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28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No. 933180

Comparison of toxicity profiles between

CGA 329351 tech. (D-enantiomere of CGA 48988) and

CGA 48988 tech. (racemate form)

FINAL REPORT

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Study Director: Dr. rer. nat. **592.e Woo**

Testing Facility: CIBA-GEIGY Limited  
Short / Long-term Toxicology  
4332 Stein / Switzerland

Test Guidelines: OECD 407  
EEC 92/69 B.7.

Study completed: August 26, 1994

Sponsor: CIBA-GEIGY Limited  
Plant Protection Division  
4002 Basle / Switzerland

This report contains: 427 pages

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0.2. Certification of GLP and Verification of the Report

(Certification of Good Laboratory Practice and Verification of a Complete and Unaltered Copy of the Report by the Sponsor)

The Statement of Compliance with Good Laboratory Practice found on page 4 of this report, and signed by the Study Director is truthful and accurate, and this report as provided by the testing facility is complete and unaltered.

For the Sponsor:

**W. J. E. WOOD**

date: *Sept-65 17, 1994*

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0.3. Statement of Compliance with Good Laboratory Practice

This study has been performed in compliance with Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986 (Verfahren und Grundsätze der Guten Laborpraxis (GLP) in der Schweiz), issued by the Swiss Federal Department of the Interior and the Intercantonal Office for the Control of Medicaments. These procedures are in essence consistent with:

- OECD Principles of Good Laboratory Practice (Council Decision 81/30, adopted on May 12, 1981, and the OECD Recommendation 83/95 concerning the 'Mutual Recognition of Compliance with Good Laboratory Practice', adopted on July 26, 1983).
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 160 (FIFRA); Federal Register, August 17, 1989.
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 792 (TSCA); Federal Register, August 17, 1989.
- Japan Ministry of Agriculture, Forestry and Fisheries, NohSan, Notification No. 3850, Agricultural Production Bureau, August 10, 1984.

Study Director:

Dr. rer. nat. 1.2.e Woo

date:

August 26, 1994

0.4. Signatures

This report presents the results of the investigations as compiled by the undersigned.

Study Director

Dr. rer. nat. 5.1.2.e Woo

5.1.2.e Woo

date: August 26, 1994

Reviewed by

Dr. phil.-nat. 5.1.2.e Woo

Head Longterm Toxicology

5.1.2.e Woo

date: August 29, 1994

Responsible for Laboratory Investigations

Dr. med. vet.  
FVH Clinical Chemistry

5.1.2.e Woo

date: August 2, 1994

Responsible for Pathology

Dr. med. vet.  
FVH Pathology

5.1.2.e Woo

date: August 30, 1994

Study Pathologist

Dr. med. vet.  
ETA Pathology

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date: August 30, 1994

Responsible for Statistics

5.1.2.e Woo dipl. stat.

5.1.2.e Woo

date: August 31, 1994



Facility Management

Dr. med. vet. 5.1.2.e Woo  
FVH Toxicology

5.1.2.e Woo

date:

August 29, 1994

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0.6. Quality Assurance Statement

I hereby certify that the following Quality Assurance activities were performed:

Activity	Performed	Reported
Facility Inspection	September 16, 1993	September 17, 1993
Protocol Audit	January 21, 1994	January 21, 1994
Study Related Inspection	February 01, 1994	February 02, 1994
Study Related Inspection	February 24, 1994	February 24, 1994
Facility Inspection	March 23, 1994	April 08, 1994
Final Report Audit	August 16, 1994	August 18, 1994

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September 7 1994  
Date

5.1.2.e Woo

INSPECTOR QUALITY ASSOCIATION

## 1. INTRODUCTION

### **Purpose**

This study was performed in order to compare the toxicity profiles of CGA 329351 tech. (D-enantiomere of CGA 48988) and CGA 48988 tech. (racemate), when administered to rats by daily oral gavage over a period of 4 weeks under identical conditions.

### **Good laboratory practice**

This study was carried out in accordance with the Principles of Good Laboratory Practice as set forth in "Verfahren und Grundsätze der Guten Laborpraxis (GLP) in der Schweiz", Swiss Federal Department of the Interior and Intercantonal Office for the Control of Medicaments (IKS), March 1986.

The study was subjected to periodic internal quality assurance evaluation.

The inspection of the tissue processing and manufacturing of slides was performed by the quality assurance of HISZTOLABOR PANNOMIA Kft. following their standard operating procedures, according to specific inspection requests from the quality assurance of CIBA-GEIGY Limited, Basle/Switzerland.

Analytical investigations, performed at RCC Umweltchemie AG, were inspected by the Quality Assurance Unit of RCC Umweltchemie AG, 4452 Itingen / Switzerland.

### **Basis for the study**

The study was carried out according to the following guidelines:

- OECD Guideline for testing of chemicals, No.407, "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-day Study", adopted May 12, 1981.
- Annex to Commission Directive 92/69/EEC, Official Journal of the European Communities, 29 December 1992, L383A, Page 136-139, B.7. Repeated dose (28 days) toxicity (oral).

### **Sponsor**

CIBA-GEIGY Limited  
Plant Protection Division  
4002 Basle / Switzerland

### Testing facility

All in-life testing was performed at the Sisseln facility:

CIBA-GEIGY Limited  
Short/Long-term Toxicology  
4332 Stein / Switzerland

Tissue processing and slide manufacturing was performed at:

Hiszolabor Pannomia Kft.  
Laita u. 38  
H-9013 Gyöer / Hungary

Histopathological examination was performed at:

CIBA-GEIGY Limited  
Short/Long-term Toxicology (Pathology)  
4002 Basle / Switzerland

Analytical investigations were performed at:

RCC Umweltchemie AG  
4452 Itingen / Switzerland

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**Personnel and responsible scientists**

The following scientists, professionals and supervisory personnel were involved in the conduct of the study:

- Study director: Dr. rer. nat. [REDACTED] WOD  
Longterm Toxicology
- Technical assistant: [REDACTED] WOD  
Longterm Toxicology
- Supervisors: [REDACTED] WOD  
Longterm Toxicology
- Responsible for laboratory investigations: Dr. med. vet. [REDACTED]  
FVH Clinical Chemistry  
Clinical Laboratory
- Assistant laboratory investigations: [REDACTED] WOD  
Clinical Laboratory
- Responsible for necropsy: Mrs. [REDACTED] dipl. med. vet.  
Macropathology
- Responsible for pathology services: PD Dr. med. vet. [REDACTED]  
FVH Fundamental Medicine
- Assistant, Logistics / Archives: Ms. [REDACTED]
- Responsible for pathology: Dr. med. vet. [REDACTED] WOD  
FVH Pathology  
Toxicological Pathology
- Study pathologist: Dr. med. vet. [REDACTED] WOD  
FTA Pathology  
Toxicological Pathology
- Responsible for statistics: [REDACTED] dipl. stat.  
Mathematical Applications
- Responsible for analytics: [REDACTED] WOD, RCC

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

The job descriptions and the summaries of training and professional experience of personnel participating in this study are available at:

CIBA-GEIGY Limited, for Short/Long-term Toxicology  
4332 Stein / Switzerland Sisseln Facility

CIBA-GEIGY Limited, for Short/Long-term Toxicology  
4002 Basle / Switzerland (Pathology)  
and Mathematical Applications

Hisztolabor Pannomia Kft. for Hisztolabor Pannomia  
Laita u. 38  
H-9013 Gyöer/Hungary

RCC Umweltchemie AG for Analytical Laboratories  
4452 Itingen / Switzerland

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## 2. SUMMARY AND CONCLUSION

In this comparative study, the test articles CGA 329351 tech. and CGA 48988 tech. were each administered by gavage for 4 weeks at daily doses of 10, 50, 150 and 300 mg/kg bodyweight to 5 male and 5 female albino rats per dose group. The common control group consisted of 10 animals, 5 males and 5 females.

Administered quantities of the test article suspension were adjusted daily to individual bodyweight.

The results of this study are summarized as follows:

### In-life observations

After the first administration of CGA 329351 tech., all animals of groups 4 and 5 (150 and 300 mg/kg) showed hypoactivity. Two female animals of group 5 were prostrate. These signs were present for two hours post dosing on day 1 of treatment only.

No signs of toxicological relevance were observed in animals treated with CGA 48988 tech.

### Mortality

All animals survived the 28 day-treatment periods with either CGA 329351 tech. or CGA 48988 tech.

### Bodyweight

Compared with the control group, treatment with either CGA 329351 tech. or CGA 48988 tech. did not affect the bodyweight development.

### Food consumption

The overall food intake (weeks 1-4) of animals treated with either test article was considered to be uninfluenced by the treatment.

### Food consumption ratios

Mean food consumption ratios did not reveal an effect due to the treatment with either CGA 329351 tech. or CGA 48988 tech.

### Water consumption

Treatment with CGA 329351 tech. reduced the mean water consumption of the male high dose group (300 mg/kg) throughout the treatment period, whereas treatment with CGA 48988 tech. increased the mean water consumption of group 5 (300 mg/kg).

### Hematology

Treatment with CGA 329351 tech. and CGA 48988 tech. had no influence on the hematological profile of the rats.

### Blood chemistry

Minimally lower plasma sodium levels, minimally higher plasma chloride levels, and a tendency to lower urea levels were recorded among males treated with 300 mg/kg of CGA 329351 tech. or 300 mg/kg of CGA 48988 tech. In addition, males treated with 300 mg/kg of CGA 329351 tech. had minimally lower plasma bilirubin levels.

Females treated with 300 mg/kg of CGA 329351 tech. and females treated at 150 and 300 mg/kg of CGA 48988 tech. had increased plasma protein levels (albumin and globulin), and minimally lower plasma bilirubin levels.

### Organ weights

A slight increase of mean liver weights and ratios was seen in the male and female high dose group treated with CGA 48988 tech. and in the high dose females treated with CGA 329351 tech.

### Pathological findings

The few findings observed macroscopically were considered not to be related to the treatment with either CGA 329351 tech. or CGA 48988 tech.

Microscopical examination revealed the following treatment-related findings:

Minimal to moderate hypertrophy of centrilobular hepatocytes occurred in female animals of group 4 (150 mg/kg) and male and female animals of group 5 (300 mg/kg) treated with CGA 329351 tech.

Minimal hypertrophy of centrilobular hepatocytes in females of group 5 (300 mg/kg) and minimally increased incidence of extramedullary hematopoiesis in the spleen of females of groups 4 and 5 (150 and 300 mg/kg) were found after treatment with CGA 48988 tech.



### 3. MATERIALS AND METHODS

#### 3.1. Test articles

##### CGA 329351 tech.

Company code No.: CGA 329351 tech.

Batch No.: KGL-4634/6

Purity: 97.3 %

Description: liquid

Date of receipt: January 20, 1994

Storage conditions: room temperature

Stability: February 1998

##### CGA 48988 tech.

Company code No.: CGA 48988 tech.

Batch No.: EN 603107

Purity: 96.1 %

Description: solid

Date of receipt: December 30, 1993

Storage conditions: room temperature

Stability: June 1994

#### Pretest analytics

Prior to the start of the study, samples of the vehicle containing the respective test article (for CGA 329351 tech. batch KGL-4634/5 was used) at concentrations of 0, 0.1, 1, 10 and 100 mg/ml were dispatched to the analytical laboratories of RCC Umweltchemie AG, 4452 Itingen / Switzerland, for analysis of content, homogeneity and stability.

The results of the analyses (RCC Project 365894) are given in the results and appendix sections of this report.

### 3.2. Test system

#### 3.2.1. Experimental animals

Species: albino rats

Stock: Tif: RAIf (SPF),  
hybrids of RII/1 x RII/2  
(Sprague-Dawley derived)

Source: Animal Production  
CIBA-GEIGY Limited  
4332 Stein / Switzerland

Initial bodyweight:  
(at week -1) 132.4 - 146.7 g in males  
143.5 - 163.4 g in females

Initial age: approximately 5 weeks at delivery

#### 3.2.2. Husbandry

The study was carried out under specified pathogen free (SPF) standard laboratory conditions. The animals were housed in groups of 5 in macrolon cages type 4 with wire mesh tops and standardized granulated soft wood bedding (Societe Parisienne des Sciures Pantin).

The animal room was air conditioned:

Temperature:  $22 \pm 2^{\circ}\text{C}$

Relative humidity (%):  $55 \pm 10$

Ventilation: 16-20 air changes/hour

Light cycle: 12 hours light per day

Neither insecticides nor chemicals were applied in the animal room with the exception of disinfectant: BRADOPHEN<sup>tm</sup>.

#### 3.2.3. Identification

By tattoo of tail for cage number and by tattoo of right ear auricle with numbers 1 to 5 for individual identification of the animals in the cages.



3.3.2. Animal number and distribution

Number of animals: 90 (total)

For both test articles, 5 males and 5 females were used in each of the treatment groups 2, 3, 4 and 5. The common control group (group 1) consisted of 5 males and 5 females.

The general outline of the experiment is presented in the following animal distribution table: Due to technical reasons treatment with CGA 329351 tech. was defined with study number 933180, and treatment with CGA 48988 tech. was defined with study subnumber 940001. The common control was integrated within 933180.

Animal No. (cage no.)	Group 1 Control	Group 2 10 mg/kg	Group 3 50 mg/kg	Group 4 150 mg/kg	Group 5 300 mg/kg
MALES 933180	* 1-5 (1)	6-10 (2)	11-15 (3)	16-20 (4)	21-25 (5)
FEMALES 933180	* 26-30 (6)	31-35 (7)	36-40 (8)	41-45 (9)	46-50 (10)
MALES 940001	*	6-10 (2)	11-15 (3)	16-20 (4)	21-25 (5)
FEMALES 940001	*	31-35 (7)	36-40 (8)	41-45 (9)	46-50 (10)

933180 to be treated with CGA 329351 tech.  
 5 animals per sex and group for evaluation of toxicity, including laboratory investigations

940001 to be treated with CGA 48988 tech.  
 5 animals per sex and group for evaluation of toxicity, including laboratory investigations

\* Original records for the common control group were copied from 933180 to 940001





### 3.3.5. Rationale for dose selection

Dose levels were based on the results of the following previously conducted studies:

Project no. 382-106  
International Research and Development corporation, Mattawan,  
Michigan USA Acute oral toxicity (LD 50) in rats. CGA 48988.

LD50 in rats: 633 mg/kg bodyweight

and

Project no. 790325  
Ciba-Geigy Ltd., Basle  
28-days toxicity study on rats with CGA 48988 technical:

CGA 48988 was administered orally by gastric intubation to groups of 10 male and female Tif:RAIf (SPF) rats at initial daily dose levels of 0, 10, 30 and 100 mg/kg bodyweight. As the treatment provoked no overt toxic reactions, the doses were raised to 0, 30, 100 and 300 mg/kg from days 15 to 21 and finally to 0, 60, 200 and 600 mg/kg from day 22 onwards. No mortality occurred. After the dose was increased to 600 mg/kg, i.e. to a level which comes close to the acute oral LD 50 for rats, tremor was observed among the animals of this dose group. On the following days the animals adapted to the treatment until no more clinical signs were visible on days 26, 27 and 28. No treatment-related reactions were noted with respect to bodyweight gain and food consumption. Also the ophthalmological examination and the parameters of hematology, blood chemistry and urinalysis revealed no treatment-related changes. In comparison to the untreated controls, the mean absolute and relative liver weights were increased in all treated groups.

and

Project no. 933179  
Short/Long-term Toxicology, CIBA-GEIGY Limited, Stein  
Acute oral toxicity in the rat:

CGA 329351 tech. was administered orally by gavage to each of 5 male rats at dose levels of 2000, 1000, and 500 mg/kg, and to each of 5 female rats at 500 and 200 mg/kg bodyweight.

LD50 in male rats: 953 mg/kg bodyweight

LD50 in female rats: 375 mg/kg bodyweight

LD50 in rats of both sexes: 667 mg/kg bodyweight

### 3.4. Test article administration and diet

#### **Route of administration**

The test articles were administered orally by gavage.

#### **Frequency of administration**

1 dose per day, 7 times per week.

#### **Preparation of suspension**

Suspensions of each test article in the selected vehicle at the appropriate concentrations were freshly prepared every day immediately prior to the dosing of the animals and administered within about 2 hours.

#### **Vehicle**

As a standard procedure, distilled water containing 0.5% carboxymethylcellulose and 0.1% Tween 80 was used as a vehicle.

#### **Volume of suspension applied**

10 ml/kg bodyweight

#### **Control analyses**

Control analyses of the respective test article's concentration in the vehicle were carried out at all dose levels on samples collected once per experimental week. The samples were collected on completion of dosing, immediately deep frozen and sent to the analytical laboratories of RCC Umweltchemie AG, 4452 Itingen / Switzerland. The results thereof (Analytical Report No. 365894) are given in the results and appendix sections of this report.

#### **Control animals**

The control animals were dosed in the same way as the treated rats with vehicle, without the test article.

### 3.4.1. Diet

Pelleted, certified standard diet (Nafag No. 8900 FOR GLP) was provided ad libitum (except as noted under Laboratory Investigations). All batches of diet were assayed for composition and contaminant levels by the manufacturer. Analytical results are available at the animal supply office (CIBA-GEIGY Limited, Pharmaceuticals Division).

### 3.4.2. Water

Tap water was given ad libitum. The drinking water quality fulfilled the critical parameters in the specifications of the "Schweizerisches Lebensmittelbuch" (Ed. 1972). The results of the routine chemical examination of water at source (Grundwasserfassung Stein) as conducted periodically by the water authority (Baudepartement des Kantons Aargau, Abteilung Gewaesserschutz) are available to CIBA-GEIGY Limited, as well as the results of inhouse chemical analysis by the analytical laboratories of the Pharmaceuticals Division, CIBA-GEIGY Limited.

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### 3.5. Observations and records

#### **Mortality**

All animals were checked daily (a.m. and p.m. on working days, a.m. on weekends and holidays), in order to record mortalities, and to allow dead or moribund animals to be submitted to necropsy as soon as possible.

#### **In-life observations**

In order to detect changes in state of health or behaviour, or any reaction to treatment, examination was carried out daily, and observations were recorded at least weekly.

#### **Bodyweight**

The weight of all animals was recorded individually at weekly (midweek) weighing sessions. The first weights were recorded during the acclimatation period. Daily bodyweights for accurate dosing were measured but not recorded.

#### **Food consumption**

The food consumption was recorded weekly (cagewise) and was calculated for periods of one week. The calculation was based on the weight of the offered diet at the beginning of a weighing period and its difference to the re-weighed amount after several days. The individual food consumption values were calculated from the food consumption per cage and the number of animals present.

#### **Food consumption ratios**

The food consumption ratios were calculated as mean of individual ratios according to the following formula:

$$\frac{\text{weekly food consumption (g)}}{\text{midweek bodyweight (g)}} \times \frac{1000}{7}$$

Unit: g food/kg bodyweight per day

#### **Water consumption**

The water consumption was recorded weekly (cagewise).

The water consumption was calculated for periods of one week. The calculation was based on the weight of the offered water at the beginning of a weighing period and its difference to the re-weighed amount after one day.

The individual water consumption was calculated from the water consumption per cage and the number of animals present.

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### 3.6.1. Parameters and methods used in hematology

#### Parameters determined by the Technicon H\*1 <1>, <2> (Method code: M0002)

Red blood cell parameters	Abbreviation	Unit
Erythrocyte count	RBC	T/l
Hemoglobin	Hb	mmol/l
Hematocrit	Hct	l
Mean corpuscular volume	MCV	fl
Red cell volume distribution width<3>	RDW	l
Mean corpuscular hemoglobin	MCH	fmol
Mean corpuscular hemoglobin concentration	MCHC	mmol/l
Hemoglobin concentration distribution width<3>	HDW	mmol/l
<b>White blood cell parameters</b>		
Leukocyte count	WBC	G/l
Differential leukocyte count		rel. abs.
Neutrophils	Neut	1 G/l
Eosinophils	Eos	1 G/l
Basophils	Baso	1 G/l
Lymphocytes	Lympho	1 G/l
Monocytes	Mono	1 G/l
Large unstained cells	Luc	1 G/l
<b>Blood platelets</b>		
Thrombocyte Count	Plt	G/l
<b><u>Prothrombin time</u></b>		
Photometric assay using chromogenic substrate on a Cobas Bio centrifugal analyser (Method code: M0001)	PT (CS)	sec

#### References

- <1> D.T. Davies, G.V. Fisher (1991): The Validation and Application of the Technicon H\*1 for the Complete Automated Evaluation of Laboratory Animal Haematology  
Comp Haematol Int 1, 91-105
- <2> W. Groner, J. Boyett, A. Johnson, M. Scantlebury (1986): Variability of Erythrocyte Size and Hemoglobin Content Observed in Man and Four Selected Mammals  
Blood Cells 12, 65-80
- <3> C. Fossat et al. (1987): New Parameters in Erythrocyte Counting  
Arch Pathol Lab Med 111, 1150-1154

3.6.2. Parameters and methods used in blood chemistry

Parameter	Method of analysis (Method code) Instrument	Abbreviation	Unit
Glucose	Hexokinase/G6P-DH (M0001) HITACHI 737	Gluc	mmol/l
Urea	Urease/GLDH (M0001) HITACHI 737	Urea	mmol/l
Creatinine	Enzymatic colorimetric test (M0001) HITACHI 737	Creat-e	umol/l
Total bilirubin	Reaction with 2,5-Di- chlorophenyldiazonium salt (M0001) HITACHI 737	Bili-tot	umol/l
Total protein	Biuret reaction (M0001) HITACHI 737	Prot	g/l
Albumin	Bromcresol green method (M0001) HITACHI 737	Alb	g/l
Globulin	Calculated value (M0001) (Total Protein minus Albumin)	Glob	g/l
A/G Ratio	Calculated value (M0001) (Albumin/Globulins)	A/G	1
Cholesterol	Enzymatic, CHOD/PAP (M0001) HITACHI 737	Chol	mmol/l
Sodium	Ion selective electrode (M0001) HITACHI 737	Na+	mmol/l
Potassium	Ion selective electrode (M0001) HITACHI 737	K+	mmol/l
Calcium	o-Cresolphthalein complexone method (M0001) HITACHI 737	Ca++	mmol/l
Chloride	Ion selective electrode (M0001) HITACHI 737	Cl-	mmol/l



Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

Parameter	Method of analysis (Method code) Instrument	Abbreviation	Unit
Phosphorus inorganic	Phosphomolybdate reaction (M0001) HITACHI 737	PO4-in	mmol/l
Aspartate aminotransferase EC 2.6.1.1	MDH/NADH coupled reaction method (M0001) HITACHI 737	ASAT (GOT)	U/l
Alanine aminotransferase EC 2.6.1.2	LDH/NADH coupled reaction method (M0001) HITACHI 737	ALAT (GPT)	U/l
Alkaline phosphatase EC 3.1.3.1	p-Nitrophenyl-phosphate as substrate (M0001) HITACHI 737	ALP	U/l

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### 3.7. Pathology

#### 3.7.1. Macroscopical examination

At the end of the test period all controls and treated animals were bled under ether anesthesia and subjected to detailed necropsy.

At necropsy the following weights were recorded from all animals:

body (exsanguinated)  
heart  
liver  
kidneys  
adrenals  
thymus  
ovaries/testes  
spleen  
thyroid

The following organs and tissues were preserved in neutral buffered 4% formalin:

skin  
mammary area  
spleen  
mesenteric lymph node  
axillary lymph node  
sternum with bone marrow  
femur with joint  
skeletal muscle  
trachea  
lung  
heart  
aorta  
submandibular salivary gland, both  
liver  
pancreas  
esophagus  
stomach  
small intestine (duodenum, jejunum, ileum)  
large intestine (cecum, colon, rectum)  
kidney, both  
urinary bladder  
prostate  
seminal vesicle  
testis, both  
epididymis, both  
uterus  
vagina  
ovary, both  
pituitary gland  
adrenal gland, both

thyroid with parathyroid gland  
thymus  
peripheral nerve  
brain  
spinal cord  
eye with optic nerve, both  
orbital gland, both  
extraorbital lacrimal gland, both  
Zymbal gland, both  
muzzle  
tongue  
any tissue with gross lesions

### 3.7.2. Microscopical examination

After the fixation, organ samples listed below were taken, embedded in paraplast, sectioned at 3-5 microns, stained with hematoxylin and eosin, and subjected to a microscopical examination.

spleen  
heart  
liver  
kidney, both  
testis, both  
epididymis, both  
adrenal gland, both  
any organ with gross lesions

### 3.7.3. Presentation of pathology data

Where practicable, gross lesions were identified by a capital letter, e.g. A, B, C, etc. at necropsy.

At the subsequent histopathological evaluation the diagnosis or diagnoses corresponding to the macroscopically identified lesions were given the same alphabetical label in order to correlate the microscopical findings with the changes seen at necropsy.

The histopathological lesions observed were graded as to degree of severity according to the following criteria:

Grade "+" : Minimal (slight). Includes histopathological change that is a noticeable but not prominent feature of the tissue.  
Grade "++" : Moderate. Includes histopathological change that is a prominent but not dominant feature of the tissue.  
Grade "+++" : Marked. Includes histopathological change that is a dominant feature of the tissue.



### 3.8. Statistical analysis

For each time point and parameter an univariate statistical analysis was performed. Nonparametric methods <1> were applied, to allow for non normal as well as normal data distribution.

Each treated group was compared to the control group by Wilcoxon's two-sample test and tested for increasing or decreasing trends from control up to the respective dose group by Jonckheere's test for ordered alternatives <2>. The Jonckheere test is sensitive to monotone dose-related effects.

Two-sided asymptotic p-values are reported in the "statistics" tables. Flags for significant differences between groups (\*) or trends over groups (+ or -) are given in the "means" tables according to the specified significance level. Statistical tests and flags used are indicated in the header of each table.

Statistical significance does not necessarily imply biological relevance. Hence, the responsible scientist may not comment on statistically significant values lying within the physiological range and on the other hand may comment on values, which differ substantially from the expected normal values although this difference was not statistically significant.

#### References

- <1> E.L. Lehmann, Nonparametrics: Statistical Methods Based on Ranks. Holden-Day (1975): pp. 5-31, 232-238.
- <2> A.R. Jonckheere, Biometrika (1954) 41: pp. 133-145

### Explanation of statistics and flags

N the number of observations on which the calculations are based

Mean the sum of the observed values divided by N

Median the 50th percentile

Min, Max the smallest value, the largest value

p<sub>W</sub> p-value, the probability of an outcome being greater than or equal to the absolute value of Wilcoxon's standardized test statistic, if the null hypothesis is true (two-sided, with correction for ties). Not given, if sample sizes too small

\*, significant difference in location between treated group and control at the level specified in the header of the table

p<sub>J</sub> p-value, the probability of an outcome being greater than or equal to the absolute value of Jonckheere's standardized test statistic, if the null hypothesis is true (two-sided, no correction for ties). Not given, if sample sizes too small

+ or -, significant positive or negative trend from control up to the respective dose group at the level specified in the header of the table

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### 3.9. Deviations

#### 3.9.1. Amendments

##### Amendment no.1 (dated January 21, 1994)

###### Test article renamed

As was notified by the sponsor, the test article CGA 76539 tech. was renamed CGA 329351 tech. Consequently, all references to CGA 76539 tech. in the protocol were corrected to CGA 329351 tech.

###### Specification of study conduct

In this part of the amendment, an exact specification of the study conduct design was given, which is presented in chapter 3.3.2 of this report.

##### Amendment no.2 (dated February 16, 1994)

###### Specifications of the test article CGA 329351 tech.

Company code No.: CGA 329351 tech.

Batch No.: KGL-4634/6

Purity: 97.3

Description: liquid

Date of receipt: January 20, 1994

Storage conditions: room temperature

###### Tissue processing

As proposed by Short/Long-term Toxicology and after consultation with the sponsor the tissue processing and the manufacturing of histological slides was contracted to:

HISZTOLABOR PANNOMIA Kft.

Laita u. 38

H-9013 GYOER / Hungary

All material and raw data were returned to CIBA-GEIGY Limited in order to be archived as mentioned in the protocol.

The above mentioned deviations are considered to have no impact on the validity of the study.

There were no known circumstances that could have affected the quality and/or integrity of the data.

#### 4. RESULTS

##### 4.1. Analytical results

Prior to the beginning of the study, suspensions containing the respective test article at concentrations of 0.1, 1, 10 and 100 mg/ml were analyzed for determination of content, homogeneity and stability.

The results of these analyses showed that the contents of the test articles in the vehicle were in agreement with the nominal concentrations and that the samples were homogeneous and stable for 4 hours at room temperature (RCC Project no. 365894, see Appendix B of this report).

During the study, content and stability of CGA 329351 tech. and content of CGA 48988 tech. were confirmed in suspensions containing the respective test article at 1, 5, 15 and 30 mg/ml (RCC Project no. 365894, see Appendix B of this report).

As shown in the table below, the calculated mean contents of CGA 329351 tech. in the vehicle were 106, 106, 104 and 106% and of CGA 48988 tech. 123, 107, 103 and 103% of the nominal concentrations in dose groups 2, 3, 4 and 5, respectively (RCC Project no. 365894, see Appendix B of this report).

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CGA 329351 tech.

TEST MATERIAL CONTENT

	GROUP 2	GROUP 3	GROUP 4	GROUP 5
NOMINAL (mg/ml)	1	5	15	30
ANALYTICAL (mg/ml)				
study week: 1	1.126	5.359	15.59	32.33
2	1.077	5.316	15.74	31.95
3	1.141	5.406	15.89	31.99
4	0.908	5.038	15.28	30.47
MEAN 1 - 4 ( % )	106.3	105.6	104.2	105.6

CGA 48988 tech.

TEST MATERIAL CONTENT

	GROUP 2	GROUP 3	GROUP 4	GROUP 5
NOMINAL (mg/ml)	1	5	15	30
ANALYTICAL (mg/ml)				
study week: 1	1.592/1.542	5.200	14.12	30.01
2	1.120	5.203	15.59	31.33
3	1.150	5.577	15.90	31.41
4	1.092	5.395	16.18	30.80
MEAN 1 - 4 ( % )	123.2	106.9	103.0	103.0

#### 4.2. In-life observations

The clinical signs observed in the course of the study are presented in the appendix section of this report and in the following summary table. Identical observations occurring repeatedly in the same animal are indicated only once in the summary table.

##### CGA 329351 tech.

After the first administration of CGA 329351 tech., all animals of groups 4 and 5 (150 and 300 mg/kg) showed hypoactivity. Two female animals of group 5 became prostrate.

Occurrence of these signs was restricted to within the first two hours after the first dosing. For the remaining part of the treatment period, normal behaviour was observed.

Other signs noted were considered of no toxicological relevance.

##### CGA 48988 tech.

No signs of toxicological relevance were observed during the treatment period.

INCIDENCES OF IN-LIFE OBSERVATIONS

CGA 329351 tech.

OBSERVATIONS	males					females				
	1	2	3	4	5	1	2	3	4	5
Group:										
hypoactivity	-	-	-	5	5	-	-	-	5	5
prostrate	-	-	-	-	-	-	-	-	-	2
skin lesion	-	-	2	1	2	-	-	-	-	-
no findings	5	5	3	0	0	5	5	5	0	0

CGA 48988 tech.

OBSERVATIONS	males					females				
	1	2	3	4	5	1	2	3	4	5
Group:										
dyspnea	-	-	-	-	-	-	-	1	-	-
hair loss	-	-	-	-	-	-	-	-	1	-
no findings	5	5	5	5	5	5	5	4	4	5

#### 4.3. Mortality

All animals survived the 28 days treatment with either CGA 329351 tech. or CGA 48988 tech.

#### 4.4. Bodyweight

Mean bodyweight values are presented in the following tables and plots. The individual bodyweight values collected during the study and the results of the statistical analysis of these data are filed in the appendix sections of this report.

Compared with the control group, treatment with either CGA 329351 tech. or CGA 48988 tech. did not affect the bodyweight development in any treated group.

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CGA 329351 tech.

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$

JONCKHEERE: +- if  $p_J < 0.01$

Bodyweight (means) : males  
 (g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	142.8	140.9	137.5*	137.6*	139.1
1	182.2	184.3	178.1	172.8	179.4
2	232.6	236.8	225.2	223.4	224.3
3	282.6	290.4	275.2	272.5	274.6
4	322.0	325.1	317.2	310.4	311.3

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$

JONCKHEERE: +- if  $p_J < 0.01$

Bodyweight (means) : females  
 (g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	155.1	157.2	157.0	155.7	156.6
1	185.8	181.1	178.2	173.0	183.4
2	200.5	203.5	201.8	188.7	202.5
3	221.5	226.8	222.4	215.7	224.3
4	235.8	233.6	235.7	229.5	238.1

CGA 48988 tech.

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$

JONCKHEERE: +- if  $p_J < 0.01$

Bodyweight (means) : males  
 (g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	142.8	135.8*-	136.6*	136.8*	136.2*
1	182.2	177.1	175.1	175.1	182.0
2	232.6	228.9	223.1	225.3	235.5
3	282.6	288.6	276.4	276.7	287.5
4	322.0	324.1	309.7	310.9	325.5

Statistical tests and flags used:

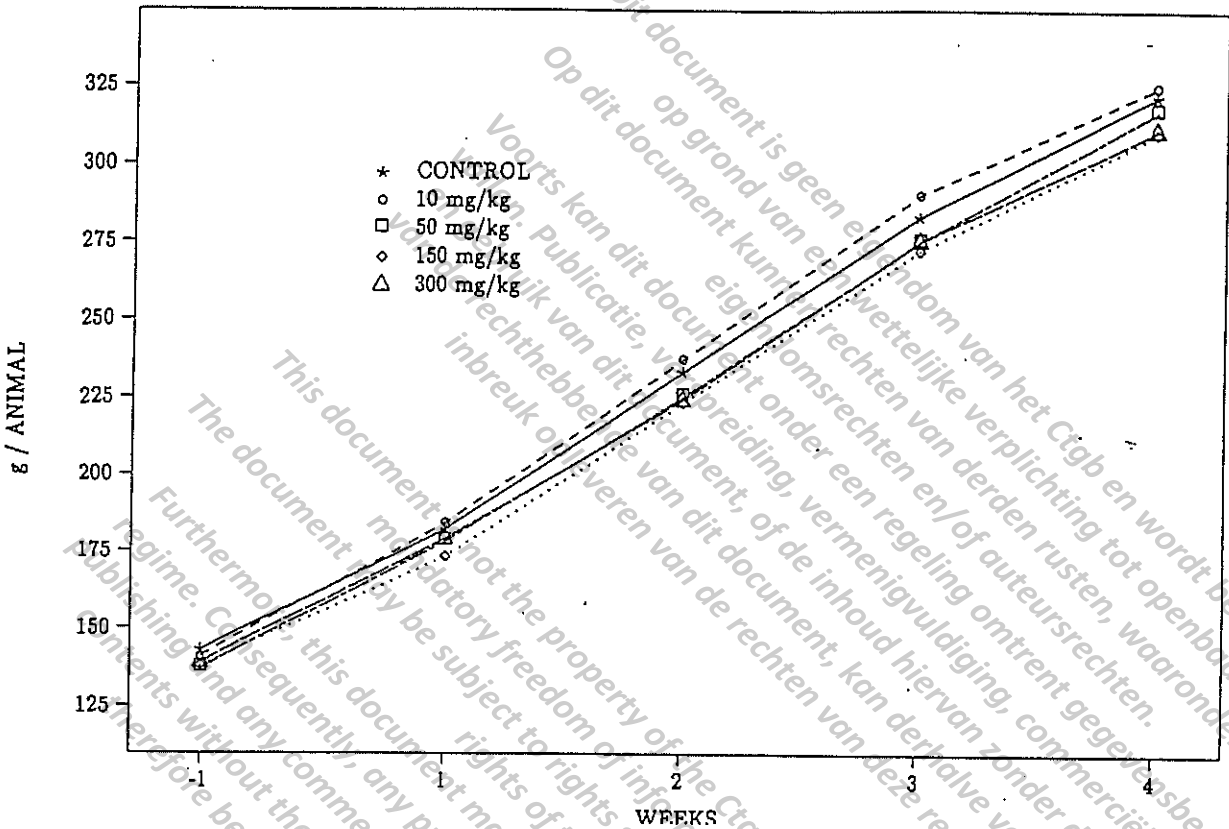
WILCOXON: \* if  $p_W < 0.05$

JONCKHEERE: +- if  $p_J < 0.01$

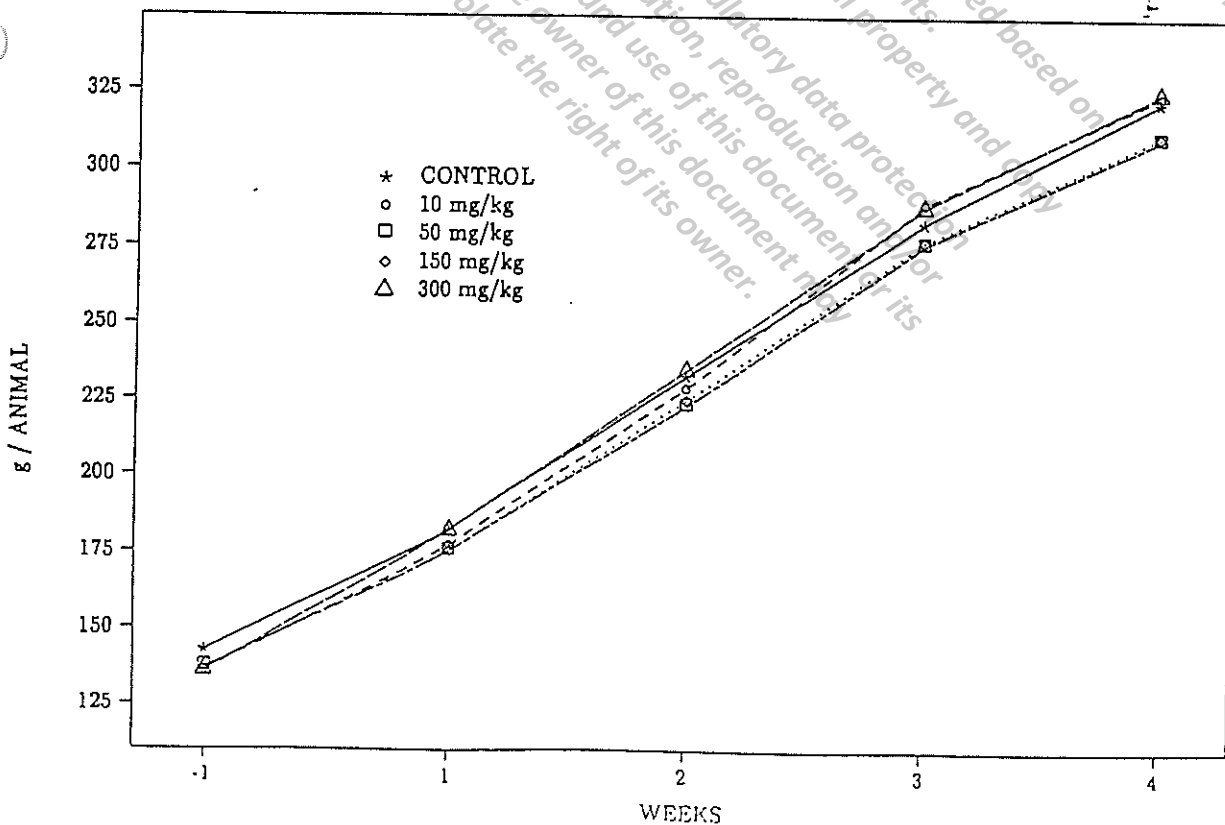
Bodyweight (means) : females  
 (g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	155.1	150.9	148.6	147.7*	151.3
1	185.8	178.1	180.3	182.9	183.1
2	200.5	200.6	203.2	208.2	203.5
3	221.5	228.1	230.1	232.7	230.2
4	235.8	248.4	244.7	243.3	246.9

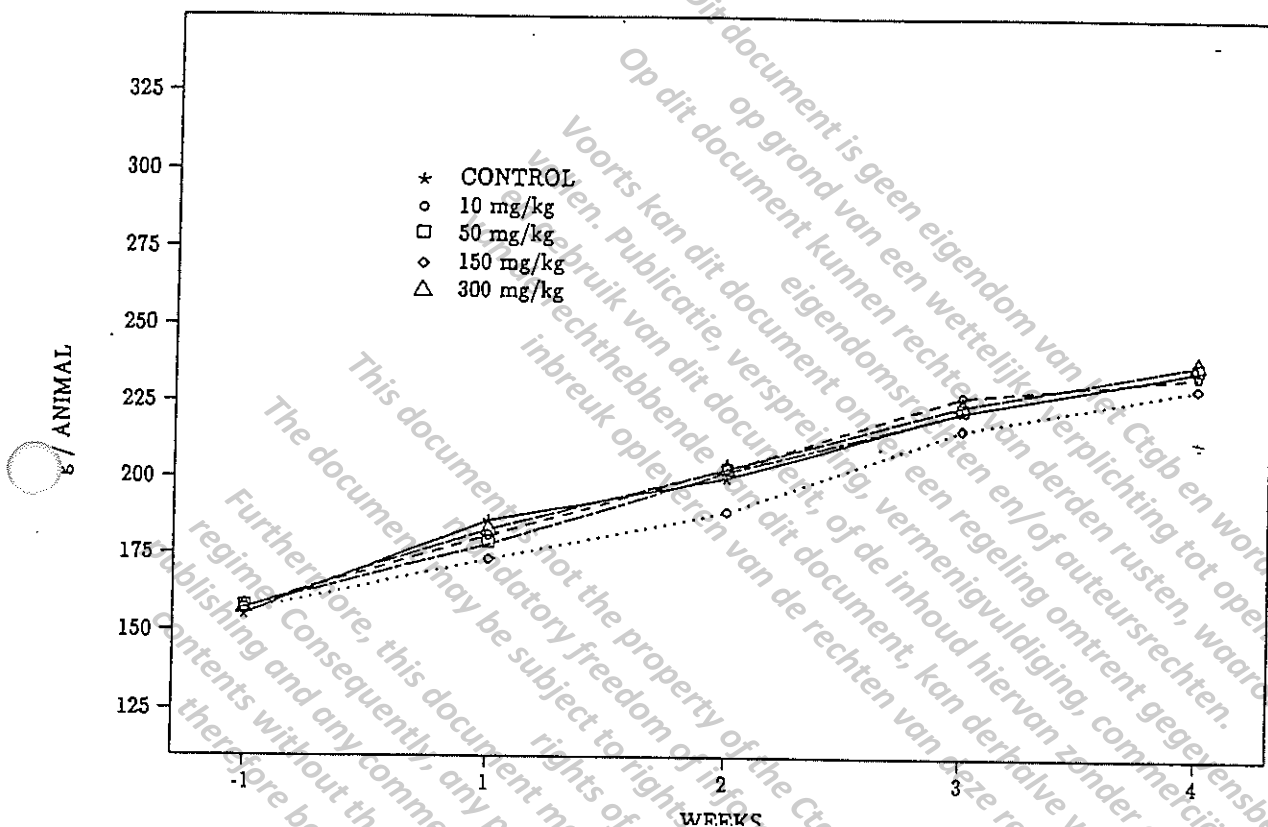
MEAN BODYWEIGHT / MALES  
CGA 329351 tech.



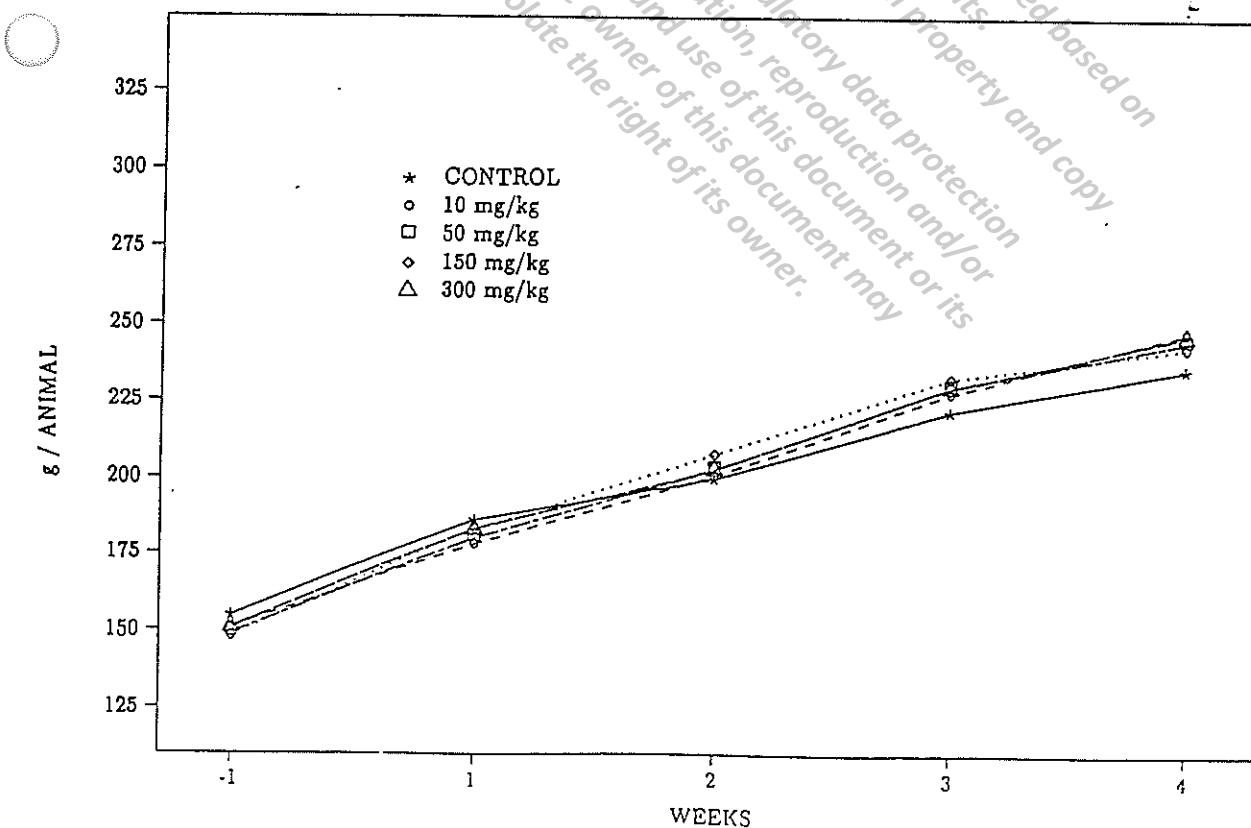
MEAN BODYWEIGHT / MALES  
CGA 48988 tech.



MEAN BODYWEIGHT / FEMALES  
 CGA 329351 tech.



MEAN BODYWEIGHT / FEMALES  
 CGA 48988 tech.





#### 4.5. Food consumption

Mean food consumption values are presented in the following tables and plots.

The individual food consumption was calculated from the food consumption per cage and the number of animals present. Therefore no statistics are given.

##### CGA 329351 tech.

The overall food intake (weeks 1-4) of animals treated with CGA 329351 tech. was comparable to that of the respective control group.

##### CGA 48988 tech.

Treatment with CGA 48988 tech. was considered not to have influenced the mean food consumption of the treated groups.

Since no logical dose dependency existed, the increased mean food intake of all treated female groups at weeks 2 and 3 was considered to reflect normal biological variability.

CGA 329351 tech.

No statistical tests performed

Food consumption (means, determined cagewise) : males  
 (g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	125.5	126.5	126.8	126.3	126.5
1	146.3	154.4	145.2	141.2	145.4
2	176.0	178.2	174.6	168.6	164.4
3	184.7	188.0	193.1	185.0	182.1
4	184.9	195.4	194.5	182.7	177.7

No statistical tests performed

Food consumption (means, determined cagewise) : females  
 (g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	124.6	121.0	116.9	117.2	121.8
1	115.7	112.2	116.1	107.0	115.0
2	124.0	127.3	129.6	125.1	127.8
3	134.1	130.3	124.8	137.8	127.7
4	139.2	129.0	132.1	135.0	125.9

CGA 48988 tech.

No statistical tests performed

Food consumption (means, determined cagewise) : males  
 (g/animal/week)

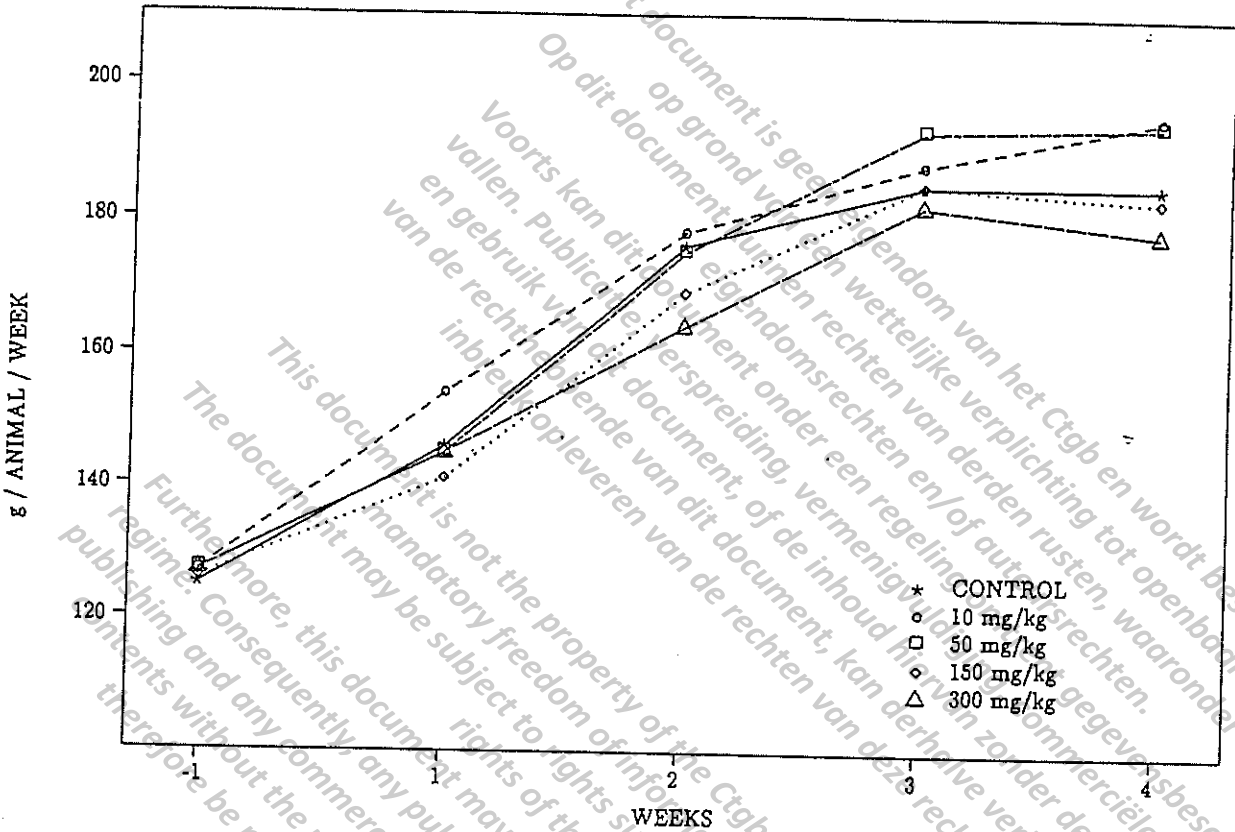
Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	125.5	125.4	125.2	126.4	126.6
1	146.3	140.2	146.0	138.8	149.8
2	176.0	179.8	172.1	169.1	169.6
3	184.7	193.0	188.5	184.2	185.1
4	184.9	191.6	185.4	183.8	185.2

No statistical tests performed

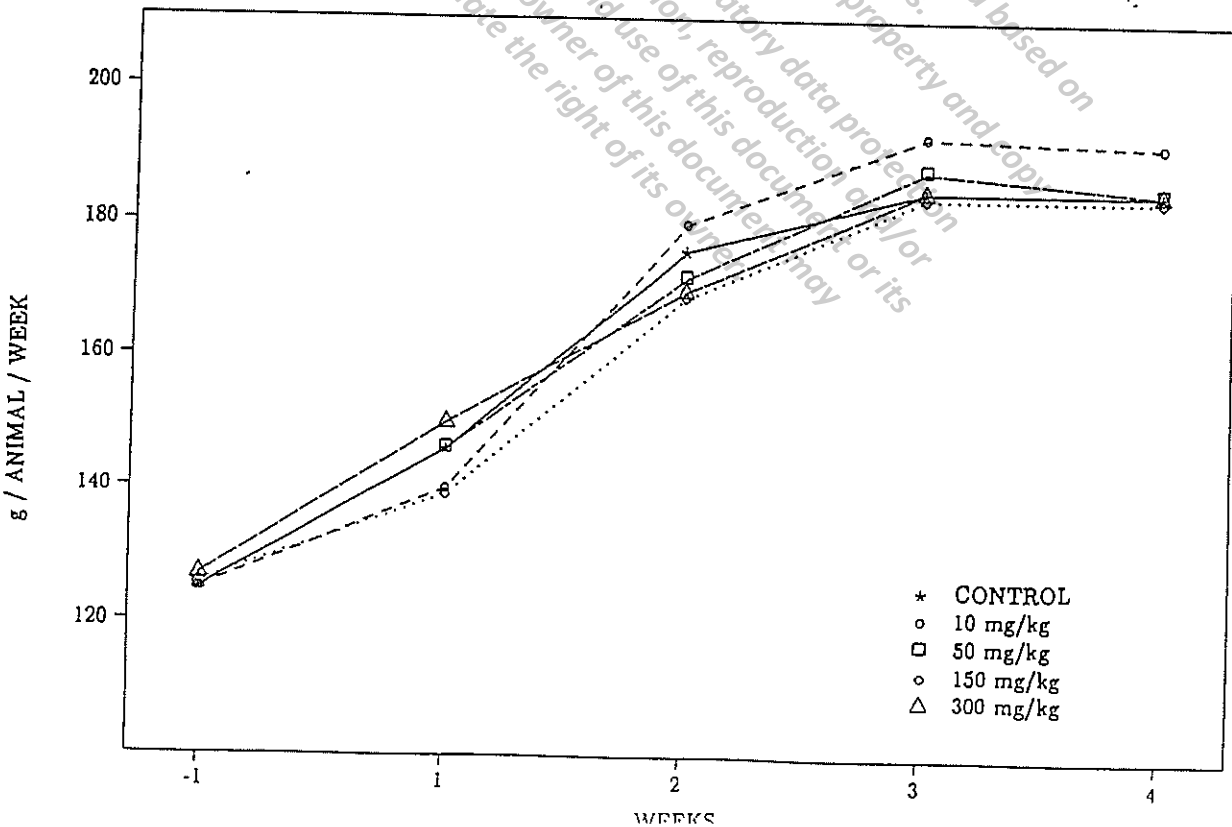
Food consumption (means, determined cagewise) : females  
 (g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	124.6	120.5	119.9	121.1	124.8
1	115.7	120.2	116.2	118.0	122.3
2	124.0	132.2	132.8	131.0	137.0
3	134.1	149.5	141.8	142.7	143.7
4	139.2	141.4	129.5	134.6	141.7

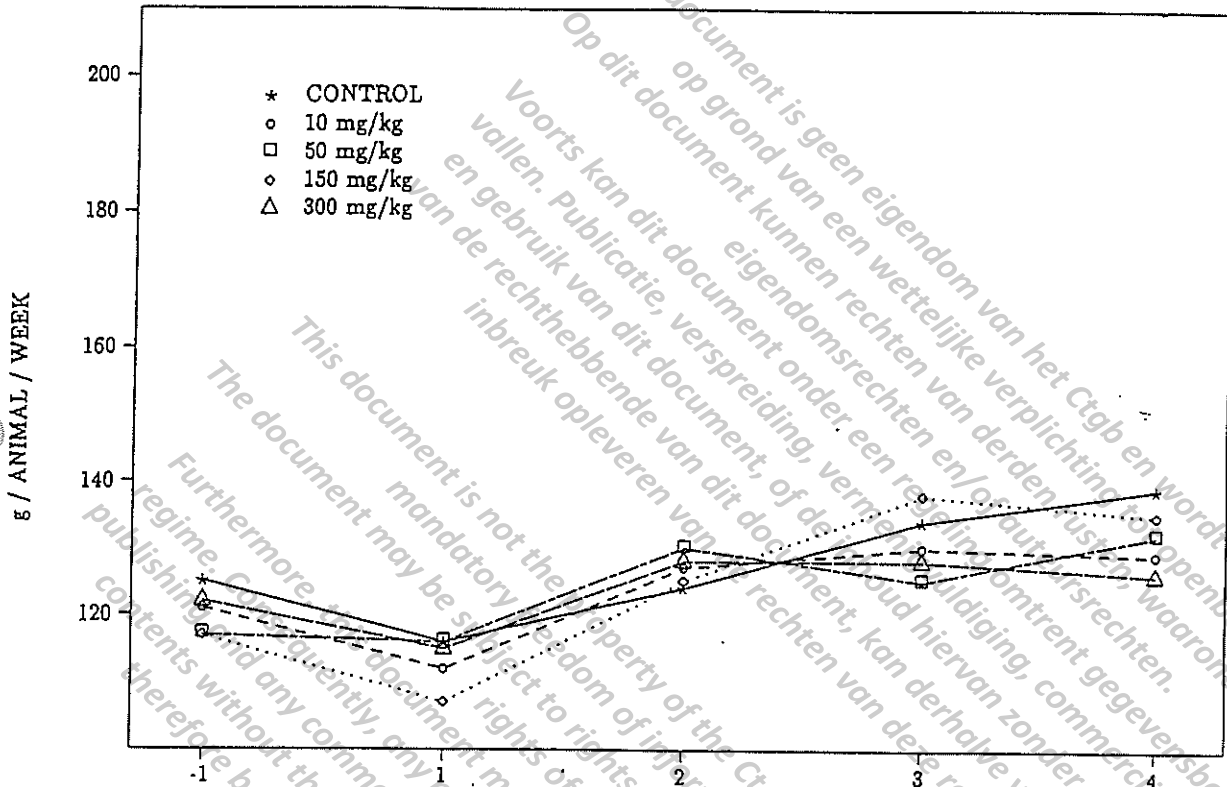
MEAN FOOD CONSUMPTION / MALES  
 CGA 329351 tech.



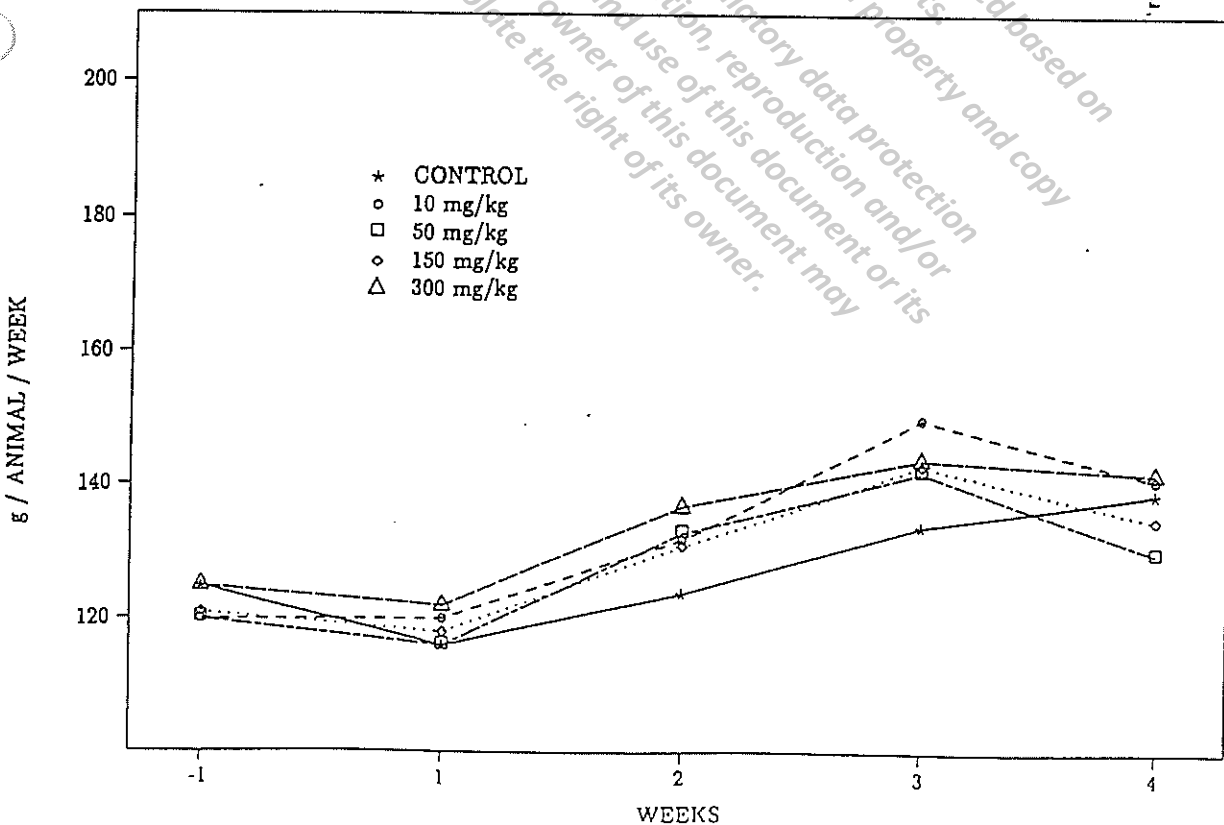
MEAN FOOD CONSUMPTION / MALES  
 CGA 48988 tech.



MEAN FOOD CONSUMPTION / FEMALES  
 CGA 329351 tech.



MEAN FOOD CONSUMPTION / FEMALES  
 CGA 48988 tech.



#### 4.6. Food consumption ratios

Mean food consumption ratios are presented in the following tables and plots. Statistical analysis of these data was not performed.

Mean food consumption ratios did not reveal an effect due to the treatment with either CGA 329351 tech. or CGA 48988 tech.

Since no dose dependency was noted, the minor differences between treated and control groups were considered a reflection of natural variability.

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.No statistical tests performedFood consumption ratios (means, determined cagewise) : males  
(g food/kg bodyweight/day)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	125.5	128.3	131.8	131.1	130.0
1	114.8	120.2	116.8	116.8	116.2
2	108.4	108.2	111.3	107.9	105.2
3	93.59	93.09	100.7	97.07	94.98
4	82.24	86.63	87.93	84.17	81.81

No statistical tests performedFood consumption ratios (means, determined cagewise) : females  
(g food/kg bodyweight/day)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	114.9	110.0	106.4	107.6	111.2
1	89.07	88.79	93.16	88.62	89.78
2	88.51	89.40	91.94	94.86	90.61
3	86.60	82.23	80.42	91.49	81.72
4	84.37	79.15	80.32	84.18	75.76

CGA 48988 tech.

No statistical tests performed

Food consumption ratios (means, determined cagewise) : males  
 (g food/kg bodyweight/day)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	125.5	132.0	131.0	132.1	132.9
1	114.8	113.6	119.1	113.4	117.8
2	108.4	112.9	110.4	107.4	103.2
3	93.59	96.09	97.58	95.36	92.21
4	82.24	84.94	85.63	84.67	81.53

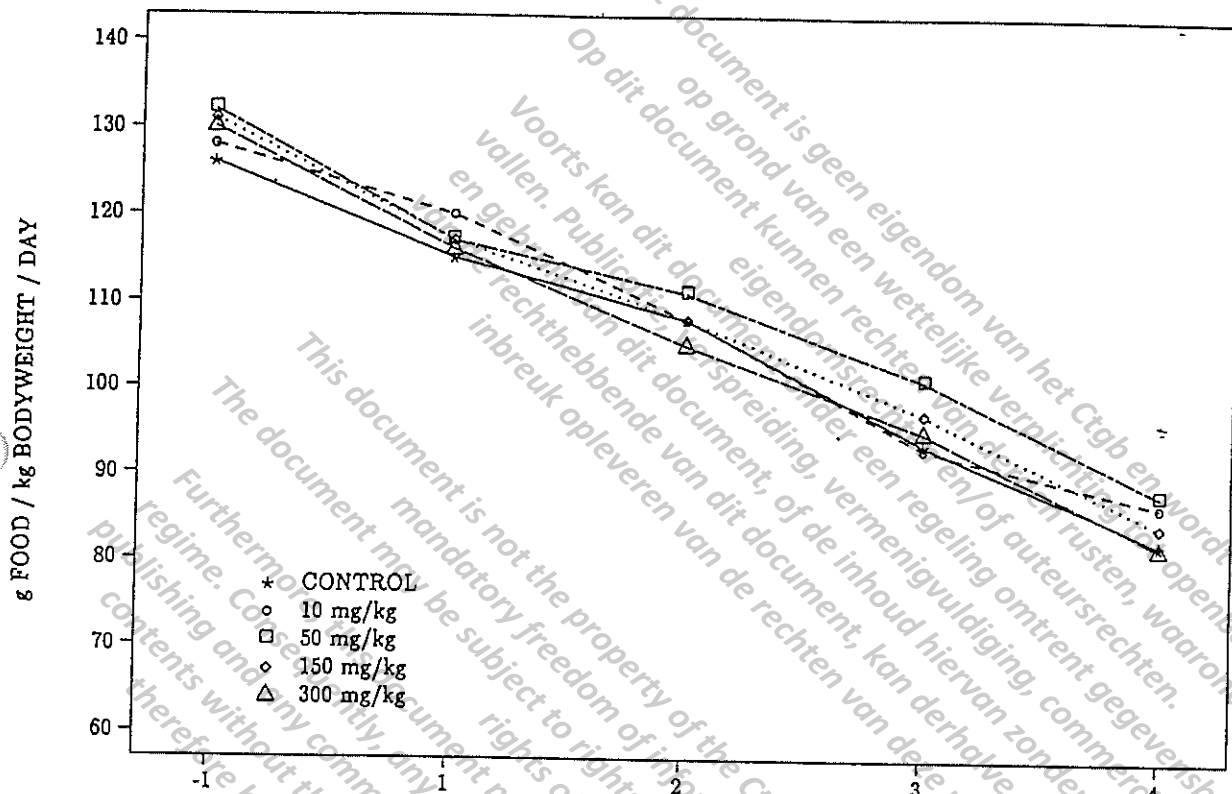
No statistical tests performed

Food consumption ratios (means, determined cagewise) : females  
 (g food/kg bodyweight/day)

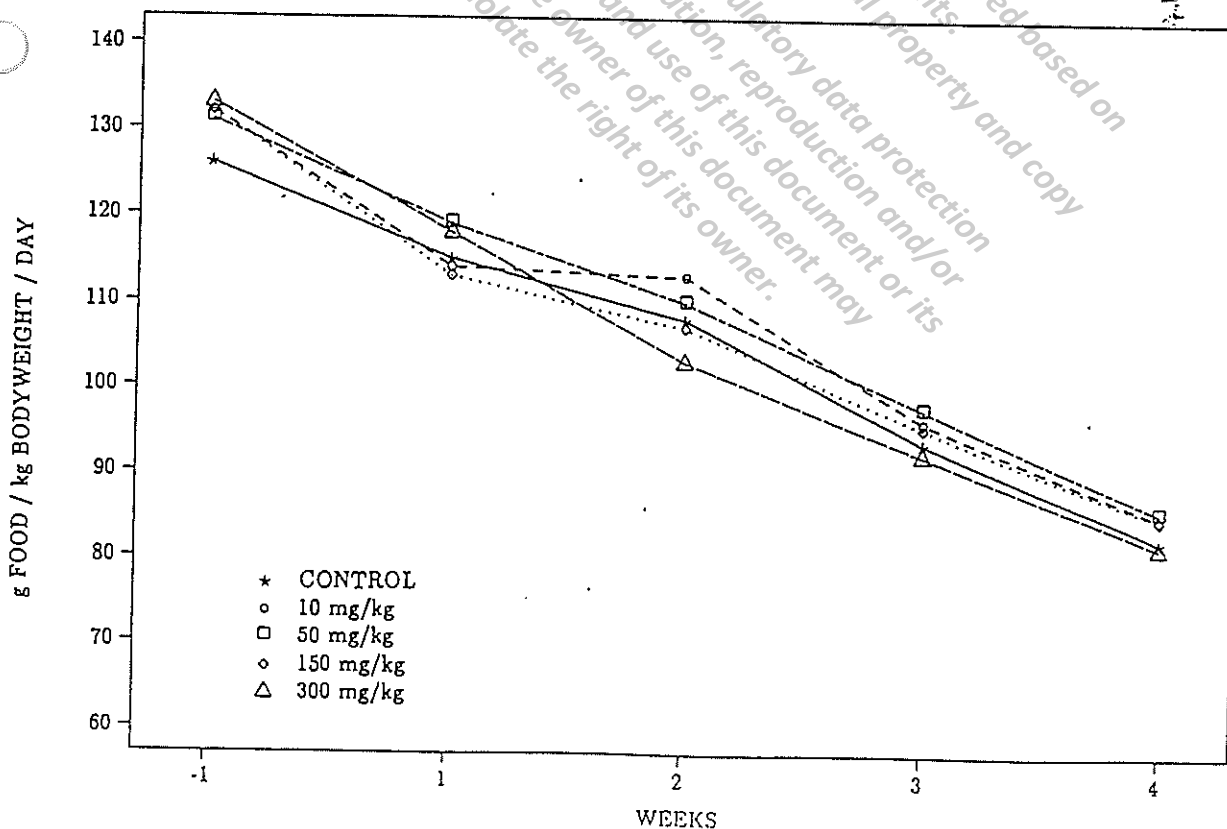
Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	114.9	114.2	115.3	117.2	117.9
1	89.07	96.45	92.10	92.62	95.59
2	88.51	94.34	93.52	90.19	96.45
3	86.60	93.71	88.49	88.16	89.37
4	84.37	81.53	75.95	79.46	82.13



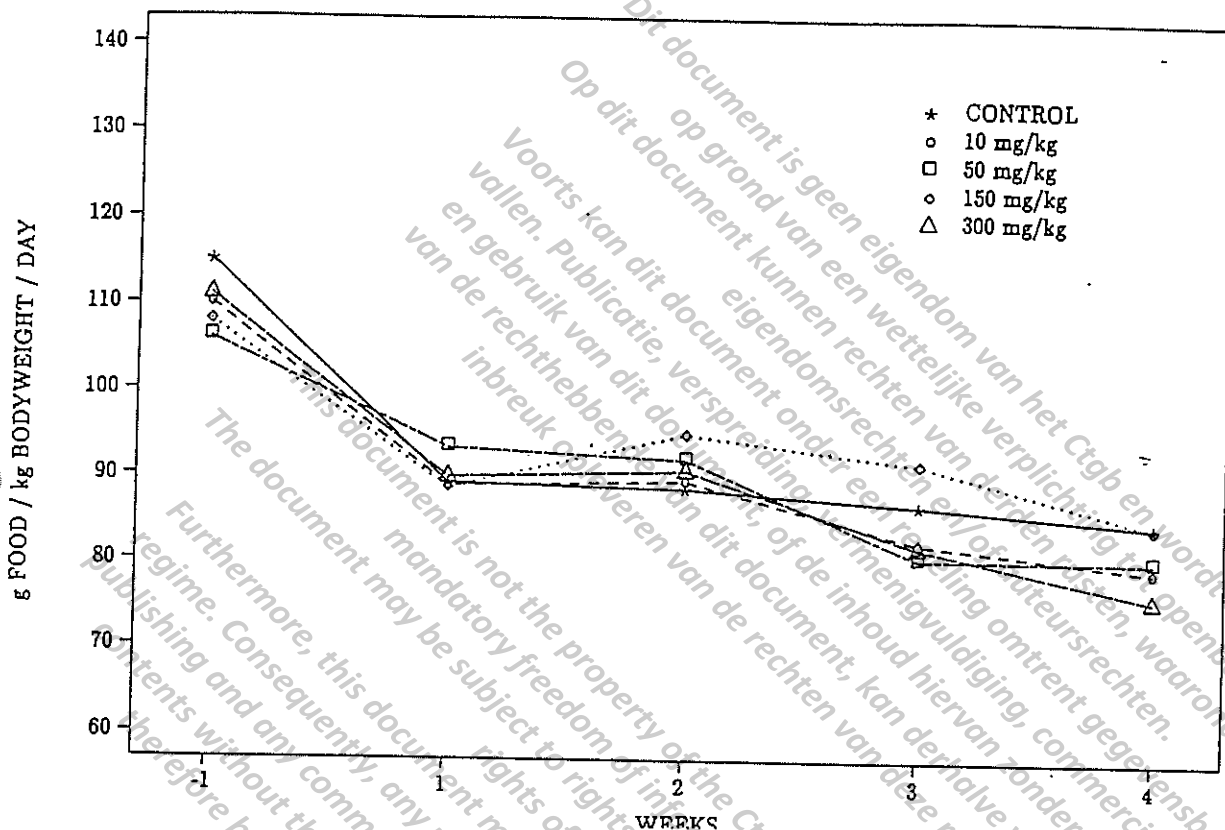
FOOD CONSUMPTION RATIOS / MALES  
 CGA 329351 tech.



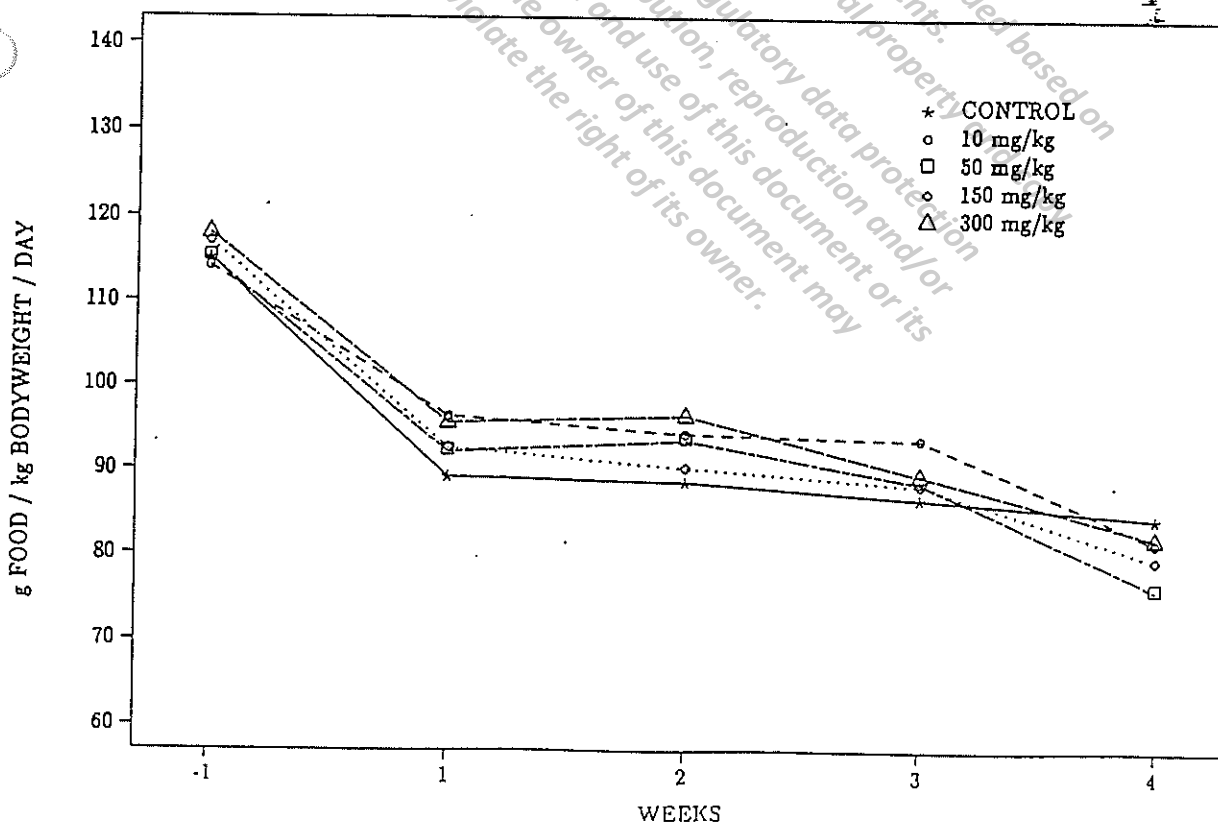
FOOD CONSUMPTION RATIOS / MALES  
 CGA 48988 tech.



FOOD CONSUMPTION RATIOS / FEMALES  
 CGA 329351 tech.



FOOD CONSUMPTION RATIOS / FEMALES  
 CGA 48988 tech.



#### 4.7. Water consumption

Mean water consumption values are presented in the following tables and plots. The individual water consumption was calculated from the water consumption per cage and the number of animals present. Therefore no statistics are given.

##### CGA 329351 tech.

The mean water consumption of the male high dose group (300 mg/kg) was reduced throughout the treatment period.

Mean water intake of the other treated groups was essentially similar to that of the respective control group.

##### CGA 48988 tech.

During the treatment period the mean water consumption of group 5 (300 mg/kg) was increased, resulting in mean overall intakes (weeks 1-4) of 10% in males and 22% in females above the respective control value.

The mean water intake of the other treated groups were considered to reflect the range of normal physiological variability.

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.No statistical tests performedWater consumption (means, determined cagewise) : males  
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	168.6	175.7	168.6	174.6	170.7
1	206.1	199.5	204.5	205.4	188.3
2	218.3	229.5	223.7	240.8	197.8
3	246.0	285.2	244.7	246.7	228.6
4	277.8	281.5	271.5	297.2	239.7

No statistical tests performedWater consumption (means, determined cagewise) : females  
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	158.8	192.6	160.4	170.2	165.5
1	178.9	174.9	176.7	182.4	184.5
2	155.0	185.4	171.5	183.5	177.0
3	197.5	220.4	196.0	222.2	182.8
4	194.6	198.2	221.6	224.3	213.1

CGA 48988 tech.

No statistical tests performed

Water consumption (means, determined cagewise) : males  
 (g/animal/week)

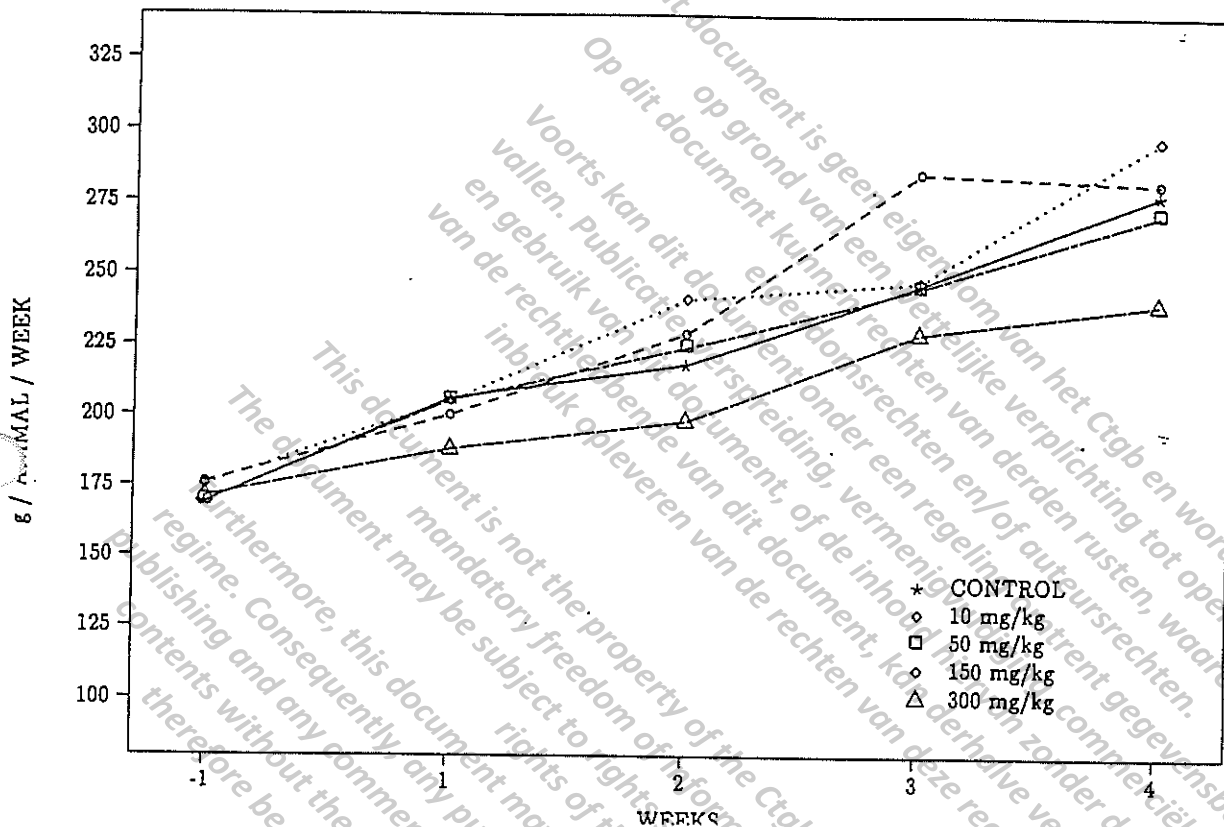
Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	168.6	139.0	173.6	156.4	163.4
1	206.1	180.7	190.0	180.3	209.0
2	218.3	235.1	208.2	194.6	232.7
3	246.0	270.2	240.8	246.5	284.6
4	277.8	264.3	245.8	249.5	321.3

No statistical tests performed

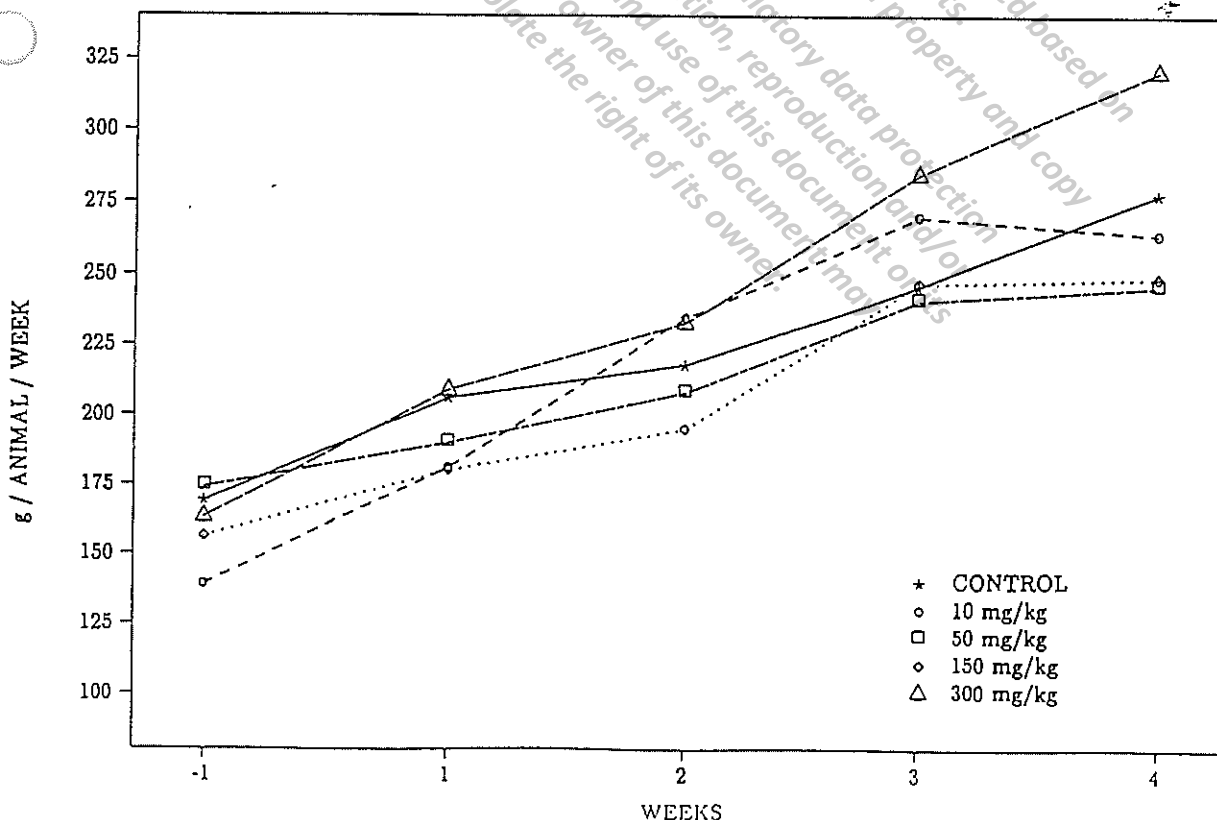
Water consumption (means, determined cagewise) : females  
 (g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: -1	158.8	175.1	184.5	156.1	180.3
1	178.9	203.7	181.3	188.7	238.8
2	155.0	194.3	189.6	182.4	199.5
3	197.5	222.2	202.9	208.9	221.2
4	194.6	214.5	173.2	172.8	227.5

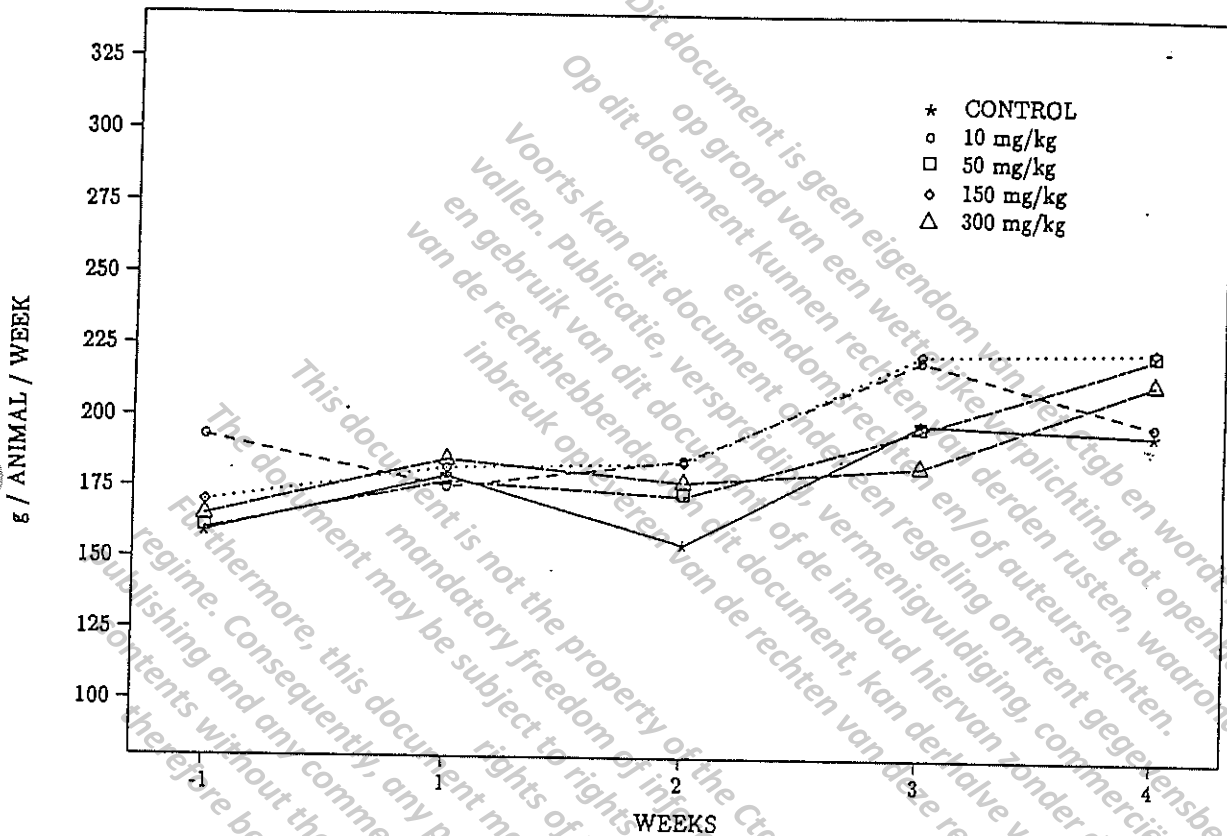
MEAN WATER CONSUMPTION / MALES  
CGA 329351 tech.



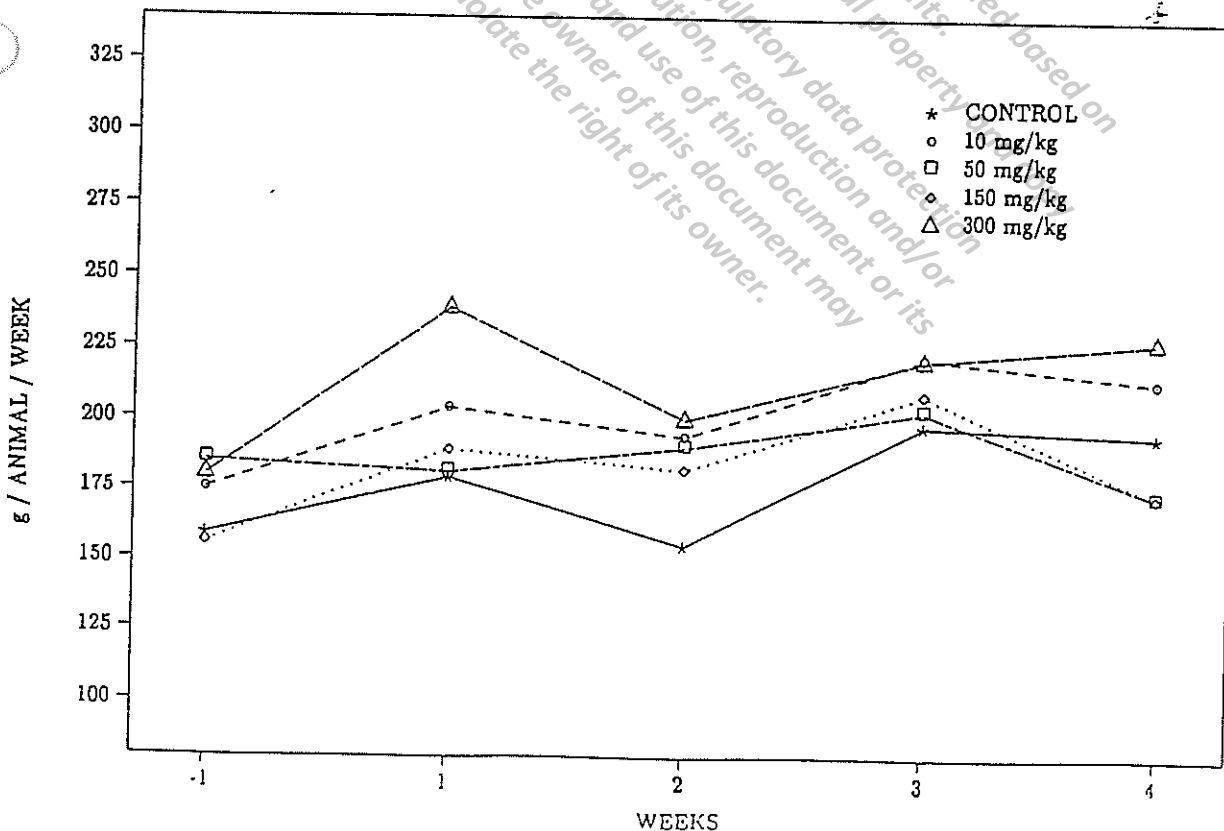
MEAN WATER CONSUMPTION / MALES  
CGA 48988 tech.



MEAN WATER CONSUMPTION / FEMALES  
 CGA 329351 tech.



MEAN WATER CONSUMPTION / FEMALES  
 CGA 48988 tech.



Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

#### 4.8. Hematology

Mean values are presented in the following tables. Individual values and their statistics are given in the Appendices A and B of this report. Reference values from previous studies are given in Appendix C.

The treatment with CGA 329351 tech. and CGA 48988 tech. had no influence on the hematological profile.

Shorter prothrombin times as observed in high dose males treated with CGA 329351 tech. are without any toxicological relevance. Other inter-group differences attaining a level of statistical significance reflect the physiological variation of the parameters and were therefore considered not to be treatment-related.

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Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

CGA 329351 tech.

Hematology (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
RBC (T/l) week: 5	7.518	7.342	7.416	7.688	7.226
Hb (mmol/l) week: 5	9.380	9.460	9.560	9.460	9.140
Hct (l) week: 5	0.452	0.455	0.450	0.455	0.440
MCV (fl) week: 5	60.08	62.01	60.72	59.24	60.86
RDW (l) week: 5	0.121	0.122	0.122	0.126*	0.121
MCH (fmol) week: 5	1.252	1.287	1.292	1.236	1.262
MCHC (mmol/l) week: 5	20.80	20.78	21.26*+	20.82	20.78
HDW (mmol/l) week: 5	1.374	1.367	1.300	1.448	1.448
WBC (G/l) week: 5	18.90	12.65*	14.19	17.08	13.00*
Neut (l) week: 5	0.074	0.103	0.084	0.075	0.106
Eos (l) week: 5	0.005	0.008	0.007	0.008	0.006

CGA 329351 tech.

Hematology (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Baso (1) week: 5	0.007	0.005*	0.006	0.006	0.005*
Lympho (1) week: 5	0.839	0.810	0.827	0.829	0.815
Mono (1) week: 5	0.040	0.037	0.043	0.043	0.037
Luc (1) week: 5	0.034	0.038	0.033	0.040	0.032
Neut (G/l) week: 5	1.394	1.213	1.146	1.260	1.282
Eos (G/l) week: 5	0.098	0.093	0.096	0.122	0.068
Baso (G/l) week: 5	0.134	0.058*	0.084	0.106	0.062*
Lympho (G/l) week: 5	15.84	10.37*	11.79	14.12	10.69*
Mono (G/l) week: 5	0.774	0.465	0.620	0.772	0.480
Luc (G/l) week: 5	0.656	0.452*	0.454*	0.688	0.426
Plt (G/l) week: 5	1054	1101	1077	1163	996.2
PT(CS) (sec) week: 5	35.82	33.43	34.24	34.83	30.22*

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Hematology (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
RBC (T/l) week: 5	7.978	7.558	7.702	7.474*	7.716
Hb (mmol/l) week: 5	9.700	9.480	9.740	9.260*	9.440
Hct (l) week: 5	0.452	0.439	0.453	0.431	0.438
MCV (fl) week: 5	56.74	58.16	58.80	57.70	56.88
RDW (1) week: 5	0.117	0.116	0.113	0.120	0.113
MCH (fmol) week: 5	1.216	1.252	1.262	1.238	1.226
MCHC (mmol/l) week: 5	21.44	21.52	21.49	21.45	21.55
HDW (mmol/l) week: 5	1.246	1.428	1.284	1.378	1.276
WBC (G/l) week: 5	11.34	14.28	12.37	12.65	13.19
Neut (1) week: 5	0.053	0.046	0.057	0.074	0.068
Eos (1) week: 5	0.010	0.007	0.009	0.016	0.008

CGA 329351 tech.

Hematology (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Baso (1) week: 5	0.005	0.006	0.005	0.004	0.005
Lympho (1) week: 5	0.855	0.884*	0.870	0.838	0.863
Mono (1) week: 5	0.047	0.031	0.034	0.039	0.030
Luc (1) week: 5	0.030	0.026	0.025	0.029	0.026
Neut (G/l) week: 5	0.606	0.638	0.720	0.942	0.870*
Eos (G/l) week: 5	0.112	0.102	0.114	0.240	0.092
Baso (G/l) week: 5	0.056	0.080	0.066	0.060	0.072
Lympho (G/l) week: 5	9.674	12.66	10.76	10.57	11.42
Mono (G/l) week: 5	0.550	0.432	0.406	0.470	0.390
Luc (G/l) week: 5	0.342	0.370	0.304	0.366	0.342
Plt (G/l) week: 5	1153	1146	1083	1089	1129
PT(CS) (sec) week: 5	27.19	30.58*	28.38	29.80	28.49

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Hematology (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
RBC (T/l) week: 5	7.518	7.432	7.206	7.380	7.262
Hb (mmol/l) week: 5	9.380	9.560	8.960	9.440	9.180
Hct (l) week: 5	0.452	0.463	0.428	0.453	0.445
MCV (fl) week: 5	60.08	62.40	59.44	61.47	61.28
RDW (l) week: 5	0.121	0.122	0.122	0.122	0.124
MCH (fmol) week: 5	1.252	1.290	1.244	1.279	1.268
MCHC (mmol/l) week: 5	20.80	20.66	20.93	20.83	20.67
HDW (mmol/l) week: 5	1.374	1.356	1.422	1.355	1.458
WBC (G/l) week: 5	18.90	20.08	17.69	18.41	16.00
Neut (l) week: 5	0.074	0.072	0.114	0.090	0.072
Eos (l) week: 5	0.005	0.005	0.005	0.009	0.007

CGA 48988 tech.

Hematology (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Baso (1) week: 5	0.007	0.008	0.006	0.007	0.006
Lympho (1) week: 5	0.839	0.843	0.808	0.824	0.854
Mono (1) week: 5	0.040	0.040	0.039	0.040	0.037
Luc (1) week: 5	0.034	0.032	0.028	0.032	0.025*-
Neut (G/l) week: 5	1.394	1.410	1.600	1.516	1.148
Eos (G/l) week: 5	0.098	0.098	0.104	0.145	0.106
Baso (G/l) week: 5	0.134	0.156	0.120	0.128	0.094
Lympho (G/l) week: 5	15.84	16.93	14.58	15.31	13.67
Mono (G/l) week: 5	0.774	0.824	0.742	0.712	0.586
Luc (G/l) week: 5	0.656	0.654	0.528	0.590	0.400*
Plt (G/l) week: 5	1054	1090	1062	1071	1179
PT(CS) (sec) week: 5	35.82	34.07	34.11	31.51	33.37

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

CGA 48988 tech.

Hematology (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
RBC (T/l) week: 5	7.978	7.654*	7.448*	7.476	7.542
Hb (mmol/l) week: 5	9.700	9.500	9.460	9.380	9.440
Hct (l) week: 5	0.452	0.444	0.443	0.439	0.443
MCV (fl) week: 5	56.74	58.00	59.56**	58.74	58.82*
RDW (l) week: 5	0.117	0.112	0.114	0.114	0.114
MCH (fmol) week: 5	1.216	1.240	1.268 +	1.260	1.256
MCHC (mmol/l) week: 5	21.44	21.37	21.29	21.40	21.30
HDW (mmol/l) week: 5	1.246	1.240	1.204	1.388	1.260
WBC (G/l) week: 5	11.34	12.75	13.20	11.54	11.64
Neut (l) week: 5	0.053	0.054	0.070	0.065	0.053
Eos (l) week: 5	0.010	0.008	0.010	0.010	0.007

CGA 48988 tech.

Hematology (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Baso (1) week: 5	0.005	0.005	0.006	0.004	0.005
Lympho (1) week: 5	0.855	0.865	0.854	0.845	0.861
Mono (1) week: 5	0.047	0.037	0.030	0.043	0.044
Luc (1) week: 5	0.030	0.032	0.030	0.032	0.031
Neut (G/l) week: 5	0.606	0.670	0.974	0.712	0.618
Eos (G/l) week: 5	0.112	0.098	0.136	0.114	0.076
Baso (G/l) week: 5	0.056	0.066	0.074	0.052	0.058
Lympho (G/l) week: 5	9.674	11.04	11.20*	9.778	9.996
Mono (G/l) week: 5	0.550	0.464	0.412	0.504	0.528
Luc (G/l) week: 5	0.342	0.404	0.406	0.380	0.364
Plt (G/l) week: 5	1153	1015	1083	1102	1083
PT(CS) (sec) week: 5	27.19	24.93	27.67	24.06	26.57



#### 4.9. Blood chemistry

Mean values are presented in the following tables. Individual values and their statistics are compiled in the Appendices A and B of this report. Reference values from previous studies are given in Appendix C.

Minimally lower plasma sodium levels, minimally higher plasma chloride levels, and a tendency to lower urea levels were recorded among males treated with 300 mg/kg of CGA 329351 tech. or 300 mg/kg of CGA 48988 tech. In addition, males treated with 300 mg/kg of CGA 329351 tech. had minimally lower plasma bilirubin levels.

Females treated with 300 mg/kg of CGA 329351 tech. and females treated at 150 and 300 mg/kg of CGA 48988 tech. had increased plasma protein levels (albumin and globulin), and minimally lower plasma bilirubin levels.

Other inter-group differences attaining a level of statistical significance reflect the physiological variation of the parameters and were therefore considered not to be treatment-related.

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Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

CGA 329351 tech.

Blood chemistry (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Gluc (mmol/l) week: 5	6.728	7.948*	7.722	7.154	7.662
Urea (mmol/l) week: 5	5.832	5.642	6.086	5.672	4.854*
Creat-e (umol/l) week: 5	57.52	59.80	56.00	59.90	51.92*
Bili-tot (umol/l) week: 5	2.384	2.172	2.242	2.290	1.776*
Prot (g/l) week: 5	66.21	66.82	64.72	66.35	66.52
Alb (g/l) week: 5	38.15	38.55	37.83	38.59	38.23
Glob (g/l) week: 5	28.06	28.27	26.89	27.76	28.30
A/G (1) week: 5	1.364	1.364	1.406	1.392	1.354
Chol (mmol/l) week: 5	2.044	1.856	2.042	1.898	2.106



Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

CGA 329351 tech.

Blood chemistry (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Gluc (mmol/l) week: 5	5.938	7.025	6.198	6.252	5.568
Urea (mmol/l) week: 5	6.030	6.894	7.590*+	6.116	6.152
Creat-e (umol/l) week: 5	57.52	57.72	57.14	51.96	54.60
Bili-tot (umol/l) week: 5	2.478	2.244	2.224	2.152	1.614*
Prot (g/l) week: 5	65.33	65.72	67.10	67.04	69.01*+
Alb (g/l) week: 5	38.58	38.60	38.95	39.40	39.73
Glob (g/l) week: 5	26.74	27.12	28.14*	27.64	29.29*+
A/G (l) week: 5	1.446	1.424	1.382	1.426	1.360*
Chol (mmol/l) week: 5	2.619	2.346	2.580	2.412	2.488



Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

Statistical tests and flags used:WILCOXON: \* if  $p_W < 0.05$ JONCKHEERE: +- if  $p_J < 0.01$ CGA 48988 tech.

## Blood chemistry (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Gluc (mmol/l) week: 5	6.728	7.808	7.568	6.800	6.064
Urea (mmol/l) week: 5	5.832	5.806	5.952	5.526	5.156*
Creat-e (umol/l) week: 5	57.52	53.40	60.00	58.32	56.70
Bili-tot (umol/l) week: 5	2.384	1.871	2.457	2.010	1.918
Prot (g/l) week: 5	66.21	66.88	65.60	66.53	66.65
Alb (g/l) week: 5	38.15	38.84	38.20	38.78	38.03
Glob (g/l) week: 5	28.06	28.35	27.49	27.75	28.62
A/G (1) week: 5	1.364	1.372	1.394	1.404	1.332
Chol (mmol/l) week: 5	2.044	2.030	1.933	1.950	2.088

CGA 48988 tech.

Blood chemistry (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Na+ (mmol/l) week: 5	144.5	141.7	140.7*	141.6	139.9*
K+ (mmol/l) week: 5	3.727	3.502	3.797	3.634	3.540
Ca++ (mmol/l) week: 5	2.774	2.762	2.678*	2.710	2.660*-
Cl- (mmol/l) week: 5	97.34	100.1*	99.60	99.46	100.2*
PO4-in (mmol/l) week: 5	2.402	2.408	2.358	2.308	2.230*
ASAT (GOT) (U/l) week: 5	56.64	55.35	68.20*	52.72	54.60
ALAT (GPT) (U/l) week: 5	38.86	41.04	42.90	32.42*	32.74
AlP (U/l) week: 5	164.8	186.7	156.9	153.7	153.8

## 28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

## Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$ JONCKHEERE: +- if  $p_J < 0.01$ CGA 48988 tech.

## Blood chemistry (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Gluc (mmol/l) week: 5	5.938	5.794	4.872*	5.412	6.384
Urea (mmol/l) week: 5	6.030	6.128	7.343	6.778	5.908
Creat-e (umol/l) week: 5	57.52	54.84	62.24	57.04	51.94
Bili-tot (umol/l) week: 5	2.478	1.894*	2.010	1.730*	1.494*+-
Prot (g/l) week: 5	65.33	65.28	66.46	68.95*	69.56*+
Alb (g/l) week: 5	38.58	38.24	37.70	39.12	40.25*
Glob (g/l) week: 5	26.74	26.95	28.53	29.92*+	29.67*+
A/G (1) week: 5	1.446	1.430	1.330*	1.308*-	1.360 -
Chol (mmol/l) week: 5	2.619	2.340	2.444	2.851	2.720



CGA 48988 tech.

Blood chemistry (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Na+ (mmol/l) week: 5	139.4	142.1*	140.0	140.7	139.9
K+ (mmol/l) week: 5	3.422	3.324	3.382	3.460	3.508
Ca++ (mmol/l) week: 5	2.672	2.586	2.656	2.771	2.621
Cl- (mmol/l) week: 5	100.4	99.70	98.97	98.62*	99.81
PO4-in (mmol/l) week: 5	1.800	1.906	1.806	2.068	1.770
ASAT (GOT) (U/l) week: 5	58.30	48.26*	126.4	53.08	49.28*
ALAT (GPT) (U/l) week: 5	31.92	27.26	46.46	35.98	42.72
AlP (U/l) week: 5	93.24	76.85	116.6	87.56	117.6

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#### 4.10. Organ weights and ratios

Mean organ weights and organ to bodyweight ratios are presented in the following summary tables. The individual organ weights and ratios and the results of the statistical analysis of these data are filed in the appendix sections of this report.

Mean carcass weights of animals treated with either CGA 329351 tech. or CGA 48988 tech. were comparable to those of the control group.

A slight increase (9-12%) in mean absolute liver weights and liver to bodyweight ratios was recorded for high dose males and females treated with CGA 48988 tech. and for high dose females treated with CGA 329351 tech.

Additionally, a few statistically significant differences in absolute and relative organ weights were found. However, these minor variations were considered of no biological relevance.

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4.10.1. Organ weights (means)

CGA 329351 tech.

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

Organ weights (means): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Body (g)	327.6	332.5	325.7	312.9	315.8
Heart (g)	1.158	1.177	1.116	1.110	1.109
Liver (g)	16.71	18.74	17.44	17.52	17.90
Kidney (both) (g)	2.529	2.531	2.435	2.312	2.480
Adrenal (both) (mg)	82.12	80.88	84.28	76.20	79.52
Thymus (mg)	823.3	738.4	767.4	668.9	768.6
Testis (both) (g)	3.445	3.418	3.402	3.370	3.428
Spleen (g)	0.726	0.701	0.671	0.737	0.637
Thyroid gland (mg)	23.40	20.32	24.70	20.74	21.20

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.Statistical tests and flags used:WILCOXON: \* if  $p_W < 0.05$ JONCKHEERE: +- if  $p_J < 0.01$ 

Organ weights (means): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Body (g)	243.7	233.1	235.3	230.7	238.5
Heart (g)	0.906	0.886	0.885	0.930	0.938
Liver (g)	11.39	11.44	11.48	11.58	12.38*
Kidney (both) (g)	1.864	1.851	1.812	1.801	1.939
Adrenal (both) (mg)	80.96	87.52	89.12	89.00	92.62
Thymus (mg)	525.2	550.6	563.3	532.4	562.9
Ovary (both) (mg)	166.6	174.0	170.9	172.6	169.5
Spleen (g)	0.606	0.633	0.633	0.683	0.604
Thyroid gland (mg)	19.34	24.44*	21.42	22.50	17.56

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.Statistical tests and flags used:WILCOXON: \* if  $p_W < 0.05$ JONCKHEERE: +- if  $p_J < 0.01$ 

Organ weights (means): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Body (g)	327.6	328.9	313.0	313.2	325.7
Heart (g)	1.158	1.120	1.092	1.114	1.091
Liver (g)	16.71	17.66	16.68	16.16	18.24
Kidney (both) (g)	2.529	2.445	2.284	2.414	2.413
Adrenal (both) (mg)	82.12	76.68	69.92*	79.24	78.84
Thymus (mg)	823.3	939.3	749.8	891.9	782.0
Testis (both) (g)	3.445	3.357	3.459	3.395	3.471
Spleen (g)	0.726	0.764	0.721	0.706	0.706
Thyroid gland (mg)	23.40	22.50	23.90	22.66	24.00

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

## Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$ JONCKHEERE: +- if  $p_J < 0.01$ 

Organ weights (means): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Body (g)	243.7	240.8	244.3	245.9	244.8
Heart (g)	0.906	0.919	0.878	0.967	0.947
Liver (g)	11.39	10.57*	11.47	12.29	12.80*
Kidney (both) (g)	1.864	2.039	2.058	2.051	2.060
Adrenal (both) (mg)	80.96	85.52	94.46	99.26*	85.62
Thymus (mg)	525.2	598.6	523.7	557.0	583.1
Ovary (both) (mg)	166.6	183.0	172.2	169.6	171.1
Spleen (g)	0.606	0.681*	0.658	0.677	0.657
Thyroid gland (mg)	19.34	20.02	18.22	20.34	18.24

4.10.2. Organ to bodyweight ratios (means)

CGA 329351 tech.

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

Organ to bodyweight ratios (means): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Heart (o/oo)	3.539	3.550	3.432	3.545	3.521
Liver (o/oo)	51.10	56.20	53.42	55.97	56.73
Kidney (both) (o/oo)	7.727	7.586	7.481	7.395	7.868
Adrenal (both) (o/oo)	0.251	0.245	0.257	0.243	0.253
Thymus (o/oo)	2.536	2.194	2.361	2.145	2.463
Testis (both) (o/oo)	10.54	10.31	10.50	10.77	10.87
Spleen (o/oo)	2.218	2.092	2.070	2.357	2.025
Thyroid gland (o/oo)	0.071	0.061	0.076	0.067	0.067

CGA 329351 tech.

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

Organ to bodyweight ratios (means): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Heart (o/oo)	3.709	3.817	3.759	4.028	3.936
Liver (o/oo)	46.76	49.09	48.76	50.17	51.90**
Kidney (both) (o/oo)	7.632	7.958	7.683	7.808	8.136
Adrenal (both) (o/oo)	0.332	0.377*	0.379	0.385	0.389*
Thymus (o/oo)	2.157	2.362	2.397	2.287	2.356
Ovary (both) (o/oo)	0.682	0.754	0.724	0.746	0.710
Spleen (o/oo)	2.489	2.731	2.696	2.966*	2.534
Thyroid gland (o/oo)	0.079	0.106*	0.091	0.097*	0.073

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CGA 48988 tech.

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

Organ to bodyweight ratios (means): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Heart (o/oo)	3.709	3.812	3.588	3.929	3.869
Liver (o/oo)	46.76	43.96	46.88	49.99	52.28*+
Kidney (both) (o/oo)	7.632	8.477	8.416	8.331	8.420
Adrenal (both) (o/oo)	0.332	0.355	0.389	0.407*	0.349
Thymus (o/oo)	2.157	2.486	2.132	2.268	2.374
Ovary (both) (o/oo)	0.682	0.760	0.705	0.690	0.697
Spleen (o/oo)	2.489	2.829*	2.685	2.773	2.691
Thyroid gland (o/oo)	0.079	0.083	0.075	0.083	0.074

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

#### 4.11. Pathology

Detailed findings for individual animals are presented in Appendix B.

The results and the tabulated summaries of the gross pathological and histopathological examination are presented below.

##### **4.11.1. Macroscopical findings**

###### **Animals treated with CGA 329351 tech.:**

A few male rats presented with scab formation on the back, microscopically diagnosed as focal chronic inflammation or ulceration of the skin. The distribution and morphological appearance of these changes did not indicate an association with the treatment.

###### **Animals treated with CGA 48988 tech.:**

In some females a dilatation of the renal pelvis was found at necropsy. Microscopically, no evidence of a treatment-related change of the renal pelvis was seen and, therefore, no toxicological relevance was attributed to the pelvic dilatation observed macroscopically.

The few other findings found in this study occurred in comparable numbers in control and treated groups and were similar to those occurring spontaneously in our colony of rats. Thus, no experimental relevance was attributed to these findings.

Summary tables of macroscopical findings (CGA 329351 tech.)  
(all diagnoses)

SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
-----					
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, selected	5	5	5	5	5
Examined macroscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5
Examined microscopically	5	5	5	5	5

Abbreviations used in pathology tables

S1, S2..... scheduled sacrifice(s)  
MS moribund sacrifice  
FD found dead  
AD accidental death

SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>SKIN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>MAMMARY AREA</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SPLEEN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>MESENTERIC LYMPH NODE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>AXILLARY LYMPH NODE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>STERNUM WITH BONE MARROW</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>FEMUR WITH JOINT</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>SKELETAL MUSCLE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>TRACHEA</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>LUNG</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>HEART</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>AORTA</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>TONGUE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SUBMANDIBULAR SALIVARY GLAND</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>LIVER</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PANCREAS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>OESOPHAGUS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>STOMACH</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SMALL INTESTINE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>LARGE INTESTINE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>KIDNEY</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

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**SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>URINARY BLADDER</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PROSTATE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SEMINAL VESICLE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>TESTIS</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>EPIDIDYMIS</b>					
One organ, damaged at autopsy	(0)	(1)	(0)	(0)	(0)
<b>NO CHANGES OBSERVED</b>					
S1	5	4	5	5	5
Total	5	4	5	5	5
<b>PITUITARY GLAND</b>					
Damaged during autopsy	(1)	(0)	(0)	(0)	(0)
<b>NO CHANGES OBSERVED</b>					
S1	4	5	5	5	5
Total	4	5	5	5	5
<b>ADRENAL GLAND</b>					
One organ, damaged at autopsy	(0)	(1)	(0)	(0)	(0)
<b>NO CHANGES OBSERVED</b>					
S1	5	4	5	5	5
Total	5	4	5	5	5



Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

## SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>THYROID WITH PARATHYROID GLAND</b>					
Damaged during autopsy	(0)	(0)	(0)	(1)	(0)
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	4	5
Total	5	5	5	4	5
<b>THYMUS</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PERIPHERAL NERVE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>BRAIN</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SPINAL CORD</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>EYE WITH OPTIC NERVE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>ORBITAL GLAND</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**EXTRAORBITAL LACRIMAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**ZYMBAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**MUZZLE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**BACK**

**SCAB FORMATION**

S1	0	0	1	1	2
Total	0	0	1	1	2

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SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)

Removal code : all                      Observation period : all

Selected experimental group(s) : all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, <u>selected</u>	5	5	5	5	5
Examined macroscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5
Examined microscopically	5	5	5	5	5

Abbreviations used in pathology tables

S1, S2..... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300

Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**SKIN**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**MAMMARY AREA**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**SPLEEN**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**MESENTERIC LYMPH NODE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**AXILLARY LYMPH NODE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**STERNUM WITH BONE MARROW**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**FEMUR WITH JOINT**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>SKELETAL MUSCLE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>TRACHEA</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>LUNG</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>HEART</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>AORTA</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>TONGUE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SUBMANDIBULAR SALIVARY GLAND</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>LIVER</b>					
<b>MASS</b>					
S1	0	0	1	0	0
Total	0	0	1	0	0
<b>NO CHANGES OBSERVED</b>					
S1	5	5	4	5	5
Total	5	5	4	5	5
<b>PANCREAS</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>OESOPHAGUS</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>STOMACH</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SMALL INTESTINE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>LARGE INTESTINE</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>KIDNEY</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300

Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**RENAL PELVIS**

**DILATATION**

S1	0	0	2	1	1
Total	0	0	2	1	1

**URINARY BLADDER**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**VAGINA**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**UTERUS**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**OVARY**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**PITUITARY GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**ADRENAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>THYROID WITH PARATHYROID GLAND</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>THYMUS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PERIPHERAL NERVE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>BRAIN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SPINAL CORD</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>EYE WITH OPTIC NERVE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>ORBITAL GLAND</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5



**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**EXTRAORBITAL LACRIMAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**ZYMBAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**MUZZLE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

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Summary tables of macroscopical findings (CGA 48988 tech.)  
 (all diagnoses)

SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300

Animals initially in study	5	5	5	5	5
----------------------------	---	---	---	---	---

Treatment ended in observation period, selected	5	5	5	5	5
---	---	---	---	---	---

Examined macroscopically	5	5	5	5	5
S1	5	5	5	5	5
Total	5	5	5	5	5

Examined microscopically	5	5	5	5	5
--------------------------	---	---	---	---	---

Abbreviations used in pathology tables

S1, S2.....	scheduled sacrifice(s)
MS	moribund sacrifice
FD	found dead
AD	accidental death

SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>SKIN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>MAMMARY AREA</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SPLEEN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>MESENTERIC LYMPH NODE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>AXILLARY LYMPH NODE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>STERNUM WITH BONE MARROW</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>FEMUR WITH JOINT</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300

Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**SKELETAL MUSCLE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**TRACHEA**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**LUNG**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**HEART**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**AORTA**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**TONGUE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**SUBMANDIBULAR SALIVARY GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

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SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>LIVER</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PANCREAS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>OESOPHAGUS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>STOMACH</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SMALL INTESTINE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>LARGE INTESTINE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>KIDNEY</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>URINARY BLADDER</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PROSTATE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SEMINAL VESICLE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>TESTIS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>EPIDIDYMIS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PITUITARY GLAND</b>					
Damaged during autopsy	(1)	(0)	(0)	(0)	(0)
NO CHANGES OBSERVED					
S1	4	5	5	5	5
Total	4	5	5	5	5
<b>ADRENAL GLAND</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

THYROID WITH PARATHYROID GLAND

NO CHANGES OBSERVED

S1	5	5	5	5	5
Total	5	5	5	5	5

THYMUS

NO CHANGES OBSERVED

S1	5	5	5	5	5
Total	5	5	5	5	5

PERIPHERAL NERVE

NO CHANGES OBSERVED

S1	5	5	5	5	5
Total	5	5	5	5	5

BRAIN

NO CHANGES OBSERVED

S1	5	5	5	5	5
Total	5	5	5	5	5

SPINAL CORD

NO CHANGES OBSERVED

S1	5	5	5	5	5
Total	5	5	5	5	5

EYE WITH OPTIC NERVE

NO CHANGES OBSERVED

S1	5	5	5	5	5
Total	5	5	5	5	5

ORBITAL GLAND

NO CHANGES OBSERVED

S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**EXTRAORBITAL LACRIMAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**ZYMBAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**MUZZLE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

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SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)

Removal code : all                      Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
-----	-----	-----	-----	-----	-----
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, selected	5	5	5	5	5
Examined macroscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5
Examined microscopically	5	5	5	5	5

=====  
Abbreviations used in pathology tables

S1, S2..... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

=====

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>SKIN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>MAMMARY AREA</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SPLEEN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>MESENTERIC LYMPH NODE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>AXILLARY LYMPH NODE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>STERNUM WITH BONE MARROW</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>FEMUR WITH JOINT</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**SKELETAL MUSCLE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**TRACHEA**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**LUNG**

**MASS**

S1	0	0	1	0	0
Total	0	0	1	0	0

**NO CHANGES OBSERVED**

S1	5	5	4	5	5
Total	5	5	4	5	5

**HEART**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**AORTA**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**TONGUE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**SUBMANDIBULAR SALIVARY GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

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**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>LIVER</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PANCREAS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>OESOPHAGUS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>STOMACH</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SMALL INTESTINE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>LARGE INTESTINE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>KIDNEY</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>RENAL PELVIS</b>					
<b>DILATATION</b>					
S1	0	1	1	1	2
Total	0	1	1	1	2
<b>URINARY BLADDER</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>VAGINA</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>UTERUS</b>					
Damaged during autopsy	(0)	(1)	(0)	(0)	(0)
<b>NO CHANGES OBSERVED</b>					
S1	5	4	5	5	5
Total	5	4	5	5	5
<b>OVARY</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PITUITARY GLAND</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>ADRENAL GLAND</b>					
<b>NO CHANGES OBSERVED</b>					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
<b>THYROID WITH PARATHYROID GLAND</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>THYMUS</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>PERIPHERAL NERVE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>BRAIN</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>SPINAL CORD</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>EYE WITH OPTIC NERVE</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5
<b>ORBITAL GLAND</b>					
NO CHANGES OBSERVED					
S1	5	5	5	5	5
Total	5	5	5	5	5

**SUMMARY OF MACROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined macroscopically	5	5	5	5	5

**EXTRAORBITAL LACRIMAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**ZYMBAL GLAND**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

**MUZZLE**

**NO CHANGES OBSERVED**

S1	5	5	5	5	5
Total	5	5	5	5	5

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4.11.2. Microscopical findings

The following findings were considered related to the treatment with either CGA 329351 tech. or CGA 48988 tech.:

Animals treated with CGA 329351 tech.:

Liver:

Hypertrophy of centrilobular hepatocytes was found in an increased incidence and severity in female animals of group 4 (150 mg/kg) and male and female animals of group 5 (300 mg/kg). Incidence and severity are listed in the table 1.

Table 1:  
 Incidence and severity of findings related to treatment with CGA 329351 tech.

Group	1	2	3	4	5
Dose (mg/kg)	0	10	50	150	300
-----					
Livers examined in males/females	5	5	5	5	5
Hepatocellular hypertrophy in males:					
minimal	0	0	0	0	2
total	0	0	0	0	2
Hepatocellular hypertrophy in females:					
minimal	1	1	0	3	3
moderate	0	0	0	0	2
total	1	1	0	3	5

Animals treated with CGA 48988 tech.:

Liver:

Minimal hypertrophy of centrilobular hepatocytes was found in an increased incidence in female animals of group 5 (300 mg/kg). Incidence and severity are listed in the table 2.

Spleen:

Extramedullary hematopoiesis is known to occur normally in the splenic red pulp of laboratory rats in a low grade; therefore, low graded hematopoiesis was not recorded in the tables. A minimally increased extent of this finding, in the tables recorded as minimal extramedullary hematopoiesis, was noted in a higher number of female animals of groups 4 and 5 (150 and 300 mg/kg) compared with the controls and low dose groups. Incidence and severity are listed in the table 2.





Summary tables of microscopical findings (CGA 329351 tech.)  
 (main diagnoses only)

SUMMARY OF MICROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, selected	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
Examined microscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5

Abbreviations used in pathology tables

S1, S2.... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

**SUMMARY OF MICROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300

Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5

**ORGANS AND TISSUES AS A WHOLE**

**NO CHANGES OBSERVED**

S1	1	0	1	1	0
Total	1	0	1	1	0

**SKIN**

**ULCERATION**

S1	0	0	0	1	1
Total	0	0	0	1	1

**CHRONIC INFLAMMATION**

S1	0	0	1	0	1
Total	0	0	1	0	1

**SPLEEN**

**EXTRAMEDULLARY HAEMATOPOIESIS**

S1	2	1	2	0	0
Total	2	1	2	0	0

**MYOCARDIUM**

**INFLAMMATORY CELL INFILTRATION**

S1	0	1	1	1	1
Total	0	1	1	1	1

**LIVER**

**INFLAMMATORY CELL INFILTRATION**

S1	2	2	1	1	2
Total	2	2	1	1	2

**EXTRAMEDULLARY HAEMATOPOIESIS**

S1	1	0	0	0	0
Total	1	0	0	0	0

**LIVER HEPATOCYTE**

**HYPERTROPHY**

S1	0	0	0	0	2
Total	0	0	0	0	2

SUMMARY OF MICROSCOPICAL FINDINGS IN MALES (CGA 329351 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5
<b>KIDNEY</b>					
<b>INFLAMMATORY CELL INFILTRATION</b>					
S1	0	0	1	0	0
Total	0	0	1	0	0
<b>RENAL TUBULE</b>					
<b>ATROPHY</b>					
S1	1	1	1	1	0
Total	1	1	1	1	0
<b>EPITHELIUM OF RENAL PELVIS</b>					
<b>HYPERPLASIA</b>					
S1	1	0	0	0	0
Total	1	0	0	0	0
<b>TESTIS</b>					
<b>TUBULAR ATROPHY</b>					
S1	1	0	0	0	0
Total	1	0	0	0	0
<b>TESTIS INTERSTITIAL CELL OF LEYDIG</b>					
<b>HYPERPLASIA</b>					
S1	0	0	0	0	1
Total	0	0	0	0	1
<b>ADRENAL CORTEX</b>					
<b>FATTY CHANGE</b>					
S1	0	3	1	2	0
Total	0	3	1	2	0

SUMMARY OF MICROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)

Removal code : all                      Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300

---

Animals initially in study	5	5	5	5	5
----------------------------	---	---	---	---	---

Treatment ended in observation period, selected	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
Examined microscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5

=====  
Abbreviations used in pathology tables

S1, S2..... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

=====

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**SUMMARY OF MICROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5
<b>SPLEEN</b>					
<b>HAEMOSIDEROSIS</b>					
S1	2	1	1	0	1
Total	2	1	1	0	1
<b>EXTRAMEDULLARY HAEMATOPOIESIS</b>					
S1	0	2	2	2	2
Total	0	2	2	2	2
<b>SPLENIC WHITE PULP</b>					
<b>ATROPHY</b>					
S1	0	1	0	1	0
Total	0	1	0	1	0
<b>MYOCARDIUM</b>					
<b>INFLAMMATORY CELL INFILTRATION</b>					
S1	0	0	0	1	0
Total	0	0	0	1	0
<b>LIVER</b>					
<b>INFLAMMATORY CELL INFILTRATION</b>					
S1	1	3	1	3	3
Total	1	3	1	3	3
<b>NODULAR HYPERPLASIA</b>					
S1	0	0	1	0	0
Total	0	0	1	0	0
<b>LIVER HEPATOCYTE</b>					
<b>HYPERTROPHY</b>					
S1	1	1	0	3	5
Total	1	1	0	3	5
<b>KIDNEY</b>					
<b>INFLAMMATORY CELL INFILTRATION</b>					
S1	0	0	1	1	0
Total	0	0	1	1	0
<b>NEPHROCALCINOSIS</b>					
S1	5	5	3	4	5
Total	5	5	3	4	5

SUMMARY OF MICROSCOPICAL FINDINGS IN FEMALES (CGA 329351 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5

RENAL TUBULE

CAST

S1	0	1	0	0	0
Total	0	1	0	0	0

ATROPHY

S1	5	4	2	2	2
Total	5	4	2	2	2

RENAL PELVIS

MACROSCOPICAL CHANGE NOT OBSERVED

S1	0	0	1	1	0
Total	0	0	1	1	0

DILATATION

S1	0	0	1	0	1
Total	0	0	1	0	1

ADRENAL GLAND

SINUSOID CYSTIC DILATATION

S1	0	0	1	0	0
Total	0	0	1	0	0

ADRENAL MEDULLA

One organ, no exam.tech. reasons	(0)	(1)	(0)	(0)	(0)
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Summary tables of microscopical findings (CGA 48988 tech.)  
 (main diagnoses only)

SUMMARY OF MICROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
-----	-----	-----	-----	-----	-----
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, selected	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
Examined microscopically	5	5	5	5	5
S1	5	5	5	5	5
Total	5	5	5	5	5

=====  
Abbreviations used in pathology tables

S1, S2.... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

=====  
 =====



**SUMMARY OF MICROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5

**ORGANS AND TISSUES AS A WHOLE**

**NO CHANGES OBSERVED**

S1	1	1	1	1	0
Total	1	1	1	1	0

**SPLEEN**

**EXTRAMEDULLARY HAEMATOPOIESIS**

S1	2	1	1	1	3
Total	2	1	1	1	3

**MYOCARDIUM**

**INFLAMMATORY CELL INFILTRATION**

S1	0	1	1	3	1
Total	0	1	1	3	1

**LIVER**

**INFLAMMATORY CELL INFILTRATION**

S1	2	2	4	2	4
Total	2	2	4	2	4

**EXTRAMEDULLARY HAEMATOPOIESIS**

S1	1	0	0	0	0
Total	1	0	0	0	0

**LIVER HEPATOCYTE**

**HYPERTROPHY**

S1	0	0	1	0	1
Total	0	0	1	0	1

**KIDNEY**

**INFLAMMATORY CELL INFILTRATION**

S1	0	0	1	1	1
Total	0	0	1	1	1

**RENAL TUBULE**

**ATROPHY**

S1	1	3	1	1	3
Total	1	3	1	1	3

SUMMARY OF MICROSCOPICAL FINDINGS IN MALES (CGA 48988 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5

EPITHELIUM OF RENAL PELVIS

HYPERPLASIA

S1	1	0	0	0	0
Total	1	0	0	0	0

TESTIS

TUBULAR ATROPHY

S1	1	0	0	1	0
Total	1	0	0	1	0

EPIDIDYMIS

INFLAMMATORY CELL INFILTRATION

S1	0	1	0	0	0
Total	0	1	0	0	0

ADRENAL CORTEX

FATTY CHANGE

S1	0	0	0	0	1
Total	0	0	0	0	1

ADRENAL MEDULLA

One organ, no exam.tech. reasons	(0)	(0)	(1)	(0)	(0)
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SUMMARY OF MICROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)

Removal code : all                      Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
-----					
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, selected	5	5	5	5	5
Examined macroscopically	5	5	5	5	5
Examined microscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5

=====  
Abbreviations used in pathology tables

S1, S2.... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

=====  
 =====

SUMMARY OF MICROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5
<b>SPLEEN</b>					
<b>HAEMOSIDEROSIS</b>					
S1	2	0	1	1	2
Total	2	0	1	1	2
<b>EXTRAMEDULLARY HAEMATOPOIESIS</b>					
S1	0	1	2	4	4
Total	0	1	2	4	4
<b>LUNG</b>					
<b>HAEMORRHAGIC INFARCT</b>					
S1	0	0	1	0	0
Total	0	0	1	0	0
<b>LIVER</b>					
<b>INFLAMMATORY CELL INFILTRATION</b>					
S1	1	3	2	4	3
Total	1	3	2	4	3
<b>LIVER HEPATOCYTE</b>					
<b>HYPERTROPHY</b>					
S1	1	0	2	1	5
Total	1	0	2	1	5
<b>KIDNEY</b>					
<b>INFLAMMATORY CELL INFILTRATION</b>					
S1	0	0	0	0	1
Total	0	0	0	0	1
<b>NEPHROCALCINOSIS</b>					
S1	5	5	4	4	5
Total	5	5	4	4	5
<b>RENAL TUBULE</b>					
<b>CAST</b>					
S1	0	0	1	0	0
Total	0	0	1	0	0
<b>NECROSIS</b>					
S1	0	0	1	0	0
Total	0	0	1	0	0

**SUMMARY OF MICROSCOPICAL FINDINGS IN FEMALES (CGA 48988 tech.)**

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300

Animals initially in study	5	5	5	5	5
Examined microscopically	5	5	5	5	5

**RENAL TUBULE (continued)**

**ATROPHY**

S1	5	4	5	2	4
Total	5	4	5	2	4

**RENAL PELVIS**

**ONE ORGAN, MACROSCOPICAL CHANGE NOT OBSERVED**

S1	0	0	1	0	1
Total	0	0	1	0	1

**MACROSCOPICAL CHANGE NOT OBSERVED**

S1	0	0	0	0	1
Total	0	0	0	0	1

**DILATATION**

S1	0	2	0	1	0
Total	0	2	0	1	0

**ADRENAL CORTEX**

**FATTY CHANGE**

S1	0	0	1	0	0
Total	0	0	1	0	0

**ADRENAL MEDULLA**

One organ, no exam.tech.reasons	(0)	(0)	(0)	(0)	(1)
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5. APPENDIX A: STATISTICAL DATA

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5.1. Bodyweight (statistics)

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

**Bodyweight (statistics) : males**  
 (g/animal)

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	150	300
week: -1 N	5	5	5	5	5
Mean	142.8	140.9	137.5	137.6	139.1
Median	143.0	141.5	136.4	137.6	139.4
Min	138.9	137.1	134.8	135.8	134.9
Max	146.7	144.4	144.2	139.3	145.0
p <sub>W</sub>		0.347	0.047 *	0.016 *	0.117
p <sub>J</sub>		0.347	0.017	0.015	0.077
week: 1 N	5	5	5	5	5
Mean	182.2	184.3	178.1	172.8	179.4
Median	180.0	181.5	172.8	176.1	176.1
Min	174.3	169.2	168.0	166.3	167.7
Max	190.5	198.7	196.0	176.9	202.2
p <sub>W</sub>		0.754	0.347	0.117	0.465
p <sub>J</sub>		0.754	0.428	0.106	0.197
week: 2 N	5	5	5	5	5
Mean	232.6	236.8	225.2	223.4	224.3
Median	231.4	231.6	223.0	223.5	223.9
Min	220.6	215.5	208.6	210.3	205.7
Max	245.5	259.0	254.2	229.8	251.1
p <sub>W</sub>		0.917	0.465	0.347	0.465
p <sub>J</sub>		0.917	0.369	0.313	0.251
week: 3 N	5	5	5	5	5
Mean	282.6	290.4	275.2	272.5	274.6
Median	278.1	290.0	273.0	274.5	274.5
Min	266.8	259.3	253.1	259.0	259.0
Max	305.4	318.0	311.3	279.2	295.4
p <sub>W</sub>		0.754	0.465	0.465	0.465
p <sub>J</sub>		0.754	0.492	0.419	0.403

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.Bodyweight (statistics) : males  
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
week: 4 N	5	5	5	5	5
Mean	322.0	325.1	317.2	310.4	311.3
Median	315.3	328.4	314.6	312.1	311.6
Min	306.6	284.4	288.7	296.4	291.0
Max	351.5	365.7	350.6	322.0	334.2
p_W		0.917	0.754	0.251	0.465
p_J		0.917	0.792	0.382	0.293

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Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Bodyweight (statistics) : females  
 (g/animal)

Dose (mg/kg)		group 1	group 2	group 3	group 4	group 5
		0	10	50	150	300
week: -1	N	5	5	5	5	5
	Mean	155.1	157.2	157.0	155.7	156.6
	Median	154.4	155.5	157.8	154.0	153.5
	Min	145.6	154.1	152.2	152.3	152.7
	Max	161.5	163.4	162.3	159.8	162.6
	p <sub>W</sub>		0.465	0.754	0.754	0.917
	p <sub>J</sub>		0.465	0.712	0.893	0.738
week: 1	N	5	5	5	5	5
	Mean	185.8	181.1	178.2	173.0	183.4
	Median	184.1	174.3	175.4	175.3	181.9
	Min	179.3	171.0	171.3	162.5	171.5
	Max	198.2	197.2	185.6	186.3	194.5
	p <sub>W</sub>		0.347	0.347	0.076	0.465
	p <sub>J</sub>		0.347	0.316	0.106	0.503
week: 2	N	5	5	5	5	5
	Mean	200.5	203.5	201.8	188.7	202.5
	Median	200.7	202.8	197.8	189.0	201.1
	Min	192.4	195.8	189.9	179.3	184.0
	Max	210.9	208.6	218.8	197.9	230.7
	p <sub>W</sub>		0.465	0.917	0.076	0.917
	p <sub>J</sub>		0.465	0.874	0.093	0.272
week: 3	N	5	5	5	5	5
	Mean	221.5	226.8	222.4	215.7	224.3
	Median	217.5	223.3	221.3	215.9	226.4
	Min	213.9	215.9	207.2	202.5	198.8
	Max	233.9	240.3	243.2	231.8	246.9
	p <sub>W</sub>		0.251	0.917	0.465	0.602
	p <sub>J</sub>		0.251	0.792	0.419	0.886
week: 4	N	5	5	5	5	5
	Mean	235.8	233.6	235.7	229.5	238.1
	Median	235.8	232.7	229.7	226.8	241.9
	Min	226.4	218.7	218.5	219.0	215.1
	Max	243.4	255.4	253.0	248.8	248.7
	p <sub>W</sub>		0.602	0.917	0.251	0.347
	p <sub>J</sub>		0.602	0.712	0.282	0.811

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Bodyweight (statistics) : males  
 (g/animal)

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	150	300
week: -1 N	5	5	5	5	5
Mean	142.8	135.8	136.6	136.8	136.2
Median	143.0	136.0	136.6	137.4	137.2
Min	138.9	132.5	133.7	132.9	132.4
Max	146.7	138.7	140.2	140.9	140.2
p <sub>W</sub>		0.009 *	0.016 *	0.028 *	0.016 *
p <sub>J</sub>		0.009 -	0.017	0.060	0.050
week: 1 N	5	5	5	5	5
Mean	182.2	177.1	175.1	175.1	182.0
Median	180.0	180.0	176.9	173.8	182.7
Min	174.3	161.2	170.7	167.0	171.1
Max	190.5	194.2	178.8	183.5	194.4
p <sub>W</sub>		0.754	0.175	0.117	0.917
p <sub>J</sub>		0.754	0.267	0.226	0.981
week: 2 N	5	5	5	5	5
Mean	232.6	228.9	223.1	225.3	235.5
Median	231.4	232.3	218.7	229.6	234.6
Min	220.6	210.1	210.4	214.1	219.9
Max	245.5	255.6	234.8	234.8	255.0
p <sub>W</sub>		0.754	0.175	0.347	0.754
p <sub>J</sub>		0.754	0.369	0.329	0.943
week: 3 N	5	5	5	5	5
Mean	282.6	288.6	276.4	276.7	287.5
Median	278.1	289.4	277.8	285.7	282.4
Min	266.8	263.1	263.3	256.4	270.7
Max	305.4	326.0	289.7	289.6	311.1
p <sub>W</sub>		0.917	0.347	0.465	0.602
p <sub>J</sub>		0.917	0.428	0.226	0.774
week: 4 N	5	5	5	5	5
Mean	322.0	324.1	309.7	310.9	325.5
Median	315.3	320.8	310.5	318.0	331.2
Min	306.6	294.7	295.6	285.5	303.1
Max	351.5	365.7	322.9	326.9	347.9
p <sub>W</sub>		0.917	0.251	0.754	0.917
p <sub>J</sub>		0.917	0.369	0.459	0.924

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Bodyweight (statistics): females  
 (g/animal)

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
0	10	50	150	300	
week: -1	N	5	5	5	5
Mean	155.1	150.9	148.6	147.7	151.3
Median	154.4	153.9	147.6	147.1	153.3
Min	145.6	143.5	144.5	144.6	145.9
Max	161.5	155.8	152.4	153.2	155.4
p <sub>W</sub>		0.465	0.076	0.047 *	0.251
p <sub>J</sub>		0.465	0.101	0.037	0.251
week: 1	N	5	5	5	5
Mean	185.8	178.1	180.3	182.9	183.1
Median	184.1	177.0	178.6	186.7	184.9
Min	179.3	173.4	176.3	167.2	172.4
Max	198.2	187.6	189.0	195.8	192.5
p <sub>W</sub>		0.076	0.076	0.917	0.917
p <sub>J</sub>		0.076	0.224	0.545	0.848
week: 2	N	5	5	5	5
Mean	200.5	200.6	203.2	208.2	203.5
Median	200.7	201.4	206.4	206.6	203.5
Min	192.4	190.5	189.0	191.7	190.1
Max	210.9	216.1	213.3	225.1	215.9
p <sub>W</sub>		0.917	0.602	0.465	0.675
p <sub>J</sub>		0.917	0.712	0.346	0.459
week: 3	N	5	5	5	5
Mean	221.5	228.1	230.1	232.7	230.2
Median	217.5	232.7	231.1	236.1	229.2
Min	213.9	217.2	203.9	211.4	219.0
Max	233.9	234.3	255.0	260.0	246.7
p <sub>W</sub>		0.251	0.347	0.602	0.117
p <sub>J</sub>		0.251	0.224	0.226	0.214
week: 4	N	5	5	5	5
Mean	235.8	248.4	244.7	243.3	246.9
Median	235.8	256.3	246.9	256.2	241.7
Min	226.4	232.3	218.8	221.6	238.9
Max	243.4	263.4	261.9	258.9	267.6
p <sub>W</sub>		0.347	0.251	0.602	0.076
p <sub>J</sub>		0.347	0.316	0.686	0.444

5.2. Hematology (statistics)

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05

JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Hematology (statistics): males

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>RBC (T/l)</b>					
week: 5 N	5	5	5	5	5
Mean	7.518	7.342	7.416	7.688	7.226
Median	7.410	7.320	7.460	7.760	7.240
Min	7.290	6.980	7.150	7.440	6.860
Max	7.880	7.740	7.720	7.900	7.550
p <sub>W</sub>		0.465	0.602	0.175	0.175
p <sub>J</sub>		0.465	0.634	0.201	0.830
<b>Hb (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	9.380	9.460	9.560	9.460	9.140
Median	9.400	9.600	9.400	9.500	9.400
Min	9.200	8.800	9.300	9.000	8.400
Max	9.600	9.800	10.20	9.800	9.400
p <sub>W</sub>		0.343	0.523	0.528	0.280
p <sub>J</sub>		0.347	0.526	0.590	0.444
<b>Hct (l)</b>					
week: 5 N	5	5	5	5	5
Mean	0.452	0.455	0.450	0.455	0.440
Median	0.453	0.459	0.446	0.452	0.441
Min	0.438	0.424	0.438	0.443	0.406
Max	0.464	0.474	0.479	0.468	0.469
p <sub>W</sub>		0.347	0.462	0.754	0.347
p <sub>J</sub>		0.347	0.792	0.840	0.416
<b>MCV (fl)</b>					
week: 5 N	5	5	5	5	5
Mean	60.08	62.01	60.72	59.24	60.86
Median	59.80	61.80	60.30	59.70	61.00
Min	59.00	59.30	57.90	56.90	59.20
Max	62.10	65.50	64.00	62.20	62.70
p <sub>W</sub>		0.117	0.753	0.675	0.402
p <sub>J</sub>		0.117	0.634	0.501	0.867

CGA 329351 tech.

Hematology (statistics) : males

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>RDW</b>					
(1)					
week: 5 N	5	5	5	5	5
Mean	0.121	0.122	0.122	0.126	0.121
Median	0.120	0.125	0.122	0.127	0.122
Min	0.117	0.114	0.117	0.123	0.117
Max	0.125	0.128	0.126	0.129	0.124
p_W		0.674	0.597	0.026 *	0.752
p_J		0.676	0.712	0.051	0.459
<b>MCH</b>					
(fmol)					
week: 5 N	5	5	5	5	5
Mean	1.252	1.287	1.292	1.236	1.262
Median	1.240	1.280	1.300	1.250	1.250
Min	1.220	1.240	1.230	1.160	1.220
Max	1.310	1.340	1.360	1.310	1.300
p_W		0.113	0.207	0.916	0.523
p_J		0.117	0.139	0.973	0.830
<b>MCHC</b>					
(mmol/l)					
week: 5 N	5	5	5	5	5
Mean	20.80	20.78	21.26	20.82	20.78
Median	20.69	20.76	21.28	21.05	20.68
Min	20.65	20.53	20.97	20.28	20.15
Max	21.05	20.97	21.56	21.07	21.31
p_W		0.754	0.016 *	0.598	1.000
p_J		0.754	0.008 +	0.148	0.519
<b>HDW</b>					
(mmol/l)					
week: 5 N	5	5	5	5	5
Mean	1.374	1.367	1.300	1.448	1.448
Median	1.280	1.245	1.240	1.260	1.340
Min	1.200	1.130	1.170	1.230	1.260
Max	1.620	1.710	1.620	1.790	1.690
p_W		0.917	0.462	0.675	0.251
p_J		0.917	0.634	0.590	0.158

CGA 329351 tech.

Hematology (statistics) : males

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
WBC (G/l)						
week:	5 N	5	5	5	5	5
	Mean	18.90	12.65	14.19	17.08	13.00
	Median	20.10	13.07	12.24	16.56	13.28
	Min	14.37	8.035	12.05	9.500	7.450
	Max	22.66	17.20	20.98	23.43	16.99
	p_W		0.028 *	0.076	0.602	0.047 *
	p_J		0.028	0.064	0.545	0.214
Neut (1)						
week:	5 N	5	5	5	5	5
	Mean	0.074	0.103	0.084	0.075	0.106
	Median	0.071	0.086	0.091	0.069	0.094
	Min	0.058	0.065	0.054	0.048	0.063
	Max	0.101	0.175	0.109	0.118	0.152
	p_W		0.175	0.347	1.000	0.173
	p_J		0.175	0.316	0.973	0.327
Eos (1)						
week:	5 N	5	5	5	5	5
	Mean	0.005	0.008	0.007	0.008	0.006
	Median	0.005	0.008	0.006	0.008	0.005
	Min	0.004	0.004	0.004	0.005	0.003
	Max	0.007	0.012	0.012	0.011	0.008
	p_W		0.207	0.456	0.090	0.829
	p_J		0.210	0.428	0.201	0.848
Baso (1)						
week:	5 N	5	5	5	5	5
	Mean	0.007	0.005	0.006	0.006	0.005
	Median	0.007	0.004	0.005	0.005	0.004
	Min	0.006	0.004	0.005	0.003	0.004
	Max	0.009	0.006	0.008	0.009	0.006
	p_W		0.015 *	0.051	0.245	0.014 *
	p_J		0.016	0.139	0.329	0.090

CGA 329351 tech.

Hematology (statistics) : males

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Lympho (1)					
week: 5 N	5	5	5	5	5
Mean	0.839	0.810	0.827	0.829	0.815
Median	0.848	0.821	0.832	0.831	0.815
Min	0.793	0.723	0.782	0.790	0.771
Max	0.862	0.867	0.859	0.857	0.857
p_W		0.530	0.347	0.465	0.251
p_J		0.531	0.460	0.523	0.293
Mono (1)					
week: 5 N	5	5	5	5	5
Mean	0.040	0.037	0.043	0.043	0.037
Median	0.035	0.040	0.041	0.050	0.038
Min	0.033	0.027	0.030	0.026	0.031
Max	0.054	0.046	0.056	0.055	0.044
p_W		0.675	0.602	0.528	0.599
p_J		0.676	0.634	0.400	0.981
Luc (1)					
week: 5 N	5	5	5	5	5
Mean	0.034	0.038	0.033	0.040	0.032
Median	0.034	0.033	0.037	0.036	0.033
Min	0.030	0.025	0.025	0.033	0.025
Max	0.041	0.053	0.040	0.052	0.037
p_W		0.917	0.916	0.209	0.674
p_J		0.917	0.712	0.545	0.867
Neut (G/l)					
week: 5 N	5	5	5	5	5
Mean	1.394	1.213	1.146	1.260	1.282
Median	1.170	1.370	1.140	1.320	1.130
Min	1.040	0.890	0.910	0.680	1.060
Max	2.100	1.430	1.310	1.900	1.660
p_W		0.465	0.347	0.754	0.602
p_J		0.465	0.224	0.459	0.702

CGA 329351 tech.

Hematology (statistics) : males

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Eos (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.098	0.093	0.096	0.122	0.068
	Median	0.100	0.100	0.090	0.120	0.060
	Min	0.070	0.045	0.070	0.080	0.050
	Max	0.130	0.130	0.150	0.170	0.100
	p_W		0.915	0.667	0.207	0.055
	p_J		0.917	0.792	0.297	0.376
Baso (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.134	0.058	0.084	0.106	0.062
	Median	0.140	0.060	0.060	0.090	0.060
	Min	0.080	0.030	0.060	0.030	0.030
	Max	0.190	0.100	0.170	0.200	0.100
	p_W		0.021 *	0.072	0.402	0.021 *
	p_J		0.022	0.139	0.590	0.205
Lympho (G/l)						
week:	5 N	5	5	5	5	5
	Mean	15.84	10.37	11.79	14.12	10.69
	Median	16.60	10.27	10.31	14.07	10.61
	Min	12.19	5.805	9.420	8.140	5.750
	Max	19.06	14.65	18.03	19.48	14.55
	p_W		0.028 *	0.076	0.602	0.047 *
	p_J		0.028	0.081	0.590	0.251
Mono (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.774	0.465	0.620	0.772	0.480
	Median	0.700	0.500	0.530	0.910	0.500
	Min	0.480	0.325	0.370	0.240	0.240
	Max	1.120	0.600	1.030	1.160	0.640
	p_W		0.076	0.347	1.000	0.117
	p_J		0.076	0.398	0.893	0.444



CGA 329351 tech.

Hematology (statistics) : males

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Luc (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.656	0.452	0.454	0.688	0.426
	Median	0.610	0.420	0.490	0.690	0.420
	Min	0.490	0.370	0.310	0.310	0.250
	Max	0.860	0.670	0.520	1.020	0.590
	p_W		0.047 *	0.036 *	0.754	0.059
	p_J		0.047	0.091	1.000	0.364
Plt (G/l)						
week:	5 N	5	5	5	5	5
	Mean	1054	1101	1077	1163	996.2
	Median	1123	1118	1110	1149	1121
	Min	705.0	1005	979.0	1073	363.0
	Max	1201	1184	1123	1276	1232
	p_W		0.917	0.402	0.465	0.917
	p_J		0.917	0.460	0.614	0.720
PT(CS) (sec)						
week:	5 N	5	5	5	5	5
	Mean	35.82	33.43	34.24	34.83	30.22
	Median	33.65	33.52	34.04	33.25	30.75
	Min	29.73	30.11	31.07	31.30	27.06
	Max	44.36	35.11	37.96	40.83	32.36
	p_W		0.754	0.917	0.754	0.047 *
	p_J		0.754	0.958	0.946	0.050

Statistical tests and flags used:

WILCOXON: \* if  $p_W < 0.05$   
 JONCKHEERE: +- if  $p_J < 0.01$

CGA 329351 tech.

Hematology (statistics) : females

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>RBC (T/l)</b>					
week: 5 N	5	5	5	5	5
Mean	7.978	7.558	7.702	7.474	7.716
Median	8.070	7.730	7.740	7.290	7.710
Min	7.630	6.930	7.430	7.140	7.690
Max	8.210	8.010	7.920	7.880	7.760
p_W		0.117	0.094	0.036 *	0.116
p_J		0.117	0.113	0.031	0.059
<b>Hb (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	9.700	9.480	9.740	9.260	9.440
Median	9.700	9.500	9.900	9.200	9.500
Min	9.300	8.900	9.300	9.100	9.000
Max	10.10	10.10	10.30	9.700	9.700
p_W		0.462	0.750	0.035 *	0.138
p_J		0.465	0.792	0.168	0.166
<b>Hct (l)</b>					
week: 5 N	5	5	5	5	5
Mean	0.452	0.439	0.453	0.431	0.438
Median	0.450	0.440	0.459	0.428	0.441
Min	0.431	0.417	0.428	0.420	0.417
Max	0.470	0.466	0.479	0.451	0.451
p_W		0.173	1.000	0.075	0.173
p_J		0.175	0.916	0.178	0.197
<b>MCV (fl)</b>					
week: 5 N	5	5	5	5	5
Mean	56.74	58.16	58.80	57.70	56.88
Median	56.50	58.30	58.00	57.90	56.90
Min	54.90	56.10	56.80	53.70	54.00
Max	59.60	60.20	60.80	60.70	58.70
p_W		0.251	0.075	0.347	0.753
p_J		0.251	0.081	0.253	0.830

CGA 329351 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>RDW</b>						
(1)						
week:	5 N	5	5	5	5	5
	Mean	0.117	0.116	0.113	0.120	0.113
	Median	0.114	0.118	0.111	0.117	0.113
	Min	0.111	0.110	0.108	0.113	0.108
	Max	0.128	0.121	0.122	0.127	0.118
	p_W		0.916	0.141	0.344	0.463
	p_J		0.917	0.291	0.614	0.702
<b>MCH</b>						
(fmol)						
week:	5 N	5	5	5	5	5
	Mean	1.216	1.252	1.262	1.238	1.226
	Median	1.200	1.260	1.250	1.240	1.230
	Min	1.190	1.220	1.230	1.180	1.170
	Max	1.290	1.280	1.300	1.290	1.270
	p_W		0.114	0.074	0.401	0.463
	p_J		0.117	0.051	0.282	0.867
<b>MCHC</b>						
(mmol/l)						
week:	5 N	5	5	5	5	5
	Mean	21.44	21.52	21.49	21.45	21.55
	Median	21.49	21.53	21.51	21.46	21.59
	Min	21.09	21.30	21.09	21.18	21.43
	Max	21.66	21.71	21.78	21.92	21.67
	p_W		0.602	0.675	0.754	0.347
	p_J		0.602	0.673	0.788	0.848
<b>HDW</b>						
(mmol/l)						
week:	5 N	5	5	5	5	5
	Mean	1.246	1.428	1.284	1.378	1.276
	Median	1.230	1.410	1.190	1.410	1.320
	Min	1.200	1.120	1.090	1.190	1.150
	Max	1.300	1.750	1.740	1.660	1.370
	p_W		0.117	0.207	0.530	0.602
	p_J		0.117	0.673	0.866	0.830

CGA 329351 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>WBC</b>						
(G/l)						
week:	5 N	5	5	5	5	5
	Mean	11.34	14.28	12.37	12.65	13.19
	Median	11.30	15.22	12.88	11.83	12.61
	Min	9.620	10.21	7.570	8.880	10.35
	Max	13.27	15.94	17.07	18.15	17.36
	p_W		0.076	0.602	0.754	0.465
	p_J		0.076	0.492	0.737	0.667
<b>Neut</b>						
(1)						
week:	5 N	5	5	5	5	5
	Mean	0.053	0.046	0.057	0.074	0.068
	Median	0.055	0.050	0.069	0.084	0.075
	Min	0.037	0.030	0.020	0.042	0.040
	Max	0.064	0.060	0.071	0.111	0.082
	p_W		0.344	0.346	0.347	0.076
	p_J		0.347	0.492	0.139	0.050
<b>Eos</b>						
(1)						
week:	5 N	5	5	5	5	5
	Mean	0.010	0.007	0.009	0.016	0.008
	Median	0.009	0.007	0.009	0.008	0.007
	Min	0.008	0.003	0.008	0.006	0.005
	Max	0.014	0.012	0.011	0.046	0.014
	p_W		0.171	0.827	0.665	0.136
	p_J		0.175	0.792	0.920	0.315
<b>Baso</b>						
(1)						
week:	5 N	5	5	5	5	5
	Mean	0.005	0.006	0.005	0.004	0.005
	Median	0.005	0.006	0.005	0.004	0.005
	Min	0.005	0.005	0.003	0.003	0.004
	Max	0.006	0.007	0.006	0.006	0.007
	p_W		0.189	0.905	0.178	0.822
	p_J		0.251	0.874	0.253	0.416

CGA 329351 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Lympho (1)						
week:	5 N	5	5	5	5	5
	Mean	0.855	0.884	0.870	0.838	0.863
	Median	0.846	0.894	0.861	0.833	0.863
	Min	0.836	0.858	0.850	0.782	0.839
	Max	0.894	0.900	0.896	0.880	0.899
	p_W		0.035 *	0.116	0.346	0.346
	p_J		0.037	0.245	0.567	0.684
Mono (1)						
week:	5 N	5	5	5	5	5
	Mean	0.047	0.031	0.034	0.039	0.030
	Median	0.051	0.037	0.033	0.039	0.032
	Min	0.020	0.020	0.029	0.026	0.024
	Max	0.061	0.037	0.039	0.055	0.032
	p_W		0.090	0.117	0.295	0.113
	p_J		0.095	0.154	0.638	0.138
Luc (1)						
week:	5 N	5	5	5	5	5
	Mean	0.030	0.026	0.025	0.029	0.026
	Median	0.030	0.027	0.026	0.030	0.026
	Min	0.023	0.022	0.017	0.022	0.022
	Max	0.035	0.029	0.030	0.033	0.029
	p_W		0.058	0.113	0.451	0.073
	p_J		0.060	0.091	0.662	0.304
Neut (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.606	0.638	0.720	0.942	0.870
	Median	0.650	0.610	0.700	0.740	0.840
	Min	0.360	0.470	0.200	0.500	0.690
	Max	0.730	0.760	1.200	2.020	1.120
	p_W		0.917	0.602	0.175	0.028 *
	p_J		0.917	0.634	0.253	0.040

CGA 329351 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Eos (G/l)	week: 5 N	5	5	5	5	5
	Mean	0.112	0.102	0.114	0.240	0.092
	Median	0.100	0.100	0.120	0.100	0.080
	Min	0.090	0.050	0.060	0.070	0.080
	Max	0.140	0.150	0.150	0.830	0.140
	p_W		0.671	0.674	0.671	0.083
	p_J		0.676	0.712	0.946	0.282
Baso (G/l)	week: 5 N	5	5	5	5	5
	Mean	0.056	0.080	0.066	0.060	0.072
	Median	0.060	0.090	0.060	0.050	0.070
	Min	0.050	0.050	0.020	0.030	0.040
	Max	0.060	0.100	0.100	0.090	0.120
	p_W		0.068	0.314	0.747	0.454
	p_J		0.076	0.291	1.000	0.886
Lympho (G/l)	week: 5 N	5	5	5	5	5
	Mean	9.674	12.66	10.76	10.57	11.42
	Median	9.590	13.71	11.42	10.34	10.69
	Min	8.590	8.760	6.430	7.360	8.690
	Max	11.23	14.34	14.64	14.20	15.60
	p_W		0.076	0.465	0.754	0.465
	p_J		0.076	0.428	0.840	0.774
Mono (G/l)	week: 5 N	5	5	5	5	5
	Mean	0.550	0.432	0.406	0.470	0.390
	Median	0.580	0.380	0.400	0.490	0.410
	Min	0.200	0.300	0.280	0.350	0.330
	Max	0.800	0.570	0.560	0.540	0.440
	p_W		0.175	0.175	0.117	0.117
	p_J		0.175	0.170	0.313	0.126

CGA 329351 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Luc (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.342	0.370	0.304	0.366	0.342
	Median	0.350	0.370	0.300	0.350	0.320
	Min	0.260	0.300	0.210	0.200	0.280
	Max	0.420	0.420	0.420	0.530	0.450
	p_W		0.459	0.530	0.753	0.917
	p_J		0.465	0.561	0.893	0.867
Plt (G/l)						
week:	5 N	5	5	5	5	5
	Mean	1153	1146	1083	1089	1129
	Median	1109	1096	1091	1094	1109
	Min	1060	1020	979.0	979.0	1066
	Max	1335	1318	1163	1167	1228
	p_W		0.754	0.295	0.465	0.834
	p_J		0.754	0.291	0.364	0.633
PT(CS) (sec)						
week:	5 N	5	5	5	5	5
	Mean	27.19	30.58	28.38	29.80	28.49
	Median	27.06	31.19	29.30	30.56	28.51
	Min	24.37	27.10	22.24	25.38	25.53
	Max	31.06	32.72	31.58	31.60	30.69
	p_W		0.047*	0.347	0.251	0.347
	p_J		0.047	0.316	0.346	0.886

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Hematology (statistics) : males

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
RBC (T/l)					
week: 5 N	5	5	5	5	5
Mean	7.518	7.432	7.206	7.380	7.262
Median	7.410	7.380	7.460	7.400	7.310
Min	7.290	6.930	6.420	7.130	6.930
Max	7.880	7.780	7.960	7.720	7.650
p <sub>W</sub>		0.602	0.754	0.465	0.175
p <sub>J</sub>		0.602	0.561	0.545	0.232
Hb (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	9.380	9.560	8.960	9.440	9.180
Median	9.400	9.500	9.300	9.500	9.000
Min	9.200	9.200	8.200	9.100	8.900
Max	9.600	9.900	9.600	9.700	9.600
p <sub>W</sub>		0.338	0.461	0.670	0.245
p <sub>J</sub>		0.347	0.526	0.946	0.339
Hct (l)					
week: 5 N	5	5	5	5	5
Mean	0.452	0.463	0.428	0.453	0.445
Median	0.453	0.465	0.445	0.456	0.442
Min	0.438	0.448	0.388	0.433	0.434
Max	0.464	0.482	0.459	0.463	0.459
p <sub>W</sub>		0.093	0.251	0.834	0.295
p <sub>J</sub>		0.095	0.460	0.762	0.293
MCV (fl)					
week: 5 N	5	5	5	5	5
Mean	60.08	62.40	59.44	61.47	61.28
Median	59.80	61.70	59.70	60.70	61.70
Min	59.00	59.80	57.70	60.00	59.80
Max	62.10	65.40	60.30	63.95	62.60
p <sub>W</sub>		0.094	0.675	0.117	0.142
p <sub>J</sub>		0.095	0.634	0.480	0.272



CGA 48988 tech.

Hematology (statistics) : males

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>RDW</b>					
(1)					
week: 5 N	5	5	5	5	5
Mean	0.121	0.122	0.122	0.122	0.124
Median	0.120	0.121	0.121	0.122	0.124
Min	0.117	0.115	0.120	0.120	0.119
Max	0.125	0.130	0.129	0.126	0.133
p_W		0.753	0.589	0.451	0.396
p_J		0.754	0.634	0.501	0.376
<b>MCH</b>					
(fmol)					
week: 5 N	5	5	5	5	5
Mean	1.252	1.290	1.244	1.279	1.268
Median	1.240	1.270	1.250	1.270	1.280
Min	1.220	1.210	1.210	1.250	1.210
Max	1.310	1.370	1.270	1.335	1.300
p_W		0.293	0.915	0.093	0.463
p_J		0.296	1.000	0.267	0.205
<b>MCHC</b>					
(mmol/l)					
week: 5 N	5	5	5	5	5
Mean	20.80	20.66	20.93	20.83	20.67
Median	20.69	20.62	20.94	20.89	20.78
Min	20.65	20.20	20.74	20.45	20.22
Max	21.05	21.15	21.11	21.01	20.90
p_W		0.465	0.175	0.834	0.465
p_J		0.465	0.492	0.711	0.519
<b>HDW</b>					
(mmol/l)					
week: 5 N	5	5	5	5	5
Mean	1.374	1.356	1.422	1.355	1.458
Median	1.280	1.280	1.300	1.290	1.360
Min	1.200	1.170	1.210	1.190	1.240
Max	1.620	1.720	1.730	1.700	1.800
p_W		1.000	0.602	0.754	0.402
p_J		1.000	0.673	0.973	0.488

CGA 48988 tech.

Hematology (statistics) : males

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
WBC (G/l)						
week:	5 N	5	5	5	5	5
	Mean	18.90	20.08	17.69	18.41	16.00
	Median	20.10	20.34	19.24	17.13	16.17
	Min	14.37	14.47	8.240	13.27	11.91
	Max	22.66	25.54	25.94	24.26	18.54
	p_W		0.602	0.754	0.917	0.175
	p_J		0.602	0.874	0.840	0.272
Neut (1)						
week:	5 N	5	5	5	5	5
	Mean	0.074	0.072	0.114	0.090	0.072
	Median	0.071	0.069	0.083	0.081	0.076
	Min	0.058	0.059	0.054	0.054	0.057
	Max	0.101	0.085	0.247	0.166	0.081
	p_W		0.917	0.602	0.917	0.754
	p_J		0.917	0.673	0.840	0.886
Eos (1)						
week:	5 N	5	5	5	5	5
	Mean	0.005	0.005	0.005	0.009	0.007
	Median	0.005	0.005	0.005	0.008	0.006
	Min	0.004	0.003	0.003	0.003	0.003
	Max	0.007	0.008	0.010	0.017	0.013
	p_W		0.915	0.670	0.207	0.525
	p_J		0.917	0.712	0.382	0.315
Baso (1)						
week:	5 N	5	5	5	5	5
	Mean	0.007	0.008	0.006	0.007	0.006
	Median	0.007	0.007	0.006	0.006	0.006
	Min	0.006	0.006	0.002	0.005	0.004
	Max	0.009	0.010	0.009	0.009	0.007
	p_W		0.667	0.456	0.456	0.084
	p_J		0.676	0.526	0.364	0.085

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Hematology (statistics) : males

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Lympho (1)						
week:	5 N	5	5	5	5	5
	Mean	0.839	0.843	0.808	0.824	0.854
	Median	0.848	0.844	0.835	0.838	0.852
	Min	0.793	0.833	0.695	0.746	0.839
	Max	0.862	0.854	0.846	0.870	0.874
	p_W		0.600	0.175	0.754	0.530
	p_J		0.602	0.126	0.297	0.667
Mono (1)						
week:	5 N	5	5	5	5	5
	Mean	0.040	0.040	0.039	0.040	0.037
	Median	0.035	0.044	0.041	0.039	0.037
	Min	0.033	0.031	0.028	0.035	0.032
	Max	0.054	0.047	0.053	0.048	0.041
	p_W		0.916	0.753	0.530	0.917
	p_J		0.917	0.673	0.946	0.633
Luc (1)						
week:	5 N	5	5	5	5	5
	Mean	0.034	0.032	0.028	0.032	0.025
	Median	0.034	0.032	0.031	0.031	0.025
	Min	0.030	0.025	0.022	0.027	0.021
	Max	0.041	0.038	0.033	0.036	0.027
	p_W		0.671	0.094	0.344	0.009 *
	p_J		0.676	0.081	0.189	0.006 -
Neut (G/l)						
week:	5 N	5	5	5	5	5
	Mean	1.394	1.410	1.600	1.516	1.148
	Median	1.170	1.510	1.590	1.380	1.070
	Min	1.040	1.200	1.180	1.200	0.930
	Max	2.100	1.540	2.030	2.200	1.440
	p_W		0.249	0.173	0.251	0.251
	p_J		0.251	0.039	0.130	0.650

CGA 48988 tech.

Hematology (statistics) : males

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Eos (G/l)					
week: 5 N	5	5	5	5	5
Mean	0.098	0.098	0.104	0.145	0.106
Median	0.100	0.090	0.060	0.130	0.100
Min	0.070	0.080	0.040	0.070	0.050
Max	0.130	0.120	0.250	0.225	0.150
p_W		0.916	0.527	0.398	0.750
p_J		0.917	0.526	0.614	0.633
Baso (G/l)					
week: 5 N	5	5	5	5	5
Mean	0.134	0.156	0.120	0.128	0.094
Median	0.140	0.140	0.110	0.090	0.100
Min	0.080	0.090	0.020	0.060	0.050
Max	0.190	0.220	0.230	0.230	0.110
p_W		0.530	0.754	0.753	0.243
p_J		0.531	0.833	0.662	0.261
Lympho (G/l)					
week: 5 N	5	5	5	5	5
Mean	15.84	16.93	14.58	15.31	13.67
Median	16.60	17.17	16.06	13.95	14.14
Min	12.19	12.12	5.720	9.890	9.990
Max	19.06	21.82	21.87	20.70	15.79
p_W		0.754	0.754	0.917	0.251
p_J		0.754	0.874	0.788	0.315
Mono (G/l)					
week: 5 N	5	5	5	5	5
Mean	0.774	0.824	0.742	0.712	0.586
Median	0.700	0.930	0.780	0.760	0.590
Min	0.480	0.480	0.230	0.520	0.440
Max	1.120	1.120	1.190	0.870	0.720
p_W		0.753	0.917	0.917	0.347
p_J		0.754	0.874	0.840	0.282

CGA 48988 tech.

Hematology (statistics) : males

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Luc</b>					
(G/l)					
week: 5 N	5	5	5	5	5
Mean	0.656	0.654	0.528	0.590	0.400
Median	0.610	0.710	0.620	0.580	0.400
Min	0.490	0.460	0.190	0.360	0.300
Max	0.860	0.820	0.810	0.870	0.490
p_W		0.754	0.602	0.602	0.012 *
p_J		0.754	0.398	0.459	0.042
<b>Plt</b>					
(G/l)					
week: 5 N	5	5	5	5	5
Mean	1054	1090	1062	1071	1179
Median	1123	1081	1043	1124	1190
Min	705.0	1035	1014	838.5	1127
Max	1201	1152	1135	1185	1218
p_W		0.465	0.347	0.917	0.175
p_J		0.465	0.224	0.686	0.115
<b>PT (CS)</b>					
(sec)					
week: 5 N	5	5	5	5	5
Mean	35.82	34.07	34.11	31.51	33.37
Median	33.65	33.72	33.10	29.73	33.81
Min	29.73	31.34	31.45	28.48	28.78
Max	44.36	39.78	39.45	36.24	37.46
p_W		0.917	0.917	0.209	0.602
p_J		0.917	0.874	0.267	0.488

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
RBC (T/l)						
week:	5 N	5	5	5	5	5
	Mean	7.978	7.654	7.448	7.476	7.542
	Median	8.070	7.610	7.390	7.720	7.510
	Min	7.630	7.320	7.120	6.880	6.940
	Max	8.210	8.050	7.760	7.970	8.370
	p <sub>W</sub>		0.047 *	0.028 *	0.076	0.251
	p <sub>J</sub>		0.047	0.011	0.029	0.059
Hb (mmol/l)						
week:	5 N	5	5	5	5	5
	Mean	9.700	9.500	9.460	9.380	9.440
	Median	9.700	9.400	9.500	9.800	9.500
	Min	9.300	9.200	9.100	8.400	8.600
	Max	10.10	9.900	9.700	9.900	10.30
	p <sub>W</sub>		0.293	0.172	0.751	0.530
	p <sub>J</sub>		0.296	0.224	0.480	0.503
Hct (l)						
week:	5 N	5	5	5	5	5
	Mean	0.452	0.444	0.443	0.439	0.443
	Median	0.450	0.442	0.446	0.449	0.454
	Min	0.431	0.429	0.428	0.399	0.400
	Max	0.470	0.461	0.453	0.462	0.481
	p <sub>W</sub>		0.289	0.346	0.401	0.753
	p <sub>J</sub>		0.296	0.342	0.400	0.616
MCV (fl)						
week:	5 N	5	5	5	5	5
	Mean	56.74	58.00	59.56	58.74	58.82
	Median	56.50	57.70	59.20	58.10	57.80
	Min	54.90	57.20	58.40	57.90	57.50
	Max	59.60	59.20	61.00	60.30	60.90
	p <sub>W</sub>		0.117	0.047 *	0.076	0.047 *
	p <sub>J</sub>		0.117	0.006 +	0.017	0.042

CGA 48988 tech.

Hematology (statistics) : females

dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>RDW</b>					
(1)					
week: 5 N	5	5	5	5	5
Mean	0.117	0.112	0.114	0.114	0.114
Median	0.114	0.112	0.114	0.114	0.114
Min	0.111	0.111	0.110	0.111	0.111
Max	0.128	0.113	0.119	0.118	0.119
p_W		0.070	0.525	0.667	0.671
p_J		0.076	0.398	0.762	0.924
<b>MCH</b>					
(fmol)					
week: 5 N	5	5	5	5	5
Mean	1.216	1.240	1.268	1.260	1.256
Median	1.200	1.240	1.270	1.260	1.240
Min	1.190	1.220	1.240	1.230	1.230
Max	1.290	1.260	1.290	1.290	1.300
p_W		0.114	0.093	0.093	0.074
p_J		0.117	0.010	0.015	0.035
<b>MCHC</b>					
(mmol/l)					
week: 5 N	5	5	5	5	5
Mean	21.44	21.37	21.29	21.40	21.30
Median	21.49	21.39	21.24	21.33	21.36
Min	21.09	21.22	21.16	21.17	20.93
Max	21.66	21.48	21.45	21.95	21.52
p_W		0.347	0.209	0.465	0.251
p_J		0.347	0.081	0.122	0.205
<b>HDW</b>					
(mmol/l)					
week: 5 N	5	5	5	5	5
Mean	1.246	1.240	1.204	1.388	1.260
Median	1.230	1.230	1.180	1.430	1.180
Min	1.200	1.180	1.110	1.200	1.140
Max	1.300	1.300	1.360	1.550	1.550
p_W		0.751	0.209	0.209	0.347
p_J		0.754	0.187	0.501	0.886

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Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
WBC (G/l)	week: 5 N	5	5	5	5	5
	Mean	11.34	12.75	13.20	11.54	11.64
	Median	11.30	13.52	12.71	11.14	12.12
	Min	9.620	8.690	11.51	8.430	9.210
	Max	13.27	15.87	16.26	15.92	14.41
	p_W		0.175	0.076	0.754	0.917
	p_J		0.175	0.126	0.893	0.905
Neut (1)	week: 5 N	5	5	5	5	5
	Mean	0.053	0.054	0.070	0.065	0.053
	Median	0.055	0.054	0.062	0.074	0.055
	Min	0.037	0.035	0.034	0.034	0.036
	Max	0.064	0.069	0.143	0.096	0.067
	p_W		0.917	0.602	0.465	1.000
	p_J		0.917	0.751	0.459	0.774
Eos (1)	week: 5 N	5	5	5	5	5
	Mean	0.010	0.008	0.010	0.010	0.007
	Median	0.009	0.008	0.009	0.008	0.007
	Min	0.008	0.005	0.006	0.008	0.004
	Max	0.014	0.011	0.015	0.014	0.009
	p_W		0.203	0.834	0.655	0.112
	p_J		0.210	0.792	0.973	0.282
Baso (1)	week: 5 N	5	5	5	5	5
	Mean	0.005	0.005	0.006	0.004	0.005
	Median	0.005	0.005	0.006	0.004	0.004
	Min	0.005	0.003	0.004	0.003	0.004
	Max	0.006	0.006	0.007	0.006	0.007
	p_W		0.905	0.369	0.178	0.214
	p_J		0.917	0.342	0.567	0.339



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Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Lympho (1)						
week:	5 N	5	5	5	5	5
	Mean	0.855	0.865	0.854	0.845	0.861
	Median	0.846	0.861	0.857	0.841	0.871
	Min	0.836	0.852	0.752	0.818	0.834
	Max	0.894	0.891	0.906	0.867	0.874
	p_W		0.116	0.249	0.600	0.463
	p_J		0.117	0.205	0.973	0.684
Mono (1)						
week:	5 N	5	5	5	5	5
	Mean	0.047	0.037	0.030	0.043	0.044
	Median	0.051	0.040	0.031	0.045	0.040
	Min	0.020	0.030	0.017	0.033	0.038
	Max	0.061	0.044	0.042	0.048	0.062
	p_W		0.116	0.076	0.169	0.463
	p_J		0.117	0.027	0.459	0.848
Luc (1)						
week:	5 N	5	5	5	5	5
	Mean	0.030	0.032	0.030	0.032	0.031
	Median	0.030	0.029	0.031	0.031	0.033
	Min	0.023	0.021	0.021	0.029	0.024
	Max	0.035	0.044	0.041	0.037	0.036
	p_W		0.917	0.917	0.599	0.528
	p_J		0.917	0.916	0.711	0.756
Neut (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.606	0.670	0.974	0.712	0.618
	Median	0.650	0.590	0.760	0.690	0.530
	Min	0.360	0.470	0.420	0.460	0.470
	Max	0.730	0.930	2.320	0.990	0.810
	p_W		0.917	0.347	0.465	0.917
	p_J		0.917	0.561	0.545	0.962

CGA 48988 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Eos (G/l)</b>						
week:	5 N	5	5	5	5	5
	Mean	0.112	0.098	0.136	0.114	0.076
	Median	0.100	0.110	0.120	0.100	0.060
	Min	0.090	0.050	0.070	0.080	0.040
	Max	0.140	0.140	0.250	0.170	0.120
	p_W		0.752	0.834	0.750	0.173
	p_J		0.754	0.673	0.814	0.282
<b>Baso (G/l)</b>						
week:	5 N	5	5	5	5	5
	Mean	0.056	0.066	0.074	0.052	0.058
	Median	0.060	0.070	0.070	0.050	0.050
	Min	0.050	0.030	0.050	0.030	0.040
	Max	0.060	0.100	0.110	0.100	0.100
	p_W		0.454	0.126	0.228	0.511
	p_J		0.465	0.187	0.762	0.519
<b>Lympho (G/l)</b>						
week:	5 N	5	5	5	5	5
	Mean	9.674	11.04	11.20	9.778	9.996
	Median	9.590	11.60	11.26	9.580	10.32
	Min	8.590	7.480	9.800	7.090	8.020
	Max	11.23	14.13	12.23	13.80	12.02
	p_W		0.175	0.028 *	0.754	0.754
	p_J		0.175	0.081	0.840	0.924
<b>Mono (G/l)</b>						
week:	5 N	5	5	5	5	5
	Mean	0.550	0.464	0.412	0.504	0.528
	Median	0.580	0.480	0.360	0.470	0.460
	Min	0.200	0.340	0.220	0.280	0.350
	Max	0.800	0.590	0.690	0.770	0.890
	p_W		0.251	0.347	0.347	0.602
	p_J		0.251	0.139	0.400	0.667

CGA 48988 tech.

Hematology (statistics) : females

dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Luc (G/l)						
week:	5 N	5	5	5	5	5
	Mean	0.342	0.404	0.406	0.380	0.364
	Median	0.350	0.390	0.380	0.350	0.440
	Min	0.260	0.250	0.260	0.240	0.220
	Max	0.420	0.600	0.670	0.570	0.470
	p_W		0.530	0.675	0.834	0.602
	p_J		0.531	0.597	0.788	0.867
Plt (G/l)						
week:	5 N	5	5	5	5	5
	Mean	1153	1015	1083	1102	1083
	Median	1109	999.0	1068	1083	1068
	Min	1060	857.0	1047	1000	949.0
	Max	1335	1146	1170	1230	1210
	p_W		0.175	0.142	0.465	0.347
	p_J		0.175	0.342	0.711	0.738
PT(CS) (sec)						
week:	5 N	5	5	5	5	5
	Mean	27.19	24.93	27.67	24.06	26.57
	Median	27.06	23.75	27.98	22.45	26.89
	Min	24.37	20.72	23.51	19.09	21.19
	Max	31.06	29.51	31.99	31.46	31.97
	p_W		0.251	0.602	0.251	0.754
	p_J		0.251	0.792	0.382	0.702

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5.3. Blood chemistry (statistics)

Statistical tests and flags used:

WILCOXON: \* if p\_W < 0.05  
 JONCKHEERE: +- if p\_J < 0.01

CGA 329351 tech.

Blood chemistry (statistics): males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Gluc (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	6.728	7.948	7.722	7.154	7.662
Median	6.860	7.840	7.630	7.220	7.780
Min	5.900	7.150	6.440	5.960	6.570
Max	7.580	9.190	9.320	8.310	9.040
p_W		0.028 *	0.076	0.465	0.076
p_J		0.028	0.081	0.346	0.315
<b>Urea (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	5.832	5.642	6.086	5.672	4.854
Median	5.810	6.290	6.020	5.500	4.440
Min	5.230	4.530	5.560	4.830	4.380
Max	6.350	6.540	6.600	7.420	5.750
p_W		0.917	0.402	0.251	0.036 *
p_J		0.917	0.597	0.662	0.040
<b>Creat-e (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	57.52	59.80	56.00	59.90	51.92
Median	57.30	56.10	54.40	60.10	52.50
Min	53.50	54.10	50.80	52.70	48.50
Max	61.50	75.60	62.80	64.60	54.50
p_W		0.754	0.754	0.347	0.016 *
p_J		0.754	0.492	0.686	0.104
<b>Bili-tot (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	2.384	2.172	2.242	2.290	1.776
Median	2.340	2.100	2.100	2.340	1.640
Min	1.870	1.870	1.870	2.100	1.400
Max	3.270	2.570	3.270	2.570	2.100
p_W		0.523	0.389	0.913	0.043 *
p_J		0.531	0.316	0.973	0.099

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Blood chemistry (statistics) : males

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Prot (g/l)	week: 5 N	5	5	5	5	5
	Mean	66.21	66.82	64.72	66.35	66.52
	Median	65.91	67.20	64.31	66.53	66.21
	Min	62.68	64.31	63.23	64.66	64.78
	Max	68.86	68.95	67.11	67.84	68.89
	p_W		0.754	0.347	0.917	0.602
	p_J		0.754	0.205	0.614	0.943
Alb (g/l)	week: 5 N	5	5	5	5	5
	Mean	38.15	38.55	37.83	38.59	38.23
	Median	38.18	38.64	37.76	38.48	38.08
	Min	36.59	37.64	36.41	38.08	37.49
	Max	39.50	39.46	39.06	39.31	39.66
	p_W		0.917	0.465	0.465	0.917
	p_J		0.917	0.316	1.000	0.756
Glob (g/l)	week: 5 N	5	5	5	5	5
	Mean	28.06	28.27	26.89	27.76	28.30
	Median	27.73	27.99	26.83	27.68	28.27
	Min	26.09	26.67	25.88	26.43	27.22
	Max	30.04	29.49	28.05	29.36	29.23
	p_W		0.754	0.175	0.834	0.754
	p_J		0.754	0.224	0.400	0.830
A/G (1)	week: 5 N	5	5	5	5	5
	Mean	1.364	1.364	1.406	1.392	1.354
	Median	1.380	1.350	1.390	1.400	1.360
	Min	1.290	1.320	1.360	1.310	1.310
	Max	1.400	1.410	1.460	1.450	1.380
	p_W		1.000	0.248	0.341	0.523
	p_J		1.000	0.205	0.189	0.962

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Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Chol (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.044	1.856	2.042	1.898	2.106
Median	2.000	1.920	1.960	1.920	2.090
Min	1.820	1.350	1.640	1.470	1.850
Max	2.330	2.300	2.470	2.160	2.400
p_W		0.347	0.917	0.465	0.602
p_J		0.347	0.916	0.638	0.702
Na+ (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	144.5	141.4	141.3	141.3	139.4
Median	144.9	142.2	140.9	142.0	139.0
Min	140.7	139.1	140.4	138.7	138.9
Max	148.8	143.4	142.2	143.7	140.7
p_W		0.175	0.209	0.175	0.009 *
p_J		0.175	0.126	0.139	0.003
K+ (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	3.727	3.751	3.788	3.825	3.512
Median	3.750	3.640	3.800	3.710	3.460
Min	3.640	3.240	3.560	3.360	3.200
Max	3.835	4.545	4.190	4.515	3.850
p_W		0.675	0.917	0.754	0.251
p_J		0.676	1.000	0.814	0.403
Ca++ (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.774	2.748	2.754	2.768	2.750
Median	2.750	2.770	2.760	2.770	2.780
Min	2.740	2.670	2.670	2.720	2.650
Max	2.830	2.770	2.800	2.810	2.800
p_W		0.916	1.000	0.752	0.597
p_J		0.917	0.958	0.788	0.867

CGA 329351 tech.

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Cl-</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	97.34	99.40	98.90	99.59	101.0
Median	97.40	99.50	99.60	99.30	100.4
Min	94.50	98.50	96.60	98.40	100.3
Max	99.70	100.5	99.70	101.2	102.6
p_W		0.142	0.207	0.076	0.009 *
p_J		0.144	0.205	0.114	> 0.001 +
<b>PO4-in</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.402	2.306	2.434	2.484	2.458
Median	2.410	2.370	2.390	2.530	2.450
Min	2.250	2.140	2.110	2.360	2.260
Max	2.570	2.450	2.790	2.630	2.680
p_W		0.347	0.917	0.346	0.465
p_J		0.347	0.874	0.459	0.327
<b>ASAT (GOT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	56.64	65.14	58.16	58.28	50.92
Median	54.60	52.70	57.10	53.30	50.80
Min	50.80	51.40	48.90	44.40	45.10
Max	63.50	115.6	72.40	85.10	56.50
p_W		0.674	0.834	0.602	0.094
p_J		0.676	0.833	0.840	0.173
<b>ALAT (GPT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	38.86	39.04	37.58	35.46	33.08
Median	39.50	36.30	41.10	31.40	33.90
Min	32.30	30.60	25.80	30.60	27.40
Max	41.90	48.40	45.20	51.60	36.30
p_W		0.917	0.834	0.140	0.059
p_J		0.917	0.958	0.382	0.166

CGA 329351 tech.

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
ALP (U/l)					
week: 5 N	5	5	5	5	5
Mean	164.8	173.8	165.2	151.3	165.2
Median	156.6	172.2	173.0	153.1	173.8
Min	148.3	118.2	124.9	129.5	126.5
Max	187.5	241.2	203.3	186.1	184.8
p_W		0.917	0.917	0.175	0.754
p_J		0.917	0.958	0.419	0.774

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Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Gluc (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	5.938	7.025	6.198	6.252	5.568
Median	5.660	6.250	6.050	6.510	5.530
Min	5.390	5.590	5.190	5.440	5.050
Max	6.730	10.13	7.640	6.930	6.140
p <sub>W</sub>		0.251	0.754	0.347	0.347
p <sub>J</sub>		0.251	0.874	0.711	0.282
<b>Urea (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	6.030	6.894	7.590	6.116	6.152
Median	6.410	6.660	7.480	6.140	6.350
Min	4.650	6.380	6.840	5.320	5.350
Max	6.930	8.090	8.790	7.630	6.930
p <sub>W</sub>		0.248	0.016 *	0.753	1.000
p <sub>J</sub>		0.251	0.010 +	0.686	0.667
<b>Creat-e (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	57.52	57.72	57.14	51.96	54.60
Median	57.80	57.70	57.50	53.90	53.80
Min	52.20	54.20	48.30	47.40	50.20
Max	65.30	60.90	62.20	54.50	63.40
p <sub>W</sub>		0.917	0.917	0.175	0.347
p <sub>J</sub>		0.917	0.958	0.093	0.081
<b>Bili-tot (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	2.478	2.244	2.224	2.152	1.614
Median	2.340	2.100	2.340	2.340	1.640
Min	2.100	1.640	1.520	1.400	1.400
Max	3.040	3.040	2.810	2.810	1.870
p <sub>W</sub>		0.396	0.523	0.395	0.009 *
p <sub>J</sub>		0.403	0.398	0.329	0.014

CGA 329351 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Prot (g/l)</b>					
week: 5 N	5	5	5	5	5
Mean	65.33	65.72	67.10	67.04	69.01
Median	66.06	65.77	67.66	67.17	69.44
Min	62.68	61.68	64.60	65.27	66.38
Max	67.72	69.07	69.21	68.42	71.43
p_W		0.917	0.251	0.117	0.016 *
p_J		0.917	0.267	0.158	0.006 +
<b>Alb (g/l)</b>					
week: 5 N	5	5	5	5	5
Mean	38.58	38.60	38.95	39.40	39.73
Median	38.29	38.87	38.67	39.37	39.95
Min	37.46	36.73	37.51	38.57	39.03
Max	39.94	39.92	41.09	40.35	40.52
p_W		0.917	0.754	0.175	0.076
p_J		0.917	0.874	0.282	0.045
<b>Glob (g/l)</b>					
week: 5 N	5	5	5	5	5
Mean	26.74	27.12	28.14	27.64	29.29
Median	26.87	26.90	28.12	27.93	29.33
Min	24.64	24.95	27.09	26.23	27.23
Max	27.80	29.15	28.99	28.47	31.48
p_W		0.465	0.028 *	0.175	0.028 *
p_J		0.465	0.030	0.080	0.003 +
<b>A/G (1)</b>					
week: 5 N	5	5	5	5	5
Mean	1.446	1.424	1.382	1.426	1.360
Median	1.440	1.420	1.380	1.440	1.360
Min	1.380	1.370	1.330	1.380	1.270
Max	1.540	1.470	1.460	1.490	1.440
p_W		0.674	0.090	0.592	0.046 *
p_J		0.676	0.081	0.459	0.056

CGA 329351 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Chol</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.619	2.346	2.580	2.412	2.488
Median	2.520	2.270	2.590	2.360	2.620
Min	2.270	2.060	2.410	2.150	2.000
Max	3.005	2.620	2.800	2.920	2.940
p_W		0.207	0.917	0.172	0.600
p_J		0.210	1.000	0.400	0.667
<b>Na+</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	139.4	140.8	140.3	138.6	138.5
Median	139.2	141.1	140.0	138.0	138.6
Min	137.6	139.8	139.2	137.1	137.6
Max	141.6	141.2	141.7	141.2	139.1
p_W		0.173	0.248	0.251	0.209
p_J		0.175	0.291	0.400	0.045
<b>K+</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	3.422	3.198	3.432	3.194	3.388
Median	3.420	3.200	3.370	3.160	3.400
Min	3.220	2.950	3.130	3.030	3.240
Max	3.660	3.490	3.840	3.440	3.610
p_W		0.117	0.917	0.047 *	0.754
p_J		0.117	0.833	0.213	0.793
<b>Ca++</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.672	2.648	2.668	2.686	2.738
Median	2.700	2.650	2.680	2.650	2.730
Min	2.550	2.570	2.600	2.590	2.680
Max	2.780	2.700	2.750	2.790	2.850
p_W		0.528	0.675	0.753	0.293
p_J		0.531	0.792	0.920	0.166

CGA 329351 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Cl-</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	100.4	100.6	100.3	101.1	101.6
Median	100.5	100.5	100.7	101.5	101.6
Min	98.80	100.1	98.30	99.40	99.80
Max	102.5	101.3	101.4	101.6	103.2
p_W		0.451	0.917	0.344	0.249
p_J		0.465	0.634	0.122	0.028
<b>PO4-in</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	1.800	1.826	1.956	1.854	2.006
Median	1.820	1.850	1.930	1.770	1.850
Min	1.560	1.500	1.650	1.570	1.750
Max	2.100	2.010	2.380	2.210	2.330
p_W		0.917	0.347	0.754	0.249
p_J		0.917	0.398	0.614	0.282
<b>ASAT (GOT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	58.30	45.65	51.06	48.52	50.80
Median	59.10	44.40	47.60	47.60	47.60
Min	52.10	40.95	45.10	40.60	47.00
Max	62.20	52.10	61.00	61.00	56.50
p_W		0.012 *	0.117	0.076	0.028 *
p_J		0.012	0.224	0.213	0.403
<b>ALAT (GPT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	31.92	34.50	31.94	37.42	39.18
Median	29.80	33.10	29.00	38.70	31.40
Min	25.00	28.20	25.00	25.00	28.20
Max	42.70	43.50	44.40	48.40	57.30
p_W		0.402	0.916	0.344	0.600
p_J		0.403	1.000	0.459	0.376

CGA 329351 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
ALP (U/l)					
week: 5 N	5	5	5	5	5
Mean	93.24	96.92	110.2	94.02	115.1
Median	83.50	91.60	121.4	91.90	95.60
Min	76.80	76.30	71.20	87.00	74.70
Max	127.0	120.6	139.4	102.3	164.4
p_W		0.754	0.465	0.465	0.465
p_J		0.754	0.369	0.567	0.403

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28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Gluc (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	6.728	7.808	7.568	6.800	6.064
Median	6.860	8.030	7.450	6.570	5.790
Min	5.900	6.550	7.190	5.750	5.540
Max	7.580	9.070	8.430	7.750	7.540
p <sub>W</sub>		0.175	0.076	0.917	0.076
p <sub>J</sub>		0.175	0.154	0.946	0.104
<b>Urea (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	5.832	5.806	5.952	5.526	5.156
Median	5.810	5.650	5.810	5.720	5.200
Min	5.230	5.320	5.200	4.160	4.770
Max	6.350	6.690	6.540	6.630	5.470
p <sub>W</sub>		0.834	0.675	0.602	0.016 *
p <sub>J</sub>		0.835	0.792	0.737	0.050
<b>Creat-e (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	57.52	53.40	60.00	58.32	56.70
Median	57.30	55.00	60.30	58.40	55.20
Min	53.50	44.60	53.30	53.50	52.50
Max	61.50	58.40	64.50	62.30	61.40
p <sub>W</sub>		0.402	0.347	0.462	0.602
p <sub>J</sub>		0.403	0.398	0.313	0.702
<b>Bili-tot (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	2.384	1.871	2.457	2.010	1.918
Median	2.340	1.870	2.570	2.100	1.870
Min	1.870	1.635	1.755	1.170	1.170
Max	3.270	2.340	2.810	2.570	2.570
p <sub>W</sub>		0.069	0.596	0.456	0.289
p <sub>J</sub>		0.076	0.751	0.840	0.459

CGA 48988 tech.

Blood chemistry (statistics) : males

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Prot (g/l)						
week:	5 N	5	5	5	5	5
	Mean	66.21	66.88	65.60	66.53	66.65
	Median	65.91	65.91	64.76	66.15	67.20
	Min	62.68	64.09	63.08	65.13	64.83
	Max	68.86	70.58	69.07	68.37	68.66
	p_W		0.675	0.754	0.917	0.917
	p_J		0.676	0.673	0.920	0.848
Alb (g/l)						
week:	5 N	5	5	5	5	5
	Mean	38.15	38.84	38.20	38.78	38.03
	Median	38.18	38.94	37.83	38.73	38.00
	Min	36.59	38.01	36.99	37.69	37.57
	Max	39.50	39.97	39.49	40.18	38.49
	p_W		0.347	0.917	0.347	0.602
	p_J		0.347	0.958	0.686	0.534
Glob (g/l)						
week:	5 N	5	5	5	5	5
	Mean	28.06	28.35	27.49	27.75	28.62
	Median	27.73	27.90	27.66	28.46	28.71
	Min	26.09	26.40	25.72	24.95	26.87
	Max	30.04	30.61	29.90	29.83	30.66
	p_W		0.602	0.530	0.754	0.602
	p_J		0.602	0.597	0.614	0.793
A/G (1)						
week:	5 N	5	5	5	5	5
	Mean	1.364	1.372	1.394	1.404	1.332
	Median	1.380	1.360	1.410	1.330	1.340
	Min	1.290	1.290	1.310	1.290	1.240
	Max	1.400	1.480	1.470	1.610	1.420
	p_W		0.834	0.249	1.000	0.401
	p_J		0.835	0.369	0.567	0.667

CGA 48988 tech.

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Chol</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.044	2.030	1.933	1.950	2.088
Median	2.000	1.900	1.940	1.900	2.050
Min	1.820	1.660	1.710	1.590	1.810
Max	2.330	2.650	2.285	2.410	2.610
p_W		0.754	0.463	0.602	0.753
p_J		0.754	0.561	0.567	0.981
<b>Na+</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	144.5	141.7	140.7	141.6	139.9
Median	144.9	141.1	140.1	140.9	140.4
Min	140.7	139.2	139.5	140.2	138.1
Max	148.8	144.7	143.7	144.6	142.1
p_W		0.175	0.028 *	0.142	0.036 *
p_J		0.175	0.030	0.168	0.050
<b>K+</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	3.727	3.502	3.797	3.634	3.540
Median	3.750	3.480	3.700	3.610	3.410
Min	3.640	3.260	3.100	3.410	3.300
Max	3.835	3.710	4.505	3.860	4.150
p_W		0.075	0.754	0.465	0.117
p_J		0.076	0.712	0.686	0.261
<b>Ca++</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.774	2.762	2.678	2.710	2.660
Median	2.750	2.760	2.710	2.720	2.660
Min	2.740	2.660	2.570	2.620	2.570
Max	2.830	2.870	2.730	2.790	2.720
p_W		0.917	0.009 *	0.059	0.009 *
p_J		0.917	0.057	0.075	0.009 -



CGA 48988 tech.

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Cl-</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	97.34	100.1	99.60	99.46	100.2
Median	97.40	99.65	100.3	99.40	100.7
Min	94.50	99.00	97.70	98.20	98.70
Max	99.70	101.8	101.2	101.1	100.9
p_W		0.047 *	0.076	0.117	0.047 *
p_J		0.047	0.081	0.178	0.085
<b>PO4-in</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.402	2.408	2.358	2.308	2.230
Median	2.410	2.440	2.380	2.310	2.180
Min	2.250	2.190	2.130	2.110	2.130
Max	2.570	2.510	2.560	2.460	2.350
p_W		0.834	0.754	0.347	0.047 *
p_J		0.835	0.751	0.297	0.030
<b>ASAT (GOT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	56.64	55.35	68.20	52.72	54.60
Median	54.60	55.20	62.20	54.00	53.30
Min	50.80	45.70	61.00	44.40	51.40
Max	63.50	64.10	89.50	59.70	59.70
p_W		0.917	0.047 *	0.295	0.465
p_J		0.917	0.051	0.973	0.416
<b>ALAT (GPT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	38.86	41.04	42.90	32.42	32.74
Median	39.50	37.90	41.90	32.30	33.10
Min	32.30	25.80	37.90	26.60	23.40
Max	41.90	64.10	51.60	37.90	42.70
p_W		0.458	0.399	0.036 *	0.249
p_J		0.465	0.673	0.106	0.033

CGA 48988 tech.

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
ALP (U/l)					
week: 5 N	5	5	5	5	5
Mean	164.8	186.7	156.9	153.7	153.8
Median	156.6	208.7	182.6	151.0	145.0
Min	148.3	136.2	59.90	141.6	112.3
Max	187.5	216.8	204.9	177.0	232.1
P_W		0.251	0.754	0.175	0.117
P_J		0.251	0.874	0.226	0.059

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Statistical tests and flags used:  
 WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Gluc (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	5.938	5.794	4.872	5.412	6.384
Median	5.660	5.770	5.080	5.470	6.300
Min	5.390	5.140	3.810	4.950	5.600
Max	6.730	6.730	5.500	5.830	7.620
p <sub>W</sub>		0.834	0.028 *	0.175	0.347
p <sub>J</sub>		0.835	0.027	0.080	0.667
<b>Urea (mmol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	6.030	6.128	7.343	6.778	5.908
Median	6.410	6.320	6.570	6.960	6.020
Min	4.650	5.230	5.440	6.170	4.740
Max	6.930	7.020	11.66	7.270	7.110
p <sub>W</sub>		0.917	0.465	0.175	0.917
p <sub>J</sub>		0.917	0.369	0.139	0.774
<b>Creat-e (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	57.52	54.84	62.24	57.04	51.94
Median	57.80	54.20	62.30	56.90	52.50
Min	52.20	45.80	51.10	51.90	50.30
Max	65.30	67.10	75.10	66.80	52.50
p <sub>W</sub>		0.465	0.465	0.463	0.085
p <sub>J</sub>		0.465	0.492	0.866	0.293
<b>Bili-tot (umol/l)</b>					
week: 5 N	5	5	5	5	5
Mean	2.478	1.894	2.010	1.730	1.494
Median	2.340	1.750	2.100	1.640	1.400
Min	2.100	1.640	1.400	1.400	1.170
Max	3.040	2.570	2.570	2.100	2.100
p <sub>W</sub>		0.046 *	0.203	0.015 *	0.014 *
p <sub>J</sub>		0.047	0.126	0.024	0.001 -

CGA 48988 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Prot (g/l)					
week: 5 N	5	5	5	5	5
Mean	65.33	65.28	66.46	68.95	69.56
Median	66.06	65.10	66.21	67.97	70.28
Min	62.68	63.29	63.01	67.59	65.83
Max	67.72	68.15	70.60	71.30	71.77
p_W		0.917	0.465	0.028 *	0.047 *
p_J		0.917	0.561	0.022 =	0.002 +
Alb (g/l)					
week: 5 N	5	5	5	5	5
Mean	38.58	38.24	37.70	39.12	40.25
Median	38.29	37.57	37.08	38.92	40.43
Min	37.46	37.16	35.80	37.34	39.08
Max	39.94	40.03	40.66	40.60	40.98
p_W		0.602	0.175	0.602	0.028 *
p_J		0.602	0.154	0.946	0.062
Glob (g/l)					
week: 5 N	5	5	5	5	5
Mean	26.74	26.95	28.53	29.92	29.67
Median	26.87	26.53	28.51	30.06	30.77
Min	24.64	25.69	27.34	29.10	26.75
Max	27.80	28.53	30.39	30.71	31.62
p_W		0.754	0.076	0.009 *	0.047 *
p_J		0.754	0.126	0.001 +	0.000 +
A/G (1)					
week: 5 N	5	5	5	5	5
Mean	1.446	1.430	1.330	1.308	1.360
Median	1.440	1.460	1.310	1.320	1.310
Min	1.380	1.350	1.300	1.230	1.300
Max	1.540	1.470	1.390	1.350	1.460
p_W		1.000	0.016 *	0.009 *	0.141
p_J		1.000	0.015	0.001 -	0.005 -

CGA 48988 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Chol</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.619	2.340	2.444	2.851	2.720
Median	2.520	2.500	2.370	2.840	2.700
Min	2.270	1.870	1.810	2.570	2.370
Max	3.005	2.700	2.970	3.265	3.150
p_W		0.249	0.463	0.173	0.463
p_J		0.251	0.428	0.329	0.223
<b>Na+</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	139.4	142.1	140.0	140.7	139.9
Median	139.2	141.1	139.4	140.8	140.5
Min	137.6	140.9	138.9	138.3	138.0
Max	141.6	145.3	142.5	143.0	141.8
p_W		0.047 *	0.463	0.251	0.600
p_J		0.047	0.634	0.590	1.000
<b>K+</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	3.422	3.324	3.382	3.460	3.508
Median	3.420	3.350	3.450	3.390	3.450
Min	3.220	3.100	3.130	3.040	3.130
Max	3.660	3.620	3.550	4.090	3.890
p_W		0.463	0.917	0.917	0.917
p_J		0.465	0.916	0.973	0.738
<b>Ca++</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	2.672	2.586	2.656	2.771	2.621
Median	2.700	2.580	2.670	2.790	2.590
Min	2.550	2.510	2.550	2.640	2.465
Max	2.780	2.710	2.740	2.880	2.760
p_W		0.142	0.753	0.076	0.465
p_J		0.144	0.874	0.060	0.430

CGA 48988 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Cl-</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	100.4	99.70	98.97	98.62	99.81
Median	100.5	99.70	99.70	98.75	99.80
Min	98.80	98.50	95.35	97.65	99.10
Max	102.5	101.8	101.7	99.55	100.4
p_W		0.173	0.207	0.028 *	0.249
p_J		0.175	0.126	0.015	0.232
<b>PO4-in</b> (mmol/l)					
week: 5 N	5	5	5	5	5
Mean	1.800	1.906	1.806	2.068	1.770
Median	1.820	1.890	1.790	2.090	1.610
Min	1.560	1.580	1.550	1.900	1.550
Max	2.100	2.110	1.960	2.170	2.250
p_W		0.346	0.917	0.059	0.463
p_J		0.347	0.958	0.099	0.738
<b>ASAT (GOT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	58.30	48.26	126.4	53.08	49.28
Median	59.10	47.00	56.50	52.70	48.90
Min	52.10	42.50	47.60	48.90	46.40
Max	62.20	56.50	395.3	57.10	55.20
p_W		0.016 *	0.917	0.059	0.016 *
p_J		0.016	0.751	0.590	0.115
<b>ALAT (GPT)</b> (U/l)					
week: 5 N	5	5	5	5	5
Mean	31.92	27.26	46.46	35.98	42.72
Median	29.80	25.00	36.30	37.10	41.10
Min	25.00	21.80	25.00	32.30	30.60
Max	42.70	34.70	99.20	37.10	56.40
p_W		0.295	0.295	0.169	0.117
p_J		0.296	0.342	0.069	0.020

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
AlP (U/l)					
week: 5 N	5	5	5	5	5
Mean	93.24	76.85	116.6	87.56	117.6
Median	83.50	75.70	121.9	83.50	130.8
Min	76.80	60.15	88.40	58.00	69.30
Max	127.0	96.70	130.5	134.6	164.7
p_W		0.175	0.076	0.675	0.251
p_J		0.175	0.154	0.662	= 0.189

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5.4. Organ weights and ratios (statistics)

5.4.1. Organ weights (statistics)

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Organ weights (statistics): males week 5

Dose (mg/kg)		group 1	group 2	group 3	group 4	group 5
		0	10	50	150	300
Body (g)	N	5	5	5	5	5
	Mean	327.6	332.5	325.7	312.9	315.8
	Median	320.9	339.0	325.2	319.5	317.9
	Min	309.7	290.2	293.9	299.9	292.6
	Max	366.4	372.9	360.3	321.7	348.5
	p <sub>W</sub>		0.917	0.602	0.347	0.465
	p <sub>J</sub>		0.917	0.874	0.419	0.251
Heart (g)	N	5	5	5	5	5
	Mean	1.158	1.177	1.116	1.110	1.109
	Median	1.140	1.179	1.130	1.147	1.119
	Min	1.065	1.065	1.010	1.006	1.027
	Max	1.279	1.352	1.180	1.208	1.163
	p <sub>W</sub>		1.000	0.602	0.465	0.465
	p <sub>J</sub>		1.000	0.526	0.329	0.223
Liver (g)	N	5	5	5	5	5
	Mean	16.71	18.74	17.44	17.52	17.90
	Median	17.24	17.74	17.85	17.55	17.45
	Min	15.34	15.11	14.07	15.36	17.05
	Max	17.36	22.56	19.23	19.40	20.25
	p <sub>W</sub>		0.347	0.347	0.117	0.175
	p <sub>J</sub>		0.347	0.492	0.382	0.444
Kidney (both) (g)	N	5	5	5	5	5
	Mean	2.529	2.531	2.435	2.312	2.480
	Median	2.436	2.708	2.349	2.390	2.421
	Min	2.392	2.092	2.225	2.112	2.318
	Max	2.721	2.880	2.649	2.468	2.656
	p <sub>W</sub>		0.754	0.175	0.076	0.347
	p <sub>J</sub>		0.754	0.428	0.122	0.315



CGA 329351 tech.

Organ weights (statistics): males week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Adrenal (both) (mg)	N	5	5	5	5	5
	Mean	82.12	80.88	84.28	76.20	79.52
	Median	80.60	83.10	78.60	75.60	77.90
	Min	73.00	72.40	69.80	60.70	72.80
	Max	90.50	87.30	111.7	87.90	91.70
	p_W		0.602	0.754	0.251	0.465
	p_J		0.602	0.634	0.329	0.430
Thymus (mg)	N	5	5	5	5	5
	Mean	823.3	738.4	767.4	668.9	768.6
	Median	839.6	718.0	728.4	696.2	732.7
	Min	694.9	550.8	635.7	532.4	662.4
	Max	995.9	1031	945.6	743.3	907.9
	p_W		0.347	0.465	0.076	0.465
	p_J		0.347	0.561	0.139	0.444
Testis (both) (g)	N	5	5	5	5	5
	Mean	3.445	3.418	3.402	3.370	3.428
	Median	3.438	3.416	3.444	3.346	3.383
	Min	3.182	3.084	2.899	3.166	3.220
	Max	3.726	3.767	3.777	3.571	3.719
	p_W		0.754	0.754	0.465	0.754
	p_J		0.754	0.874	0.737	0.774
Spleen (g)	N	5	5	5	5	5
	Mean	0.726	0.701	0.671	0.737	0.637
	Median	0.738	0.664	0.643	0.756	0.632
	Min	0.579	0.528	0.603	0.690	0.600
	Max	0.796	0.935	0.809	0.774	0.695
	p_W		0.754	0.465	0.754	0.117
	p_J		0.754	0.561	0.840	0.339
Thyroid gland (mg)	N	5	5	5	5	5
	Mean	23.40	20.32	24.70	20.74	21.20
	Median	22.90	19.80	26.30	22.20	23.90
	Min	15.10	12.90	20.30	15.50	13.60
	Max	29.20	28.50	27.50	24.10	25.70
	p_W		0.465	0.917	0.465	0.602
	p_J		0.465	0.874	0.590	0.566

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Organ weights (statistics): females week 5

Dose (mg/kg)		group 1	group 2	group 3	group 4	group 5
		0	10	50	150	300
Body (g)	N	5	5	5	5	5
	Mean	243.7	233.1	235.3	230.7	238.5
	Median	244.6	234.6	237.8	233.3	237.1
	Min	233.4	206.0	220.6	211.2	227.6
	Max	255.3	256.4	251.7	245.9	253.3
	p <sub>W</sub>		0.465	0.347	0.076	0.465
	p <sub>J</sub>		0.465	0.428	0.201	0.534
Heart (g)	N	5	5	5	5	5
	Mean	0.906	0.886	0.885	0.930	0.938
	Median	0.902	0.865	0.892	0.891	0.942
	Min	0.777	0.836	0.789	0.830	0.807
	Max	1.104	0.964	0.961	1.049	1.039
	p <sub>W</sub>		0.917	0.754	0.917	0.602
	p <sub>J</sub>		0.917	0.958	0.737	0.416
Liver (g)	N	5	5	5	5	5
	Mean	11.39	11.44	11.48	11.58	12.38
	Median	11.49	11.76	11.15	11.41	12.45
	Min	10.67	9.871	10.76	10.50	11.34
	Max	11.89	12.53	13.28	12.48	13.57
	p <sub>W</sub>		0.754	0.754	0.754	0.047 *
	p <sub>J</sub>		0.754	0.874	0.840	0.115
Kidney (both) (g)	N	5	5	5	5	5
	Mean	1.864	1.851	1.812	1.801	1.939
	Median	1.881	1.853	1.704	1.821	1.897
	Min	1.639	1.678	1.518	1.635	1.635
	Max	2.220	2.095	2.386	1.924	2.390
	p <sub>W</sub>		0.754	0.602	0.602	0.602
	p <sub>J</sub>		0.754	0.369	0.545	0.774

CGA 329351 tech.

Organ weights (statistics): females week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Adrenal (both) (mg)	N	5	5	5	5	5
	Mean	80.96	87.52	89.12	89.00	92.62
	Median	76.40	85.70	89.20	92.00	92.30
	Min	70.70	81.20	73.90	70.90	79.10
	Max	92.90	98.80	101.1	106.0	110.7
	p_W		0.347	0.251	0.251	0.175
	p_J		0.347	0.187	0.201	0.120
Thymus (mg)	N	5	5	5	5	5
	Mean	525.2	550.6	563.3	532.4	562.9
	Median	558.9	573.3	541.3	618.1	595.3
	Min	374.7	473.2	281.4	264.4	481.9
	Max	605.1	623.7	842.7	656.8	650.5
	p_W		0.754	0.754	0.465	0.602
	p_J		0.754	0.634	0.545	0.550
Ovary (both) (mg)	N	5	5	5	5	5
	Mean	166.6	174.0	170.9	172.6	169.5
	Median	169.7	184.6	158.9	175.3	170.0
	Min	129.2	148.3	142.4	135.2	146.4
	Max	196.8	191.0	218.0	208.5	196.4
	p_W		0.917	0.917	0.602	0.334
	p_J		0.917	0.916	0.866	0.962
Spleen (g)	N	5	5	5	5	5
	Mean	0.606	0.633	0.633	0.683	0.604
	Median	0.606	0.583	0.615	0.662	0.577
	Min	0.534	0.532	0.584	0.625	0.481
	Max	0.691	0.748	0.753	0.818	0.777
	p_W		0.917	0.465	0.076	0.602
	p_J		0.917	0.428	0.051	0.503
Thyroid gland (mg)	N	5	5	5	5	5
	Mean	19.34	24.44	21.42	22.50	17.56
	Median	18.10	24.10	17.90	23.50	16.70
	Min	16.20	19.70	17.00	16.00	13.80
	Max	25.30	27.50	28.30	27.00	22.60
	p_W		0.047 *	0.754	0.251	0.402
	p_J		0.047	0.492	0.590	0.304

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Organ weights (statistics): males week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Body (g)	N	5	5	5	5	5
	Mean	327.6	328.9	313.0	313.2	325.7
	Median	320.9	328.2	313.4	321.8	336.5
	Min	309.7	295.6	294.5	290.8	296.9
	Max	366.4	375.0	331.8	325.2	349.0
	p <sub>W</sub>		0.917	0.347	0.754	0.917
	p <sub>J</sub>		0.917	0.369	0.313	0.774
Heart (g)	N	5	5	5	5	5
	Mean	1.158	1.120	1.092	1.114	1.091
	Median	1.140	1.092	1.107	1.081	1.069
	Min	1.065	1.051	1.009	0.999	0.957
	Max	1.279	1.289	1.135	1.321	1.213
	p <sub>W</sub>		0.347	0.251	0.465	0.251
	p <sub>J</sub>		0.347	0.316	0.282	0.251
Liver (g)	N	5	5	5	5	5
	Mean	16.71	17.66	16.68	16.16	18.24
	Median	17.24	18.05	16.95	16.12	18.89
	Min	15.34	16.63	15.40	15.16	15.26
	Max	17.36	18.72	17.45	17.51	20.70
	p <sub>W</sub>		0.175	0.917	0.465	0.347
	p <sub>J</sub>		0.175	0.958	0.226	0.962
Kidney (both) (g)	N	5	5	5	5	5
	Mean	2.529	2.445	2.284	2.414	2.413
	Median	2.436	2.336	2.342	2.451	2.408
	Min	2.392	2.285	1.968	2.057	2.180
	Max	2.721	2.814	2.536	2.871	2.860
	p <sub>W</sub>		0.347	0.076	0.754	0.251
	p <sub>J</sub>		0.347	0.101	0.346	0.389

CGA 48988 tech.

Organ weights (statistics): males week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Adrenal (both) (mg)	N	5	5	5	5	5
	Mean	82.12	76.68	69.92	79.24	78.84
	Median	80.60	78.50	71.20	83.40	80.20
	Min	73.00	65.30	63.90	62.00	67.20
	Max	90.50	84.60	77.00	84.30	88.80
	p_W		0.347	0.016 *	0.917	0.602
	p_J		0.347	0.013	0.382	0.811
Thymus (mg)	N	5	5	5	5	5
	Mean	823.3	939.3	749.8	891.9	782.0
	Median	839.6	947.3	768.7	923.9	764.0
	Min	694.9	892.6	582.8	763.2	585.4
	Max	995.9	972.3	882.4	1058	919.7
	p_W		0.117	0.465	0.347	0.917
	p_J		0.117	0.369	1.000	0.444
Testis (both) (g)	N	5	5	5	5	5
	Mean	3.445	3.357	3.459	3.395	3.471
	Median	3.438	3.408	3.517	3.263	3.578
	Min	3.182	3.106	3.038	3.129	2.994
	Max	3.726	3.650	3.880	3.972	3.804
	p_W		0.465	0.917	0.347	0.754
	p_J		0.465	0.958	0.638	0.562
Spleen (g)	N	5	5	5	5	5
	Mean	0.726	0.764	0.721	0.706	0.706
	Median	0.738	0.778	0.715	0.717	0.699
	Min	0.579	0.615	0.601	0.656	0.632
	Max	0.796	0.917	0.801	0.741	0.806
	p_W		0.602	0.754	0.347	0.754
	p_J		0.602	0.792	0.382	0.339
Thyroid gland (mg)	N	5	5	5	5	5
	Mean	23.40	22.50	23.90	22.66	24.00
	Median	22.90	21.50	22.50	22.50	24.20
	Min	15.10	20.00	20.20	16.60	18.40
	Max	29.20	26.60	30.40	32.80	29.20
	p_W		0.465	0.917	0.917	1.000
	p_J		0.465	0.874	0.711	0.924

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Organ weights (statistics): females week 5

Dose (mg/kg)		group 1	group 2	group 3	group 4	group 5
		0	10	50	150	300
Body (g)	N	5	5	5	5	5
	Mean	243.7	240.8	244.3	245.9	244.8
	Median	244.6	241.3	243.7	246.6	242.3
	Min	233.4	230.9	218.5	218.0	238.1
	Max	255.3	247.2	272.2	265.0	257.9
	p <sub>W</sub>		0.602	0.917	0.754	0.834
	p <sub>J</sub>		0.602	0.874	0.840	0.830
Heart (g)	N	5	5	5	5	5
	Mean	0.906	0.919	0.878	0.967	0.947
	Median	0.902	0.935	0.843	0.991	0.944
	Min	0.777	0.822	0.746	0.854	0.912
	Max	1.104	0.990	1.004	1.106	0.976
	p <sub>W</sub>		0.602	0.602	0.347	0.117
	p <sub>J</sub>		0.602	0.874	0.346	0.214
Liver (g)	N	5	5	5	5	5
	Mean	11.39	10.57	11.47	12.29	12.80
	Median	11.49	10.52	10.95	13.12	13.03
	Min	10.67	9.798	10.08	10.61	11.74
	Max	11.89	11.48	13.18	13.64	13.83
	p <sub>W</sub>		0.028 *	0.754	0.465	0.028 *
	p <sub>J</sub>		0.028	0.428	0.459	0.040
Kidney (both) (g)	N	5	5	5	5	5
	Mean	1.864	2.039	2.058	2.051	2.060
	Median	1.881	2.046	2.090	1.955	2.036
	Min	1.639	1.872	1.624	1.824	1.782
	Max	2.220	2.262	2.441	2.374	2.338
	p <sub>W</sub>		0.175	0.251	0.251	0.175
	p <sub>J</sub>		0.175	0.154	0.253	0.251

CGA 48988 tech.

Organ weights (statistics): females week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Adrenal (both) (mg)	N	5	5	5	5	5
	Mean	80.96	85.52	94.46	99.26	85.62
	Median	76.40	80.00	90.60	96.90	79.70
	Min	70.70	71.10	86.50	89.40	75.40
	Max	92.90	99.10	108.7	109.2	99.50
	p_W		0.346	0.175	0.028 *	0.347
	p_J		0.347	0.101	0.013	0.151
Thymus (mg)	N	5	5	5	5	5
	Mean	525.2	598.6	523.7	557.0	583.1
	Median	558.9	580.7	429.9	573.3	661.0
	Min	374.7	550.9	405.9	380.8	350.0
	Max	605.1	689.1	693.6	760.6	735.1
	p_W		0.347	0.917	0.917	0.465
	p_J		0.347	0.874	1.000	0.667
Ovary (both) (mg)	N	5	5	5	5	5
	Mean	166.6	183.0	172.2	169.6	171.1
	Median	169.7	196.6	179.5	163.2	172.6
	Min	129.2	147.2	150.7	149.8	135.3
	Max	196.8	212.3	192.6	200.5	207.2
	p_W		0.251	0.754	0.754	0.754
	p_J		0.251	0.792	0.946	0.981
Spleen (g)	N	5	5	5	5	5
	Mean	0.606	0.681	0.658	0.677	0.657
	Median	0.606	0.690	0.673	0.653	0.606
	Min	0.534	0.630	0.493	0.605	0.567
	Max	0.691	0.713	0.834	0.822	0.843
	p_W		0.047 *	0.347	0.175	0.754
	p_J		0.047	0.267	0.382	0.774
Thyroid gland (mg)	N	5	5	5	5	5
	Mean	19.34	20.02	18.22	20.34	18.24
	Median	18.10	19.80	18.00	19.30	16.90
	Min	16.20	15.60	14.90	17.70	15.50
	Max	25.30	25.00	22.20	25.70	25.00
	p_W		0.602	0.602	0.402	0.251
	p_J		0.602	0.712	0.788	0.459

5.4.2. Organ to bodyweight ratios (statistics)

Statistical tests and flags used:  
 WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Organ to bodyweight ratios (statistics): males week 5

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	150	300
<b>Heart</b>					
(o/oo) N	5	5	5	5	5
Mean	3.539	3.550	3.432	3.545	3.521
Median	3.491	3.622	3.439	3.568	3.558
Min	3.341	3.160	3.211	3.355	3.165
Max	3.921	3.760	3.629	3.753	3.795
p <sub>W</sub>		0.602	0.602	0.602	0.602
p <sub>J</sub>		0.602	0.561	0.946	0.848
<b>Liver</b>					
(o/oo) N	5	5	5	5	5
Mean	51.10	56.20	53.42	55.97	56.73
Median	50.62	58.60	53.36	54.94	58.11
Min	47.39	50.24	47.89	51.23	53.64
Max	54.05	60.51	58.90	60.32	59.19
p <sub>W</sub>		0.117	0.347	0.076	0.076
p <sub>J</sub>		0.117	0.369	0.122	0.085
<b>Kidney (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	7.727	7.586	7.481	7.395	7.868
Median	7.610	7.620	7.324	7.480	8.008
Min	7.423	6.955	7.053	6.566	7.291
Max	8.311	8.010	8.145	8.037	8.213
p <sub>W</sub>		0.754	0.175	0.465	0.602
p <sub>J</sub>		0.754	0.267	0.282	0.811
<b>Adrenal (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	0.251	0.245	0.257	0.243	0.253
Median	0.247	0.233	0.242	0.241	0.258
Min	0.226	0.223	0.218	0.201	0.209
Max	0.284	0.290	0.310	0.275	0.288
p <sub>W</sub>		0.602	0.754	0.602	0.754
p <sub>J</sub>		0.602	0.874	0.686	1.000



CGA 329351 tech.

Organ to bodyweight ratios (statistics): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Thymus</b>					
(o/oo) N	5	5	5	5	5
Mean	2.536	2.194	2.361	2.145	2.463
Median	2.616	2.118	2.163	2.179	2.254
Min	1.897	1.898	2.022	1.655	1.901
Max	3.216	2.764	2.944	2.478	3.103
p_W		0.347	0.602	0.175	0.917
p_J		0.347	0.712	0.459	0.962
<b>Testis (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	10.54	10.31	10.50	10.77	10.87
Median	10.27	10.10	10.20	10.75	11.00
Min	9.383	9.919	8.838	10.36	10.18
Max	11.56	11.22	12.31	11.16	11.48
p_W		0.347	0.917	0.602	0.754
p_J		0.347	0.634	0.590	0.364
<b>Spleen</b>					
(o/oo) N	5	5	5	5	5
Mean	2.218	2.092	2.070	2.357	2.025
Median	2.240	2.206	2.026	2.351	2.070
Min	1.816	1.697	1.780	2.166	1.723
Max	2.571	2.507	2.519	2.574	2.187
p_W		0.465	0.347	0.251	0.117
p_J		0.465	0.369	0.459	0.566
<b>Thyroid gland</b>					
(o/oo) N	5	5	5	5	5
Mean	0.071	0.061	0.076	0.067	0.067
Median	0.072	0.059	0.073	0.074	0.069
Min	0.047	0.038	0.062	0.049	0.043
Max	0.091	0.079	0.094	0.080	0.082
p_W		0.602	0.754	0.917	0.602
p_J		0.602	0.561	0.840	0.962

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 329351 tech.

Organ to bodyweight ratios (statistics): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Heart</b>					
(o/oo) N	5	5	5	5	5
Mean	3.709	3.817	3.759	4.028	3.936
Median	3.652	3.909	3.770	3.929	3.719
Min	3.327	3.375	3.575	3.724	3.546
Max	4.322	4.130	3.943	4.449	4.416
p <sub>W</sub>		0.347	0.251	0.076	0.251
p <sub>J</sub>		0.347	0.428	0.069	0.151
<b>Liver</b>					
(o/oo) N	5	5	5	5	5
Mean	46.76	49.09	48.76	50.17	51.90
Median	46.20	48.85	48.79	49.94	52.03
Min	44.75	47.04	44.76	48.06	48.21
Max	50.17	52.62	52.75	52.96	54.85
p <sub>W</sub>		0.076	0.251	0.076	0.016 *
p <sub>J</sub>		0.076	0.154	0.019	0.001 +
<b>Kidney (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	7.632	7.958	7.683	7.808	8.136
Median	7.588	8.171	7.532	7.742	7.664
Min	6.915	7.151	6.276	7.558	7.181
Max	8.696	8.533	9.479	8.162	10.16
p <sub>W</sub>		0.465	0.917	0.465	0.602
p <sub>J</sub>		0.465	0.958	0.840	0.702
<b>Adrenal (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	0.332	0.377	0.379	0.385	0.389
Median	0.322	0.394	0.375	0.394	0.391
Min	0.294	0.326	0.306	0.336	0.312
Max	0.380	0.403	0.450	0.431	0.463
p <sub>W</sub>		0.047 *	0.117	0.076	0.047 *
p <sub>J</sub>		0.047	0.081	0.060	0.077

CGA 329351 tech.

Organ to bodyweight ratios (statistics): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Thymus</b>					
(o/oo) N	5	5	5	5	5
Mean	2.157	2.362	2.397	2.287	2.356
Median	2.254	2.444	2.454	2.514	2.511
Min	1.532	2.117	1.164	1.252	2.014
Max	2.593	2.547	3.544	2.888	2.568
p_W		0.347	0.347	0.602	0.602
p_J		0.347	0.224	0.253	0.293
<b>Ovary (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	0.682	0.754	0.724	0.746	0.710
Median	0.665	0.771	0.720	0.771	0.717
Min	0.545	0.612	0.613	0.639	0.637
Max	0.794	0.927	0.866	0.894	0.776
p_W		0.465	0.602	0.465	0.917
p_J		0.465	0.561	0.382	0.633
<b>Spleen</b>					
(o/oo) N	5	5	5	5	5
Mean	2.489	2.731	2.696	2.966	2.534
Median	2.509	2.583	2.597	2.809	2.435
Min	2.154	2.273	2.442	2.728	2.008
Max	2.706	3.348	3.166	3.596	3.304
p_W		0.602	0.465	0.009 *	0.254
p_J		0.602	0.428	0.037	0.503
<b>Thyroid gland</b>					
(o/oo) N	5	5	5	5	5
Mean	0.079	0.106	0.091	0.097	0.073
Median	0.075	0.111	0.077	0.101	0.071
Min	0.066	0.077	0.074	0.076	0.059
Max	0.099	0.123	0.126	0.114	0.089
p_W		0.028 *	0.347	0.047 *	0.465
p_J		0.028	0.267	0.226	0.566

Statistical tests and flags used:

WILCOXON: \* if p<sub>W</sub> < 0.05  
 JONCKHEERE: +- if p<sub>J</sub> < 0.01

CGA 48988 tech.

Organ to bodyweight ratios (statistics): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Heart</b>					
(o/oo) N	5	5	5	5	5
Mean	3.539	3.412	3.498	3.552	3.351
Median	3.491	3.438	3.383	3.435	3.442
Min	3.341	3.208	3.219	3.322	3.070
Max	3.921	3.635	3.854	4.067	3.544
p <sub>W</sub>		0.602	0.602	0.917	0.251
p <sub>J</sub>		0.602	0.792	1.000	0.503
<b>Liver</b>					
(o/oo) N	5	5	5	5	5
Mean	51.10	53.86	53.34	51.69	55.88
Median	50.62	54.14	52.61	53.17	54.74
Min	47.39	49.93	50.83	46.62	51.39
Max	54.05	56.49	56.58	54.61	60.09
p <sub>W</sub>		0.117	0.175	0.754	0.028 *
p <sub>J</sub>		0.117	0.224	0.737	0.104
<b>Kidney (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	7.727	7.444	7.291	7.689	7.399
Median	7.610	7.498	7.341	7.538	7.224
Min	7.423	6.903	6.498	7.074	7.031
Max	8.311	7.874	7.870	8.843	8.195
p <sub>W</sub>		0.602	0.175	0.754	0.076
p <sub>J</sub>		0.602	0.154	0.590	0.251
<b>Adrenal (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	0.251	0.234	0.223	0.254	0.243
Median	0.247	0.239	0.228	0.256	0.238
Min	0.226	0.211	0.205	0.193	0.195
Max	0.284	0.250	0.235	0.290	0.297
p <sub>W</sub>		0.175	0.047 *	0.347	0.754
p <sub>J</sub>		0.175	0.023	0.893	0.962

CGA 48988 tech.

Organ to bodyweight ratios (statistics): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Thymus</b>					
(o/oo) N	5	5	5	5	5
Mean	2.536	2.874	2.396	2.851	2.395
Median	2.616	2.960	2.317	2.845	2.532
Min	1.897	2.526	1.860	2.395	1.972
Max	3.216	3.166	2.811	3.253	2.733
p_W		0.347	0.917	0.251	0.602
p_J		0.347	0.634	0.545	0.633
<b>Testis (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	10.54	10.26	11.07	10.85	10.70
Median	10.27	9.733	11.10	10.56	10.93
Min	9.383	9.378	9.693	9.636	8.692
Max	11.56	11.53	12.81	12.34	12.05
p_W		0.465	0.602	0.602	0.754
p_J		0.465	0.792	0.638	0.702
<b>Spleen</b>					
(o/oo) N	5	5	5	5	5
Mean	2.218	2.324	2.312	2.259	2.167
Median	2.240	2.299	2.214	2.269	2.138
Min	1.816	2.002	1.919	2.093	2.028
Max	2.571	2.719	2.643	2.466	2.395
p_W		0.754	0.754	0.917	0.465
p_J		0.754	0.874	0.946	0.444
<b>Thyroid gland</b>					
(o/oo) N	5	5	5	5	5
Mean	0.071	0.069	0.077	0.072	0.074
Median	0.072	0.070	0.074	0.070	0.076
Min	0.047	0.061	0.064	0.051	0.061
Max	0.091	0.079	0.094	0.101	0.087
p_W		0.347	0.754	0.917	0.754
p_J		0.347	0.792	0.946	0.811

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

Statistical tests and flags used:WILCOXON: \* if p<sub>W</sub> < 0.05JONCKHEERE: +- if p<sub>J</sub> < 0.01CGA 48988 tech.

Organ to bodyweight ratios (statistics): females week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
Heart (o/oo)	N	5	5	5	5	5
	Mean	3.709	3.812	3.588	3.929	3.869
	Median	3.652	3.800	3.555	3.916	3.842
	Min	3.327	3.561	3.400	3.725	3.784
	Max	4.322	4.003	3.978	4.174	3.974
	p <sub>W</sub>		0.251	0.465	0.117	0.117
	p <sub>J</sub>		0.251	0.561	0.282	0.126
Liver (o/oo)	N	5	5	5	5	5
	Mean	46.76	43.96	46.88	49.99	52.28
	Median	46.20	42.76	46.13	49.87	51.41
	Min	44.75	41.06	44.78	43.90	48.44
	Max	50.17	49.70	50.19	56.07	57.39
	p <sub>W</sub>		0.076	0.917	0.251	0.016 *
	p <sub>J</sub>		0.076	0.958	0.158	0.005 +
Kidney (both) (o/oo)	N	5	5	5	5	5
	Mean	7.632	8.477	8.416	8.331	8.420
	Median	7.588	8.313	8.154	8.365	8.487
	Min	6.915	7.671	7.434	7.517	7.353
	Max	8.696	9.373	10.02	9.021	9.558
	p <sub>W</sub>		0.076	0.175	0.175	0.117
	p <sub>J</sub>		0.076	0.154	0.178	0.151
Adrenal (both) (o/oo)	N	5	5	5	5	5
	Mean	0.332	0.355	0.389	0.407	0.349
	Median	0.322	0.346	0.396	0.368	0.329
	Min	0.294	0.298	0.333	0.363	0.313
	Max	0.380	0.404	0.464	0.478	0.399
	p <sub>W</sub>		0.347	0.076	0.047 *	0.347
	p <sub>J</sub>		0.347	0.081	0.019	0.251

CGA 48988 tech.

Organ to bodyweight ratios (statistics): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 150	group 5 300
<b>Thymus</b>					
(o/oo) N	5	5	5	5	5
Mean	2.157	2.486	2.132	2.268	2.374
Median	2.254	2.469	1.968	2.163	2.702
Min	1.532	2.229	1.608	1.747	1.452
Max	2.593	2.800	2.757	3.216	3.034
p_W		0.175	0.917	0.917	0.465
p_J		0.175	0.874	0.840	0.774
<b>Ovary (both)</b>					
(o/oo) N	5	5	5	5	5
Mean	0.682	0.760	0.705	0.690	0.697
Median	0.665	0.795	0.717	0.690	0.712
Min	0.545	0.598	0.643	0.574	0.568
Max	0.794	0.880	0.737	0.757	0.803
p_W		0.175	0.754	0.917	0.754
p_J		0.175	0.634	0.946	0.886
<b>Spleen</b>					
(o/oo) N	5	5	5	5	5
Mean	2.489	2.829	2.685	2.773	2.691
Median	2.509	2.938	2.631	2.745	2.546
Min	2.154	2.547	2.254	2.284	2.200
Max	2.706	2.990	3.304	3.477	3.498
p_W		0.028 *	0.465	0.251	0.602
p_J		0.028	0.316	0.346	0.667
<b>Thyroid gland</b>					
(o/oo) N	5	5	5	5	5
Mean	0.079	0.083	0.075	0.083	0.074
Median	0.075	0.082	0.074	0.081	0.071
Min	0.066	0.063	0.059	0.067	0.064
Max	0.099	0.105	0.095	0.109	0.097
p_W		0.602	0.465	0.754	0.251
p_J		0.602	0.492	0.840	0.293

6. APPENDIX B: INDIVIDUAL DATA

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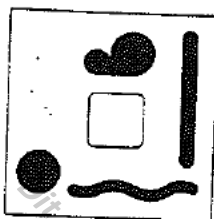
6.1. Analytical results

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**Study Title:**

DETERMINATION OF CONTENT, HOMOGENEITY  
AND STABILITY OF CGA 329351 TECH. AND CGA 48988 TECH.  
IN DISTILLED WATER CONTAINING 0.5 % CMC AND 0.1 % TWEEN 80

**ANALYTICAL REPORT TO:**

28 DAYS SUBACUTE, ORAL TOXICITY STUDY  
IN RATS (GAVAGE)

COMPARISON OF TOXICITY PROFILES BETWEEN CGA 329351 TECH.  
(D-ENANTIOMERE OF CGA 48988) AND CGA 48988 TECH.  
(RACEMATE FORM)

**Author:**

July 08, 1994

**Performing Laboratory:**

R C C UMWELTCHEMIE AG  
P.O. Box  
CH-4452 Itingen/BL  
Switzerland

**Study Project No.:**

RCC PROJECT 365894  
CIBA-GEIGY PROJECT 933180

Page 1 of 25

**RCC**  
Group

PROJECT STAFF

---

RESPONSIBLE FOR ANALYTICS:

Mr. 

Date: *July 8, 1994*

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MANAGING DIRECTOR:

Dr. 

Date: *July 8, 1994*

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## GENERAL INFORMATION

### GENERAL

---

RCC Project: 365894  
CIBA-GEIGY Project: 933180  
Sponsor: CIBA-GEIGY Limited  
Short/Long-term Toxicology  
4332 Stein / Switzerland  
Study Director: Dr. rer. nat. 512e W00  
Test Article: CGA 329351 tech. and CGA 48988 tech.  
Testing Facility: R C C  
UMWELTCHEMIE AG  
Department of Chemistry  
CH-4452 Itingen / Switzerland

### PROJECT STAFF

---

Responsible for Analytics: 512e W00

### SCHEDULE

---

Dates of Analysis: see section 2.2  
Study Completion Date: July 08, 1994/stb

### ARCHIVING

---

Raw data, copy of protocol, analytical report and copy  
of analytical report for at least 10 years:

R C C AG  
CH-4452 Itingen / Switzerland





# QUALITY ASSURANCE UNIT

R C C UMWELTCHEMIE AG, CH-4452 ITINGEN / SWITZERLAND

## STATEMENT

PROJECT NUMBER:

365894

TEST ARTICLE:

CGA 329351 tech. and CGA 48988 tech.

RESPONSIBLE FOR ANALYTICS:

5.12e Woo

TITLE:

DETERMINATION OF CONTENT, HOMOGENEITY  
AND STABILITY OF CGA 329351 TECH. AND  
CGA 48988 TECH. IN DISTILLED WATER  
CONTAINING 0.5 % CMC AND 0.1 % TWEEN 80.

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

Dates of QAU Inspections / Audits	Dates of Reports to the Study Director and to Management
February 16, 1994	February 16, 1994
July 05, 1994	July 05, 1994

Manager, Quality Assurance Unit

5.12e Woo

Date: July 11, 1994



## ABSTRACT

This chemical analysis determined content, homogeneity and stability of CGA 329351 tech. and CGA 48988 tech. in distilled water containing 0.5 % CMC and 0.1 % Tween 80.

### Pretest

The mean CGA 329351 tech. concentrations in the vehicle were found to be 113.0 %, 106.5 %, 104.4 % and 101.9 % of the nominal concentrations for dose groups 2 (0.1 mg/ml), 3 (1 mg/ml), 4 (10 mg/ml) and 5 (100 mg/ml), respectively. The homogeneity varied in the range from -2 % to +2 % of the mean concentrations.

The mean CGA 48988 tech. concentrations in the vehicle were found to be 104.1 %, 101.8 %, 102.3 % and 102.1 % of the nominal concentrations for dose groups 2 (0.1 mg/ml), 3 (1 mg/ml), 4 (10 mg/ml) and 5 (100 mg/ml), respectively. The homogeneity varied in the range from -1 % to +1 % of the mean concentrations.

CGA 329351 tech. and CGA 48988 tech. were found to be stable in distilled water containing 0.5 % CMC and 0.1 % Tween 80 at room temperature ( $22\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ ) over a period of four hours.

### Test

The overall mean concentrations of CGA 329351 tech. in the vehicle were found to be 106.3 %, 105.6 %, 104.2 % and 105.6 % of the nominal concentrations for dose groups 2 (1 mg/ml), 3 (5 mg/ml), 4 (15 mg/ml) and 5 (30 mg/ml), respectively.

The overall mean concentrations of CGA 48988 tech. in the vehicle were found to be 123.2 %, 106.9 %, 103.0 % and 103.0 % of the nominal concentrations for dose groups 2 (1 mg/ml), 3 (5 mg/ml), 4 (15 mg/ml) and 5 (30 mg/ml), respectively.

## 1. INTRODUCTION

This report describes the analytical method used and the results obtained for content, homogeneity and stability of CGA 329351 tech. and CGA 48988 tech. in distilled water containing 0.5 % CMC and 0.1 % Tween 80. The analyses were performed by a HPLC method.

Analysis of homogeneity was performed by analyzing samples of each dose group from three different segments (top, middle, bottom) of the respective mixing container.

## 2. MATERIALS AND METHODS

### 2.1. DESCRIPTION OF TEST ARTICLES

---

(according to the information provided by the sponsor)

#### CGA 329351 tech.

Company code No.: CGA 329351 tech.  
Batch No.: KGL-4634/6\*  
Purity: 97.3 %  
Description: liquid  
Date of receipt: January 20, 1994  
Storage conditions: room temperature  
Stability: February 1998

#### CGA 48988 tech.

Company code No.: CGA 48988 tech.  
Batch No.: EN 603107  
Purity: 96.1 %  
Description: solid  
Date of receipt: December 30, 1993  
Storage conditions: room temperature  
Stability: June 1994

Estimated quantities  
of test articles need: 250 g per test article

Safety precautions: All personnel which was exposed to the test material during weighing, dissolving or applying of the test substance wore dust masks, protective glasses and disposable plastic gloves.

---

\* For analyses of pretest samples batch no.: KGL-4634/5 was used.

## 2.2. SAMPLES

---

### Pretest

- Prepared by sponsor on: 22-DEC-93\*
- Sampled by sponsor on: 22-DEC-93
- Received at RCC on: 23-DEC-93
- Date of analysis: 03-JAN-94
  
- Prepared by sponsor on: 05-JAN-94\*\*
- Sampled by sponsor on: 05-JAN-94
- Received at RCC on: 06-JAN-94
- Date of analysis: 11-JAN-94

### Test

- Prepared by sponsor on: 26-JAN-94\*\*\*
- Sampled by sponsor on: 26-JAN-94
- Received at RCC on: 27-JAN-94
- Date of analysis: 09-FEB-94
  
- Prepared by sponsor on: 26-JAN-94 (Reserve sample)\*\*
- Sampled by sponsor on: 26-JAN-94
- Received at RCC on: 17-FEB-94
- Date of analysis: 18-FEB-94
  
- Prepared by sponsor on: 02-FEB-94\*\*\*
- Sampled by sponsor on: 02-FEB-94
- Received at RCC on: 04-FEB-94
- Date of analysis: 09-FEB-94
  
- Prepared by sponsor on: 09-FEB-94\*\*\*
- Sampled by sponsor on: 09-FEB-94
- Received at RCC on: 10-FEB-94
- Date of analysis: 15-FEB-94
  
- Prepared by sponsor on: 16-FEB-94\*\*\*
- Sampled by sponsor on: 16-FEB-94
- Received at RCC on: 17-FEB-94
- Date of analysis: 18-FEB-94

\* Determination of CGA 329351 tech.

\*\* Determination of CGA 48988 tech.

\*\*\* Determination of CGA 329351 tech. and CGA 48988 tech.

## 2.3. STORAGE

---

Test article/vehicle mixtures were prepared, samples were collected and immediately deepfrozen by the sponsor until shipment to RCC Umweltchemie AG. The samples of the stability test were kept at room temperature (22 °C ± 2 °C) over a period of four hours prior to deepfreezing. All samples were shipped to RCC Umweltchemie AG deepfrozen in a cool box and were, upon arrival, stored deepfrozen until sample work-up and analysis by HPLC.

## 2.4. ANALYTICAL PROCEDURE

---

### 2.4.1. Standard Solutions

First, stock solutions of each test article (see section 2.1) in methanol with concentrations ranging from 0.5 mg/ml to 1.0 mg/ml were prepared as follows: 50 mg to 100 mg of CGA 329351 tech. or CGA 48988 tech. were each weighed into 100 ml volumetric flasks and dissolved in about 70 ml of methanol by ultrasonic treatment. Next, the volumetric flasks were filled to volume with methanol. Then, various standard solutions were prepared by respective dilution of these stock solutions with HPLC-eluent (see section 2.4.3) to yield concentrations in the range from 0.5 µg/ml to 58.7 µg/ml. These standard solutions were used to calibrate the HPLC.

### 2.4.2. Analysis of Samples

The total weight (about 2 g\*, weighed to the fourth decimal place) of each sample was dissolved in 10 ml of bidistilled water by treatment in an ultrasonic bath. Then, these solutions were quantitatively transferred to 100 ml volumetric flasks with about 60 ml of methanol and after treatment in the ultrasonic bath, the flasks were filled to volume with methanol. These sample solutions were diluted with HPLC-eluent (see section 2.4.3) to yield a concentration within the calibration range. Finally, a 10 µl aliquot was analyzed by HPLC.

### 2.4.3. HPLC-Determination

(Typical Operating Conditions)

Apparatus:	Merck L-6000	pump
	Merck L-4000	photometer
	Merck D-2000	integrator
	Merck 655A 40	sampling unit
Column:	Lichrospher RP-18; 5 µm; 125 x 4.6 mm	
Temperature:	Room temperature	
Eluent:	Acetonitrile	50 % v/v
	Bidistilled water	50 % v/v
Flow rate:	1.0 ml/min	
Detection:	UV, 210 nm	
Injection volume:	10 µl	

---

\* In the case of the group 1 (untreated) samples, a 2 g aliquot was taken from about 20-30 ml sample volume.

#### 2.4.4. Evaluation of Results

Injected samples were quantified by peak area or peak height with reference to the calibration curves. The latter were obtained by correlation of the peak area or peak height (in counts) of the analytical standards with their corresponding CGA 329351 tech. or CGA 48988 tech. concentration in µg/ml.

An example of a calibration curve of CGA 329351 tech. is listed in Table 1, and of CGA 48988 tech. in Table 2. From these or similar curves, the concentrations Y of CGA 329351 tech. or CGA 48988 tech. in µg/ml of an injected sample were calculated from equation 1.

$$Y = a + b \cdot X \quad (1)$$

where

Y = µg/ml of CGA 329351 tech. or CGA 48988 tech. of injected sample

a = y-axis intercept

b = slope

X = peak area or peak height of injected sample in counts

The concentration of CGA 329351 tech. or CGA 48988 tech. in the vehicle was calculated according to equation 2.

$$C = \frac{Y \cdot V \cdot D}{W \cdot 1000} \quad (2)$$

where

C = Concentration of CGA 329351 tech. or CGA 48988 tech. in the vehicle (mg/ml)

Y = µg/ml of injected sample calculated by equation 1

V = Volume of solvent used for dissolution (100 ml)

D = Dilution factor

W = Weight of sample (about 2 g, weighed to the fourth decimal place)

The density of the test article/vehicle mixtures was assumed to be 1.0 g/ml.

### 3. RESULTS

The results obtained for the content, homogeneity and stability of CGA 329351 tech. and CGA 48988 tech. in distilled water containing 0.5 % CMC and 0.1 % Tween 80 are summarized in the attached tables on pages 17 to 21.

The tabulated values represent rounded-off results obtained by calculations based on the exact raw data.

#### Pretest

The mean CGA 329351 tech. concentrations in the vehicle were found to be 113.0 %, 106.5 %, 104.4 % and 101.9 % of the nominal concentrations for dose groups 2 (0.1 mg/ml), 3 (1 mg/ml), 4 (10 mg/ml) and 5 (100 mg/ml), respectively. The homogeneity varied in the range from -2 % to +2 % of the mean concentrations.

The mean CGA 48988 tech. concentrations in the vehicle were found to be 104.1 %, 101.8 %, 102.3 % and 102.1 % of the nominal concentrations for dose groups 2 (0.1 mg/ml), 3 (1 mg/ml), 4 (10 mg/ml) and 5 (100 mg/ml), respectively. The homogeneity varied in the range from -1 % to +1 % of the mean concentrations.

CGA 329351 tech. and CGA 48988 tech. were found to be stable in distilled water containing 0.5 % CMC and 0.1 % Tween 80 at room temperature ( $22\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ ) over a period of four hours.

#### Test

The overall mean concentrations of CGA 329351 tech. in the vehicle were found to be 106.3 %, 105.6 %, 104.2 % and 105.6 % of the nominal concentrations for dose groups 2 (1 mg/ml), 3 (5 mg/ml), 4 (15 mg/ml) and 5 (30 mg/ml), respectively.

The overall mean concentrations of CGA 48988 tech. in the vehicle were found to be 123.2 %, 106.9 %, 103.0 % and 103.0 % of the nominal concentrations for dose groups 2 (1 mg/ml), 3 (5 mg/ml), 4 (15 mg/ml) and 5 (30 mg/ml), respectively.

An example of a calibration curve of CGA 329351 tech. is listed in Table 1 and of CGA 48988 tech. in Table 2. Typical chromatograms of standard solutions and samples of CGA 329351 tech. are shown in Figures 1 and 2, respectively. Typical chromatograms of standard solutions and samples of CGA 48988 tech. are shown in Figures 3 and 4, respectively.



Table 1: Example of a calibration curve of CGA 329351 tech.

Standard (µg/ml)	Peak area (counts)	
	before samples	after samples
5.9	75946	
11.7	156067	
23.5	307045	
58.7	779173	
5.6		72881
11.2		145910
22.4		291125
56.0		732954

$$Y = 1.37 E-1 + 7.57 E-5 \cdot X \quad (R^2 = 1.00)$$

where

Y = µg/ml CGA 329351 tech. in injected sample  
 X = peak area of injected sample (in counts)

Table 2: Example of a calibration curve of CGA 48988 tech.

Standard (µg/ml)	Peak area (counts)	
	before samples	after samples
5	61105	62264
10	122097	123452
20	246371	250553
50	621588	621676

$$Y = 8.09 E-2 + 8.03 E-5 \cdot X \quad (R^2 = 1.00)$$

where

Y = µg/ml CGA 48988 tech. in injected sample  
 X = peak area of injected sample (in counts)



RCC PROJECT 365894  
CIBA-GEIGY PROJECT 933180  
CGA 329351 tech. and CGA 48988 tech.

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Table 4:

## CGA 329351 TECH. IN VEHICLE CONTENT

DATE OF PREPARATION: 26-JAN-94 TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentrat. ppm	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	09-FEB-94	0.000	---	---	---	---	---
2S	1	09-FEB-94	1.126	112.6	---	---	---	---
3S	5	09-FEB-94	5.359	107.2	---	---	---	---
4S	15	09-FEB-94	15.59	103.9	---	---	---	---
5S	30	09-FEB-94	32.33	107.8	---	---	---	---

DATE OF PREPARATION: 02-FEB-94 TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentrat. ppm	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	09-FEB-94	0.000	---	---	---	---	---
2S	1	09-FEB-94	1.077	107.7	---	---	---	---
3S	5	09-FEB-94	5.316	106.3	---	---	---	---
4S	15	09-FEB-94	15.74	105.0	---	---	---	---
5S	30	09-FEB-94	31.95	106.5	---	---	---	---

DATE OF PREPARATION: 09-FEB-94 TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentrat. ppm	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	15-FEB-94	0.000	---	---	---	---	---
2S	1	15-FEB-94	1.141	114.1	---	---	---	---
3S	5	15-FEB-94	5.406	108.1	---	---	---	---
4S	15	15-FEB-94	15.89	105.9	---	---	---	---
5S	30	15-FEB-94	31.99	106.6	---	---	---	---

DATE OF PREPARATION: 16-FEB-94 TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentrat. ppm	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	18-FEB-94	0.000	---	---	---	---	---
2S	1	18-FEB-94	0.908	90.8	---	---	---	---
3S	5	18-FEB-94	5.038	100.8	---	---	---	---
4S	15	18-FEB-94	15.28	101.9	---	---	---	---
5S	30	18-FEB-94	30.47	101.6	---	---	---	---

## OVERALL MEAN CONCENTRATIONS

Dose Group	Nominal mg/ml	N	Mean % of Nom.	St. dev. % of Nom.
Group 2	1	4	106.3	10.7
Group 3	5	4	105.6	3.3
Group 4	15	4	104.2	1.7
Group 5	30	4	105.6	2.8

Table 5:

## CGA 48988 TECH. IN VEHICLE STABILITY, CONTENT AND HOMOGENEITY

DATE OF PREPARATION: 05-JAN-94      PRETEST

Dose Group Time	Nominal mg/ml	Date of analysis		Concentrat. mg/ml	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	11-JAN-94		0.000	—	—	—	—	—
2A	0.1	11-JAN-94	T	0.104	103.5	104.1	-1 / +1	—	—
2B			M	0.103	103.4				
2C			B	0.105	105.3				
2S			*	0.104	104.4				
3A	1	11-JAN-94	T	1.016	101.6	101.8	-0 / +0	—	—
3B			M	1.016	101.6				
3C			B	1.023	102.3				
3S			*	1.032	103.2				
4A	10	11-JAN-94	T	10.27	102.7	102.3	-1 / +1	—	—
4B			M	10.29	102.9				
4C			B	10.14	101.4				
4S			*	10.26	102.6				
5A	100	11-JAN-94	T	101.2	101.2	102.1	-1 / +1	—	—
5B			M	101.7	101.7				
5C			B	103.3	103.3				
5S			*	103.5	103.5				

T: Top )  
 M: Middle ) of mixing container  
 B: Bottom )

\* : Stability test over a period of 4 hours at room temperature (22 °C ± 2 °C)

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**Table 6:**

**CGA 48988 TECH. IN VEHICLE  
 CONTENT**

DATE OF PREPARATION: 26-JAN-94

TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentrat. found ppm	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	09-FEB-94	0.000	---	---	---	---	---
2S	1	09-FEB-94	1.592	159.2*	---	---	---	---
2SR	1	18-FEB-94	1.542	154.2*	---	---	---	---
3S	5	09-FEB-94	5.200	104.0	---	---	---	---
4S	15	09-FEB-94	14.12	94.11	---	---	---	---
5S	30	09-FEB-94	30.01	100.0	---	---	---	---

DATE OF PREPARATION: 02-FEB-94

TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentrat. found ppm	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	09-FEB-94	0.000	---	---	---	---	---
2S	1	09-FEB-94	1.120	112.0	---	---	---	---
3S	5	09-FEB-94	5.203	104.1	---	---	---	---
4S	15	09-FEB-94	15.59	103.9	---	---	---	---
5S	30	09-FEB-94	31.33	104.4	---	---	---	---

DATE OF PREPARATION: 09-FEB-94

TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentrat. found ppm	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	15-FEB-94	0.000	---	---	---	---	---
2S	1	15-FEB-94	1.150	115.0	---	---	---	---
3S	5	15-FEB-94	5.577	111.5	---	---	---	---
4S	15	15-FEB-94	15.90	106.0	---	---	---	---
5S	30	15-FEB-94	31.41	104.7	---	---	---	---

\* Mean concentration of sample 2S and sample 2 SR was calculated and found to be 156.7 % of nominal. This value was used for calculation of the overall mean concentration.

**Table 6: CONT'D.**

DATE OF PREPARATION: 16-FEB-94 TEST

Dose Group Day	Nominal ppm	Date of analysis	Concentration found ppm	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery ppm added	%
1S	0	18-FEB-94	0.000	---	---	---	---	---
2S	1	18-FEB-94	1.092	109.2	---	---	---	---
3S	5	18-FEB-94	5.395	107.9	---	---	---	---
4S	15	18-FEB-94	16.18	107.8	---	---	---	---
5S	30	18-FEB-94	30.80	102.7	---	---	---	---

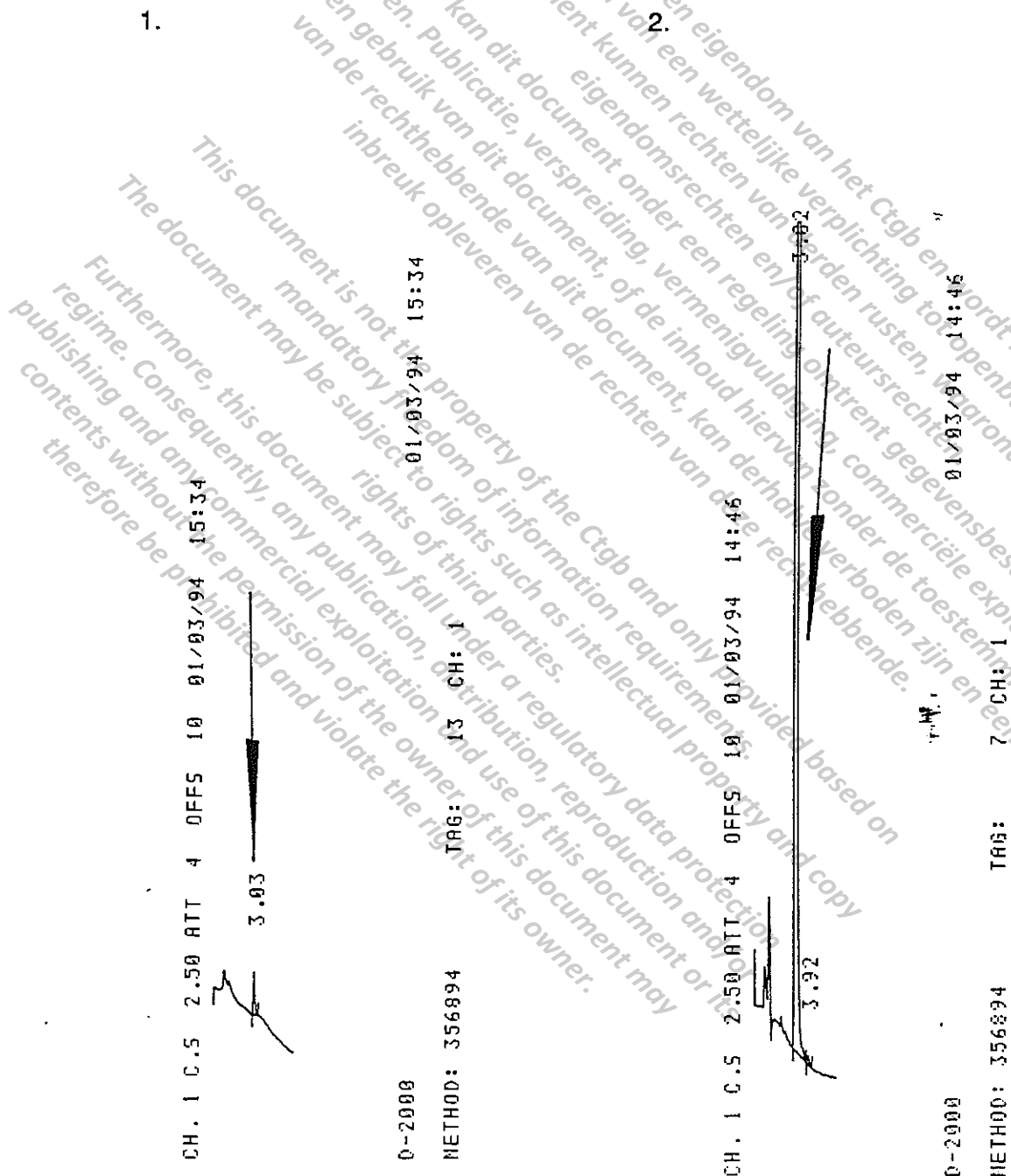
**OVERALL MEAN CONCENTRATIONS**

Dose Group	Nominal mg/ml	N	Mean % of Nom.	St. dev. % of Nom.
Group 2	1	4	123.2	22.4
Group 3	5	4	106.9	3.6
Group 4	15	4	103.0	6.1
Group 5	30	4	103.0	2.2

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Figure 1: Typical Chromatograms of CGA 329351 tech.:

1. Standard solution 0.5 µg/ml, before samples
2. Standard solution 50 µg/ml, before samples



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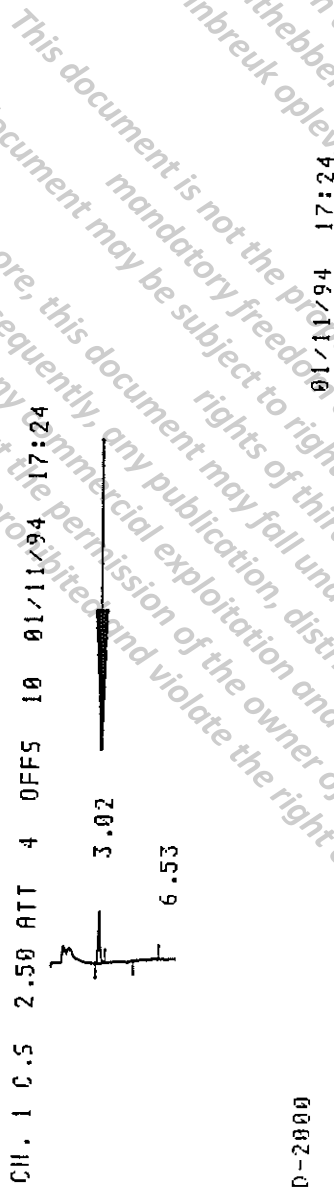




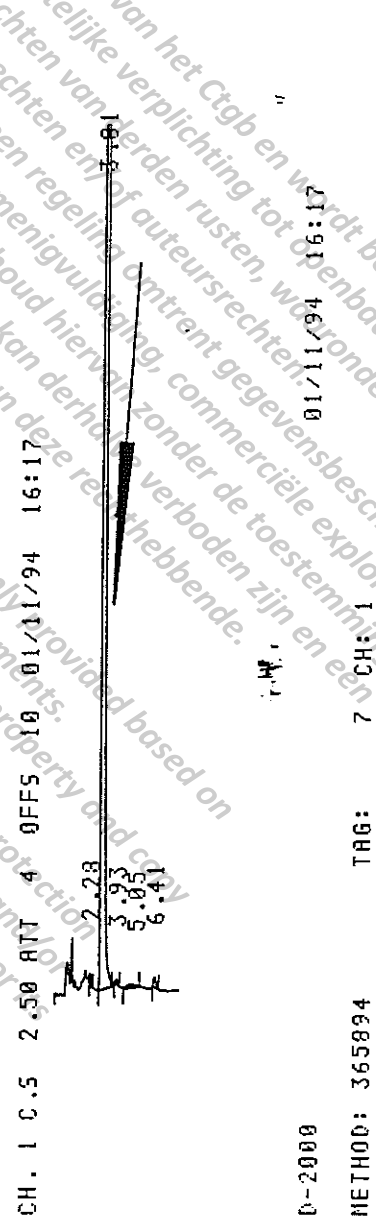
Figure 3: Typical Chromatograms of CGA 48988 tech.:

1. Standard solution 0.5 µg/ml, before samples
2. Standard solution 50 µg/ml, before samples

1.



2.

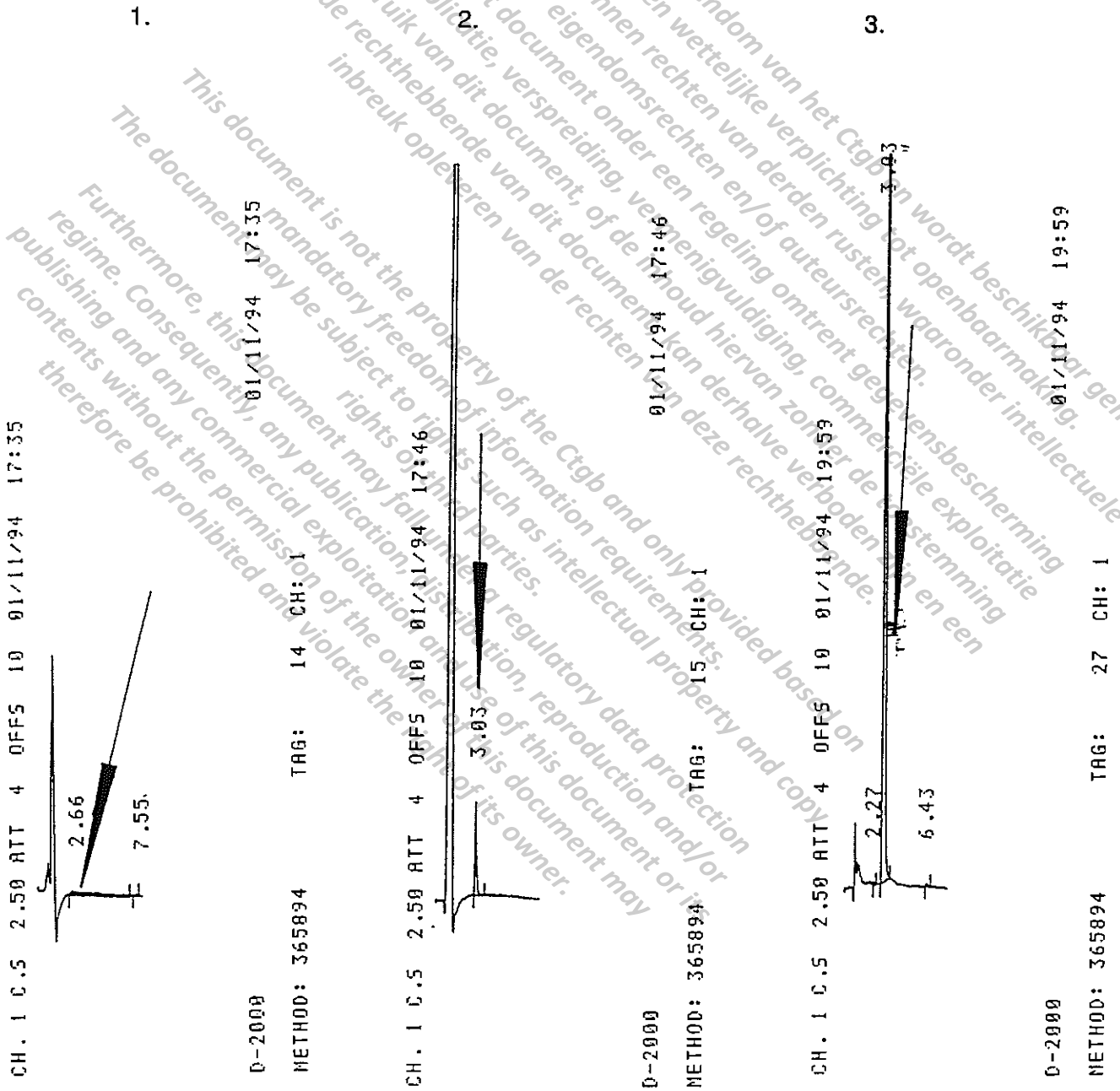


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Figure 4: Typical Chromatograms of CGA 48988 tech.:

1. Control sample
2. Sample, nominal 0.1 mg/ml
3. Sample, nominal 100 mg/ml, diluted 50x



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**RCC**  
**UMWELTCHEMIE AG**

**RCC PROJECT 365894**

**First Amendment to Report**

(9 pages)

**Title:**

**DETERMINATION OF CONTENT, HOMOGENEITY  
AND STABILITY OF CGA 329351 TECH. AND CGA  
48988 TECH. IN DISTILLED WATER CONTAINING  
0.5 % CMC AND 0.1 % TWEEN 80**

**Analytical Report to:**

**28 DAYS SUBACUTE, ORAL TOXICITY STUDY  
IN RATS (GAVAGE)**

**Sponsor:**

**CIBA-GEIGY Limited  
Short/Long-term Toxicology  
4332 Stein / Switzerland**

**Study Director:**

**Dr. rer. nat. [REDACTED]**

P.O. Box CH-4452 Itingen/Switzerland

Phone 061/975 [REDACTED] Telex 966 136 RCC CH

Telefax 061/971 [REDACTED]

RCC PROJECT 365894  
 CIBA-GEIGY PROJECT 933180  
 CGA 329351 tech. and CGA 48988 tech.

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## CONCERNING:

- 1) Legend Table 3 and Table 5
- 2) Header Table 4 and Table 6

## PAGES:

- 1) 17 and 19
- 2) 18, 20-21

## PRESENT:

- 1) Nominal ppm, Concentrat. ppm and Recovery ppm added
- 2) Top, Middle and Bottom

## NEW:

- 1) Nominal mg/ml, Concentrat. mg/ml and Recovery mg/ml added
- 2) A, B and C

## REASON FOR THE

## ALTERATION:

- 1) Mistake in the report
- 2) Mistake in the report

The corrected page are attached as amendment page

RCC PROJECT 365894  
CIBA-GEIGY PROJECT 933180  
CGA 329351 tech. and CGA 48988 tech.

**QUALITY ASSURANCE UNIT**

R C C UMWELTCHEMIE AG, CH-4452 ITINGEN / SWITZERLAND

STATEMENT

PROJECT NUMBER: 365894  
TEST ARTICLE: CGA 329351 tech. and CGA 48988 tech.  
RESPONSIBLE FOR ANALYTICS: 5.1.2.e Woo  
TITLE: DETERMINATION OF CONTENT  
HOMOGENEITY  
AND STABILITY OF CGA 329351 TECH. AND  
CGA 48988 TECH. IN DISTILLED WATER  
CONTAINING 0.5 % CMC AND  
0.1 % TWEEN 80

This Amendment to Report was audited by the Quality Assurance Unit.  
The date is given below.

Dates of QAU Inspections / Audits	Dates of Reports to the Study Director and to Management
19-AUG-94	19-AUG-94

Manager; Quality Assurance Unit

Mrs. 5.1.2.e Woo

5.1.2.e Woo

Date: August 22, 1994

RCC PROJECT 365894  
CIBA-GEIGY PROJECT 933180  
CGA 329351 tech. and CGA 48988 tech.

Responsible for Analytics:

For the Sponsor:

5.1.2.e WOO

5.1.2.e WOO

Date: 18.08.1994/rmma

Date: August 23, 1994

Distribution

Sponsor:	1 x (copy)
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**AMENDMENT PAGE**

Table 3:

**CGA 329351 TECH. IN VEHICLE  
 STABILITY, CONTENT AND HOMOGENEITY**

DATE OF PREPARATION: 22-DEC-93      PRETEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. found mg/ml	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	03-JAN-94	0.000	—	—	—	—	—
2A	0.1	03-JAN-94	A	0.115	114.9	113.0	—	—
2B			B	0.111	111.3			
2C			C	0.113	112.9			
2S			*	0.115	114.8			
3A	1	03-JAN-94	A	1.067	106.7	106.5	—	—
3B			B	1.064	106.4			
3C			C	1.064	106.4			
3S			*	1.071	107.2			
4A	10	03-JAN-94	A	10.42	104.2	104.4	—	—
4B			B	10.38	103.8			
4C			C	10.53	105.3			
4S			*	10.25	102.5			
5A	100	03-JAN-94	A	101.8	101.8	101.9	—	—
5B			B	101.9	101.9			
5C			C	102.1	102.1			
5S			*	102.9	102.9			

A: Top )  
 B: Middle ) of mixing container  
 C: Bottom )

\*: Stability test over a period of 4 hours at room temperature (22 °C ± 2 °C)

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 CIBA-GEIGY PROJECT 933180  
 CGA 329351 tech. and CGA 48988 tech.

Table 4: **AMENDMENT PAGE**

**CGA 329351 TECH. IN VEHICLE  
 CONTENT**

DATE OF PREPARATION: 26-JAN-94 TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. found mg/ml	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	09-FEB-94	0.000	---	---	---	---	---
2S	1	09-FEB-94	1.126	112.6	---	---	---	---
3S	5	09-FEB-94	5.359	107.2	---	---	---	---
4S	15	09-FEB-94	15.59	103.9	---	---	---	---
5S	30	09-FEB-94	32.33	107.8	---	---	---	---

DATE OF PREPARATION: 02-FEB-94 TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. found mg/ml	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	09-FEB-94	0.000	---	---	---	---	---
2S	1	09-FEB-94	1.077	107.7	---	---	---	---
3S	5	09-FEB-94	5.316	106.3	---	---	---	---
4S	15	09-FEB-94	15.74	105.0	---	---	---	---
5S	30	09-FEB-94	31.95	106.5	---	---	---	---

DATE OF PREPARATION: 09-FEB-94 TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. found mg/ml	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	15-FEB-94	0.000	---	---	---	---	---
2S	1	15-FEB-94	1.141	114.1	---	---	---	---
3S	5	15-FEB-94	5.406	108.1	---	---	---	---
4S	15	15-FEB-94	15.89	105.9	---	---	---	---
5S	30	15-FEB-94	31.99	106.6	---	---	---	---

DATE OF PREPARATION: 16-FEB-94 TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. found mg/ml	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	18-FEB-94	0.000	---	---	---	---	---
2S	1	18-FEB-94	0.908	90.8	---	---	---	---
3S	5	18-FEB-94	5.038	100.8	---	---	---	---
4S	15	18-FEB-94	15.28	101.9	---	---	---	---
5S	30	18-FEB-94	30.47	101.6	---	---	---	---

OVERALL MEAN CONCENTRATIONS

Dose Group	Nominal mg/ml	N	Mean % of Nom.	St. dev. % of Nom.
Group 2	1	4	106.3	10.7
Group 3	5	4	105.6	3.3
Group 4	15	4	104.2	1.7
Group 5	30	4	105.6	2.8



RCC PROJECT 365894  
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 CGA 329351 tech. and CGA 48988 tech.

**Table 5: AMENDMENT PAGE**

**CGA 48988 TECH. IN VEHICLE STABILITY, CONTENT AND HOMOGENEITY**

DATE OF PREPARATION: 05-JAN-94 PRETEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. found mg/ml	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	11-JAN-94	0.000	---	---	---	---	---
2A	0.1	11-JAN-94	A	0.104	103.5	104.1	---	---
2B			B	0.103	103.4			
2C			C	0.105	105.3			
2S			*	0.104	104.4			
3A	1	11-JAN-94	A	1.016	101.6	101.8	---	---
3B			B	1.016	101.6			
3C			C	1.023	102.3			
3S			*	1.032	103.2			
4A	10	11-JAN-94	A	10.27	102.7	102.3	---	---
4B			B	10.29	102.9			
4C			C	10.14	101.4			
4S			*	10.26	102.6			
5A	100	11-JAN-94	A	101.2	101.2	102.1	---	---
5B			B	101.7	101.7			
5C			C	103.3	103.3			
5S			*	103.5	103.5			

A: Top )  
 B: Middle ) of mixing container  
 C: Bottom )

\* : Stability test over a period of 4 hours at room temperature (22 °C ± 2 °C)

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Table 6:

**AMENDMENT PAGE****CGA 48988 TECH. IN VEHICLE  
CONTENT**

DATE OF PREPARATION: 26-JAN-94

TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. mg/ml	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	09-FEB-94	0.000	—	—	—	—	—
2S	1	09-FEB-94	1.592	159.2*	—	—	—	—
2SR	1	18-FEB-94	1.542	154.2*	—	—	—	—
3S	5	09-FEB-94	5.200	104.0	—	—	—	—
4S	15	09-FEB-94	14.12	94.11	—	—	—	—
5S	30	09-FEB-94	30.01	100.0	—	—	—	—

DATE OF PREPARATION: 02-FEB-94

TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. mg/ml	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	09-FEB-94	0.000	—	—	—	—	—
2S	1	09-FEB-94	1.120	112.0	—	—	—	—
3S	5	09-FEB-94	5.203	104.1	—	—	—	—
4S	15	09-FEB-94	15.59	103.9	—	—	—	—
5S	30	09-FEB-94	31.33	104.4	—	—	—	—

DATE OF PREPARATION: 09-FEB-94

TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. mg/ml	found % of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	15-FEB-94	0.000	—	—	—	—	—
2S	1	15-FEB-94	1.150	115.0	—	—	—	—
3S	5	15-FEB-94	5.577	111.5	—	—	—	—
4S	15	15-FEB-94	15.90	106.0	—	—	—	—
5S	30	15-FEB-94	31.41	104.7	—	—	—	—

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- \* Mean concentration of sample 2S and sample 2 SR was calculated and found to be 156.7 % of nominal. This value was used for calculation of the overall mean concentration.

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Table 6: CONT'D.

**AMENDMENT PAGE**

DATE OF PREPARATION: 16-FEB-94 TEST

Dose Group Time	Nominal mg/ml	Date of analysis	Concentrat. found mg/ml	% of Nom.	Mean % of Nom.	± Dev. in % of Mean	Recovery mg/ml added	%
1S	0	18-FEB-94	0.000	—	—	—	—	—
2S	1	18-FEB-94	1.092	109.2	—	—	—	—
3S	5	18-FEB-94	5.395	107.9	—	—	—	—
4S	15	18-FEB-94	16.18	107.8	—	—	—	—
5S	30	18-FEB-94	30.80	102.7	—	—	—	—

## OVERALL MEAN CONCENTRATIONS

Dose Group	Nominal mg/ml	N	Mean % of Nom.	St. dev. % of Nom.
Group 2	1	4	123.2	22.4
Group 3	5	4	106.9	3.6
Group 4	15	4	103.0	6.1
Group 5	30	4	103.0	2.2

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

6.2. In-life observations (individuals)

- : clinical sign observed until scheduled sacrifice

CGA 329351 tech.

Antemortem findings (individuals) : males group 1 : 0 mg/kg

No.	Finding	start day	end day
01	no findings noted		
02	no findings noted		
03	no findings noted		
04	no findings noted		
05	no findings noted		

CGA 329351 tech.

Antemortem findings (individuals) : males group 2 : 10 mg/kg

No.	Finding	start day	end day
06	no findings noted		
07	no findings noted		
08	no findings noted		
09	no findings noted		
10	no findings noted		

CGA 329351 tech.

Antemortem findings (individuals) : males group 3 : 50 mg/kg

No.	Finding	start day	end day
11	no findings noted		
12	skin lesion neck	24	29
13	skin lesion neck	24	-
14	no findings noted		
15	no findings noted		

CGA 329351 tech.

Antemortem findings (individuals) : males group 4 : 150 mg/kg

No.	Finding	start day	end day
16	hypoactivity	1	1
16	skin lesion neck	24	-
17	hypoactivity	1	1
18	hypoactivity	1	1
19	hypoactivity	1	1
20	hypoactivity	1	1

CGA 329351 tech.

Antemortem findings (individuals) : males group 5 : 300 mg/kg

No.	Finding	start day	end day
21	hypoactivity	1	1
22	hypoactivity	1	1
23	hypoactivity	1	1
24	hypoactivity	1	1
24	skin lesion neck	24	-
25	hypoactivity	1	1
25	skin lesion neck	24	-

CGA329351 tech.

Antemortem findings (individuals) : females group 1 : 0 mg/kg

No.	Finding	start day	end day
26	no findings noted		
27	no findings noted		
28	no findings noted		
29	no findings noted		
30	no findings noted		

CGA 329351 tech.

Antemortem findings (individuals) : females group 2 : 10 mg/kg

No.	Finding	start day	end day
31	no findings noted		
32	no findings noted		
33	no findings noted		
34	no findings noted		
35	no findings noted		

CGA 329351 tech.

Antemortem findings (individuals) : females group 3 : 50 mg/kg

No.	Finding	start day	end day
36	no findings noted		
37	no findings noted		
38	no findings noted		
39	no findings noted		
40	no findings noted		

CGA 329351 tech.

Antemortem findings (individuals) : females group 4 : 150 mg/kg

No.	Finding	start day	end day
41	hypoactivity	1	1
42	hypoactivity	1	1
43	hypoactivity	1	1
44	hypoactivity	1	1
45	hypoactivity	1	1

CGA 329351 tech.

Antemortem findings (individuals) : females group 5 : 300 mg/kg

No.	Finding	start day	end day
46	hypoactivity	1	1
46	prostrate	1	1
47	hypoactivity	1	1
48	hypoactivity	1	1
48	prostrate	1	1
49	hypoactivity	1	1
50	hypoactivity	1	1

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CGA 48988 tech.

Antemortem findings (individuals) : males group 1 : 0 mg/kg

No.	Finding	start day	end day
01	no findings noted		
02	no findings noted		
03	no findings noted		
04	no findings noted		
05	no findings noted		

CGA 48988 tech.

Antemortem findings (individuals) : males group 2 : 10 mg/kg

No.	Finding	start day	end day
06	no findings noted		
07	no findings noted		
08	no findings noted		
09	no findings noted		
10	no findings noted		

CGA 48988 tech.

Antemortem findings (individuals) : males group 3 : 50 mg/kg

No.	Finding	start day	end day
11	no findings noted		
12	no findings noted		
13	no findings noted		
14	no findings noted		
15	no findings noted		





CGA 48988 tech.

Antemortem findings (individuals) : females group 1 : 0 mg/kg

No.	Finding	start day	end day
26	no findings noted		
27	no findings noted		
28	no findings noted		
29	no findings noted		
30	no findings noted		

CGA 48988 tech.

Antemortem findings (individuals) : females group 2 : 10 mg/kg

No.	Finding	start day	end day
31	no findings noted		
32	no findings noted		
33	no findings noted		
34	no findings noted		
35	no findings noted		

CGA 48988 tech.

Antemortem findings (individuals) : females group 3 : 50 mg/kg

No.	Finding	start day	end day
36	no findings noted		
37	no findings noted		
38	no findings noted		
39	no findings noted		
40	dyspnea	28	29

CGA 48988 tech.

Antemortem findings (individuals) : females group 4 : 150 mg/kg

No.	Finding	start day	end day
41	hair loss forelimbs	31	-
42	no findings noted		
43	no findings noted		
44	no findings noted		
45	no findings noted		

CGA 48988 tech.

Antemortem findings (individuals) : females group 5 : 300 mg/kg

No.	Finding	start day	end day
46	no findings noted		
47	no findings noted		
48	no findings noted		
49	no findings noted		
50	no findings noted		

6.3. Mortality (individuals)

CGA 329351 tech.

Mortality (individuals) : males group 1 : 0 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
1	1	23 Feb 94	5	30	yes	Sacrifice 1
2	1	23 Feb 94	5	30	yes	Sacrifice 1
3	1	23 Feb 94	5	30	yes	Sacrifice 1
4	1	23 Feb 94	5	30	yes	Sacrifice 1
5	1	23 Feb 94	5	30	yes	Sacrifice 1

CGA 329351 tech.

Mortality (individuals) : males group 2 : 10 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
6	2	23 Feb 94	5	30	yes	Sacrifice 1
7	2	23 Feb 94	5	30	yes	Sacrifice 1
8	2	23 Feb 94	5	30	yes	Sacrifice 1
9	2	23 Feb 94	5	30	yes	Sacrifice 1
10	2	23 Feb 94	5	30	yes	Sacrifice 1

CGA 329351 tech.

Mortality (individuals) : males group 3 : 50 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
11	3	23 Feb 94	5	30	yes	Sacrifice 1
12	3	23 Feb 94	5	30	yes	Sacrifice 1
13	3	23 Feb 94	5	30	yes	Sacrifice 1
14	3	23 Feb 94	5	30	yes	Sacrifice 1
15	3	23 Feb 94	5	30	yes	Sacrifice 1



CGA 329351 tech.

Mortality (individuals) : females group 1 : 0 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
26	6	24 Feb 94	5	31	yes	Sacrifice 1
27	6	24 Feb 94	5	31	yes	Sacrifice 1
28	6	24 Feb 94	5	31	yes	Sacrifice 1
29	6	24 Feb 94	5	31	yes	Sacrifice 1
30	6	24 Feb 94	5	31	yes	Sacrifice 1

CGA 329351 tech.

Mortality (individuals) : females group 2 : 10 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
31	7	24 Feb 94	5	31	yes	Sacrifice 1
32	7	24 Feb 94	5	31	yes	Sacrifice 1
33	7	24 Feb 94	5	31	yes	Sacrifice 1
34	7	24 Feb 94	5	31	yes	Sacrifice 1
35	7	24 Feb 94	5	31	yes	Sacrifice 1

CGA 329351 tech.

Mortality (individuals) : females group 3 : 50 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
36	8	24 Feb 94	5	31	yes	Sacrifice 1
37	8	24 Feb 94	5	31	yes	Sacrifice 1
38	8	24 Feb 94	5	31	yes	Sacrifice 1
39	8	24 Feb 94	5	31	yes	Sacrifice 1
40	8	24 Feb 94	5	31	yes	Sacrifice 1

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.

Mortality (individuals) : females group 4 : 150 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
41	9	24 Feb 94	5	31	yes	Sacrifice 1
42	9	24 Feb 94	5	31	yes	Sacrifice 1
43	9	24 Feb 94	5	31	yes	Sacrifice 1
44	9	24 Feb 94	5	31	yes	Sacrifice 1
45	9	24 Feb 94	5	31	yes	Sacrifice 1

CGA 329351 tech.

Mortality (individuals) : females group 5 : 300 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
46	10	24 Feb 94	5	31	yes	Sacrifice 1
47	10	24 Feb 94	5	31	yes	Sacrifice 1
48	10	24 Feb 94	5	31	yes	Sacrifice 1
49	10	24 Feb 94	5	31	yes	Sacrifice 1
50	10	24 Feb 94	5	31	yes	Sacrifice 1

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Mortality (individuals) : males group 1 : 0 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
1	1	23 Feb 94	5	30	yes	Sacrifice 1
2	1	23 Feb 94	5	30	yes	Sacrifice 1
3	1	23 Feb 94	5	30	yes	Sacrifice 1
4	1	23 Feb 94	5	30	yes	Sacrifice 1
5	1	23 Feb 94	5	30	yes	Sacrifice 1

CGA 48988 tech.

Mortality (individuals) : males group 2 : 10 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
6	2	23 Feb 94	5	30	yes	Sacrifice 1
7	2	23 Feb 94	5	30	yes	Sacrifice 1
8	2	23 Feb 94	5	30	yes	Sacrifice 1
9	2	23 Feb 94	5	30	yes	Sacrifice 1
10	2	23 Feb 94	5	30	yes	Sacrifice 1

CGA 48988 tech.

Mortality (individuals) : males group 3 : 50 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
11	3	23 Feb 94	5	30	yes	Sacrifice 1
12	3	23 Feb 94	5	30	yes	Sacrifice 1
13	3	23 Feb 94	5	30	yes	Sacrifice 1
14	3	23 Feb 94	5	30	yes	Sacrifice 1
15	3	23 Feb 94	5	30	yes	Sacrifice 1



CGA 48988 tech.

Mortality (individuals) : males group 4 : 150 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
16	4	23 Feb 94	5	30	yes	Sacrifice 1
17	4	23 Feb 94	5	30	yes	Sacrifice 1
18	4	23 Feb 94	5	30	yes	Sacrifice 1
19	4	23 Feb 94	5	30	yes	Sacrifice 1
20	4	23 Feb 94	5	30	yes	Sacrifice 1

CGA 48988 tech.

Mortality (individuals) : males group 5 : 300 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
21	5	23 Feb 94	5	30	yes	Sacrifice 1
22	5	23 Feb 94	5	30	yes	Sacrifice 1
23	5	23 Feb 94	5	30	yes	Sacrifice 1
24	5	23 Feb 94	5	30	yes	Sacrifice 1
25	5	23 Feb 94	5	30	yes	Sacrifice 1

CGA 48988 tech.

Mortality (individuals) : females group 1 : 0 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
26	6	24 Feb 94	5	31	yes	Sacrifice 1
27	6	24 Feb 94	5	31	yes	Sacrifice 1
28	6	24 Feb 94	5	31	yes	Sacrifice 1
29	6	24 Feb 94	5	31	yes	Sacrifice 1
30	6	24 Feb 94	5	31	yes	Sacrifice 1

CGA 48988 tech.

Mortality (individuals) : females group 2 : 10 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
31	7	24 Feb 94	5	31	yes	Sacrifice 1
32	7	24 Feb 94	5	31	yes	Sacrifice 1
33	7	24 Feb 94	5	31	yes	Sacrifice 1
34	7	24 Feb 94	5	31	yes	Sacrifice 1
35	7	24 Feb 94	5	31	yes	Sacrifice 1

CGA 48988 tech.

Mortality (individuals) : females group 3 : 50 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
36	8	24 Feb 94	5	31	yes	Sacrifice 1
37	8	24 Feb 94	5	31	yes	Sacrifice 1
38	8	24 Feb 94	5	31	yes	Sacrifice 1
39	8	24 Feb 94	5	31	yes	Sacrifice 1
40	8	24 Feb 94	5	31	yes	Sacrifice 1

## 28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Mortality (individuals) : females group 4 : 150 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
41	9	24 Feb 94	5	31	yes	Sacrifice 1
42	9	24 Feb 94	5	31	yes	Sacrifice 1
43	9	24 Feb 94	5	31	yes	Sacrifice 1
44	9	24 Feb 94	5	31	yes	Sacrifice 1
45	9	24 Feb 94	5	31	yes	Sacrifice 1

CGA 48988 tech.

Mortality (individuals) : females group 5 : 300 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
46	10	24 Feb 94	5	31	yes	Sacrifice 1
47	10	24 Feb 94	5	31	yes	Sacrifice 1
48	10	24 Feb 94	5	31	yes	Sacrifice 1
49	10	24 Feb 94	5	31	yes	Sacrifice 1
50	10	24 Feb 94	5	31	yes	Sacrifice 1

6.4. Bodyweight (individuals)

CGA 329351 tech.

Bodyweight (individuals): males group 1 : 0 mg/kg  
 (g/animal)

	1	2	3	4	5	Animal no
week: -1	146.7	138.9	145.1	140.6	143.0	
1	190.1	174.3	190.5	176.2	180.0	
2	244.9	220.6	245.5	220.6	231.4	
3	305.4	271.1	291.5	266.8	278.1	
4	351.5	312.6	323.9	306.6	315.3	

CGA 329351 tech.

Bodyweight (individuals): males group 2 : 10 mg/kg  
 (g/animal)

	6	7	8	9	10	Animal no
week: -1	143.0	141.5	138.4	137.1	144.4	
1	197.2	181.5	169.2	174.8	198.7	
2	258.3	231.6	219.9	215.5	259.0	
3	318.0	290.0	271.0	259.3	313.7	
4	365.7	328.4	297.7	284.4	349.1	

CGA 329351 tech.

Bodyweight (individuals): males group 3 : 50 mg/kg  
 (g/animal)

	11	12	13	14	15	Animal no
week: -1	135.3	134.8	144.2	136.6	136.4	
1	171.9	168.0	196.0	172.8	181.8	
2	223.0	208.6	254.2	213.5	226.6	
3	273.0	263.9	311.3	253.1	274.6	
4	313.9	318.2	350.6	288.7	314.6	

CGA 329351 tech.

Bodyweight (individuals) : males group 4 : 150 mg/kg  
 (g/animal)

	16	17	18	19	Animal no 20
week: -1	138.7	135.8	137.6	136.8	139.3
1	176.9	168.2	176.1	176.6	166.3
2	223.4	223.5	229.7	229.8	210.3
3	276.0	274.5	273.6	279.2	259.0
4	319.7	312.1	301.8	322.0	296.4

CGA 329351 tech.

Bodyweight (individuals) : males group 5 : 300 mg/kg  
 (g/animal)

	21	22	23	24	Animal no 25
week: -1	139.4	136.8	134.9	139.4	145.0
1	176.3	174.9	176.1	167.7	202.2
2	223.9	215.8	224.9	205.7	251.1
3	283.6	260.6	274.5	259.0	295.4
4	325.9	293.8	311.6	291.0	334.2

CGA 329351 tech.

Bodyweight (individuals) : females group 1 : 0 mg/kg  
 (g/animal)

	26	27	28	29	Animal no 30
week: -1	153.8	154.4	145.6	160.4	161.5
1	184.1	184.6	179.3	183.0	198.2
2	210.9	193.6	192.4	204.6	200.7
3	233.9	217.5	213.9	226.9	215.5
4	238.9	235.8	234.4	243.4	226.4

CGA 329351 tech.

Bodyweight (individuals) : females group 2 : 10 mg/kg  
 (g/animal)

	31	32	33	34	Animal no 35
week: -1	154.1	157.9	155.2	163.4	155.5
1	171.0	190.3	172.8	197.2	174.3
2	202.5	207.8	195.8	202.8	208.6
3	223.3	237.2	215.9	217.6	240.3
4	232.7	241.6	218.7	219.5	255.4

CGA 329351 tech.

Bodyweight (individuals) : females group 3 : 50 mg/kg  
 (g/animal)

	36	37	38	39	Animal no 40
week: -1	162.3	158.5	157.8	152.2	153.9
1	173.9	171.3	185.0	185.6	175.4
2	197.8	189.9	205.6	218.8	197.0
3	227.0	207.2	221.3	243.2	213.4
4	248.9	218.5	228.6	253.0	229.7

28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.

Bodyweight (individuals) : females group 4 : 150 mg/kg  
(g/animal)

	41	42	43	44	Animal no 45
week: -1	159.8	158.7	153.9	154.0	152.3
1	186.3	178.1	162.5	175.3	163.0
2	197.9	197.1	179.3	189.0	180.1
3	231.8	218.1	202.5	215.9	210.1
4	248.8	224.6	219.0	226.8	228.6

CGA 329351 tech.

Bodyweight (individuals) : females group 5 : 300 mg/kg  
(g/animal)

	46	47	48	49	Animal no 50
week: -1	161.2	153.0	153.5	152.7	162.6
1	192.4	171.5	176.7	181.9	194.5
2	230.7	184.0	195.7	201.1	201.2
3	246.9	198.8	218.8	230.7	226.4
4	248.7	215.1	241.9	241.6	243.1

CGA 48988 tech.

Bodyweight (individuals) : males group 1 : 0 mg/kg  
 (g/animal)

	1	2	3	4	5
week: -1	146.7	138.9	145.1	140.6	143.0
1	190.1	174.3	190.5	176.2	180.0
2	244.9	220.6	245.5	220.6	231.4
3	305.4	271.1	291.5	266.8	278.1
4	351.5	312.6	323.9	306.6	315.3

CGA 48988 tech.

Bodyweight (individuals) : males group 2 : 10 mg/kg  
 (g/animal)

	6	7	8	9	10
week: -1	136.0	138.7	134.4	137.2	132.5
1	182.7	194.2	161.2	180.0	167.3
2	236.4	255.6	210.1	232.3	210.1
3	289.4	326.0	263.1	296.1	268.6
4	320.8	365.7	294.7	333.7	305.5

CGA 48988 tech.

Bodyweight (individuals) : males group 3 : 50 mg/kg  
 (g/animal)

	11	12	13	14	15
week: -1	135.8	140.2	133.7	136.7	136.6
1	176.9	171.0	178.1	178.8	170.7
2	234.8	210.4	217.0	234.8	218.7
3	289.7	263.3	264.5	286.6	277.8
4	322.9	295.6	297.9	321.7	310.5



CGA 48988 tech.

Bodyweight (individuals) : males group 4 : 150 mg/kg  
 (g/animal)

	16	17	18	19	Animal no 20
week: -1	133.8	140.9	132.9	138.8	137.4
1	171.7	179.4	167.0	183.5	173.8
2	216.0	231.9	214.1	234.8	229.6
3	262.8	288.8	256.4	285.7	289.6
4	299.1	324.9	285.5	318.0	326.9

CGA 48988 tech.

Bodyweight (individuals) : males group 5 : 300 mg/kg  
 (g/animal)

	21	22	23	24	Animal no 25
week: -1	137.2	137.8	133.1	132.4	140.2
1	177.8	183.8	182.7	171.1	194.4
2	231.6	234.6	236.2	219.9	255.0
3	282.4	277.1	296.5	270.7	311.1
4	331.2	305.2	339.9	303.1	347.9

CGA 48988 tech.

Bodyweight (individuals) : females group 1 : 0 mg/kg  
 (g/animal)

	26	27	28	29	Animal no 30
week: -1	153.8	154.4	145.6	160.4	161.5
1	184.1	184.6	179.3	183.0	198.2
2	210.9	193.6	192.4	204.6	200.7
3	233.9	217.5	213.9	226.9	215.5
4	238.9	235.8	234.4	243.4	226.4

CGA 48988 tech.

Bodyweight (individuals) : females group 2 : 10 mg/kg  
 (g/animal)

	31	32	33	34	Animal no 35
week: -1	146.3	143.5	153.9	155.8	155.0
1	173.4	177.0	178.6	174.0	187.6
2	193.5	190.5	201.4	216.1	201.8
3	217.2	223.0	234.3	232.7	233.4
4	233.3	232.3	263.4	256.3	256.7

CGA 48988 tech.

Bodyweight (individuals) : females group 3 : 50 mg/kg  
 (g/animal)

	36	37	38	39	Animal no 40
week: -1	147.2	147.6	144.5	152.4	151.2
1	178.5	179.0	178.6	176.3	189.0
2	189.0	213.3	199.7	206.4	207.6
3	203.9	255.0	231.1	223.7	236.8
4	218.8	259.2	246.9	236.9	261.9

CGA 48988 tech.

Bodyweight (individuals) : females group 4 : 150 mg/kg  
 (g/animal)

	41	42	43	44	Animal no 45
week: -1	148.5	147.1	153.2	144.6	145.2
1	195.8	167.2	194.7	186.7	169.9
2	218.7	199.0	225.1	206.6	191.7
3	236.1	211.4	260.0	242.1	213.7
4	258.9	223.4	256.3	256.2	221.6

CGA 48988 tech.

Bodyweight (individuals) : females group 5 : 300 mg/kg  
 (g/animal)

	46	47	48	49	Animal no 50
week: -1	153.3	148.1	153.6	145.9	155.4
1	184.9	172.4	189.4	176.6	192.5
2	203.5	193.6	215.9	190.1	214.4
3	219.3	229.2	236.6	219.0	246.7
4	240.6	245.6	241.7	238.9	267.6

6.5. Food consumption (individuals)

CGA 329351 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	1
week: -1	125.5
1	146.3
2	176.0
3	184.7
4	184.9

CGA 329351 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	2
week: -1	126.5
1	154.4
2	178.2
3	188.0
4	195.4

CGA 329351 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	3
week: -1	126.8
1	145.2
2	174.6
3	193.1
4	194.5

CGA 329351 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	4
week: -1	126.3
1	141.2
2	168.6
3	185.0
4	182.7

CGA 329351 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	5
week: -1	126.5
1	145.4
2	164.4
3	182.1
4	177.7

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	6
week: -1	124.6
1	115.7
2	124.0
3	134.1
4	139.2

CGA 329351 tech.Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	7
week: -1	121.0
1	112.2
2	127.3
3	130.3
4	129.0

CGA 329351 tech.Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	8
week: -1	116.9
1	116.1
2	129.6
3	124.8
4	132.1

CGA 329351 tech.

Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	9
week: -1	117.2
1	107.0
2	125.1
3	137.8
4	135.0

CGA 329351 tech.

Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	10
week: -1	121.8
1	115.0
2	127.8
3	127.7
4	125.9

CGA 48988 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	1
week: -1	125.5
1	146.3
2	176.0
3	184.7
4	184.9

CGA 48988 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	2
week: -1	125.4
1	140.2
2	179.8
3	193.0
4	191.6

CGA 48988 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	3
week: -1	125.2
1	146.0
2	172.1
3	188.5
4	185.4



CGA 48988 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	4
week: -1	126.4
1	138.8
2	169.1
3	184.2
4	183.8

CGA 48988 tech.

Food consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	5
week: -1	126.6
1	149.8
2	169.6
3	185.1
4	185.2

CGA 48988 tech.

Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	6
week: -1	124.6
1	115.7
2	124.0
3	134.1
4	139.2

CGA 48988 tech.

Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	7
week: -1	120.5
1	120.2
2	132.2
3	149.5
4	141.4

CGA 48988 tech.

Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	8
week: -1	119.9
1	116.2
2	132.8
3	141.8
4	129.5

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	9
week: -1	121.1
1	118.0
2	131.0
3	142.7
4	134.6

CGA 48988 tech.Food consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	10
week: -1	124.8
1	122.3
2	137.0
3	143.7
4	141.7

6.6. Water consumption (individuals)

CGA 329351 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	1
week: -1	168.6
1	206.1
2	218.3
3	246.0
4	277.8

CGA 329351 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	2
week: -1	175.7
1	199.5
2	229.5
3	285.2
4	281.5

CGA 329351 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	3
week: -1	168.6
1	204.5
2	223.7
3	244.7
4	271.5

CGA 329351 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	4
week: -1	174.6
1	205.4
2	240.8
3	246.7
4	297.2

CGA 329351 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	5
week: -1	170.7
1	188.3
2	197.8
3	228.6
4	239.7

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	6
week: -1	158.8
1	178.9
2	155.0
3	197.5
4	194.6

CGA 329351 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	7
week: -1	192.6
1	174.9
2	185.4
3	220.4
4	198.2

CGA 329351 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	8
week: -1	160.4
1	176.7
2	171.5
3	196.0
4	221.6

CGA 329351 tech.

Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	9
week: -1	170.2
1	182.4
2	183.5
3	222.2
4	224.3

CGA 329351 tech.

Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	10
week: -1	165.5
1	184.5
2	177.0
3	182.8
4	213.1

CGA 48988 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	1
week: -1	168.6
1	206.1
2	218.3
3	246.0
4	277.8

CGA 48988 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	2
week: -1	139.0
1	180.7
2	235.1
3	270.2
4	264.3

CGA 48988 tech.

Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	3
week: -1	173.6
1	190.0
2	208.2
3	240.8
4	245.8



Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	4
week: -1	156.4
1	180.3
2	194.6
3	246.5
4	249.5

CGA 48988 tech.Water consumption (individuals, determined cagewise) : males  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	5
week: -1	163.4
1	209.0
2	232.7
3	284.6
4	321.3

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 1 : 0 mg/kg

	Cage no
	6
week: -1	158.8
1	178.9
2	155.0
3	197.5
4	194.6

CGA 48988 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 2 : 10 mg/kg

	Cage no
	7
week: -1	175.1
1	203.7
2	194.3
3	222.2
4	214.5

CGA 48988 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 3 : 50 mg/kg

	Cage no
	8
week: -1	184.5
1	181.3
2	189.6
3	202.9
4	173.2

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 4 : 150 mg/kg

	Cage no
	9
week: -1	156.1
1	188.7
2	182.4
3	208.9
4	172.8

CGA 48988 tech.Water consumption (individuals, determined cagewise) : females  
(g/animal/week)

group 5 : 300 mg/kg

	Cage no
	10
week: -1	180.3
1	238.8
2	199.5
3	221.2
4	227.5

6.7. Hematology (individuals)

CGA 329351 tech.

Hematology (individuals): males

group 1  
 0 mg/kg

		Animal no				
		1	2	3	4	5
RBC (T/l)						
week:	5	7.290	7.410	7.880	7.620	7.390
Hb (mmol/l)						
week:	5	9.500	9.200	9.600	9.400	9.200
Hct (l)						
week:	5	0.453	0.447	0.464	0.456	0.438
MCV (fl)						
week:	5	62.10	60.30	59.00	59.80	59.20
RDW (l)						
week:	5	0.123	0.120	0.120	0.125	0.117
MCH (fmol)						
week:	5	1.310	1.250	1.220	1.240	1.240
MCHC (mmol/l)						
week:	5	21.05	20.65	20.67	20.69	20.92
HDW (mmol/l)						
week:	5	1.530	1.200	1.280	1.240	1.620
WBC (G/l)						
week:	5	16.42	20.10	22.66	14.37	20.93

CGA 329351 tech.

Hematology (individuals): males

group 1  
 0 mg/kg

		Animal no				
		1	2	3	4	5
Neut (1) week:	5	0.071	0.058	0.066	0.072	0.101
Eos (1) week:	5	0.004	0.007	0.005	0.006	0.005
Baso (1) week:	5	0.006	0.008	0.009	0.006	0.007
Lympho (1) week:	5	0.852	0.862	0.841	0.848	0.793
Mono (1) week:	5	0.034	0.035	0.044	0.033	0.054
Luc (1) week:	5	0.032	0.030	0.035	0.034	0.041
Neut (G/1) week:	5	1.160	1.170	1.500	1.040	2.100
Eos (G/1) week:	5	0.070	0.130	0.100	0.090	0.100
Baso (G/1) week:	5	0.100	0.160	0.190	0.080	0.140
Lympho (G/1) week:	5	14.00	17.34	19.06	12.19	16.60
Mono (G/1) week:	5	0.560	0.700	1.010	0.480	1.120

28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.

Hematology (individuals): males

group 1  
0 mg/kg

		1	2	3	4	5	Animal no
Luc (G/l) week:	5	0.530	0.610	0.790	0.490	0.860	
Plt (G/l) week:	5	1123	1077	1201	1166	705.0	
PT(CS) (sec) week:	5	38.61	33.65	32.73	29.73	44.36	

CGA 329351 tech.

Hematology (individuals): males

group 2  
10 mg/kg

		6	7	8	9	10	Animal no
RBC (T/l) week:	5	6.980	7.740	7.010	7.660	7.320	
Hb (mmol/l) week:	5	9.400	9.600	8.800	9.800	9.700	
Hct (l) week:	5	0.457	0.459	0.424	0.474	0.461	
MCV (fl) week:	5	65.50	59.30	60.45	61.80	63.00	
RDW (l) week:	5	0.125	0.126	0.128	0.114	0.115	



CGA 329351 tech.

Hematology (individuals): males

group 2  
10 mg/kg

		6	7	8	9	10
Eos (G/l) week:	5	0.070	0.120	0.045	0.130	0.100
Baso (G/l) week:	5	0.100	0.060	0.030	0.040	0.060
Lympho (G/l) week:	5	14.65	11.89	5.805	9.220	10.27
Mono (G/l) week:	5	0.520	0.380	0.325	0.500	0.600
Luc (G/l) week:	5	0.430	0.370	0.420	0.370	0.670
Plt (G/l) week:	5	1174	1184	1025	1118	1005
PT(CS) (sec) week:	5	33.46	34.93	30.11	33.52	35.11

CGA 329351 tech.

Hematology (individuals): males

group 3  
50 mg/kg

		11	12	13	14	15
RBC (T/l) week:	5	7.150	7.480	7.460	7.270	7.720



CGA 329351 tech.

Hematology (individuals): males

group 3  
 50 mg/kg

		11	12	13	14	15
		Animal no				
Hb (mmol/l) week: 5		9.300	10.20	9.400	9.400	9.500
Hct (1) week: 5		0.446	0.479	0.440	0.438	0.447
MCV (fl) week: 5		62.40	64.00	59.00	60.30	57.90
RDW (1) week: 5		0.122	0.122	0.123	0.126	0.117
MCH (fmol) week: 5		1.310	1.360	1.260	1.300	1.230
MCHC (mmol/l) week: 5		20.97	21.28	21.32	21.56	21.19
HDW (mmol/l) week: 5		1.240	1.170	1.620	1.250	1.220
WBC (G/l) week: 5		20.98	13.61	12.05	12.07	12.24
Neut (1) week: 5		0.054	0.093	0.109	0.091	0.074
Eos (1) week: 5		0.004	0.005	0.008	0.006	0.012
Baso (1) week: 5		0.008	0.005	0.005	0.005	0.005

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CGA 329351 tech.

Hematology (individuals): males

group 3  
 50 mg/kg

		11	12	13	14	15
		Animal no				
Lympho (1) week:	5	0.859	0.820	0.782	0.832	0.842
Mono (1) week:	5	0.049	0.039	0.056	0.041	0.030
Luc (1) week:	5	0.025	0.037	0.040	0.025	0.037
Neut (G/l) week:	5	1.140	1.270	1.310	1.100	0.910
Eos (G/l) week:	5	0.090	0.070	0.100	0.070	0.150
Baso (G/l) week:	5	0.170	0.070	0.060	0.060	0.060
Lympho (G/l) week:	5	18.03	11.16	9.420	10.05	10.31
Mono (G/l) week:	5	1.030	0.530	0.670	0.500	0.370
Luc (G/l) week:	5	0.520	0.500	0.490	0.310	0.450
Plt (G/l) week:	5	1110	979.0	1049	1122	1123
PT(CS) (sec) week:	5	34.96	34.04	31.07	37.96	33.15



CGA 329351 tech.

Hematology (individuals): males

group 4  
 150 mg/kg

		16	17	18	19	20
		Animal no				
Eos (1) week:	5	0.011	0.009	0.005	0.008	0.006
Baso (1) week:	5	0.005	0.003	0.009	0.005	0.007
Lympho (1) week:	5	0.790	0.857	0.831	0.850	0.818
Mono (1) week:	5	0.035	0.026	0.050	0.055	0.050
Luc (1) week:	5	0.043	0.033	0.036	0.034	0.052
Neut (G/l) week:	5	1.900	0.680	1.610	0.790	1.320
Eos (G/l) week:	5	0.170	0.080	0.120	0.130	0.110
Baso (G/l) week:	5	0.070	0.030	0.200	0.090	0.140
Lympho (G/l) week:	5	12.80	8.140	19.48	14.07	16.13
Mono (G/l) week:	5	0.560	0.240	1.160	0.910	0.990
Luc (G/l) week:	5	0.690	0.310	0.850	0.570	1.020

CGA 329351 tech.

Hematology (individuals): males

group 4  
150 mg/kg

		16	17	18	19	20
		Animal no				
Plt (G/l) week: 5		1234	1073	1084	1276	1149
PT(CS) (sec) week: 5		40.83	31.30	36.26	33.25	32.52

CGA 329351 tech.

Hematology (individuals): males

group 5  
300 mg/kg

		21	22	23	24	25
		Animal no				
RBC (T/l) week: 5		7.460	7.240	6.860	7.020	7.550
Hb (mmol/l) week: 5		9.400	9.400	8.400	9.100	9.400
Hct (l) week: 5		0.443	0.441	0.406	0.440	0.469
MCV (fl) week: 5		59.40	61.00	59.20	62.70	62.00
RDW (l) week: 5		0.121	0.117	0.123	0.122	0.124
MCH (fmol) week: 5		1.250	1.300	1.220	1.290	1.250



CGA 329351 tech.

Hematology (individuals): males

group 5  
 300 mg/kg

		21	22	23	24	25
		Animal no				
Baso (G/l) week:	5	0.050	0.100	0.030	0.070	0.060
Lympho (G/l) week:	5	10.61	14.55	5.750	13.24	9.280
Mono (G/l) week:	5	0.530	0.640	0.240	0.490	0.500
Luc (G/l) week:	5	0.340	0.590	0.250	0.530	0.420
Plt (G/l) week:	5	363.0	1232	1036	1121	1229
PT(CS) (sec) week:	5	29.01	31.92	30.75	27.06	32.36

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CGA 329351 tech.

Hematology (individuals): females group 1  
0 mg/kg

		26	27	28	29	30
		Animal no				
RBC (T/l) week:	5	8.070	8.100	7.880	7.630	8.210
Hb (mmol/l) week:	5	9.700	9.600	10.10	9.300	9.800
Hct (l) week:	5	0.461	0.450	0.470	0.431	0.450
MCV (fl) week:	5	57.10	55.60	59.60	56.50	54.90
RDW (l) week:	5	0.128	0.116	0.114	0.111	0.114
MCH (fmol) week:	5	1.200	1.190	1.290	1.210	1.190
MCHC (mmol/l) week:	5	21.09	21.37	21.57	21.49	21.66
HDW (mmol/l) week:	5	1.200	1.300	1.230	1.210	1.290
WBC (G/l) week:	5	9.620	11.33	11.30	11.18	13.27
Neut (l) week:	5	0.037	0.055	0.064	0.060	0.049



CGA 329351 tech.

Hematology (individuals): females

group 1  
 0 mg/kg

		26	27	28	29	30
		Animal no				
Eos (1) week:	5	0.014	0.012	0.008	0.009	0.008
Baso (1) week:	5	0.005	0.005	0.005	0.006	0.005
Lympho (1) week:	5	0.894	0.846	0.851	0.836	0.846
Mono (1) week:	5	0.020	0.051	0.048	0.055	0.061
Luc (1) week:	5	0.030	0.030	0.023	0.035	0.032
Neut (G/1) week:	5	0.360	0.620	0.730	0.670	0.650
Eos (G/1) week:	5	0.130	0.140	0.090	0.100	0.100
Baso (G/1) week:	5	0.050	0.060	0.050	0.060	0.060
Lympho (G/1) week:	5	8.590	9.590	9.620	9.340	11.23
Mono (G/1) week:	5	0.200	0.580	0.550	0.620	0.800
Luc (G/1) week:	5	0.290	0.350	0.260	0.390	0.420

CGA 329351 tech.

Hematology (individuals): females group 1  
0 mg/kg

		26	27	28	29	30	Animal no
Plt (G/l) week: 5		1109	1335	1060	1091	1170	
PT(CS) (sec) week: 5		25.74	24.37	27.70	31.06	27.06	

CGA 329351 tech.

Hematology (individuals): females group 2  
10 mg/kg

		31	32	33	34	35	Animal no
RBC (T/l) week: 5		7.980	6.930	8.010	7.730	7.140	
Hb (mmol/l) week: 5		10.10	8.900	9.800	9.500	9.100	
Hct (l) week: 5		0.466	0.417	0.449	0.440	0.423	
MCV (fl) week: 5		58.30	60.20	56.10	56.90	59.30	
RDW (l) week: 5		0.110	0.121	0.120	0.118	0.110	
MCH (fmol) week: 5		1.260	1.280	1.220	1.220	1.280	

CGA 329351 tech.

Hematology (individuals): females

group 2  
 10 mg/kg

		31	32	33	34	35	Animal no
MCHC (mmol/l) week:	5	21.60	21.30	21.71	21.48	21.53	
HDW (mmol/l) week:	5	1.120	1.750	1.410	1.310	1.550	
WBC (G/l) week:	5	14.51	15.52	15.94	15.22	10.21	
Neut (1) week:	5	0.052	0.030	0.037	0.050	0.060	
Eos (1) week:	5	0.007	0.006	0.009	0.003	0.012	
Baso (1) week:	5	0.007	0.006	0.006	0.005	0.005	
Lympho (1) week:	5	0.868	0.894	0.900	0.900	0.858	
Mono (1) week:	5	0.037	0.037	0.024	0.020	0.037	
Luc (1) week:	5	0.029	0.027	0.023	0.022	0.029	
Neut (G/l) week:	5	0.760	0.470	0.590	0.760	0.610	
Eos (G/l) week:	5	0.100	0.090	0.150	0.050	0.120	

CGA 329351 tech.

Hematology (individuals): females

group 2  
10 mg/kg

		31	32	33	34	35
		Animal no				
Baso (G/l) week: 5		0.090	0.090	0.100	0.070	0.050
Lympho (G/l) week: 5		12.59	13.88	14.34	13.71	8.760
Mono (G/l) week: 5		0.540	0.570	0.380	0.300	0.370
Luc (G/l) week: 5		0.420	0.420	0.370	0.340	0.300
Plt (G/l) week: 5		1020	1079	1096	1215	1318
PT(CS) (sec) week: 5		29.45	27.10	32.46	31.19	32.72

CGA 329351 tech.

Hematology (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40
		Animal no				
RBC (T/l) week: 5		7.880	7.430	7.920	7.540	7.740
Hb (mmol/l) week: 5		10.30	9.300	9.900	9.300	9.900

CGA 329351 tech.

Hematology (individuals): females

group 3  
 50 mg/kg

		36	37	38	39	40
		Animal no				
Hct (1) week:	5	0.479	0.428	0.459	0.429	0.470
MCV (fl) week:	5	60.80	57.60	58.00	56.80	60.80
RDW (1) week:	5	0.108	0.122	0.110	0.111	0.112
MCH (fmol) week:	5	1.300	1.250	1.250	1.230	1.280
MCHC (mmol/l) week:	5	21.44	21.78	21.51	21.63	21.09
HDW (mmol/l) week:	5	1.090	1.740	1.190	1.210	1.190
WBC (G/l) week:	5	10.41	17.07	12.88	7.570	13.90
Neut (1) week:	5	0.020	0.071	0.054	0.071	0.069
Eos (1) week:	5	0.011	0.009	0.009	0.008	0.009
Baso (1) week:	5	0.005	0.006	0.005	0.003	0.006
Lympho (1) week:	5	0.896	0.857	0.887	0.850	0.861

CGA 329351 tech.

Hematology (individuals): females

group 3  
 50 mg/kg

		36	37	38	39	40
		Animal no				
Mono (1) week:	5	0.039	0.033	0.030	0.037	0.029
Luc (1) week:	5	0.029	0.025	0.017	0.030	0.026
Neut (G/l) week:	5	0.200	1.200	0.700	0.540	0.960
Eos (G/l) week:	5	0.120	0.150	0.110	0.060	0.130
Baso (G/l) week:	5	0.060	0.100	0.060	0.020	0.090
Lympho (G/l) week:	5	9.330	14.64	11.42	6.430	11.96
Mono (G/l) week:	5	0.400	0.560	0.380	0.280	0.410
Luc (G/l) week:	5	0.300	0.420	0.210	0.230	0.360
Plt (G/l) week:	5	979.0	1091	1163	1092	1088
PT(CS) (sec) week:	5	22.24	27.52	29.30	31.58	31.24

CGA 329351 tech.

Hematology (individuals): females

group 4  
 150 mg/kg

		41	42	43	44	45
		Animal no				
RBC (T/l) week:	5	7.880	7.290	7.810	7.140	7.250
Hb (mmol/l) week:	5	9.700	9.100	9.200	9.200	9.100
Hct (l) week:	5	0.451	0.422	0.420	0.433	0.428
MCV (fl) week:	5	57.20	57.90	53.70	60.70	59.00
RDW (l) week:	5	0.117	0.113	0.127	0.117	0.126
MCH (fmol) week:	5	1.230	1.240	1.180	1.290	1.250
MCHC (mmol/l) week:	5	21.46	21.48	21.92	21.23	21.18
HDW (mmol/l) week:	5	1.190	1.200	1.410	1.660	1.430
WBC (G/l) week:	5	11.83	8.990	18.15	15.38	8.880
Neut (l) week:	5	0.042	0.088	0.111	0.043	0.084

CGA 329351 tech.

Hematology (individuals): females

group 4  
 150. mg/kg

		41	42	43	44	45	Animal no
Eos (1) week:	5	0.008	0.012	0.046	0.006	0.008	
Baso (1) week:	5	0.004	0.003	0.005	0.006	0.004	
Lympho (1) week:	5	0.874	0.819	0.782	0.880	0.833	
Mono (1) week:	5	0.042	0.055	0.026	0.035	0.039	
Luc (1) week:	5	0.030	0.022	0.029	0.030	0.033	
Neut (G/1) week:	5	0.500	0.790	2.020	0.660	0.740	
Eos (G/1) week:	5	0.090	0.110	0.830	0.100	0.070	
Baso (G/1) week:	5	0.050	0.030	0.090	0.090	0.040	
Lympho (G/1) week:	5	10.34	7.360	14.20	13.53	7.400	
Mono (G/1) week:	5	0.490	0.500	0.470	0.540	0.350	
Luc (G/1) week:	5	0.350	0.200	0.530	0.460	0.290	

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CGA 329351 tech.

Hematology (individuals): females group 4  
150 mg/kg

		41	42	43	44	45	Animal no
Plt (G/l)							
week:	5	1088	979.0	1116	1167	1094	
PT(CS) (sec)							
week:	5	30.56	30.48	31.60	25.38	30.97	

CGA 329351 tech.

Hematology (individuals): females group 5  
300 mg/kg

		46	47	48	49	50	Animal no
RBC (T/l)							
week:	5	7.690	7.710	7.690	7.760	7.730	
Hb (mmol/l)							
week:	5	9.700	9.500	9.500	9.500	9.000	
Hct (l)							
week:	5	0.451	0.438	0.445	0.441	0.417	
MCV (fl)							
week:	5	58.70	56.90	57.90	56.90	54.00	
RDW (l)							
week:	5	0.108	0.118	0.113	0.109	0.117	
MCH (fmol)							
week:	5	1.270	1.230	1.240	1.220	1.170	

CGA 329351 tech.

Hematology (individuals): females

group 5  
 300 mg/kg

		46	47	48	49	50
		Animal no				
MCHC (mmol/l) week: 5		21.60	21.59	21.44	21.43	21.67
HDW (mmol/l) week: 5		1.180	1.320	1.150	1.370	1.360
WBC (G/l) week: 5		14.85	17.36	10.76	12.61	10.35
Neut (1) week: 5		0.075	0.040	0.066	0.078	0.082
Eos (1) week: 5		0.005	0.005	0.008	0.007	0.014
Baso (1) week: 5		0.005	0.007	0.004	0.006	0.004
Lympho (1) week: 5		0.863	0.899	0.865	0.848	0.839
Mono (1) week: 5		0.030	0.024	0.032	0.032	0.032
Luc (1) week: 5		0.022	0.026	0.026	0.029	0.029
Neut (G/l) week: 5		1.120	0.690	0.710	0.990	0.840
Eos (G/l) week: 5		0.080	0.080	0.080	0.080	0.140

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.

Hematology (individuals): females

group 5  
300 mg/kg

		46	47	48	49	50
						Animal no
Baso (G/l)						
week:	5	0.080	0.120	0.040	0.070	0.050
Lympho (G/l)						
week:	5	12.81	15.60	9.310	10.69	8.690
Mono (G/l)						
week:	5	0.440	0.420	0.350	0.410	0.330
Luc (G/l)						
week:	5	0.320	0.450	0.280	0.360	0.300
Plt (G/l)						
week:	5	1083	1066	1157	1109	1228
PT(CS) (sec)						
week:	5	28.42	29.29	28.51	30.69	25.53

CGA 48988 tech.

Hematology (individuals): males

group 1  
 0 mg/kg

		Animal no				
		1	2	3	4	5
RBC (T/l) week:	5	7.290	7.410	7.880	7.620	7.390
Hb (mmol/l) week:	5	9.500	9.200	9.600	9.400	9.200
Hct (l) week:	5	0.453	0.447	0.464	0.456	0.438
MCV (fl) week:	5	62.10	60.30	59.00	59.80	59.20
RDW (l) week:	5	0.123	0.120	0.120	0.125	0.117
MCH (fmol) week:	5	1.310	1.250	1.220	1.240	1.240
MCHC (mmol/l) week:	5	21.05	20.65	20.67	20.69	20.92
HDW (mmol/l) week:	5	1.530	1.200	1.280	1.240	1.620
WBC (G/l) week:	5	16.42	20.10	22.66	14.37	20.93
Neut (l) week:	5	0.071	0.058	0.066	0.072	0.101

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CGA 48988 tech.

Hematology (individuals): males

group 1  
 0 mg/kg

		Animal no				
		1	2	3	4	5
Eos (1) week:	5	0.004	0.007	0.005	0.006	0.005
Baso (1) week:	5	0.006	0.008	0.009	0.006	0.007
Lympho (1) week:	5	0.852	0.862	0.841	0.848	0.793
Mono (1) week:	5	0.034	0.035	0.044	0.033	0.054
Luc (1) week:	5	0.032	0.030	0.035	0.034	0.041
Neut (G/l) week:	5	1.160	1.170	1.500	1.040	2.100
Eos (G/l) week:	5	0.070	0.130	0.100	0.090	0.100
Baso (G/l) week:	5	0.100	0.160	0.190	0.080	0.140
Lympho (G/l) week:	5	14.00	17.34	19.06	12.19	16.60
Mono (G/l) week:	5	0.560	0.700	1.010	0.480	1.120
Luc (G/l) week:	5	0.530	0.610	0.790	0.490	0.860

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CGA 48988 tech.

Hematology (individuals): males group 1  
0 mg/kg

		1	2	3	4	5
		Animal no				
Plt (G/l)						
week:	5	1123	1077	1201	1166	705.0
PT(CS) (sec)						
week:	5	38.61	33.65	32.73	29.73	44.36

CGA 48988 tech.

Hematology (individuals): males group 2  
10 mg/kg

		6	7	8	9	10
		Animal no				
RBC (T/l)						
week:	5	7.780	6.930	7.700	7.370	7.380
Hb (mmol/l)						
week:	5	9.400	9.500	9.800	9.900	9.200
Hct (l)						
week:	5	0.465	0.448	0.465	0.482	0.456
MCV (fl)						
week:	5	59.80	64.70	60.40	65.40	61.70
RDW (l)						
week:	5	0.127	0.115	0.130	0.121	0.119
MCH (fmol)						
week:	5	1.210	1.370	1.270	1.350	1.250

CGA 48988 tech.

Hematology (individuals): males

group 2  
 10 mg/kg

		Animal no				
		6	7	8	9	10
MCHC (mmol/l)						
week:	5	20.20	21.15	21.04	20.62	20.28
HDW (mmol/l)						
week:	5	1.720	1.170	1.350	1.280	1.260
WBC (G/l)						
week:	5	21.92	14.47	25.54	18.14	20.34
Neut (1)						
week:	5	0.069	0.083	0.059	0.085	0.064
Eos (1)						
week:	5	0.004	0.008	0.003	0.007	0.005
Baso (1)						
week:	5	0.010	0.006	0.008	0.007	0.007
Lympho (1)						
week:	5	0.833	0.838	0.854	0.844	0.844
Mono (1)						
week:	5	0.047	0.033	0.044	0.031	0.046
Luc (1)						
week:	5	0.038	0.032	0.032	0.025	0.035
Neut (G/l)						
week:	5	1.510	1.200	1.510	1.540	1.290
Eos (G/l)						
week:	5	0.090	0.110	0.080	0.120	0.090

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CGA 48988 tech.

Hematology (individuals): males

group 2  
10 mg/kg

		6	7	8	9	10
		Animal no				
Baso (G/l) week:	5	0.220	0.090	0.200	0.130	0.140
Lympho (G/l) week:	5	18.25	12.12	21.82	15.31	17.17
Mono (G/l) week:	5	1.020	0.480	1.120	0.570	0.930
Luc (G/l) week:	5	0.820	0.470	0.810	0.460	0.710
Plt (G/l) week:	5	1081	1035	1065	1119	1152
PT(CS) (sec) week:	5	31.74	33.72	39.78	31.34	33.79

CGA 48988 tech.

Hematology (individuals): males

group 3  
50 mg/kg

		11	12	13	14	15
		Animal no				
RBC (T/l) week:	5	7.460	6.630	7.960	7.560	6.420
Hb (mmol/l) week:	5	9.300	8.300	9.600	9.400	8.200



CGA 48988 tech.

Hematology (individuals): males

group 3  
 50 mg/kg

		Animal no				
		11	12	13	14	15
Hct (1) week:	5	0.445	0.398	0.459	0.450	0.388
MCV (fl) week:	5	59.70	60.00	57.70	59.50	60.30
RDW (1) week:	5	0.120	0.120	0.129	0.121	0.121
MCH (fmol) week:	5	1.240	1.250	1.210	1.250	1.270
MCHC (mmol/l) week:	5	20.86	20.74	20.94	21.02	21.11
HDW (mmol/l) week:	5	1.230	1.640	1.730	1.210	1.300
WBC (G/l) week:	5	19.24	13.10	25.94	21.91	8.240
Neut (1) week:	5	0.083	0.123	0.061	0.054	0.247
Eos (1) week:	5	0.003	0.003	0.010	0.006	0.005
Baso (1) week:	5	0.006	0.005	0.009	0.008	0.002
Lympho (1) week:	5	0.835	0.819	0.843	0.846	0.695

CGA 48988 tech.

Hematology (individuals): males

group 3  
50 mg/kg

		Animal no				
		11	12	13	14	15
Mono (1) week:	5	0.041	0.028	0.046	0.053	0.028
Luc (1) week:	5	0.032	0.022	0.031	0.033	0.023
Neut (G/l) week:	5	1.590	1.610	1.590	1.180	2.030
Eos (G/l) week:	5	0.060	0.040	0.250	0.130	0.040
Baso (G/l) week:	5	0.110	0.060	0.230	0.180	0.020
Lympho (G/l) week:	5	16.06	10.73	21.87	18.54	5.720
Mono (G/l) week:	5	0.780	0.360	1.190	1.150	0.230
Luc (G/l) week:	5	0.620	0.290	0.810	0.730	0.190
Plt (G/l) week:	5	1014	1037	1043	1135	1083
PT(CS) (sec) week:	5	31.45	33.75	39.45	32.78	33.10

CGA 48988 tech.

Hematology (individuals): males

group 4  
 150 mg/kg

		16	17	18	19	20
		Animal no				
RBC (T/l) week:	5	7.720	7.130	7.140	7.400	7.510
Hb (mmol/l) week:	5	9.700	9.500	9.100	9.500	9.400
Hct (l) week:	5	0.463	0.456	0.433	0.463	0.451
MCV (fl) week:	5	60.00	63.95	60.70	62.60	60.10
RDW (l) week:	5	0.122	0.120	0.126	0.124	0.120
MCH (fmol) week:	5	1.250	1.335	1.270	1.280	1.260
MCHC (mmol/l) week:	5	20.89	20.87	21.01	20.45	20.92
HDW (mmol/l) week:	5	1.290	1.195	1.700	1.190	1.400
WBC (G/l) week:	5	24.26	13.27	22.10	17.13	15.28
Neut (l) week:	5	0.057	0.166	0.054	0.091	0.081

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CGA 48988 tech.

Hematology (individuals): males

group 4  
 150 mg/kg

		16	17	18	19	20
		Animal no				
Eos (1) week:	5	0.009	0.017	0.003	0.008	0.006
Baso (1) week:	5	0.009	0.005	0.008	0.005	0.006
Lympho (1) week:	5	0.853	0.746	0.870	0.814	0.838
Mono (1) week:	5	0.036	0.040	0.035	0.048	0.039
Luc (1) week:	5	0.036	0.027	0.030	0.034	0.031
Neut (G/l) week:	5	1.380	2.200	1.200	1.560	1.240
Eos (G/l) week:	5	0.210	0.225	0.070	0.130	0.090
Baso (G/l) week:	5	0.230	0.060	0.170	0.090	0.090
Lympho (G/l) week:	5	20.70	9.890	19.22	13.95	12.81
Mono (G/l) week:	5	0.870	0.520	0.760	0.820	0.590
Luc (G/l) week:	5	0.870	0.360	0.670	0.580	0.470

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CGA 48988 tech.

Hematology (individuals): males group 4  
150 mg/kg

		16	17	18	19	20	Animal no
Plt (G/l)							
week:	5	1185	838.5	1076	1131	1124	
PT(CS) (sec)							
week:	5	34.39	28.73	28.48	36.24	29.73	

CGA 48988 tech.

Hematology (individuals): males group 5  
300 mg/kg

		21	22	23	24	25	Animal no
RBC (T/l)							
week:	5	6.930	7.310	7.650	7.040	7.380	
Hb (mmol/l)							
week:	5	9.000	9.400	9.600	9.000	8.900	
Hct (l)							
week:	5	0.434	0.451	0.459	0.438	0.442	
MCV (fl)							
week:	5	62.60	61.70	60.10	62.20	59.80	
RDW (l)							
week:	5	0.125	0.120	0.124	0.133	0.119	
MCH (fmol)							
week:	5	1.300	1.290	1.260	1.280	1.210	

CGA 48988 tech.

Hematology (individuals): males

group 5  
 300 mg/kg

		21	22	23	24	25
		Animal no				
MCHC (mmol/l)						
week:	5	20.78	20.85	20.90	20.59	20.22
HDW (mmol/l)						
week:	5	1.240	1.800	1.290	1.360	1.600
WBC (G/l)						
week:	5	17.43	15.97	11.91	16.17	18.54
Neut (1)						
week:	5	0.076	0.067	0.081	0.057	0.078
Eos (1)						
week:	5	0.006	0.009	0.013	0.005	0.003
Baso (1)						
week:	5	0.006	0.006	0.004	0.007	0.005
Lympho (1)						
week:	5	0.844	0.859	0.839	0.874	0.852
Mono (1)						
week:	5	0.041	0.037	0.037	0.032	0.036
Luc (1)						
week:	5	0.027	0.021	0.025	0.025	0.026
Neut (G/l)						
week:	5	1.330	1.070	0.970	0.930	1.440
Eos (G/l)						
week:	5	0.100	0.150	0.150	0.080	0.050

CGA 48988 tech.

Hematology (individuals): males

group 5  
 300 mg/kg

		21	22	23	24	25
		Animal no				
Baso (G/l) week:	5	0.110	0.100	0.050	0.110	0.100
Lympho (G/l) week:	5	14.71	13.72	9.990	14.14	15.79
Mono (G/l) week:	5	0.720	0.590	0.440	0.510	0.670
Luc (G/l) week:	5	0.470	0.340	0.300	0.400	0.490
Plt (G/l) week:	5	1162	1127	1190	1198	1218
PT(CS) (sec) week:	5	28.78	36.90	29.89	33.81	37.46

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Hematology (individuals): females

group 1

0 mg/kg

		26	27	28	29	30
		Animal no				
RBC (T/l) week:	5	8.070	8.100	7.880	7.630	8.210
Hb (mmol/l) week:	5	9.700	9.600	10.10	9.300	9.800
Hct (l) week:	5	0.461	0.450	0.470	0.431	0.450
MCV (fl) week:	5	57.10	55.60	59.60	56.50	54.90
RDW (l) week:	5	0.128	0.116	0.114	0.111	0.114
MCH (fmol) week:	5	1.200	1.190	1.290	1.210	1.190
MCHC (mmol/l) week:	5	21.09	21.37	21.57	21.49	21.66
HDW (mmol/l) week:	5	1.200	1.300	1.230	1.210	1.290
WBC (G/l) week:	5	9.620	11.33	11.30	11.18	13.27
Neut (l) week:	5	0.037	0.055	0.064	0.060	0.049



Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Hematology (individuals): females

group 1  
0 mg/kg

		26	27	28	29	30	Animal no
Eos (1) week:	5	0.014	0.012	0.008	0.009	0.008	
Baso (1) week:	5	0.005	0.005	0.005	0.006	0.005	
Lympho (1) week:	5	0.894	0.846	0.851	0.836	0.846	
Mono (1) week:	5	0.020	0.051	0.048	0.055	0.061	
Luc (1) week:	5	0.030	0.030	0.023	0.035	0.032	
Neut (G/l) week:	5	0.360	0.620	0.730	0.670	0.650	
Eos (G/l) week:	5	0.130	0.140	0.090	0.100	0.100	
Baso (G/l) week:	5	0.050	0.060	0.050	0.060	0.060	
Lympho (G/l) week:	5	8.590	9.590	9.620	9.340	11.23	
Mono (G/l) week:	5	0.200	0.580	0.550	0.620	0.800	
Luc (G/l) week:	5	0.290	0.350	0.260	0.390	0.420	

CGA 48988 tech.

Hematology (individuals): females group 1  
0 mg/kg

		26	27	28	29	30
		Animal no				
Plt (G/l)						
week:	5	1109	1335	1060	1091	1170
PT(CS) (sec)						
week:	5	25.74	24.37	27.70	31.06	27.06

CGA 48988 tech.

Hematology (individuals): females group 2  
10 mg/kg

		31	32	33	34	35
		Animal no				
RBC (T/l)						
week:	5	7.730	7.320	8.050	7.560	7.610
Hb (mmol/l)						
week:	5	9.400	9.200	9.900	9.400	9.600
Hct (l)						
week:	5	0.442	0.429	0.461	0.436	0.450
MCV (fl)						
week:	5	57.30	58.60	57.20	57.70	59.20
RDW (l)						
week:	5	0.112	0.113	0.113	0.111	0.111
MCH (fmol)						
week:	5	1.220	1.260	1.220	1.240	1.260

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Hematology (individuals): females

group 2  
10 mg/kg

		31	32	33	34	35
						Animal no
MCHC (mmol/l)						
week:	5	21.31	21.47	21.39	21.48	21.22
HDW (mmol/l)						
week:	5	1.200	1.180	1.290	1.230	1.300
WBC (G/l)						
week:	5	13.98	8.690	15.87	13.52	11.68
Neut (1)						
week:	5	0.067	0.054	0.035	0.044	0.069
Eos (1)						
week:	5	0.008	0.006	0.009	0.005	0.011
Baso (1)						
week:	5	0.005	0.003	0.006	0.006	0.005
Lympho (1)						
week:	5	0.862	0.861	0.891	0.858	0.852
Mono (1)						
week:	5	0.030	0.040	0.030	0.044	0.042
Luc (1)						
week:	5	0.028	0.037	0.029	0.044	0.021
Neut (G/l)						
week:	5	0.930	0.470	0.560	0.590	0.800
Eos (G/l)						
week:	5	0.110	0.050	0.140	0.060	0.130

CGA 48988 tech.

Hematology (individuals): females

group 2  
10 mg/kg

		31	32	33	34	35
		Animal no				
Baso (G/l) week:	5	0.070	0.030	0.100	0.080	0.050
Lympho (G/l) week:	5	12.04	7.480	14.13	11.60	9.950
Mono (G/l) week:	5	0.420	0.340	0.480	0.590	0.490
Luc (G/l) week:	5	0.390	0.320	0.460	0.600	0.250
Plt (G/l) week:	5	1146	857.0	999.0	933.0	1139
PT(CS) (sec) week:	5	23.75	20.72	23.04	29.51	27.64

CGA 48988 tech.

Hematology (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40
		Animal no				
RBC (T/l) week:	5	7.760	7.120	7.320	7.390	7.650
Hb (mmol/l) week:	5	9.600	9.100	9.500	9.400	9.700

CGA 48988 tech.

Hematology (individuals): females

group 3  
 50 mg/kg

		36	37	38	39	40
		Animal no				
Hct (1) week:	5	0.453	0.428	0.446	0.437	0.452
MCV (fl) week:	5	58.40	60.10	61.00	59.20	59.10
RDW (1) week:	5	0.110	0.111	0.114	0.119	0.115
MCH (fmol) week:	5	1.240	1.280	1.290	1.270	1.260
MCHC (mmol/l) week:	5	21.16	21.22	21.24	21.45	21.37
HDW (mmol/l) week:	5	1.180	1.110	1.210	1.160	1.360
WBC (G/l) week:	5	11.51	13.08	12.43	12.71	16.26
Neut (1) week:	5	0.066	0.044	0.034	0.062	0.143
Eos (1) week:	5	0.013	0.007	0.006	0.009	0.015
Baso (1) week:	5	0.005	0.004	0.007	0.006	0.007
Lympho (1) week:	5	0.852	0.903	0.906	0.857	0.752

CGA 48988 tech.

Hematology (individuals): females

group 3  
 50 mg/kg

		36	37	38	39	40
		Animal no				
		36	37	38	39	40
Mono (1) week:	5	0.031	0.017	0.027	0.035	0.042
Luc (1) week:	5	0.033	0.024	0.021	0.031	0.041
Neut (G/l) week:	5	0.760	0.580	0.420	0.790	2.320
Eos (G/l) week:	5	0.150	0.090	0.070	0.120	0.250
Baso (G/l) week:	5	0.050	0.060	0.080	0.070	0.110
Lympho (G/l) week:	5	9.800	11.81	11.26	10.89	12.23
Mono (G/l) week:	5	0.360	0.220	0.340	0.450	0.690
Luc (G/l) week:	5	0.380	0.320	0.260	0.400	0.670
Plt (G/l) week:	5	1068	1052	1079	1170	1047
PT(CS) (sec) week:	5	28.24	27.98	26.63	31.99	23.51

CGA 48988 tech.

Hematology (individuals): females

group 4  
 150 mg/kg

		41	42	43	44	45
		Animal no				
RBC (T/l) week:	5	7.720	7.970	6.880	7.780	7.030
Hb (mmol/l) week:	5	9.900	9.800	8.400	9.800	9.000
Hct (l) week:	5	0.449	0.461	0.399	0.462	0.424
MCV (fl) week:	5	58.10	57.90	58.00	59.40	60.30
RDW (l) week:	5	0.111	0.116	0.111	0.118	0.114
MCH (fmol) week:	5	1.280	1.240	1.230	1.260	1.290
MCHC (mmol/l) week:	5	21.95	21.36	21.17	21.18	21.33
HDW (mmol/l) week:	5	1.200	1.550	1.260	1.500	1.430
WBC (G/l) week:	5	8.430	11.86	10.37	11.14	15.92
Neut (l) week:	5	0.082	0.074	0.096	0.041	0.034

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CGA 48988 tech.

Hematology (individuals): females

group 4  
 150 mg/kg

		41	42	43	44	45
		Animal no				
		41	42	43	44	45
Eos (1) week:	5	0.011	0.014	0.008	0.008	0.008
Baso (1) week:	5	0.004	0.004	0.003	0.005	0.006
Lympho (1) week:	5	0.841	0.839	0.818	0.860	0.867
Mono (1) week:	5	0.033	0.040	0.045	0.048	0.048
Luc (1) week:	5	0.029	0.029	0.031	0.037	0.036
Neut (G/l) week:	5	0.690	0.880	0.990	0.460	0.540
Eos (G/l) week:	5	0.100	0.170	0.080	0.090	0.130
Baso (G/l) week:	5	0.030	0.050	0.030	0.050	0.100
Lympho (G/l) week:	5	7.090	9.940	8.480	9.580	13.80
Mono (G/l) week:	5	0.280	0.470	0.460	0.540	0.770
Luc (G/l) week:	5	0.240	0.350	0.330	0.410	0.570

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CGA 48988 tech.

Hematology (individuals): females

group 4  
150 mg/kg

		41	42	43	44	Animal no 45
Plt (G/l) week:	5	1067	1230	1083	1000	1131
PT(CS) (sec) week:	5	31.46	26.54	19.09	22.45	20.75

CGA 48988 tech.

Hematology (individuals): females

group 5  
300 mg/kg

		46	47	48	49	Animal no 50
RBC (T/l) week:	5	7.510	8.370	6.960	7.930	6.940
Hb (mmol/l) week:	5	9.500	10.30	8.600	9.800	9.000
Hct (l) week:	5	0.454	0.481	0.400	0.459	0.423
MCV (fl) week:	5	60.40	57.50	57.50	57.80	60.90
RDW (l) week:	5	0.111	0.119	0.115	0.114	0.112
MCH (fmol) week:	5	1.270	1.230	1.240	1.240	1.300

CGA 48988 tech.

Hematology (individuals): females

group 5  
 300 mg/kg

		46	47	48	49	50
		Animal no				
MCHC (mmol/l)						
week:	5	20.93	21.43	21.52	21.36	21.27
HDW (mmol/l)						
week:	5	1.140	1.270	1.550	1.180	1.160
WBC (G/l)						
week:	5	9.390	14.41	12.12	13.08	9.210
Neut (1)						
week:	5	0.056	0.055	0.067	0.036	0.053
Eos (1)						
week:	5	0.005	0.009	0.004	0.009	0.007
Baso (1)						
week:	5	0.004	0.007	0.004	0.005	0.004
Lympho (1)						
week:	5	0.874	0.834	0.852	0.872	0.871
Mono (1)						
week:	5	0.038	0.062	0.038	0.043	0.040
Luc (1)						
week:	5	0.024	0.033	0.036	0.035	0.025
Neut (G/l)						
week:	5	0.530	0.790	0.810	0.470	0.490
Eos (G/l)						
week:	5	0.040	0.120	0.050	0.110	0.060

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CGA 48988 tech.

Hematology (individuals): females

group 5  
 300 mg/kg

		46	47	48	49	50	Animal no
Baso (G/l) week:	5	0.040	0.100	0.050	0.060	0.040	
Lympho (G/l) week:	5	8.210	12.02	10.32	11.41	8.020	
Mono (G/l) week:	5	0.350	0.890	0.460	0.570	0.370	
Luc (G/l) week:	5	0.220	0.470	0.440	0.460	0.230	
Plt (G/l) week:	5	949.0	1210	1161	1068	1027	
PT(CS) (sec) week:	5	29.24	21.19	23.54	26.89	31.97	

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

6.8. Blood chemistry (individuals)CGA 329351 tech.

Blood chemistry (individuals): males

group 1  
0 mg/kg

		Animal no				
		1	2	3	4	5
Gluc (mmol/l)						
week:	5	6.860	5.900	6.910	6.390	7.580
Urea (mmol/l)						
week:	5	5.230	6.020	6.350	5.750	5.810
Creat-e (umol/l)						
week:	5	57.30	58.30	57.00	61.50	53.50
Bili-tot (umol/l)						
week:	5	3.270	2.100	2.340	1.870	2.340
Prot (g/l)						
week:	5	65.91	62.68	64.89	68.72	68.86
Alb (g/l)						
week:	5	38.18	36.59	37.81	38.68	39.50
Glob (g/l)						
week:	5	27.73	26.09	27.08	30.04	29.36
A/G (1)						
week:	5	1.380	1.400	1.400	1.290	1.350
Chol (mmol/l)						
week:	5	2.000	1.820	1.880	2.330	2.190



CGA 329351 tech.

Blood chemistry (individuals): males

group 2  
10 mg/kg

		Animal no				
		6	7	8	9	10
Gluc (mmol/l) week: 5		9.190	7.150	8.170	7.390	7.840
Urea (mmol/l) week: 5		6.540	4.530	6.290	6.320	4.530
Creat-e (umol/l) week: 5		54.10	55.20	75.60	58.00	56.10
Bili-tot (umol/l) week: 5		2.100	2.570	2.100	2.220	1.870
Prot (g/l) week: 5		67.93	65.71	64.31	67.20	68.95
Alb (g/l) week: 5		38.64	37.78	37.64	39.21	39.46
Glob (g/l) week: 5		29.29	27.93	26.67	27.99	29.49
A/G (1) week: 5		1.320	1.350	1.410	1.400	1.340
Chol (mmol/l) week: 5		2.300	1.350	1.750	1.920	1.960
Na+ (mmol/l) week: 5		143.0	139.1	139.5	143.4	142.2

CGA 329351 tech.

Blood chemistry (individuals): males

group 2  
10 mg/kg

		6	7	8	9	10
		Animal no				
K+	(mmol/l)					
week:	5	3.420	3.910	4.545	3.640	3.240
Ca++	(mmol/l)					
week:	5	2.770	2.770	2.670	2.770	2.760
Cl-	(mmol/l)					
week:	5	100.5	98.50	99.50	99.70	98.80
PO4-in	(mmol/l)					
week:	5	2.140	2.450	2.370	2.170	2.400
ASAT (GOT)	(U/l)					
week:	5	52.70	51.40	115.6	54.60	51.40
ALAT (GPT)	(U/l)					
week:	5	48.40	30.60	44.40	35.50	36.30
ALP	(U/l)					
week:	5	241.2	172.2	133.2	118.2	204.4

CGA 329351 tech.

Blood chemistry (individuals): males

group 3  
50 mg/kg

		11	12	13	14	15
		Animal no				
Gluc	(mmol/l)					
week:	5	7.090	8.130	9.320	6.440	7.630

CGA 329351 tech.

Blood chemistry (individuals): males

group 3  
50 mg/kg

		11	12	13	14	15
		Animal no				
Urea (mmol/l)						
week:	5	5.990	6.600	6.020	5.560	6.260
Creat-e (umol/l)						
week:	5	54.40	62.80	50.80	58.40	53.60
Bili-tot (umol/l)						
week:	5	1.870	3.270	2.100	1.870	2.100
Prot (g/l)						
week:	5	63.23	63.64	67.11	64.31	65.33
Alb (g/l)						
week:	5	36.41	37.76	39.06	37.43	38.50
Glob (g/l)						
week:	5	26.82	25.88	28.05	26.88	26.83
A/G (l)						
week:	5	1.360	1.460	1.390	1.390	1.430
Chol (mmol/l)						
week:	5	2.240	1.960	2.470	1.900	1.640
Na+ (mmol/l)						
week:	5	142.2	140.8	140.9	140.4	142.1
K+ (mmol/l)						
week:	5	3.830	3.560	3.560	4.190	3.800
Ca++ (mmol/l)						
week:	5	2.760	2.800	2.780	2.670	2.760



CGA 329351 tech.

Blood chemistry (individuals): males

group 3  
50 mg/kg

		11	12	13	14	15
		Animal no				
Cl-	(mmol/l)					
week:	5	99.60	96.60	99.00	99.60	99.70
PO4-in	(mmol/l)					
week:	5	2.790	2.610	2.270	2.110	2.390
ASAT (GOT)	(U/l)					
week:	5	54.60	57.80	48.90	72.40	57.10
ALAT (GPT)	(U/l)					
week:	5	31.40	44.40	25.80	41.10	45.20
ALP	(U/l)					
week:	5	203.3	179.4	145.6	173.0	124.9

CGA 329351 tech.

Blood chemistry (individuals): males

group 4  
150 mg/kg

		16	17	18	19	20
		Animal no				
Gluc	(mmol/l)					
week:	5	5.980	7.220	8.310	5.960	8.300
Urea	(mmol/l)					
week:	5	4.830	4.960	5.500	5.650	7.420
Creat-e	(umol/l)					
week:	5	64.30	52.70	57.80	60.10	64.60

CGA 329351 tech.

Blood chemistry (individuals): males

group 4  
 150. mg/kg

		16	17	18	19	20
		Animal no				
Bili-tot (umol/l)						
week:	5	2.100	2.100	2.570	2.340	2.340
Prot (g/l)						
week:	5	65.88	66.53	66.85	67.84	64.66
Alb (g/l)						
week:	5	38.08	38.85	39.31	38.48	38.23
Glob (g/l)						
week:	5	27.80	27.68	27.54	29.36	26.43
A/G (1)						
week:	5	1.370	1.400	1.430	1.310	1.450
Chol (mmol/l)						
week:	5	1.470	1.830	2.110	2.160	1.920
Na+ (mmol/l)						
week:	5	142.0	143.7	142.2	139.8	138.7
K+ (mmol/l)						
week:	5	3.850	3.710	3.360	3.690	4.515
Ca++ (mmol/l)						
week:	5	2.740	2.720	2.770	2.810	2.800
Cl- (mmol/l)						
week:	5	98.40	99.30	101.2	100.0	99.05
PO4-in (mmol/l)						
week:	5	2.530	2.360	2.360	2.540	2.630

CGA 329351 tech.

Blood chemistry (individuals): males

group 4  
150 mg/kg

		16	17	18	19	20	Animal no
ASAT (GOT) (U/l)							
week:	5	53.30	52.70	55.90	44.40	85.10	
ALAT (GPT) (U/l)							
week:	5	30.60	31.40	31.40	32.30	51.60	
AlP (U/l)							
week:	5	154.2	129.5	153.1	133.8	186.1	

CGA 329351 tech.

Blood chemistry (individuals): males

group 5  
300 mg/kg

		21	22	23	24	25	Animal no
Gluc (mmol/l)							
week:	5	7.780	7.110	9.040	6.570	7.810	
Urea (mmol/l)							
week:	5	4.440	4.380	5.750	5.290	4.410	
Creat-e (umol/l)							
week:	5	54.50	48.50	52.50	53.00	51.10	
Bili-tot (umol/l)							
week:	5	1.400	2.100	1.640	2.100	1.640	
Prot (g/l)							
week:	5	66.12	68.89	66.61	64.78	66.21	

CGA 329351 tech.

Blood chemistry (individuals): males

group 5  
300 mg/kg

		21	22	23	24	25
		Animal no				
Alb (g/l)						
week:	5	38.08	39.66	38.34	37.56	37.49
Glob (g/l)						
week:	5	28.04	29.23	28.27	27.22	28.72
A/G (1)						
week:	5	1.360	1.360	1.360	1.380	1.310
Chol (mmol/l)						
week:	5	2.090	2.400	2.060	1.850	2.130
Na+ (mmol/l)						
week:	5	139.0	138.9	140.7	138.9	139.5
K+ (mmol/l)						
week:	5	3.710	3.200	3.850	3.460	3.340
Ca++ (mmol/l)						
week:	5	2.780	2.780	2.800	2.740	2.650
Cl- (mmol/l)						
week:	5	102.6	100.4	100.3	100.3	101.5
PO4-in (mmol/l)						
week:	5	2.680	2.270	2.630	2.450	2.260
ASAT (GOT) (U/l)						
week:	5	56.50	50.80	52.70	45.10	49.50
ALAT (GPT) (U/l)						
week:	5	27.40	35.50	36.30	33.90	32.30

CGA 329351 tech.

Blood chemistry (individuals): males

group 5  
 300 mg/kg

		21	22	23	24	25
ALP (U/l) week:	5	184.8	158.7	173.8	126.5	182.1

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CGA 329351 tech.

Blood chemistry (individuals): females

group 1  
 0 mg/kg

		26	27	28	29	30
		Animal no				
Gluc (mmol/l) week: 5		5.480	5.660	6.730	6.430	5.390
Urea (mmol/l) week: 5		4.650	6.410	6.930	5.560	6.600
Creat-e (umol/l) week: 5		52.20	52.50	59.80	57.80	65.30
Bili-tot (umol/l) week: 5		2.100	3.040	2.340	2.810	2.100
Prot (g/l) week: 5		66.09	67.72	66.06	62.68	64.08
Alb (g/l) week: 5		38.29	39.94	39.19	38.04	37.46
Glob (g/l) week: 5		27.80	27.78	26.87	24.64	26.62
A/G (1) week: 5		1.380	1.440	1.460	1.540	1.410
Chol (mmol/l) week: 5		2.520	2.520	2.780	2.270	3.005
Na+ (mmol/l) week: 5		138.6	141.6	140.0	139.2	137.6

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Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.

Blood chemistry (individuals): females

group 1  
0 mg/kg

		26	27	28	29	30
		Animal no				
K+	(mmol/l)					
week:	5	3.420	3.540	3.660	3.220	3.270
Ca++	(mmol/l)					
week:	5	2.700	2.780	2.710	2.550	2.620
Cl-	(mmol/l)					
week:	5	102.5	99.90	100.5	100.5	98.80
PO4-in	(mmol/l)					
week:	5	2.100	1.820	1.900	1.620	1.560
ASAT (GOT)	(U/l)					
week:	5	58.40	59.10	52.10	59.70	62.20
ALAT (GPT)	(U/l)					
week:	5	25.00	29.80	33.10	29.00	42.70
AlP	(U/l)					
week:	5	76.80	98.60	127.0	83.50	80.30

CGA 329351 tech.

Blood chemistry (individuals): females

group 2  
10 mg/kg

		31	32	33	34	35
		Animal no				
Gluc	(mmol/l)					
week:	5	6.250	6.230	6.930	10.13	5.590

CGA 329351 tech.

Blood chemistry (individuals): females

group 2  
 10 mg/kg

		31	32	33	34	35
		Animal no				
Urea (mmol/l) week: 5		6.660	6.380	6.410	8.090	6.930
Creat-e (umol/l) week: 5		56.10	59.70	54.20	57.70	60.90
Bili-tot (umol/l) week: 5		1.640	3.040	1.870	2.100	2.570
Prot (g/l) week: 5		65.77	67.37	64.72	61.68	69.07
Alb (g/l) week: 5		38.87	39.51	37.98	36.73	39.92
Glob (g/l) week: 5		26.90	27.86	26.74	24.95	29.15
A/G (1) week: 5		1.440	1.420	1.420	1.470	1.370
Chol (mmol/l) week: 5		2.270	2.620	2.220	2.060	2.560
Na+ (mmol/l) week: 5		140.9	139.8	141.1	141.1	141.2
K+ (mmol/l) week: 5		3.360	3.490	3.200	2.950	2.990
Ca++ (mmol/l) week: 5		2.650	2.670	2.700	2.570	2.650



CGA 329351 tech.

Blood chemistry (individuals): females

group 2  
10. mg/kg

		31	32	33	34	35
		Animal no				
Cl-						
(mmol/l)						
week:	5	100.6	100.5	100.1	100.5	101.3
PO4-in						
(mmol/l)						
week:	5	1.850	1.980	2.010	1.790	1.500
ASAT (GOT)						
(U/l)						
week:	5	44.40	52.10	47.00	40.95	43.80
ALAT (GPT)						
(U/l)						
week:	5	28.20	33.10	36.30	43.50	31.40
ALP						
(U/l)						
week:	5	120.6	91.60	105.0	91.10	76.30

CGA 329351 tech.

Blood chemistry (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40
		Animal no				
Gluc						
(mmol/l)						
week:	5	5.190	7.640	6.110	6.000	6.050
Urea						
(mmol/l)						
week:	5	7.570	6.840	7.480	7.270	8.790
Creat-e						
(umol/l)						
week:	5	62.20	55.50	57.50	48.30	62.20

CGA 329351 tech.

Blood chemistry (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40
		Animal no				
Bili-tot (umol/l)						
week:	5	2.810	2.810	1.520	2.340	1.640
Prot (g/l)						
week:	5	68.07	69.21	65.94	64.60	67.66
Alb (g/l)						
week:	5	39.46	41.09	38.03	37.51	38.67
Glob (g/l)						
week:	5	28.61	28.12	27.91	27.09	28.99
A/G (1)						
week:	5	1.380	1.460	1.360	1.380	1.330
Chol (mmol/l)						
week:	5	2.800	2.590	2.410	2.610	2.490
Na+ (mmol/l)						
week:	5	140.0	139.2	139.4	141.2	141.7
K+ (mmol/l)						
week:	5	3.840	3.460	3.370	3.360	3.130
Ca++ (mmol/l)						
week:	5	2.750	2.690	2.600	2.620	2.680
Cl- (mmol/l)						
week:	5	101.4	98.30	100.7	101.1	99.80
PO4-in (mmol/l)						
week:	5	2.380	2.030	1.650	1.790	1.930

CGA 329351 tech.

Blood chemistry (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40
		Animal no				
ASAT (GOT) (U/l)						
week:	5	61.00	54.60	47.60	47.00	45.10
ALAT (GPT) (U/l)						
week:	5	29.00	44.40	33.90	25.00	27.40
ALP (U/l)						
week:	5	71.20	139.4	121.4	83.30	135.9

CGA 329351 tech.

Blood chemistry (individuals): females

group 4  
150 mg/kg

		41	42	43	44	45
		Animal no				
Gluc (mmol/l)						
week:	5	6.930	6.510	6.520	5.860	5.440
Urea (mmol/l)						
week:	5	6.140	5.320	6.140	7.630	5.350
Creat-e (umol/l)						
week:	5	53.90	54.40	54.50	49.60	47.40
Bili-tot (umol/l)						
week:	5	1.870	1.400	2.810	2.340	2.340
Prot (g/l)						
week:	5	65.27	67.84	66.50	68.42	67.17

CGA 329351 tech.

Blood chemistry (individuals): females

group 4  
 150. mg/kg

		41	42	43	44	45
		Animal no				
Alb (g/l) week:	5	39.04	39.37	38.57	40.35	39.67
Glob (g/l) week:	5	26.23	28.47	27.93	28.07	27.50
A/G (1) week:	5	1.490	1.380	1.380	1.440	1.440
Chol (mmol/l) week:	5	2.150	2.150	2.480	2.920	2.360
Na+ (mmol/l) week:	5	141.2	137.1	139.2	138.0	137.4
K+ (mmol/l) week:	5	3.440	3.160	3.030	3.150	3.190
Ca++ (mmol/l) week:	5	2.790	2.590	2.620	2.780	2.650
Cl- (mmol/l) week:	5	99.40	101.2	101.5	101.6	101.6
PO4-in (mmol/l) week:	5	2.060	1.660	1.770	2.210	1.570
ASAT (GOT) (U/l) week:	5	47.60	45.10	61.00	40.60	48.30
ALAT (GPT) (U/l) week:	5	48.40	25.00	42.70	32.30	38.70

CGA 329351 tech.

Blood chemistry (individuals): females

group 4  
150 mg/kg

		41	42	43	44	45
AlP (U/l) week: 5		97.80	87.00	102.3	91.90	91.10

CGA 329351 tech.

Blood chemistry (individuals): females

group 5  
300 mg/kg

		46	47	48	49	50
Gluc (mmol/l) week: 5		5.050	5.530	6.140	5.200	5.920
Urea (mmol/l) week: 5		5.350	6.350	5.350	6.930	6.780
Creat-e (umol/l) week: 5		53.80	63.40	51.10	54.50	50.20
Bili-tot (umol/l) week: 5		1.640	1.870	1.520	1.640	1.400
Prot (g/l) week: 5		67.96	69.44	69.85	66.38	71.43
Alb (g/l) week: 5		39.03	39.98	40.52	39.15	39.95
Glob (g/l) week: 5		28.93	29.46	29.33	27.23	31.48

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.

Blood chemistry (individuals): females

group 5

300 .mg/kg

		46	47	48	49	50
		Animal no				
A/G (1)						
week:	5	1.350	1.360	1.380	1.440	1.270
Chol (mmol/l)						
week:	5	2.700	2.000	2.620	2.180	2.940
Na+ (mmol/l)						
week:	5	137.6	138.6	139.1	139.0	138.2
K+ (mmol/l)						
week:	5	3.260	3.610	3.240	3.400	3.430
Ca++ (mmol/l)						
week:	5	2.680	2.850	2.700	2.730	2.730
Cl- (mmol/l)						
week:	5	101.6	99.80	103.2	101.1	102.3
PO4-in (mmol/l)						
week:	5	1.850	2.250	1.750	2.330	1.850
ASAT (GOT) (U/l)						
week:	5	47.00	55.90	47.60	56.50	47.00
ALAT (GPT) (U/l)						
week:	5	28.20	50.80	28.20	31.40	57.30
AlP (U/l)						
week:	5	95.60	164.4	151.5	74.70	89.20

CGA 48988 tech.

Blood chemistry (individuals): males

group 1  
0 mg/kg

		Animal no				
		1	2	3	4	5
Gluc (mmol/l)						
week:	5	6.860	5.900	6.910	6.390	7.580
Urea (mmol/l)						
week:	5	5.230	6.020	6.350	5.750	5.810
Creat-e (umol/l)						
week:	5	57.30	58.30	57.00	61.50	53.50
Bili-tot (umol/l)						
week:	5	3.270	2.100	2.340	1.870	2.340
Prot (g/l)						
week:	5	65.91	62.68	64.89	68.72	68.86
Alb (g/l)						
week:	5	38.18	36.59	37.81	38.68	39.50
Glob (g/l)						
week:	5	27.73	26.09	27.08	30.04	29.36
A/G (1)						
week:	5	1.380	1.400	1.400	1.290	1.350
Chol (mmol/l)						
week:	5	2.000	1.820	1.880	2.330	2.190
Na+ (mmol/l)						
week:	5	144.9	140.7	147.2	140.9	148.8

CGA 48988 tech.

Blood chemistry (individuals): males

group 1  
0 mg/kg

		1	2	3	4	5
		Animal no				
K+	(mmol/l)					
week:	5	3.835	3.650	3.750	3.760	3.640
Ca++	(mmol/l)					
week:	5	2.830	2.750	2.740	2.800	2.750
Cl-	(mmol/l)					
week:	5	97.40	98.90	96.20	99.70	94.50
PO4-in	(mmol/l)					
week:	5	2.440	2.570	2.340	2.250	2.410
ASAT (GOT)	(U/l)					
week:	5	63.50	54.60	54.00	60.30	50.80
ALAT (GPT)	(U/l)					
week:	5	41.10	41.90	39.50	39.50	32.30
AlP	(U/l)					
week:	5	155.0	148.3	156.6	176.7	187.5

CGA 48988 tech.

Blood chemistry (individuals): males

group 2  
10 mg/kg

		6	7	8	9	10
		Animal no				
Gluc	(mmol/l)					
week:	5	6.650	8.740	6.550	9.070	8.030



CGA 48988 tech.

Blood chemistry (individuals): males

group 2  
 10 mg/kg

		Animal no				
		6	7	8	9	10
Urea (mmol/l) week:	5	6.020	5.350	5.320	5.650	6.690
Creat-e (umol/l) week:	5	55.00	44.60	58.30	50.70	58.40
Bili-tot (umol/l) week:	5	2.340	1.870	1.640	1.870	1.635
Prot (g/l) week:	5	70.58	65.91	64.71	69.12	64.09
Alb (g/l) week:	5	39.97	38.01	38.15	38.94	39.13
Glob (g/l) week:	5	30.61	27.90	26.64	30.18	26.40
A/G (1) week:	5	1.310	1.360	1.420	1.290	1.480
Chol (mmol/l) week:	5	1.900	2.220	1.660	2.650	1.720
Na+ (mmol/l) week:	5	141.1	139.2	143.5	140.2	144.7
K+ (mmol/l) week:	5	3.710	3.710	3.350	3.260	3.480
Ca++ (mmol/l) week:	5	2.870	2.670	2.660	2.850	2.760

CGA 48988 tech.

Blood chemistry (individuals): males

group 2  
10 mg/kg

		6	7	8	9	10
		Animal no				
Cl-						
(mmol/l)						
week:	5	99.20	101.8	99.65	100.6	99.00
PO4-in						
(mmol/l)						
week:	5	2.390	2.190	2.440	2.510	2.510
ASAT (GOT)						
(U/l)						
week:	5	55.20	45.70	59.05	52.70	64.10
ALAT (GPT)						
(U/l)						
week:	5	37.90	25.80	39.50	37.90	64.10
ALP						
(U/l)						
week:	5	158.2	136.2	216.8	208.7	213.5

CGA 48988 tech.

Blood chemistry (individuals): males

group 3  
50 mg/kg

		11	12	13	14	15
		Animal no				
Gluc						
(mmol/l)						
week:	5	7.190	8.430	7.220	7.550	7.450
Urea						
(mmol/l)						
week:	5	6.540	6.430	5.810	5.200	5.780
Creat-e						
(umol/l)						
week:	5	60.30	64.20	53.30	57.70	64.50

CGA 48988 tech.

Blood chemistry (individuals): males

group 3  
50 mg/kg

		Animal no				
		11	12	13	14	15
Bili-tot (umol/l)						
week:	5	1.755	2.340	2.810	2.810	2.570
Prot (g/l)						
week:	5	64.76	67.55	69.07	63.55	63.08
Alb (g/l)						
week:	5	37.52	39.49	39.17	37.83	36.99
Glob (g/l)						
week:	5	27.66	28.06	29.90	25.72	26.09
A/G (1)						
week:	5	1.360	1.410	1.310	1.470	1.420
Chol (mmol/l)						
week:	5	2.285	2.020	1.940	1.710	1.710
Na+ (mmol/l)						
week:	5	139.7	140.3	139.5	143.7	140.1
K+ (mmol/l)						
week:	5	3.700	4.505	3.680	3.100	4.000
Ca++ (mmol/l)						
week:	5	2.720	2.710	2.730	2.660	2.570
Cl- (mmol/l)						
week:	5	97.70	101.2	101.0	100.3	97.80
PO4-in (mmol/l)						
week:	5	2.130	2.260	2.460	2.560	2.380

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CGA 48988 tech.

Blood chemistry (individuals): males

group 3  
50 mg/kg

		11	12	13	14	15
		Animal no				
ASAT (GOT) (U/l)						
week:	5	61.00	89.50	62.20	61.60	66.70
ALAT (GPT) (U/l)						
week:	5	41.90	51.60	45.20	37.90	37.90
ALP (U/l)						
week:	5	182.6	59.90	204.9	182.6	154.4

CGA 48988 tech.

Blood chemistry (individuals): males

group 4  
150 mg/kg

		16	17	18	19	20
		Animal no				
Gluc (mmol/l)						
week:	5	6.400	7.530	5.750	7.750	6.570
Urea (mmol/l)						
week:	5	6.200	4.920	6.630	5.720	4.160
Creat-e (umol/l)						
week:	5	62.30	58.40	60.10	57.30	53.50
Bili-tot (umol/l)						
week:	5	2.100	2.570	1.870	2.340	1.170
Prot (g/l)						
week:	5	67.78	66.15	68.37	65.21	65.13

CGA 48988 tech.

Blood chemistry (individuals): males

group 4  
 150. mg/kg

		16	17	18	19	20	Animal no
Alb (g/l) week:	5	38.73	37.69	38.54	38.76	40.18	
Glob (g/l) week:	5	29.05	28.46	29.83	26.45	24.95	
A/G (1) week:	5	1.330	1.320	1.290	1.470	1.610	
Chol (mmol/l) week:	5	1.590	2.410	2.040	1.900	1.810	
Na+ (mmol/l) week:	5	141.8	140.2	144.6	140.9	140.3	
K+ (mmol/l) week:	5	3.820	3.860	3.470	3.610	3.410	
Ca++ (mmol/l) week:	5	2.790	2.720	2.740	2.680	2.620	
Cl- (mmol/l) week:	5	98.40	101.1	99.40	98.20	100.2	
PO4-in (mmol/l) week:	5	2.460	2.260	2.310	2.400	2.110	
ASAT (GOT) (U/l) week:	5	59.70	59.10	54.00	44.40	46.40	
ALAT (GPT) (U/l) week:	5	37.90	30.60	32.30	34.70	26.60	

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CGA 48988 tech.

Blood chemistry (individuals): males

group 4  
150 mg/kg

		16	17	18	19	20
		Animal no				
AlP (U/l) week: 5		153.4	177.0	141.6	151.0	145.3

CGA 48988 tech.

Blood chemistry (individuals): males

group 5  
300 mg/kg

		21	22	23	24	25
		Animal no				
Gluc (mmol/l) week: 5		5.590	5.540	5.790	5.860	7.540
Urea (mmol/l) week: 5		5.470	5.140	5.200	4.770	5.200
Creat-e (umol/l) week: 5		54.40	52.50	61.40	60.00	55.20
Bili-tot (umol/l) week: 5		1.170	2.570	1.870	1.640	2.340
Prot (g/l) week: 5		68.66	65.01	67.55	64.83	67.20
Alb (g/l) week: 5		38.00	38.14	37.94	37.57	38.49
Glob (g/l) week: 5		30.66	26.87	29.61	27.26	28.71

CGA 48988 tech.

Blood chemistry (individuals): males

group 5  
 300 mg/kg

		21	22	23	24	25	Animal no
A/G (1) week: 5		1.240	1.420	1.280	1.380	1.340	
Chol (mmol/l) week: 5		2.160	1.810	2.610	1.810	2.050	
Na+ (mmol/l) week: 5		140.4	138.1	140.7	138.3	142.1	
K+ (mmol/l) week: 5		3.410	3.510	4.150	3.330	3.300	
Ca++ (mmol/l) week: 5		2.720	2.630	2.720	2.570	2.660	
Cl- (mmol/l) week: 5		99.60	100.9	100.9	100.7	98.70	
PO4-in (mmol/l) week: 5		2.180	2.180	2.350	2.130	2.310	
ASAT (GOT) (U/l) week: 5		53.30	52.10	56.50	59.70	51.40	
ALAT (GPT) (U/l) week: 5		42.70	34.70	23.40	29.80	33.10	
AlP (U/l) week: 5		145.3	134.3	112.3	145.0	232.1	

CGA 48988 tech.

Blood chemistry (individuals): females

group 1  
 0 mg/kg

		26	27	28	29	30
		Animal no				
Gluc (mmol/l)						
week:	5	5.480	5.660	6.730	6.430	5.390
Urea (mmol/l)						
week:	5	4.650	6.410	6.930	5.560	6.600
Creat-e (umol/l)						
week:	5	52.20	52.50	59.80	57.80	65.30
Bili-tot (umol/l)						
week:	5	2.100	3.040	2.340	2.810	2.100
Prot (g/l)						
week:	5	66.09	67.72	66.06	62.68	64.08
Alb (g/l)						
week:	5	38.29	39.94	39.19	38.04	37.46
Glob (g/l)						
week:	5	27.80	27.78	26.87	24.64	26.62
A/G (1)						
week:	5	1.380	1.440	1.460	1.540	1.410
Chol (mmol/l)						
week:	5	2.520	2.520	2.780	2.270	3.005
Na+ (mmol/l)						
week:	5	138.6	141.6	140.0	139.2	137.6



CGA 48988 tech.

Blood chemistry (individuals): females

group 1  
0 mg/kg

		26	27	28	29	30	Animal no
K+	(mmol/l)						
week:	5	3.420	3.540	3.660	3.220	3.270	
Ca++	(mmol/l)						
week:	5	2.700	2.780	2.710	2.550	2.620	
Cl-	(mmol/l)						
week:	5	102.5	99.90	100.5	100.5	98.80	
PO4-in	(mmol/l)						
week:	5	2.100	1.820	1.900	1.620	1.560	
ASAT (GOT)	(U/l)						
week:	5	58.40	59.10	52.10	59.70	62.20	
ALAT (GPT)	(U/l)						
week:	5	25.00	29.80	33.10	29.00	42.70	
AlP	(U/l)						
week:	5	76.80	98.60	127.0	83.50	80.30	

CGA 48988 tech.

Blood chemistry (individuals): females

group 2  
10 mg/kg

		31	32	33	34	35	Animal no
Gluc	(mmol/l)						
week:	5	5.470	6.730	5.140	5.860	5.770	

CGA 48988 tech.

Blood chemistry (individuals): females

group 2  
 10 mg/kg

		31	32	33	34	35
		Animal no				
Urea (mmol/l)						
week:	5	5.230	6.780	6.320	7.020	5.290
Creat-e (umol/l)						
week:	5	50.20	45.80	67.10	54.20	56.90
Bili-tot (umol/l)						
week:	5	1.870	1.750	1.640	2.570	1.640
Prot (g/l)						
week:	5	68.15	64.53	65.35	63.29	65.10
Alb (g/l)						
week:	5	40.03	38.87	37.16	37.57	37.56
Glob (g/l)						
week:	5	28.53	26.29	27.73	25.69	26.53
A/G (1)						
week:	5	1.410	1.470	1.350	1.460	1.460
Chol (mmol/l)						
week:	5	2.700	1.870	2.500	1.950	2.680
Na+ (mmol/l)						
week:	5	141.0	140.9	142.1	145.3	141.1
K+ (mmol/l)						
week:	5	3.100	3.350	3.620	3.100	3.450
Ca++ (mmol/l)						
week:	5	2.540	2.510	2.580	2.710	2.590

CGA 48988 tech.

Blood chemistry (individuals): females

group 2  
10. mg/kg

		31	32	33	34	35	Animal no
Cl-	(mmol/l)						
week:	5	99.70	99.80	98.50	101.8	98.70	
PO4-in	(mmol/l)						
week:	5	1.580	1.840	1.890	2.110	2.110	
ASAT (GOT)	(U/l)						
week:	5	42.50	47.00	56.50	48.30	47.00	
ALAT (GPT)	(U/l)						
week:	5	25.00	23.40	21.80	34.70	31.40	
ALP	(U/l)						
week:	5	87.80	60.15	63.90	96.70	75.70	

CGA 48988 tech.

Blood chemistry (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40	Animal no
Gluc	(mmol/l)						
week:	5	5.370	5.500	4.600	5.080	3.810	
Urea	(mmol/l)						
week:	5	5.780	5.440	7.270	6.570	11.66	
Creat-e	(umol/l)						
week:	5	62.30	51.10	57.30	65.40	75.10	

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 48988 tech.

Blood chemistry (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40
		Animal no				
Bili-tot ( $\mu\text{mol/l}$ ) week: 5		2.570	1.400	1.640	2.340	2.100
Prot (g/l) week: 5		66.21	70.60	67.48	64.99	63.01
Alb (g/l) week: 5		37.08	40.66	37.94	37.00	35.80
Glob (g/l) week: 5		27.54	30.39	28.88	28.51	27.34
A/G (1) week: 5		1.390	1.340	1.310	1.300	1.310
Chol ( $\text{mmol/l}$ ) week: 5		2.970	2.220	2.850	2.370	1.810
Na+ ( $\text{mmol/l}$ ) week: 5		139.4	140.3	142.5	138.9	138.9
K+ ( $\text{mmol/l}$ ) week: 5		3.460	3.550	3.450	3.320	3.130
Ca++ ( $\text{mmol/l}$ ) week: 5		2.550	2.740	2.610	2.670	2.710
Cl- ( $\text{mmol/l}$ ) week: 5		101.7	99.90	98.20	99.70	95.35
PO4-in ( $\text{mmol/l}$ ) week: 5		1.770	1.550	1.790	1.960	1.960

**CGA 48988 tech.**

Blood chemistry (individuals): females

group 3  
50 mg/kg

		36	37	38	39	40	Animal no
ASAT (GOT) (U/l)							
week:	5	56.50	47.60	54.00	78.70	395.3	
ALAT (GPT) (U/l)							
week:	5	37.90	25.00	33.90	36.30	99.20	
AlP (U/l)							
week:	5	88.40	121.9	130.5	128.4	113.6	

**CGA 48988 tech.**

Blood chemistry (individuals): females

group 4  
150 mg/kg

		41	42	43	44	45	Animal no
Gluc (mmol/l)							
week:	5	5.470	4.950	5.230	5.830	5.580	
Urea (mmol/l)							
week:	5	6.960	6.320	6.170	7.270	7.170	
Creat-e (umol/l)							
week:	5	51.90	51.90	56.90	57.70	66.80	
Bili-tot (umol/l)							
week:	5	1.400	1.870	1.640	1.640	2.100	
Prot (g/l)							
week:	5	67.59	70.29	67.97	71.30	67.60	

CGA 48988 tech.

Blood chemistry (individuals): females

group 4  
 150 mg/kg

		41	42	43	44	45
		Animal no				
		41	42	43	44	45
Alb (g/l)						
week:	5	38.16	40.58	37.34	40.60	38.92
Glob (g/l)						
week:	5	29.33	30.06	30.38	30.71	29.10
A/G (l)						
week:	5	1.300	1.350	1.230	1.320	1.340
Chol (mmol/l)						
week:	5	2.880	2.840	3.265	2.700	2.570
Na+ (mmol/l)						
week:	5	140.3	143.0	138.3	141.3	140.8
K+ (mmol/l)						
week:	5	3.390	3.280	4.090	3.500	3.040
Ca++ (mmol/l)						
week:	5	2.640	2.880	2.750	2.795	2.790
Cl- (mmol/l)						
week:	5	98.75	98.05	99.10	99.55	97.65
PO4-in (mmol/l)						
week:	5	1.900	2.090	2.110	2.070	2.170
ASAT (GOT) (U/l)						
week:	5	52.70	52.10	57.10	48.90	54.60
ALAT (GPT) (U/l)						
week:	5	32.30	37.10	36.30	37.10	37.10

CGA 48988 tech.

Blood chemistry (individuals): females

group 4  
150 mg/kg

		41	42	43	44	45	Animal no
AlP (U/l) week: 5		71.70	90.00	58.00	83.50	134.6	

CGA 48988 tech.

Blood chemistry (individuals): females

group 5  
300 mg/kg

		46	47	48	49	50	Animal no
Gluc (mmol/l) week: 5		6.300	5.890	5.600	6.510	7.620	
Urea (mmol/l) week: 5		6.020	7.110	4.740	6.080	5.590	
Creat-e (umol/l) week: 5		52.50	50.30	51.90	52.50	52.50	
Bili-tot (umol/l) week: 5		1.170	2.100	1.400	1.400	1.400	
Prot (g/l) week: 5		71.77	70.28	71.56	68.37	65.83	
Alb (g/l) week: 5		40.70	40.43	40.98	40.08	39.08	
Glob (g/l) week: 5		30.96	30.77	31.62	28.26	26.75	

CGA 48988 tech.

Blood chemistry (individuals): females

group 5  
 300 mg/kg

		46	47	48	49	50
		Animal no				
A/G (1)						
week:	5	1.310	1.310	1.300	1.420	1.460
Chol (mmol/l)						
week:	5	2.530	2.700	3.150	2.850	2.370
Na+ (mmol/l)						
week:	5	141.2	138.0	140.5	141.8	138.0
K+ (mmol/l)						
week:	5	3.130	3.860	3.450	3.890	3.210
Ca++ (mmol/l)						
week:	5	2.465	2.540	2.760	2.750	2.590
Cl- (mmol/l)						
week:	5	99.60	99.80	100.4	99.10	100.2
PO4-in (mmol/l)						
week:	5	1.550	2.250	1.550	1.890	1.610
ASAT (GOT) (U/l)						
week:	5	46.40	48.90	48.90	55.20	47.00
ALAT (GPT) (U/l)						
week:	5	41.10	56.40	30.60	53.20	32.30
AlP (U/l)						
week:	5	130.8	164.7	87.60	135.6	69.30



6.9. Organ weights and ratios (individuals)

6.9.1. Organ weights (individuals)

CGA 329351 tech.

Organ weights (individuals) : males

group 1 : 0 mg/kg

week 5

	Animal no				
	1	2	3	4	5
Body (g)	366.4	322.3	320.9	318.9	309.7
Heart (g)	1.279	1.092	1.140	1.065	1.214
Liver (g)	17.36	16.31	17.30	17.24	15.34
Kidney (both) (g)	2.721	2.392	2.667	2.427	2.436
Adrenal (both) (mg)	90.50	73.00	80.60	78.40	88.10
Thymus (mg)	694.9	724.3	839.6	861.7	995.9
Testis (both) (g)	3.438	3.726	3.614	3.265	3.182
Spleen (g)	0.793	0.722	0.738	0.579	0.796
Thyroid gland (mg)	27.40	15.10	29.20	22.90	22.40

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CGA 329351 tech.

Organ weights (individuals) : males

group 2 : 10 mg/kg

week 5

	Animal no				
	6	7	8	9	10
Body (g)	372.9	339.0	300.8	290.2	359.5
Heart (g)	1.179	1.199	1.090	1.065	1.352
Liver (g)	22.56	17.74	15.11	17.21	21.07
Kidney (both) (g)	2.842	2.708	2.092	2.135	2.880
Adrenal (both) (mg)	83.10	78.00	87.30	72.40	83.60
Thymus (mg)	1031	718.0	585.5	550.8	806.7
Testis (both) (g)	3.767	3.416	3.084	3.257	3.566
Spleen (g)	0.935	0.575	0.664	0.528	0.802
Thyroid gland (mg)	19.80	12.90	23.30	17.10	28.50

CGA 329351 tech.

Organ weights (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Body (g)	321.2	328.0	360.3	293.9	325.2
Heart (g)	1.105	1.130	1.157	1.010	1.180

CGA 329351 tech.

Organ weights (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Liver (g)	16.87	17.85	19.23	14.07	19.15
Kidney (both) (g)	2.349	2.313	2.639	2.225	2.649
Adrenal (both) (mg)	89.70	71.60	111.7	69.80	78.60
Thymus (mg)	945.6	672.4	728.4	635.7	854.8
Testis (both) (g)	3.276	2.899	3.444	3.617	3.777
Spleen (g)	0.809	0.603	0.642	0.643	0.659
Thyroid gland (mg)	27.10	22.30	26.30	27.50	20.30

CGA 329351 tech.

Organ weights (individuals) : males

group 4 : 150 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Body (g)	321.7	319.5	299.9	321.6	301.7
Heart (g)	1.208	1.152	1.006	1.147	1.039
Liver (g)	17.34	17.55	15.36	19.40	17.94
Kidney (both) (g)	2.468	2.390	2.166	2.112	2.425

CGA 329351 tech.

Organ weights (individuals) : males

group 4 : 150 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Adrenal (both) (mg)	84.40	87.90	72.40	75.60	60.70
Thymus (mg)	532.4	696.2	743.3	662.2	710.3
Testis (both) (g)	3.571	3.436	3.346	3.333	3.166
Spleen (g)	0.756	0.692	0.772	0.774	0.690
Thyroid gland (mg)	18.00	15.50	24.10	23.90	22.20

CGA 329351 tech.

Organ weights (individuals) : males

group 5 : 300 mg/kg

week 5

	Animal no				
	21	22	23	24	25
Body (g)	325.1	292.6	317.9	294.8	348.5
Heart (g)	1.163	1.027	1.131	1.119	1.103
Liver (g)	17.51	17.22	17.05	17.45	20.25
Kidney (both) (g)	2.603	2.401	2.318	2.421	2.656
Adrenal (both) (mg)	77.90	79.00	91.70	76.20	72.80
Thymus (mg)	732.7	907.9	680.0	860.2	662.4



CGA 329351 tech.

Organ weights (individuals) : females

group 1 : 0 mg/kg

week 5

	Animal no				
	26	27	28	29	30
Body (g)	255.3	244.6	233.4	248.0	237.0
Heart (g)	1.104	0.902	0.777	0.906	0.843
Liver (g)	11.80	11.49	10.67	11.10	11.89
Kidney (both) (g)	2.220	1.881	1.697	1.882	1.639
Adrenal (both) (mg)	91.80	92.90	70.70	73.00	76.40
Thymus (mg)	592.2	374.7	605.1	558.9	495.1
Ovary (both) (mg)	169.7	191.1	146.4	196.8	129.2
Spleen (g)	0.691	0.614	0.606	0.534	0.588
Thyroid gland (mg)	25.30	16.20	19.30	18.10	17.80

CGA 329351 tech.

Organ weights (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no				
	31	32	33	34	35
Body (g)	234.6	256.4	206.0	223.5	244.9
Heart (g)	0.917	0.865	0.851	0.836	0.964

CGA 329351 tech.

Organ weights (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no				
	31	32	33	34	35
Liver (g)	11.04	12.53	9.871	11.76	12.01
Kidney (both) (g)	1.678	2.095	1.758	1.853	1.872
Adrenal (both) (mg)	85.70	83.50	81.20	88.40	98.80
Thymus (mg)	573.3	578.0	504.8	473.2	623.7
Ovary (both) (mg)	148.3	157.0	191.0	184.6	188.9
Spleen (g)	0.732	0.583	0.532	0.748	0.571
Thyroid gland (mg)	23.80	19.70	24.10	27.50	27.10

CGA 329351 tech.

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	36	37	38	39	40
Body (g)	241.8	220.6	237.8	251.7	224.8
Heart (g)	0.892	0.789	0.896	0.961	0.886
Liver (g)	10.82	10.76	11.39	13.28	11.15
Kidney (both) (g)	1.518	1.662	1.704	2.386	1.790

Test No.: 933180 (Comparison of toxicity profiles)

Test Articles: CGA 329351 tech. and CGA 48988 tech.

CGA 329351 tech.

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	36	37	38	39	40
Adrenal (both) (mg)	73.90	81.90	89.20	99.50	101.1
Thymus (mg)	281.4	541.3	842.7	628.3	522.8
Ovary (both) (mg)	148.3	158.9	187.1	218.0	142.4
Spleen (g)	0.597	0.619	0.753	0.615	0.584
Thyroid gland (mg)	17.90	17.00	17.50	26.40	28.30

CGA 329351 tech.

Organ weights (individuals) : females

group 4 : 150 mg/kg

week 5

	Animal no				
	41	42	43	44	45
Body (g)	245.9	233.3	211.2	227.4	235.7
Heart (g)	1.013	0.869	0.830	0.891	1.049
Liver (g)	12.28	11.21	10.50	11.41	12.48
Kidney (both) (g)	1.861	1.763	1.635	1.821	1.924
Adrenal (both) (mg)	106.0	92.00	70.90	94.50	81.60
Thymus (mg)	618.1	472.1	264.4	656.8	650.5



CGA 329351 tech.

Organ weights (individuals) : females

group 4 : 150 mg/kg week 5

	Animal no				
	41	42	43	44	45
Ovary (both) (mg)	193.6	208.5	135.2	175.3	150.6
Spleen (g)	0.674	0.637	0.625	0.818	0.662
Thyroid gland (mg)	27.00	23.50	16.00	26.00	20.00

CGA 329351 tech.

Organ weights (individuals) : females

group 5 : 300 mg/kg week 5

	Animal no				
	46	47	48	49	50
Body (g)	253.3	227.6	237.1	235.2	239.3
Heart (g)	0.942	0.807	1.015	1.039	0.889
Liver (g)	13.57	12.48	12.05	11.34	12.45
Kidney (both) (g)	1.897	1.635	1.940	2.390	1.834
Adrenal (both) (mg)	79.10	88.40	92.60	92.30	110.7
Thymus (mg)	650.5	486.1	595.3	600.6	481.9
Ovary (both) (mg)	196.4	146.4	170.0	182.5	152.4
Spleen (g)	0.661	0.527	0.577	0.777	0.481

CGA 329351 tech.

Organ weights (individuals) : females

group 5 : 300 mg/kg

week 5

	Animal no				
	46	47	48	49	50
Thyroid gland (mg)	22.60	16.20	16.70	13.80	18.50

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CGA 48988 tech.

Organ weights (individuals) : males

group 1 : 0 mg/kg week 5

	Animal no				
	1	2	3	4	5
Body (g)	366.4	322.3	320.9	318.9	309.7
Heart (g)	1.279	1.092	1.140	1.065	1.214
Liver (g)	17.36	16.31	17.30	17.24	15.34
Kidney (both) (g)	2.721	2.392	2.667	2.427	2.436
Adrenal (both) (mg)	90.50	73.00	80.60	78.40	88.10
Thymus (mg)	694.9	724.3	839.6	861.7	995.9
Testis (both) (g)	3.438	3.726	3.614	3.265	3.182
Spleen (g)	0.793	0.722	0.738	0.579	0.796
Thyroid gland (mg)	27.40	15.10	29.20	22.90	22.40

CGA 48988 tech.

Organ weights (individuals) : males

group 2 : 10 mg/kg week 5

	Animal no				
	6	7	8	9	10
Body (g)	328.2	375.0	295.6	338.4	307.1
Heart (g)	1.053	1.289	1.051	1.092	1.116

CGA 48988 tech.

Organ weights (individuals) : males

group 2 : 10 mg/kg

week 5

	Animal no				
	6	7	8	9	10
Liver (g)	18.05	18.72	16.70	18.18	16.63
Kidney (both) (g)	2.461	2.814	2.328	2.336	2.285
Adrenal (both) (mg)	78.50	79.20	65.30	84.60	75.80
Thymus (mg)	971.5	947.3	892.6	913.0	972.3
Testis (both) (g)	3.106	3.650	3.408	3.173	3.445
Spleen (g)	0.708	0.917	0.804	0.778	0.615
Thyroid gland (mg)	20.00	23.40	21.00	26.60	21.50

CGA 48988 tech.

Organ weights (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Body (g)	331.8	302.9	294.5	322.2	313.4
Heart (g)	1.123	1.107	1.135	1.089	1.009
Liver (g)	17.45	15.40	16.66	16.95	16.95
Kidney (both) (g)	2.415	1.968	2.162	2.536	2.342

CGA 48988 tech.

Organ weights (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Adrenal (both) (mg)	77.00	71.20	63.90	66.20	71.30
Thymus (mg)	768.7	851.5	663.4	882.4	582.8
Testis (both) (g)	3.517	3.880	3.268	3.591	3.038
Spleen (g)	0.715	0.801	0.775	0.714	0.601
Thyroid gland (mg)	21.30	22.50	25.10	30.40	20.20

CGA 48988 tech.

Organ weights (individuals) : males

group 4 : 150 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Body (g)	303.3	325.2	290.8	321.8	324.7
Heart (g)	1.008	1.163	0.999	1.081	1.321
Liver (g)	16.56	15.16	15.46	16.12	17.51
Kidney (both) (g)	2.152	2.451	2.057	2.540	2.871
Adrenal (both) (mg)	83.90	83.40	84.30	62.00	82.60
Thymus (mg)	763.2	1058	943.5	770.8	923.9

CGA 48988 tech.

Organ weights (individuals) : males

group 4 : 150 mg/kg week 5

	Animal no				
	16	17	18	19	20
Testis (both) (g)	3.177	3.435	3.263	3.972	3.129
Spleen (g)	0.656	0.681	0.717	0.741	0.737
Thyroid gland (mg)	18.20	16.60	23.20	22.50	32.80

CGA 48988 tech.

Organ weights (individuals) : males

group 5 : 300 mg/kg week 5

	Animal no				
	21	22	23	24	25
Body (g)	336.5	301.7	344.4	296.9	349.0
Heart (g)	1.158	1.069	1.057	0.957	1.213
Liver (g)	19.86	16.52	20.70	15.26	18.89
Kidney (both) (g)	2.408	2.180	2.422	2.193	2.860
Adrenal (both) (mg)	80.20	69.70	67.20	88.30	88.80
Thymus (mg)	919.7	764.0	888.3	585.4	752.7
Testis (both) (g)	3.683	3.298	2.994	3.578	3.804
Spleen (g)	0.806	0.632	0.699	0.647	0.746

CGA 48988 tech.

Organ weights (individuals) : males

group 5 : 300 mg/kg

week 5

	Animal no				
	21	22	23	24	25
Thyroid gland (mg)	29.20	18.40	26.10	24.20	22.10

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CGA 48988 tech.

Organ weights (individuals) : females

group 1 : 0 mg/kg week 5

	26	27	28	29	30	Animal no
Body (g)	255.3	244.6	233.4	248.0	237.0	
Heart (g)	1.104	0.902	0.777	0.906	0.843	
Liver (g)	11.80	11.49	10.67	11.10	11.89	
Kidney (both) (g)	2.220	1.881	1.697	1.882	1.639	
Adrenal (both) (mg)	91.80	92.90	70.70	73.00	76.40	
Thymus (mg)	592.2	374.7	605.1	558.9	495.1	
Ovary (both) (mg)	169.7	191.1	146.4	196.8	129.2	
Spleen (g)	0.691	0.614	0.606	0.534	0.588	
Thyroid gland (mg)	25.30	16.20	19.30	18.10	17.80	

CGA 48988 tech.

Organ weights (individuals) : females

group 2 : 10 mg/kg week 5

	31	32	33	34	35	Animal no
Body (g)	230.9	238.6	247.2	241.3	246.1	
Heart (g)	0.822	0.902	0.990	0.945	0.935	



CGA 48988 tech.

Organ weights (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no				
	31	32	33	34	35
Liver (g)	11.48	9.798	10.46	10.62	10.52
Kidney (both) (g)	2.121	1.872	1.896	2.262	2.046
Adrenal (both) (mg)	80.00	71.10	99.10	97.40	80.00
Thymus (mg)	570.1	602.2	550.9	580.7	689.1
Ovary (both) (mg)	159.3	199.4	196.6	212.3	147.2
Spleen (g)	0.690	0.701	0.630	0.713	0.669
Thyroid gland (mg)	20.70	25.00	15.60	19.80	19.00

CGA 48988 tech.

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	36	37	38	39	40
Body (g)	218.5	272.2	243.7	234.4	252.5
Heart (g)	0.746	0.968	0.829	0.843	1.004
Liver (g)	10.08	13.18	10.95	10.50	12.67
Kidney (both) (g)	1.624	2.090	2.441	1.911	2.221

CGA 48988 tech.

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	36	37	38	39	40
Adrenal (both) (mg)	86.50	90.60	96.70	108.7	89.80
Thymus (mg)	429.9	693.6	671.9	417.4	405.9
Ovary (both) (mg)	157.4	192.6	179.5	150.7	181.0
Spleen (g)	0.493	0.674	0.673	0.617	0.834
Thyroid gland (mg)	15.90	20.10	18.00	22.20	14.90

CGA 48988 tech.

Organ weights (individuals) : females

group 4 : 150 mg/kg

week 5

	Animal no				
	41	42	43	44	45
Body (g)	265.0	218.0	263.2	246.6	236.5
Heart (g)	1.106	0.854	1.003	0.991	0.881
Liver (g)	13.64	10.61	13.12	10.83	13.26
Kidney (both) (g)	2.249	1.824	2.374	1.854	1.955
Adrenal (both) (mg)	96.50	104.3	96.90	89.40	109.2
Thymus (mg)	573.3	380.8	492.6	577.5	760.6

CGA 48988 tech.

Organ weights (individuals) : females

group 4 : 150 mg/kg

week 5

	41	42	43	44	Animal no 45
Ovary (both) (mg)	200.5	149.8	151.1	183.2	163.2
Spleen (g)	0.605	0.628	0.653	0.677	0.822
Thyroid gland (mg)	19.00	19.30	17.70	20.00	25.70

CGA 48988 tech.

Organ weights (individuals) : females

group 5 : 300 mg/kg

week 5

	46	47	48	49	Animal no 50
Body (g)	242.3	241.0	244.6	238.1	257.9
Heart (g)	0.931	0.944	0.972	0.912	0.976
Liver (g)	11.74	13.83	13.03	12.12	13.26
Kidney (both) (g)	1.782	2.123	2.338	2.021	2.036
Adrenal (both) (mg)	79.70	75.40	97.70	75.80	99.50
Thymus (mg)	735.1	350.0	661.0	452.4	716.9
Ovary (both) (mg)	172.6	183.2	157.1	135.3	207.2
Spleen (g)	0.686	0.843	0.583	0.606	0.567

CGA 48988 tech.

Organ weights (individuals) : females

group 5 : 300 mg/kg

week 5

	46	47	48	49	50
Thyroid gland (mg)	16.40	15.50	17.40	16.90	25.00

6.9.2. Organ to bodyweight ratios (individuals)

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : males

group 1 : 0 mg/kg

week 5

	1	2	3	4	5
Heart (o/oo)	3.491	3.388	3.553	3.341	3.921
Liver (o/oo)	47.39	50.62	53.92	54.05	49.52
Kidney (both) (o/oo)	7.427	7.423	8.311	7.610	7.865
Adrenal (both) (o/oo)	0.247	0.226	0.251	0.246	0.284
Thymus (o/oo)	1.897	2.247	2.616	2.702	3.216
Testis (both) (o/oo)	9.383	11.56	11.26	10.24	10.27
Spleen (o/oo)	2.163	2.240	2.301	1.816	2.571
Thyroid gland (o/oo)	0.075	0.047	0.091	0.072	0.072

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : males

group 2 : 10 mg/kg

week 5

	Animal no				
	6	7	8	9	10
Heart (o/oo)	3.160	3.538	3.622	3.671	3.760
Liver (o/oo)	60.51	52.32	50.24	59.31	58.60
Kidney (both) (o/oo)	7.620	7.987	6.955	7.356	8.010
Adrenal (both) (o/oo)	0.223	0.230	0.290	0.249	0.233
Thymus (o/oo)	2.764	2.118	1.946	1.898	2.244
Testis (both) (o/oo)	10.10	10.08	10.25	11.22	9.919
Spleen (o/oo)	2.507	1.697	2.206	1.818	2.231
Thyroid gland (o/oo)	0.053	0.038	0.077	0.059	0.079

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Heart (o/oo)	3.439	3.445	3.211	3.437	3.629
Liver (o/oo)	52.52	54.43	53.36	47.89	58.90
Kidney (both) (o/oo)	7.314	7.053	7.324	7.570	8.145

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Adrenal (both) (o/oo)	0.279	0.218	0.310	0.237	0.242
Thymus (o/oo)	2.944	2.050	2.022	2.163	2.629
Testis (both) (o/oo)	10.20	8.838	9.559	12.31	11.61
Spleen (o/oo)	2.519	1.838	1.780	2.186	2.026
Thyroid gland (o/oo)	0.084	0.068	0.073	0.094	0.062

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : males

group 4 : 150 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Heart (o/oo)	3.753	3.605	3.355	3.568	3.445
Liver (o/oo)	53.90	54.94	51.23	60.32	59.47
Kidney (both) (o/oo)	7.670	7.480	7.223	6.566	8.037
Adrenal (both) (o/oo)	0.262	0.275	0.241	0.235	0.201
Thymus (o/oo)	1.655	2.179	2.478	2.059	2.354
Testis (both) (o/oo)	11.10	10.75	11.16	10.36	10.49

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : males

group 4 : 150 mg/kg week 5

	Animal no				
	16	17	18	19	20
Spleen (o/oo)	2.351	2.166	2.574	2.407	2.287
Thyroid gland (o/oo)	0.056	0.049	0.080	0.074	0.074

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : males

group 5 : 300 mg/kg week 5

	Animal no				
	21	22	23	24	25
Heart (o/oo)	3.576	3.511	3.558	3.795	3.165
Liver (o/oo)	53.86	58.86	53.64	59.19	58.11
Kidney (both) (o/oo)	8.008	8.206	7.291	8.213	7.622
Adrenal (both) (o/oo)	0.240	0.270	0.288	0.258	0.209
Thymus (o/oo)	2.254	3.103	2.139	2.918	1.901
Testis (both) (o/oo)	11.02	11.00	10.18	11.48	10.67
Spleen (o/oo)	1.985	2.159	2.187	2.070	1.723
Thyroid gland (o/oo)	0.079	0.082	0.043	0.063	0.069

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : females

group 1 : 0 mg/kg week 5

	Animal no				
	26	27	28	29	30
Heart (o/oo)	4.322	3.689	3.327	3.652	3.556
Liver (o/oo)	46.20	46.99	45.70	44.75	50.17
Kidney (both) (o/oo)	8.696	7.688	7.272	7.588	6.915
Adrenal (both) (o/oo)	0.360	0.380	0.303	0.294	0.322
Thymus (o/oo)	2.320	1.532	2.593	2.254	2.089
Ovary (both) (o/oo)	0.665	0.781	0.627	0.794	0.545
Spleen (o/oo)	2.706	2.509	2.594	2.154	2.481
Thyroid gland (o/oo)	0.099	0.066	0.083	0.073	0.075

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : females

group 2 : 10 mg/kg week 5

	Animal no				
	31	32	33	34	35
Heart (o/oo)	3.909	3.375	4.130	3.738	3.934
Liver (o/oo)	47.04	48.85	47.92	52.62	49.03
Kidney (both) (o/oo)	7.151	8.171	8.533	8.291	7.644



CGA 329351 tech.

Organ to bodyweight ratios (individuals) : females

group 2 : 10 mg/kg week 5

	Animal no				
	31	32	33	34	35
Adrenal (both) (o/oo)	0.365	0.326	0.394	0.396	0.403
Thymus (o/oo)	2.444	2.254	2.450	2.117	2.547
Ovary (both) (o/oo)	0.632	0.612	0.927	0.826	0.771
Spleen (o/oo)	3.120	2.273	2.583	3.348	2.332
Thyroid gland (o/oo)	0.101	0.077	0.117	0.123	0.111

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : females

group 3 : 50 mg/kg week 5

	Animal no				
	36	37	38	39	40
Heart (o/oo)	3.691	3.575	3.770	3.819	3.943
Liver (o/oo)	44.76	48.79	47.91	52.75	49.61
Kidney (both) (o/oo)	6.276	7.532	7.165	9.479	7.963
Adrenal (both) (o/oo)	0.306	0.371	0.375	0.395	0.450
Thymus (o/oo)	1.164	2.454	3.544	2.496	2.326
Ovary (both) (o/oo)	0.613	0.720	0.787	0.866	0.633

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : females

group 3 : 50 mg/kg week 5

	36	37	38	39	40
	Animal no				
Spleen (o/oo)	2.467	2.808	3.166	2.442	2.597
Thyroid gland (o/oo)	0.074	0.077	0.074	0.105	0.126

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : females

group 4 : 150 mg/kg week 5

	41	42	43	44	45
	Animal no				
Heart (o/oo)	4.121	3.724	3.929	3.920	4.449
Liver (o/oo)	49.94	48.06	49.73	50.16	52.96
Kidney (both) (o/oo)	7.569	7.558	7.742	8.008	8.162
Adrenal (both) (o/oo)	0.431	0.394	0.336	0.416	0.346
Thymus (o/oo)	2.514	2.024	1.252	2.888	2.760
Ovary (both) (o/oo)	0.787	0.894	0.640	0.771	0.639
Spleen (o/oo)	2.739	2.728	2.957	3.596	2.809
Thyroid gland (o/oo)	0.110	0.101	0.076	0.114	0.085

CGA 329351 tech.

Organ to bodyweight ratios (individuals) : females

group 5 : 300 mg/kg

week 5

	Animal no				
	46	47	48	49	50
Heart (o/oo)	3.719	3.546	4.282	4.416	3.716
Liver (o/oo)	53.57	54.85	50.83	48.21	52.03
Kidney (both) (o/oo)	7.489	7.181	8.182	10.16	7.664
Adrenal (both) (o/oo)	0.312	0.388	0.391	0.392	0.463
Thymus (o/oo)	2.568	2.136	2.511	2.554	2.014
Ovary (both) (o/oo)	0.775	0.643	0.717	0.776	0.637
Spleen (o/oo)	2.609	2.314	2.435	3.304	2.008
Thyroid gland (o/oo)	0.089	0.071	0.070	0.059	0.077

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CGA 48988 tech.

Organ to bodyweight ratios (individuals) : males

group 1 : 0 mg/kg week 5

	Animal no				
	1	2	3	4	5
Heart (o/oo)	3.491	3.388	3.553	3.341	3.921
Liver (o/oo)	47.39	50.62	53.92	54.05	49.52
Kidney (both) (o/oo)	7.427	7.423	8.311	7.610	7.865
Adrenal (both) (o/oo)	0.247	0.226	0.251	0.246	0.284
Thymus (o/oo)	1.897	2.247	2.616	2.702	3.216
Testis (both) (o/oo)	9.383	11.56	11.26	10.24	10.27
Spleen (o/oo)	2.163	2.240	2.301	1.816	2.571
Thyroid gland (o/oo)	0.075	0.047	0.091	0.072	0.072

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : males

group 2 : 10 mg/kg week 5

	Animal no				
	6	7	8	9	10
Heart (o/oo)	3.208	3.438	3.554	3.226	3.635
Liver (o/oo)	55.00	49.93	56.49	53.73	54.14
Kidney (both) (o/oo)	7.498	7.504	7.874	6.903	7.441

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : males

group 2 : 10 mg/kg week 5

	Animal no				
	6	7	8	9	10
Adrenal (both) (o/oo)	0.239	0.211	0.221	0.250	0.247
Thymus (o/oo)	2.960	2.526	3.020	2.698	3.166
Testis (both) (o/oo)	9.464	9.733	11.53	9.378	11.22
Spleen (o/oo)	2.157	2.445	2.719	2.299	2.002
Thyroid gland (o/oo)	0.061	0.062	0.071	0.079	0.070

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : males

group 3 : 50 mg/kg week 5

	Animal no				
	11	12	13	14	15
Heart (o/oo)	3.383	3.655	3.854	3.378	3.219
Liver (o/oo)	52.59	50.83	56.58	52.61	54.08
Kidney (both) (o/oo)	7.277	6.498	7.341	7.870	7.472
Adrenal (both) (o/oo)	0.232	0.235	0.217	0.205	0.228
Thymus (o/oo)	2.317	2.811	2.253	2.739	1.860
Testis (both) (o/oo)	10.60	12.81	11.10	11.14	9.693

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : males

group 3 : 50 mg/kg week 5

	Animal no				
	11	12	13	14	15
Spleen (o/oo)	2.154	2.643	2.630	2.214	1.919
Thyroid gland (o/oo)	0.064	0.074	0.085	0.094	0.064

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : males

group 4 : 150 mg/kg week 5

	Animal no				
	16	17	18	19	20
Heart (o/oo)	3.322	3.577	3.435	3.360	4.067
Liver (o/oo)	54.61	46.62	53.17	50.10	53.93
Kidney (both) (o/oo)	7.095	7.538	7.074	7.894	8.843
Adrenal (both) (o/oo)	0.277	0.256	0.290	0.193	0.254
Thymus (o/oo)	2.516	3.253	3.244	2.395	2.845
Testis (both) (o/oo)	10.47	10.56	11.22	12.34	9.636
Spleen (o/oo)	2.163	2.093	2.466	2.303	2.269
Thyroid gland (o/oo)	0.060	0.051	0.080	0.070	0.101

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : males

group 5 : 300 mg/kg

week 5

	Animal no				
	21	22	23	24	25
Heart (o/oo)	3.442	3.544	3.070	3.222	3.475
Liver (o/oo)	59.02	54.74	60.09	51.39	54.14
Kidney (both) (o/oo)	7.157	7.224	7.031	7.387	8.195
Adrenal (both) (o/oo)	0.238	0.231	0.195	0.297	0.254
Thymus (o/oo)	2.733	2.532	2.579	1.972	2.157
Testis (both) (o/oo)	10.95	10.93	8.692	12.05	10.90
Spleen (o/oo)	2.395	2.094	2.028	2.178	2.138
Thyroid gland (o/oo)	0.087	0.061	0.076	0.082	0.063

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CGA 48988 tech.

Organ to bodyweight ratios (individuals) : females

group 1 : 0 mg/kg week 5

	Animal no				
	26	27	28	29	30
Heart (o/oo)	4.322	3.689	3.327	3.652	3.556
Liver (o/oo)	46.20	46.99	45.70	44.75	50.17
Kidney (both) (o/oo)	8.696	7.688	7.272	7.588	6.915
Adrenal (both) (o/oo)	0.360	0.380	0.303	0.294	0.322
Thymus (o/oo)	2.320	1.532	2.593	2.254	2.089
Ovary (both) (o/oo)	0.665	0.781	0.627	0.794	0.545
Spleen (o/oo)	2.706	2.509	2.594	2.154	2.481
Thyroid gland (o/oo)	0.099	0.066	0.083	0.073	0.075

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : females

group 2 : 10 mg/kg week 5

	Animal no				
	31	32	33	34	35
Heart (o/oo)	3.561	3.779	4.003	3.918	3.800
Liver (o/oo)	49.70	41.06	42.31	43.99	42.76
Kidney (both) (o/oo)	9.184	7.845	7.671	9.373	8.313



CGA 48988 tech.

Organ to bodyweight ratios (individuals) : females

group 2 : 10 mg/kg week 5

	Animal no				
	31	32	33	34	35
Adrenal (both) (o/oo)	0.346	0.298	0.401	0.404	0.325
Thymus (o/oo)	2.469	2.524	2.229	2.407	2.800
Ovary (both) (o/oo)	0.690	0.836	0.795	0.880	0.598
Spleen (o/oo)	2.990	2.938	2.547	2.954	2.720
Thyroid gland (o/oo)	0.090	0.105	0.063	0.082	0.077

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : females

group 3 : 50 mg/kg week 5

	Animal no				
	36	37	38	39	40
Heart (o/oo)	3.415	3.555	3.400	3.595	3.978
Liver (o/oo)	46.13	48.41	44.91	44.78	50.19
Kidney (both) (o/oo)	7.434	7.677	10.02	8.154	8.797
Adrenal (both) (o/oo)	0.396	0.333	0.397	0.464	0.356
Thymus (o/oo)	1.968	2.548	2.757	1.781	1.608
Ovary (both) (o/oo)	0.720	0.708	0.737	0.643	0.717

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : females

group 3 : 50 mg/kg week 5

	Animal no				
	36	37	38	39	40
Spleen (o/oo)	2.254	2.474	2.762	2.631	3.304
Thyroid gland (o/oo)	0.073	0.074	0.074	0.095	0.059

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : females

group 4 : 150 mg/kg week 5

	Animal no				
	41	42	43	44	45
Heart (o/oo)	4.174	3.916	3.811	4.018	3.725
Liver (o/oo)	51.49	48.65	49.87	43.90	56.07
Kidney (both) (o/oo)	8.486	8.365	9.021	7.517	8.266
Adrenal (both) (o/oo)	0.364	0.478	0.368	0.363	0.462
Thymus (o/oo)	2.163	1.747	1.872	2.342	3.216
Ovary (both) (o/oo)	0.757	0.687	0.574	0.743	0.690
Spleen (o/oo)	2.284	2.881	2.481	2.745	3.477
Thyroid gland (o/oo)	0.072	0.089	0.067	0.081	0.109

CGA 48988 tech.

Organ to bodyweight ratios (individuals) : females

group 5 : 300 mg/kg week 5

	Animal no				
	46	47	48	49	50
Heart (o/oo)	3.842	3.917	3.974	3.828	3.784
Liver (o/oo)	48.44	57.39	53.27	50.91	51.41
Kidney (both) (o/oo)	7.353	8.809	9.558	8.487	7.895
Adrenal (both) (o/oo)	0.329	0.313	0.399	0.318	0.386
Thymus (o/oo)	3.034	1.452	2.702	1.900	2.780
Ovary (both) (o/oo)	0.712	0.760	0.642	0.568	0.803
Spleen (o/oo)	2.830	3.498	2.382	2.546	2.200
Thyroid gland (o/oo)	0.068	0.064	0.071	0.071	0.097

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6.10. Macroscopical and microscopical findings (individuals):

6.10.1. List of findings in individual males  
 (CGA 329351 tech.)

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings: all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, <u>selected</u>	5	5	5	5	5
Examined macroscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5
Examined microscopically	5	5	5	5	5

Abbreviations used in pathology tables

S1, S2..... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Exposure: 0 mg/kg

Male Nr. 1 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Renal tubule : Atrophy + unilateral

Male Nr. 2 / Days on study: 30 / Scheduled sacrifice 1

Macro

Pituitary gland : Damaged during autopsy

Micro

Liver : Inflammatory cell infiltration +

Male Nr. 3 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Epithelium of renal pelvis : Hyperplasia + focal  
unilateral

Male Nr. 4 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Organs and tissues as a whole : No changes observed

Male Nr. 5 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver : Extramedullary haematopoiesis +  
Testis : Tubular atrophy + unilateral

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Exposure: 10 mg/kg

Male Nr. 6 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Renal tubule : Atrophy + unilateral  
Adrenal cortex : Fatty change + diffuse bilateral

Male Nr. 7 / Days on study: 30 / Scheduled sacrifice 1

Macro

Epididymis : One organ, damaged during autopsy right

Micro

Liver : Inflammatory cell infiltration +

Male Nr. 8 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +

Male Nr. 9 / Days on study: 30 / Scheduled sacrifice 1

Macro

Adrenal gland : One organ, damaged during autopsy right

Micro

Myocardium : Inflammatory cell infiltration ++  
Adrenal cortex : Fatty change + diffuse bilateral

Male Nr. 10 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Adrenal cortex : Fatty change + diffuse bilateral

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES**

Exposure: 50 mg/kg

Male Nr. 11 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Adrenal cortex : Fatty change + diffuse bilateral

Male Nr. 12 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Myocardium : Inflammatory cell infiltration +  
Kidney : Inflammatory cell infiltration + unilateral

Male Nr. 13 / Days on study: 30 / Scheduled sacrifice 1

Macro

A Back : Scab formation

Micro

A Skin : Chronic inflammation ++ focal  
A ->A Epidermis : Hyperkeratosis ++ focal  
A ->A Epidermis : Acanthosis ++ focal  
Spleen : Extramedullary haematopoiesis +

Male Nr. 14 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Organs and tissues as a whole : No changes observed

Male Nr. 15 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Renal tubule : Atrophy + unilateral

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Exposure: 150 mg/kg

Male Nr. 16 / Days on study: 30 / Scheduled sacrifice 1

Macro

A Back : Scab formation

Micro

A Skin : Ulceration ++ focal  
Adrenal cortex : Fatty change + diffuse bilateral

Male Nr. 17 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Organs and tissues as a whole : No changes observed

Male Nr. 18 / Days on study: 30 / Scheduled sacrifice 1

Macro

Thyroid with parathyroid gland : Damaged during autopsy

Micro

Myocardium : Inflammatory cell infiltration +  
Liver : Inflammatory cell infiltration +

Male Nr. 19 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Renal tubule : Atrophy + unilateral

Male Nr. 20 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Adrenal cortex : Fatty change + diffuse bilateral



**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES**

Exposure: 300 mg/kg

Male Nr. 21 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver hepatocyte : Hypertrophy +

Male Nr. 22 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +

Male Nr. 23 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +

Liver hepatocyte : Hypertrophy +

Testis interstitial cell of leydig : Hyperplasia + focal unilateral

Male Nr. 24 / Days on study: 30 / Scheduled sacrifice 1

Macro

A Back : Scab formation

Micro

A Skin : Chronic inflammation + focal

A ->A Epidermis : Hyperkeratosis + focal

A ->A Epidermis : Acanthosis ++ focal

Male Nr. 25 / Days on study: 30 / Scheduled sacrifice 1

Macro

A Back : Scab formation

Micro

A Skin : Ulceration ++ focal

Myocardium : Inflammatory cell infiltration +

6.10.2. List of findings in individual females  
 (CGA 329351 tech.)

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
-----	-----	-----	-----	-----	-----
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, <u>selected</u>	5	5	5	5	5
Examined macroscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5
Examined microscopically	5	5	5	5	5

Abbreviations used in pathology tables

S1, S2.... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 0 mg/kg

Female Nr. 26 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +

Liver hepatocyte : Hypertrophy +

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy ++ bilateral

Female Nr. 27 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + unilateral

Female Nr. 28 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Haemosiderosis +

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + unilateral

Female Nr. 29 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Haemosiderosis +

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + unilateral

Female Nr. 30 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + unilateral

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES

Exposure: 10 mg/kg

Female Nr. 31 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

Female Nr. 32 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Cast + contralateral  
Renal tubule : Atrophy + unilateral

Female Nr. 33 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Splenic white pulp : Atrophy +  
Liver : Inflammatory cell infiltration +  
Kidney : Nephrocalcinosis + bilateral  
Adrenal medulla : One organ, no examination for technical reasons

Female Nr. 34 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

Female Nr. 35 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 10 mg/kg

Micro

Spleen : Haemosiderosis +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

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**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 50 mg/kg

Female Nr. 36 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Liver : Mass up to 1 cm one  
B Renal pelvis : Dilatation bilateral

Micro

Spleen : Extramedullary haematopoiesis +  
A Liver : Nodular hyperplasia +  
B Renal pelvis : Macroscopical change not observed

Female Nr. 37 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Haemosiderosis +  
Spleen : Extramedullary haematopoiesis +  
Kidney : Inflammatory cell infiltration + unilateral

Female Nr. 38 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +  
Kidney : Nephrocalcinosis + bilateral

Female Nr. 39 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation bilateral

Micro

Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + bilateral  
A Renal pelvis : Dilatation + unilateral  
Adrenal gland : Sinusoid cystic dilatation + unilateral

Female Nr. 40 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 150 mg/kg

Female Nr. 41 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

Female Nr. 42 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Myocardium : Inflammatory cell infiltration +  
Liver : Inflammatory cell infiltration +

Female Nr. 43 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation bilateral

Micro

Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral

A Renal pelvis : Macroscopical change not observed

Female Nr. 44 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral

Female Nr. 45 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Splenic white pulp : Atrophy +  
Liver hepatocyte : Hypertrophy +  
Kidney : Inflammatory cell infiltration + contralateral  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 300 mg/kg

Female Nr. 46 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral

Female Nr. 47 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy ++  
Kidney : Nephrocalcinosis + bilateral

Female Nr. 48 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + bilateral

Female Nr. 49 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation left

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration ++  
Liver hepatocyte : Hypertrophy ++  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy ++ bilateral

A Renal pelvis : Dilatation ++ unilateral

Female Nr. 50 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Haemosiderosis +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral



6.10.3. List of findings in individual males  
 (CGA 48988 tech.)

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, <u>selected</u>	5	5	5	5	5
Examined macroscopically					
SI	5	5	5	5	5
Total	5	5	5	5	5
Examined microscopically	5	5	5	5	5

Abbreviations used in pathology tables

SI, S2.... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Exposure: 0 mg/kg

Male Nr. 1 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Renal tubule : Atrophy + unilateral

Male Nr. 2 / Days on study: 30 / Scheduled sacrifice 1

Macro

Pituitary gland : Damaged during autopsy

Micro

Liver : Inflammatory cell infiltration +

Male Nr. 3 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Epithelium of renal pelvis : Hyperplasia + focal  
unilateral

Male Nr. 4 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Organs and tissues as a whole : No changes observed

Male Nr. 5 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver : Extramedullary haematopoiesis +  
Testis : Tubular atrophy + unilateral

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES**

Exposure: 10 mg/kg

Male Nr. 6 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Renal tubule : Atrophy + unilateral

Male Nr. 7 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +

Renal tubule : Atrophy + unilateral

Male Nr. 8 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Organs and tissues as a whole : No changes observed

Male Nr. 9 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +

Liver : Inflammatory cell infiltration +

Renal tubule : Atrophy + bilateral

Epididymis : Inflammatory cell infiltration + unilateral

Male Nr. 10 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Myocardium : Inflammatory cell infiltration +

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Exposure: 50 mg/kg

Male Nr. 11 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +  
Kidney : Inflammatory cell infiltration + unilateral

Male Nr. 12 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Renal tubule : Atrophy + unilateral

Male Nr. 13 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Organs and tissues as a whole : No changes observed

Male Nr. 14 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Myocardium : Inflammatory cell infiltration +  
Liver : Inflammatory cell infiltration +  
Adrenal medulla : One organ, no examination for technical reasons

Male Nr. 15 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES**

Exposure: 150 mg/kg

Male Nr. 16 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +

Male Nr. 17 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Myocardium : Inflammatory cell infiltration +  
Renal tubule : Atrophy + unilateral

Male Nr. 18 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Organs and tissues as a whole : No changes observed

Male Nr. 19 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Myocardium : Inflammatory cell infiltration +  
Liver : Inflammatory cell infiltration +  
Kidney : Inflammatory cell infiltration + unilateral

Male Nr. 20 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Myocardium : Inflammatory cell infiltration +  
Testis : Tubular atrophy + bilateral

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL MALES

Exposure: 300 mg/kg

Male Nr. 21 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Renal tubule : Atrophy + unilateral

Male Nr. 22 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Renal tubule : Atrophy + unilateral

Male Nr. 23 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +

Male Nr. 24 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Myocardium : Inflammatory cell infiltration +  
Liver : Inflammatory cell infiltration +  
Renal tubule : Atrophy + unilateral

Male Nr. 25 / Days on study: 30 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Inflammatory cell infiltration + unilateral  
Adrenal cortex : Fatty change + diffuse bilateral

6.10.4. List of findings in individual females  
 (CGA 48988 tech.)

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES

Removal code : all Observation period : all

Selected experimental group(s) : all

Selected animals: all

Selected findings : all

Group	1	2	3	4	5
Exposure : mg/kg	0	10	50	150	300
Animals initially in study	5	5	5	5	5
Treatment ended in observation period, selected	5	5	5	5	5
Examined macroscopically					
S1	5	5	5	5	5
Total	5	5	5	5	5
Examined microscopically	5	5	5	5	5

Abbreviations used in pathology tables

S1, S2..... scheduled sacrifice(s)  
 MS moribund sacrifice  
 FD found dead  
 AD accidental death

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 0 mg/kg

Female Nr. 26 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy ++ bilateral

Female Nr. 27 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

Female Nr. 28 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Haemosiderosis +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

Female Nr. 29 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Haemosiderosis +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

Female Nr. 30 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral



**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 10 mg/kg

Female Nr. 31 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation left

Micro

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + bilateral

A Renal pelvis : Dilatation + unilateral

Female Nr. 32 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +

Liver : Inflammatory cell infiltration +

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + unilateral

Female Nr. 33 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Kidney : Nephrocalcinosis + unilateral

Renal tubule : Atrophy + unilateral

Renal pelvis : Dilatation + unilateral

Female Nr. 34 / Days on study: 31 / Scheduled sacrifice 1

Macro

Uterus : Damaged during autopsy

Micro

Liver : Inflammatory cell infiltration +

Kidney : Nephrocalcinosis ++ bilateral

Renal tubule : Atrophy + bilateral

Female Nr. 35 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver : Inflammatory cell infiltration +

Kidney : Nephrocalcinosis + bilateral

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES

Exposure: 50 mg/kg

Female Nr. 36 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation left

Micro

Spleen : Haemosiderosis +

Liver : Inflammatory cell infiltration +

Renal tubule : Atrophy + unilateral

A Renal pelvis : One organ, macroscopical change not observed

Female Nr. 37 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +

Liver : Inflammatory cell infiltration +

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + unilateral

Female Nr. 38 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver hepatocyte : Hypertrophy +

Kidney : Nephrocalcinosis ++ bilateral

Renal tubule : Atrophy ++ unilateral

Female Nr. 39 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver hepatocyte : Hypertrophy +

Kidney : Nephrocalcinosis + bilateral

Renal tubule : Atrophy + unilateral

Adrenal cortex : Fatty change + focal unilateral

Female Nr. 40 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Lung : Mass 1 - 5 cm one

Micro

Spleen : Extramedullary haematopoiesis +

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES

Exposure: 50 mg/kg

- A Lung : Haemorrhagic infarct +++  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Cast + unilateral  
Renal tubule : Necrosis + bilateral  
Renal tubule : Atrophy ++ bilateral

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**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 150 mg/kg

Female Nr. 41 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy ++ bilateral

Female Nr. 42 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Haemosiderosis +  
Spleen : Extramedullary haematopoiesis +

Female Nr. 43 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation bilateral

Micro

Liver : Inflammatory cell infiltration +  
Kidney : Nephrocalcinosis + bilateral

A Renal pelvis : Dilatation + unilateral

Female Nr. 44 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Kidney : Nephrocalcinosis + bilateral

Female Nr. 45 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral

MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES

Exposure: 300 mg/kg

Female Nr. 46 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + bilateral

Female Nr. 47 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral

Female Nr. 48 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation bilateral

Micro

Spleen : Haemosiderosis +  
Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Inflammatory cell infiltration + unilateral  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + bilateral

A Renal pelvis : Macroscopical change not observed

Female Nr. 49 / Days on study: 31 / Scheduled sacrifice 1

Macro

A Renal pelvis : Dilatation left

Micro

Spleen : Extramedullary haematopoiesis +  
Liver : Inflammatory cell infiltration +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + bilateral

A Renal pelvis : One organ, macroscopical change not observed

Female Nr. 50 / Days on study: 31 / Scheduled sacrifice 1

Macro

Body as a whole : No changes observed

**MACROSCOPICAL AND MICROSCOPICAL FINDINGS IN INDIVIDUAL FEMALES**

Exposure: 300 mg/kg

Micro

Spleen : Haemosiderosis +  
Spleen : Extramedullary haematopoiesis +  
Liver hepatocyte : Hypertrophy +  
Kidney : Nephrocalcinosis + bilateral  
Renal tubule : Atrophy + unilateral  
Adrenal medulla : One organ, no examination for technical reasons

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7. APPENDIX C: REFERENCE VALUES

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7.1. Reference values: Hematology

HEMATOLOGY REFERENCE VALUES  
 UNTREATED MALE RATS Tif: RAIF (SPF)

Age : 9 - 12 weeks Period : 08.04.91 - 20.01.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	452	7.250	7.760	8.350
Hb	M0002	mmol/l	452	9.000	9.500	10.05
Hct	M0002	l	452	0.427	0.454	0.483
MCV	M0002	fl	452	55.00	58.30	62.10
RDW	M0002	l	452	0.105	0.118	0.143
MCH	M0002	fmol	452	1.150	1.230	1.290
MCHC	M0002	mmol/l	452	20.04	20.87	21.95
HDW	M0002	mmol/l	452	1.290	1.550	2.170
Reti	M0002	l	79	0.016	0.030	0.044
	M0003	l	15	0.045	0.059	0.083
WBC	M0002	G/l	452	8.310	12.79	19.47
Neut	M0002	l	452	0.048	0.080	0.159
Eos	M0002	l	452	0.003	0.007	0.014
Baso	M0002	l	452	0.002	0.004	0.007
Lympho	M0002	l	452	0.762	0.852	0.901
Mono	M0002	l	452	0.018	0.032	0.057
Luc	M0002	l	452	0.009	0.020	0.039
Neut	M0002	G/l	94	0.610	1.125	2.380
Eos	M0002	G/l	94	0.040	0.080	0.210
Baso	M0002	G/l	94	0.020	0.060	0.130
Lympho	M0002	G/l	94	7.050	11.26	16.41
Mono	M0002	G/l	94	0.230	0.440	1.040
Luc	M0002	G/l	94	0.140	0.320	0.780
Plt	M0002	G/l	452	818.5	1002	1159
PT(CS)	M0001	sec	334	29.84	39.60	52.88
MethHb	M0001	l	218	0.005	0.007	0.011



HEMATOLOGY REFERENCE VALUES  
 UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks      Period : 08.04.91 - 20.01.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	357	7.070	7.655	8.190
Hb	M0002	mmol/l	357	8.700	9.400	10.00
Hct	M0002	l	357	0.410	0.441	0.470
MCV	M0002	fl	357	54.50	57.70	60.90
RDW	M0002	l	357	0.103	0.118	0.149
MCH	M0002	fmol	357	1.160	1.220	1.290
MCHC	M0002	mmol/l	357	20.36	21.23	22.25
HDW	M0002	mmol/l	357	1.220	1.440	1.950
Reti	M0001	l	10	0.011	0.030	0.035
	M0002	l	85	0.014	0.026	0.054
	M0003	l	15	0.032	0.054	0.083
WBC	M0002	G/l	357	4.850	8.230	12.84
Neut	M0002	l	357	0.044	0.080	0.167
Eos	M0002	l	357	0.005	0.010	0.020
Baso	M0002	l	357	0.001	0.003	0.005
Lympho	M0002	l	357	0.763	0.852	0.906
Mono	M0002	l	357	0.016	0.031	0.055
Luc	M0002	l	357	0.008	0.018	0.037
Neut	M0002	G/l	95	0.360	0.680	1.345
Eos	M0002	G/l	95	0.050	0.090	0.160
Baso	M0002	G/l	95	0.010	0.020	0.060
Lympho	M0002	G/l	95	3.870	6.960	11.57
Mono	M0002	G/l	95	0.100	0.270	0.510
Luc	M0002	G/l	95	0.080	0.180	0.340
Plt	M0002	G/l	357	869.0	1038	1219
PT(CS)	M0001	sec	341	23.39	30.77	37.78
MetHb	M0001	l	219	0.005	0.007	0.011

7.2. Reference values: Blood chemistry

BLOOD CHEMISTRY REFERENCE VALUES  
 UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks Period : 08.04.91 - 20.01.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	453	5.280	7.040	8.920
Urea	M0001	mmol/l	453	4.460	6.180	8.320
Creat-e	M0001	umol/l	353	40.20	61.10	79.80
Bili-tot	M0001	umol/l	348	1.850	2.390	3.210
Prot	M0001	g/l	453	60.40	64.13	69.32
Alb	M0001	g/l	343	34.69	36.80	38.70
Glob	M0001	g/l	343	24.52	26.98	31.12
A/G	M0001	l	343	1.200	1.360	1.510
Chol	M0001	mmol/l	453	1.400	1.770	2.210
Trigly	M0001	mmol/l	228	0.430	0.740	1.530
Phos-Lip	M0001	mmol/l	5	1.270	1.510	1.790
Na+	M0001	mmol/l	453	141.3	143.6	146.8
K+	M0001	mmol/l	453	3.020	3.540	3.990
Ca++	M0001	mmol/l	343	2.580	2.690	2.850
Cl-	M0001	mmol/l	343	94.67	98.20	101.1
PO4-in	M0001	mmol/l	343	1.800	2.120	2.540
ASAT (GOT)	M0001	U/l	453	45.40	56.40	71.50
ALAT (GPT)	M0001	U/l	453	22.40	33.90	51.90
AlP	M0001	U/l	453	119.8	184.2	332.6
GGT	M0001	U/l	278	0.000	0.000	0.000
ChE-Pl	M0001	U/l	25	180.0	316.0	506.0
ChE-RBC	M0002	U/l	5	1677	1764	1834
ChE-Br	M0002	U/g	5	3.111	3.324	3.680

BLOOD CHEMISTRY REFERENCE VALUES  
 UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks      Period : 08.04.91 - 20.01.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	357	4.840	6.040	7.940
Urea	M0001	mmol/l	357	4.590	6.700	8.660
Creat-e	M0001	umol/l	352	38.20	59.30	82.40
Bili-tot	M0001	umol/l	342	1.930	2.720	3.760
Prot	M0001	g/l	357	59.43	64.25	70.34
Alb	M0001	g/l	342	35.36	37.77	40.00
Glob	M0001	g/l	342	23.12	26.51	30.94
A/G	M0001	l	342	1.240	1.420	1.610
Chol	M0001	mmol/l	357	1.460	2.010	2.580
Trigly	M0001	mmol/l	223	0.370	0.550	1.140
Na+	M0001	mmol/l	357	139.2	142.7	147.0
K+	M0001	mmol/l	357	2.720	3.250	3.780
Ca++	M0001	mmol/l	342	2.510	2.620	2.790
Cl-	M0001	mmol/l	342	95.40	99.30	103.2
PO4-in	M0001	mmol/l	342	1.410	1.805	2.250
ASAT (GOT)	M0001	U/l	377	44.80	57.00	74.50
ALAT (GPT)	M0001	U/l	377	18.50	29.00	46.30
ALP	M0001	U/l	377	78.15	125.1	215.6
GGT	M0001	U/l	208	0.000	0.000	0.000
ChE-Pl	M0001	U/l	20	657.0	1256	1825
ChE-RBC	M0002	U/l	5	1752	1892	2047
ChE-Br	M0002	U/g	5	3.768	3.923	4.267

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