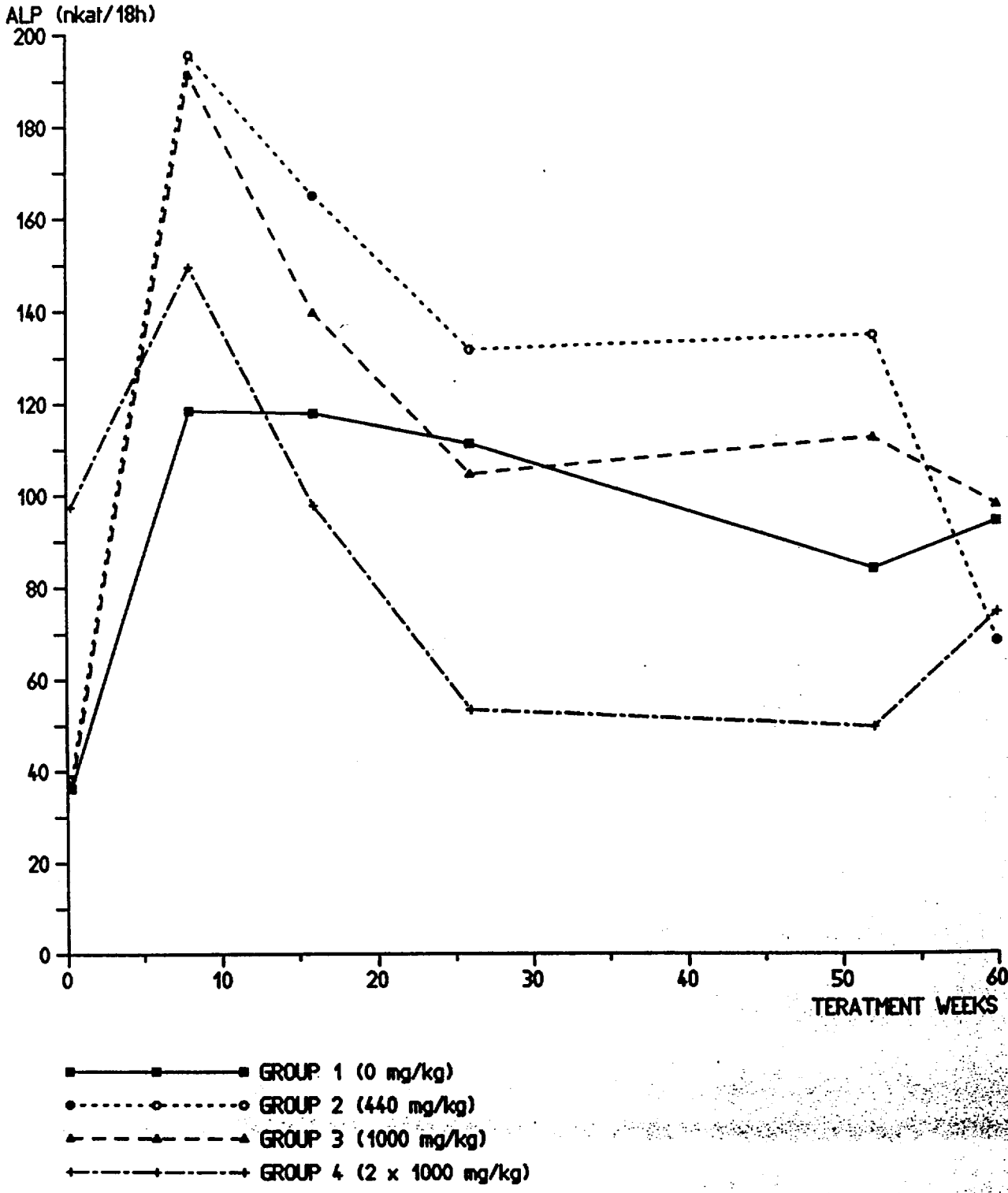
FEMALES



URINARY INDICATORS OF NEPHROTOXICITY

ALP: BRUSH BORDER ENZYME

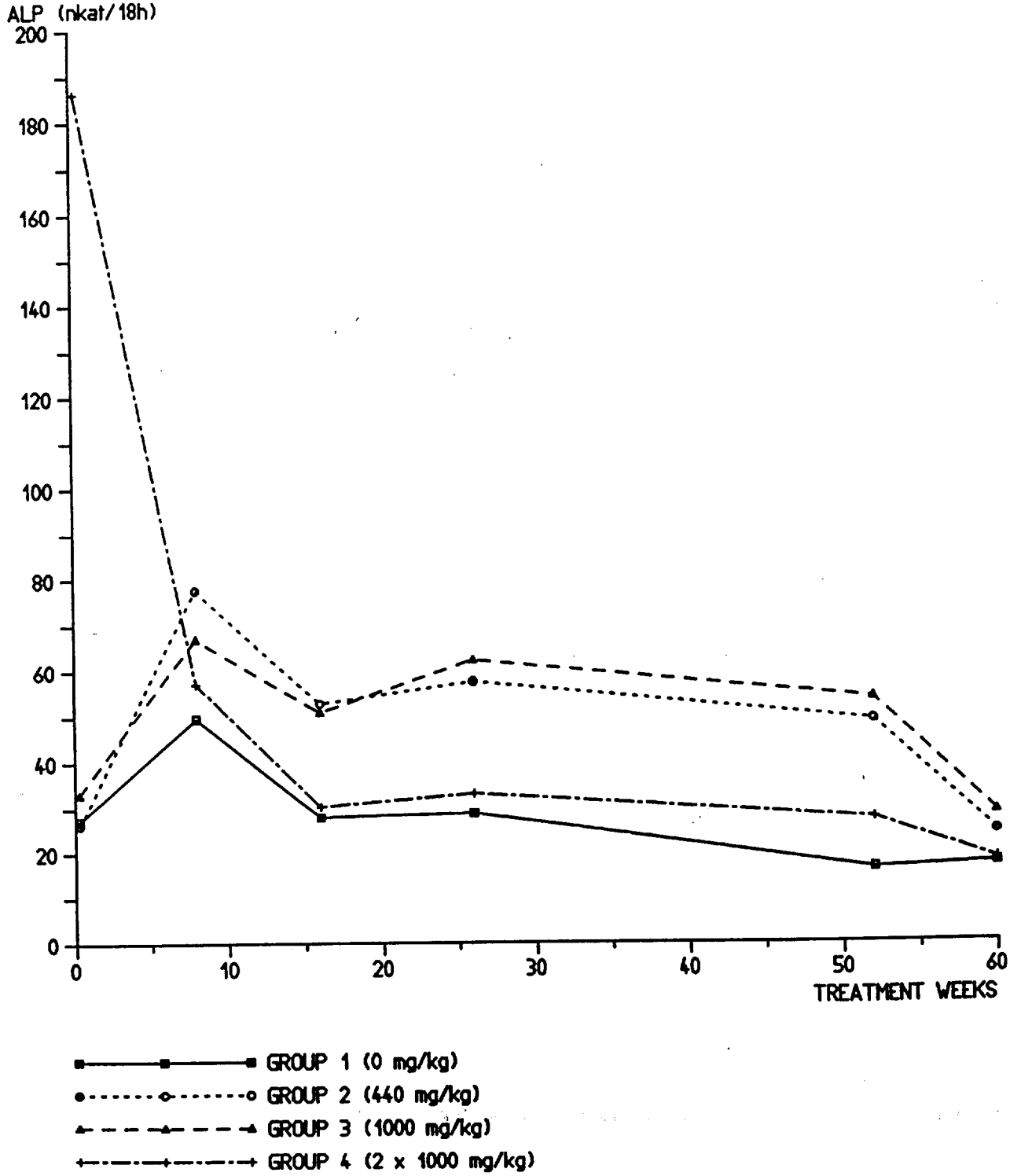
MALES



URINARY INDICATORS OF NEPHROTOXICITY

ALP: BRUSH BORDER ENZYME

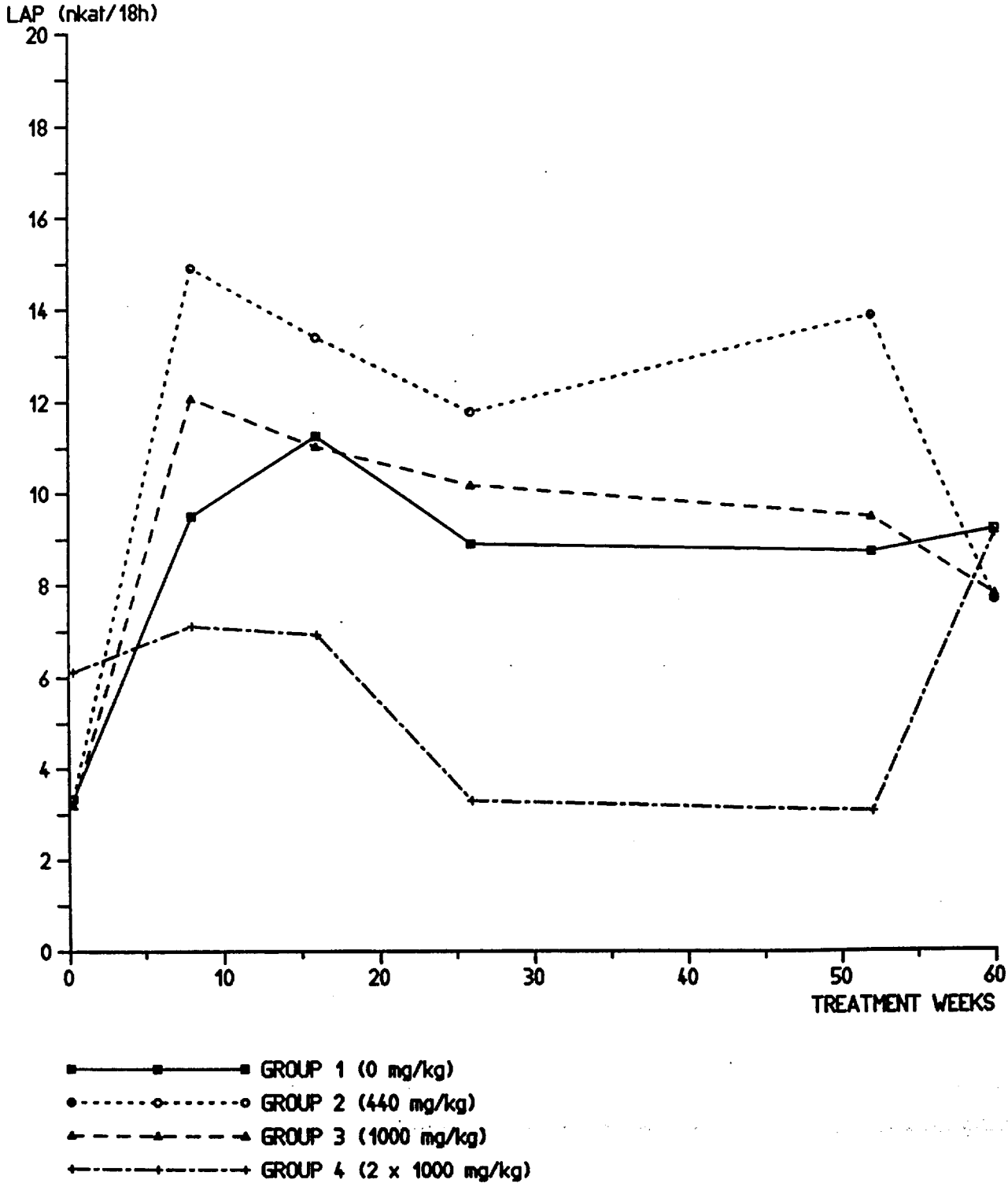
FEMALES



URINARY INDICATORS OF NEPHROTOXICITY

LAP: BRUSH BORDER ENZYME

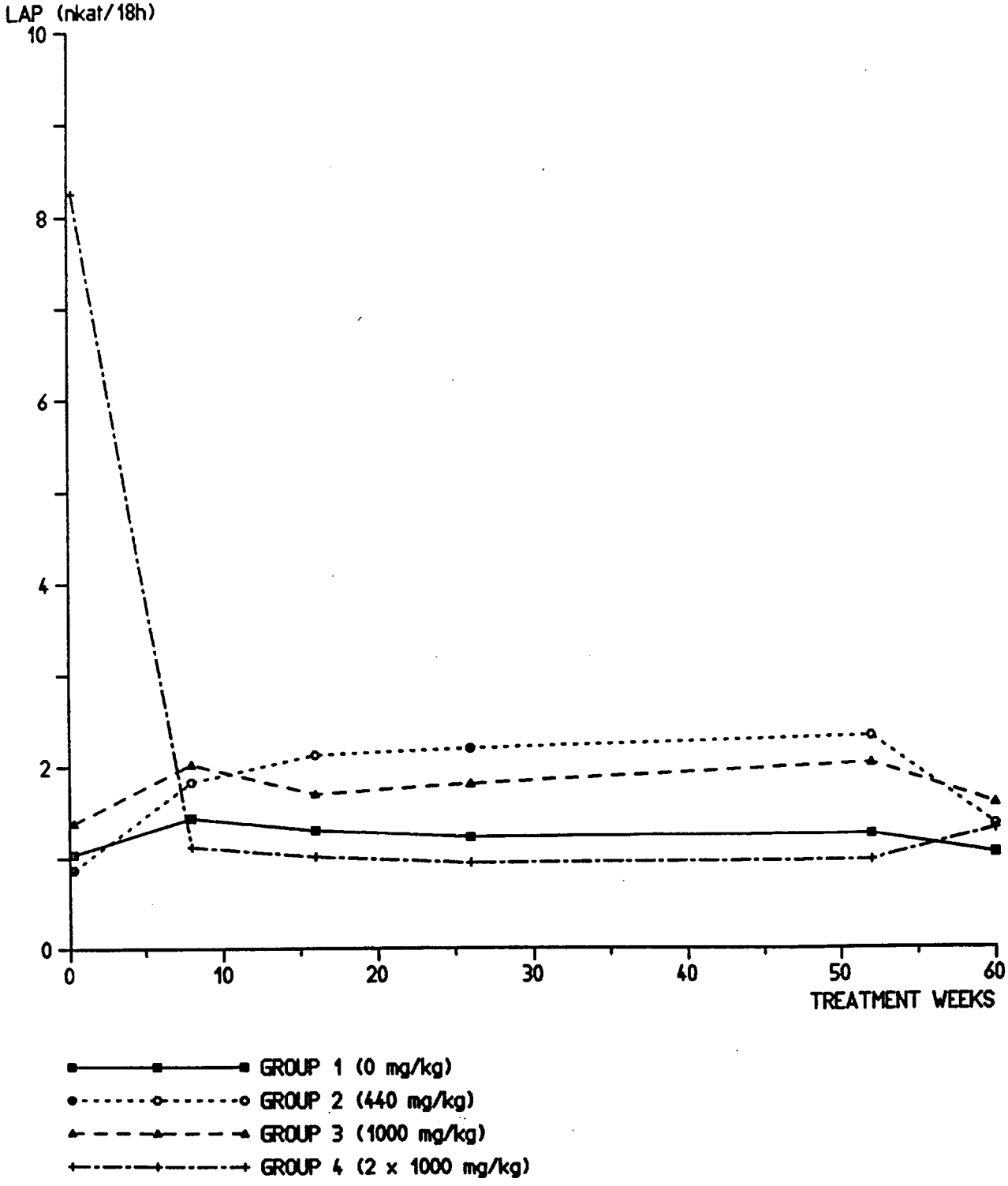
MALES



URINARY INDICATORS OF NEPHROTOXICITY

LAP: BRUSH BORDER ENZYME

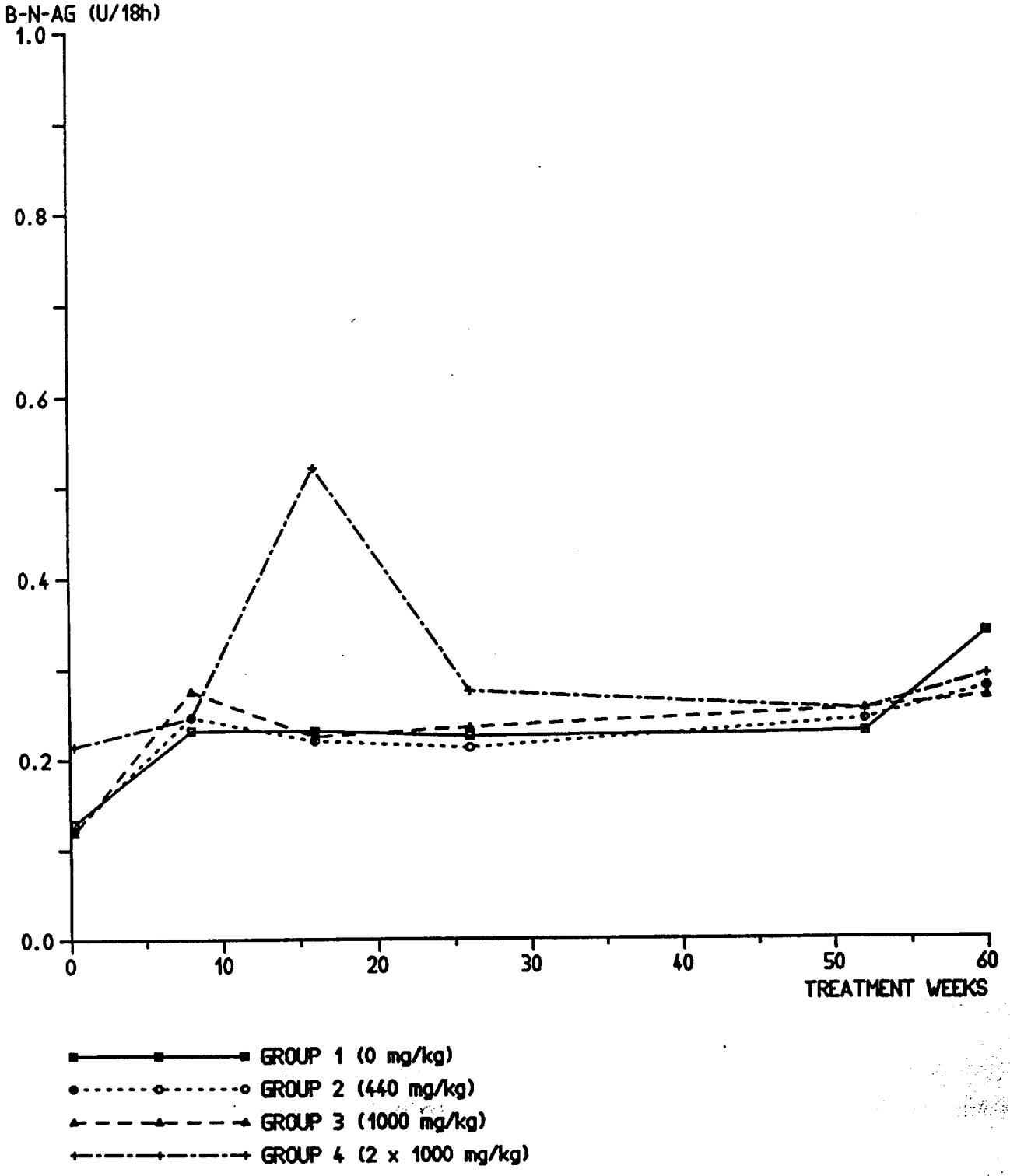
FEMALES



URINARY INDICATORS OF NEPHROTOXICITY

B-N-AG: PROXIMAL CONVOLUTED TUBULE

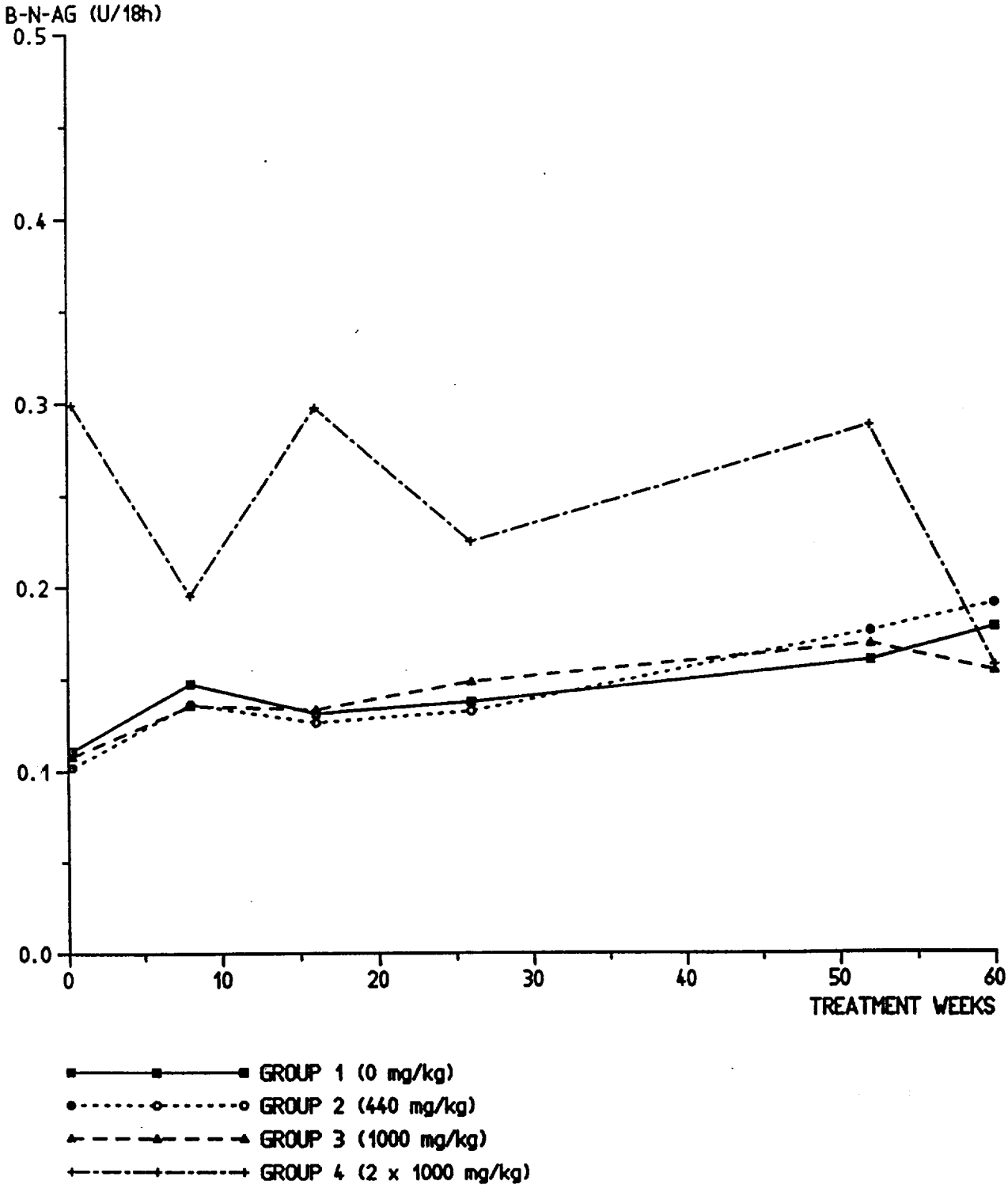
MALES



URINARY INDICATORS OF NEPHROTOXICITY

B-N-AG: PROXIMAL CONVOLUTED TUBULE

FEMALES



PATHOLOGY

ORGAN WEIGHTS (see pp. 67-70, 810-862)

The assessment of organ weights is based on the absolute weight as well as on the organ/body weight and organ brain weight ratios.

The following statistically significant differences from control means are considered to be treatment-related.

- At the end of treatment, the kidney weight was increased in males at 2 x 1000 mg SAMe/kg by approximately 28 % in terms of kidney/body weight ratio and by approximately 14 % in terms of kidney/brain weight ratio. In females at 1000 and 2 x 1000 mg SAMe/kg the kidney weight was increased in a dose-related manner. The differences from controls were approximately 29 % and 58 % in terms of kidney/ body weight ratios and approximately 20 % and 40 % in terms of kidney/brain weight ratios.

- The only changes noted at the end of the recovery period were increased kidney weights in females at 1000 and 2 x 1000 mg SAMe/kg.

A higher spleen weight was noted in females at 2 x 1000 mg SAMe/kg at the end of the treatment period the increases being approximately 30% and 15% in terms of spleen/body weight and spleen/brain weight ratio. In view of the absence of any histopathological correlate and the known high variability of spleen weight this finding is considered to be spurious.

All other statistically significant differences from controls are considered to be due the distinctly reduced terminal body weight recorded for both sexes at 1000 and 2 x 1000 mg SAMe/kg.

MACROSCOPICAL FINDINGS (see Pathology Report, page 912)

A variety of macroscopic findings were recorded in rats of all groups. The incidence of most macroscopic findings recorded, were considered similar in both control and treated rats and were amongst those which may be observed in this strain of rat and at these ages.

One macroscopic finding which distinguished treated rats from controls at the end of the main study period, was the observation of dilated cecum with liquid contents seen chiefly in animals at 1 x 1000 and 2 x 1000 mg SAMe/kg. This finding was no longer in evidence at the end of the recovery period.

MICROSCOPICAL FINDINGS (see Pathology Report, page 912)

Microscopic Findings - Non-neoplastic

Most of the non-neoplastic lesions recorded were age associated and degenerative, inflammatory or proliferative in nature and showed little difference in either incidence or severity between the control and treated groups.

No microscopic correlate to the dilated ceca seen at necropsy was found an microscopic examination.

The following findings were noted at increased incidences:

Kidneys - tubular vacuolation, tubular dilation;
Testes - interstitial cell hyperplasia;
Sciatic nerve - mineralization.

Reversible kidney alterations consisted of tubular vacuolation and tubular dilation. Renal tubular vacuolation was characterised by foci of cortical tubules with hypertrophic epithelium and highly vacuolated cytoplasm and was seen only in rats of the treated groups, with a higher incidence in males. In both sexes the incidence increased with dose and in males the severity also increased slightly with increasing dose. Following the recovery period there were only two treated males (low dose, high dose) seen with this finding at minor grades of severity.

In contrast to the above finding, tubular dilation was more common in females where it showed a dose related increase in incidence. Severity was minor and did not increase with dose. Again, following the recovery period this alteration had largely been reversed.

These renal findings may therefore be classified as reversible adaptive responses, possibly due to an osmotic effect of the test article.

Focal mineralization of the nutrient blood vessels of the sciatic nerve was noted in some animals from all dose groups including controls at both sacrifices, chiefly at minor degrees of severity and almost exclusively in males. The presence of this alteration did not adversely affect the incidence of other lesions in the nerve itself and there were no other unusual sites of vascular mineralization in other organs. Although the incidence of this finding did increase with dose, it was not found in a two year study carried out almost concurrently with SAMe SD_4 administered at similar doses (RCC project 280708, Knoll project MPF/WT 9115 E) in the same strain of rat, and therefore the relationship to the test article was regarded as equivocal.

In the testes there was a dose-related increase in incidence and severity (minimal to moderate) of interstitial cell hyperplasia. This was seen in all treated groups, was not present in control males and was also seen in males at 1000 and 2 x 1000 mg SAMe/kg at the termination of the recovery phase.

Again, in the two year study (RCC project 280708), the incidence of interstitial cell hyperplasia in the testes was very low, there were only isolated cases of benign interstitial cell tumors and the incidence of neither alteration was affected by treatment with the test article. Hence, it was considered that the incidences recorded in this study may have been due to chance or may also have been transitory in nature.

The remainder of morphologic alterations occurred at similar incidences and severity across the dose groups and were within the range of spontaneous findings which may be encountered in Sprague-Dawley rats at these ages.

MICROSCOPICAL FINDINGS (cont'd)

The most noteworthy non-neoplastic findings are listed below according to organ system.

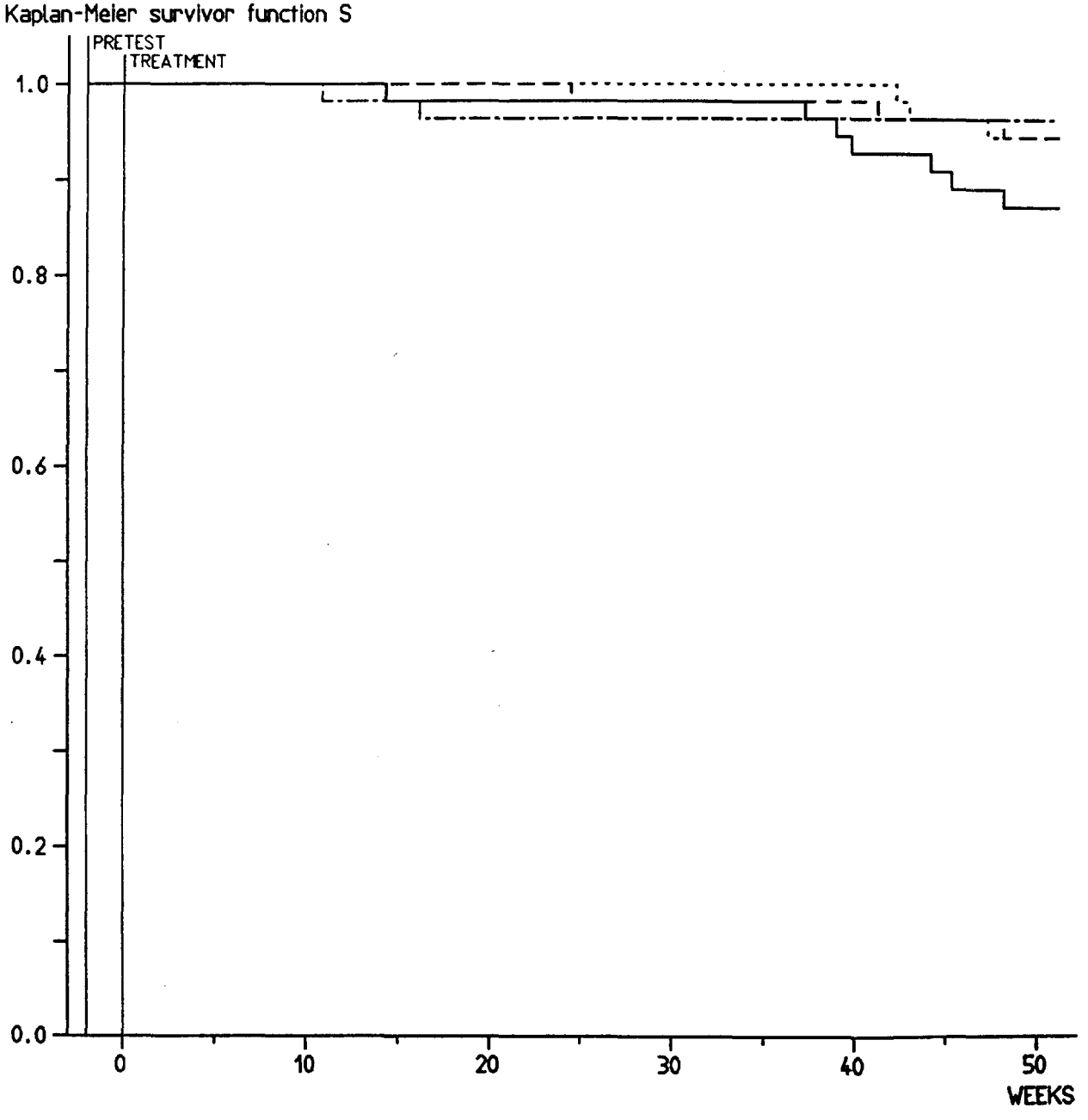
Nervous System:		
	Sciatic Nerve	- mineralization
Cardiovascular System:		
	Heart	- cardiomyopathy
Digestive System:		
	Liver	- single cell necrosis, cholangiofibrosis and clear cell foci
Urinary System:		
	Kidneys	- chronic nephropathy and associated inflammatory and degenerative lesions; tubular vacuolation and tubular dilation
Reproductive System:		
	Testes	- interstitial cell hyperplasia
	Ovaries	- senile involution
	Uterus	- cystic endometrial hyperplasia
Endocrine System:		
	Pituitary Gland	- focal hypertrophy and hyperplasia
	Thyroid Glands	- parafollicular (C-cell) hyperplasia
	Adrenal Glands	- focal hypertrophy and angiectasis
Hemopoietic and Lymphoid Systems:		
	Spleen	- hemosiderosis and hemopoiesis
	Thymus	- atrophy and epithelial hyperplasia
	Lymph Nodes	- histiocytosis, plasmacytosis and lymphoid hyperplasia
Integumentary System:		
	Mammary Glands	- glandular hyperplasia

<u>Microscopic Findings - Neoplastic</u>

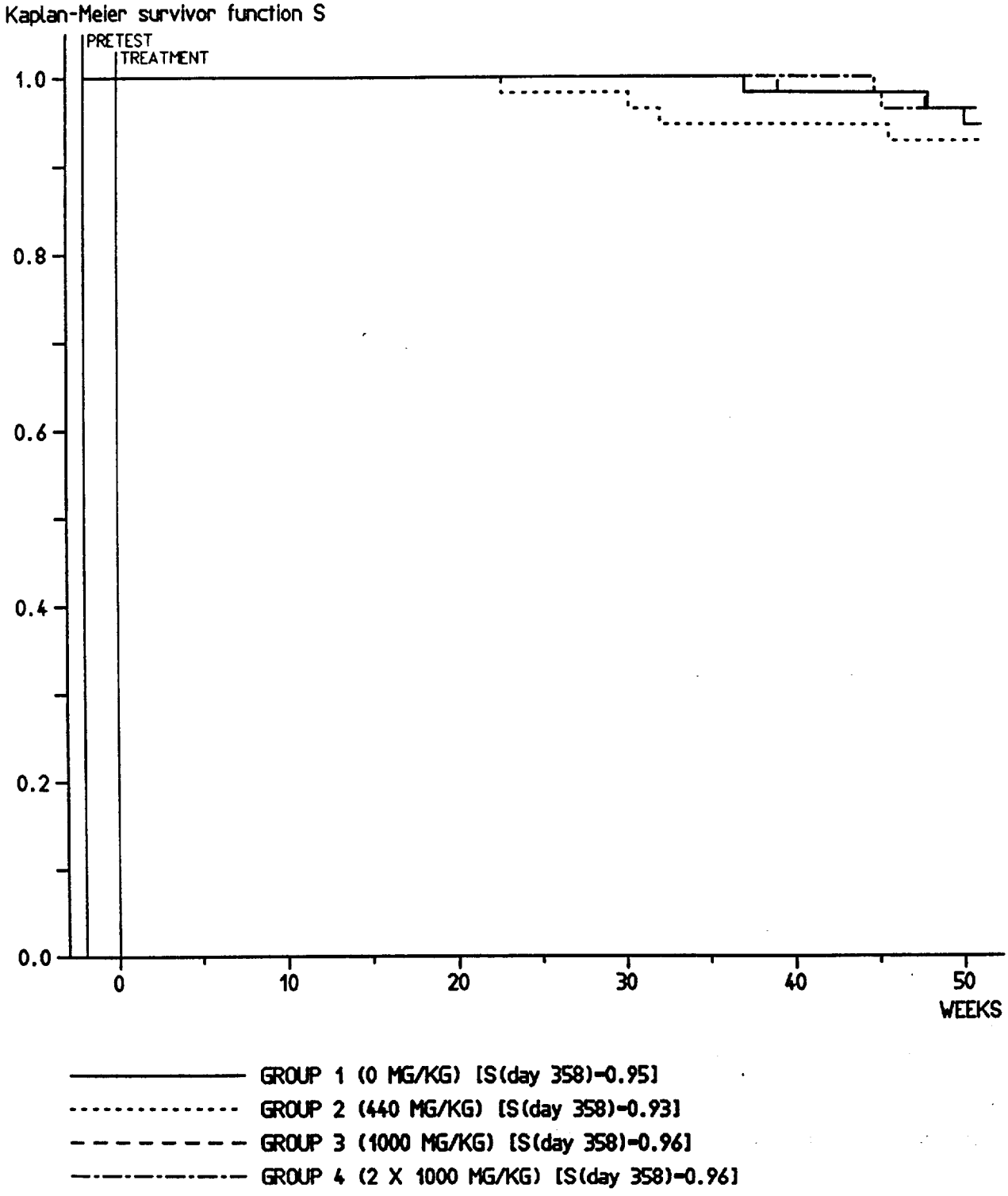
A total of 84 primary neoplasms were recorded in 73 rats. These were distributed across the dose groups with a higher incidence in the control group at both sacrifices than in the treated groups. Of the total number of primary tumors in males (23), 17 were benign and 6 were malignant; in females (total 61) 47 were benign and 14 malignant. Again the incidences of benign and malignant tumors were slightly higher in controls than in the treated rats.

The most commonly occurring neoplasms were pituitary adenomas and mammary gland fibroadenomas and carcinomas.

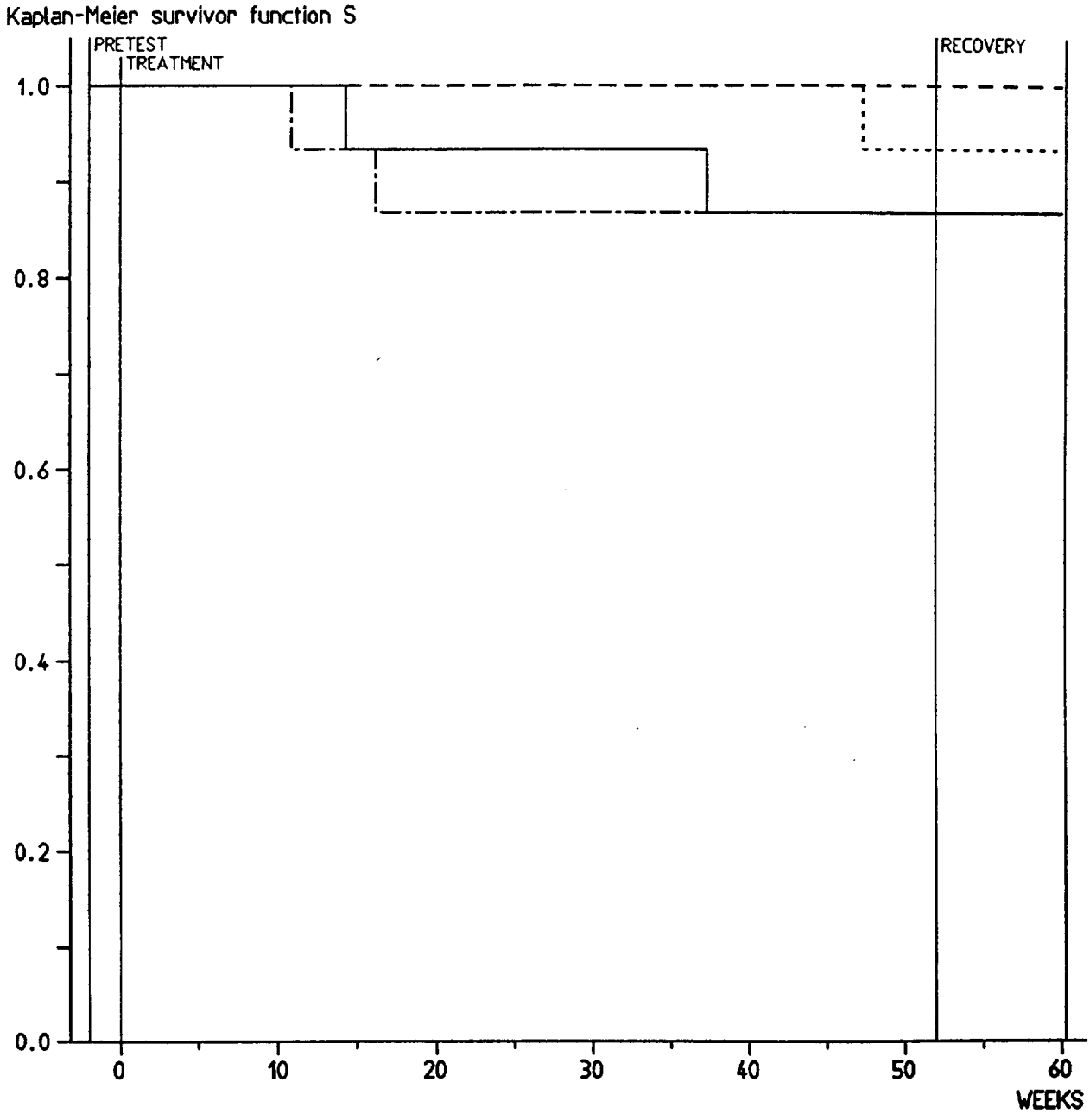
SURVIVAL RATE
MALES



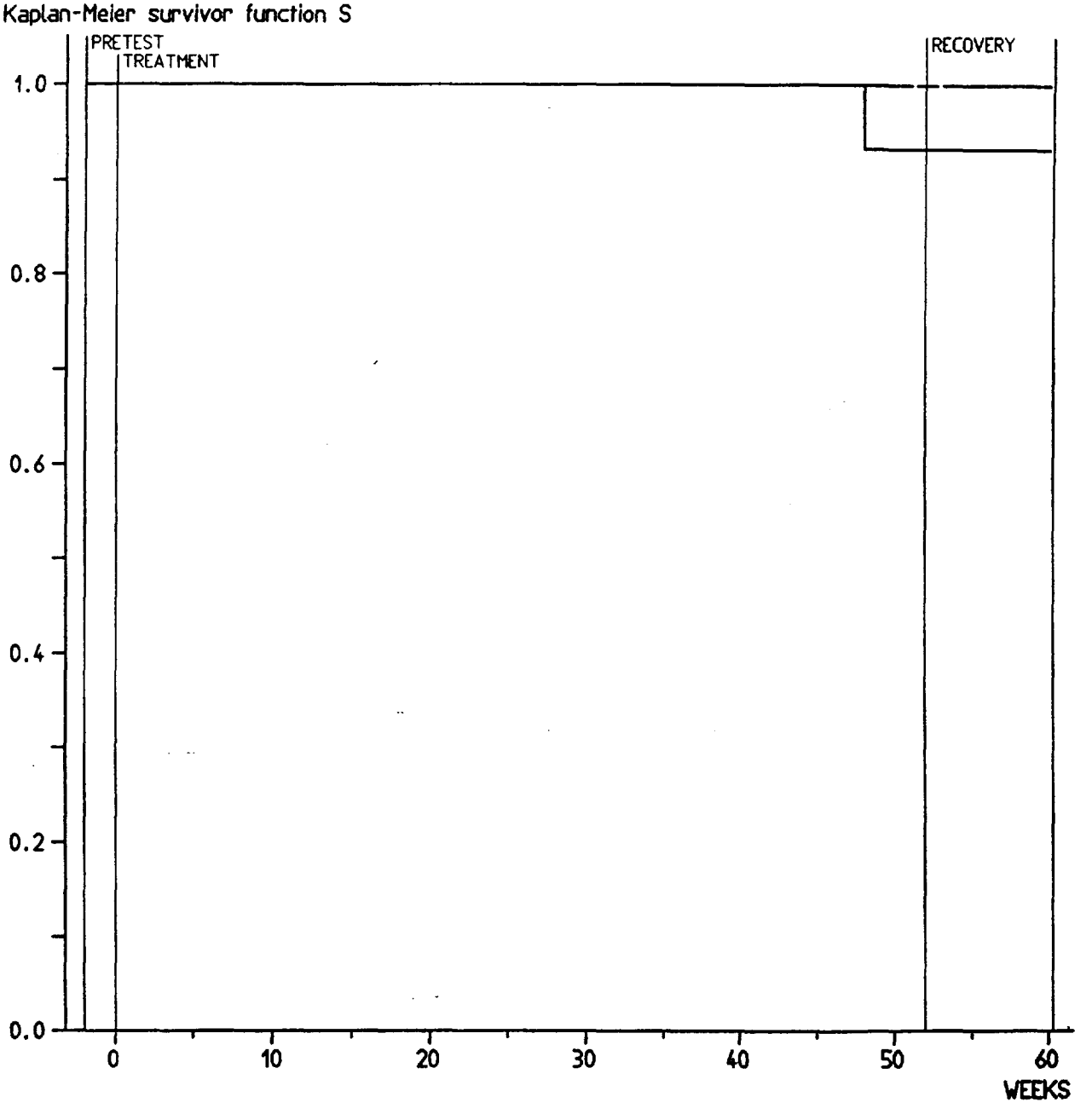
SURVIVAL RATE
FEMALES



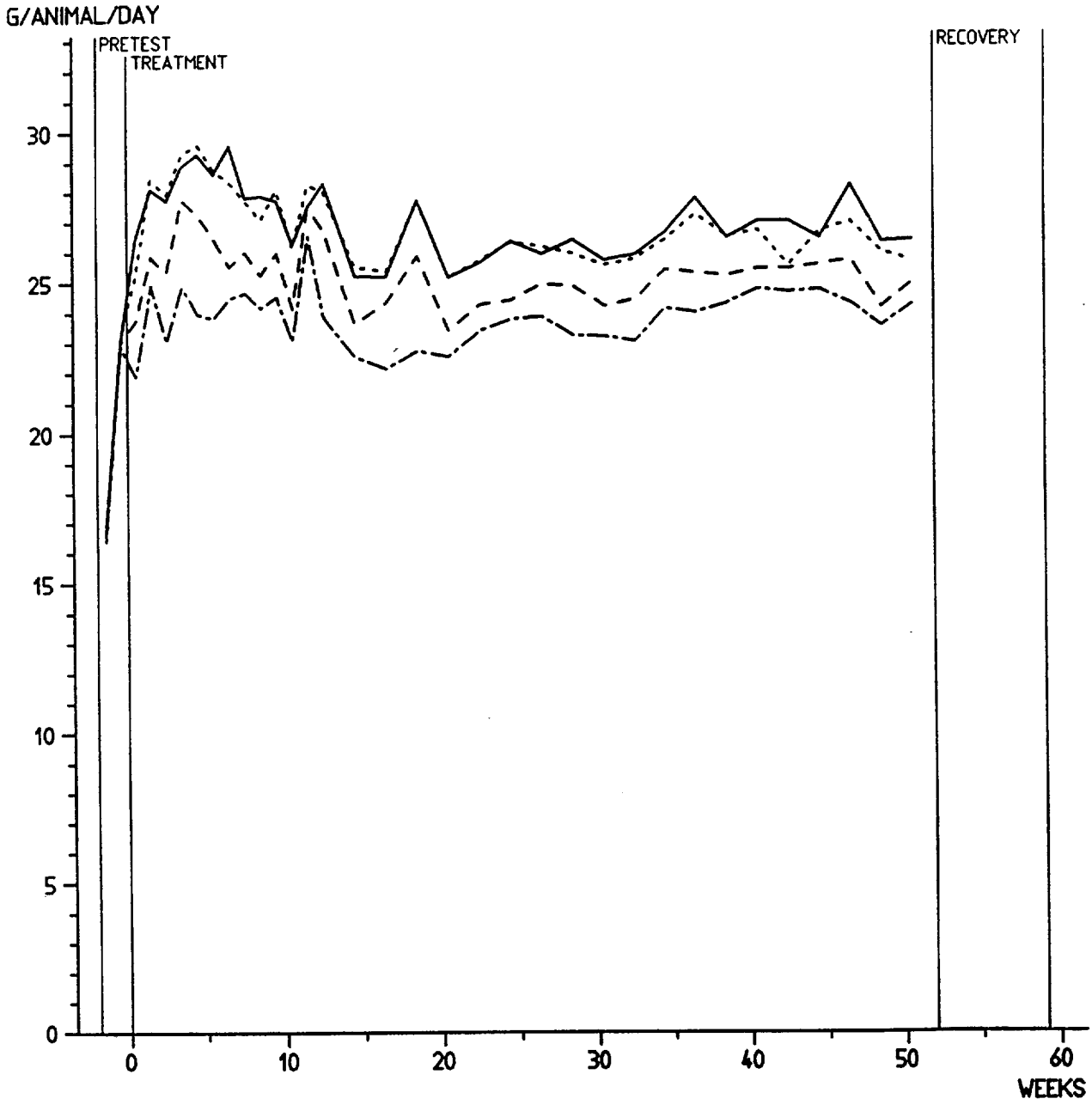
SURVIVAL RATE
CLINICAL LABORATORY/RECOVERY / MALES



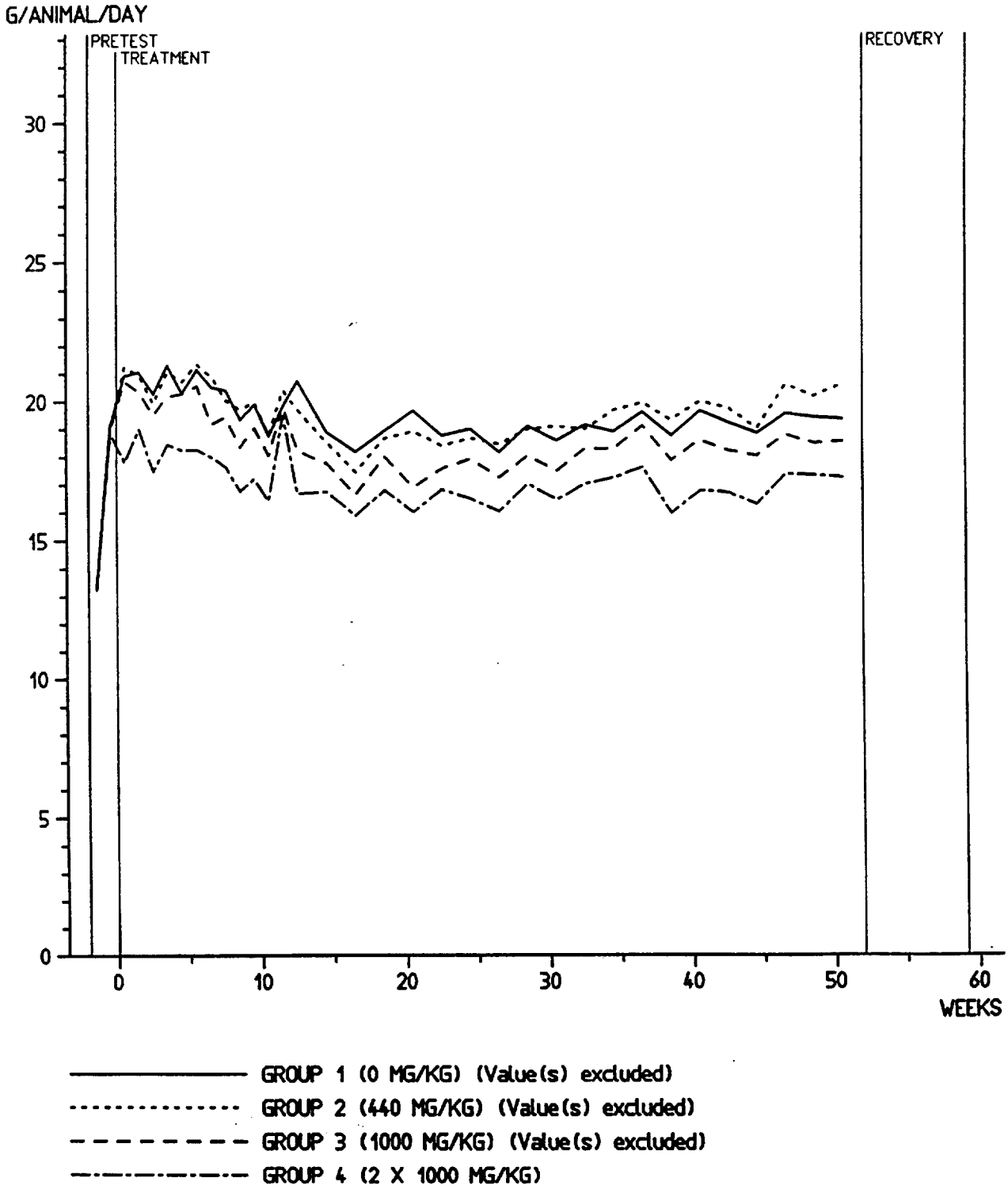
SURVIVAL RATE
CLINICAL LABORATORY/RECOVERY / FEMALES



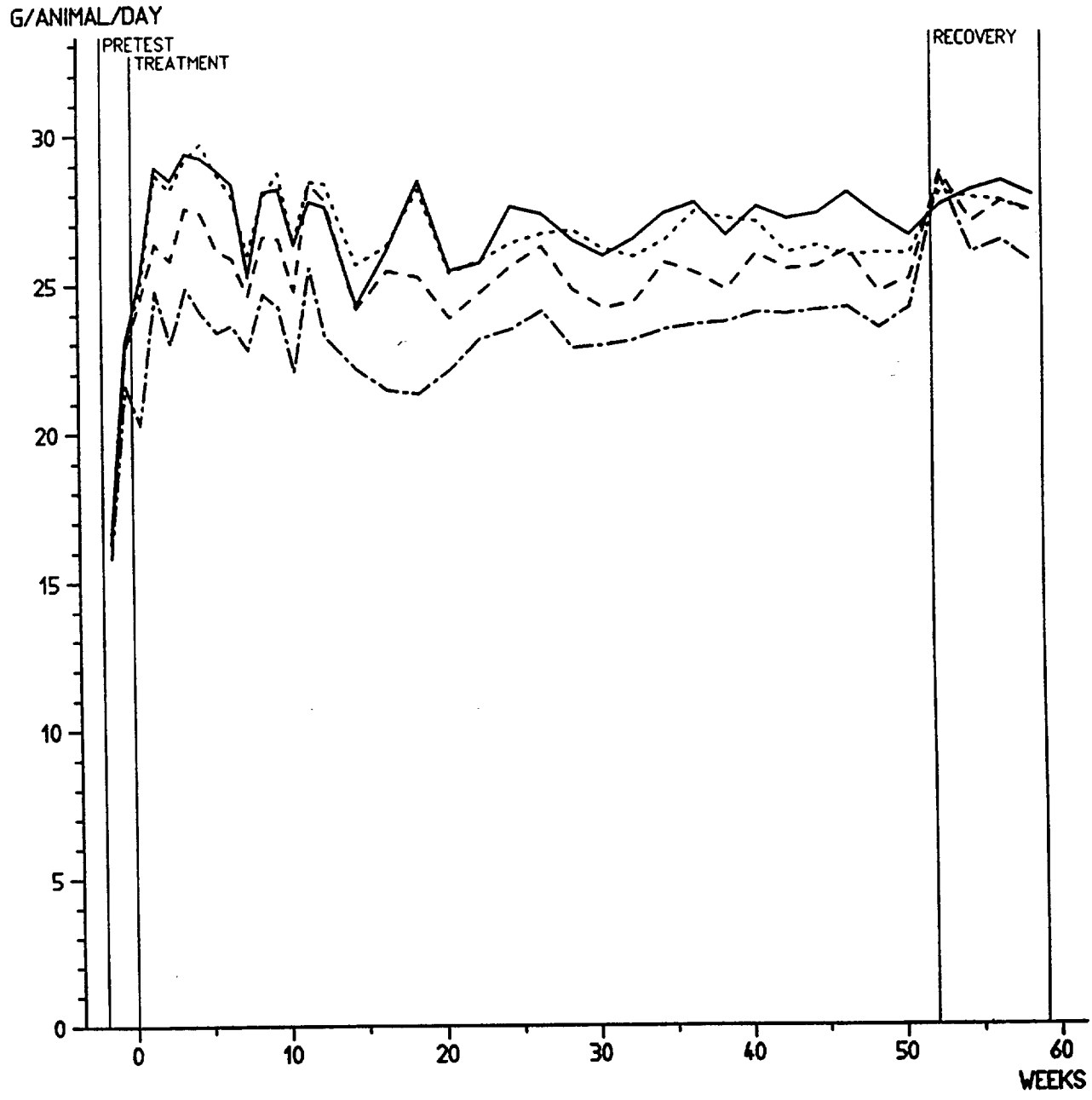
FOOD CONSUMPTION
MALES



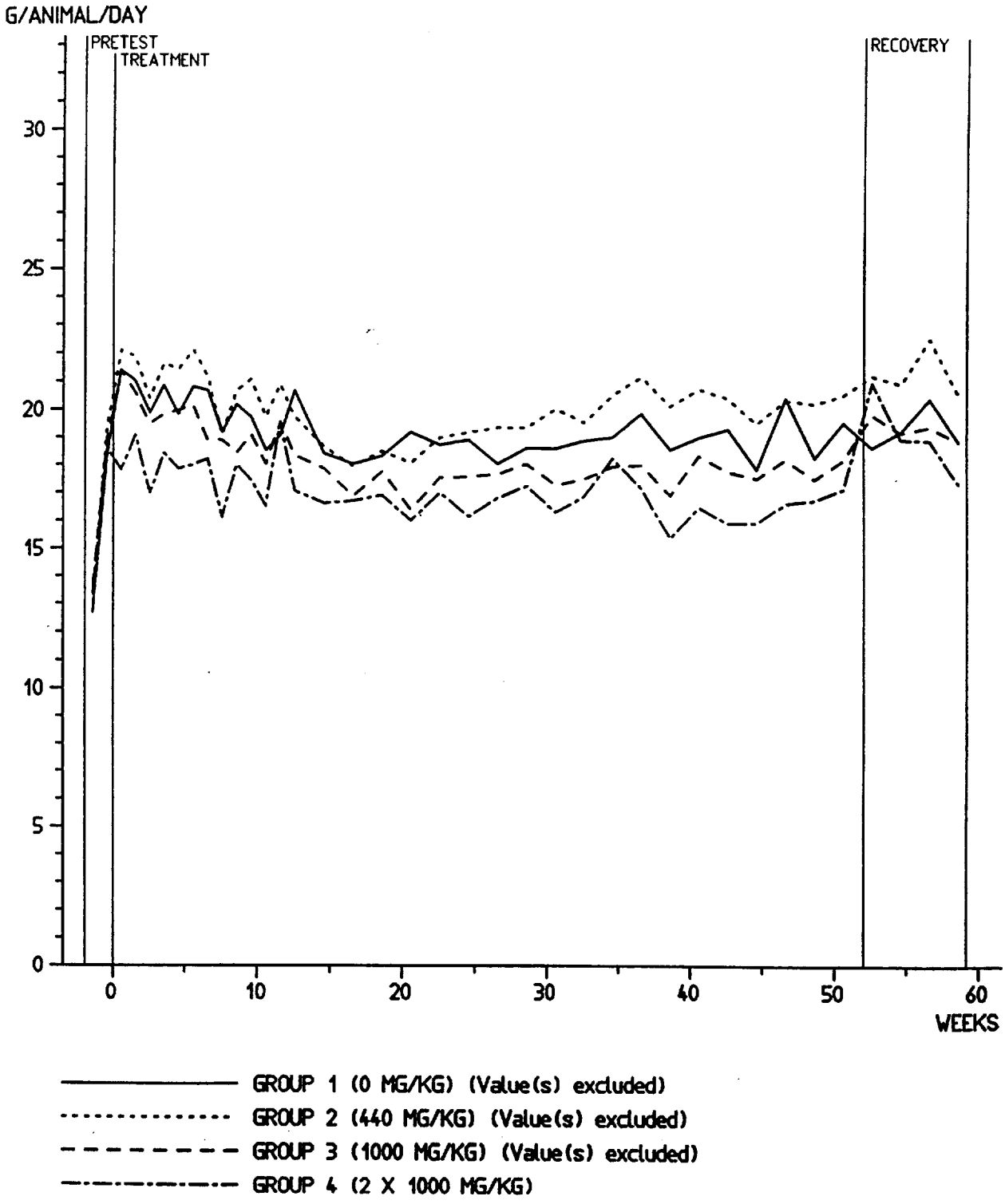
FOOD CONSUMPTION
FEMALES



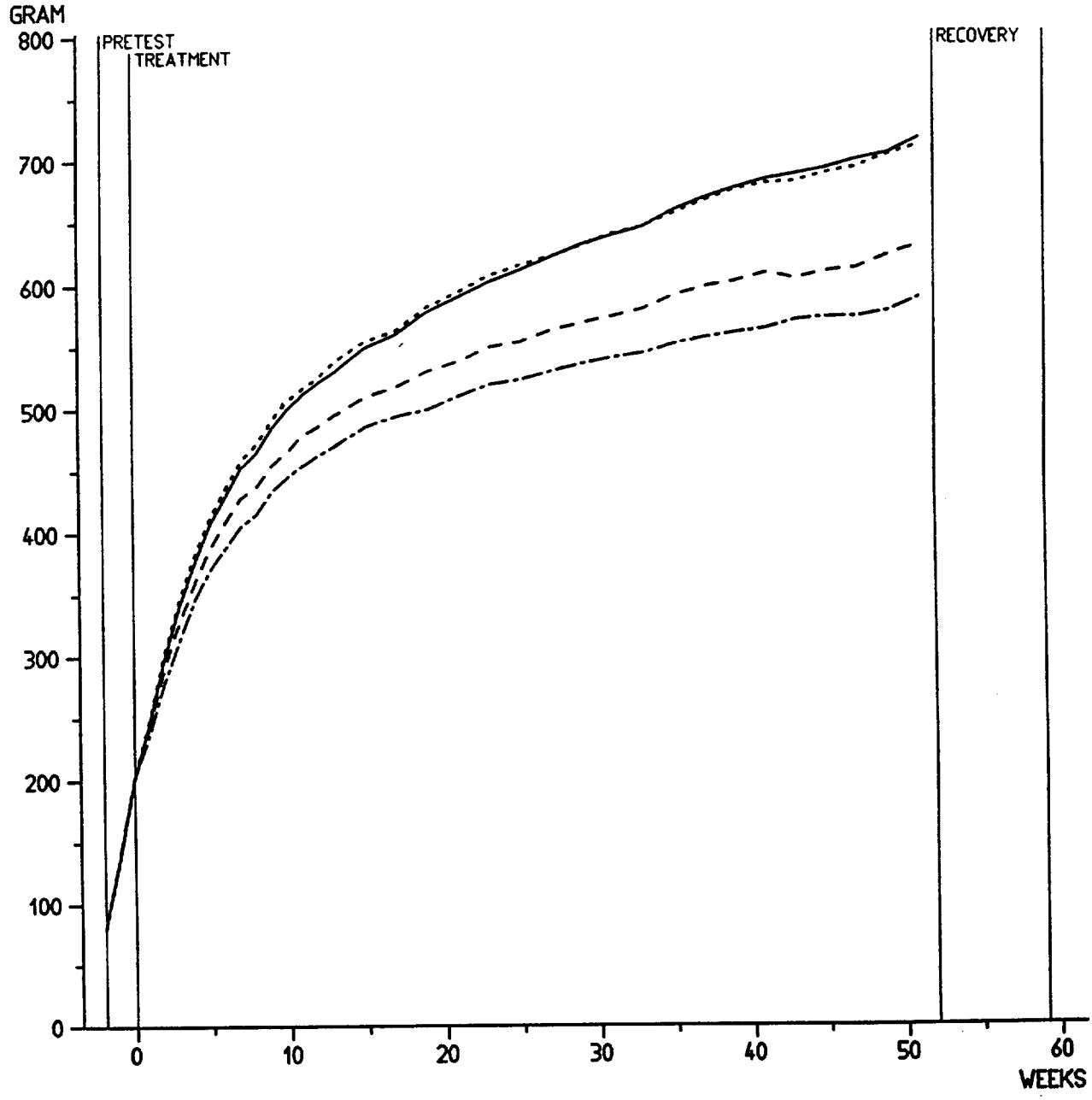
FOOD CONSUMPTION
CLINICAL LABORATORY/RECOVERY MALES



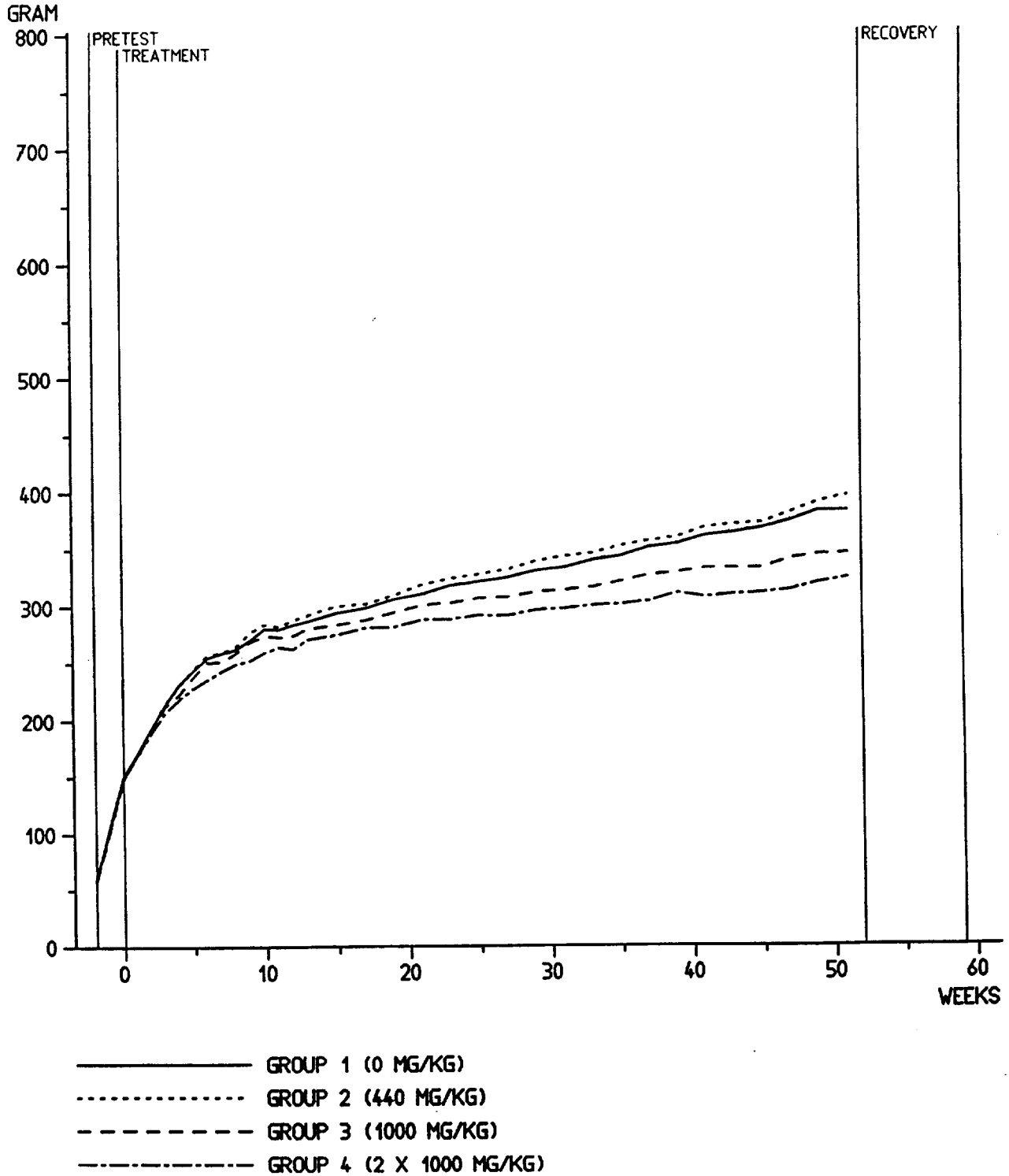
FOOD CONSUMPTION
CLINICAL LABORATORY/RECOVERY FEMALES



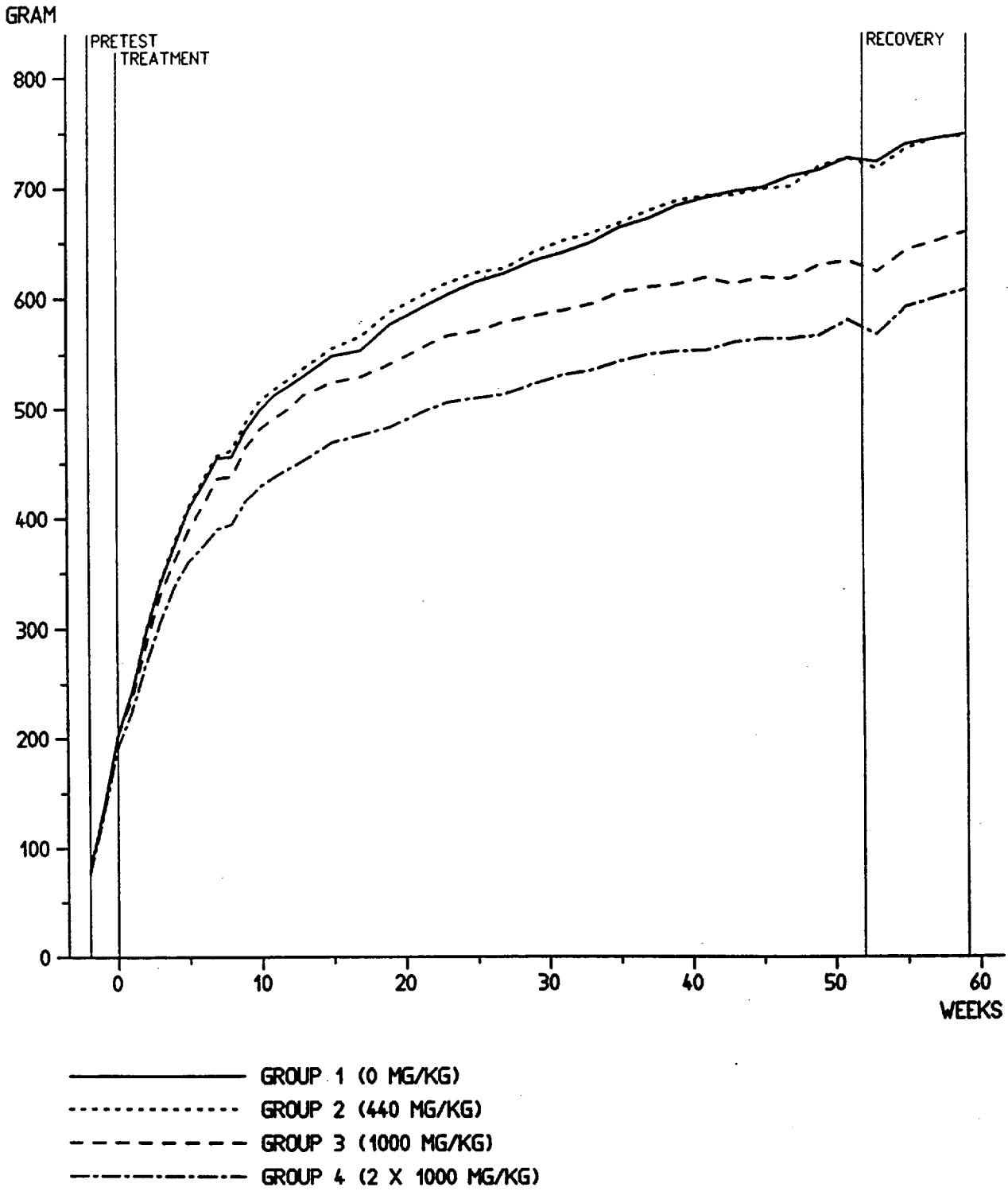
BODY WEIGHTS
MALES



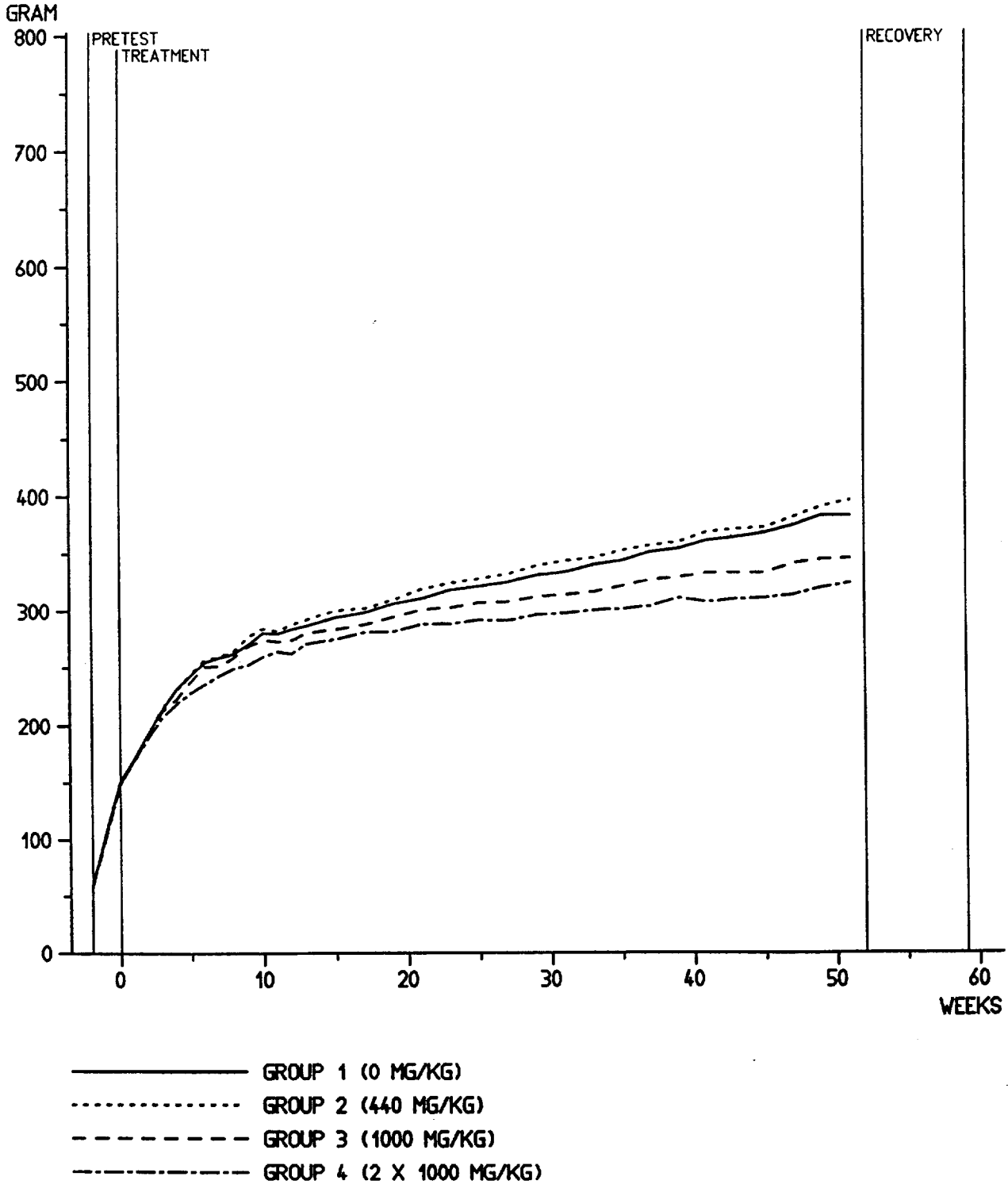
BODY WEIGHTS
FEMALES



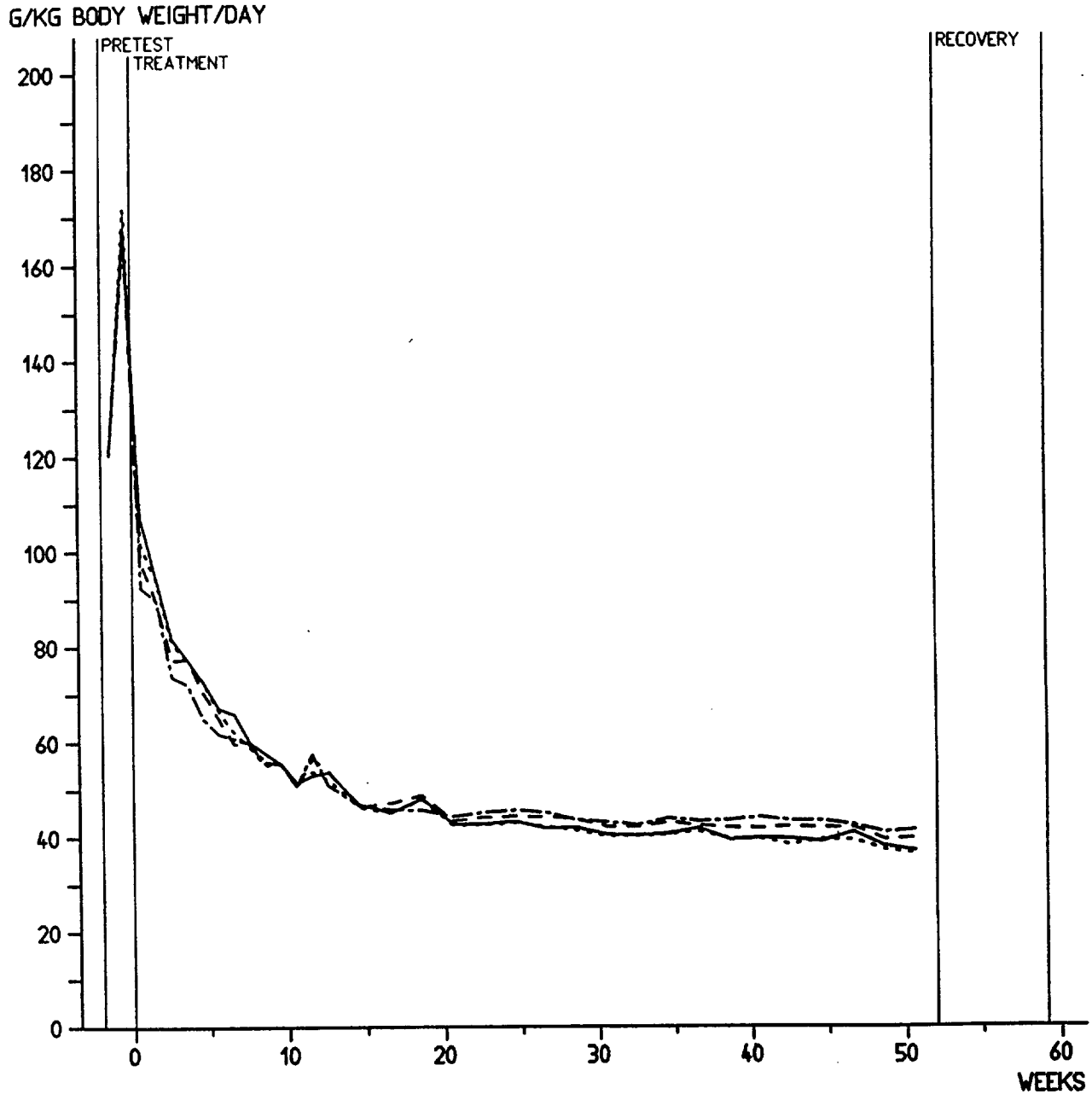
BODY WEIGHTS
CLINICAL LABORATORY/RECOVERY MALES



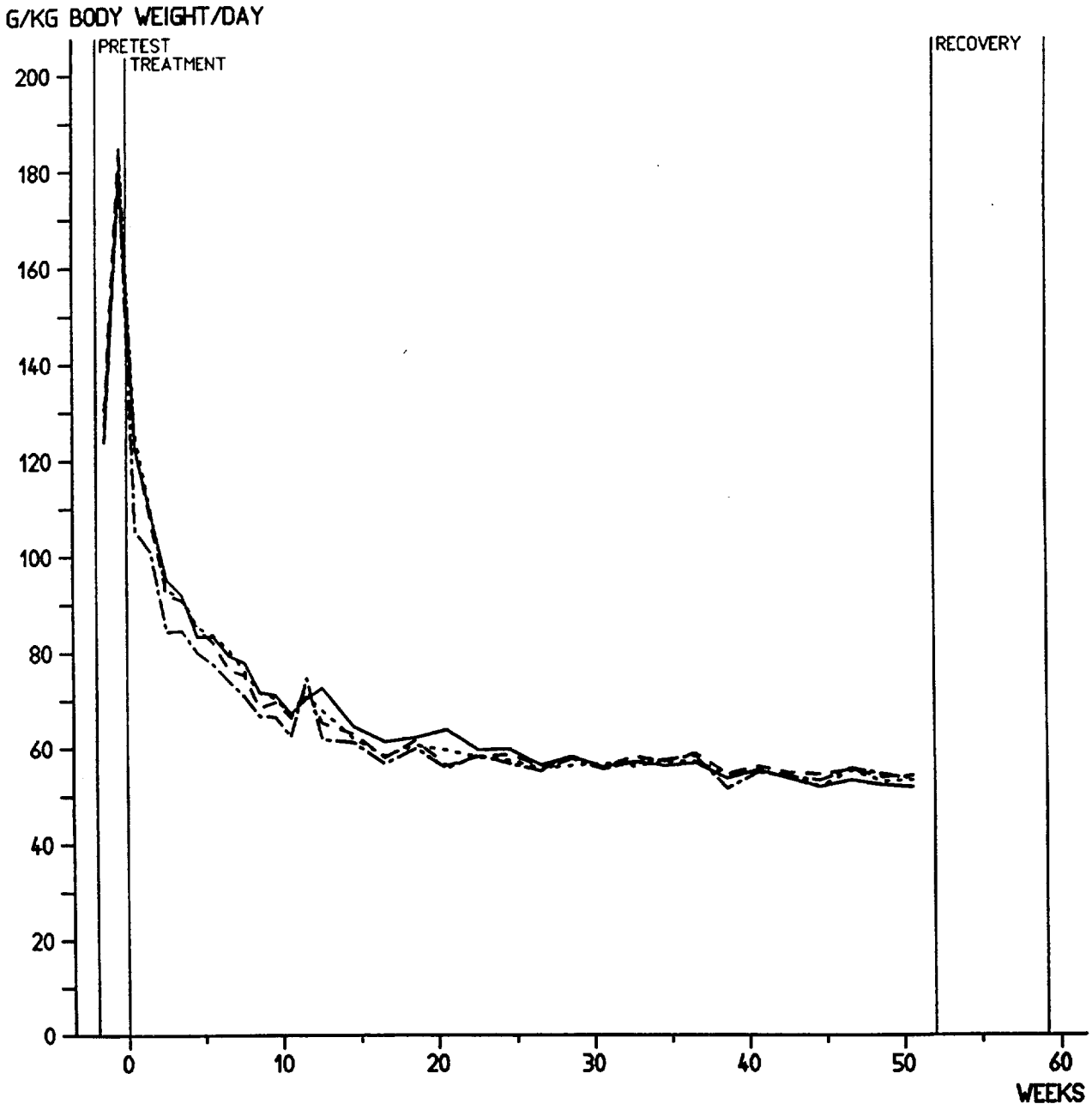
BODY WEIGHTS
FEMALES



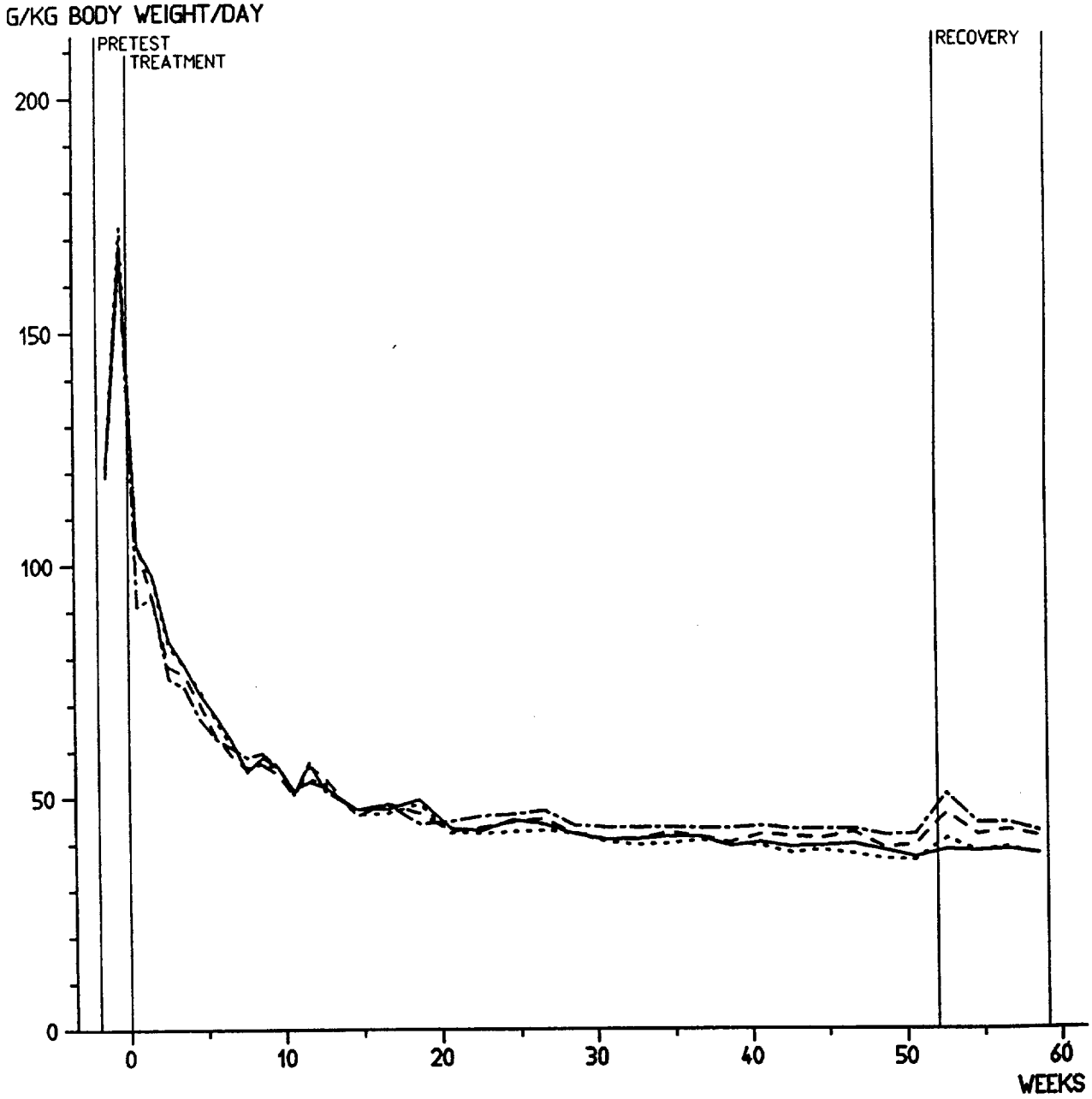
RELATIVE FOOD CONSUMPTION
MALES



RELATIVE FOOD CONSUMPTION
FEMALES

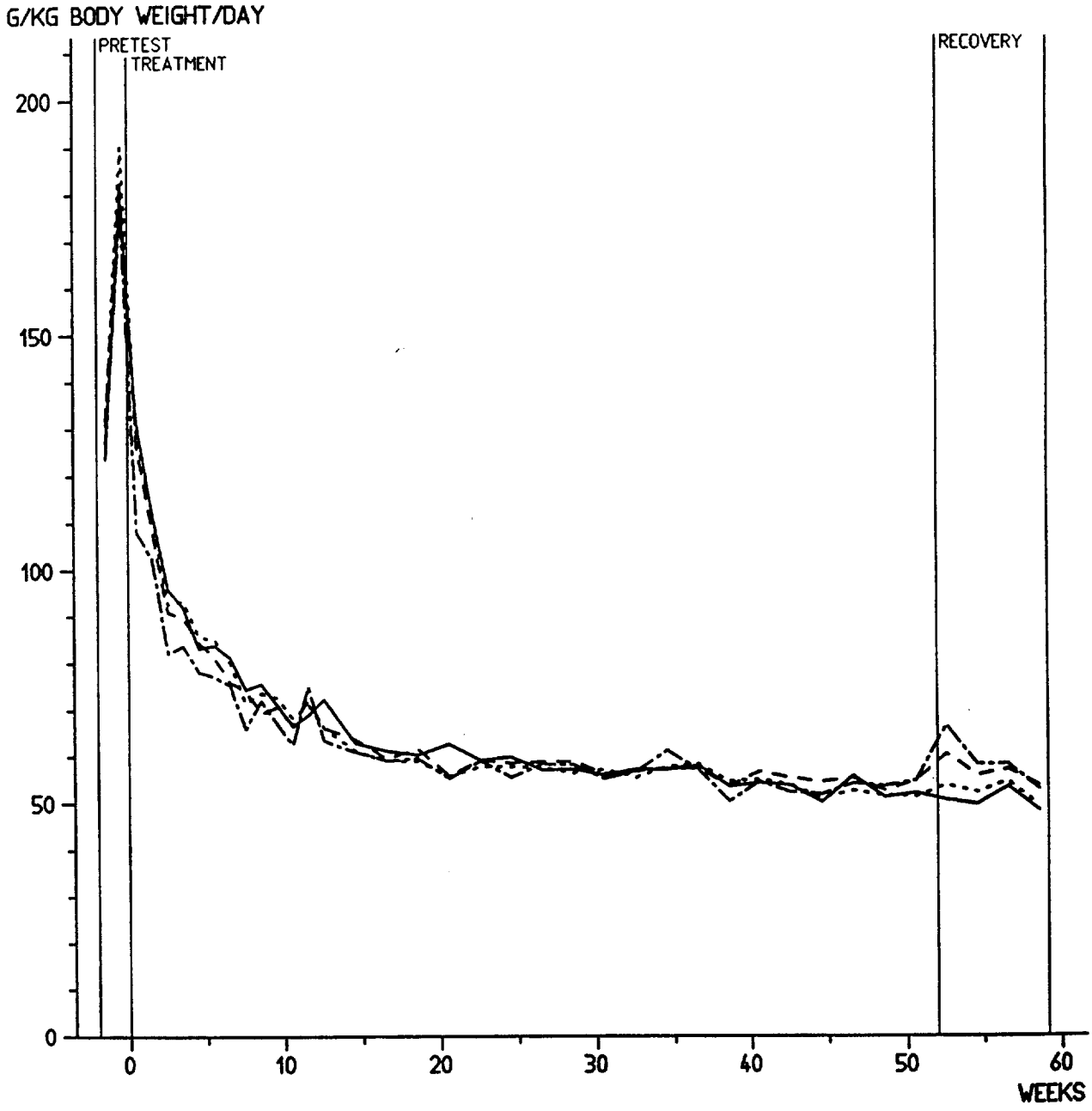


RELATIVE FOOD CONSUMPTION
CLINICAL LABORATORY/RECOVERY MALES



GROUP 1 (0 MG/KG) (Value(s) excluded)
GROUP 2 (440 MG/KG) (Value(s) excluded)
GROUP 3 (1000 MG/KG) (Value(s) excluded)
GROUP 4 (2 X 1000 MG/KG)

RELATIVE FOOD CONSUMPTION
CLINICAL LABORATORY/RECOVERY FEMALES



FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	16.7	16.4	16.9	16.6
WEEKS 1/2	ST.DEV.	2.0	2.2	2.0	2.3
	N	55	55	55	55
DAYS 8-15	MEAN	23.0	23.2	23.0	22.9
WEEKS 2/3	ST.DEV.	2.1	2.0	2.4	2.6
	N	55	55	55	55
MEAN OF MEANS OVER PRETEST		19.9	19.8	20.0	19.7

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

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	26.4	25.2	23.7 **	21.9 **
WEEKS 1/2	ST.DEV.	2.7	2.1	2.9	3.3
	N	55	55	55	55
DAYS 8-15	MEAN	28.1	28.4	25.8 **	24.9 **
WEEKS 2/3	ST.DEV.	2.4	2.1	2.5	3.0
	N	54 x	55	54 x	55
DAYS 15-22	MEAN	27.7	27.9	25.3 **	23.0 **
WEEKS 3/4	ST.DEV.	2.7	2.2	2.7	3.2
	N	54 x	55	55	55
DAYS 22-29	MEAN	28.8	29.3	27.7	24.8 **
WEEKS 4/5	ST.DEV.	2.5	2.0	2.9	3.0
	N	53 x	53 x	55	55
DAYS 29-36	MEAN	29.2	29.6	27.2 **	23.9 **
WEEKS 5/6	ST.DEV.	2.3	2.1	3.0	2.8
	N	51 x	52 x	55	55
DAYS 36-43	MEAN	28.6	28.7	26.5 **	23.8 **
WEEKS 6/7	ST.DEV.	2.4	3.2	2.9	2.6
	N	53 x	52 x	55	55
DAYS 43-50	MEAN	29.5	28.3	25.5 **	24.4 **
WEEKS 7/8	ST.DEV.	2.6	2.8	2.9	2.4
	N	52 x	54 x	55	55
DAYS 50-57	MEAN	27.8	27.7	26.0 **	24.6 **
WEEKS 8/9	ST.DEV.	3.1	2.8	3.0	3.0
	N	55	54 x	55	55
DAYS 57-64	MEAN	27.9	27.0	25.2 **	24.1 **
WEEKS 9/10	ST.DEV.	2.4	2.5	3.0	2.6
	N	55	55	55	55
DAYS 64-71	MEAN	27.7	28.1	25.9 **	24.5 **
WEEKS 10/11	ST.DEV.	2.7	2.4	3.1	2.6
	N	55	55	55	55
DAYS 71-78	MEAN	26.2	26.1	24.1 **	23.0 **
WEEKS 11/12	ST.DEV.	2.5	2.4	2.8	2.9
	N	55	55	55	55
DAYS 78-85	MEAN	27.5	28.2	27.5	26.5
WEEKS 12/13	ST.DEV.	3.0	2.5	3.1	2.8
	N	55	55	55	54
DAYS 85-92	MEAN	28.3	28.0	26.7 **	23.8 **
WEEKS 13/14	ST.DEV.	2.7	2.5	3.1	2.6
	N	54 x	55	55	54
DAYS 99-106	MEAN	25.2	25.5	23.6 *	22.5 **
WEEKS 15/16	ST.DEV.	4.3	2.5	2.9	2.4
	N	55	55	55	54
DAYS 113-120	MEAN	25.2	25.3	24.3	22.1 **
WEEKS 17/18	ST.DEV.	2.8	2.6	3.3	3.8
	N	54	55	54 x	54
DAYS 127-134	MEAN	27.7	27.7	25.8 **	22.7 **
WEEKS 19/20	ST.DEV.	2.9	2.4	3.0	3.0
	N	54	54 x	55	53
DAYS 141-148	MEAN	25.1	25.1	23.4 **	22.5 **
WEEKS 21/22	ST.DEV.	2.8	2.6	3.5	2.5
	N	54	55	55	53

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 155-162	MEAN	25.6	25.7	24.2 *	23.4 **
WEEKS 23/24	ST.DEV.	2.6	2.4	3.5	2.9
	N	54	55	55	53
DAYS 169-176	MEAN	26.3	26.3	24.4 **	23.7 **
WEEKS 25/26	ST.DEV.	3.0	2.7	4.0	2.8
	N	54	55	55	53
DAYS 183-190	MEAN	25.9	26.1	24.9	23.8 **
WEEKS 27/28	ST.DEV.	2.9	2.6	3.7	2.8
	N	54	55	54	53
DAYS 197-204	MEAN	26.3	25.9	24.8 *	23.2 **
WEEKS 29/30	ST.DEV.	2.7	2.4	3.3	2.8
	N	54	55	54	53
DAYS 211-218	MEAN	25.7	25.5	24.2 *	23.2 **
WEEKS 31/32	ST.DEV.	2.6	3.0	3.5	2.8
	N	54	55	54	53
DAYS 225-232	MEAN	25.8	25.7	24.4	23.0 **
WEEKS 33/34	ST.DEV.	3.0	2.7	3.6	3.9
	N	54	55	54	53
DAYS 239-246	MEAN	26.6	26.3	25.3	24.1 **
WEEKS 35/36	ST.DEV.	3.2	2.5	3.6	3.2
	N	54	55	54	53
DAYS 253-260	MEAN	27.7	27.2	25.3 **	23.9 **
WEEKS 37/38	ST.DEV.	3.2	2.7	3.6	3.1
	N	54	55	54	53
DAYS 267-274	MEAN	26.4	26.4	25.2	24.2 **
WEEKS 39/40	ST.DEV.	3.2	2.7	3.6	3.3
	N	53	55	54	53
DAYS 281-288	MEAN	26.9	26.6	25.4 *	24.7 **
WEEKS 41/42	ST.DEV.	3.0	2.4	3.8	3.3
	N	51	55	54	53
DAYS 295-302	MEAN	26.9	25.5	25.4	24.6 **
WEEKS 43/44	ST.DEV.	3.3	4.0	3.8	3.2
	N	51	55	53	53
DAYS 309-316	MEAN	26.4	26.6	25.5	24.7 *
WEEKS 45/46	ST.DEV.	3.9	2.8	4.0	3.1
	N	51	51 x	53	53
DAYS 323-330	MEAN	28.2	26.9	25.7 **	24.2 **
WEEKS 47/48	ST.DEV.	3.1	3.8	4.0	3.3
	N	47 x	52 x	53	53
DAYS 337-344	MEAN	26.3	25.9	24.1 *	23.5 **
WEEKS 49/50	ST.DEV.	3.9	3.0	4.7	3.2
	N	49	52	53	53
DAYS 351-358	MEAN	26.3	25.7	24.9	24.2 **
WEEKS 51/52	ST.DEV.	3.2	3.1	4.0	3.3
	N	48	52	52	53
MEAN OF MEANS OVER TREATMENT		27.0	26.8	25.2	23.8

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	13.2	13.3	13.4	13.4
WEEKS 1/2	ST.DEV.	1.2	1.2	1.2	1.3
	N	55	55	55	55
DAYS 8-15	MEAN	19.1	19.1	19.0	18.9
WEEKS 2/3	ST.DEV.	1.5	1.3	1.4	1.5
	N	55	55	55	55
MEAN OF MEANS OVER PRETEST		16.2	16.2	16.2	16.1

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

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	20.9	21.2	20.7	17.8 **
WEEKS 1/2	ST.DEV.	1.9	1.8	2.0	1.9
	N	55	55	55	55
DAYS 8-15	MEAN	21.0	20.9	20.3	19.0 **
WEEKS 2/3	ST.DEV.	1.7	1.7	1.9	1.9
	N	55	53 x	55	55
DAYS 15-22	MEAN	20.3	19.9	19.5	17.5 **
WEEKS 3/4	ST.DEV.	1.8	2.1	1.8	2.2
	N	52 x	55	55	55
DAYS 22-29	MEAN	21.3	21.1	20.2 **	18.4 **
WEEKS 4/5	ST.DEV.	1.9	1.9	1.8	1.8
	N	55	54 x	54 x	55
DAYS 29-36	MEAN	20.3	20.7	20.3	18.2 **
WEEKS 5/6	ST.DEV.	1.8	2.0	2.1	1.8
	N	55	53 x	55	55
DAYS 36-43	MEAN	21.1	21.3	20.5	18.3 **
WEEKS 6/7	ST.DEV.	2.0	2.1	1.9	1.6
	N	53 x	43 x	55	55
DAYS 43-50	MEAN	20.5	20.9	19.2 **	18.0 **
WEEKS 7/8	ST.DEV.	1.9	2.2	1.7	1.6
	N	55	55	55	55
DAYS 50-57	MEAN	20.4	20.0	19.4 *	17.6 **
WEEKS 8/9	ST.DEV.	2.2	2.2	2.1	1.9
	N	55	55	55	55
DAYS 57-64	MEAN	19.3	19.7	18.3 *	16.7 **
WEEKS 9/10	ST.DEV.	2.0	2.1	1.9	1.6
	N	55	54 x	55	55
DAYS 64-71	MEAN	19.9	19.9	19.0	17.2 **
WEEKS 10/11	ST.DEV.	2.0	2.3	1.9	1.5
	N	55	54 x	55	55
DAYS 71-78	MEAN	18.7	18.8	18.0	16.4 **
WEEKS 11/12	ST.DEV.	2.2	2.5	1.8	1.7
	N	55	55	55	55
DAYS 78-85	MEAN	19.8	20.4	19.8	19.5
WEEKS 12/13	ST.DEV.	1.8	2.7	2.1	1.3
	N	54 x	55	55	55
DAYS 85-92	MEAN	20.7	19.7 *	18.2 **	16.7 **
WEEKS 13/14	ST.DEV.	2.0	2.3	1.9	1.6
	N	55	54 x	55	55
DAYS 99-106	MEAN	18.9	18.5	17.8 **	16.7 **
WEEKS 15/16	ST.DEV.	2.3	2.0	1.8	1.7
	N	55	55	55	55
DAYS 113-120	MEAN	18.2	17.4	16.6 **	15.9 **
WEEKS 17/18	ST.DEV.	2.3	2.0	1.8	1.6
	N	55	54 x	55	55
DAYS 127-134	MEAN	18.9	18.7	18.0	16.8 **
WEEKS 19/20	ST.DEV.	2.3	2.5	1.8	1.7
	N	55	55	55	55
DAYS 141-148	MEAN	19.6	18.9	16.9 **	16.0 **
WEEKS 21/22	ST.DEV.	2.2	3.0	2.3	1.6
	N	54 x	54 x	55	55

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 155-162	MEAN	18.7	18.4	17.6 **	16.8 **
WEEKS 23/24	ST.DEV.	2.1	2.6	1.9	1.6
	N	52 x	54 x	55	55
DAYS 169-176	MEAN	19.0	18.7	17.9 *	16.5 **
WEEKS 25/26	ST.DEV.	2.2	2.1	2.1	1.6
	N	54 x	53 x	55	55
DAYS 183-190	MEAN	18.1	18.4	17.2	16.0 **
WEEKS 27/28	ST.DEV.	2.2	2.6	2.4	2.0
	N	54 x	54	55	55
DAYS 197-204	MEAN	19.1	19.0	18.0 *	17.0 **
WEEKS 29/30	ST.DEV.	2.6	2.1	2.2	1.7
	N	54 x	54	55	55
DAYS 211-218	MEAN	18.6	19.1	17.5 *	16.4 **
WEEKS 31/32	ST.DEV.	2.4	2.9	2.2	1.6
	N	55	53 x	55	55
DAYS 225-232	MEAN	19.1	19.0	18.3	17.0 **
WEEKS 33/34	ST.DEV.	2.5	2.7	2.6	1.8
	N	53 x	52 x	55	55
DAYS 239-246	MEAN	18.9	19.6	18.2	17.2 **
WEEKS 35/36	ST.DEV.	2.3	2.3	2.4	2.1
	N	52 x	48 x	55	55
DAYS 253-260	MEAN	19.6	19.9	19.1	17.6 **
WEEKS 37/38	ST.DEV.	2.5	2.3	2.6	1.9
	N	53 x	49 x	55	55
DAYS 267-274	MEAN	18.7	19.3	17.8	15.9 **
WEEKS 39/40	ST.DEV.	2.7	2.5	2.7	1.9
	N	53 x	50 x	55	55
DAYS 281-288	MEAN	19.6	19.9	18.6	16.7 **
WEEKS 41/42	ST.DEV.	2.8	2.4	2.5	1.9
	N	52 x	50 x	54	55
DAYS 295-302	MEAN	19.2	19.7	18.2	16.7 **
WEEKS 43/44	ST.DEV.	2.3	2.5	2.8	1.7
	N	53 x	50 x	54	55
DAYS 309-316	MEAN	18.8	19.0	18.0	16.2 **
WEEKS 45/46	ST.DEV.	2.5	2.6	2.4	2.7
	N	53 x	51 x	54	55
DAYS 323-330	MEAN	19.5	20.5	18.8	17.3 **
WEEKS 47/48	ST.DEV.	2.7	2.2	2.8	1.9
	N	52 x	49 x	54	53
DAYS 337-344	MEAN	19.4	20.1	18.4	17.3 **
WEEKS 49/50	ST.DEV.	3.7	2.3	2.8	2.1
	N	54	48 x	53	53
DAYS 351-358	MEAN	19.3	20.6 *	18.5	17.2 **
WEEKS 51/52	ST.DEV.	2.9	2.2	2.2	2.6
	N	52 x	49 x	53	53
MEAN OF MEANS OVER TREATMENT		19.5	19.7	18.6	17.1

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	16.6	16.4	16.3	15.8
WEEKS 1/2	ST.DEV.	2.7	2.8	2.2	2.5
	N	15	15	15	15
DAYS 8-15	MEAN	23.1	23.0	22.8	21.6
WEEKS 2/3	ST.DEV.	2.3	2.7	2.7	2.7
	N	15	15	15	15
MEAN OF MEANS OVER PRETEST		19.8	19.7	19.5	18.7

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

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	25.2	24.9	24.4	20.3 **
WEEKS 1/2	ST.DEV.	3.6	2.7	2.4	2.3
	N	15	15	15	15
DAYS 8-15	MEAN	28.9	28.7	26.3 *	24.8 **
WEEKS 2/3	ST.DEV.	2.9	2.3	2.6	2.6
	N	15	15	15	15
DAYS 15-22	MEAN	28.5	28.1	25.8 *	23.0 **
WEEKS 3/4	ST.DEV.	3.1	2.3	3.4	2.8
	N	15	15	15	15
DAYS 22-29	MEAN	29.4	29.2	27.5	24.8 **
WEEKS 4/5	ST.DEV.	3.2	2.0	3.8	3.2
	N	15	14 x	15	15
DAYS 29-36	MEAN	29.2	29.7	27.4	24.0 **
WEEKS 5/6	ST.DEV.	2.6	2.1	4.1	2.4
	N	14 x	14 x	15	15
DAYS 36-43	MEAN	28.8	28.7	26.1	23.4 **
WEEKS 6/7	ST.DEV.	3.0	2.3	4.1	2.2
	N	14 x	14 x	15	15
DAYS 43-50	MEAN	28.3	27.9	25.9	23.6 **
WEEKS 7/8	ST.DEV.	3.4	3.0	4.1	2.1
	N	15	15	15	15
DAYS 50-57	MEAN	25.2	26.0	24.6	22.8
WEEKS 8/9	ST.DEV.	3.5	2.5	4.0	3.2
	N	15	15	15	15
DAYS 57-64	MEAN	28.1	27.9	26.6	24.6 **
WEEKS 9/10	ST.DEV.	2.5	2.0	4.0	2.7
	N	15	15	15	15
DAYS 64-71	MEAN	28.2	28.7	26.5	24.2 **
WEEKS 10/11	ST.DEV.	3.5	2.6	3.9	2.4
	N	15	15	15	15
DAYS 71-78	MEAN	26.3	26.3	24.7	22.0 **
WEEKS 11/12	ST.DEV.	2.8	2.5	3.9	2.5
	N	15	15	15	15
DAYS 78-85	MEAN	27.7	28.4	28.4	25.5
WEEKS 12/13	ST.DEV.	3.0	2.6	4.3	2.7
	N	15	15	15	14
DAYS 85-92	MEAN	27.6	28.3	27.8	23.2 **
WEEKS 13/14	ST.DEV.	2.9	2.9	4.3	2.8
	N	15	15	15	14
DAYS 99-106	MEAN	24.3	25.6	24.1	22.1
WEEKS 15/16	ST.DEV.	7.1	2.9	4.2	2.0
	N	15	15	15	14
DAYS 113-120	MEAN	26.1	26.2	25.4	21.4 *
WEEKS 17/18	ST.DEV.	2.8	2.8	4.2	6.4
	N	14	15	14 x	14
DAYS 127-134	MEAN	28.4	28.1	25.2 *	21.3 **
WEEKS 19/20	ST.DEV.	3.1	2.4	4.1	2.6
	N	14	14 x	15	13
DAYS 141-148	MEAN	25.4	25.3	23.8	22.1 *
WEEKS 21/22	ST.DEV.	2.8	3.0	5.2	2.6
	N	14	15	15	13

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 155-162	MEAN	25.7	25.7	24.7	23.1
WEEKS 23/24	ST.DEV.	2.6	2.9	5.0	2.6
	N	14	15	15	13
DAYS 169-176	MEAN	27.5	26.3	25.6	23.4 *
WEEKS 25/26	ST.DEV.	3.3	3.2	5.1	2.5
	N	14	15	15	13
DAYS 183-190	MEAN	27.3	26.6	26.2	24.0
WEEKS 27/28	ST.DEV.	2.8	2.6	5.2	2.7
	N	14	15	15	13
DAYS 197-204	MEAN	26.4	26.7	24.7	22.8 *
WEEKS 29/30	ST.DEV.	2.5	2.6	4.9	2.6
	N	14	15	15	13
DAYS 211-218	MEAN	25.9	26.1	24.1	22.9
WEEKS 31/32	ST.DEV.	2.5	3.3	4.9	2.3
	N	14	15	15	13
DAYS 225-232	MEAN	26.4	25.8	24.3	23.0 *
WEEKS 33/34	ST.DEV.	2.9	2.8	4.9	2.7
	N	14	15	15	13
DAYS 239-246	MEAN	27.3	26.4	25.6	23.4 *
WEEKS 35/36	ST.DEV.	3.1	2.2	4.9	2.3
	N	14	15	15	13
DAYS 253-260	MEAN	27.6	27.3	25.3	23.5 *
WEEKS 37/38	ST.DEV.	3.3	2.6	5.2	2.4
	N	14	15	15	13
DAYS 267-274	MEAN	26.5	27.1	24.7	23.6
WEEKS 39/40	ST.DEV.	2.8	2.6	5.4	2.1
	N	13	15	15	13
DAYS 281-288	MEAN	27.5	27.0	25.9	23.9 *
WEEKS 41/42	ST.DEV.	2.4	2.3	5.4	2.5
	N	13	15	15	13
DAYS 295-302	MEAN	27.1	25.9	25.4	23.9
WEEKS 43/44	ST.DEV.	2.9	2.6	5.2	2.8
	N	13	15	15	13
DAYS 309-316	MEAN	27.2	26.2	25.5	24.0
WEEKS 45/46	ST.DEV.	2.6	2.5	5.6	2.6
	N	13	14 x	15	13
DAYS 323-330	MEAN	27.9	25.8	26.0	24.1
WEEKS 47/48	ST.DEV.	2.6	5.8	5.0	3.3
	N	13	14 x	15	13
DAYS 337-344	MEAN	27.1	25.9	24.6	23.4 *
WEEKS 49/50	ST.DEV.	2.3	2.7	5.2	2.8
	N	13	14	15	13
DAYS 351-358	MEAN	26.5	25.9	25.1	24.1
WEEKS 51/52	ST.DEV.	2.7	3.1	4.9	2.7
	N	13	14	15	13
MEAN OF MEANS OVER TREATMENT		27.2	27.0	25.6	23.3

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	27.5	28.0	28.6	28.5
WEEKS 1/2	ST.DEV.	2.3	1.9	5.2	2.9
	N	13	12 x	14 x	13
DAYS 15-22	MEAN	28.0	27.8	27.0	26.0
WEEKS 3/4	ST.DEV.	2.3	2.7	5.5	2.4
	N	13	14	15	13
DAYS 29-36	MEAN	28.3	27.7	27.7	26.3
WEEKS 5/6	ST.DEV.	1.8	2.6	5.5	2.2
	N	13	12 x	14 x	13
DAYS 43-50	MEAN	27.9	27.2	27.3	25.6
WEEKS 7/8	ST.DEV.	2.0	2.4	5.3	1.9
	N	13	13 x	15	13
MEAN OF MEANS OVER RECOVERY		27.9	27.7	27.6	26.6

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	12.7	13.3	13.7 *	13.4
WEEKS 1/2	ST.DEV.	0.9	1.0	1.3	1.3
	N	15	15	15	15
DAYS 8-15	MEAN	18.3	19.4	19.0	18.6
WEEKS 2/3	ST.DEV.	0.9	1.2	1.5	1.6
	N	15	15	15	15
MEAN OF MEANS OVER PRETEST		15.5	16.4	16.3	16.0

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FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	21.4	22.1	21.3	17.8 **
WEEKS 1/2	ST.DEV.	1.2	1.8	2.3	2.1
	N	15	15	15	15
DAYS 8-15	MEAN	21.0	21.9	20.6	19.0 *
WEEKS 2/3	ST.DEV.	1.4	1.4	2.4	2.0
	N	15	14 x	15	15
DAYS 15-22	MEAN	19.9	20.4	19.5	17.0 **
WEEKS 3/4	ST.DEV.	1.6	1.7	2.0	2.4
	N	14 x	15	15	15
DAYS 22-29	MEAN	20.8	21.6	19.8	18.4 **
WEEKS 4/5	ST.DEV.	1.5	1.5	1.8	2.2
	N	15	14 x	15	15
DAYS 29-36	MEAN	19.8	21.4	19.9	17.8 *
WEEKS 5/6	ST.DEV.	1.5	2.0	2.2	2.0
	N	15	15	15	15
DAYS 36-43	MEAN	20.8	22.1	20.1	18.0 **
WEEKS 6/7	ST.DEV.	2.0	1.6	1.9	2.0
	N	14 x	14 x	15	15
DAYS 43-50	MEAN	20.7	21.1	18.9 *	18.2 **
WEEKS 7/8	ST.DEV.	1.8	2.0	1.9	1.9
	N	15	15	15	15
DAYS 50-57	MEAN	19.2	19.0	18.9	16.1 **
WEEKS 8/9	ST.DEV.	2.2	2.0	2.5	1.8
	N	15	15	15	15
DAYS 57-64	MEAN	20.1	20.6	18.4 *	18.0 **
WEEKS 9/10	ST.DEV.	2.3	1.6	2.2	1.4
	N	15	15	15	15
DAYS 64-71	MEAN	19.7	21.0	19.1	17.4 **
WEEKS 10/11	ST.DEV.	2.2	1.8	1.7	1.7
	N	15	15	15	15
DAYS 71-78	MEAN	18.5	19.7	18.0	16.5 *
WEEKS 11/12	ST.DEV.	2.5	2.0	1.7	2.0
	N	15	15	15	15
DAYS 78-85	MEAN	19.0	20.9 *	19.5	19.5
WEEKS 12/13	ST.DEV.	1.7	2.1	1.9	1.5
	N	14 x	15	15	15
DAYS 85-92	MEAN	20.6	19.7	18.3 **	17.0 **
WEEKS 13/14	ST.DEV.	2.4	1.5	2.0	1.7
	N	15	15	15	15
DAYS 99-106	MEAN	18.4	18.6	17.9	16.6 *
WEEKS 15/16	ST.DEV.	2.7	1.7	1.8	1.8
	N	15	15	15	15
DAYS 113-120	MEAN	18.0	17.9	16.8	16.7
WEEKS 17/18	ST.DEV.	2.4	1.6	2.0	1.4
	N	15	15	15	15
DAYS 127-134	MEAN	18.3	18.5	17.7	16.9
WEEKS 19/20	ST.DEV.	2.6	1.8	1.9	1.9
	N	15	15	15	15
DAYS 141-148	MEAN	19.2	18.0	16.4 **	16.0 **
WEEKS 21/22	ST.DEV.	2.3	1.4	2.3	1.7
	N	14 x	15	15	15

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

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 155-162	MEAN	18.7	19.0	17.5	17.0 *
WEEKS 23/24	ST.DEV.	2.7	1.3	2.0	1.3
	N	15	15	15	15
DAYS 169-176	MEAN	18.9	19.1	17.5	16.1 **
WEEKS 25/26	ST.DEV.	1.8	1.9	1.7	1.9
	N	14 x	15	15	15
DAYS 183-190	MEAN	18.0	19.3	17.6	16.8
WEEKS 27/28	ST.DEV.	2.0	2.5	2.6	1.5
	N	14 x	15	15	15
DAYS 197-204	MEAN	18.6	19.3	18.0	17.2
WEEKS 29/30	ST.DEV.	2.7	1.9	2.1	1.5
	N	14 x	15	15	15
DAYS 211-218	MEAN	18.6	20.0	17.2	16.3 *
WEEKS 31/32	ST.DEV.	2.4	2.2	2.2	1.4
	N	15	15	15	15
DAYS 225-232	MEAN	18.8	19.5	17.5	16.8 *
WEEKS 33/34	ST.DEV.	2.2	2.3	1.7	1.3
	N	14 x	15	15	15
DAYS 239-246	MEAN	19.0	20.5	17.9	18.2
WEEKS 35/36	ST.DEV.	1.8	2.0	1.9	1.8
	N	14 x	14 x	15	15
DAYS 253-260	MEAN	19.8	21.1	18.0	17.1 **
WEEKS 37/38	ST.DEV.	2.6	2.0	2.3	1.3
	N	14 x	15	15	15
DAYS 267-274	MEAN	18.5	20.1	16.9	15.3 **
WEEKS 39/40	ST.DEV.	2.6	2.4	2.0	1.3
	N	14 x	15	15	15
DAYS 281-288	MEAN	19.0	20.7	18.3	16.4 **
WEEKS 41/42	ST.DEV.	2.5	1.8	2.2	1.5
	N	14 x	15	15	15
DAYS 295-302	MEAN	19.3	20.4	17.7	15.9 **
WEEKS 43/44	ST.DEV.	2.8	2.0	2.2	1.5
	N	15	15	15	15
DAYS 309-316	MEAN	17.8	19.5	17.5	15.9 *
WEEKS 45/46	ST.DEV.	2.4	2.3	2.1	1.6
	N	14 x	15	15	15
DAYS 323-330	MEAN	20.4	20.3	18.2 *	16.6 **
WEEKS 47/48	ST.DEV.	3.2	2.0	2.4	1.9
	N	14 x	15	15	15
DAYS 337-344	MEAN	18.2	20.2	17.4	16.7
WEEKS 49/50	ST.DEV.	5.6	1.9	2.6	1.7
	N	15	14 x	15	15
DAYS 351-358	MEAN	19.5	20.5	18.1	17.1
WEEKS 51/52	ST.DEV.	2.2	2.3	2.1	3.7
	N	13 x	15	15	15
MEAN OF MEANS OVER TREATMENT		19.3	20.1	18.3	17.1

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	18.6	21.2 **	19.8	20.9 *
WEEKS 1/2	ST.DEV.	1.9	2.2	2.2	1.8
	N	12 x	14 x	14 x	15
DAYS 15-22	MEAN	19.2	20.9	19.1	18.9
WEEKS 3/4	ST.DEV.	2.6	1.5	2.5	1.5
	N	13 x	13 x	15	15
DAYS 29-36	MEAN	20.4	22.5 *	19.4	18.9
WEEKS 5/6	ST.DEV.	1.8	1.6	2.4	1.8
	N	12 x	14 x	14 x	15
DAYS 43-50	MEAN	18.9	20.5	18.8	17.3
WEEKS 7/8	ST.DEV.	1.3	2.0	2.9	1.4
	N	13 x	14 x	15	15
MEAN OF MEANS OVER RECOVERY		19.3	21.3	19.3	19.0

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHTS (GRAM) SUMMARY
MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 1	MEAN	81	79	82	81
WEEK 1	ST.DEV.	12.1	14.7	12.8	14.8
	N	55	55	55	55
DAY 8	MEAN	138	137	140	137
WEEK 2	ST.DEV.	16.6	19.8	17.2	21.2
	N	55	55	55	55

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

BODY WEIGHTS (GRAM) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 1	MEAN	202	203	203	202
WEEK 1	ST.DEV.	19.7	23.1	21.6	27.3
	N	55	55	55	55
DAY 8	MEAN	247	250	243	237
WEEK 2	ST.DEV.	23.0	25.1	23.5	31.7
	N	55	55	55	55
DAY 15	MEAN	299	304	290	279 **
WEEK 3	ST.DEV.	25.3	26.7	25.9	35.8
	N	55	55	55	55
DAY 22	MEAN	341	347	328	313 **
WEEK 4	ST.DEV.	28.8	26.3	28.3	40.0
	N	55	55	55	55
DAY 29	MEAN	376	382	360 *	346 **
WEEK 5	ST.DEV.	32.6	29.0	32.3	42.8
	N	55	55	55	55
DAY 36	MEAN	407	412	387 *	370 **
WEEK 6	ST.DEV.	34.9	31.6	36.0	45.0
	N	55	55	55	55
DAY 43	MEAN	429	436	408 *	387 **
WEEK 7	ST.DEV.	37.5	37.0	38.1	46.2
	N	55	55	55	55
DAY 50	MEAN	452	458	428 **	405 **
WEEK 8	ST.DEV.	40.2	38.5	40.6	47.0
	N	55	55	55	55
DAY 57	MEAN	464	471	436 **	415 **
WEEK 9	ST.DEV.	41.1	40.8	41.8	49.1
	N	55	55	55	55
DAY 64	MEAN	485	491	454 **	433 **
WEEK 10	ST.DEV.	43.2	41.9	45.0	51.1
	N	55	55	55	55
DAY 71	MEAN	500	507	465 **	445 **
WEEK 11	ST.DEV.	46.7	43.6	47.3	51.4
	N	55	55	55	55
DAY 78	MEAN	511	516	479 **	454 **
WEEK 12	ST.DEV.	47.1	45.7	48.6	52.2
	N	55	55	55	54
DAY 85	MEAN	521	525	486 **	462 **
WEEK 13	ST.DEV.	48.7	47.0	49.4	51.9
	N	55	55	55	54
DAY 92	MEAN	529	538	494 **	469 **
WEEK 14	ST.DEV.	51.3	48.4	49.2	52.8
	N	55	55	55	54
DAY 106	MEAN	549	554	509 **	485 **
WEEK 16	ST.DEV.	54.2	52.0	52.2	53.3
	N	54	55	55	54
DAY 120	MEAN	560	563	517 **	494 **
WEEK 18	ST.DEV.	56.9	51.8	52.9	54.6
	N	54	55	55	53
DAY 134	MEAN	578	582	530 **	499 **
WEEK 20	ST.DEV.	60.1	54.6	53.9	55.5
	N	54	55	55	53

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

BODY WEIGHTS (GRAM) SUMMARY
MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 148	MEAN	590	594	537 **	509 **
WEEK 22	ST.DEV.	62.8	57.5	57.3	55.6
	N	54	55	55	53
DAY 162	MEAN	601	606	549 **	519 **
WEEK 24	ST.DEV.	64.4	58.5	59.8	56.1
	N	54	55	55	53
DAY 176	MEAN	610	615	553 **	522 **
WEEK 26	ST.DEV.	66.2	62.3	61.5	56.9
	N	54	55	54	53
DAY 190	MEAN	621	621	562 **	529 **
WEEK 28	ST.DEV.	67.8	63.1	62.3	59.0
	N	54	55	54	53
DAY 204	MEAN	631	630	568 **	535 **
WEEK 30	ST.DEV.	69.6	65.5	62.0	58.7
	N	54	55	54	53
DAY 218	MEAN	638	639	573 **	540 **
WEEK 32	ST.DEV.	71.0	66.2	62.7	59.2
	N	54	55	54	53
DAY 232	MEAN	645	645	579 **	543 **
WEEK 34	ST.DEV.	72.0	69.5	64.4	60.9
	N	54	55	54	53
DAY 246	MEAN	658	656	590 **	551 **
WEEK 36	ST.DEV.	75.5	70.4	65.4	60.8
	N	54	55	54	53
DAY 260	MEAN	668	666	597 **	556 **
WEEK 38	ST.DEV.	78.9	72.8	66.8	61.3
	N	54	55	54	53
DAY 274	MEAN	676	674	601 **	560 **
WEEK 40	ST.DEV.	80.7	75.4	67.9	62.0
	N	53	55	54	53
DAY 288	MEAN	683	680	608 **	563 **
WEEK 42	ST.DEV.	82.6	76.5	70.8	62.9
	N	51	55	54	53
DAY 302	MEAN	687	681	603 **	570 **
WEEK 44	ST.DEV.	84.9	77.6	71.6	63.5
	N	51	53	53	53
DAY 316	MEAN	692	688	609 **	572 **
WEEK 46	ST.DEV.	86.6	80.4	72.6	65.2
	N	50	53	53	53
DAY 330	MEAN	699	693	612 **	572 **
WEEK 48	ST.DEV.	88.2	83.2	73.9	65.9
	N	49	53	53	53
DAY 344	MEAN	704	703	622 **	577 **
WEEK 50	ST.DEV.	88.1	84.5	74.3	66.0
	N	48	52	52	53
DAY 358	MEAN	716	711	630 **	588 **
WEEK 52	ST.DEV.	91.1	87.0	75.8	68.2
	N	48	52	52	53

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

BODY WEIGHTS (GRAM) SUMMARY
FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 1	MEAN	60	59	58	60
WEEK 1	ST.DEV.	7.4	6.3	6.3	6.9
	N	55	55	55	55
DAY 8	MEAN	107	104	103	106
WEEK 2	ST.DEV.	11.4	9.5	9.2	10.6
	N	55	55	55	55

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BODY WEIGHTS (GRAM) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 1	MEAN	151	149	148	148
WEEK 1	ST.DEV.	13.5	10.4	10.1	12.9
	N	55	55	55	55
DAY 8	MEAN	171	170	168	169
WEEK 2	ST.DEV.	13.9	13.0	11.4	14.0
	N	55	55	55	55
DAY 15	MEAN	193	193	190	188
WEEK 3	ST.DEV.	15.4	15.1	14.4	15.8
	N	55	55	55	55
DAY 22	MEAN	213	215	212	207
WEEK 4	ST.DEV.	16.6	18.4	15.6	17.7
	N	55	55	55	55
DAY 29	MEAN	232	231	223 *	219 **
WEEK 5	ST.DEV.	17.9	19.9	16.3	18.0
	N	55	55	55	55
DAY 36	MEAN	243	244	238	228 **
WEEK 6	ST.DEV.	18.8	22.1	18.1	18.4
	N	55	55	55	55
DAY 43	MEAN	255	257	251	236 **
WEEK 7	ST.DEV.	20.4	24.3	19.2	18.8
	N	55	55	55	55
DAY 50	MEAN	258	259	251	243 **
WEEK 8	ST.DEV.	20.5	24.5	19.0	18.5
	N	55	55	55	55
DAY 57	MEAN	262	264	258	249 **
WEEK 9	ST.DEV.	21.0	25.4	19.3	18.5
	N	55	55	55	55
DAY 64	MEAN	270	277	268	252 **
WEEK 10	ST.DEV.	21.6	25.3	20.9	18.1
	N	55	55	55	55
DAY 71	MEAN	280	283	273	259 **
WEEK 11	ST.DEV.	22.2	26.1	21.4	18.6
	N	55	55	55	55
DAY 78	MEAN	279	281	272	263 **
WEEK 12	ST.DEV.	22.8	27.5	19.8	19.2
	N	55	55	55	55
DAY 85	MEAN	283	287	274	262 **
WEEK 13	ST.DEV.	23.2	28.1	20.5	19.1
	N	55	55	55	55
DAY 92	MEAN	286	291	280	270 **
WEEK 14	ST.DEV.	23.3	30.1	20.8	19.4
	N	55	55	55	55
DAY 106	MEAN	293	299	283	274 **
WEEK 16	ST.DEV.	24.4	29.7	20.7	18.7
	N	55	55	55	55
DAY 120	MEAN	297	301	287	280 **
WEEK 18	ST.DEV.	26.1	31.2	21.6	18.3
	N	55	55	55	55
DAY 134	MEAN	305	309	293 *	281 **
WEEK 20	ST.DEV.	26.2	32.2	22.7	19.4
	N	55	55	55	55

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BODY WEIGHTS (GRAM) SUMMARY
FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 148 WEEK 22	MEAN	310	318	300	287 **
	ST.DEV.	26.8	35.2	23.2	18.4
	N	55	55	55	55
DAY 162 WEEK 24	MEAN	317	323	302 **	287 **
	ST.DEV.	29.3	33.1	23.8	19.9
	N	55	54	55	55
DAY 176 WEEK 26	MEAN	320	327	306 *	290 **
	ST.DEV.	29.8	32.9	24.9	19.9
	N	55	54	55	55
DAY 190 WEEK 28	MEAN	324	331	306 **	290 **
	ST.DEV.	31.6	34.9	27.1	21.2
	N	55	54	55	55
DAY 204 WEEK 30	MEAN	330	338	311 **	295 **
	ST.DEV.	34.8	35.5	26.0	20.5
	N	55	54	55	55
DAY 218 WEEK 32	MEAN	332	342	312 **	296 **
	ST.DEV.	33.7	39.5	26.9	19.8
	N	55	53	55	55
DAY 232 WEEK 34	MEAN	339	345	315 **	299 **
	ST.DEV.	38.6	41.0	29.5	20.6
	N	55	52	55	55
DAY 246 WEEK 36	MEAN	342	351	320 **	300 **
	ST.DEV.	39.8	43.8	30.2	21.9
	N	55	52	55	55
DAY 260 WEEK 38	MEAN	349	355	325 **	302 **
	ST.DEV.	40.8	45.4	32.8	21.1
	N	55	52	55	55
DAY 274 WEEK 40	MEAN	353	359	328 **	310 **
	ST.DEV.	44.3	47.5	36.2	23.0
	N	54	52	55	55
DAY 288 WEEK 42	MEAN	360	367	331 **	306 **
	ST.DEV.	46.8	50.6	33.3	22.3
	N	54	52	54	55
DAY 302 WEEK 44	MEAN	363	370	332 **	308 **
	ST.DEV.	46.4	48.7	35.5	21.3
	N	54	52	54	55
DAY 316 WEEK 46	MEAN	366	371	332 **	309 **
	ST.DEV.	49.0	52.2	36.4	24.5
	N	54	52	54	54
DAY 330 WEEK 48	MEAN	373	380	339 **	312 **
	ST.DEV.	52.8	51.2	38.3	23.8
	N	54	51	54	53
DAY 344 WEEK 50	MEAN	381	389	343 **	318 **
	ST.DEV.	51.2	53.0	40.9	25.8
	N	53	51	53	53
DAY 358 WEEK 52	MEAN	381	395	344 **	323 **
	ST.DEV.	49.4	53.6	42.5	26.7
	N	52	51	53	53

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

BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 1	MEAN	80	77	78	76
WEEK 1	ST.DEV.	15.7	15.7	14.3	14.4
	N	15	15	15	15
DAY 8	MEAN	138	135	137	131
WEEK 2	ST.DEV.	21.4	24.8	18.4	21.4
	N	15	15	15	15

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BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG	
DAY 1	MEAN	203	201	203	191	
WEEK 1	ST.DEV.	23.0	31.1	20.9	27.2	
	N	15	15	15	15	
DAY 8	MEAN	242	241	235	224	
WEEK 2	ST.DEV.	26.1	32.1	18.6	29.1	
	N	15	15	15	15	
DAY 15	MEAN	296	297	284	267	*
WEEK 3	ST.DEV.	29.1	34.1	19.5	33.5	
	N	15	15	15	15	
DAY 22	MEAN	340	342	329	305	*
WEEK 4	ST.DEV.	33.0	32.6	26.1	39.2	
	N	15	15	15	15	
DAY 29	MEAN	374	377	360	337	*
WEEK 5	ST.DEV.	37.2	35.7	34.3	40.2	
	N	15	15	15	15	
DAY 36	MEAN	408	410	388	360	**
WEEK 6	ST.DEV.	41.0	38.6	41.7	44.3	
	N	15	15	15	15	
DAY 43	MEAN	430	434	411	373	**
WEEK 7	ST.DEV.	45.1	38.1	44.0	43.8	
	N	15	15	15	15	
DAY 50	MEAN	454	457	435	390	**
WEEK 8	ST.DEV.	48.2	38.7	49.3	44.2	
	N	15	15	15	15	
DAY 57	MEAN	455	461	437	394	**
WEEK 9	ST.DEV.	43.7	38.9	51.8	43.9	
	N	15	15	15	15	
DAY 64	MEAN	480	487	464	415	**
WEEK 10	ST.DEV.	46.7	38.4	57.3	46.4	
	N	15	15	15	15	
DAY 71	MEAN	498	507	481	428	**
WEEK 11	ST.DEV.	53.0	40.0	59.4	47.5	
	N	15	15	15	15	
DAY 78	MEAN	512	517	491	437	**
WEEK 12	ST.DEV.	51.6	43.1	62.1	47.7	
	N	15	15	15	14	
DAY 85	MEAN	520	527	499	445	**
WEEK 13	ST.DEV.	52.7	44.3	63.7	48.3	
	N	15	15	15	14	
DAY 92	MEAN	529	536	512	452	**
WEEK 14	ST.DEV.	54.2	47.6	63.5	49.4	
	N	15	15	15	14	
DAY 106	MEAN	548	554	523	468	**
WEEK 16	ST.DEV.	55.7	51.7	70.2	50.7	
	N	14	15	15	14	
DAY 120	MEAN	553	565	529	475	**
WEEK 18	ST.DEV.	56.5	52.9	70.3	51.0	
	N	14	15	15	13	
DAY 134	MEAN	575	586	540	482	**
WEEK 20	ST.DEV.	58.3	54.0	72.3	54.9	
	N	14	15	15	13	

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BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 148 WEEK 22	MEAN	589	600	553	494 **
	ST.DEV.	59.8	58.7	78.1	53.4
	N	14	15	15	13
DAY 162 WEEK 24	MEAN	602	612	565	505 **
	ST.DEV.	60.6	62.4	81.3	55.6
	N	14	15	15	13
DAY 176 WEEK 26	MEAN	613	621	569	508 **
	ST.DEV.	64.5	66.1	82.3	56.1
	N	14	15	15	13
DAY 190 WEEK 28	MEAN	621	625	577	512 **
	ST.DEV.	63.9	66.7	84.5	55.4
	N	14	15	15	13
DAY 204 WEEK 30	MEAN	632	640	582	521 **
	ST.DEV.	62.9	68.1	84.1	56.2
	N	14	15	15	13
DAY 218 WEEK 32	MEAN	639	650	587	529 **
	ST.DEV.	61.2	70.7	85.0	56.0
	N	14	15	15	13
DAY 232 WEEK 34	MEAN	649	657	593	533 **
	ST.DEV.	62.7	75.3	89.8	58.9
	N	14	15	15	13
DAY 246 WEEK 36	MEAN	662	666	603	542 **
	ST.DEV.	65.6	74.4	88.6	59.9
	N	14	15	15	13
DAY 260 WEEK 38	MEAN	670	677	608	548 **
	ST.DEV.	69.5	76.6	91.7	59.0
	N	14	15	15	13
DAY 274 WEEK 40	MEAN	682	687	610 *	551 **
	ST.DEV.	70.2	78.6	94.8	55.5
	N	13	15	15	13
DAY 288 WEEK 42	MEAN	689	691	617 *	552 **
	ST.DEV.	69.4	79.6	97.8	56.9
	N	13	15	15	13
DAY 302 WEEK 44	MEAN	695	691	611 *	559 **
	ST.DEV.	70.1	80.4	95.8	57.2
	N	13	15	15	13
DAY 316 WEEK 46	MEAN	698	697	617 *	562 **
	ST.DEV.	71.5	82.8	98.1	60.1
	N	13	15	15	13
DAY 330 WEEK 48	MEAN	709	699	616 *	562 **
	ST.DEV.	71.8	90.1	97.7	58.1
	N	13	15	15	13
DAY 344 WEEK 50	MEAN	714	718	628 *	565 **
	ST.DEV.	72.8	87.7	99.3	59.1
	N	13	14	15	13
DAY 358 WEEK 52	MEAN	726	726	632 *	579 **
	ST.DEV.	75.0	92.8	100.6	61.4
	N	13	14	15	13

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BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY MALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 8	MEAN	723	716	623 **	566 **
WEEK 2	ST.DEV.	75.5	92.7	96.9	59.7
	N	13	14	15	13
DAY 22	MEAN	739	735	642 *	591 **
WEEK 4	ST.DEV.	78.0	94.0	100.5	60.1
	N	13	14	15	13
DAY 36	MEAN	744	744	651 *	599 **
WEEK 6	ST.DEV.	78.2	97.2	105.1	62.5
	N	13	14	15	13
DAY 50	MEAN	748	747	659 *	607 **
WEEK 8	ST.DEV.	78.1	97.3	105.9	59.9
	N	13	14	15	13

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BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 1	MEAN	57	57	58	61
WEEK 1	ST.DEV.	6.6	3.6	7.3	7.2
	N	15	15	15	15
DAY 8	MEAN	103	102	104	106
WEEK 2	ST.DEV.	8.6	6.4	11.0	10.5
	N	15	15	15	15

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BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 1	MEAN	143	150	150	147
WEEK 1	ST.DEV.	8.0	8.4	11.2	13.4
	N	15	15	15	15
DAY 8	MEAN	162	171	169	165
WEEK 2	ST.DEV.	7.7	10.8	13.3	14.4
	N	15	15	15	15
DAY 15	MEAN	186	197	189	186
WEEK 3	ST.DEV.	11.0	13.7	16.6	15.8
	N	15	15	15	15
DAY 22	MEAN	208	220	214	206
WEEK 4	ST.DEV.	11.0	16.4	17.2	18.4
	N	15	15	15	15
DAY 29	MEAN	227	235	221	220
WEEK 5	ST.DEV.	13.2	17.8	16.8	18.8
	N	15	15	15	15
DAY 36	MEAN	239	250	236	229
WEEK 6	ST.DEV.	14.2	19.5	18.2	21.1
	N	15	15	15	15
DAY 43	MEAN	251	264	248	233 *
WEEK 7	ST.DEV.	19.1	19.2	19.6	21.8
	N	15	15	15	15
DAY 50	MEAN	255	265	249	242
WEEK 8	ST.DEV.	17.1	20.4	19.8	23.5
	N	15	15	15	15
DAY 57	MEAN	258	267	255	245
WEEK 9	ST.DEV.	17.4	22.5	19.6	22.3
	N	15	15	15	15
DAY 64	MEAN	267	282	266	251
WEEK 10	ST.DEV.	21.6	20.7	23.1	21.6
	N	15	15	15	15
DAY 71	MEAN	277	291	271	260
WEEK 11	ST.DEV.	19.5	23.8	20.5	22.9
	N	15	15	15	15
DAY 78	MEAN	278	289	270	264
WEEK 12	ST.DEV.	20.5	23.4	19.3	23.0
	N	15	15	15	15
DAY 85	MEAN	279	294	271	262
WEEK 13	ST.DEV.	20.8	24.5	19.3	23.9
	N	15	15	15	15
DAY 92	MEAN	286	299	278	270
WEEK 14	ST.DEV.	21.1	25.7	19.9	23.3
	N	15	15	15	15
DAY 106	MEAN	292	305	280	273
WEEK 16	ST.DEV.	24.2	26.4	19.6	21.3
	N	15	15	15	15
DAY 120	MEAN	294	304	283	283
WEEK 18	ST.DEV.	24.8	26.3	19.8	21.2
	N	15	15	15	15
DAY 134	MEAN	303	314	288	284
WEEK 20	ST.DEV.	25.8	29.1	21.3	23.5
	N	15	15	15	15

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BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 148	MEAN	309	325	293	290
WEEK 22	ST.DEV.	27.3	29.1	20.4	21.9
	N	15	15	15	15
DAY 162	MEAN	316	330	296	288 *
WEEK 24	ST.DEV.	30.8	28.0	23.0	23.2
	N	15	15	15	15
DAY 176	MEAN	320	333	300	291 *
WEEK 26	ST.DEV.	30.6	30.1	22.6	22.3
	N	15	15	15	15
DAY 190	MEAN	322	336	299	289 **
WEEK 28	ST.DEV.	34.4	29.2	23.8	21.7
	N	15	15	15	15
DAY 204	MEAN	332	343	305 *	297 **
WEEK 30	ST.DEV.	39.6	27.2	23.6	23.5
	N	15	15	15	15
DAY 218	MEAN	332	351	307	296 **
WEEK 32	ST.DEV.	35.7	31.0	25.0	21.7
	N	15	15	15	15
DAY 232	MEAN	338	353	308 *	298 **
WEEK 34	ST.DEV.	40.6	32.8	24.3	21.0
	N	15	15	15	15
DAY 246	MEAN	341	360	313 *	298 **
WEEK 36	ST.DEV.	39.6	33.6	24.6	22.1
	N	15	15	15	15
DAY 260	MEAN	350	364	314 *	301 **
WEEK 38	ST.DEV.	44.4	32.6	26.2	22.5
	N	15	15	15	15
DAY 274	MEAN	356	369	315 **	306 **
WEEK 40	ST.DEV.	49.2	36.4	26.0	22.3
	N	15	15	15	15
DAY 288	MEAN	359	378	323 *	303 **
WEEK 42	ST.DEV.	48.9	36.9	28.1	22.5
	N	15	15	15	15
DAY 302	MEAN	360	380	321 **	304 **
WEEK 44	ST.DEV.	49.7	35.9	28.6	21.5
	N	15	15	15	15
DAY 316	MEAN	365	383	321 **	307 **
WEEK 46	ST.DEV.	54.3	37.6	28.5	24.2
	N	15	15	15	15
DAY 330	MEAN	372	390	329 *	307 **
WEEK 48	ST.DEV.	61.4	40.0	29.2	24.1
	N	15	15	15	15
DAY 344	MEAN	385	399	332 **	313 **
WEEK 50	ST.DEV.	49.9	38.9	31.0	27.4
	N	14	15	15	15
DAY 358	MEAN	387	402	333 **	315 **
WEEK 52	ST.DEV.	56.4	40.4	31.5	28.7
	N	14	15	15	15

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BODY WEIGHTS (GRAM) SUMMARY
CLINICAL LABORATORY/RECOVERY FEMALES

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAY 8	MEAN	386	401	331 **	315 **
WEEK 2	ST.DEV.	59.7	41.8	33.7	27.5
	N	14	15	15	15
DAY 22	MEAN	395	413	343 **	326 **
WEEK 4	ST.DEV.	58.7	43.9	35.7	27.2
	N	14	15	15	15
DAY 36	MEAN	403	420	346 **	325 **
WEEK 6	ST.DEV.	62.5	43.4	38.7	28.7
	N	14	15	15	15
DAY 50	MEAN	405	424	351 **	329 **
WEEK 8	ST.DEV.	62.6	42.7	41.3	26.2
	N	14	15	15	15

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

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	121	120	121	121
WEEKS 1/2	ST.DEV.	5.9	5.0	7.0	5.6
	N	55	55	55	55
DAYS 8-15	MEAN	168	172	166	168
WEEKS 2/3	ST.DEV.	13.7	15.3	14.3	15.1
	N	55	55	55	55
MEAN OF MEANS OVER PRETEST		144	146	144	145

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

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	107	101 **	98 **	93 **
WEEKS 1/2	ST.DEV.	6.8	6.8	8.8	9.3
	N	55	55	55	55
DAYS 8-15	MEAN	94	94	89 **	90 **
WEEKS 2/3	ST.DEV.	5.1	5.7	5.7	6.4
	N	54 x	55	54 x	55
DAYS 15-22	MEAN	81	81	77 **	74 **
WEEKS 3/4	ST.DEV.	4.8	5.2	5.1	5.3
	N	54 x	55	55	55
DAYS 22-29	MEAN	77	77	77	72 **
WEEKS 4/5	ST.DEV.	4.1	4.4	6.6	5.1
	N	53 x	53 x	55	55
DAYS 29-36	MEAN	73	72	70 *	65 **
WEEKS 5/6	ST.DEV.	3.3	4.3	5.1	4.2
	N	51 x	52 x	55	55
DAYS 36-43	MEAN	67	66	65 *	62 **
WEEKS 6/7	ST.DEV.	3.5	5.3	3.9	3.5
	N	53 x	52 x	55	55
DAYS 43-50	MEAN	66	62 **	60 **	61 **
WEEKS 7/8	ST.DEV.	4.1	3.7	4.2	3.7
	N	52 x	54 x	55	55
DAYS 50-57	MEAN	60	59	60	60
WEEKS 8/9	ST.DEV.	5.8	4.1	4.8	7.2
	N	55	54 x	55	55
DAYS 57-64	MEAN	58	55 **	56 **	56 *
WEEKS 9/10	ST.DEV.	3.1	3.0	3.5	3.7
	N	55	55	55	55
DAYS 64-71	MEAN	55	55	56	55
WEEKS 10/11	ST.DEV.	2.9	2.8	3.5	3.4
	N	55	55	55	55
DAYS 71-78	MEAN	51	51	50	51
WEEKS 11/12	ST.DEV.	3.5	2.5	2.7	3.1
	N	55	55	55	54
DAYS 78-85	MEAN	53	54	57 **	57 **
WEEKS 12/13	ST.DEV.	4.0	2.8	3.1	3.6
	N	55	55	55	54
DAYS 85-92	MEAN	54	52 *	54	51 **
WEEKS 13/14	ST.DEV.	3.1	2.9	3.6	3.2
	N	54 x	55	55	54
DAYS 99-106	MEAN	47	46	46	46
WEEKS 15/16	ST.DEV.	2.6	2.5	3.0	2.6
	N	54	55	55	54
DAYS 113-120	MEAN	45	45	47 **	46
WEEKS 17/18	ST.DEV.	3.0	2.9	3.7	3.6
	N	54	55	54 x	53
DAYS 127-134	MEAN	48	48	49	46 **
WEEKS 19/20	ST.DEV.	2.6	2.7	3.1	4.0
	N	54	54 x	55	53

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 141-148	MEAN	43	42	43	44 *
WEEKS 21/22	ST.DEV.	2.5	2.3	3.8	3.1
	N	54	55	55	53
DAYS 155-162	MEAN	43	42	44 *	45 **
WEEKS 23/24	ST.DEV.	2.4	2.3	3.4	3.3
	N	54	55	55	53
DAYS 169-176	MEAN	43	43	44	46 **
WEEKS 25/26	ST.DEV.	2.8	2.7	3.3	3.1
	N	54	55	54	53
DAYS 183-190	MEAN	42	42	44 **	45 **
WEEKS 27/28	ST.DEV.	2.8	2.6	3.8	3.1
	N	54	55	54	53
DAYS 197-204	MEAN	42	41	44 **	43 *
WEEKS 29/30	ST.DEV.	2.3	2.5	3.4	3.1
	N	54	55	54	53
DAYS 211-218	MEAN	40	40	42 **	43 **
WEEKS 31/32	ST.DEV.	2.2	3.2	3.7	2.9
	N	54	55	54	53
DAYS 225-232	MEAN	40	40	42 *	42 **
WEEKS 33/34	ST.DEV.	2.5	2.2	3.4	5.6
	N	54	55	54	53
DAYS 239-246	MEAN	40	40	43 **	44 **
WEEKS 35/36	ST.DEV.	2.4	2.6	3.0	3.4
	N	54	55	54	53
DAYS 253-260	MEAN	42	41	42	43 *
WEEKS 37/38	ST.DEV.	2.7	2.2	3.2	3.2
	N	54	55	54	53
DAYS 267-274	MEAN	39	39	42 **	43 **
WEEKS 39/40	ST.DEV.	2.9	2.4	3.4	3.3
	N	53	55	54	53
DAYS 281-288	MEAN	40	39	42 **	44 **
WEEKS 41/42	ST.DEV.	2.4	2.7	3.3	3.3
	N	51	55	54	53
DAYS 295-302	MEAN	39	38	42 **	43 **
WEEKS 43/44	ST.DEV.	2.6	2.6	3.4	3.1
	N	51	53	53	53
DAYS 309-316	MEAN	39	39	42 **	43 **
WEEKS 45/46	ST.DEV.	2.6	2.9	3.6	3.1
	N	50	51 x	53	53
DAYS 323-330	MEAN	41	39	42	42
WEEKS 47/48	ST.DEV.	2.7	4.5	3.5	3.2
	N	47 x	52 x	53	53
DAYS 337-344	MEAN	38	37	39 *	41 **
WEEKS 49/50	ST.DEV.	2.5	2.4	3.0	3.1
	N	48	52	52	53
DAYS 351-358	MEAN	37	36	40 **	41 **
WEEKS 51/52	ST.DEV.	2.3	2.8	4.5	2.9
	N	48	52	52	53

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

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

MEAN OF MEANS OVER TREATMENT	GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
MEAN OF MEANS OVER TREATMENT	53	52	53	52

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

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

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	124	128 *	130 **	127 *
WEEKS 1/2	ST.DEV.	6.6	6.9	7.5	7.1
	N	55	55	55	55
DAYS 8-15	MEAN	179	183	185	180
WEEKS 2/3	ST.DEV.	13.9	13.5	16.2	15.2
	N	55	55	55	55
MEAN OF MEANS OVER PRETEST		152	155	158	153

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

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	123	125	123	105 **
WEEKS 1/2	ST.DEV.	10.6	7.1	7.7	8.3
	N	55	55	55	55
DAYS 8-15	MEAN	109	109	107	101 **
WEEKS 2/3	ST.DEV.	6.2	5.9	5.8	6.2
	N	55	53 x	55	55
DAYS 15-22	MEAN	95	93	92 *	84 **
WEEKS 3/4	ST.DEV.	6.1	6.1	4.9	6.2
	N	52 x	55	55	55
DAYS 22-29	MEAN	92	92	91	84 **
WEEKS 4/5	ST.DEV.	5.4	4.8	5.5	4.9
	N	55	54 x	54 x	55
DAYS 29-36	MEAN	83	85	85	80 **
WEEKS 5/6	ST.DEV.	4.6	5.4	4.5	4.9
	N	55	53 x	55	55
DAYS 36-43	MEAN	83	84	82	78 **
WEEKS 6/7	ST.DEV.	4.9	5.8	4.9	4.5
	N	53 x	43 x	55	55
DAYS 43-50	MEAN	79	81	76 **	74 **
WEEKS 7/8	ST.DEV.	4.9	6.0	4.3	4.8
	N	55	55	55	55
DAYS 50-57	MEAN	78	76	75	71 **
WEEKS 8/9	ST.DEV.	6.0	6.9	7.0	5.7
	N	55	55	55	55
DAYS 57-64	MEAN	72	72	68 **	67 **
WEEKS 9/10	ST.DEV.	4.9	5.7	4.3	5.4
	N	55	54 x	55	55
DAYS 64-71	MEAN	71	70	70	66 **
WEEKS 10/11	ST.DEV.	4.9	5.3	4.2	4.2
	N	55	54 x	55	55
DAYS 71-78	MEAN	67	67	66	62 **
WEEKS 11/12	ST.DEV.	5.3	5.6	4.6	4.8
	N	55	55	55	55
DAYS 78-85	MEAN	70	71	73	75 **
WEEKS 12/13	ST.DEV.	4.7	6.0	5.5	3.7
	N	54 x	55	55	55
DAYS 85-92	MEAN	72	68 **	65 **	62 **
WEEKS 13/14	ST.DEV.	5.4	4.8	4.8	5.0
	N	55	54 x	55	55
DAYS 99-106	MEAN	64	62 *	63	61 **
WEEKS 15/16	ST.DEV.	5.3	4.1	4.5	4.8
	N	55	55	55	55
DAYS 113-120	MEAN	61	58 **	58 **	57 **
WEEKS 17/18	ST.DEV.	5.1	3.7	4.8	4.9
	N	55	54 x	55	55
DAYS 127-134	MEAN	62	60	61	60
WEEKS 19/20	ST.DEV.	5.7	6.1	4.6	4.4
	N	55	55	55	55

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 141-148	MEAN	64	59 **	56 **	56 **
WEEKS 21/22	ST.DEV.	5.6	6.4	5.4	4.2
	N	54 x	54 x	55	55
DAYS 155-162	MEAN	60	58	58	58
WEEKS 23/24	ST.DEV.	4.4	4.7	4.3	4.0
	N	52 x	53 x	55	55
DAYS 169-176	MEAN	60	57	59	57 **
WEEKS 25/26	ST.DEV.	6.4	4.9	4.5	4.1
	N	54 x	53 x	55	55
DAYS 183-190	MEAN	56	56	56	55
WEEKS 27/28	ST.DEV.	4.8	4.8	5.5	4.9
	N	54 x	54	55	55
DAYS 197-204	MEAN	58	56	58	58
WEEKS 29/30	ST.DEV.	5.1	4.1	5.1	4.8
	N	54 x	54	55	55
DAYS 211-218	MEAN	56	57	56	55
WEEKS 31/32	ST.DEV.	5.3	4.6	5.0	4.0
	N	55	52 x	55	55
DAYS 225-232	MEAN	57	56	58	57
WEEKS 33/34	ST.DEV.	4.7	5.0	6.5	4.6
	N	53 x	51 x	55	55
DAYS 239-246	MEAN	56	57	57	57
WEEKS 35/36	ST.DEV.	5.4	4.8	5.6	5.0
	N	52 x	48 x	55	55
DAYS 253-260	MEAN	57	57	59	58
WEEKS 37/38	ST.DEV.	5.6	5.0	5.8	4.5
	N	53 x	49 x	55	55
DAYS 267-274	MEAN	54	54	54	51
WEEKS 39/40	ST.DEV.	5.3	4.0	5.9	4.4
	N	53 x	50 x	55	55
DAYS 281-288	MEAN	55	55	56	55
WEEKS 41/42	ST.DEV.	5.0	4.4	4.9	4.9
	N	52 x	50 x	54	55
DAYS 295-302	MEAN	54	54	55	54
WEEKS 43/44	ST.DEV.	5.1	5.0	5.4	4.1
	N	53 x	50 x	54	55
DAYS 309-316	MEAN	52	52	54 *	53
WEEKS 45/46	ST.DEV.	4.2	4.7	4.7	4.5
	N	53 x	51 x	54	54
DAYS 323-330	MEAN	53	55	55	56 *
WEEKS 47/48	ST.DEV.	5.0	5.6	5.5	4.7
	N	52 x	49 x	54	53
DAYS 337-344	MEAN	52	53	54	54
WEEKS 49/50	ST.DEV.	5.5	4.3	5.3	4.4
	N	53	48 x	53	53
DAYS 351-358	MEAN	52	53	54	53
WEEKS 51/52	ST.DEV.	4.8	4.3	5.2	7.5
	N	51 x	49 x	53	53

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

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

MEAN OF MEANS OVER TREATMENT	GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
MEAN OF MEANS OVER TREATMENT	68	68	67	65

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

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

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	120	121	119	121
WEEKS 1/2	ST.DEV.	7.5	5.5	5.6	5.2
	N	15	15	15	15
DAYS 8-15	MEAN	169	173	167	167
WEEKS 2/3	ST.DEV.	16.2	16.0	17.8	14.3
	N	15	15	15	15
MEAN OF MEANS OVER PRETEST		144	147	143	144

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

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	104	104	104	91 **
WEEKS 1/2	ST.DEV.	9.1	8.6	9.2	6.9
	N	15	15	15	15
DAYS 8-15	MEAN	98	97	93 *	93
WEEKS 2/3	ST.DEV.	4.8	6.7	6.4	5.4
	N	15	15	15	15
DAYS 15-22	MEAN	84	83	78 *	76 **
WEEKS 3/4	ST.DEV.	3.9	6.1	6.2	5.3
	N	15	15	15	15
DAYS 22-29	MEAN	79	78	76	74 *
WEEKS 4/5	ST.DEV.	4.0	4.7	5.6	3.7
	N	15	14 x	15	15
DAYS 29-36	MEAN	72	73	70	67 **
WEEKS 5/6	ST.DEV.	3.5	4.2	5.5	3.8
	N	14 x	14 x	15	15
DAYS 36-43	MEAN	68	67	63 *	63 **
WEEKS 6/7	ST.DEV.	2.9	4.2	5.8	2.5
	N	14 x	14 x	15	15
DAYS 43-50	MEAN	62	61	59	61
WEEKS 7/8	ST.DEV.	4.1	4.1	5.5	2.6
	N	15	15	15	15
DAYS 50-57	MEAN	56	56	56	59
WEEKS 8/9	ST.DEV.	6.8	4.8	6.2	12.8
	N	15	15	15	15
DAYS 57-64	MEAN	59	57	57	59
WEEKS 9/10	ST.DEV.	3.7	2.6	4.3	2.8
	N	15	15	15	15
DAYS 64-71	MEAN	56	57	55	57
WEEKS 10/11	ST.DEV.	3.7	2.7	3.9	3.2
	N	15	15	15	15
DAYS 71-78	MEAN	51	51	50	51
WEEKS 11/12	ST.DEV.	3.5	2.4	3.9	2.3
	N	15	15	15	14
DAYS 78-85	MEAN	53	54	57 *	57 **
WEEKS 12/13	ST.DEV.	3.9	3.2	4.1	3.2
	N	15	15	15	14
DAYS 85-92	MEAN	52	53	54	51
WEEKS 13/14	ST.DEV.	3.3	2.9	5.3	3.0
	N	15	15	15	14
DAYS 99-106	MEAN	47	46	46	47
WEEKS 15/16	ST.DEV.	3.3	2.6	4.0	2.1
	N	14	15	15	14
DAYS 113-120	MEAN	47	46	48	48
WEEKS 17/18	ST.DEV.	3.9	2.8	5.1	2.5
	N	14	15	14 x	13
DAYS 127-134	MEAN	49	48	47 *	44 **
WEEKS 19/20	ST.DEV.	3.0	2.3	3.7	2.6
	N	14	14 x	15	13

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

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 141-148	MEAN	43	42	43	45
WEEKS 21/22	ST.DEV.	3.0	2.3	6.1	2.3
	N	14	15	15	13
DAYS 155-162	MEAN	43	42	43	46 *
WEEKS 23/24	ST.DEV.	2.2	2.3	5.2	2.0
	N	14	15	15	13
DAYS 169-176	MEAN	45	42	44	46
WEEKS 25/26	ST.DEV.	2.9	2.6	5.0	2.5
	N	14	15	15	13
DAYS 183-190	MEAN	44	43	45	47
WEEKS 27/28	ST.DEV.	3.0	2.7	6.0	2.1
	N	14	15	15	13
DAYS 197-204	MEAN	42	42	42	44
WEEKS 29/30	ST.DEV.	2.6	2.3	4.7	2.1
	N	14	15	15	13
DAYS 211-218	MEAN	41	40	41	43
WEEKS 31/32	ST.DEV.	2.5	2.7	5.6	1.4
	N	14	15	15	13
DAYS 225-232	MEAN	41	39	41	43
WEEKS 33/34	ST.DEV.	2.6	2.5	4.7	2.2
	N	14	15	15	13
DAYS 239-246	MEAN	41	40	42	43
WEEKS 35/36	ST.DEV.	3.0	2.5	4.4	1.8
	N	14	15	15	13
DAYS 253-260	MEAN	41	40	41	43
WEEKS 37/38	ST.DEV.	2.4	2.2	4.8	2.4
	N	14	15	15	13
DAYS 267-274	MEAN	39	40	40	43 *
WEEKS 39/40	ST.DEV.	4.4	2.9	5.0	2.1
	N	13	15	15	13
DAYS 281-288	MEAN	40	39	42	43 *
WEEKS 41/42	ST.DEV.	2.4	2.5	4.7	2.5
	N	13	15	15	13
DAYS 295-302	MEAN	39	38	41	43 *
WEEKS 43/44	ST.DEV.	2.2	2.5	4.9	2.3
	N	13	15	15	13
DAYS 309-316	MEAN	39	38	41	43 *
WEEKS 45/46	ST.DEV.	2.6	3.1	5.4	2.7
	N	13	14 x	15	13
DAYS 323-330	MEAN	40	37	42	43
WEEKS 47/48	ST.DEV.	2.3	7.8	3.9	3.1
	N	13	14 x	15	13
DAYS 337-344	MEAN	38	36	39	41 *
WEEKS 49/50	ST.DEV.	2.2	2.2	4.2	2.9
	N	13	14	15	13
DAYS 351-358	MEAN	37	36	39	42 **
WEEKS 51/52	ST.DEV.	2.5	4.4	3.9	1.6
	N	13	14	15	13

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

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

MEAN OF MEANS OVER TREATMENT	GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
MEAN OF MEANS OVER TREATMENT	53	52	52	53

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

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

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	38	41	46 **	50 **
WEEKS 1/2	ST.DEV.	2.7	2.5	4.3	2.8
	N	13	12 x	14 x	13
DAYS 15-22	MEAN	38	38	42 **	44 **
WEEKS 3/4	ST.DEV.	2.6	2.5	4.0	2.3
	N	13	14	15	13
DAYS 29-36	MEAN	38	39	43 **	44 **
WEEKS 5/6	ST.DEV.	3.0	2.6	3.7	2.6
	N	13	12 x	14 x	13
DAYS 43-50	MEAN	37	37	41 *	42 **
WEEKS 7/8	ST.DEV.	3.2	2.8	3.7	3.0
	N	13	13 x	15	13
MEAN OF MEANS OVER RECOVERY		38	39	43	45

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

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

PRETEST		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	124	131 *	132 **	127
WEEKS 1/2	ST.DEV.	4.8	6.7	7.0	7.8
	N	15	15	15	15
DAYS 8-15	MEAN	179	190	183	176
WEEKS 2/3	ST.DEV.	12.1	10.9	17.9	14.5
	N	15	15	15	15
MEAN OF MEANS OVER PRETEST		151	161	158	152

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

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 2-8	MEAN	132	129	126	108 **
WEEKS 1/2	ST.DEV.	5.6	5.1	9.0	10.1
	N	15	15	15	15
DAYS 8-15	MEAN	113	112	108	102 **
WEEKS 2/3	ST.DEV.	5.2	4.3	7.0	6.8
	N	15	14 x	15	15
DAYS 15-22	MEAN	96	93	91 *	82 **
WEEKS 3/4	ST.DEV.	6.4	4.3	4.4	5.9
	N	14 x	15	15	15
DAYS 22-29	MEAN	92	93	90	83 **
WEEKS 4/5	ST.DEV.	3.6	4.1	5.0	5.3
	N	15	14 x	15	15
DAYS 29-36	MEAN	83	85	84	78 *
WEEKS 5/6	ST.DEV.	4.0	5.3	5.4	4.3
	N	15	15	15	15
DAYS 36-43	MEAN	84	85	81	77 **
WEEKS 6/7	ST.DEV.	5.1	4.5	4.5	5.2
	N	14 x	14 x	15	15
DAYS 43-50	MEAN	81	80	76 **	75 **
WEEKS 7/8	ST.DEV.	4.2	5.2	4.4	4.9
	N	15	15	15	15
DAYS 50-57	MEAN	74	71	74	66 **
WEEKS 8/9	ST.DEV.	5.4	6.0	9.8	6.2
	N	15	15	15	15
DAYS 57-64	MEAN	75	73	69 **	72 *
WEEKS 9/10	ST.DEV.	3.9	4.9	3.2	3.5
	N	15	15	15	15
DAYS 64-71	MEAN	71	73	70	67 *
WEEKS 10/11	ST.DEV.	4.7	4.5	3.8	4.3
	N	15	15	15	15
DAYS 71-78	MEAN	66	68	67	62
WEEKS 11/12	ST.DEV.	5.2	5.2	5.3	5.5
	N	15	15	15	15
DAYS 78-85	MEAN	69	71	72	75 **
WEEKS 12/13	ST.DEV.	4.1	4.2	4.4	4.2
	N	14 x	15	15	15
DAYS 85-92	MEAN	72	66 **	66 **	63 **
WEEKS 13/14	ST.DEV.	3.8	4.1	5.9	5.5
	N	15	15	15	15
DAYS 99-106	MEAN	63	61	64	61
WEEKS 15/16	ST.DEV.	5.1	3.9	4.5	4.7
	N	15	15	15	15
DAYS 113-120	MEAN	61	59	59	59
WEEKS 17/18	ST.DEV.	3.9	3.4	5.0	3.3
	N	15	15	15	15
DAYS 127-134	MEAN	60	59	62	60
WEEKS 19/20	ST.DEV.	4.4	3.5	4.6	4.8
	N	15	15	15	15

x Explanations for excluded data are listed in the tables of individual values
* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

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

TREATMENT		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 141-148	MEAN	63	56 **	56 **	55 **
WEEKS 21/22	ST.DEV.	4.6	3.7	6.0	4.4
	N	14 x	15	15	15
DAYS 155-162	MEAN	59	58	59	59
WEEKS 23/24	ST.DEV.	4.4	4.1	4.1	3.3
	N	15	15	15	15
DAYS 169-176	MEAN	60	58	58	55 *
WEEKS 25/26	ST.DEV.	3.4	4.3	3.4	5.0
	N	14 x	15	15	15
DAYS 183-190	MEAN	57	57	59	58
WEEKS 27/28	ST.DEV.	3.8	6.3	5.9	4.6
	N	14 x	15	15	15
DAYS 197-204	MEAN	57	56	59	58
WEEKS 29/30	ST.DEV.	5.5	4.4	3.9	5.0
	N	14 x	15	15	15
DAYS 211-218	MEAN	56	57	56	55
WEEKS 31/32	ST.DEV.	4.7	4.3	4.8	4.0
	N	15	15	15	15
DAYS 225-232	MEAN	57	55	57	57
WEEKS 33/34	ST.DEV.	5.1	5.3	3.7	3.6
	N	14 x	15	15	15
DAYS 239-246	MEAN	57	58	57	61
WEEKS 35/36	ST.DEV.	3.9	6.1	4.1	4.5
	N	14 x	14 x	15	15
DAYS 253-260	MEAN	58	58	57	57
WEEKS 37/38	ST.DEV.	4.5	5.8	5.9	3.5
	N	14 x	15	15	15
DAYS 267-274	MEAN	53	55	53	50
WEEKS 39/40	ST.DEV.	4.7	3.9	4.1	3.9
	N	14 x	15	15	15
DAYS 281-288	MEAN	54	55	57	54
WEEKS 41/42	ST.DEV.	5.2	4.8	4.1	3.9
	N	14 x	15	15	15
DAYS 295-302	MEAN	54	54	55	52
WEEKS 43/44	ST.DEV.	4.9	4.8	4.8	4.1
	N	15	15	15	15
DAYS 309-316	MEAN	50	51	54 **	52
WEEKS 45/46	ST.DEV.	3.0	4.9	3.5	3.4
	N	14 x	15	15	15
DAYS 323-330	MEAN	56	52	55	54
WEEKS 47/48	ST.DEV.	4.6	6.9	4.5	5.0
	N	14 x	15	15	15
DAYS 337-344	MEAN	51	51	52	53
WEEKS 49/50	ST.DEV.	5.3	4.9	5.7	4.0
	N	14	14 x	15	15
DAYS 351-358	MEAN	52	51	54	55
WEEKS 51/52	ST.DEV.	4.0	4.8	4.3	11.6
	N	13 x	15	15	15

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

MEAN OF MEANS OVER TREATMENT	GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
MEAN OF MEANS OVER TREATMENT	68	68	67	65

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

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

RECOVERY		GROUP 1 0 MG/KG	GROUP 2 440 MG/KG	GROUP 3 1000 MG/KG	GROUP 4 2 X 1000 MG/KG
DAYS 1-8	MEAN	50	54	60 **	66 **
WEEKS 1/2	ST.DEV.	2.5	4.5	4.1	3.3
	N	12 x	14 x	14 x	15
DAYS 15-22	MEAN	50	52	56 **	58 **
WEEKS 3/4	ST.DEV.	5.5	4.2	4.7	2.9
	N	13 x	13 x	15	15
DAYS 29-36	MEAN	53	55	57 *	58 **
WEEKS 5/6	ST.DEV.	4.9	3.3	4.0	3.2
	N	12 x	14 x	14 x	15
DAYS 43-50	MEAN	48	49	54 *	53
WEEKS 7/8	ST.DEV.	4.6	4.7	4.8	5.9
	N	13 x	14 x	15	15
MEAN OF MEANS OVER RECOVERY		50	52	57	59

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