

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

Test No. 963128

CGA 108906 tech.

(Intermediate of CGA 48988)

FINAL REPORT

Study Director: Dr. rer. nat. 5.1.2.e/loc

Testing Facility: Novartis Crop Protection AG
(successor in business of Sandoz
Ltd. and Ciba-Geigy Ltd.)
Toxicology/Experimental Toxicology
4332 Stein / Switzerland

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

Study completed: June 6, 1997

Sponsor: Novartis Crop Protection
Human Safety Assessment
4002 Basel / Switzerland

This report contains: 555 pages

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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0.2. Certification of Good Laboratory Practices

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 89/87 concerning the 'Compliance with Principles of Good Laboratory Practice', adopted on October 2, 1989).
- 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.
- Japanese Ministry of Agriculture, Forestry and Fisheries, NohSan, Notification No. 3850, Agricultural Production Bureau, August 10, 1984.

Study Director: Dr. rer. nat.

date: June 6, 1997

For Facility Management: PD Dr. med. vet.
EVH Fundamental Medicine

date: June 4, 1997

For the Sponsor:

5.1.2.e Woo

date: June 09, 1997

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1. SUMMARY AND CONCLUSION

The test article CGA 108906 tech. (Intermediate of CGA 48988, batch KI-5240/3, purity 99%) was administered by gavage for 4 weeks at daily doses of 0, 10, 50, 200, and 1000 mg/kg body weight to a total of 80 albino rats. In each dose group 5 animals per sex and group were sacrificed at the end of the treatment period; 5 animals per sex in the control group and the two upper dose groups, were kept for a 4-week recovery period before sacrifice. Clinical signs, body weight, food consumption, water consumption and mortality were monitored throughout the study for all animals. Neurotoxicologic investigations were performed weekly (detailed clinical observations) and at weeks 4 and 8 (functional observational battery, motor activity). Hematological, blood chemistry and urine analyses were performed at the end of the treatment period on all animals, and at the end of the recovery period on animals of experimental group II. At sacrifices, animals were examined macroscopically and organ weights were recorded. Organs and tissues were collected and prepared for histopathological evaluation.

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

The results of this study are summarized as follows:

Clinical signs, detailed clinical observations, functional observational battery (FOB) and motor activity

Neither daily clinical observations, weekly detailed clinical observations, nor functional measurements performed at weeks 4 and 8 revealed any relevant changes during the treatment and recovery periods.

Mortality

There was no mortality during this study which was attributed to the treatment with the test article.

Body weight

The body weight development was not influenced by the treatment with the test article.

Food consumption

The food intake was not influenced by the treatment with the test article.

Food consumption ratios

The mean food consumption ratios of treated groups were essentially comparable to those of the control group.

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Water consumption

The water intake was not considered influenced by the treatment.

Hematology

No test article-related differences were apparent by the end of the treatment and recovery periods.

Blood chemistry

Slightly higher mean values for plasma glucose and potassium levels were recorded at week 5 for males treated at 1000 mg/kg which by the end of the recovery period had reversed to mean values similar to those of the control group.

Urine analysis

At week 5, both males and females of group 5 (1000 mg/kg) excreted a more acidic urine than the controls although by the end of the recovery period the pH-value of the urine from previously treated rats was similar to that of the controls. At weeks 5 and 9, males of group 5 (1000 mg/kg) excreted a statistically significantly lower volume of urine with a higher relative density, a finding which does not reflect a toxic effect.

Organ weights

At treatment end, the mean heart weight and the mean heart to body weight ratio of males treated at 1000 mg/kg were 6% and 11%, respectively, higher than the values of the control group. This finding was reversible within the following 4-week recovery period.

Macroscopical and microscopical findings

Macroscopical and microscopical examination revealed no treatment-related changes.

Conclusion

Under the conditions of this test, treatment with CGA 108906 tech. was well tolerated up to the limit dose of 1000 mg/kg body weight where, at treatment end, the heart weight was slightly increased in males and only minor changes to few blood chemistry (males) and urine parameters (both sexes) were noted.

For both sexes, a "no-observable-adverse-effect level" (NOAEL) for both sexes was defined at 1000 mg/kg body weight.

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2. INTRODUCTION

Purpose

The present study was designed to determine the oral toxicity of the test article in rats upon daily administration by gavage for 28 consecutive days, to estimate a no-observed-adverse-effect level of exposure (NOAEL), and for observation of reversibility, persistence of, or delayed occurrence of toxic effects after a 4-week recovery period.

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.

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:

- The OECD Guideline for testing of chemicals, No. 407, "Repeated Dose 28-day Oral Toxicity Study in Rodents: 28-day or 14-day Study", adopted July 27, 1995.
- 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

Novartis Crop Protection
Human Safety Assessment
4002 Basel / 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]
Longterm Toxicology

Technical assistant: [redacted]
Longterm Toxicology

Supervisors: [redacted]
Longterm Toxicology

Responsible for Neurotoxicology: Dr. sc. nat. [redacted]
Neurotoxicology

Responsible for laboratory investigations: Dr. med. vet. [redacted]
FVH Clinical Chemistry
Toxicology Services

Assistant laboratory investigations: [redacted]
Clinical Laboratory

Responsible for necropsy: Dr. med. vet. [redacted]
FVH Clinical Chemistry
Toxicology Services

Responsible for pathology services: Dr. med. vet. [redacted]
FVH Clinical Chemistry
Toxicology Services

Responsible for pathology: Dr. med. vet. [redacted]
FVH Pathology
Toxicologic Pathology

Study pathologist: Dr. med. [redacted]
Toxicologic Pathology

Responsible for statistics: [redacted], dipl.stat.
Toxicology Services

Analytics,
Principal Investigator: [redacted], RCC

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

Novartis Crop Protection, for Experimental Toxicology
4332 Stein / Switzerland Sisseln Facility

Novartis Crop Protection, for Toxicologic Pathology
4002 Basel / Switzerland and Toxicology Services

RCC Umweltchemie AG for Analytical Laboratories
4452 Itingen / Switzerland

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Testing facility

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

Novartis Crop Protection
Toxicology/Experimental Toxicology
4332 Stein / Switzerland

Histopathological examination was performed at:

Novartis Crop Protection
Toxicology/Toxicologic Pathology
4002 Basel / Switzerland

Analytical investigations were performed at:

RCC Umweltchemie
4452 Itingen / Switzerland

Study dates

Study initiation: November 14, 1996 (protocol date)

Completion date: January 8, 1997 (final sacrifice)

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Archivation and distribution

Archives are located at Novartis Crop Protection, Toxicology, Werk Stein WST 460, 4332 Stein / Switzerland. Raw data, protocol and report, specimens and raw data of laboratory investigations are stored at this location.

Raw data of the analytical determinations are stored in the archives of RCC Research and Consulting Company Ltd., 4452 Itingen / Switzerland.

Raw data of the histopathological examination and specimens (wet tissues, tissue blocks or histological slides) are stored in the archives of Toxicology/Toxicologic Pathology, Novartis Crop Protection, 4002 Basel / Switzerland.

This report was distributed to:

Dr. 5123 Wpo (Sponsor)

Archive

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2.1. Deviations from the protocol

According to the requirement stated in the test order, the test material was stored at $<10^{\circ}\text{C}$.

As per December 31, 1996, Dr. med. vet. [REDACTED], responsible for laboratory investigations and pathology services, left the company. Her responsibilities were assumed by Dr. med. vet. [REDACTED]

The company Novartis Crop Protection AG has resulted from the merger of the companies Ciba-Geigy Ltd. and Sandoz Ltd. and is partial successor in business from above-named companies. This applies also to all aspects concerned with the requirements of Good Laboratory Practice.

The following organizational changes in the Toxicology department, which became effective as per January, 15, 1997, concerned this study: Dr. [REDACTED] became head of Novartis Crop Protection Toxicology, Dr. [REDACTED] became head of Experimental Toxicology, Dr. [REDACTED] of Toxicologic Pathology and Dr. [REDACTED] of Toxicology Services, respectively.

To harmonize terminology in the report, the term 'number of vertical movements' as used in the protocol has been changed to 'number of rearings'.

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

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3. MATERIALS AND METHODS

3.1. Test article

Company code No.: CGA 108906 tech.

Batch No.: KI-5240/3

Description: solid

Purity: 99 %

Date of receipt: October 23, 1996

Stability: October 1999

Storage conditions: <10°C

Pretest analytics

Prior to the start of the study, samples of the vehicle containing the test article at concentrations of 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 no. 641531) are given in the results and appendix sections of this report.

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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

Date and number received: November 28, 1996,
45 animals/sex

Body weight at week -1: 153.3 - 184.9 g in males
129.4 - 156.0 g in females

Initial age: approximately 5 weeks at delivery

3.2.2. Husbandry

The experiment was carried out under specified pathogen free (SPF) standard laboratory conditions. The animals were housed individually in Macrolon cages type 3 (area: 900 square centimeters) with wire mesh tops and standardized granulated soft wood bedding (Societe Parisienne des Sciures Pantin). Neither insecticides nor chemicals were applied in the animal room with the exception of disinfectant: BRADOPHENtm. Cages were allocated to racks by sex and group. Cages and water bottles were changed at 1-week intervals. The animal room was air conditioned:

Temperature: 22±2°C
Relative humidity (%): 55±10
Ventilation: 16-20 air changes/hour
Light cycle: 12 hours light per day

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3.2.3. Identification

By tattoo of tail for individual identification. The animal number was identical with the cage number.

3.3. Procedures

A written protocol, dated November 14, 1996, was prepared prior to the initiation of this study. A copy of the protocol is included in Appendix D. Procedures were performed according to Toxicology Standard Operating Procedures.

3.3.1. Study schedule

Study initiation (protocol date):	November 14, 1996
Delivery of animals:	November 28, 1996
Start of acclimatization:	November 29, 1996
Treatment start:	December 10, 1996
Laboratory investigations:	January 7, 1997
Date of sacrifice 1:	January 8, 1997
Recovery start:	January 7, 1997
Recovery end:	February 5, 1997
Laboratory investigations:	February 4, 1997 (recovery group)
Date of sacrifice 2 (experimental end date):	February 5, 1997 (recovery group)

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3.3.2. Animal number and distribution

Number of animals: 80 (total)

The general outline of the experiment is presented in the following animal distribution table:

Animal No. (=cage no.)	Group 1 Control	Group 2 10mg/kg	Group 3 50mg/kg	Group 4 200mg/kg	Group 5 1000mg/kg
MALES I	1- 5	11- 15	16- 20	21- 25	31- 35
MALES II	6- 10			26- 30	36- 40
FEMALES I	41- 45	51- 55	56- 60	61- 65	71- 75
FEMALES II	46- 50			66- 70	76- 80

I EXPERIMENTAL GROUP I

5 animals per sex and group for evaluation of toxicity, including laboratory investigations

II EXPERIMENTAL GROUP II

5 animals per sex and group for reversibility evaluation after 4 weeks of recovery, including laboratory investigations

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3.3.3. Acclimatization

An acclimatization period of 11 days was allowed between delivery and start of the treatment. Immediately after delivery, the animals were distributed into groups. In order to set up a fully randomized experiment, they were assigned to these groups by means of computer-generated random numbers. Furthermore, they were weighed during this period.

From the same batch of animals a small number was retained for possible replacement during the acclimatization period of animals deemed not suitable for study. These animals were subjected to identical conditions during this period, and those not used were removed at the start of the experiment.

3.3.4. Treatment

The treatment was performed over a period of 4 weeks on a main group (experimental group I) and a recovery group (experimental group II) of animals. The animals of experimental group I were sacrificed at the end of the treatment period.

3.3.5. Recovery

After the treatment period, animals of experimental group II were kept for a consecutive recovery phase of 4 weeks before sacrifice.

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3.3.6. Rationale for dose selection

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

Project no. 943085
Short/Long-term Toxicology, CIBA-GEIGY Limited, Stein
Acute Oral Toxicity in the Rat
LD50 > 2000 mg/kg body weight

The following dose levels were selected:

10 mg/kg bw. per day	this dose is expected to cause no observable effects
50 mg/kg bw. per day	this dose is expected to cause no or minimal observable effects
200 mg/kg bw. per day	this dose is expected to cause slight effects, if any
1000 mg/kg bw. per day	this dose is expected to cause observable effects, but no or few fatalities to permit a meaningful evaluation of the study. According to the guidelines on which this study is based, this dose represents the limit dose which needs not be exceeded.

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3.4. Test article administration and diet

Route of administration

The test article was administered orally by gavage (rubber catheter).

Frequency of administration

1 dose per day, 7 times per week.

Preparation of suspension

Suspensions of the 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 body weight

Control analyses

Control analyses of the test article 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 RCC 641531) 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.

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3.4.1. Diet

Pelleted, certified standard diet (Nafag No. 8900 FOR GLP) was provided ad libitum (except for overnight fasting prior to blood collection). All batches of diet were assayed for composition and contaminant levels by the manufacturer. Contaminant levels were within the acceptable limits and were not considered to have affected the conduct of the study or the interpretation of the data. Analytical results are archived at Experimental Toxicology, Novartis Crop Protection, 4332 Stein / Switzerland.

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 Novartis Crop Protection, as well as the results of inhouse chemical analysis by the analytical laboratories of Novartis Pharma AG. Contaminant levels were within the acceptable limits and were not considered to have affected the conduct of the study or the interpretation of the data.

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3.5. Observations and records

Mortality

All animals were checked daily (a.m. and p.m.) 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 behavior, or any reaction to treatment, examination was carried out daily, and observations were recorded.

Body weight

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

Food consumption

The food consumption was recorded weekly 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.

Food consumption ratios

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

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

Unit: g food/kg body weight per day

Water consumption

The water consumption was recorded weekly and 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.

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3.6. Detailed clinical observations

Detailed clinical observations were performed pretest and once weekly thereafter, at about the same time each day. To control for variations in test conditions and to make experimenters unaware of the animals' treatment, animals were randomized and the cage labels covered with the corresponding FOB number. Animals were observed in the home cage, during handling, and in an openfield. Observations were conducted identical to those performed as part of the FOB and also included test for sensorimotor functions. Therefore, data from detailed clinical observations were evaluated together with that of the FOB.

3.7. Functional observational battery (FOB)

FOBs were conducted at week 4 and 8 (recovery groups only), at about the same time each day and were always conducted before the assessment of motor activity. To control for variations in test conditions and to make experimenters unaware of the animals' treatment, animals were randomized and the cage labels covered with the corresponding FOB number.

Animals were observed in the home cage, during handling, and in an openfield. Observations covered the functional domains of CNS activity, CNS excitation, sensorimotor, autonomic, and physiological functions and included, but were not limited to, the following signs:

recumbency	salivation
posture/gait	lacrimation
gait abnormalities	chromodacryorrhea
paddling movements	rhinorrhea
muscle tone	chromorhinorrhea
fasciculations	piloerection
spasms	palpebral closure
tremor	eye prominence
convulsions	fecal consistency
ease of removal	urination
ease of handling	respiratory abnormalities
vocalisation	unkempt fur
Straub tail	emaciation
stereotypies	dehydration
click response	distended abdomen
paralysis	pupil size

Neurological examinations included tests for

- sensorimotor functions (approach, touch, vision, audition, pain, vestibular)

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- autonomic functions (pupillary reflex, body temperature)
- sensorimotor coordination (grip strength, landing foot splay)

A detailed description of the scoring criteria is given in Appendix C. Individual scores for observations and neurological tests were summarized according to their functional domain and mean scores calculated for each group.

Body temperature was measured rectally using a digital thermometer (Ellab DM 852; sensor Ellab PRR-04004-A). Grip strength was measured using a horizontal grid connected to a push-pull strain gauge (Mecmesin Typ FS 3.0 K; Bruetsch/Ruegger AG, 8010 Zuerich, Switzerland) according to Mattsson et al. (1986). For landing foot splay, the rats' hindfeet were powdered with China clay and the animals dropped from a prone position 30 cm above ground. Landing foot splay was measured as distance between prints of interdigital pads of the hindfeet according to Edward et al. (1977). Individual data for grip strength and landing foot splay are the means of two readings. In cases of insufficient collaboration by the animal or incorrect trials, readings were excluded from evaluation and the measurements repeated.

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3.8. Motor activity

Motor activity was assessed after conducting the FOBs using an automated openfield device (DIGISCAN Animal Activity Monitor; Omnitech Electronics Inc., Columbus, OH, USA). This system has been shown to allow measurement of increased and decreased motor activity. Each of the 8 transparent plexiglass test boxes (40 x 40 x 35 cm) is divided by 16 infrared photobeams per side (2.5 cm apart, 3 cm above floor) to measure horizontal activity. Vertical activity is measured by a further set of 16 infrared photobeams at an approximate height of 3/4 of the rats' body length. Motor activity data are automatically recorded and processed by the DIGISCAN Analyser for 10 consecutive 3-minute intervals and stored for further evaluation on an IBM PC according to Fitzgerald et al. (1988). Activity measurements were performed between 8 a.m. and 3 p.m. in an air conditioned (same temperature and humidity as in animal room) and illuminated room with background noise (about 45 db) provided by the PC's fan. Animals were allocated to the different runs and test boxes by means of a latin square design so that treatment groups were balanced across test boxes and time. Males and females were tested on separate days. The following parameters were evaluated and reported:

Horizontal activity: total distance (in cm)
number of movements (counts)
movement time (in sec)

Vertical activity: vertical activity (counts)
number of rearings (counts)
movement time (in sec)

Other parameters: time in central quadrant (center time; in sec)

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3.9. Laboratory investigations

Laboratory investigations (hematology, blood chemistry and urine analysis) were carried out on all surviving animals of each dose group at the end of the treatment period (January 7, 1997), and additionally at the end of the recovery period (February 4, 1997) on animals of the control group and dose groups 4 and 5 kept for reversibility evaluation.

With respect to biological variability due to circadian rhythms, blood was consistently sampled in the morning. Ether was used to anesthetize the animals. Blood was withdrawn from the orbital sinus using glass capillary tubes. The following anticoagulants were used: EDTA for performing the complete blood count, 3.8% sodium citrate for coagulation testing and heparin for blood chemistry investigations. Food was withheld overnight prior to blood removal.

Urine for analysis was collected overnight. The individual animals were housed in special metabolism cages. Food and water was withheld during the time of urine collection.

The parameters and methods used are listed in the following tables.

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3.9.1. Parameters and methods used in hematology

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

Red blood cell parameters	Abbreviation	SI Unit<2>
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<4>	HDW	mmol/l
White blood cell parameters		
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
Blood platelets		
Thrombocyte Count	Plt	G/l
<u>Prothrombin time</u>		
Photometric assay using chromogenic substrate on a Hitachi 917 analyser (Method code: M0001)	PT	rel. 1

<1> Method code is used for assignment of valid reference values (see Appendix section)

<2> A table which lists SI units, conventional units and factors to convert data from SI units to conventional units is given in the Appendix section

<3> RDW is derived as a coefficient of variation of the volume histogram

<4> HDW is derived as the standard deviation of the hemoglobin concentration histogram

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3.9.2. Parameters and methods used in blood chemistry

Parameter	Method of analysis (Method code) <1> Instrument	Abbre- viation	Unit
Glucose	Hexokinase/G6P-DH (M0001) HITACHI 737/917	Gluc	mmol/l
Urea	Urease/GLDH (M0001) HITACHI 737/917	Urea	mmol/l
Creatinine	Enzymatic colorimetric test (M0002) HITACHI 917	Creat	umol/l
Total bilirubin	Reaction with 2,5-Di- chlorophenyldiazonium salt (M0001) HITACHI 737/917	Bili-tot	umol/l
Total protein	Biuret reaction (M0001) HITACHI 737/917	Prot	g/l
Albumin	Bromcresol green method (M0001) HITACHI 737/917	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 737/917	Chol	mmol/l
Sodium	Ion selective electrode (M0001) HITACHI 737/917	Na+	mmol/l
Potassium	Ion selective electrode (M0001) HITACHI 737/917	K+	mmol/l
Calcium	o-Cresolphthalein complexone method (M0001) HITACHI 737/917	Ca++	mmol/l

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Parameter	Method of analysis (Method code) <1> Instrument	Abbreviation	Unit
Chloride	Ion selective electrode (M0001) HITACHI 737/917	Cl-	mmol/l
Phosphorus inorganic	Phosphomolybdate reaction (M0001) HITACHI 737/917	PO4-in	mmol/l
Aspartate amino- transferase EC 2.6.1.1	MDH/NADH coupled reaction method (M0002) HITACHI 917	ASAT (GOT)	U/l
Alanine amino- transferase EC 2.6.1.2	LDH/NADH coupled reaction method (M0002) HITACHI 917	ALAT (GPT)	U/l
Alkaline phosphatase EC 3.1.3.1	p-Nitrophenyl-phosphate as substrate (M0001) HITACHI 737/917	ALP	U/l

<1> Method code is used for assignment of valid reference values
(see Appendix section)

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3.9.3. Parameters and methods used in urinalysis

Physical and chemical examination

<u>Parameter</u>	<u>Abbreviation</u>	<u>Unit</u>	<u>Method and method code</u> <1>
Urine volume	Volume	ml	Gravimetric (M0001)
Relative density	Rel dens	1	Refractometer (M0002)
Urine color	Color	score	Visual inspection
	N = normal		
	C = colorless		
	YB = yellow-brown		
	YG = yellow-green		
	R = red		
	B = brown		
	RB = red-brown		

The following urine components were investigated using an automated test strip analyser Miditron (Boehringer Mannheim) applying reflectance spectroscopy. Results are given as discrete values representing a concentration range (semi-quantitative results).

<u>Parameter</u>	<u>Abbreviation</u>	<u>Method code</u> <1>	<u>Unit</u>	<u>Set points</u>
pH-value	pH	M0002	1	5.0, 6.0, 6.5, 7.0, 8.0, 9.0
Protein	PRO	M0001	g/l	0, 0.25, 0.75, 1.50, 5.00
Glucose	GLU	M0001	mmol/l	0, 3, 6, 17, 56
Ketones	KET	M0001	mmol/l	0, 0.5, 1.5, 5.0, 15.0
Urobilinogen	UBG	M0001	umol/l	0, 17, 68, 135, 203
Bilirubin	BIL	M0001	umol/l	0, 17, 50, 100
Erythrocytes	ERY	M0001	per ul	0, 10, 25, 50, 150, 250
Leukocytes	LEU	M0001	per ul	0, 25, 100, 500

<1> Method code is used for assignment of valid reference values (see Appendix Section)

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3.10. Pathology

3.10.1. Macroscopical examination

At scheduled sacrifices all surviving controls and treated animals were exsanguinated under ether anesthesia and subjected to detailed necropsy.

At necropsy the following weights were recorded from all animals:

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

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

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

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epididymis, both
uterus
vagina
ovary, both
pituitary gland
adrenal gland, both
thyroid with parathyroid gland
thymus
peripheral nerve (sciatic nerve)
brain (incl. medulla, pons, cerebral and cerebellar cortex)
spinal cord
eye with optic nerve, both
orbital gland, both
extraorbital lacrimal gland, both
Zymbal gland, both
muzzle
tongue
any tissue with gross lesions

A complete necropsy with tissue preservation was performed also on all animals which died during the test period or which had to be sacrificed in moribund condition.

3.10.2. 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
mesenteric lymph node
axillary lymph node
femur with joint
bone marrow (femur)
trachea
lung
heart
liver
stomach
small intestine (duodenum, ileum, jejunum)
large intestine (cecum, colon, rectum)
Peyer's patches (small and large intestine)
kidney, both
urinary bladder
testis, both
epididymis, both
prostate
uterus
ovary, both
pituitary gland
adrenal gland, both

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thyroid with parathyroid gland
thymus
peripheral nerve (sciatic nerve)
brain (incl. medulla, pons, cerebral and cerebellar cortex)
spinal cord
any organ with gross lesions

3.10.3. Acquisition and presentation of pathology data

All data observed at necropsy were recorded, whenever possible, on line on a TANDEM computer using a software package specifically designed for the purpose of the testing facility and simultaneously written by hand on raw data sheets. Subsequently, all these data were electronically transferred into a DEC/VAX computer to enable the use of the PathData system V3.6B. The handwritten raw data were archived.

The microscopical findings were directly entered during the microscopy sessions using the PathData system V3.6B. The microscopic terms were taken from the corresponding PathData glossary.

Where practicable, gross lesions were identified by a capital letter, e.g. A, B, C, etc. at necropsy. All macroscopical findings were additionally numbered per organ and animal by the PathData system. At the subsequent histopathological evaluation the diagnosis or diagnoses corresponding to the macroscopically identified lesions were correlated, using the corresponding number of the PathData system, with the changes seen at necropsy.

The codes listed and defined below are used to add the grading to a given pathological finding in order to describe the lesion as accurate as possible:

- Grade "1": Minimal/very few/very small.
- Grade "2": Slight/few/small.
- Grade "3": Moderate/moderate number/moderate size.
- Grade "4": Marked/many/large.
- Grade "5": Massive/extensive number/extensive size.
- Grade "P": Finding present, grading not scored.

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3.11. Statistical analysis

For each time point and parameter an univariate statistical analysis was performed. Nonparametric methods (Lehmann, 1975) were applied, to allow for non normal as well as normal data distribution.

Each treated group was compared to the control group by Lepage's (Lepage, 1971) or 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 (Jonckheere, 1954). The Lepage test is a combination of Wilcoxon and Ansari-Bradley statistics, i.e. a combined test for location and dispersion. The Lepage test has a good power against the more general alternative that the distributions differ not only in location but also in dispersion. 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.

At each time point FOB data and motor activity data (session totals named as 'area under the curve' (AUC)) of treated groups were compared to the control group using multiple t tests (SAS, Technical Report P-229, 1992). Raw and multiplicity-adjusted p-values based on bootstrap resampling were given.

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.

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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

SD the standard deviation

Median the 50th percentile

IQ-Range the interquartile range, the difference between the 75th and the 25th percentile

Min, Max the smallest value, the largest value

p_L p-value, the probability of an outcome being greater than or equal to Lepage's test statistic, if the null hypothesis is true. Not given, if sample sizes too small

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

a, indicative of a difference in location

b, indicative of a difference in dispersion

p_J 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

If the WILCOXON option is chosen, the following are printed in place of p_L:

p_W 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

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4. RESULTS

Figures and Summary Tables (mean values and their statistics, where performed) are given in Sections 7. "FIGURES" and 8. "TABLES", respectively. Individual values are given in Appendix A of this report. Reference values are given in Appendix C.

4.1. Dose levels

4.1.1. Analytical results

Detailed analytical results are given in Section 8.1 and in the Analytical Report (Analytical Report RCC 641531) which is included in Appendix B of this report.

Acceptability criteria

(According to Standard Operation Procedures of Toxicology/Experimental Toxicology)

Content: An analytical result of test article content in vehicle in the range between 75 % and 125 % is considered acceptable.

Homogeneity: A preparation of the test article in vehicle is considered homogeneous, when of 3 samples (A,B,C) taken at top, middle, and bottom of the mixing vessel no sample differs from the mean value by more than 20 %.

Stability: The test article in vehicle is considered stable, when the content after 4 hours at room temperature does not differ by more than $\pm 10\%$ from the value determined immediately after preparation.

Homogeneity

The analytical procedure for homogeneity determination yielded values within the limits of acceptance.

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Stability

The analytical procedure for stability determination yielded values within the limits of acceptance.

Concentrations

The analytical procedure for content determination yielded values close to the targeted concentrations and within the limits of acceptance.

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4.2. In-life observations

4.2.1. Clinical observations

During this study neither changes to the behavior nor clinical signs attributed to the administration of the test article were noted.

4.2.2. Functional observational battery

Clinical observations and functional measurements did not reveal any relevant changes throughout the treatment and recovery periods.

The minor changes in CNS activity and/or CNS excitation seen in males reflect slightly reduced activity and increased reactivity in individual animals. In females, CNS activity was increased mainly in animals of group 3. Since these observations were seen in individual animals and at few examinations only and did not show any relation to dose or treatment, they all were considered to be incidental.

4.2.3. Motor activity

No treatment-related effects were seen in any of the motor activity parameters measured. Overall means of horizontal and vertical activity and of center time were comparable across control and treated groups and within-session habituation did not reveal any treatment-related effect.

4.2.4. Mortality

There was no mortality during this study which could be attributed to the treatment with the test article.

During the treatment period, one male and two females of group 4 were found dead. Histopathological findings indicated missintubation as probable cause of the deaths.

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4.2.5. Body weight

The body weight development was not influenced by the treatment with the test article.

Minor inter-group differences were considered reflections of biological variability.

4.2.6. Food consumption

The food intake was not influenced by treatment with the test article.

In view of dose-independence, the slightly higher food intake of males of group 3, in comparison to that of the control group, was considered to reflect normal biological variability.

4.2.7. Food consumption ratios

The mean food consumption ratios of treated groups were essentially comparable to those of the control group, and thus not considered influenced by treatment with the test article.

4.2.8. Water consumption

The water intake was not considered influenced by treatment.

Males of group 5 had a higher water consumption than the control animals. However, as it continued to be increased during the whole recovery period, and no corroborative findings were noted by organ weight and pathology evaluations, it was considered as biological variability. The same is true for the higher water intake of male group 3, which, moreover, was not dose-dependent.

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4.3. Hematology

No test article-related differences were apparent by the end of the treatment and recovery periods.

Although some inter-group differences were statistically significant, they were not related to treatment as they did not form a dose-response relationship and/or the magnitude of the change was too small to be of toxicological relevance. All these minor changes were judged to reflect the physiological variation of the parameters because individual values recorded for treated rats were within the range of reference values for untreated rats of this age and strain. In males, these differences included a small increase in hemoglobin concentration and in white blood cell and monocyte counts in group 3 at week 5; a small increase in monocyte count in group 5 at week 5, and a small increase in MCH in group 5 at week 9. In females, these differences included a small increase in relative basophil count in group 5, and in large unstained cell count in group 2 at week 5. Similarly, also the slightly lower prothrombin activities recorded for females of groups 4 and 5 at treatment end were considered to be random events as all values of group 4 were within the range of reference values and only 2 of 10 values in group 5 were minimally below the lower limit of reference values.

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4.5. Urine analysis

At week 5, both males and females of group 5 (1000 mg/kg) excreted a more acidic urine than the controls although by the end of the recovery period the pH-value of the urine from previously treated rats was similar to that of the controls. At weeks 5 and 9, males of group 5 (1000 mg/kg) excreted a statistically significantly lower volume of urine with a higher relative density, a finding which does not reflect a toxic effect.

Other differences which attained a level of statistical significance were considered not to be related to treatment as they did not form a dose-response relationship and/or were too small to be of toxicological relevance because the values recorded for treated rats were within the range of reference values for untreated rats of this age and strain. In males these differences included a slightly higher bilirubin value for group 5 at week 5, and a higher erythrocyte value at week 9 for group 4. A lower leucocyte content in the urine observed at week 5 for males of groups 4 and 5 was not considered toxicologically relevant. In females, at week 5, these differences included a higher urobilinogen value for group 5 and higher bilirubin values for groups 3 and 5; and at week 9, a lower volume for group 4.

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4.6. Postmortem findings

4.6.1. Organ weights and ratios

At treatment end, the mean heart weight and the mean heart to body weight ratio of males treated at 1000 mg/kg were 6% and 11 %, respectively, higher than the values of the control group. This finding was reversible within the following 4-week recovery period.

At treatment end, males of group 3 presented significantly higher liver weights. Since, however, there was no dose-dependency, and, moreover, all individual values were well within the range of our reference data, no experimental significance was attributed to them. Other differences which attained a level of statistical significance were within the expected range and, therefore, not considered of toxicological relevance.

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4.7. Pathology

Detailed findings for individual animals are presented in Appendix A.

The results are presented below and the tabulated summaries of the gross pathological and histopathological examination are presented in the Tables section. Since no microscopic finding at all was recorded in male recovery animals, no incidence table of microscopic findings for this group of animals will appear in the Tables section.

4.7.1. Macroscopical findings

No treatment-related macroscopical changes were detected. The few findings observed occurred in comparable numbers in all experimental groups and were similar to those occurring spontaneously in our colony of rats. Thus no experimental relevance is attributed to these findings.

4.7.2. Microscopical findings

There were no microscopical changes which were considered to be treatment-related.

Slight to marked fibrinous inflammation of the pleura was observed in one male and two females of group 4 which were found dead, in absence of a dose-relationship. These findings may be compatible with an incident during gavage. A variety of other different non-neoplastic lesions was found in this study, concerning both animals for evaluation of toxicity and for reversibility evaluation after four weeks of recovery. They commonly occur in our colony of rats, and, neither their incidences nor their distribution and morphologic appearance gave any indication of a treatment-related association.

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5. DISCUSSION

Oral administration by gavage of CGA 108906 tech. to albino rats at daily doses of 0, 10, 50, 200, and 1000 mg/kg body weight for 4 weeks was well tolerated. Neither clinical observations nor neurotoxicity tests (functional observational battery, motor activity) revealed any effects indicating potential neurotoxicity. Compared to the control group, the body weight development, and food and water intake of the treated groups were not influenced by the treatment with the test article.

At the high dose level (1000 mg/kg), male animals presented with slightly increased mean absolute and relative heart weights at treatment end. Blood chemistry examination revealed slightly higher values for plasma glucose and potassium levels in males, and urine analysis a more acidic urine in both sexes. However, these findings are not considered to be adverse effects, especially in the light of reversibility after the 4-week recovery period and in the absence of any further histopathological findings.

Therefore, for both sexes the no-observable-adverse-effect level (NOAEL) was at 1000 mg/kg body weight.

Test No.: 963128

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6. REFERENCES

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7. FIGURES

Figures of neurotoxicological investigations, mean body weight, mean food consumption, mean food consumption ratios, and water consumption are given on the following pages.

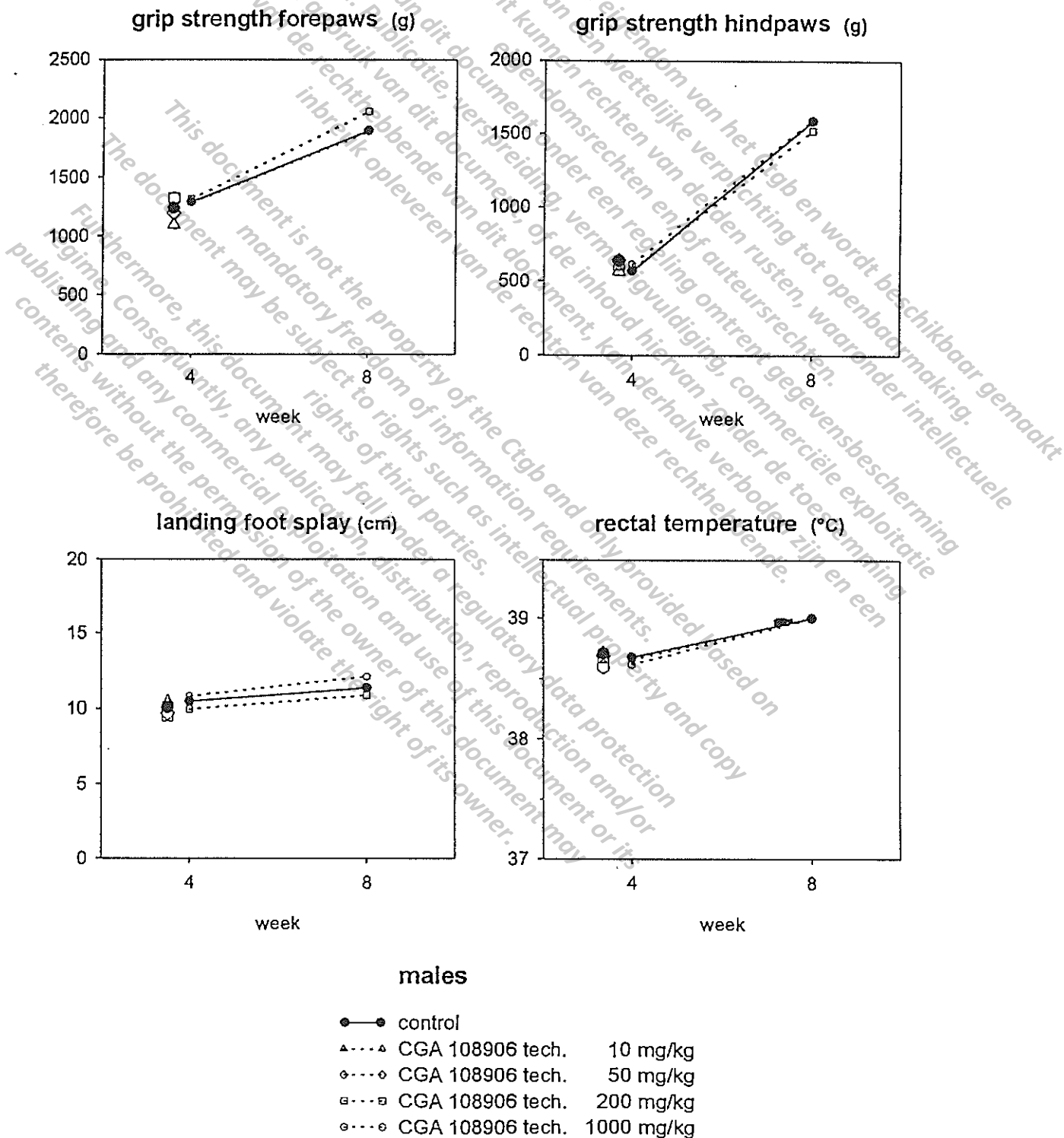
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7.1. Functional Observational Battery (Measurements)

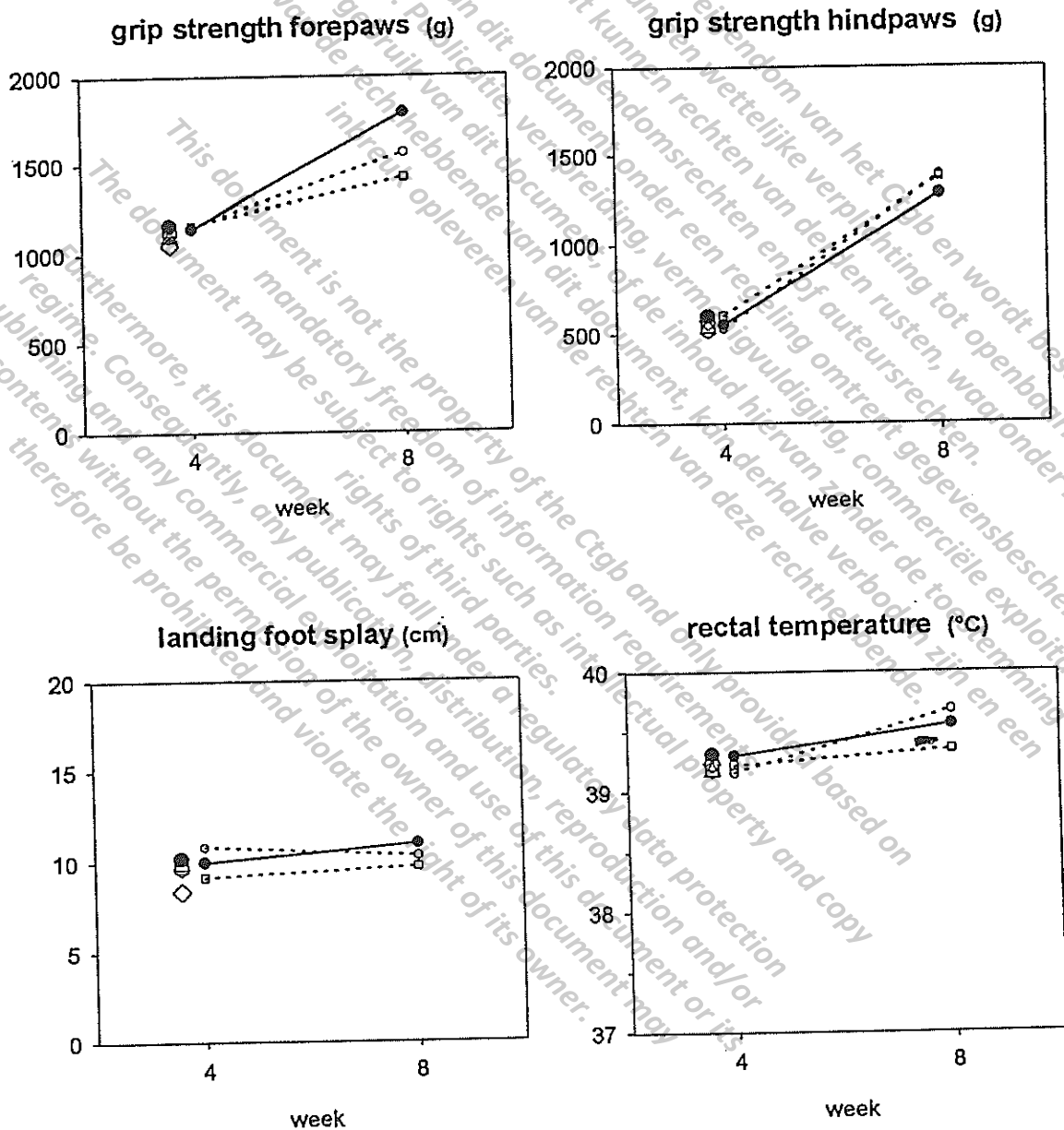
Group means for functional measurements measured at each of the time points.
 (large symbols shown at week 4 represent data of entire groups, small symbols that of recovery animals only)



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7.1. Functional Observational Battery (Measurements) (cont'd)



females

- control
- ▲---▲ CGA 108906 tech. 10 mg/kg
- ◇---◇ CGA 108906 tech. 50 mg/kg
- CGA 108906 tech. 200 mg/kg
- CGA 108906 tech. 1000 mg/kg

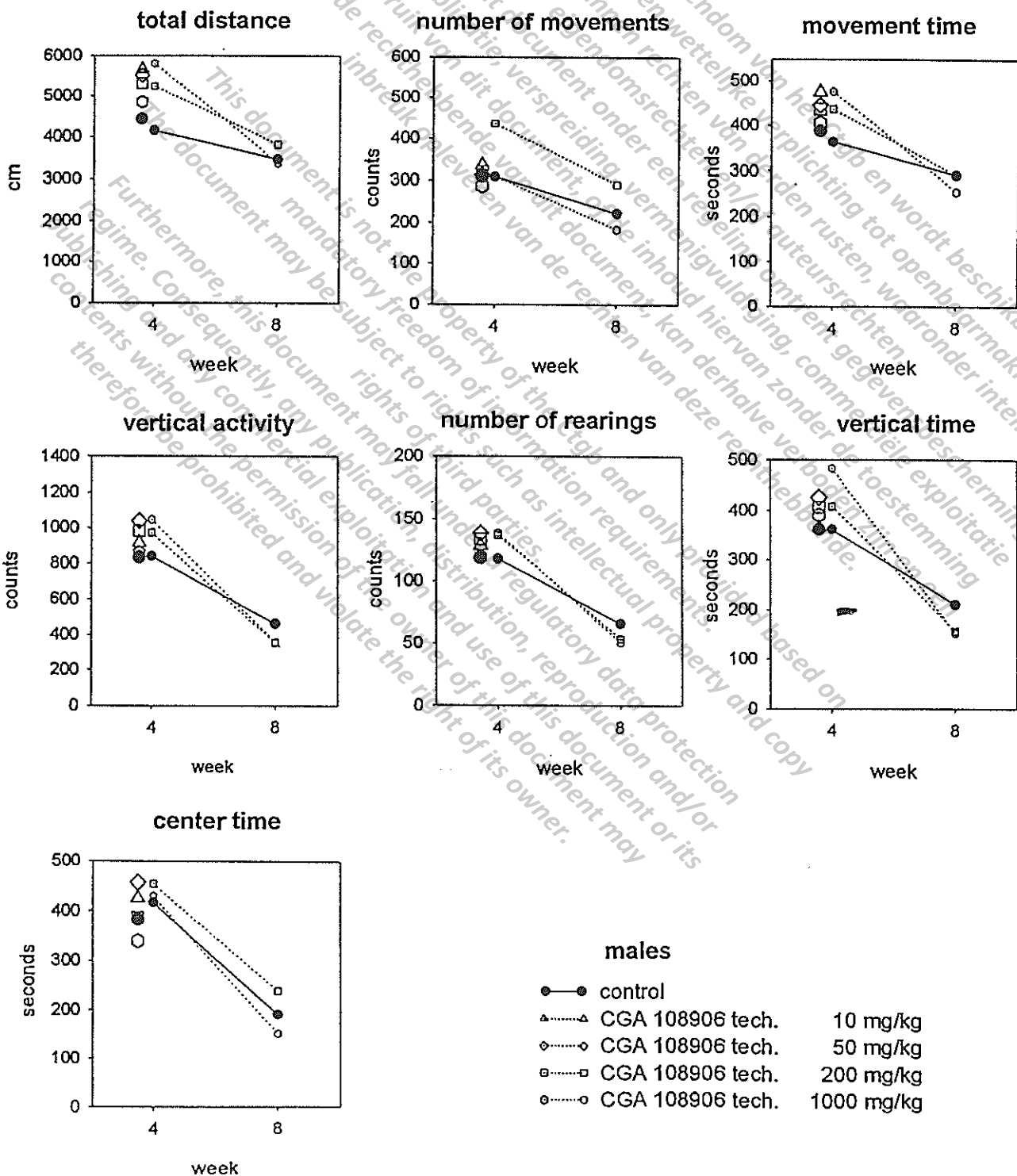
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7.2. Motor activity

7.2.1. Mean session totals males

Group means of session totals for horizontal and vertical motor activity parameters and for center time for each of the time points measured (large symbols shown at week 4 represent data of entire groups, small symbols that of recovery animals only)

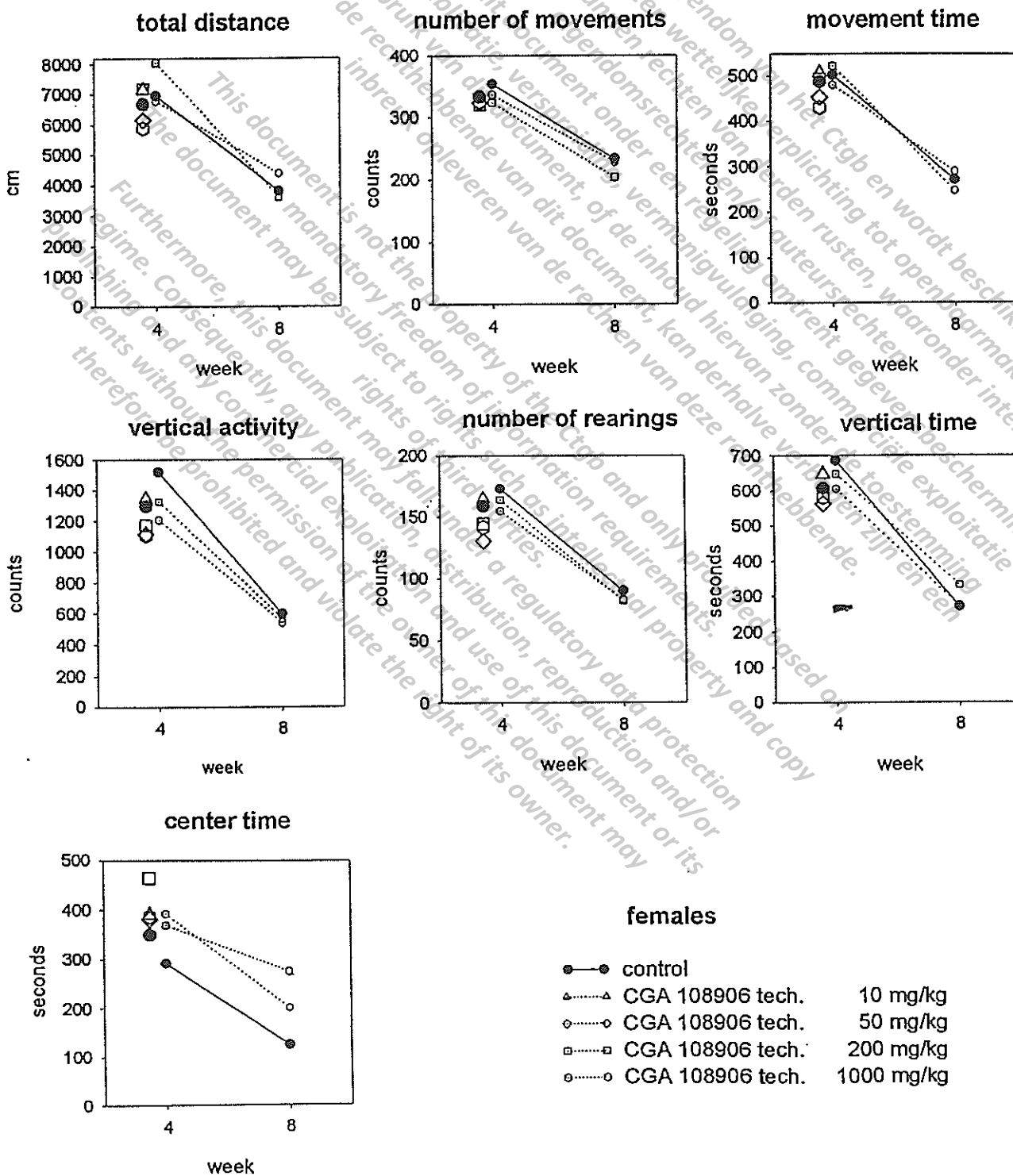


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7.2.2. Mean session totals females

explanations see legend Figure 7.2.1

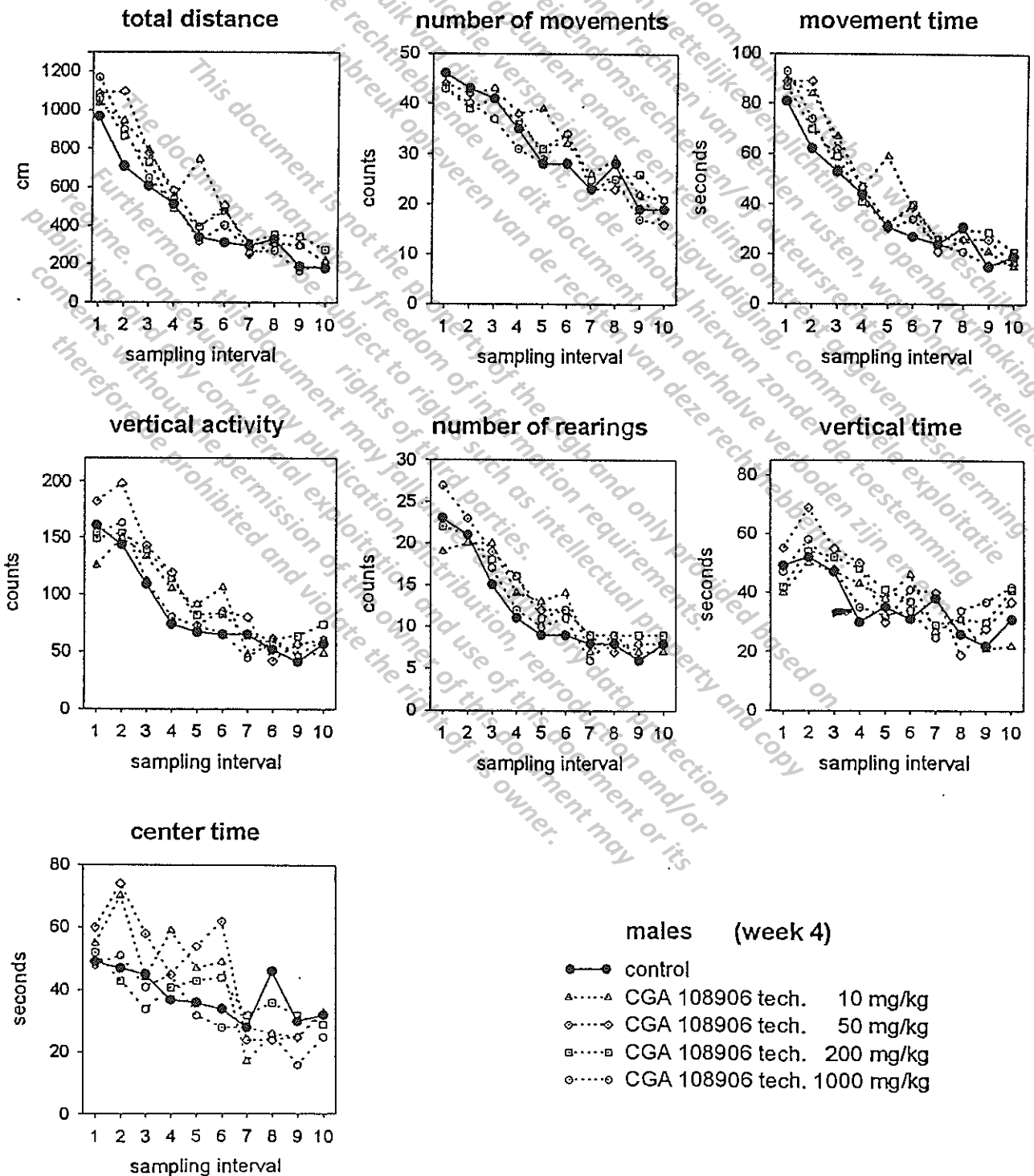


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7.2.3. Motor activity (within-session time course) males

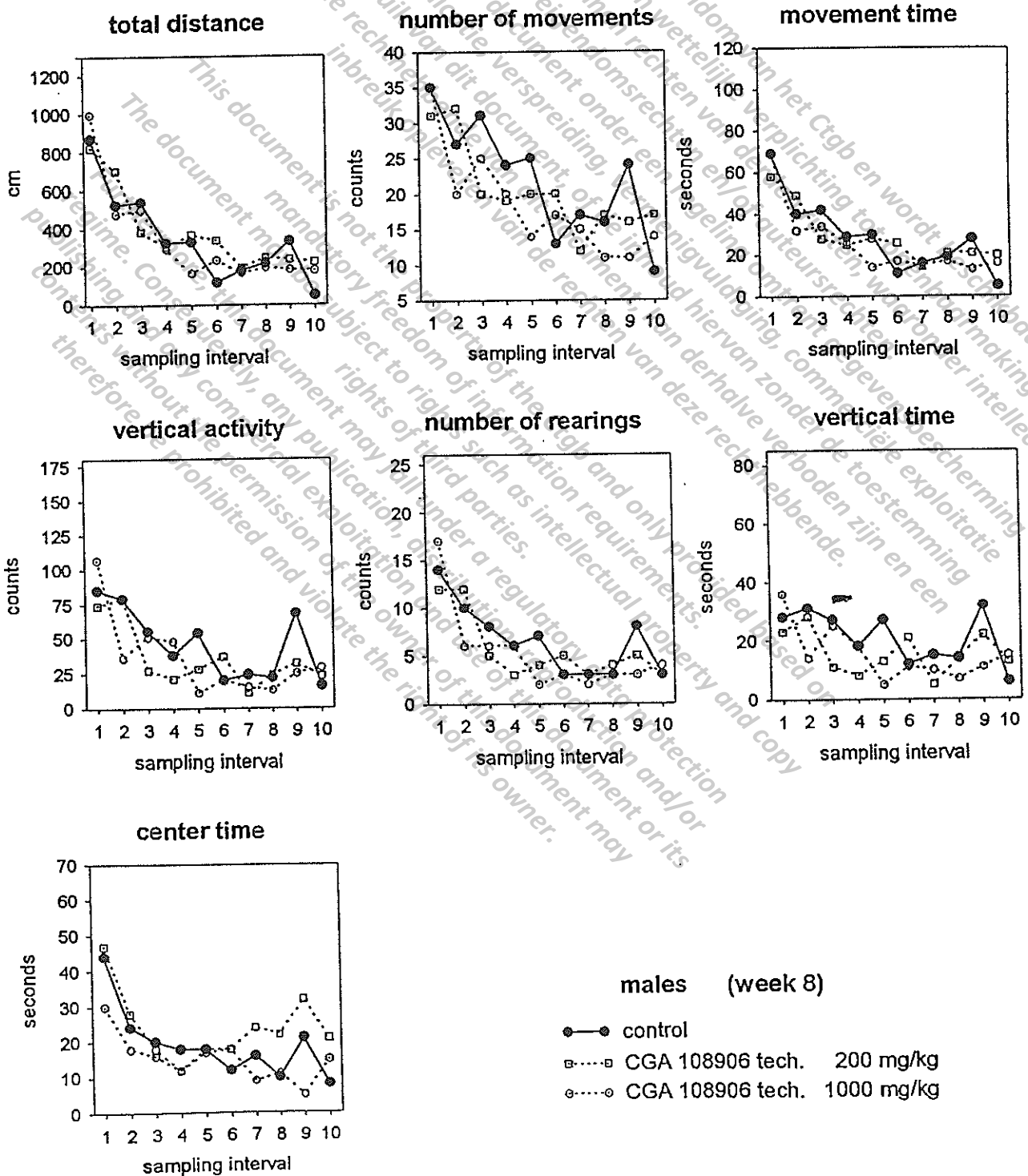
Group means for horizontal and vertical motor activity parameters and for center time for each of the 10 sampling intervals of a session.



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7.2.3. Motor activity (within-session time course) males (cont'd)



males (week 8)

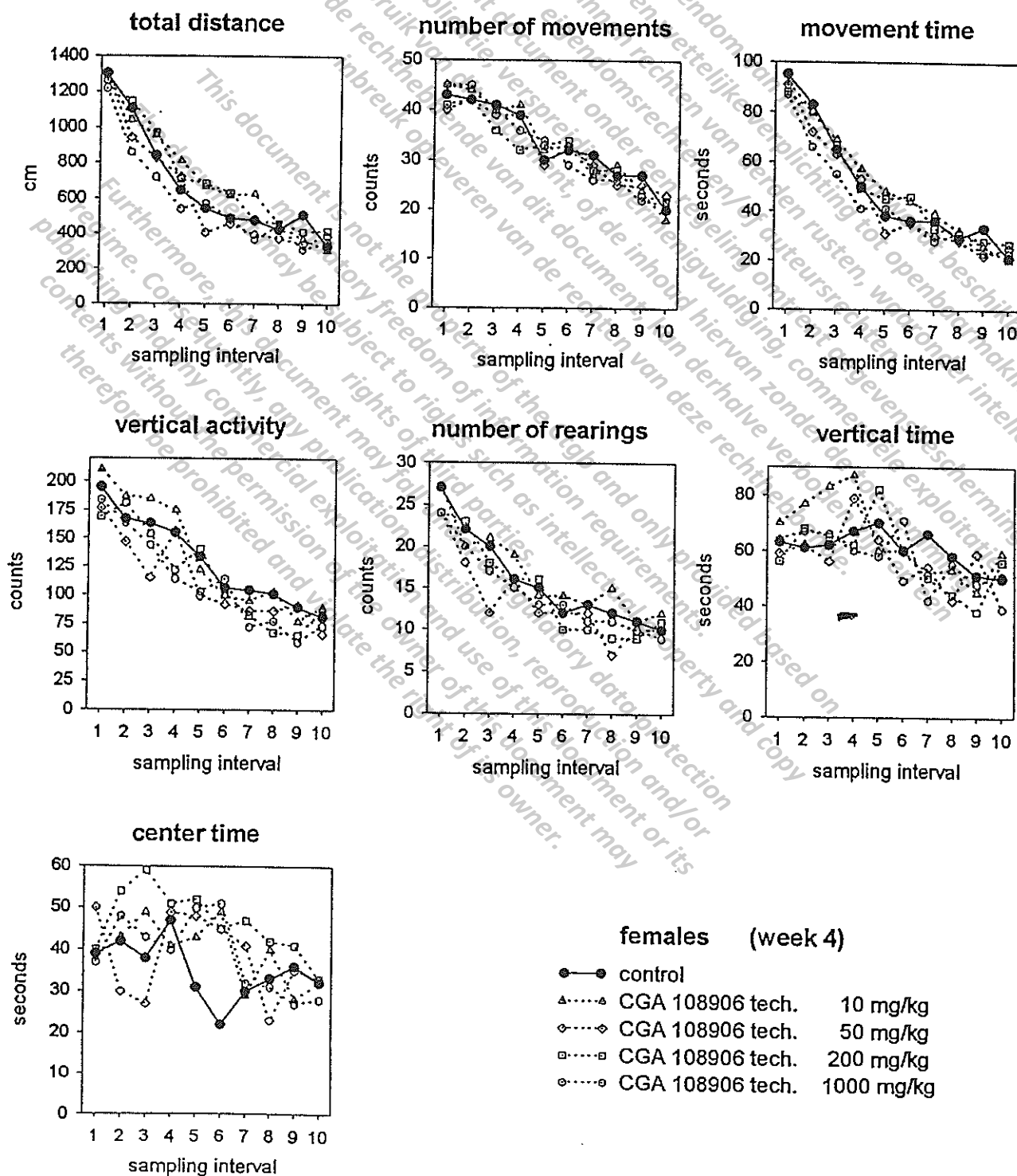
- control
- CGA 108906 tech. 200 mg/kg
- CGA 108906 tech. 1000 mg/kg

Test No.: 963128

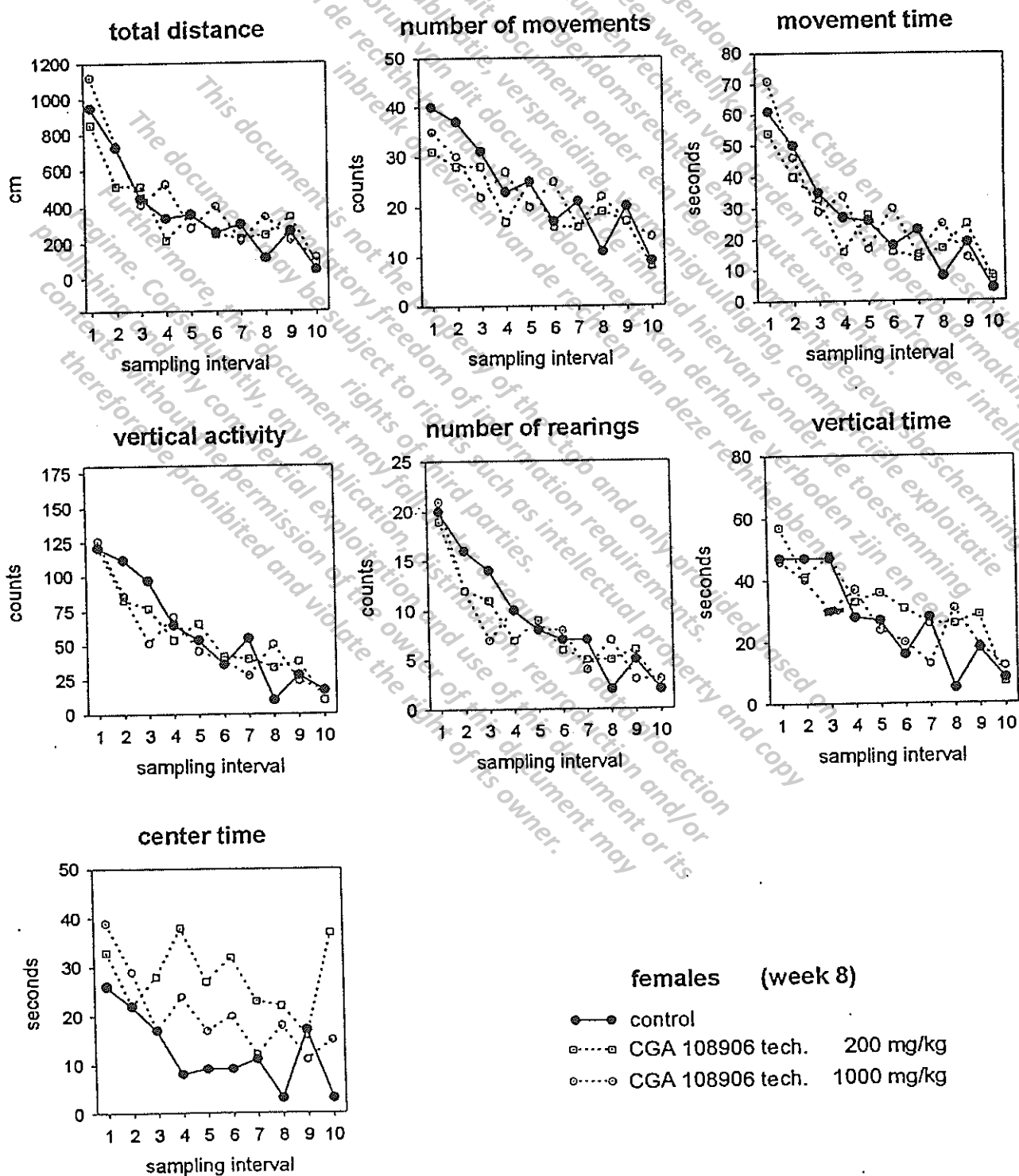
Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

7.2.4. Motor activity (within-session time course) females

explanations see legend Figure 7.2.3



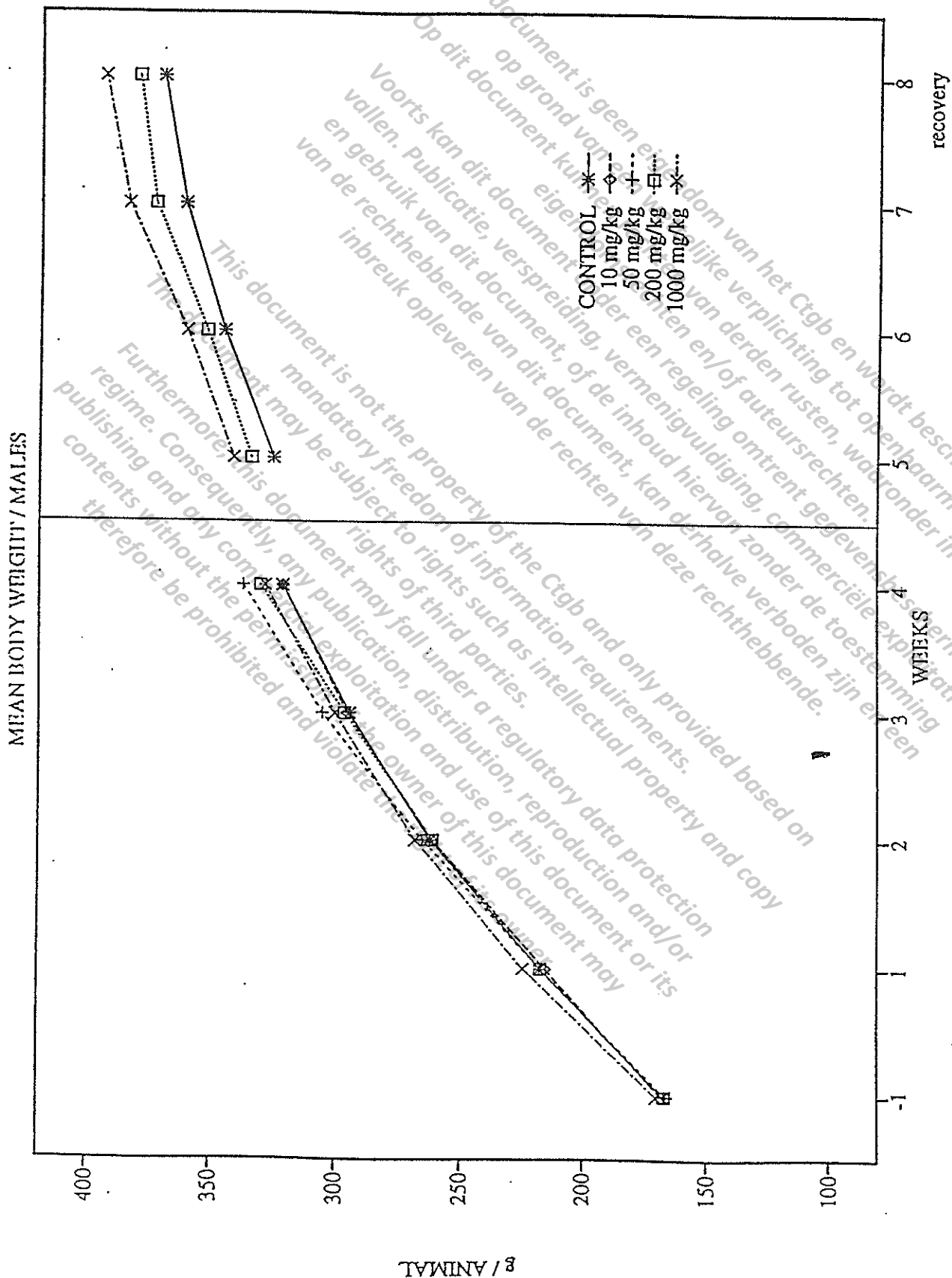
7.2.4. Motor activity (within-session time course) females (cont'd)



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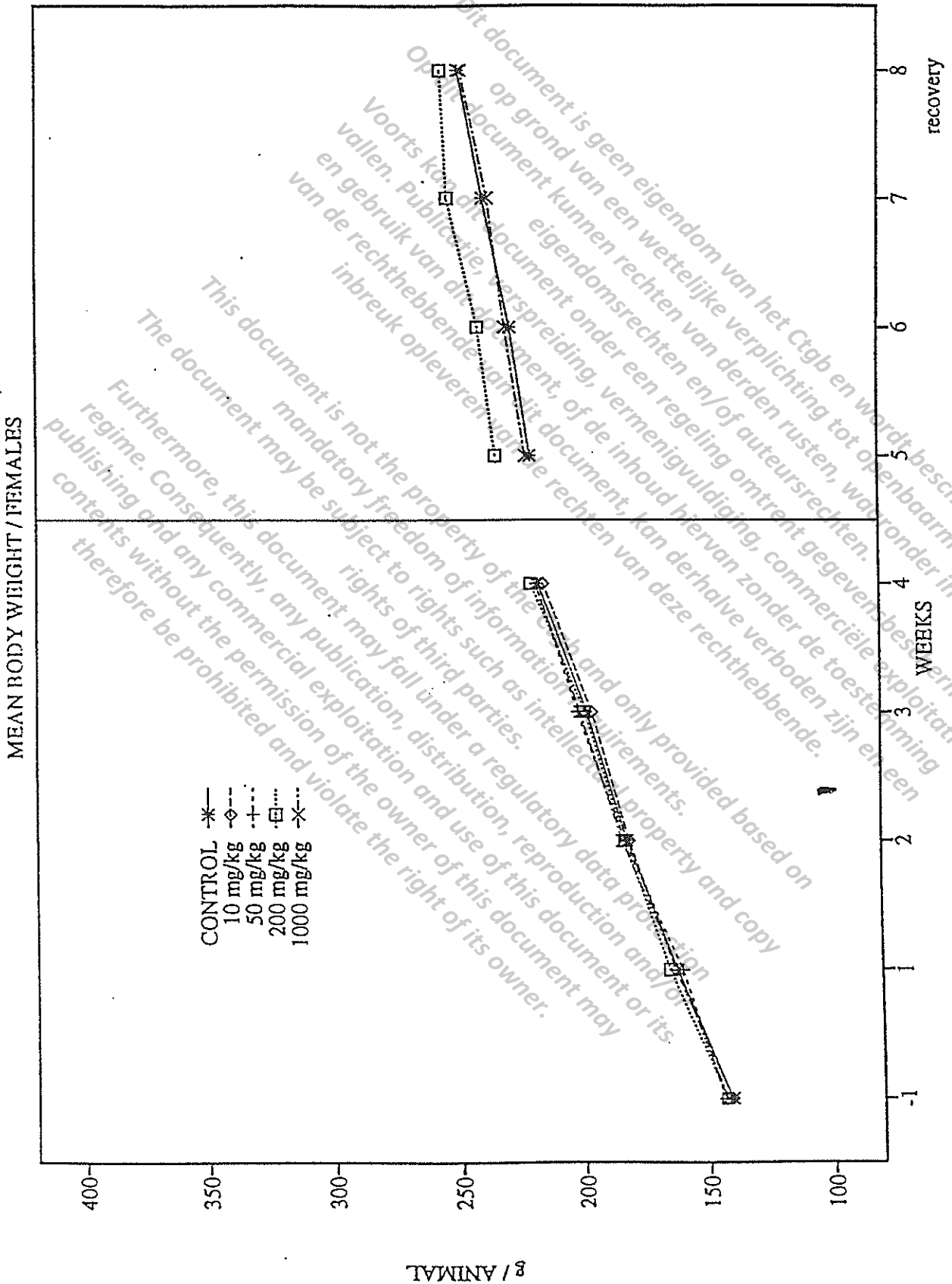
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7.3. Body weight



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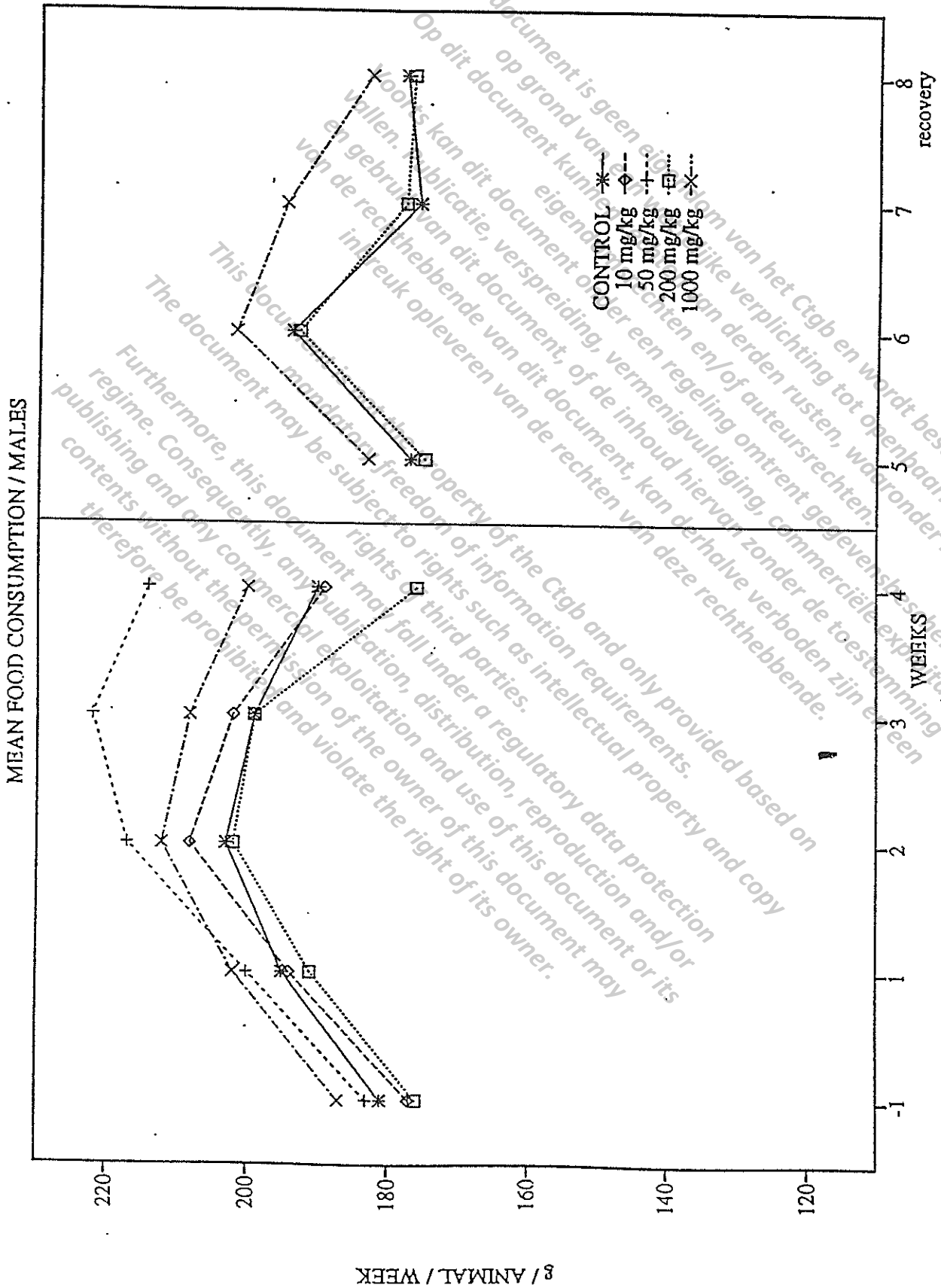
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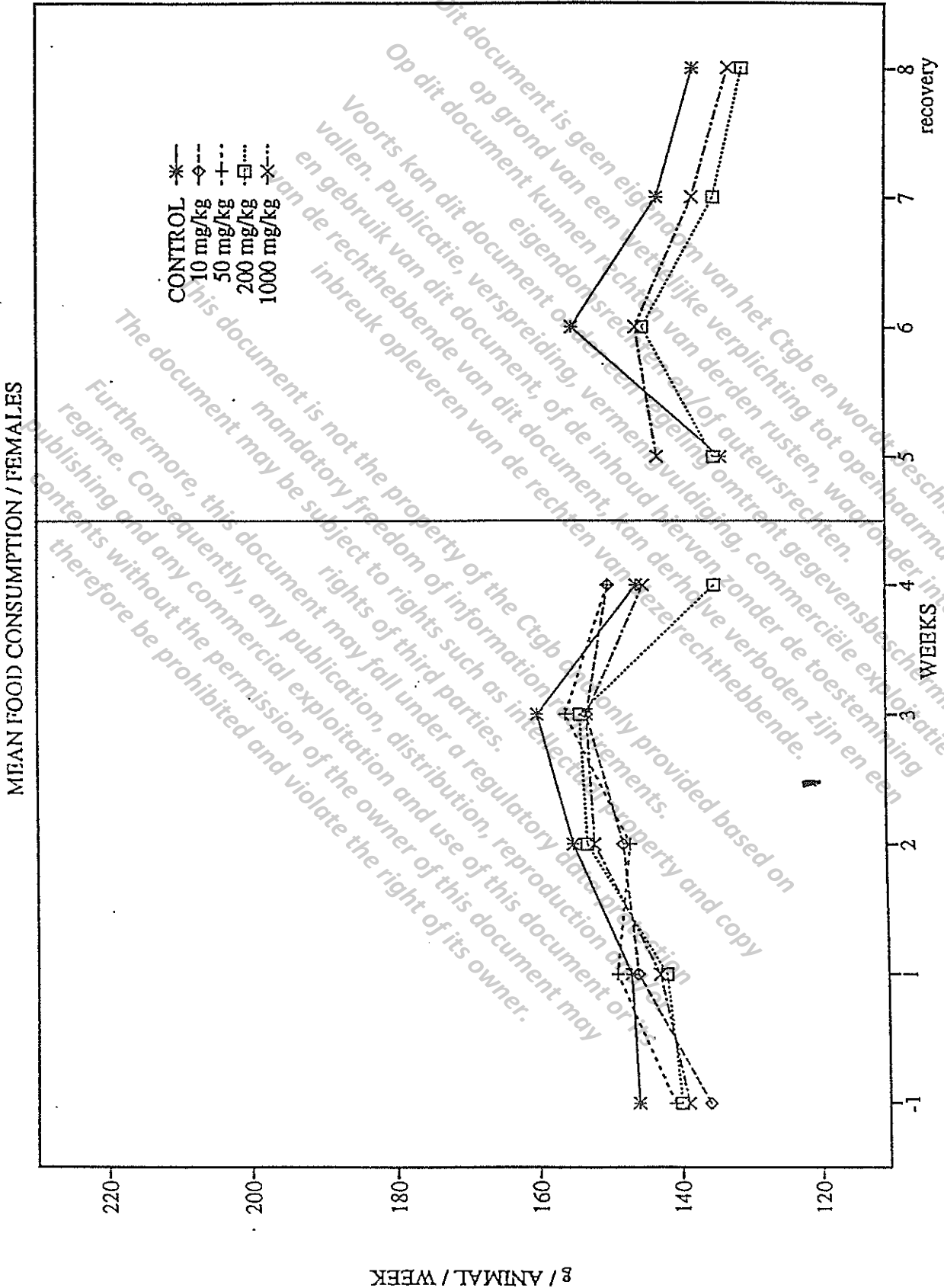
7.4. Food consumption



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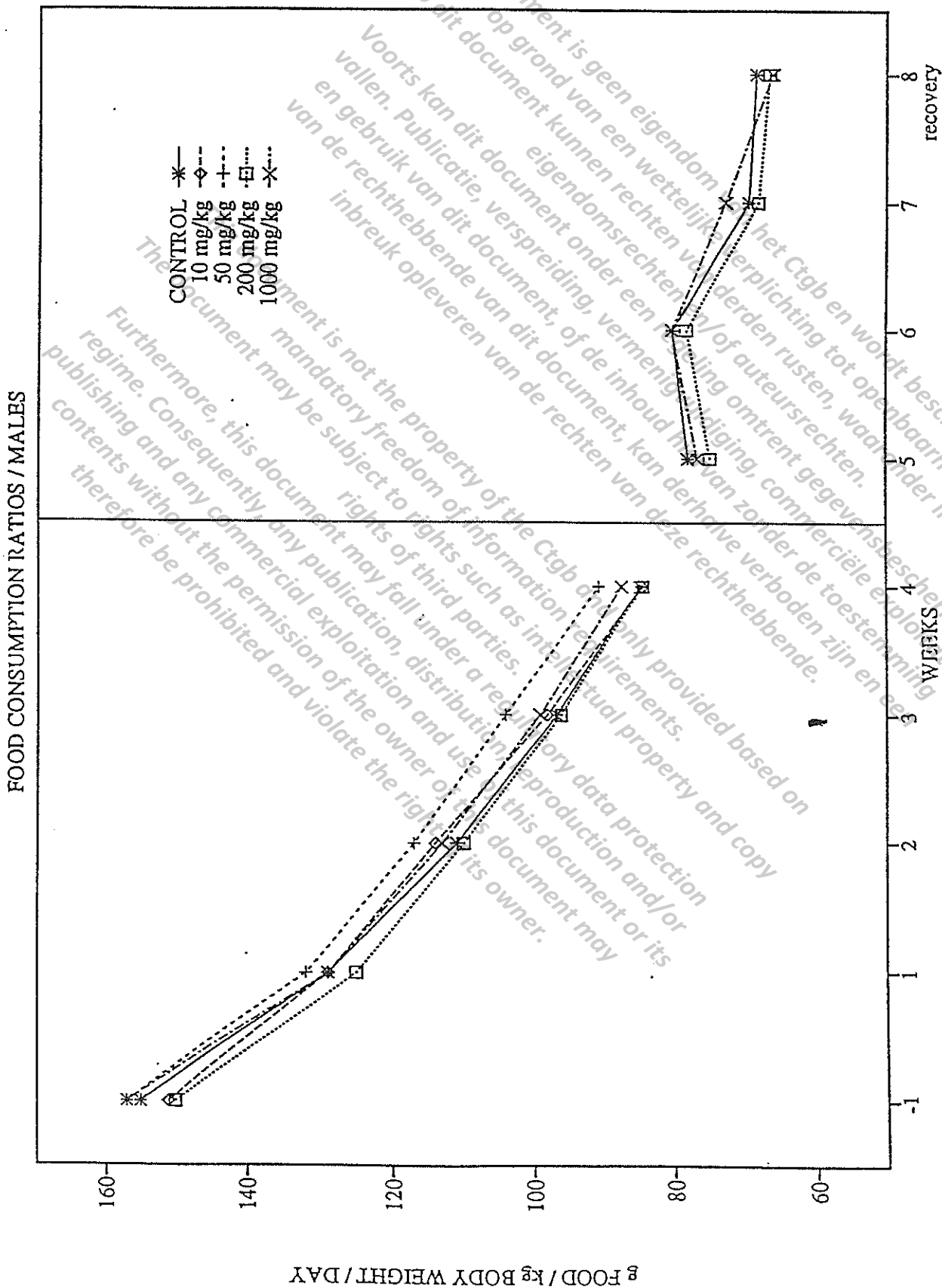
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7.5. Food consumption ratios



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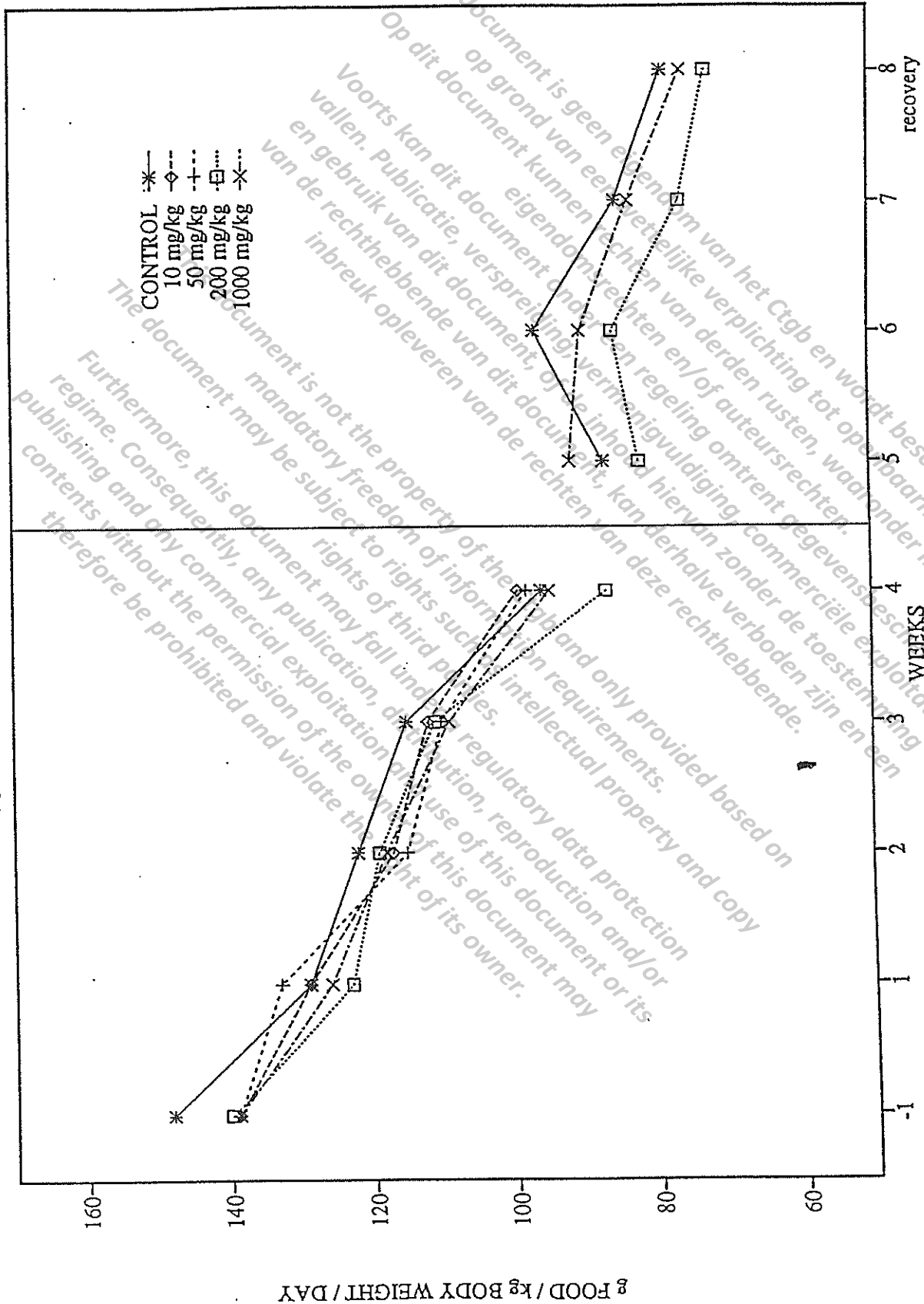
FOOD CONSUMPTION RATIOS / MALES

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Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

FOOD CONSUMPTION RATIOS / FEMALES



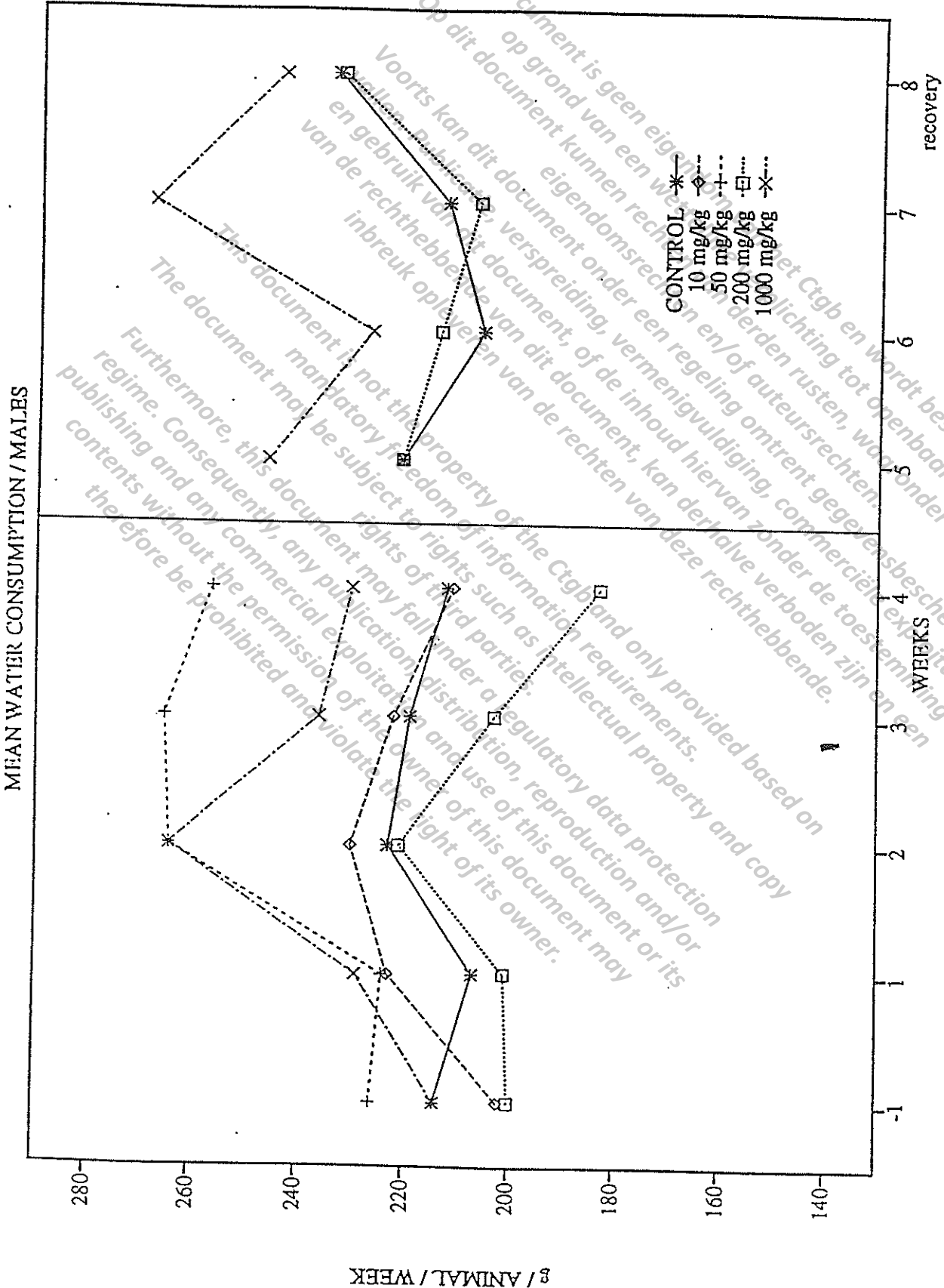
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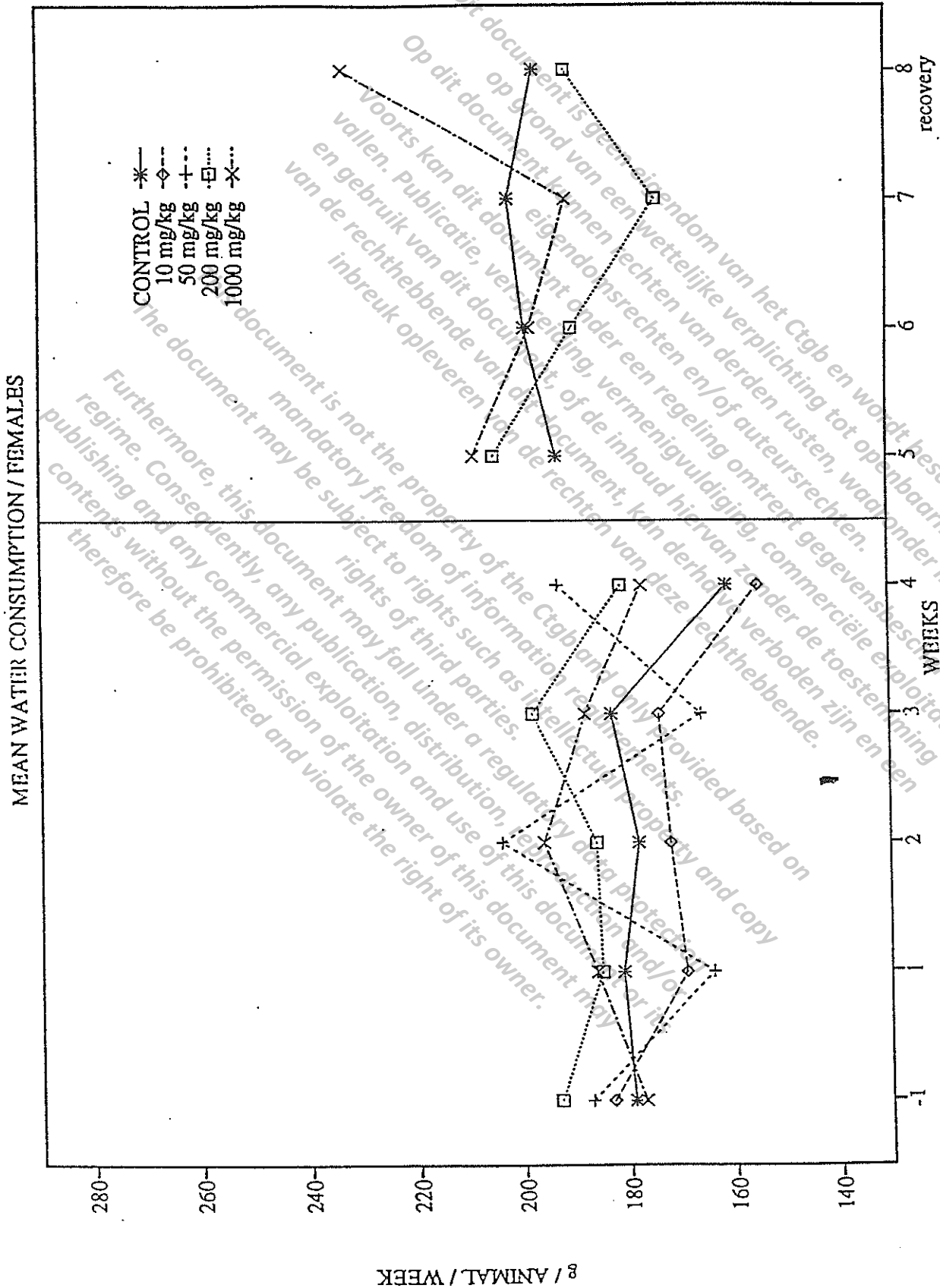
7.6. Water consumption



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8. TABLES (MEANS, STATISTICS)

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8.1. Analytical results

Detailed analytical results are given in the Analytical Report (RCC 641531) which is included in the Appendix section of this report.

Homogeneity and stability (pretest)

CGA 108906 tech.

HOMOGENEITY AND STABILITY

	GROUP 2	GROUP 3	GROUP 4
NOMINAL (mg/ml)	1	10	100
ANALYTICAL (mg/ml)			
pretest: A	0.893	9.89	98.8
B	0.961	10.27	96.5
C	0.950	9.73	98.2
S	1.061	9.87	97.1

Test material content

CGA 108906 tech.

TEST MATERIAL CONTENT

	GROUP 2	GROUP 3	GROUP 4	GROUP 5
NOMINAL (mg/ml)	1	5	20	100
ANALYTICAL (mg/ml)				
study week: 1	1.015	4.914	20.05	96.0
2	1.151	4.951	19.50	97.6
3	1.013	5.001	19.53	100.1
4	1.001	4.886	19.50	99.1
MEAN 1 - 4 (mg/ml)	1.045	4.938	19.65	98.2
MEAN (%)	104.5	98.8	98.3	98.2

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8.3. Functional Observational Battery (means)

Functional domains (mean scores):

males

Dose	group 1 0 mg/kg	group 2 10 mg/kg	group 3 50 mg/kg	group 4 200 mg/kg	group 5 1000 mg/kg
CNS activity (-4,+7)^a					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	-1	-1
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0
CNS excitation (-4,+27)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	1	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0
Autonomic functions (-3,+13)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0
Sensorimotor (-12,0)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0

^a range of scores

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Dose	group 1 0 mg/kg	group 2 10 mg/kg	group 3 50 mg/kg	group 4 200 mg/kg	group 5 1000 mg/kg
Physiological functions (0,+19)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0
Non-specific signs (0,+9)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	2	0	0	0
week 3	0	2	0	0	0
week 4	2	2	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0

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Functional domains (mean scores):

females

Dose	group 1 0 mg/kg	group 2 10 mg/kg	group 3 50 mg/kg	group 4 200 mg/kg	group 5 1000 mg/kg
CNS activity (-4,+7)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	.2	0	0
week 3	0	0	.4	0	0
week 4	0	0	0	.1	0
week 5	0	0	0	0	0
week 6	0	0	0	0	.2
week 7	.2	0	0	0	0
week 8	0	0	0	0	0
CNS excitation (-4,+27)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0
Autonomic functions (-3,+13)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0
Sensorimotor (-12,0)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0

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Dose	group 1 0 mg/kg	group 2 10 mg/kg	group 3 50 mg/kg	group 4 200 mg/kg	group 5 1000 mg/kg
Physiological functions (0,+19)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0
Non-specific signs (0,+9)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
week 5	0	0	0	0	0
week 6	0	0	0	0	0
week 7	0	0	0	0	0
week 8	0	0	0	0	0

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Functional measurements

Abbreviations used: GSF grip strength forepaws (g)
 GSH grip strength hindpaws (g)
 LFS landing foot splay (cm)
 TMP rectal temperature (°C)
 rec. recovery animals

Statistical tests and flags used:

T-test: * if Adj_p ≤ 0.05

Trend test: +/- if Adj_p ≤ 0.05

Measurements (means):

males

Parameter	Dose (mg/kg) Week	group 1	group 2	group 3	group 4	group 5
		0	10	50	200	1000
GSF	4	1217	1076	1180	1305	1305
	4 rec.	1288	.	.	1316	1283
	8 rec.	1893	.	.	2053	1883
GSH	4	639	565	641	611	620
	4 rec.	571	.	.	585	617
	8 rec.	1590	.	.	1523	1600
LFS	4	10.25	10.60	9.90	9.75	10.40
	4 rec.	10.45	.	.	9.95	10.80
	8 rec.	11.35	.	.	10.85	12.10
TMP	4	38.70	38.70	38.68	38.67	38.59
	4 rec.	38.68	.	.	38.66	38.62
	8 rec.	39.00	.	.	39.00	39.00

Measurements (means):

females

Parameter	Dose (mg/kg) Week	group 1	group 2	group 3	group 4	group 5
		0	10	50	200	1000
GSF	4	1152	1084	1039	1134	1113
	4 rec.	1144	.	.	1166	1158
	8 rec.	1790	.	.	1422	1563
GSH	4	599	532	573	552	524
	4 rec.	554	.	.	605	534
	8 rec.	1283	.	.	1378	1390
LFS	4	10.18	9.85	8.35	9.78	9.68
	4 rec.	10.00	.	.	9.15	10.85
	8 rec.	10.95	.	.	9.69	10.30
TMP	4	39.30	39.16	39.22	39.22	39.17
	4 rec.	39.30	.	.	39.22	39.16
	8 rec.	39.56	.	.	39.35	39.68

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.4. Functional observational battery (statistics)

MULTTEST PROCEDURE

Test for continuous variables: T-test of mean
 Tails for continuous tests: Two-tailed
 Strata adjustment? No
 P-value adjustments: Bootstrap
 Center continuous variables? Yes
 Number of resamples: 10000

MULTTEST COEFFICIENTS

Test	1	2	3	4	5
group 2 vs 1	-1	1	0	0	0
group 3 vs 1	-1	0	1	0	0
group 4 vs 1	-1	0	0	1	0
group 5 vs 1	-1	0	0	0	1
trend 1 to 4	-3	-1	1	3	0
trend 1 to 5	-2	-1	0	1	2

MULTTEST COEFFICIENTS (Recovery group)

Contrast	1	4	5
group 4 vs 1	-1	1	0
group 5 vs 1	-1	0	1

Abbreviations used:

GSF grip strength forepaws (g)
 GSH grip strength hindpaws (g)
 LFS landing foot splay (cm)
 TMP body temperature, rectal (° C)

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

78

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

males

week 4

Seed:

53722

MULTTEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
GSF	Mean	1217.000	1076.000	1180.000	1305.000	1304.500
	Std Dev	146.8030	149.3904	156.9235	234.9232	105.7894
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.1328		0.8740	
	group 3 vs 1		0.6888		1.0000	
	group 4 vs 1		0.2474		0.9824	
	group 5 vs 1		0.2500		0.9831	
	trend 1 to 4		0.1469		0.9024	
	trend 1 to 5		0.0273		0.3524	
GSH	Mean	639.0000	565.0000	641.0000	610.5000	619.5000
	Std Dev	104.5573	47.0372	118.2899	132.3600	94.5295
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.2154		0.9685	
	group 3 vs 1		0.9730		1.0000	
	group 4 vs 1		0.5556		1.0000	
	group 5 vs 1		0.6863		1.0000	
	trend 1 to 4		0.9526		1.0000	
	trend 1 to 5		0.9542		1.0000	
LFS	Mean	10.2500	10.6000	9.9000	9.7500	10.4000
	Std Dev	1.5679	0.8023	0.4183	1.7989	2.0823
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.6983		1.0000	
	group 3 vs 1		0.6983		1.0000	
	group 4 vs 1		0.4986		0.9999	
	group 5 vs 1		0.8386		1.0000	
	trend 1 to 4		0.3705		0.9988	
	trend 1 to 5		0.7503		1.0000	
TMP	Mean	38.7000	38.7000	38.6800	38.6667	38.5900
	Std Dev	0.2055	0.1000	0.1643	0.1225	0.2601
	N	10.0000	5.0000	5.0000	9.0000	10.0000

NOTE: Missing values for this variable are not included.

Contrast	Raw_p	Boot_p
group 2 vs 1	1.0000	1.0000
group 3 vs 1	0.8505	1.0000
group 4 vs 1	0.7083	1.0000
group 5 vs 1	0.2095	0.9651
trend 1 to 4	0.6833	1.0000
trend 1 to 5	0.2199	0.9707

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements males week 4 (recovery)

Seed: 53735

MULTTEST TABLES

Variable	Statistic	Class		
		1	4	5
GSF	Mean	1288.000	1316.000	1283.000
	Std Dev	148.8959	206.6216	114.9239
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.7884	1.0000	
	group 5 vs 1	0.9617	1.0000	
GSH	Mean	571.0000	585.0000	617.0000
	Std Dev	62.1892	67.9154	134.1454
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.8177	1.0000	
	group 5 vs 1	0.4538	0.9791	
LFS	Mean	10.4500	9.9500	10.8000
	Std Dev	1.3158	1.0811	2.5824
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.6659	0.9995	
	group 5 vs 1	0.7620	1.0000	
TMP	Mean	38.6800	38.6600	38.6200
	Std Dev	0.2387	0.1140	0.1643
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.8633	1.0000	
	group 5 vs 1	0.6074	0.9989	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

males

week 8 (recovery)

Seed:

53738

MULTTEST TABLES

Variable	Statistic	Class		
		1	4	5
GSF	Mean	1892.500	2052.500	1882.500
	Std Dev	258.3905	279.4246	172.6630
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.3151	0.9101	
	group 5 vs 1	0.9488	1.0000	
GSH	Mean	1590.000	1522.500	1600.000
	Std Dev	89.8784	216.2175	177.4384
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.5410	0.9945	
	group 5 vs 1	0.9273	1.0000	
LFS	Mean	11.3500	10.8500	12.1000
	Std Dev	1.1806	1.0093	2.7191
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.6697	0.9992	
	group 5 vs 1	0.5243	0.9918	
TMP	Mean	39.0000	39.0000	39.0000
	Std Dev	0.2121	0.2121	0.1581
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	1.0000	1.0000	
	group 5 vs 1	1.0000	1.0000	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements females week 4

Seed: 53770

MULTTEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
GSF	Mean	1152.000	1084.000	1039.000	1133.500	1113.000
	Std Dev	89.2935	71.0106	106.2662	92.6778	101.1380
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.1932		0.9533	
	group 3 vs 1		0.0341		0.4217	
	group 4 vs 1		0.6612		1.0000	
	group 5 vs 1		0.3577		0.9982	
	trend 1 to 4		0.4738		0.9999	
	trend 1 to 5		0.7732		1.0000	
GSH	Mean	598.5000	532.0000	573.0000	552.0000	524.0000
	Std Dev	148.2500	64.6723	86.5014	91.2323	83.1932
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.2528		0.9853	
	group 3 vs 1		0.6585		1.0000	
	group 4 vs 1		0.3262		0.9964	
	group 5 vs 1		0.1196		0.8442	
	trend 1 to 4		0.5289		1.0000	
	trend 1 to 5		0.2468		0.9836	
LFS	Mean	10.1750	9.8500	8.3500	9.7750	9.6750
	Std Dev	1.4145	1.3987	1.2575	2.1553	2.1475
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.7459		1.0000	
	group 3 vs 1		0.0751		0.6882	
	group 4 vs 1		0.6255		1.0000	
	group 5 vs 1		0.5422		1.0000	
	trend 1 to 4		0.3231		0.9961	
	trend 1 to 5		0.5761		1.0000	
TMP	Mean	39.3000	39.1600	39.2200	39.2200	39.1700
	Std Dev	0.1826	0.2074	0.1304	0.1814	0.1252
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.1350		0.8790	
	group 3 vs 1		0.3880		0.9991	
	group 4 vs 1		0.2916		0.9936	
	group 5 vs 1		0.0907		0.7575	
	trend 1 to 4		0.4725		0.9999	
	trend 1 to 5		0.2615		0.9874	

Measurements females week 4 (recovery)

Seed:

53778

MULTTEST TABLES

Variable	Statistic	Class		
		1	4	5
GSF	Mean	1144.000	1166.000	1158.000
	Std Dev	50.9166	102.1274	89.6242
	N	5.0000	5.0000	5.0000
Contrast		Raw_p	Boot_p	
group 4 vs 1		0.6853	0.9998	
group 5 vs 1		0.7961	1.0000	
GSH	Mean	554.0000	605.0000	534.0000
	Std Dev	173.1112	99.5615	65.5172
	N	5.0000	5.0000	5.0000
Contrast		Raw_p	Boot_p	
group 4 vs 1		0.5189	0.9930	
group 5 vs 1		0.7988	1.0000	
LFS	Mean	10.0000	9.1500	10.8500
	Std Dev	1.7139	1.4853	2.2122
	N	5.0000	5.0000	5.0000
Contrast		Raw_p	Boot_p	
group 4 vs 1		0.4766	0.9870	
group 5 vs 1		0.4766	0.9870	
TMP	Mean	39.3000	39.2200	39.1600
	Std Dev	0.2449	0.1789	0.1342
	N	5.0000	5.0000	5.0000
Contrast		Raw_p	Boot_p	
group 4 vs 1		0.5214	0.9934	
group 5 vs 1		0.2702	0.8767	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

females

week 8 (recovery)

Seed:

53781

MULTITEST TABLES

Variable	Statistic	Class		
		1	4	5
GSF	Mean	1790.000	1421.875	1562.500
	Std Dev	219.8010	215.1489	213.4171
	N	5.0000	4.0000	5.0000
	Contrast		Raw_p	Boot_p
	group 4 vs 1		0.0276	0.1715
	group 5 vs 1		0.1244	0.5757
GSH	Mean	1282.500	1378.125	1390.000
	Std Dev	72.1327	198.5298	211.2833
	N	5.0000	4.0000	5.0000
	Contrast		Raw_p	Boot_p
	group 4 vs 1		0.4194	0.9710
	group 5 vs 1		0.3387	0.9315
LFS	Mean	10.9500	9.6875	10.3000
	Std Dev	1.3393	1.4631	1.1911
	N	5.0000	4.0000	5.0000
	Contrast		Raw_p	Boot_p
	group 4 vs 1		0.1828	0.7284
	group 5 vs 1		0.4539	0.9824
TMP	Mean	39.5600	39.3500	39.6800
	Std Dev	0.2881	0.3000	0.2387
	N	5.0000	4.0000	5.0000
	Contrast		Raw_p	Boot_p
	group 4 vs 1		0.2786	0.8816
	group 5 vs 1		0.5040	0.9914

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.5. Motor activity (means)

Statistical tests and flags used:

T-test: * if Adj_p ≤ 0.05

Trend test: +/- if Adj_p ≤ 0.05

Total distance (means): males
(cm)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	967	707	606	512	337	310	292	329	187	180	4426
	2	5	1033	941	791	551	744	472	309	304	293	218	5657
	3	5	1084	1094	778	583	393	504	251	309	300	208	5504
	4	9	1062	862	728	490	396	479	311	355	346	275	5304
	5	10	1168	899	647	513	318	403	260	269	164	203	4842
4 rec.	1	5	896	562	578	458	297	356	242	307	273	183	4153
	4	5	1059	856	721	447	394	501	284	318	392	262	5234
	5	5	1308	1037	784	598	433	481	343	404	123	289	5799
8 rec.	1	5	869	523	536	324	329	114	178	217	333	49	3471
	4	5	822	700	383	306	367	338	195	247	238	225	3820
	5	5	995	476	495	293	165	233	164	196	185	180	3383

No. of movements (means): males
(counts)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	46	43	41	35	28	28	23	28	19	19	309
	2	5	44	42	43	38	39	32	26	29	22	21	336
	3	5	44	42	43	38	29	34	23	23	22	16	314
	4	9	43	39	41	36	31	34	25	25	26	21	320
	5	10	43	40	37	31	28	28	23	25	17	16	287
4 rec.	1	5	46	41	41	36	27	28	21	28	24	19	309
	4	5	43	44	40	39	32	36	26	27	23	17	326
	5	5	42	40	39	32	33	32	27	33	14	17	310
8 rec.	1	5	35	27	31	24	25	13	17	16	24	9	221
	4	5	31	32	20	19	20	20	12	17	16	17	204
	5	5	35	20	25	20	14	17	15	11	11	14	183

Movement time (means): males
(sec)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	81	62	53	44	31	27	24	31	15	19	387
	2	5	90	84	67	47	59	39	26	26	21	15	475
	3	5	89	89	62	47	32	39	21	26	26	16	445
	4	9	87	70	59	41	32	40	26	30	29	21	436
	5	10	93	74	54	43	30	34	24	21	16	17	405
4 rec.	1	5	73	51	48	41	28	29	19	30	22	21	363
	4	5	89	73	59	39	33	42	24	28	31	18	436
	5	5	101	82	64	49	42	41	31	32	11	25	476
8 rec.	1	5	69	40	42	29	30	11	16	19	28	5	290
	4	5	58	49	28	25	28	26	14	21	21	20	290
	5	5	69	32	34	26	14	17	15	17	13	16	254

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

85

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical activity (means): males
(counts)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	161	143	109	74	67	65	65	52	41	57	834
	2	5	125	150	133	105	91	106	48	62	47	49	916
	3	5	182	198	143	119	73	85	80	42	57	60	1040
	4	9	149	154	139	114	82	83	64	61	64	74	983
	5	10	154	163	112	80	72	66	45	59	46	61	857
4 rec.	1	5	141	148	96	79	55	57	67	64	71	62	841
	4	5	135	159	144	86	83	91	68	60	65	81	972
	5	5	161	180	138	101	102	82	57	93	57	77	1047
8 rec.	1	5	85	79	55	38	54	20	24	22	68	16	462
	4	5	74	79	27	21	28	37	11	24	32	23	354
	5	5	107	36	51	48	11	20	15	13	25	29	356

No. of rearings (means): males
(counts)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	23	21	15	11	9	9	8	8	6	8	120
	2	5	19	20	20	14	13	14	7	9	7	7	130
	3	5	27	23	19	16	12	12	9	7	8	8	140
	4	9	22	21	18	16	11	12	9	9	9	9	135
	5	10	23	21	17	12	10	11	6	9	6	8	121
4 rec.	1	5	20	21	14	11	8	9	8	9	10	9	118
	4	5	22	23	20	13	12	12	10	8	10	8	137
	5	5	23	22	20	14	12	13	8	13	6	9	139
8 rec.	1	5	14	10	8	6	7	3	3	3	8	3	66
	4	5	12	12	5	3	4	5	3	4	5	3	54
	5	5	17	6	6	6	2	3	2	3	3	4	51

Vertical time (means): males
(sec)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	49	52	47	30	35	31	38	26	22	31	361
	2	5	40	50	47	43	38	46	27	31	21	22	365
	3	5	55	69	55	50	30	41	40	19	28	37	426
	4	9	42	54	52	48	41	37	29	31	30	41	406
	5	10	47	58	48	35	32	34	25	34	37	42	391
4 rec.	1	5	48	55	44	30	24	25	35	28	38	34	361
	4	5	37	60	51	35	48	41	32	31	32	41	409
	5	5	49	61	60	43	46	40	31	49	51	54	484
8 rec.	1	5	28	31	27	18	27	12	15	14	32	6	211
	4	5	23	28	11	8	13	21	5	14	22	13	158
	5	5	36	14	25	18	5	11	10	7	11	15	153

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Center time (means): males
(sec)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	49	47	45	37	36	34	28	46	30	32	383
	2	5	55	70	44	59	47	49	17	26	25	33	426
	3	5	60	74	58	45	54	62	24	24	25	32	458
	4	9	52	43	34	41	43	44	32	36	32	29	387
	5	10	48	51	41	45	32	28	28	26	16	25	340
4 rec.	1	5	43	48	46	36	43	41	26	50	47	37	417
	4	5	56	50	36	49	49	56	38	42	41	40	455
	5	5	50	63	52	57	43	42	46	38	14	26	430
8 rec.	1	5	44	24	20	18	18	12	16	10	21	8	191
	4	5	47	28	18	12	18	18	24	22	32	21	239
	5	5	30	18	16	12	17	18	9	11	5	15	152

Total distance (means): females
(cm)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	1301	1105	843	645	542	486	475	425	507	328	6655
	2	5	1287	1042	957	812	668	618	626	453	369	307	7139
	3	5	1292	944	828	721	406	457	395	373	340	387	6142
	4	10	1264	1146	971	709	684	632	475	458	412	416	7166
	5	10	1219	858	721	540	570	491	366	446	310	353	5873
4 rec.	1	5	1389	1093	901	688	595	451	514	469	504	341	6947
	4	5	1307	1222	1118	876	782	704	588	477	528	448	8051
	5	5	1392	955	896	669	621	608	392	469	311	462	6776
8 rec.	1	5	949	724	449	337	359	258	301	114	265	47	3802
	4	4	852	516	515	217	357	247	228	245	343	90	3610
	5	5	1121	742	417	528	284	406	214	345	217	118	4390

No. of movements (means): females
(counts)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	43	42	41	39	30	32	31	27	27	20	332
	2	5	45	44	40	41	32	33	27	29	24	18	331
	3	5	40	42	39	39	29	33	29	25	25	23	323
	4	10	41	42	36	32	33	34	28	28	23	22	319
	5	10	45	45	40	36	34	29	26	26	22	21	325
4 rec.	1	5	45	42	44	40	33	34	36	30	26	22	353
	4	5	41	41	38	30	34	34	31	27	24	23	323
	5	5	44	48	39	37	33	34	25	25	24	27	336
8 rec.	1	5	40	37	31	23	25	17	21	11	20	9	233
	4	4	31	28	28	17	25	16	16	19	17	8	204
	5	5	35	30	22	27	20	25	16	22	17	14	228

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Movement time (means): females
(sec)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	95	83	65	50	38	36	36	29	33	21	486
	2	5	92	80	69	57	48	44	39	32	26	20	506
	3	5	91	72	63	53	31	35	30	28	22	25	452
	4	10	88	80	67	49	45	46	33	31	28	27	493
	5	10	87	66	55	41	41	35	28	31	23	23	429
4 rec.	1	5	95	84	69	54	42	34	38	31	32	22	502
	4	5	88	79	73	57	49	50	35	31	32	28	523
	5	5	96	72	68	46	43	43	29	30	23	29	480
8 rec.	1	5	61	50	35	27	26	18	23	8	19	4	271
	4	4	54	40	33	16	28	16	14	17	25	7	248
	5	5	71	46	29	34	17	30	15	25	14	8	290

Vertical activity (means): females
(counts)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	195	167	163	155	134	106	104	101	89	81	1294
	2	5	210	187	185	175	122	99	95	103	77	89	1343
	3	5	177	147	115	157	99	92	86	86	91	66	1116
	4	10	169	181	154	122	141	101	82	67	65	86	1169
	5	10	184	163	144	114	103	114	72	77	59	73	1104
4 rec.	1	5	206	196	208	187	145	126	134	109	101	108	1520
	4	5	177	171	180	132	154	134	120	90	86	85	1327
	5	5	182	175	167	148	104	117	72	89	65	89	1208
8 rec.	1	5	121	112	97	65	54	36	55	10	28	17	596
	4	4	122	83	77	54	66	42	40	34	38	10	566
	5	5	126	86	52	71	46	39	28	51	24	17	539

No. of rearings (means): females
(counts)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	27	22	20	16	15	12	13	12	11	10	160
	2	5	27	20	21	19	14	14	13	15	11	12	166
	3	5	24	18	12	16	12	12	12	7	10	10	132
	4	10	24	23	18	16	16	10	10	9	9	11	146
	5	10	24	20	17	15	13	13	11	11	10	9	143
4 rec.	1	5	27	24	22	18	14	12	15	14	13	13	173
	4	5	26	24	22	16	18	11	12	11	12	12	164
	5	5	25	20	19	17	14	14	11	13	10	11	155
8 rec.	1	5	20	16	14	10	8	7	7	2	5	2	90
	4	4	19	12	11	7	9	6	5	5	6	2	82
	5	5	21	12	7	10	8	8	4	7	3	3	83

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical time (means): females
(sec)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	63	61	62	67	70	60	66	58	51	50	606
	2	5	70	77	83	87	60	60	52	53	45	59	647
	3	5	59	62	56	79	64	49	54	42	59	39	563
	4	10	56	68	65	62	82	60	50	44	38	56	581
	5	10	64	67	66	60	58	71	42	55	48	51	580
4 rec.	1	5	62	65	75	76	74	70	82	57	54	69	685
	4	5	59	65	71	63	87	79	70	58	46	49	648
	5	5	61	64	70	73	53	61	44	60	56	63	605
8 rec.	1	5	47	47	47	28	27	16	28	5	18	8	271
	4	4	57	41	48	33	36	31	26	26	29	7	333
	5	5	46	40	30	37	24	20	13	31	19	12	272

Center time (means): females
(sec)

Week	Group	n	S a m p l i n g i n t e r v a l										Session total
			1	2	3	4	5	6	7	8	9	10	
4	1	10	39	42	38	47	31	22	30	33	36	32	350
	2	5	38	43	49	41	43	49	29	40	28	32	391
	3	5	50	30	27	49	48	45	41	23	35	33	381
	4	10	40	54	59	51	52	45	47	42	41	33	464
	5	10	37	48	43	40	50	51	32	31	27	28	387
4 rec.	1	5	35	38	36	34	27	20	23	24	30	23	292
	4	5	39	42	37	32	42	42	43	43	28	23	370
	5	5	38	43	48	50	52	48	39	19	26	29	393
8 rec.	1	5	26	22	17	8	9	9	11	3	17	3	125
	4	4	33	22	28	38	27	32	23	22	16	37	276
	5	5	39	29	17	24	17	20	12	18	11	15	202

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.6. Motor activity (statistics)

MULTTEST PROCEDURE

Test for continuous variables: Mean t-test
 Tails for continuous tests: Two-tailed
 Strata adjustment? No
 P-value adjustments: Bootstrap
 Center continuous variables? Yes
 Number of resamples: 10000

MULTTEST COEFFICIENTS

Contrast	1	2	3	4	5
group 2 vs 1	-1	1	0	0	0
group 3 vs 1	-1	0	1	0	0
group 4 vs 1	-1	0	0	1	0
group 5 vs 1	-1	0	0	0	1
trend 1 to 4	-3	-1	1	3	0
trend 1 to 5	-2	-1	0	1	2

MULTTEST COEFFICIENTS (recovery)

Contrast	1	4	5
group 4 vs 1	-1	1	0
group 5 vs 1	-1	0	1

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

males

week 4

Seed:

39591

MULTTEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
TD_AUC	Mean	4425.500	5657.200	5503.600	5303.556	4841.800
	Std Dev	1348.962	1181.056	2003.537	1737.237	1627.063
	N	10.0000	5.0000	5.0000	9.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.1664		0.8687	
	group 3 vs 1		0.2243		0.9385	
	group 4 vs 1		0.2378		0.9490	
	group 5 vs 1		0.5622		0.9998	
	trend 1 to 4		0.3110		0.9853	
	trend 1 to 5		0.7768		1.0000	
NM_AUC	Mean	309.3000	336.4000	314.2000	320.1111	287.3000
	Std Dev	66.0001	32.3697	54.6461	43.4006	58.7217
	N	10.0000	5.0000	5.0000	9.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.3714		0.9949	
	group 3 vs 1		0.8709		1.0000	
	group 4 vs 1		0.6694		1.0000	
	group 5 vs 1		0.3741		0.9954	
	trend 1 to 4		0.9024		1.0000	
	trend 1 to 5		0.3024		0.9820	
MT_AUC	Mean	387.1000	475.4000	444.6000	435.6667	404.8000
	Std Dev	109.4810	91.5030	137.4929	126.6383	122.9488
	N	10.0000	5.0000	5.0000	9.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.1844		0.8954	
	group 3 vs 1		0.3838		0.9966	
	group 4 vs 1		0.3806		0.9963	
	group 5 vs 1		0.7414		1.0000	
	trend 1 to 4		0.5285		0.9998	
	trend 1 to 5		0.9726		1.0000	
VA_AUC	Mean	834.3000	916.2000	1039.600	982.7778	856.5000
	Std Dev	194.3462	287.7303	369.8206	297.6557	338.0382
	N	10.0000	5.0000	5.0000	9.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.6153		1.0000	
	group 3 vs 1		0.2122		0.9278	
	group 4 vs 1		0.2808		0.9746	
	group 5 vs 1		0.8673		1.0000	
	trend 1 to 4		0.2119		0.9274	
	trend 1 to 5		0.7232		1.0000	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

VM_AUC	Mean	120.0000	129.8000	140.0000	135.4444	121.2000
	Std Dev	27.5600	30.9629	39.8623	35.6024	39.4174
	N	10.0000	5.0000	5.0000	9.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.6104	1.0000
group 3 vs 1	0.3013	0.9816
group 4 vs 1	0.3408	0.9910
group 5 vs 1	0.9390	1.0000
trend 1 to 4	0.2915	0.9787
trend 1 to 5	0.8277	1.0000

VT_AUC	Mean	360.6000	365.0000	426.4000	405.8889	391.0000
	Std Dev	87.8726	128.4971	182.4563	114.8264	192.5236
	N	10.0000	5.0000	5.0000	9.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.9559	1.0000
group 3 vs 1	0.4109	0.9981
group 4 vs 1	0.4991	0.9998
group 5 vs 1	0.6405	1.0000
trend 1 to 4	0.3736	0.9954
trend 1 to 5	0.5082	0.9998

CT_AUC	Mean	383.0000	426.2000	458.0000	386.7778	340.0000
	Std Dev	255.4360	188.3260	269.6359	197.7927	141.6427
	N	10.0000	5.0000	5.0000	9.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.7108	1.0000
group 3 vs 1	0.5207	0.9998
group 4 vs 1	0.9691	1.0000
group 5 vs 1	0.6515	1.0000
trend 1 to 4	0.8936	1.0000
trend 1 to 5	0.5765	0.9999

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

92 -A

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

males

week 4 (recovery)

Seed:

39606

MULTTEST TABLES

Variable	Statistic	Class		
		1	4	5
TD_AUC	Mean	4152.600	5233.800	5799.000
	Std Dev	1649.237	1469.725	1076.013
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.2514	0.8478	
	group 5 vs 1	0.0914	0.4780	
NM_AUC	Mean	309.4000	326.2000	309.6000
	Std Dev	83.3924	30.2109	36.0597
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.6395	0.9997	
	group 5 vs 1	0.9955	1.0000	
MT_AUC	Mean	362.6000	436.4000	476.4000
	Std Dev	135.3322	102.8922	92.2865
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.3167	0.9145	
	group 5 vs 1	0.1331	0.6094	
VA_AUC	Mean	840.6000	972.4000	1047.000
	Std Dev	226.9775	90.9852	228.4743
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.3020	0.9020	
	group 5 vs 1	0.1170	0.5625	
VM_AUC	Mean	118.4000	137.2000	139.2000
	Std Dev	32.6849	25.2131	21.2297
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.2891	0.8913	
	group 5 vs 1	0.2433	0.8349	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

VT_AUC	Mean	360.8000	408.8000	484.0000
	Std Dev	107.1340	54.3755	167.3574
	N	5.0000	5.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.5354	0.9943
group 5 vs 1	0.1274	0.5921

CT_AUC	Mean	417.0000	455.4000	430.2000
	Std Dev	287.9609	209.8912	63.6333
	N	5.0000	5.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.7764	1.0000
group 5 vs 1	0.9221	1.0000

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

males

week 8 (recovery)

Seed:

39611

MULTTEST TABLES

Variable	Statistic	Class		
		1	4	5
TD_AUC	Mean	3470.600	3820.200	3383.000
	Std Dev	1697.825	2858.088	1572.909
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.7990	0.9999	
	group 5 vs 1	0.9491	1.0000	
NM_AUC	Mean	221.0000	203.6000	183.2000
	Std Dev	84.5311	100.9024	64.0679
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.7504	0.9995	
	group 5 vs 1	0.4930	0.9413	
MT_AUC	Mean	289.6000	290.4000	253.8000
	Std Dev	155.8470	191.0466	96.8747
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.9935	1.0000	
	group 5 vs 1	0.7177	0.9982	
VA_AUC	Mean	461.8000	354.2000	355.8000
	Std Dev	254.0722	230.8673	141.1425
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.4427	0.9078	
	group 5 vs 1	0.4493	0.9120	
VM_AUC	Mean	65.6000	54.4000	51.0000
	Std Dev	29.6699	35.2605	15.4110
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.5397	0.9634	
	group 5 vs 1	0.4266	0.8959	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

VT_AUC	Mean	210.8000	158.0000	152.6000
	Std Dev	108.9367	102.7132	60.2354
	N	5.0000	5.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.3879	0.8617
group 5 vs 1	0.3428	0.8112

CT_AUC	Mean	191.2000	239.2000	152.0000
	Std Dev	132.4507	242.9438	142.2428
	N	5.0000	5.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.6801	0.9956
group 5 vs 1	0.7360	0.9990

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

females

week 4

Seed: 39624

MULTTEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
TD_AUC	Mean	6655.000	7139.000	6142.200	7166.300	5872.600
	Std Dev	1859.469	4345.959	2111.777	3879.520	2448.329
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.7697		1.0000	
	group 3 vs 1		0.7564		1.0000	
	group 4 vs 1		0.7049		1.0000	
	group 5 vs 1		0.5628		0.9999	
	trend 1 to 4		0.9045		1.0000	
	trend 1 to 5		0.6275		1.0000	
NM_AUC	Mean	332.4000	331.0000	323.4000	318.8000	324.5000
	Std Dev	54.1955	33.8600	79.3870	36.3709	50.4474
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.9603		1.0000	
	group 3 vs 1		0.7492		1.0000	
	group 4 vs 1		0.5548		0.9999	
	group 5 vs 1		0.7311		1.0000	
	trend 1 to 4		0.5265		0.9998	
	trend 1 to 5		0.6040		1.0000	
MT_AUC	Mean	486.1000	505.6000	451.6000	493.2000	420.5000
	Std Dev	111.8674	215.7587	158.6484	191.9038	135.1618
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.8251		1.0000	
	group 3 vs 1		0.6961		1.0000	
	group 4 vs 1		0.9215		1.0000	
	group 5 vs 1		0.4261		0.9992	
	trend 1 to 4		0.8912		1.0000	
	trend 1 to 5		0.4520		0.9994	
VA_AUC	Mean	1294.300	1342.800	1115.800	1169.400	1104.400
	Std Dev	508.9759	353.5827	449.2457	469.5800	411.2777
	N	10.0000	5.0000	5.0000	10.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.8458		1.0000	
	group 3 vs 1		0.4755		0.9995	
	group 4 vs 1		0.5405		0.9998	
	group 5 vs 1		0.3538		0.9951	
	trend 1 to 4		0.3754		0.9968	
	trend 1 to 5		0.2510		0.9721	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

VM_AUC	Mean	159.8000	166.2000	132.4000	145.8000	142.5000
	Std Dev	41.8298	54.7239	49.5510	44.5541	28.3833
	N	10.0000	5.0000	5.0000	10.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.7841	1.0000
group 3 vs 1	0.2451	0.9690
group 4 vs 1	0.4643	0.9994
group 5 vs 1	0.3668	0.9962
trend 1 to 4	0.2352	0.9645
trend 1 to 5	0.2235	0.9576

VT_AUC	Mean	606.2000	647.4000	562.6000	580.6000	580.1000
	Std Dev	166.8305	80.5779	199.2368	202.9621	215.1167
	N	10.0000	5.0000	5.0000	10.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.6898	1.0000
group 3 vs 1	0.6728	1.0000
group 4 vs 1	0.7612	1.0000
group 5 vs 1	0.7567	1.0000
trend 1 to 4	0.5637	0.9999
trend 1 to 5	0.5477	0.9999

CT_AUC	Mean	349.5000	390.6000	381.0000	464.0000	386.6000
	Std Dev	129.7495	151.4804	203.5203	205.6594	228.6847
	N	10.0000	5.0000	5.0000	10.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.6949	1.0000
group 3 vs 1	0.7636	1.0000
group 4 vs 1	0.1859	0.9231
group 5 vs 1	0.6647	1.0000
trend 1 to 4	0.2435	0.9684
trend 1 to 5	0.4633	0.9994

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

females

week 4 (recovery)

Seed:

39639

MULTTEST TABLES

Variable	Statistic	Class		
		1	4	5
TD_AUC	Mean	6947.400	8051.000	6775.800
	Std Dev	2004.191	5235.316	2747.827
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.6370	0.9983	
	group 5 vs 1	0.9412	1.0000	
NM_AUC	Mean	352.8000	322.8000	335.6000
	Std Dev	43.6772	32.6680	47.9302
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.2799	0.8359	
	group 5 vs 1	0.5287	0.9897	
MT_AUC	Mean	501.8000	522.6000	480.4000
	Std Dev	130.9569	257.8600	131.6028
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.8607	1.0000	
	group 5 vs 1	0.8567	1.0000	
VA_AUC	Mean	1519.600	1327.400	1208.000
	Std Dev	595.9105	554.0828	436.2253
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.5791	0.9958	
	group 5 vs 1	0.3736	0.9259	
VM_AUC	Mean	172.6000	164.2000	155.0000
	Std Dev	44.1509	52.5328	25.0200
	N	5.0000	5.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.7582	1.0000	
	group 5 vs 1	0.5218	0.9893	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

VT_AUC	Mean	684.6000	648.2000	604.8000
	Std Dev	159.6490	202.4727	172.1459
	N	5.0000	5.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.7533	1.0000
group 5 vs 1	0.4943	0.9841

CT_AUC	Mean	291.8000	370.4000	392.6000
	Std Dev	114.1433	201.9228	245.2230
	N	5.0000	5.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.5356	0.9908
group 5 vs 1	0.4294	0.9612

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements

females

week 8 (recovery)

Seed:

39644

MULTTEST TABLES

Variable	Statistic	Class		
		1	4	5
TD_AUC	Mean	3802.200	3610.000	4390.400
	Std Dev	2264.702	2572.942	3366.167
	N	5.0000	4.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.9201	1.0000	
	group 5 vs 1	0.7452	0.9978	
NM_AUC	Mean	232.6000	203.7500	227.8000
	Std Dev	113.2974	124.3205	110.0486
	N	5.0000	4.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.7162	0.9964	
	group 5 vs 1	0.9487	1.0000	
MT_AUC	Mean	270.8000	247.5000	290.4000
	Std Dev	148.5251	175.3710	187.0422
	N	5.0000	4.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.8425	0.9999	
	group 5 vs 1	0.8592	1.0000	
VA_AUC	Mean	595.6000	565.5000	538.6000
	Std Dev	413.6729	430.9196	361.7559
	N	5.0000	4.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.9128	1.0000	
	group 5 vs 1	0.8261	0.9999	
VM_AUC	Mean	90.2000	81.7500	83.0000
	Std Dev	59.5206	59.8686	47.3075
	N	5.0000	4.0000	5.0000
	Contrast	Raw_p	Boot_p	
	group 4 vs 1	0.8246	0.9999	
	group 5 vs 1	0.8412	0.9999	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

VT_AUC	Mean	271.2000	332.7500	272.4000
	Std Dev	153.4852	285.8804	202.5890
	N	5.0000	4.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.6763	0.9915
group 5 vs 1	0.9931	1.0000

CT_AUC	Mean	125.0000	275.7500	202.0000
	Std Dev	82.2101	343.4389	150.0117
	N	5.0000	4.0000	5.0000

Contrast	Raw_p	Boot_p
group 4 vs 1	0.3006	0.7269
group 5 vs 1	0.5681	0.9642

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.7. Body weight (means)Statistical tests and flags used:LEPAGE: * if $p_L < 0.05$ JONCKHEERE: +- if $p_J < 0.01$ Body weight (means) : males
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	166.9	167.6	165.8	167.4	170.2
1	216.8	215.0	217.3	217.1	223.6
2	261.9	260.7	265.4	261.0	268.2
3	294.2	294.8	304.8	296.0*	299.6
4	321.0	320.5	336.6	329.9	327.9
recovery					
week: 5	324.7			333.7	340.8
6	344.8			352.4	359.8
7	360.8			372.9	384.0
8	370.4			379.8	394.1

Statistical tests and flags used:LEPAGE: * if $p_L < 0.05$ JONCKHEERE: +- if $p_J < 0.01$ Body weight (means) : females
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	141.1	140.8	144.3	143.1	142.7
1	162.5	162.5	159.7	164.6	162.4
2	181.8	180.7	182.6	182.9	184.3
3	197.8	195.9	202.3	198.8	200.7
4	218.0	216.1	219.0	220.8	218.5
recovery					
week: 5	221.4			235.0	222.7
6	229.1			242.2	231.3
7	240.0			253.8	237.7
8	250.1			257.0	249.4

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.8. Body weight (statistics)

Statistical tests and flags used:

LEPAGE: * if $p_L < 0.05$

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if $p_J < 0.01$ Body weight (statistics) : males
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1 N	10	5	5	10	10
Mean	166.9	167.6	165.8	167.4	170.2
SD	4.940	4.499	10.98	8.036	9.321
Median	166.4	169.3	163.1	169.0	169.1
IQ-Range	7.000	1.685	17.71	9.571	9.200
Min	160.7	159.7	153.3	155.3	158.0
Max	176.4	170.4	178.5	180.9	184.9
p_L		0.875	0.120	0.698	0.531
p_J		0.624	0.972	0.751	0.382
week: 1 N	10	5	5	10	10
Mean	216.8	215.0	217.3	217.1	223.6
SD	8.257	10.82	14.07	12.43	12.82
Median	215.8	219.6	213.2	215.6	223.1
IQ-Range	13.83	8.128	20.01	14.17	14.74
Min	205.5	197.3	204.2	198.8	207.1
Max	227.8	224.8	237.3	239.6	244.5
p_L		0.786	0.431	0.891	0.610
p_J		0.806	0.972	0.985	0.297
week: 2 N	10	5	5	10	10
Mean	261.9	260.7	265.4	261.0	268.2
SD	9.236	11.06	18.12	16.83	12.05
Median	260.6	258.5	256.1	259.7	269.2
IQ-Range	16.17	9.586	26.56	25.86	20.50
Min	251.4	248.1	250.3	231.6	249.1
Max	276.0	277.4	290.8	287.7	286.6
p_L		0.987	0.203	0.097	0.460
p_J		1.000	0.915	0.751	0.382

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

104

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Body weight (statistics) : males
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 3 N	10	5	5	10	10
Mean	294.2	294.8	304.8	296.0	299.6
SD	10.39	13.90	22.80	24.06	13.74
Median	293.1	287.6	295.3	292.7	301.3
IQ-Range	15.51	12.19	30.61	32.16 b	18.82
Min	273.7	283.8	286.4	250.7	275.1
Max	308.5	317.5	338.9	324.2	320.9
p_L		0.536	0.475	0.024 *	0.463
p_J		0.713	0.749	0.925	0.657
week: 4 N	10	5	5	9	10
Mean	321.0	320.5	336.6	329.9	327.9
SD	15.38	16.24	28.17	21.21	15.66
Median	323.8	321.0	333.1	328.6	333.3
IQ-Range	13.52	14.70	46.66	37.76	23.24
Min	293.6	304.5	308.8	303.3	302.6
Max	351.3	345.8	372.5	353.9	353.7
p_L		0.875	0.126	0.101	0.249
p_J		0.624	0.499	0.377	0.326
recovery					
week: 5 N	5			5	5
Mean	324.7			333.7	340.8
SD	13.98			20.80	18.91
Median	325.2			323.6	339.2
IQ-Range	11.16			25.23	15.96
Min	303.0			312.6	318.0
Max	339.9			363.1	368.6
p_L				0.664	0.472
p_J				0.754	0.316
week: 6 N	5			5	5
Mean	344.8			352.4	359.8
SD	16.76			22.45	20.77
Median	347.9			343.0	354.7
IQ-Range	25.26			26.16	9.257
Min	324.1			327.7	343.2
Max	364.0			383.6	395.6
p_L				0.797	0.449
p_J				0.602	0.224

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Body weight (statistics) : males
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 7 N	5			5	5
Mean	360.8			372.9	384.0
SD	19.58			27.17	26.41
Median	362.1			363.3	381.3
IQ-Range	32.37			26.59	26.84
Min	337.0			341.6	359.2
Max	381.8			412.0	425.4
p_L				0.700	0.398
p_J				0.465	0.154
week: 8 N	5			5	5
Mean	370.4			379.8	394.1
SD	21.35			24.18	26.07
Median	370.8			371.6	389.4
IQ-Range	41.14			18.24	13.16
Min	348.0			355.7	374.7
Max	392.2			418.6	439.0
p_L				0.609	0.152
p_J				0.602	0.154

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

LEPAGE: * if p_L < 0.05

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if p_J < 0.01Body weight (statistics) : females
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1 N	10	5	5	10	10
Mean	141.1	140.8	144.3	143.1	142.7
SD	8.299	7.186	6.296	7.294	6.721
Median	140.4	142.5	140.1	143.0	143.7
IQ-Range	10.34	6.471	10.07	9.728	6.471
Min	129.4	129.8	139.2	130.0	130.4
Max	153.3	148.6	152.3	156.0	151.9
p _L		0.667	0.268	0.660	0.513
p _J		0.903	0.414	0.421	0.408
week: 1 N	10	5	5	10	10
Mean	162.5	162.5	159.7	164.6	162.4
SD	13.90	5.720	6.977	9.543	8.861
Median	159.3	163.7	159.5	163.7	163.3
IQ-Range	22.54	6.572	9.571	10.04	10.91
Min	144.1	153.6	151.4	148.3	145.4
Max	183.1	167.3	168.6	183.8	175.8
p _L		0.103	0.361	0.216	0.182
p _J		0.806	0.804	0.588	0.675
week: 2 N	10	5	5	10	10
Mean	181.8	180.7	182.6	182.9	184.3
SD	11.68	9.984	10.97	10.16	12.65
Median	177.6	183.0	178.3	181.6	184.1
IQ-Range	19.71	1.257	11.13	11.34	18.36
Min	166.2	163.6	172.5	167.7	161.1
Max	201.2	189.9	199.8	203.1	199.7
p _L		0.861	0.914	0.596	0.751
p _J		0.713	0.804	0.667	0.422
week: 3 N	10	5	5	10	10
Mean	197.8	195.9	202.3	198.8	200.7
SD	11.14	4.591	11.97	7.756	13.36
Median	196.7	195.0	200.7	199.8	201.8
IQ-Range	16.91	4.486	8.157	11.40	18.61
Min	180.8	192.1	191.7	181.8	181.2
Max	214.1	203.4	222.2	207.3	220.4
p _L		0.557	0.826	0.457	0.698
p _J		0.540	0.859	0.537	0.479

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Body weight (statistics) : females
(g/animal)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 4 N	10	5	5	10	10
Mean	218.0	216.1	219.0	220.8	218.5
SD	16.32	9.979	17.28	14.86	13.08
Median	218.4	213.8	214.7	215.6	219.7
IQ-Range	28.99	9.957	4.872	25.50	23.76
Min	196.4	202.8	202.6	202.0	200.4
Max	246.7	228.9	248.3	246.4	238.5
p_L		0.628	0.810	0.899	0.861
p_J		0.713	0.804	0.911	0.811
recovery					
week: 5 N	5			4	5
Mean	221.4			235.0	222.7
SD	18.79			24.92	15.44
Median	215.5			237.2	219.9
IQ-Range	20.04			41.81	10.60
Min	203.8			207.0	211.4
Max	250.6			258.5	249.0
p_L				0.536	0.424
p_J					0.770
week: 6 N	5			4	5
Mean	229.1			242.2	231.3
SD	18.70			24.24	12.68
Median	221.1			243.9	230.4
IQ-Range	22.32			38.31	9.386
Min	214.1			213.0	220.8
Max	258.1			268.2	252.3
p_L				0.769	0.207
p_J					0.953
week: 7 N	5			4	5
Mean	240.0			253.8	237.7
SD	17.22			25.78	13.57
Median	237.1			254.3	235.7
IQ-Range	18.63			44.04	8.757
Min	223.7			227.6	224.3
Max	266.7			278.9	259.9
p_L				0.536	0.694
p_J					0.953

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Body weight (statistics) : females
(g/animal)

Dose(mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	8 N	5			4	5
	Mean	250.1			257.0	249.4
	SD	21.80			24.29	13.83
	Median	250.6			257.3	245.1
	IQ-Range	31.94			39.97	5.415
	Min	226.4			230.1	239.4
	Max	278.7			283.2	273.5
	p _L				0.769	0.236
	p _J					0.953

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.9. Food consumption (means)

Statistical tests and flags used:

LEPAGE: * if $p_L < 0.05$ JONCKHEERE: +- if $p_J < 0.01$ Food consumption (means): males
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	181.5	177.2	182.6	175.9	186.9
1	195.1	194.3	200.5	190.6	201.9
2	203.4	207.8	217.4	202.0	212.5
3	199.1	202.1	222.2	199.2*	207.9
4	190.2	189.0	213.6	176.0*	200.2
recovery					
week: 5	177.1			174.8	183.3
6	193.7			193.1	202.1
7	175.7			178.1	195.4
8	177.7			177.2	182.7

Statistical tests and flags used:

LEPAGE: * if $p_L < 0.05$ JONCKHEERE: +- if $p_J < 0.01$ Food consumption (means): females
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	146.5	136.3	140.7	140.0	138.8
1	146.7	146.4	149.0	141.7	143.4
2	154.9	148.0	146.9	152.6	151.5
3	159.6	153.3	155.9	154.3	153.5
4	146.3	149.5	150.2	134.7	144.7
recovery					
week: 5	134.4			134.9	142.9
6	154.7			144.9	145.9
7	142.9			135.1	138.3
8	137.7			130.8	132.6

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.10. Food consumption (statistics)Statistical tests and flags used:LEPAGE: * if $p_L < 0.05$

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if $p_J < 0.01$ Food consumption (statistics) : males
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1 N	10	5	5	10	10
Mean	181.5	177.2	182.6	175.9	186.9
SD	11.47	8.495	17.15	14.85	14.25
Median	181.5	180.7	174.7	174.0	185.8
IQ-Range	17.10	1.300	18.80	25.70	24.60
Min	163.7	162.0	164.4	156.8	167.7
Max	198.9	181.6	207.2	202.1	205.9
p_L		0.145	0.362	0.463	0.347
p_J		0.540	0.722	0.270	0.692
week: 1 N	10	5	5	10	10
Mean	195.1	194.3	200.5	190.6	201.9
SD	13.01	7.797	20.77	17.00	12.14
Median	192.8	193.0	199.1	188.2	203.1
IQ-Range	22.60	9.400	16.30	24.80	19.20
Min	178.2	185.2	170.2	171.7	182.5
Max	212.7	205.0	226.1	218.6	217.6
p_L		0.268	0.826	0.195	0.474
p_J		1.000	0.499	0.640	0.395
week: 2 N	10	5	5	10	10
Mean	203.4	207.8	217.4	202.0	212.5
SD	12.65	6.038	18.61	19.07	11.42
Median	206.5	210.6	218.7	202.6	212.7
IQ-Range	12.60	9.200	33.00	30.80	18.20
Min	179.8	200.3	195.1	171.5	197.1
Max	220.4	214.0	235.8	231.9	234.4
p_L		0.638	0.203	0.245	0.352
p_J		0.391	0.145	0.911	0.344

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (statistics) : males
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 3 N	10	5	5	10	10
Mean	199.1	202.1	222.2	199.2	207.9
SD	10.58	4.545	21.16	18.60	12.91
Median	201.7	203.7	230.8	202.1	208.2
IQ-Range	16.50	6.900	32.70	31.60 b	20.90
Min	182.0	196.8	198.8	170.2	189.4
Max	211.6	207.3	246.5	220.3	229.1
p_L		0.062	0.157	0.014 *	0.211
p_J		0.903	0.110	0.614	0.286
week: 4 N	10	5	5	10	10
Mean	190.2	189.0	213.6	176.0	200.2
SD	11.37	6.540	21.06	64.48	10.40
Median	189.8	188.0	219.3	193.1	201.8
IQ-Range	17.15	5.250	36.63	42.00 b	12.25
Min	172.4	181.7	189.5	1.400	182.8
Max	209.1	199.0	235.6	220.2	216.2
p_L		0.213	0.157	0.004 *	0.143
p_J		0.854	0.102	0.708	0.250
recovery					
week: 5 N	5			5	5
Mean	177.1			174.8	183.3
SD	10.05			14.81	16.82
Median	180.4			169.1	180.4
IQ-Range	17.03			25.08	20.30
Min	164.5			158.9	161.8
Max	186.6			191.0	204.5
p_L				0.442	0.639
p_J				0.917	0.460
week: 6 N	5			5	5
Mean	193.7			193.1	202.1
SD	15.01			16.25	13.51
Median	190.4			189.7	202.5
IQ-Range	24.60			17.70	20.60
Min	175.7			176.8	187.2
Max	209.4			217.8	219.2
p_L				0.995	0.472
p_J				0.917	0.267

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (statistics) : males
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 7 N	5			5	5
Mean	175.7			178.1	195.4
SD	7.839			13.20	11.36
Median	172.9			173.8	198.3
IQ-Range	13.60			18.70	11.60
Min	167.6			165.6	182.0
Max	184.5			196.7	211.1
p_L				0.424	0.082
p_J				0.754	0.023
week: 8 N	5			5	5
Mean	177.7			177.2	182.7
SD	11.10			15.51	17.46
Median	177.0			175.5	179.7
IQ-Range	12.95			16.92	7.583
Min	162.4			161.9	159.8
Max	190.8			200.9	208.4
p_L				0.870	0.873
p_J				0.754	0.712

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

113

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

LEPAGE: * if p_L < 0.05
 a/b ind. of diff. in loc./disp.
 JONCKHEERE: +- if p_J < 0.01

Food consumption (statistics): females
 (g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1 N	10	5	5	10	10
Mean	146.5	136.3	140.7	140.0	138.8
SD	11.89	4.209	10.78	9.706	9.743
Median	147.6	137.2	137.8	142.7	136.6
IQ-Range	20.40	2.800	6.000	16.40	10.00
Min	129.0	129.6	131.5	124.7	123.3
Max	163.4	140.8	159.0	150.3	158.7
p _L		0.091	0.611	0.318	0.274
p _J		0.142	0.189	0.322	0.204
week: 1 N	10	5	5	10	10
Mean	146.7	146.4	149.0	141.7	143.4
SD	15.14	5.827	13.90	7.420	11.66
Median	145.5	147.1	149.1	141.7	137.9
IQ-Range	26.70	5.500	12.50	10.70	19.90
Min	127.4	138.5	137.0	129.9	128.9
Max	168.2	154.0	171.3	150.4	163.3
p _L		0.062	0.465	0.119	0.383
p _J		0.903	0.696	0.513	0.408
week: 2 N	10	5	5	10	10
Mean	154.9	148.0	146.9	152.6	151.5
SD	14.78	30.35	17.88	15.82	12.34
Median	152.5	140.8	144.0	153.2	150.8
IQ-Range	26.20	15.50	5.600	23.10	20.90
Min	135.9	119.4	124.5	126.9	134.6
Max	175.5	198.8	174.3	177.0	170.6
p _L		0.312	0.753	0.957	0.739
p _J		0.270	0.374	0.970	0.990
week: 3 N	10	5	5	10	10
Mean	159.6	153.3	155.9	154.3	153.5
SD	13.88	11.65	9.461	15.17	14.35
Median	165.8	152.0	152.7	147.6	151.5
IQ-Range	21.30	9.600	6.100	20.80	24.00
Min	136.4	136.0	146.5	138.6	138.2
Max	174.1	166.8	171.3	186.1	177.3
p _L		0.268	0.361	0.520	0.592
p _J		0.391	0.546	0.239	0.231

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (statistics) : females
(g/animal/week)

Dose(mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 4 N	10	5	5	10	10
Mean	146.3	149.5	150.2	134.7	144.7
SD	13.03	14.49	14.05	27.58	11.41
Median	145.9	147.1	143.0	132.4	143.4
IQ-Range	20.18	6.883	16.57	35.70	15.52
Min	127.6	134.4	137.9	96.02	130.3
Max	167.0	173.3	171.4	187.7	167.2
p_L		0.861	0.764	0.128	0.644
p_J		0.713	0.619	0.304	0.510
recovery					
week: 5 N	5			4	5
Mean	134.4			134.9	142.9
SD	12.11			17.50	15.42
Median	137.0			135.2	141.8
IQ-Range	12.02			30.10	15.05
Min	119.1			117.7	128.8
Max	150.7			151.3	167.3
p_L				0.326	0.643
p_J					0.447
week: 6 N	5			4	5
Mean	154.7			144.9	145.9
SD	13.57			12.46	16.28
Median	157.7			146.1	142.5
IQ-Range	15.60			20.40	21.80
Min	133.7			130.2	130.3
Max	166.8			157.2	169.5
p_L				0.313	0.449
p_J					0.320
week: 7 N	5			4	5
Mean	142.9			135.1	138.3
SD	14.24			12.43	13.61
Median	152.1			134.7	135.3
IQ-Range	19.60			18.90	26.40
Min	122.8			120.8	125.6
Max	154.3			150.0	153.2
p_L				0.313	0.603
p_J					0.520

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (statistics) : females
(g/animal/week)

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	8 N	5			4	5
	Mean	137.7			130.8	132.6
	SD	12.29			18.53	8.274
	Median	140.2			126.0	133.5
	IQ-Range	14.35			22.34	11.32
	Min	125.8			114.0	121.0
	Max	155.5			157.3	141.1
	p _L				0.456	0.609
	p _J					0.770

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.11. Food consumption ratios (means)No statistical tests performedFood consumption ratios (means) : males
(g food/kg body weight/day)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	155.3	150.9	157.2	150.0	156.7
1	128.7	129.3	131.6	125.3	129.1
2	111.0	114.0	117.0	110.4	113.2
3	96.67	98.05	104.1	96.09	99.13
4	84.69	84.43	90.59	84.43	87.27
recovery					
week: 5	78.03			74.75	76.71
6	80.24			78.27	80.32
7	69.63			68.25	72.78
8	68.53			66.63	66.15

No statistical tests performedFood consumption ratios (means) : females
(g food/kg body weight/day)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	148.3	138.8	139.2	139.9	139.0
1	129.1	128.9	133.3	123.2	126.2
2	121.7	116.7	114.7	119.2	117.5
3	115.2	111.8	110.1	110.9	109.3
4	95.92	99.21	97.96	86.70	94.74
recovery					
week: 5	86.86			81.85	91.55
6	96.54			85.55	90.04
7	85.03			76.16	83.24
8	78.74			72.68	76.04

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.12. Water consumption (means)Statistical tests and flags used:LEPAGE: * if $p_L < 0.05$ JONCKHEERE: +- if $p_J < 0.01$ Water consumption (means) : males
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	213.5	202.2	225.7	199.9	213.9
1	207.5	222.6	223.6	201.0	229.3
2	223.2	230.4	264.0	220.9	263.7**
3	218.9	222.5	264.6	202.7	236.4*
4	212.4	211.1	255.9	182.6	229.9
recovery					
week: 5	220.9			220.5	246.3
6	205.7			213.5	226.5
7	213.2			206.5	268.0
8	233.8			233.0	243.9

Statistical tests and flags used:LEPAGE: * if $p_L < 0.05$ JONCKHEERE: +- if $p_J < 0.01$ Water consumption (means) : females
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1	179.5	182.7	187.3	193.5	177.2
1	181.3	169.0	163.8	185.4	185.6
2	178.2	172.1	204.1	186.1	195.6
3	183.3	173.6	166.0	197.9	187.6
4	161.4	155.0	193.1	181.0	177.0
recovery					
week: 5	193.3			204.9	209.2
6	198.5			189.9	198.4
7	201.9			174.1	190.5
8	197.4			190.6	233.0

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.13. Water consumption (statistics)Statistical tests and flags used:LEPAGE: * if p_L < 0.05

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if p_J < 0.01

Water consumption (statistics) : males

(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1 N	10	5	5	10	10
Mean	213.5	202.2	225.7	199.9	213.9
SD	34.00	9.358	40.71	11.01	15.17
Median	199.5	198.1	210.0	198.1	212.8
IQ-Range	20.30	4.200	21.00	16.80	18.90
Min	182.7	195.3	186.9	184.8	191.1
Max	288.4	218.4	293.3	214.9	241.5
p _L		0.860	0.586	0.823	0.146
p _J		0.713	0.455	0.562	0.338
week: 1 N	10	5	5	10	10
Mean	207.5	222.6	223.6	201.0	229.3
SD	32.37	26.76	32.58	21.69	18.80
Median	200.6	214.9	222.6	203.0	233.5
IQ-Range	28.00	9.100	27.30	31.50	18.20
Min	174.3	203.7	191.1	159.6	191.8
Max	279.3	269.5	275.1	230.3	247.8
p _L		0.184	0.611	0.997	0.126
p _J		0.126	0.136	0.970	0.061
week: 2 N	10	5	5	10	10
Mean	223.2	230.4	264.0	220.9	263.7
SD	35.97	21.32	46.49	16.88	26.22
Median	216.7	235.2	243.6	221.2	261.5 a
IQ-Range	28.00	37.10	25.20	11.20	25.20
Min	175.0	206.5	231.0	191.8	232.4
Max	303.1	253.4	344.4	252.7	320.6
p _L		0.699	0.124	0.267	0.008 *
p _J		0.426	0.043	0.808	0.007 +

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (statistics) : males
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 3 N	10	5	5	10	10
Mean	218.9	222.5	264.6	202.7	236.4
SD	58.51	27.90	79.17	29.67	26.82
Median	191.8	234.5	250.6	204.1	232.1
IQ-Range	75.60	39.90	37.10	49.00	32.90
Min	168.7	184.8	200.9	166.6	193.2
Max	358.4	249.9	400.4	245.7	276.5
p_L		0.320	0.178	0.859	0.019 *
p_J		0.540	0.110	0.667	0.303
week: 4 N	10	5	5	10	10
Mean	212.4	211.1	255.9	182.6	229.9
SD	44.54	47.40	76.15	35.76	32.15
Median	201.3	197.4	237.3	194.6	228.6
IQ-Range	46.20	67.90	18.90	28.70	54.60
Min	165.2	153.3	189.7	94.50	186.2
Max	315.0	266.0	387.1	220.5	287.7
p_L		0.845	0.335	0.296	0.212
p_J		0.903	0.241	0.369	0.388
recovery					
week: 5 N	5			5	5
Mean	220.9			220.5	246.3
SD	22.18			24.69	13.89
Median	222.6			219.1	245.7
IQ-Range	21.00			16.10	20.30
Min	196.7			186.2	232.4
Max	254.1			254.1	265.3
p_L				0.977	0.095
p_J				1.000	0.057
week: 6 N	5			5	5
Mean	205.7			213.5	226.5
SD	40.61			15.46	43.64
Median	212.8			206.5	231.7
IQ-Range	20.30			5.600	70.70
Min	138.6			204.4	173.6
Max	246.4			240.8	274.4
p_L				0.514	0.341
p_J				0.676	0.751

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (statistics) : males
(g/animal/week)

Dose(mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 7 N	5			5	5
Mean	213.2			206.5	268.0
SD	58.96			29.12	59.20
Median	195.3			192.5	241.5
IQ-Range	79.10			38.50	95.90
Min	161.0			176.4	202.3
Max	300.3			245.7	331.1
p_L				0.442	0.278
p_J				0.917	0.101
week: 8 N	5			5	5
Mean	233.8			233.0	243.9
SD	43.95			72.36	25.15
Median	226.1			196.7	254.8
IQ-Range	33.60			21.00	42.70
Min	198.8			192.5	216.3
Max	307.3			361.2	270.2
p_L				0.224	0.700
p_J				0.251	0.673

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

LEPAGE: * if p_L < 0.05

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if p_J < 0.01

Water consumption (statistics) : females
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: -1 N	10	5	5	10	10
Mean	179.5	182.7	187.3	193.5	177.2
SD	22.81	32.90	15.56	22.29	21.13
Median	174.7	184.8	184.1	195.0	183.1
IQ-Range	25.20	28.00	16.10	30.80	16.80
Min	154.7	143.5	167.3	165.2	126.0
Max	232.4	231.0	207.9	233.8	200.9
p _L		0.569	0.441	0.266	0.750
p _J		0.903	0.394	0.100	0.557
week: 1 N	10	5	5	10	10
Mean	181.3	169.0	163.8	185.4	185.6
SD	25.31	39.58	13.45	48.24	28.53
Median	180.3	147.0	163.1	182.0	183.8
IQ-Range	11.90	44.10	21.00	49.70	16.80
Min	134.4	140.7	147.0	106.4	123.2
Max	231.0	231.7	178.5	261.8	238.7
p _L		0.251	0.153	0.340	0.679
p _J		0.540	0.214	0.955	0.344
week: 2 N	10	5	5	10	10
Mean	178.2	172.1	204.1	186.1	195.6
SD	31.77	26.79	35.54	33.20	27.11
Median	181.3	177.1	200.9	182.0	198.8
IQ-Range	47.60	18.20	24.50	53.90	44.80
Min	127.4	129.5	173.6	143.5	156.1
Max	226.8	200.9	263.2	242.9	239.4
p _L		0.361	0.383	0.830	0.459
p _J		0.713	0.320	0.454	0.200
week: 3 N	10	5	5	10	10
Mean	183.3	173.6	166.0	197.9	187.6
SD	38.28	27.44	51.55	57.78	26.09
Median	186.9	172.2	147.0	186.9	184.5
IQ-Range	45.50	44.10	39.90	84.70	33.60
Min	134.4	140.7	129.5	132.3	145.6
Max	256.9	204.4	253.4	305.9	233.8
p _L		0.989	0.229	0.465	0.931
p _J		0.903	0.241	0.955	0.565

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (statistics) : females
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 4 N	10	5	5	10	10
Mean	161.4	155.0	193.1	181.0	177.0
SD	40.18	31.65	42.01	51.98	35.92
Median	173.6	165.2	172.2	161.4	170.5
IQ-Range	66.50	41.30	51.10	106.4	39.20
Min	106.4	107.1	156.8	123.2	135.1
Max	215.6	181.3	256.2	255.5	249.2
p_L		0.785	0.629	0.751	0.474
p_J		0.806	0.477	0.525	0.472
recovery					
week: 5 N	5			4	5
Mean	193.3			204.9	209.2
SD	29.24			37.10	29.76
Median	200.2			201.6	200.2
IQ-Range	15.40			61.95	4.900
Min	150.5			169.4	182.7
Max	231.0			247.1	260.4
p_L				0.569	0.861
p_J					0.520
week: 6 N	5			4	5
Mean	198.5			189.9	198.4
SD	23.00			46.79	38.79
Median	200.9			185.5	186.2
IQ-Range	20.30			76.65	36.40
Min	165.9			143.5	148.4
Max	227.5			245.0	249.9
p_L				0.137	0.424
p_J					0.953
week: 7 N	5			4	5
Mean	201.9			174.1	190.5
SD	51.04			14.03	31.13
Median	207.2			174.7	198.1
IQ-Range	67.20			22.05	26.60
Min	135.1			157.5	144.2
Max	262.5			189.7	226.8
p_L				0.175	0.207
p_J					0.815

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (statistics) : females
(g/animal/week)

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 8 N	5			4	5
Mean	197.4			190.6	233.0
SD	51.60			52.05	65.23
Median	224.0			177.5	216.3
IQ-Range	80.50			64.05	109.2
Min	135.8			142.8	162.4
Max	249.9			264.6	308.7
p _L				0.913	0.765
p _J					0.320

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.14. Hematology (means)

Statistical tests and flags used:

LEPAGE: * if p_L < 0.05
 JONCKHEERE: +- if p_J < 0.01

Hematology (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
RBC (T/l)					
week: 5	8.151	8.176	8.208	8.077	8.071
9	9.094			8.728	8.724
Hb (mmol/l)					
week: 5	9.620	9.700	9.780*	9.633	9.670
9	9.720			9.700	9.760
Hct (l)					
week: 5	0.470	0.471	0.475	0.469	0.475
9	0.484			0.477	0.484
MCV (fl)					
week: 5	57.65	57.68	57.94	58.09	58.81
9	53.18			54.72	55.44
RDW (l)					
week: 5	0.118	0.117	0.114	0.115	0.120
9	0.140			0.133	0.128
MCH (fmol)					
week: 5	1.183	1.188	1.190	1.193	1.198
9	1.066			1.114	1.118*+
MCHC (mmol/l)					
week: 5	20.49	20.60	20.54	20.53	20.39
9	20.08			20.35	20.20

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

Test No.: 963128

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Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
HDW (mmol/l)					
week: 5	1.698	1.710	1.556	1.651	1.602
9	1.512			1.674	1.684
WBC (G/l)					
week: 5	10.59	12.22	12.69*	11.55	11.92
9	9.322			11.14	10.55
Neut (1)					
week: 5	0.092	0.095	0.079	0.085	0.096
9	0.097			0.134	0.101
Eos (1)					
week: 5	0.008	0.005	0.008	0.008	0.009
9	0.012			0.011	0.009
Baso (1)					
week: 5	0.006	0.007	0.006	0.005	0.006
9	0.005			0.006	0.005
Lympho (1)					
week: 5	0.845	0.839	0.846	0.849	0.829
9	0.826			0.785	0.823
Mono (1)					
week: 5	0.030	0.034	0.040	0.034	0.040*
9	0.034			0.042	0.039
Luc (1)					
week: 5	0.020	0.021	0.022	0.019	0.021
9	0.025			0.022	0.021

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Neut (G/l)					
week: 5	0.960	1.136	0.994	0.978	1.115
9	0.920			1.520	1.048
Eos (G/l)					
week: 5	0.084	0.060	0.094	0.090	0.100
9	0.114			0.124	0.102
Baso (G/l)					
week: 5	0.062	0.088	0.082	0.062	0.069
9	0.054			0.064	0.054
Lympho (G/l)					
week: 5	8.951	10.29	10.73	9.808	9.928
9	7.656			8.716	8.706
Mono (G/l)					
week: 5	0.320	0.406	0.508*	0.400	0.465*
9	0.330			0.458	0.424
Luc (G/l)					
week: 5	0.211	0.242	0.274	0.218	0.242
9	0.248			0.254	0.220
Plt (G/l)					
week: 5	1081	1106	1133	1108	1056
9	1015			1069	1033
PT (rel. 1)					
week: 5	0.730	0.743	0.770	0.745	0.754
9	0.823			0.881	0.850

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

LEPAGE: * if $p_L < 0.05$ JONCKHEERE: +- if $p_J < 0.01$

Hematology (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
RBC (T/l)					
week: 5	8.033	7.870	8.106	7.900	8.017
9	8.388			8.158	8.420
Hb (mmol/l)					
week: 5	9.420	9.300	9.520	9.425	9.460
9	9.520			9.500	9.760
Hct (l)					
week: 5	0.452	0.451	0.458	0.453	0.454
9	0.468			0.459	0.472
MCV (fl)					
week: 5	56.28	57.46	56.50	57.40	56.64
9	55.82			56.25	56.02
RDW (l)					
week: 5	0.123	0.115	0.129	0.130	0.124
9	0.126			0.139	0.128
MCH (fmol)					
week: 5	1.173	1.182	1.174	1.194	1.179
9	1.136			1.165	1.160
MCHC (mmol/l)					
week: 5	20.82	20.62	20.79	20.80	20.81
9	20.34			20.74	20.69

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
HDW (mmol/l)					
week: 5	1.499	1.428	1.322	1.423	1.382
9	1.350			1.358	1.260
WBC (G/l)					
week: 5	7.971	9.506	8.778	9.355	8.731
9	5.886			6.445	5.516
Neut (1)					
week: 5	0.098	0.105	0.074	0.078	0.078
9	0.120			0.072	0.098
Eos (1)					
week: 5	0.008	0.009	0.011	0.009	0.011
9	0.016			0.017	0.015
Baso (1)					
week: 5	0.004	0.004	0.005	0.006	0.006 +
9	0.004			0.004	0.003
Lympho (1)					
week: 5	0.845	0.835	0.863	0.860	0.851
9	0.799			0.854	0.823
Mono (1)					
week: 5	0.029	0.032	0.031	0.031	0.035
9	0.042			0.034	0.041
Luc (1)					
week: 5	0.016	0.015	0.017	0.017	0.019
9	0.019			0.020	0.020

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

129

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Neut (G/l)					
week: 5	0.700	0.972	0.632	0.665	0.660
9	0.690			0.475	0.542
Eos (G/l)					
week: 5	0.065	0.086	0.098	0.083	0.099
9	0.092			0.103	0.082
Baso (G/l)					
week: 5	0.035	0.036	0.046	0.054	0.050
9	0.024			0.023	0.020
Lympho (G/l)					
week: 5	6.810	7.972	7.584	8.104	7.449
9	4.728			5.490	4.536
Mono (G/l)					
week: 5	0.232	0.296	0.266	0.296	0.299
9	0.242			0.228	0.228
Luc (G/l)					
week: 5	0.126	0.144*	0.150	0.158	0.170
9	0.108			0.125	0.110
Plt (G/l)					
week: 5	1099	1078	1079	1023	1104
9	1038			1080	1006
PT (rel. 1)					
week: 5	0.988	0.974	0.964	0.920*-	0.915 -
9	1.013			0.942	0.920

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.15. Hematology (statistics)

Statistical tests and flags used:

LEPAGE: * if p_L < 0.05

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if p_J < 0.01

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
RBC (T/l)					
week: 5 N	10	5	5	9	10
Mean	8.151	8.176	8.208	8.077	8.071
SD	0.310	0.263	0.387	0.277	0.290
Median	8.250	8.190	8.280	8.020	8.050
IQ-Range	0.350	0.410	0.150	0.270	0.450
Min	7.590	7.850	7.580	7.560	7.730
Max	8.620	8.470	8.630	8.490	8.580
p _L		0.841	0.716	0.704	0.623
p _J		0.903	0.670	0.596	0.332
week: 9 N	5			5	5
Mean	9.094			8.728	8.724
SD	0.323			0.406	0.199
Median	9.150			8.780	8.700
IQ-Range	0.410			0.560	0.180
Min	8.670			8.220	8.430
Max	9.480			9.220	8.950
p _L				0.398	0.204
p _J				0.175	0.113
Hb (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	9.620	9.700	9.780	9.633	9.670
SD	0.361	0.187	0.179	0.229	0.302
Median	9.500	9.800	9.700	9.600	9.650
IQ-Range	0.600	0.300	0.000	0.400	0.600
Min	9.200	9.500	9.700	9.400	9.200
Max	10.20	9.900	10.10	10.00	10.00
p _L		0.215	0.045 *	0.479	0.667
p _J		0.582	0.374	0.953	0.901

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	9.720			9.700	9.760
SD	0.342			0.292	0.219
Median	9.600			9.700	9.900
IQ-Range	0.100			0.200	0.200
Min	9.400			9.300	9.400
Max	10.30			10.10	9.900
p_L				0.953	0.737
p_J				0.835	0.428
Hct (1)					
week: 5 N	10	5	5	9	10
Mean	0.470	0.471	0.475	0.469	0.475
SD	0.016	0.018	0.011	0.010	0.018
Median	0.468	0.474	0.472	0.467	0.475
IQ-Range	0.021	0.017	0.005	0.013	0.026
Min	0.446	0.450	0.468	0.455	0.452
Max	0.495	0.496	0.495	0.487	0.511
p_L		0.823	0.138	0.290	0.892
p_J		0.806	0.644	0.922	0.709
week: 9 N	5			5	5
Mean	0.484			0.477	0.484
SD	0.018			0.013	0.013
Median	0.477			0.480	0.483
IQ-Range	0.007			0.014	0.019
Min	0.467			0.461	0.467
Max	0.515			0.494	0.500
p_L				0.956	0.905
p_J				0.835	0.751
MCV (fl)					
week: 5 N	10	5	5	9	10
Mean	57.65	57.68	57.94	58.09	58.81
SD	1.522	1.728	2.439	1.101	1.634
Median	57.50	57.30	57.10	58.00	58.65
IQ-Range	1.800	1.300	0.400	1.200	1.300
Min	55.80	56.40	56.00	56.40	55.70
Max	60.90	60.60	62.20	60.10	62.10
p_L		0.785	0.868	0.513	0.218
p_J		0.806	0.831	0.356	0.033

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

132

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	53.18			54.72	55.44
SD	1.099			1.141	1.345
Median	53.70			54.70	55.40
IQ-Range	1.900			1.900	1.000
Min	52.00			53.50	53.90
Max	54.30			56.10	57.50
p_L				0.274	0.067
p_J				0.144	0.020
RDW (1)					
week: 5 N	10	5	5	9	10
Mean	0.118	0.117	0.114	0.115	0.120
SD	0.006	0.009	0.004	0.006	0.017
Median	0.118	0.115	0.113	0.114	0.116
IQ-Range	0.009	0.013	0.007	0.002	0.015
Min	0.110	0.107	0.110	0.109	0.106
Max	0.130	0.128	0.119	0.129	0.164
p_L		0.346	0.351	0.284	0.537
p_J		0.759	0.241	0.182	0.494
week: 9 N	5			5	5
Mean	0.140			0.133	0.128
SD	0.015			0.007	0.008
Median	0.148			0.128	0.124
IQ-Range	0.021			0.007	0.013
Min	0.121			0.128	0.121
Max	0.155			0.145	0.137
p_L				0.061	0.255
p_J				0.403	0.126
MCH (fmol)					
week: 5 N	10	5	5	9	10
Mean	1.183	1.188	1.190	1.193	1.198
SD	0.037	0.023	0.045	0.026	0.023
Median	1.170	1.190	1.170	1.190	1.200
IQ-Range	0.060	0.040	0.010	0.040	0.040
Min	1.140	1.160	1.160	1.160	1.160
Max	1.260	1.210	1.270	1.240	1.230
p_L		0.564	0.716	0.306	0.125
p_J		0.624	0.722	0.336	0.100

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	1.066			1.114	1.118
SD	0.024			0.019	0.015
Median	1.060			1.100	1.120 a
IQ-Range	0.030			0.030	0.010
Min	1.040			1.100	1.100
Max	1.100			1.140	1.140
p_L				0.057	0.042 *
p_J				0.022	0.007 +
MCHC (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	20.49	20.60	20.54	20.53	20.39
SD	0.205	0.370	0.145	0.198	0.383
Median	20.57	20.62	20.47	20.55	20.41
IQ-Range	0.320	0.170	0.210	0.180	0.420
Min	20.16	20.02	20.41	20.20	19.63
Max	20.71	21.03	20.74	20.79	20.88
p_L		0.423	0.921	0.970	0.383
p_J		0.358	0.670	0.860	0.601
week: 9 N	5			5	5
Mean	20.08			20.35	20.20
SD	0.247			0.201	0.273
Median	20.06			20.41	20.15
IQ-Range	0.160			0.370	0.420
Min	19.79			20.12	19.85
Max	20.46			20.54	20.48
p_L				0.137	0.449
p_J				0.060	0.398
HDW (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	1.698	1.710	1.556	1.651	1.602
SD	0.259	0.397	0.159	0.279	0.307
Median	1.610	1.470	1.530	1.540	1.430
IQ-Range	0.420	0.660	0.100	0.380	0.530
Min	1.370	1.330	1.410	1.370	1.370
Max	2.090	2.150	1.820	2.140	2.210
p_L		0.125	0.505	0.710	0.161
p_J		0.903	0.434	0.623	0.223

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			5	5
	Mean	1.512			1.674	1.684
	SD	0.078			0.219	0.194
	Median	1.510			1.580	1.730
	IQ-Range	0.150			0.290	0.290
	Min	1.430			1.470	1.450
	Max	1.590			1.990	1.910
	p_L				0.469	0.265
	p_J				0.251	0.187
WBC (G/l)						
week:	5 N	10	5	5	9	10
	Mean	10.59	12.22	12.69	11.55	11.92
	SD	1.389	2.784	1.498	1.838	2.460
	Median	10.90	11.65	11.98 a	11.32	12.25
	IQ-Range	2.210	2.910	1.120	2.040	3.090
	Min	8.770	8.750	11.58	7.880	7.660
	Max	13.22	16.01	15.21	13.91	16.69
	p_L		0.166	0.031 *	0.407	0.171
	p_J		0.270	0.021	0.146	0.179
week:	9 N	5			5	5
	Mean	9.322			11.14	10.55
	SD	1.648			2.120	1.950
	Median	8.640			11.86	9.660
	IQ-Range	1.780			2.830	2.860
	Min	7.990			8.770	8.930
	Max	11.94			13.84	13.32
	p_L				0.268	0.230
	p_J				0.117	0.267
Neut (l)						
week:	5 N	10	5	5	9	10
	Mean	0.092	0.095	0.079	0.085	0.096
	SD	0.029	0.035	0.013	0.014	0.037
	Median	0.087	0.090	0.073	0.084	0.095
	IQ-Range	0.024	0.035	0.008	0.005	0.042
	Min	0.042	0.060	0.071	0.065	0.058
	Max	0.151	0.149	0.101	0.118	0.187
	p_L		0.720	0.279	0.298	0.566
	p_J		1.000	0.320	0.530	0.950

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	0.097			0.134	0.101
SD	0.030			0.042	0.021
Median	0.101			0.128	0.089
IQ-Range	0.023			0.028	0.033
Min	0.056			0.087	0.085
Max	0.138			0.201	0.130
p_L				0.293	0.658
p_J				0.117	0.792
Eos (1)					
week: 5 N	10	5	5	9	10
Mean	0.008	0.005	0.008	0.008	0.009
SD	0.003	0.002	0.003	0.002	0.003
Median	0.008	0.005	0.008	0.007	0.008
IQ-Range	0.004	0.002	0.002	0.003	0.003
Min	0.003	0.003	0.004	0.004	0.005
Max	0.014	0.009	0.012	0.011	0.015
p_L		0.224	0.910	0.937	0.824
p_J		0.111	0.594	0.783	0.290
week: 9 N	5			5	5
Mean	0.012			0.011	0.009
SD	0.008			0.003	0.002
Median	0.009			0.011	0.009
IQ-Range	0.007			0.004	0.001
Min	0.006			0.008	0.007
Max	0.025			0.015	0.012
p_L				0.363	0.165
p_J				0.602	0.874
Baso (1)					
week: 5 N	10	5	5	9	10
Mean	0.006	0.007	0.006	0.005	0.006
SD	0.001	0.000	0.001	0.001	0.001
Median	0.006	0.007	0.007	0.005	0.006
IQ-Range	0.001	0.000	0.001	0.001	0.001
Min	0.004	0.006	0.005	0.004	0.004
Max	0.007	0.007	0.007	0.007	0.008
p_L		0.090	0.342	0.509	0.915
p_J		0.043	0.102	0.543	0.455

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	0.005			0.006	0.005
SD	0.002			0.001	0.002
Median	0.005			0.006	0.005
IQ-Range	0.001			0.001	0.001
Min	0.003			0.005	0.004
Max	0.008			0.007	0.008
p_L				0.495	0.888
p_J				0.602	0.597
Lympho (1)					
week: 5 N	10	5	5	9	10
Mean	0.845	0.839	0.846	0.849	0.829
SD	0.030	0.051	0.026	0.021	0.039
Median	0.847	0.840	0.854	0.853	0.833
IQ-Range	0.050	0.072	0.046	0.007	0.023
Min	0.787	0.768	0.818	0.802	0.728
Max	0.887	0.890	0.872	0.881	0.871
p_L		0.303	0.978	0.212	0.466
p_J		0.903	1.000	0.860	0.419
week: 9 N	5			5	5
Mean	0.826			0.785	0.823
SD	0.040			0.052	0.023
Median	0.828			0.805	0.832
IQ-Range	0.021			0.052	0.021
Min	0.760			0.708	0.789
Max	0.867			0.841	0.847
p_L				0.293	0.664
p_J				0.117	0.792
Mono (1)					
week: 5 N	10	5	5	9	10
Mean	0.030	0.034	0.040	0.034	0.040
SD	0.006	0.014	0.009	0.008	0.007
Median	0.030	0.032	0.044	0.035	0.039 a
IQ-Range	0.006	0.023	0.010	0.012	0.009
Min	0.020	0.018	0.027	0.021	0.030
Max	0.039	0.050	0.049	0.047	0.054
p_L		0.153	0.060	0.273	0.020 *
p_J		0.759	0.145	0.271	0.037

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	0.034			0.042	0.039
SD	0.010			0.013	0.006
Median	0.033			0.034	0.038
IQ-Range	0.006			0.016	0.003
Min	0.022			0.032	0.034
Max	0.049			0.062	0.050
p_L				0.697	0.278
p_J				0.465	0.170
Luc (1)					
week: 5 N	10	5	5	9	10
Mean	0.020	0.021	0.022	0.019	0.021
SD	0.006	0.005	0.009	0.004	0.006
Median	0.019	0.021	0.018	0.020	0.020
IQ-Range	0.005	0.006	0.003	0.005	0.007
Min	0.012	0.015	0.015	0.014	0.015
Max	0.030	0.027	0.038	0.026	0.033
p_L		0.892	0.997	0.981	0.813
p_J		0.668	0.859	0.937	0.852
week: 9 N	5			5	5
Mean	0.025			0.022	0.021
SD	0.008			0.005	0.006
Median	0.021			0.023	0.020
IQ-Range	0.014			0.005	0.005
Min	0.018			0.014	0.016
Max	0.036			0.026	0.032
p_L				0.541	0.643
p_J				0.835	0.398
Neut (G/l)					
week: 5 N	10	5	5	9	10
Mean	0.960	1.136	0.994	0.978	1.115
SD	0.270	0.401	0.143	0.183	0.351
Median	0.895	1.120	1.020	1.020	1.130
IQ-Range	0.440	0.660	0.210	0.140	0.410
Min	0.480	0.700	0.830	0.660	0.560
Max	1.320	1.620	1.170	1.210	1.850
p_L		0.253	0.509	0.449	0.742
p_J		0.540	0.696	0.922	0.364

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			5	5
	Mean	0.920			1.520	1.048
	SD	0.424			0.715	0.147
	Median	0.860			1.240	1.060
	IQ-Range	0.220			0.190	0.150
	Min	0.560			1.030	0.820
	Max	1.640			2.780	1.190
	p_L				0.092	0.361
	p_J				0.076	0.561
Eos (G/l)						
week:	5 N	10	5	5	9	10
	Mean	0.084	0.060	0.094	0.090	0.100
	SD	0.044	0.028	0.032	0.032	0.043
	Median	0.075	0.040	0.090	0.090	0.085
	IQ-Range	0.030	0.040	0.040	0.020	0.050
	Min	0.030	0.040	0.060	0.030	0.060
	Max	0.190	0.100	0.140	0.140	0.180
	p_L		0.450	0.757	0.599	0.614
	p_J		0.298	0.722	0.326	0.213
week:	9 N	5			5	5
	Mean	0.114			0.124	0.102
	SD	0.082			0.036	0.035
	Median	0.110			0.130	0.100
	IQ-Range	0.060			0.040	0.020
	Min	0.050			0.070	0.070
	Max	0.250			0.160	0.160
	p_L				0.486	0.218
	p_J				0.347	0.958
Baso (G/l)						
week:	5 N	10	5	5	9	10
	Mean	0.062	0.088	0.082	0.062	0.069
	SD	0.019	0.024	0.015	0.019	0.027
	Median	0.060	0.090	0.080	0.060	0.070
	IQ-Range	0.020	0.030	0.010	0.020	0.020
	Min	0.030	0.060	0.060	0.040	0.030
	Max	0.100	0.120	0.100	0.090	0.130
	p_L		0.127	0.147	0.640	0.650
	p_J		0.050	0.036	0.953	0.921

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	0.054			0.064	0.054
SD	0.023			0.018	0.026
Median	0.050			0.060	0.040
IQ-Range	0.020			0.010	0.010
Min	0.030			0.040	0.040
Max	0.090			0.090	0.100
p_L				0.531	0.878
p_J				0.347	0.916
Lympho (G/l)					
week: 5 N	10	5	5	9	10
Mean	8.951	10.29	10.73	9.808	9.928
SD	1.273	2.650	1.334	1.595	2.327
Median	9.210	10.36	10.45	9.780	10.25
IQ-Range	2.100	2.850	0.380	1.750	3.130
Min	6.910	7.350	9.470	6.750	6.360
Max	10.81	14.15	12.99	11.87	14.43
p_L		0.126	0.097	0.355	0.092
p_J		0.327	0.060	0.202	0.279
week: 9 N	5			5	5
Mean	7.656			8.716	8.706
SD	1.029			1.564	1.739
Median	7.140			9.750	8.180
IQ-Range	1.470			2.390	2.540
Min	6.730			6.660	7.050
Max	9.080			9.980	11.12
p_L				0.230	0.472
p_J				0.251	0.224
Mono (G/l)					
week: 5 N	10	5	5	9	10
Mean	0.320	0.406	0.508	0.400	0.465
SD	0.074	0.188	0.144	0.130	0.094
Median	0.310	0.290	0.520 a	0.400	0.470 a
IQ-Range	0.070	0.230	0.220	0.140	0.130
Min	0.230	0.260	0.320	0.230	0.300
Max	0.490	0.690	0.660	0.620	0.610
p_L		0.473	0.033 *	0.230	0.011 *
p_J		0.759	0.043	0.141	0.022

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			5	5
	Mean	0.330			0.458	0.424
	SD	0.149			0.147	0.129
	Median	0.300			0.410	0.370
	IQ-Range	0.030			0.170	0.200
	Min	0.180			0.290	0.310
	Max	0.580			0.660	0.600
	p_L				0.364	0.138
	p_J				0.175	0.205
Luc (G/l)						
week:	5 N	10	5	5	9	10
	Mean	0.211	0.242	0.274	0.218	0.242
	SD	0.083	0.041	0.124	0.042	0.068
	Median	0.175	0.230	0.210	0.210	0.225
	IQ-Range	0.040	0.010	0.100	0.020	0.090
	Min	0.140	0.200	0.180	0.150	0.160
	Max	0.400	0.310	0.480	0.280	0.380
	p_L		0.116	0.223	0.426	0.162
	p_J		0.086	0.076	0.263	0.196
week:	9 N	5			5	5
	Mean	0.248			0.254	0.220
	SD	0.126			0.089	0.051
	Median	0.180			0.260	0.230
	IQ-Range	0.180			0.100	0.030
	Min	0.150			0.130	0.150
	Max	0.430			0.360	0.290
	p_L				0.687	0.192
	p_J				0.917	0.792
Plt (G/l)						
week:	5 N	10	5	5	9	10
	Mean	1081	1106	1133	1108	1056
	SD	107.5	97.99	81.76	97.91	73.20
	Median	1107	1053	1151	1113	1066
	IQ-Range	122.0	137.0	101.0	144.0	120.0
	Min	826.0	1014	1050	973.0	938.0
	Max	1191	1239	1248	1276	1158
	p_L		0.569	0.724	0.948	0.408
	p_J		0.903	0.455	0.724	0.351

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	1015			1069	1033
SD	53.46			64.99	55.05
Median	1011			1072	1031
IQ-Range	71.00			58.00	51.00
Min	963.0			964.0	962.0
Max	1092			1124	1109
p_L				0.364	0.870
p_J				0.175	0.874
PT (rel. 1)					
week: 5 N	10	5	5	9	10
Mean	0.730	0.743	0.770	0.745	0.754
SD	0.041	0.051	0.062	0.073	0.070
Median	0.742	0.742	0.787	0.722	0.736
IQ-Range	0.075	0.075	0.083	0.092	0.127
Min	0.670	0.676	0.682	0.630	0.676
Max	0.772	0.798	0.833	0.864	0.873
p_L		0.706	0.146	0.592	0.898
p_J		0.540	0.145	0.432	0.559
week: 9 N	5			5	5
Mean	0.823			0.881	0.850
SD	0.039			0.059	0.041
Median	0.819			0.839	0.850
IQ-Range	0.053			0.083	0.016
Min	0.777			0.839	0.799
Max	0.872			0.964	0.913
p_L				0.268	0.449
p_J				0.175	0.428

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

LEPAGE: * if $p_L < 0.05$

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if $p_J < 0.01$

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
RBC (T/l)					
week: 5 N	10	5	5	8	10
Mean	8.033	7.870	8.106	7.900	8.017
SD	0.292	0.422	0.323	0.273	0.269
Median	8.025	8.080	8.040	7.935	8.005
IQ-Range	0.420	0.730	0.270	0.215	0.400
Min	7.520	7.410	7.840	7.380	7.670
Max	8.520	8.290	8.640	8.340	8.560
p_L		0.638	0.628	0.543	0.889
p_J		0.624	0.972	0.457	0.717
week: 9 N	5	5	4	5	
Mean	8.388		8.158	8.420	
SD	0.252		0.219	0.178	
Median	8.490		8.230	8.400	
IQ-Range	0.030		0.315	0.090	
Min	7.940		7.850	8.200	
Max	8.540		8.320	8.690	
p_L			0.152	0.765	
p_J				0.770	
Hb (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	9.420	9.300	9.520	9.425	9.460
SD	0.352	0.158	0.277	0.311	0.263
Median	9.450	9.300	9.400	9.400	9.450
IQ-Range	0.400	0.200	0.100	0.450	0.400
Min	9.000	9.100	9.300	9.100	9.200
Max	10.20	9.500	10.00	10.00	10.00
p_L		0.335	0.694	0.915	0.740
p_J		0.462	0.887	0.788	0.493

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	9.520			9.500	9.760
SD	0.303			0.294	0.195
Median	9.400			9.500	9.700
IQ-Range	0.200			0.500	0.200
Min	9.200			9.200	9.500
Max	10.00			9.800	10.00
p_L				0.720	0.183
p_J					0.178
Hct (1)					
week: 5 N	10	5	5	8	10
Mean	0.452	0.451	0.458	0.453	0.454
SD	0.016	0.006	0.011	0.016	0.013
Median	0.453	0.451	0.453	0.452	0.452
IQ-Range	0.009	0.003	0.005	0.022	0.018
Min	0.426	0.443	0.450	0.434	0.437
Max	0.486	0.461	0.477	0.482	0.476
p_L		0.575	0.252	0.438	0.957
p_J		0.854	0.477	0.649	0.708
week: 9 N	5			4	5
Mean	0.468			0.459	0.472
SD	0.021			0.018	0.007
Median	0.464			0.465	0.474
IQ-Range	0.024			0.026	0.013
Min	0.450			0.433	0.464
Max	0.501			0.473	0.478
p_L				0.809	0.220
p_J					0.349
MCV (fl)					
week: 5 N	10	5	5	8	10
Mean	56.28	57.46	56.50	57.40	56.64
SD	1.257	2.775	1.049	2.023	1.785
Median	56.35	56.60	56.80	58.00	56.00
IQ-Range	2.100	3.800	1.800	3.350	1.400
Min	54.50	54.10	55.20	54.20	54.70
Max	58.40	60.80	57.50	59.90	60.80
p_L		0.428	0.875	0.067	0.996
p_J		0.582	0.619	0.247	0.708

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	55.82			56.25	56.02
SD	2.156			2.164	1.460
Median	56.10			56.75	55.50
IQ-Range	2.100			2.700	1.200
Min	53.00			53.20	54.50
Max	58.70			58.30	58.30
p_L				0.809	0.694
p_J					0.907
RDW (1)					
week: 5 N	10	5	5	8	10
Mean	0.123	0.115	0.129	0.130	0.124
SD	0.017	0.006	0.008	0.018	0.010
Median	0.119	0.115	0.130	0.128	0.130
IQ-Range	0.016	0.005	0.001	0.016	0.016
Min	0.107	0.106	0.117	0.108	0.107
Max	0.165	0.122	0.138	0.168	0.134
p_L		0.629	0.334	0.484	0.751
p_J		0.426	0.255	0.102	0.166
week: 9 N	5			4	5
Mean	0.126			0.139	0.128
SD	0.011			0.026	0.014
Median	0.124			0.132	0.123
IQ-Range	0.006			0.037	0.016
Min	0.113			0.116	0.115
Max	0.142			0.176	0.150
p_L				0.762	0.812
p_J					1.000
MCH (fmol)					
week: 5 N	10	5	5	8	10
Mean	1.173	1.182	1.174	1.194	1.179
SD	0.034	0.066	0.013	0.043	0.032
Median	1.170	1.170	1.180	1.205	1.170
IQ-Range	0.070	0.120	0.020	0.075	0.050
Min	1.120	1.120	1.160	1.130	1.140
Max	1.210	1.260	1.190	1.240	1.230
p_L		0.277	0.077	0.273	0.764
p_J		0.903	0.915	0.321	0.578

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	1.136			1.165	1.160
SD	0.044			0.025	0.035
Median	1.130			1.170	1.150
IQ-Range	0.060			0.030	0.020
Min	1.080			1.130	1.130
Max	1.190			1.190	1.220
p_L				0.362	0.227
p_J					0.520
MCHC (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	20.82	20.62	20.79	20.80	20.81
SD	0.371	0.509	0.182	0.219	0.320
Median	20.89	20.77	20.79	20.88	20.92
IQ-Range	0.290	0.510	0.120	0.365	0.420
Min	19.90	19.83	20.55	20.44	20.29
Max	21.28	21.12	21.05	21.00	21.17
p_L		0.475	0.570	0.856	0.901
p_J		0.540	0.434	0.605	1.000
week: 9 N	5			4	5
Mean	20.34			20.74	20.69
SD	0.369			0.395	0.240
Median	20.24			20.63	20.80
IQ-Range	0.340			0.460	0.330
Min	20.00			20.38	20.35
Max	20.93			21.30	20.91
p_L				0.306	0.177
p_J					0.143
HDW (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	1.499	1.428	1.322	1.423	1.382
SD	0.284	0.175	0.121	0.240	0.159
Median	1.425	1.390	1.270	1.325	1.360
IQ-Range	0.380	0.090	0.060	0.345	0.170
Min	1.180	1.260	1.230	1.210	1.170
Max	1.990	1.720	1.530	1.830	1.650
p_L		0.624	0.436	0.726	0.349
p_J		0.713	0.166	0.255	0.326

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			4	5
	Mean	1.350			1.358	1.260
	SD	0.158			0.252	0.163
	Median	1.250			1.305	1.170
	IQ-Range	0.240			0.385	0.250
	Min	1.220			1.130	1.090
	Max	1.560			1.690	1.450
	p_L				0.289	0.273
	p_J					0.219
WBC (G/l)						
week:	5 N	10	5	5	8	10
	Mean	7.971	9.506	8.778	9.355	8.731
	SD	2.564	1.694	1.645	2.387	1.692
	Median	7.450	9.890	8.210	10.24	9.025
	IQ-Range	3.870	2.330	2.430	3.420	2.390
	Min	4.870	7.170	7.290	4.850	6.180
	Max	13.14	11.28	11.08	11.84	11.63
	p_L		0.275	0.325	0.400	0.243
	p_J		0.142	0.241	0.121	0.415
week:	9 N	5			4	5
	Mean	5.886			6.445	5.516
	SD	0.953			1.160	1.003
	Median	5.880			6.525	5.950
	IQ-Range	0.490			1.470	0.760
	Min	4.720			4.950	3.900
	Max	7.340			7.780	6.470
	p_L				0.536	0.909
	p_J					0.815
Neut (1)						
week:	5 N	10	5	5	8	10
	Mean	0.098	0.105	0.074	0.078	0.078
	SD	0.060	0.034	0.025	0.053	0.033
	Median	0.074	0.085	0.060	0.060	0.072
	IQ-Range	0.100	0.033	0.037	0.043	0.026
	Min	0.041	0.081	0.050	0.026	0.036
	Max	0.213	0.160	0.106	0.188	0.141
	p_L		0.067	0.628	0.672	0.479
	p_J		0.327	0.915	0.374	0.438

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	0.120			0.072	0.098
SD	0.039			0.014	0.030
Median	0.098			0.070	0.082
IQ-Range	0.049			0.024	0.043
Min	0.087			0.060	0.070
Max	0.177			0.090	0.137
p_L				0.088	0.278
p_J					0.266
Eos (1)					
week: 5 N	10	5	5	8	10
Mean	0.008	0.009	0.011	0.009	0.011
SD	0.002	0.003	0.007	0.004	0.005
Median	0.008	0.008	0.010	0.008	0.010
IQ-Range	0.001	0.001	0.004	0.005	0.008
Min	0.004	0.006	0.004	0.004	0.006
Max	0.011	0.014	0.022	0.018	0.022
p_L		0.957	0.083	0.348	0.081
p_J		0.903	0.594	0.918	0.272
week: 9 N	5			4	5
Mean	0.016			0.017	0.015
SD	0.005			0.010	0.006
Median	0.014			0.016	0.014
IQ-Range	0.006			0.017	0.007
Min	0.011			0.008	0.009
Max	0.022			0.029	0.023
p_L				0.078	0.639
p_J					0.725
Baso (1)					
week: 5 N	10	5	5	8	10
Mean	0.004	0.004	0.005	0.006	0.006
SD	0.001	0.000	0.001	0.001	0.001
Median	0.005	0.004	0.005	0.006	0.006
IQ-Range	0.002	0.000	0.001	0.002	0.002
Min	0.002	0.003	0.004	0.003	0.004
Max	0.006	0.004	0.006	0.007	0.008
p_L		0.089	0.483	0.201	0.061
p_J		0.391	0.644	0.041	0.002 +

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			4	5
	Mean	0.004			0.004	0.003
	SD	0.001			0.000	0.001
	Median	0.004			0.004	0.003
	IQ-Range	0.002			0.000	0.001
	Min	0.003			0.003	0.002
	Max	0.006			0.004	0.005
	p_L				0.252	0.621
	p_J					0.320
Lympho (1)						
week:	5 N	10	5	5	8	10
	Mean	0.845	0.835	0.863	0.860	0.851
	SD	0.058	0.049	0.028	0.052	0.039
	Median	0.872	0.863	0.860	0.879	0.862
	IQ-Range	0.092	0.046	0.032	0.046	0.064
	Min	0.733	0.756	0.822	0.750	0.776
	Max	0.901	0.873	0.892	0.898	0.900
	p_L		0.166	0.729	0.658	0.560
	p_J		0.327	0.831	0.444	0.846
week:	9 N	5			4	5
	Mean	0.799			0.854	0.823
	SD	0.043			0.021	0.035
	Median	0.820			0.858	0.842
	IQ-Range	0.075			0.030	0.047
	Min	0.746			0.826	0.773
	Max	0.836			0.874	0.852
	p_L				0.127	0.278
	p_J					0.320
Mono (1)						
week:	5 N	10	5	5	8	10
	Mean	0.029	0.032	0.031	0.031	0.035
	SD	0.004	0.012	0.007	0.008	0.008
	Median	0.029	0.027	0.027	0.031	0.035
	IQ-Range	0.004	0.010	0.009	0.010	0.004
	Min	0.022	0.024	0.026	0.024	0.021
	Max	0.035	0.052	0.042	0.046	0.050
	p_L		0.278	0.409	0.352	0.098
	p_J		0.806	0.943	0.820	0.124

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	0.042			0.034	0.041
SD	0.009			0.012	0.008
Median	0.045			0.031	0.045
IQ-Range	0.017			0.015	0.011
Min	0.032			0.025	0.029
Max	0.051			0.051	0.048
p_L				0.141	0.639
p_J					0.682
Luc (1)					
week: 5 N	10	5	5	8	10
Mean	0.016	0.015	0.017	0.017	0.019
SD	0.003	0.003	0.005	0.002	0.008
Median	0.015	0.015	0.015	0.016	0.017
IQ-Range	0.004	0.005	0.001	0.002	0.003
Min	0.012	0.012	0.012	0.014	0.013
Max	0.021	0.019	0.026	0.021	0.042
p_L		0.892	0.907	0.184	0.341
p_J		0.903	0.804	0.215	0.093
week: 9 N	5			4	5
Mean	0.019			0.020	0.020
SD	0.002			0.002	0.005
Median	0.019			0.020	0.018
IQ-Range	0.001			0.003	0.003
Min	0.015			0.017	0.015
Max	0.021			0.023	0.028
p_L				0.885	0.651
p_J					0.815
Neut (G/1)					
week: 5 N	10	5	5	8	10
Mean	0.700	0.972	0.632	0.665	0.660
SD	0.309	0.233	0.169	0.364	0.267
Median	0.635	0.960	0.670	0.620	0.565
IQ-Range	0.470	0.330	0.200	0.245	0.390
Min	0.280	0.680	0.370	0.280	0.380
Max	1.230	1.250	0.780	1.490	1.150
p_L		0.186	0.667	0.935	0.955
p_J		0.086	0.749	0.508	0.386

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			4	5
	Mean	0.690			0.475	0.542
	SD	0.162			0.171	0.195
	Median	0.720			0.450	0.490
	IQ-Range	0.260			0.250	0.190
	Min	0.480			0.300	0.310
	Max	0.850			0.700	0.820
	p_L				0.230	0.398
	p_J					0.178
Eos (G/l)						
week:	5 N	10	5	5	8	10
	Mean	0.065	0.086	0.098	0.083	0.099
	SD	0.021	0.039	0.083	0.032	0.052
	Median	0.065	0.080	0.080	0.090	0.095
	IQ-Range	0.030	0.030	0.040	0.040	0.040
	Min	0.030	0.050	0.030	0.040	0.050
	Max	0.100	0.150	0.240	0.140	0.220
	p_L		0.510	0.282	0.165	0.129
	p_J		0.327	0.414	0.222	0.064
week:	9 N	5			4	5
	Mean	0.092			0.103	0.082
	SD	0.029			0.045	0.043
	Median	0.100			0.110	0.060
	IQ-Range	0.020			0.075	0.050
	Min	0.050			0.050	0.050
	Max	0.130			0.140	0.150
	p_L				0.244	0.552
	p_J					0.770
Baso (G/l)						
week:	5 N	10	5	5	8	10
	Mean	0.035	0.036	0.046	0.054	0.050
	SD	0.020	0.009	0.013	0.020	0.016
	Median	0.035	0.030	0.040	0.055	0.050
	IQ-Range	0.030	0.010	0.020	0.030	0.020
	Min	0.010	0.030	0.030	0.020	0.030
	Max	0.060	0.050	0.060	0.080	0.080
	p_L		0.078	0.351	0.197	0.197
	p_J		0.903	0.271	0.028	0.028

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	0.024			0.023	0.020
SD	0.011			0.005	0.010
Median	0.020			0.020	0.020
IQ-Range	0.010			0.005	0.020
Min	0.010			0.020	0.010
Max	0.040			0.030	0.030
p_L				0.413	0.852
p_J					0.598
Lympho (G/1)					
week: 5 N	10	5	5	8	10
Mean	6.810	7.972	7.584	8.104	7.449
SD	2.507	1.673	1.492	2.317	1.591
Median	6.215	8.630	7.010	9.055	7.595
IQ-Range	4.080	1.520	2.110	3.570	2.830
Min	4.240	5.420	5.990	3.940	5.410
Max	11.83	9.730	9.530	10.42	10.47
p_L		0.383	0.325	0.400	0.069
p_J		0.221	0.271	0.102	0.415
week: 9 N	5			4	5
Mean	4.728			5.490	4.536
SD	0.954			0.894	0.833
Median	4.510			5.630	4.600
IQ-Range	0.530			1.190	0.900
Min	3.520			4.280	3.310
Max	6.140			6.420	5.450
p_L				0.536	0.909
p_J					0.682
Mono (G/1)					
week: 5 N	10	5	5	8	10
Mean	0.232	0.296	0.266	0.296	0.299
SD	0.083	0.076	0.034	0.122	0.093
Median	0.200	0.300	0.260	0.300	0.305
IQ-Range	0.110	0.130	0.050	0.175	0.150
Min	0.110	0.200	0.220	0.150	0.180
Max	0.390	0.370	0.300	0.510	0.480
p_L		0.264	0.119	0.475	0.216
p_J		0.126	0.155	0.207	0.137

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	0.242			0.228	0.228
SD	0.042			0.115	0.065
Median	0.230			0.200	0.250
IQ-Range	0.060			0.145	0.100
Min	0.200			0.120	0.140
Max	0.300			0.390	0.290
p_L				0.306	0.664
p_J					0.639
Luc (G/l)					
week: 5 N	10	5	5	8	10
Mean	0.126	0.144	0.150	0.158	0.170
SD	0.052	0.015	0.075	0.056	0.089
Median	0.110	0.150	0.130	0.150	0.150
IQ-Range	0.100	0.010	0.030	0.085	0.040
Min	0.070	0.120	0.090	0.080	0.080
Max	0.200	0.160	0.280	0.250	0.400
p_L		0.050 *	0.390	0.388	0.240
p_J		0.426	0.594	0.282	0.174
week: 9 N	5			4	5
Mean	0.108			0.125	0.110
SD	0.011			0.030	0.035
Median	0.110			0.130	0.100
IQ-Range	0.000			0.050	0.020
Min	0.090			0.090	0.080
Max	0.120			0.150	0.170
p_L				0.279	0.436
p_J					0.682
Plt (G/l)					
week: 5 N	10	5	5	8	10
Mean	1099	1078	1079	1023	1104
SD	55.46	59.76	89.95	202.7	92.04
Median	1096	1074	1067	1055	1095
IQ-Range	100.0	4.000	21.00	166.0	66.00
Min	1032	1001	982.0	568.0	956.0
Max	1181	1169	1227	1203	1285
p_L		0.667	0.932	0.078	0.944
p_J		0.903	0.570	0.457	0.846

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	1038			1080	1006
SD	62.37			104.0	48.12
Median	1030			1060	993.0
IQ-Range	33.00			165.5	22.00
Min	986.0			988.0	951.0
Max	1144			1212	1082
p_L				0.769	0.643
p_J					0.447
PT (rel. 1)					
week: 5 N	10	5	5	8	10
Mean	0.988	0.974	0.964	0.920	0.915
SD	0.049	0.031	0.049	0.054	0.076
Median	0.979	0.955	0.954	0.907 a	0.941
IQ-Range	0.065	0.047	0.039	0.060	0.071
Min	0.925	0.947	0.925	0.860	0.746
Max	1.095	1.014	1.046	1.032	0.997
p_L		0.860	0.525	0.023 *	0.105
p_J		0.713	0.320	0.005	0.004
week: 9 N	5			4	5
Mean	1.013			0.942	0.920
SD	0.050			0.093	0.051
Median	0.995			0.922	0.910
IQ-Range	0.057			0.125	0.059
Min	0.974			0.853	0.851
Max	1.093			1.072	0.982
p_L				0.106	0.081
p_J					0.040

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.16. Blood chemistry (means)

Statistical tests and flags used:

* if p_L < 0.05
+- if p_J < 0.01

Blood chemistry (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Gluc (mmol/l)					
week: 5	7.908	8.010	8.440	7.858	8.911*+
9	7.486			8.108	7.886
Urea (mmol/l)					
week: 5	5.662	6.768	5.676	6.097	6.177
9	6.416			6.312	6.526
Creat (umol/l)					
week: 5	17.66	18.74	18.46	19.13	19.85
9	17.92			19.96	18.98
Bili-tot (umol/l)					
week: 5	1.388	1.042	1.262	1.426	1.446
9	1.565			1.803	1.850
Prot (g/l)					
week: 5	66.80	66.87	68.04	67.34	66.61
9	67.38			66.26*	67.80
Alb (g/l)					
week: 5	34.57	34.54	34.73	34.63	34.63
9	34.66			34.27*	35.14
Glob (g/l)					
week: 5	32.23	32.32	33.31	32.72	31.98
9	32.71			31.99	32.66

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
A/G (1)					
week: 5	1.075	1.072	1.042	1.058*	1.084
9	1.060			1.070	1.078
Chol (mmol/l)					
week: 5	1.723	1.884	1.908	1.848	1.847
9	1.656			1.898	1.874
Na+ (mmol/l)					
week: 5	144.3	143.1	143.7	144.9	143.6
9	144.0			144.0	144.7
K+ (mmol/l)					
week: 5	3.492	3.716	3.730	3.613	3.941**
9	3.452			3.526	3.624
Ca++ (mmol/l)					
week: 5	2.634	2.674	2.706	2.659	2.696
9	2.610			2.620	2.634
Cl- (mmol/l)					
week: 5	98.93	98.96	100.0	98.54	97.84
9	101.9			101.8	99.42
PO4-in (mmol/l)					
week: 5	2.208	2.066	2.046	2.114	2.297
9	1.704			1.698	1.824
ASAT (GOT) (U/l)					
week: 5	68.07	66.94	65.26*	64.41	74.08
9	76.14			82.21	76.18

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
ALAT (GPT) (U/l)					
week: 5	33.08	29.08	29.34	28.72	39.79
9	39.64			29.92	35.70
ALP (U/l)					
week: 5	164.6	159.7	163.9	150.2	187.8
9	126.3			116.7	126.3

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

157

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

LEPAGE: * if p_L < 0.05

JONCKHEERE: +- if p_J < 0.01

Blood chemistry (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Gluc (mmol/l)					
week: 5	7.504	7.942	7.382	6.499	7.046
9	7.646			7.295	6.936
Urea (mmol/l)					
week: 5	6.791	7.658	6.754	7.249	7.516
9	6.648			7.758	7.272
Creat (umol/l)					
week: 5	21.01	23.88	22.42	24.65	23.36
9	19.76			27.75*	26.96*+
Bili-tot (umol/l)					
week: 5	1.645	1.583	1.706	1.658	1.700
9	1.964			1.866	1.916
Prot (g/l)					
week: 5	66.67	67.35	65.39	64.96	65.88
9	68.20			67.60	65.68
Alb (g/l)					
week: 5	35.60	36.01	34.67*	35.10	35.46
9	36.57			36.67	35.46
Glob (g/l)					
week: 5	31.07	31.33	30.73	29.86	30.41
9	31.62			30.93	30.23

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
A/G (1)					
week: 5	1.147	1.150	1.130	1.179	1.169
9	1.160			1.190	1.172
Chol (mmol/l)					
week: 5	2.209	2.246	2.216	2.088	2.268
9	2.324			1.795	2.000
Na+ (mmol/l)					
week: 5	144.4	143.8	144.4	145.0	144.2
9	143.7			142.6	143.3
K+ (mmol/l)					
week: 5	3.328	3.458	3.524	3.354	3.460
9	3.096			3.183	3.042
Ca++ (mmol/l)					
week: 5	2.646	2.610	2.620	2.604	2.650
9	2.602			2.585	2.546
Cl- (mmol/l)					
week: 5	100.3	100.5	101.9	101.5	100.7
9	102.5			103.1	102.3
PO4-in (mmol/l)					
week: 5	2.083	1.978	1.958	1.986	2.065
9	1.258			1.378	1.264
ASAT (GOT) (U/l)					
week: 5	67.96	66.62	64.90	72.85	70.42
9	62.94			63.90	64.40

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
ALAT (GPT) (U/l)					
week: 5	24.70	27.66	25.34	24.23	26.50
9	24.08			23.04	24.38*
ALP (U/l)					
week: 5	111.3	125.1	115.4	103.1	140.4
9	75.98			68.50	80.98

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.17. Blood chemistry (statistics)Statistical tests and flags used:LEPAGE: * if p_L < 0.05

a/b ind. of diff. in loc./disp.

JONCKHEERE: +- if p_J < 0.01Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Gluc (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	7.908	8.010	8.440	7.858	8.911
SD	0.963	0.385	0.328	0.775	0.707
Median	7.510	7.810	8.520	7.710	8.780
IQ-Range	1.250	0.460	0.230	1.000	1.260
Min	6.900	7.700	7.970	6.440	8.200
Max	10.07	8.600	8.860	8.800	10.22
p _L		0.070	0.090	0.943	0.021 *
p _J		0.178	0.030	0.444	0.006 +
week: 9 N	5			5	5
Mean	7.486			8.108	7.886
SD	0.441			0.596	0.690
Median	7.480			7.800	8.260
IQ-Range	0.270			0.550	0.740
Min	6.790			7.650	6.800
Max	7.970			9.080	8.430
p _L				0.224	0.278
p _J				0.095	0.170
Urea (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	5.662	6.768	5.676	6.097	6.177
SD	1.050	1.124	1.335	0.580	0.808
Median	5.660	7.040	5.120	6.100	6.310
IQ-Range	1.810	1.910	2.060	0.880	1.180
Min	4.200	5.360	4.300	5.100	5.000
Max	7.330	7.850	7.340	6.800	7.420
p _L		0.218	0.698	0.264	0.318
p _J		0.086	0.546	0.517	0.426

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	6.416			6.312	6.526
SD	1.222			0.832	1.140
Median	6.550			6.540	6.780
IQ-Range	0.760			1.430	0.260
Min	4.410			5.300	4.660
Max	7.600			7.130	7.770
p_L				0.609	0.609
p_J				0.602	0.874
Creat (umol/l)					
week: 5 N	10	5	5	9	10
Mean	17.66	18.74	18.46	19.13	19.85
SD	1.852	2.011	1.885	2.230	2.641
Median	17.75	18.60	19.50	19.10	19.85
IQ-Range	1.900	0.300	2.900	1.900	4.400
Min	13.30	16.30	15.90	16.30	15.00
Max	19.90	21.90	20.00	22.70	23.10
p_L		0.717	0.138	0.321	0.089
p_J		0.624	0.414	0.195	0.034
week: 9 N	5			5	5
Mean	17.92			19.96	18.98
SD	2.711			1.144	2.309
Median	18.20			20.40	18.80
IQ-Range	4.000			1.400	1.100
Min	14.20			18.30	15.60
Max	20.60			21.10	22.00
p_L				0.268	0.609
p_J				0.117	0.492
Bili-tot (umol/l)					
week: 5 N	10	5	5	9	10
Mean	1.388	1.042	1.262	1.426	1.446
SD	0.373	0.145	0.295	0.319	0.285
Median	1.285	0.970	1.290	1.400	1.455
IQ-Range	0.630	0.100	0.190	0.190	0.410
Min	1.010	0.950	0.850	1.050	1.090
Max	2.080	1.290	1.660	2.110	1.980
p_L		0.063	0.861	0.488	0.451
p_J		0.027	0.286	0.387	0.108

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	1.565			1.803	1.850
SD	0.329			0.423	0.220
Median	1.480			1.830	1.980
IQ-Range	0.210			0.310	0.390
Min	1.195			1.325	1.600
Max	2.080			2.450	2.040
p_L				0.643	0.230
p_J				0.347	0.154
Prot (g/l)					
week: 5 N	10	5	5	9	10
Mean	66.80	66.87	68.04	67.34	66.61
SD	2.211	2.060	1.157	1.387	2.329
Median	66.50	66.95	67.72	67.08	67.08
IQ-Range	1.510	2.490	1.090	1.110	3.530
Min	63.73	64.01	66.65	65.39	62.42
Max	71.50	69.24	69.69	69.75	69.81
p_L		0.921	0.186	0.478	0.567
p_J		0.806	0.145	0.246	0.765
week: 9 N	5			5	5
Mean	67.38			66.26	67.80
SD	0.769			2.715	1.706
Median	66.98			65.95	67.84
IQ-Range	1.350			4.780 b	1.390
Min	66.67			63.32	65.18
Max	68.26			69.31	69.69
p_L				0.034 *	0.700
p_J				0.602	0.561
Alb (g/l)					
week: 5 N	10	5	5	9	10
Mean	34.57	34.54	34.73	34.63	34.63
SD	0.907	0.651	0.605	0.744	1.091
Median	34.71	34.31	34.58	34.41	34.62
IQ-Range	1.370	0.750	0.580	1.020	2.070
Min	33.23	33.93	34.25	33.39	33.12
Max	36.15	35.53	35.72	35.60	36.46
p_L		0.855	0.525	0.901	0.952
p_J		0.854	0.943	0.875	0.891

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	34.66			34.27	35.14
SD	0.505			1.429	0.846
Median	34.49			33.33	35.05
IQ-Range	0.615			2.390 b	0.220
Min	34.14			33.15	34.05
Max	35.39			36.04	36.42
p_L				0.034 *	0.588
p_J				0.602	0.492
Glob (g/l)					
week: 5 N	10	5	5	9	10
Mean	32.23	32.32	33.31	32.72	31.98
SD	1.708	1.675	0.619	0.709	1.412
Median	31.60	32.10	33.28	32.66	32.52
IQ-Range	1.120	2.200	0.640	0.240	2.540
Min	30.20	30.08	32.39	31.78	29.30
Max	36.50	34.21	33.97	34.15	33.35
p_L		0.841	0.105	0.055	0.795
p_J		0.624	0.070	0.087	0.610
week: 9 N	5			5	5
Mean	32.71			31.99	32.66
SD	0.888			1.440	1.509
Median	32.53			32.62	32.40
IQ-Range	0.890			2.320	2.220
Min	31.59			30.10	31.13
Max	33.92			33.27	34.71
p_L				0.797	0.424
p_J				0.602	0.958
A/G (1)					
week: 5 N	10	5	5	9	10
Mean	1.075	1.072	1.042	1.058	1.084
SD	0.049	0.049	0.013	0.014	0.034
Median	1.090	1.090	1.040	1.060	1.080
IQ-Range	0.050	0.040	0.020	0.020	0.040
Min	0.960	1.000	1.030	1.040	1.030
Max	1.130	1.130	1.060	1.080	1.140
p_L		0.952	0.118	0.035 *	0.895
p_J		0.759	0.088	0.125	0.891

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	1.060			1.070	1.078
SD	0.040			0.030	0.055
Median	1.050			1.080	1.080
IQ-Range	0.020			0.010	0.040
Min	1.010			1.020	1.010
Max	1.120			1.100	1.160
p_L				0.637	0.648
p_J				0.403	0.428
Chol (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	1.723	1.884	1.908	1.848	1.847
SD	0.203	0.388	0.188	0.162	0.263
Median	1.710	1.900	1.900	1.800	1.735
IQ-Range	0.130	0.120	0.100	0.120	0.460
Min	1.400	1.290	1.630	1.620	1.500
Max	2.190	2.370	2.150	2.140	2.280
p_L		0.069	0.161	0.194	0.706
p_J		0.142	0.076	0.195	0.478
week: 9 N	5			5	5
Mean	1.656			1.898	1.874
SD	0.117			0.334	0.320
Median	1.670			1.700	1.880
IQ-Range	0.080			0.290	0.330
Min	1.470			1.670	1.530
Max	1.780			2.450	2.350
p_L				0.369	0.186
p_J				0.210	0.369
Na+ (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	144.3	143.1	143.7	144.9	143.6
SD	2.026	1.102	0.841	1.394	0.948
Median	143.4	143.0	143.6	144.6	143.5
IQ-Range	3.600	0.300	0.700	1.500	1.600
Min	142.3	141.9	143.0	142.2	142.5
Max	147.3	144.9	145.1	146.8	145.2
p_L		0.319	0.170	0.178	0.270
p_J		0.327	0.972	0.175	0.794

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	144.0			144.0	144.7
SD	0.856			0.887	0.630
Median	144.1			144.3	144.4
IQ-Range	1.200			0.100	0.700
Min	143.0			142.4	144.2
Max	145.1			144.5	145.7
p_L				0.442	0.230
p_J				0.917	0.342
K+ (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	3.492	3.716	3.730	3.613	3.941
SD	0.233	0.255	0.113	0.198	0.280
Median	3.380	3.810	3.730	3.580	3.955 a
IQ-Range	0.370	0.200	0.090	0.180	0.330
Min	3.270	3.320	3.620	3.280	3.530
Max	3.930	3.990	3.910	3.880	4.555
p_L		0.243	0.120	0.175	0.009 *
p_J		0.142	0.082	0.326	0.002 +
week: 9 N	5			5	5
Mean	3.452			3.526	3.624
SD	0.215			0.163	0.119
Median	3.590			3.490	3.610
IQ-Range	0.290			0.230	0.160
Min	3.150			3.360	3.500
Max	3.630			3.750	3.790
p_L				0.801	0.470
p_J				0.531	0.139
Ca++ (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	2.634	2.674	2.706	2.659	2.696
SD	0.066	0.051	0.056	0.046	0.103
Median	2.665	2.680	2.710	2.650	2.690
IQ-Range	0.090	0.060	0.060	0.070	0.140
Min	2.530	2.600	2.620	2.610	2.550
Max	2.720	2.730	2.760	2.750	2.890
p_L		0.496	0.082	0.601	0.255
p_J		0.245	0.028	0.377	0.204

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	2.610			2.620	2.634
SD	0.023			0.028	0.081
Median	2.620			2.620	2.620
IQ-Range	0.010			0.000	0.120
Min	2.570			2.580	2.530
Max	2.630			2.660	2.720
p_L				0.825	0.338
p_J				0.602	0.597
Cl- (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	98.93	98.96	100.0	98.54	97.84
SD	1.778	1.936	1.409	1.255	1.808
Median	99.20	100.0	99.90	98.80	98.20
IQ-Range	2.200	1.000	2.200	1.400	2.600
Min	95.60	95.60	98.50	96.50	95.00
Max	101.0	100.2	101.8	100.7	100.8
p_L		0.854	0.526	0.469	0.328
p_J		0.854	0.414	0.492	0.062
week: 9 N	5			5	5
Mean	101.9			101.8	99.42
SD	1.363			1.193	1.525
Median	101.7			101.3	100.0
IQ-Range	1.800			1.700	2.600
Min	100.2			100.6	97.50
Max	103.6			103.4	100.8
p_L				0.870	0.082
p_J				0.754	0.017
PO4-in (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	2.208	2.066	2.046	2.114	2.297
SD	0.284	0.131	0.225	0.201	0.321
Median	2.220	2.120	2.140	2.070	2.245
IQ-Range	0.520	0.140	0.340	0.320	0.230
Min	1.750	1.870	1.740	1.820	1.930
Max	2.660	2.200	2.250	2.410	3.040
p_L		0.093	0.497	0.557	0.914
p_J		0.270	0.255	0.444	0.542

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	1.704			1.698	1.824
SD	0.184			0.167	0.203
Median	1.670			1.740	1.820
IQ-Range	0.170			0.260	0.160
Min	1.540			1.490	1.500
Max	2.000			1.880	2.020
p_L				0.812	0.588
p_J				1.000	0.316
ASAT (GOT) (U/l)					
week: 5 N	10	5	5	9	10
Mean	68.07	66.94	65.26	64.41	74.08
SD	9.473	6.782	4.791	9.444	19.57
Median	72.65	66.70	67.40	63.30	64.75
IQ-Range	15.10	8.000	6.500	10.10	17.00
Min	53.20	57.40	59.00	55.00	59.70
Max	81.20	74.60	70.40	85.00	120.6
p_L		0.361	0.044 *	0.346	0.914
p_J		0.713	0.414	0.169	0.746
week: 9 N	5			5	5
Mean	76.14			82.21	76.18
SD	14.05			16.34	9.997
Median	81.40			80.20	73.30
IQ-Range	10.80			5.800	16.00
Min	54.80			63.00	66.10
Max	91.90			108.1	88.90
p_L				0.952	0.995
p_J				0.754	0.958
ALAT (GPT) (U/l)					
week: 5 N	10	5	5	9	10
Mean	33.08	29.08	29.34	28.72	39.79
SD	5.053	3.642	2.402	4.007	17.88
Median	33.35	30.60	28.60	30.70	33.00
IQ-Range	7.700	1.700	2.400	5.600	15.60
Min	25.40	22.70	27.30	22.00	28.00
Max	39.70	31.40	33.20	33.30	87.00
p_L		0.167	0.271	0.106	0.941
p_J		0.159	0.076	0.087	0.700

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	39.64			29.92	35.70
SD	9.456			4.866	7.022
Median	44.10			28.40	34.90
IQ-Range	8.500			4.500	7.400
Min	24.30			26.00	29.60
Max	47.50			37.90	46.80
p_L				0.177	0.700
p_J				0.175	0.712
ALP (U/l)					
week: 5 N	10	5	5	9	10
Mean	164.6	159.7	163.9	150.2	187.8
SD	29.79	41.74	29.16	16.58	32.87
Median	154.7	158.2	149.2	149.7	192.9
IQ-Range	57.10	35.00	24.30	23.90	40.50
Min	130.8	105.7	144.4	122.6	142.4
Max	207.0	218.3	212.9	172.9	245.1
p_L		0.845	0.463	0.439	0.328
p_J		0.903	0.804	0.479	0.204
week: 9 N	5			5	5
Mean	126.3			116.7	126.3
SD	19.39			12.42	12.40
Median	126.2			121.7	118.8
IQ-Range	13.50			5.200	13.30
Min	96.50			95.00	117.6
Max	148.6			125.2	146.0
p_L				0.278	0.873
p_J				0.175	0.428

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

169

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

LEPAGE: * if $p_L < 0.05$
 a/b ind. of diff. in loc./disp.
 JONCKHEERE: +- if $p_J < 0.01$

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Gluc (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	7.504	7.942	7.382	6.499	7.046
SD	0.935	1.229	0.355	0.571	1.079
Median	7.650	7.930	7.420	6.475	6.615
IQ-Range	1.620	1.200	0.390	0.800	1.030
Min	6.100	6.270	7.030	5.630	6.120
Max	8.810	9.530	7.910	7.350	9.570
p_L		0.627	0.238	0.054	0.502
p_J		0.501	0.831	0.010	0.023
week: 9 N	5	5	4	5	
Mean	7.646		7.295		6.936
SD	0.744		1.243		1.123
Median	7.560		7.330		6.760
IQ-Range	1.020		1.950		1.070
Min	6.810		5.830		6.010
Max	8.640		8.690		8.760
p_L			0.413		0.230
p_J					0.349
Urea (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	6.791	7.658	6.754	7.249	7.516
SD	0.962	0.919	0.452	1.047	1.152
Median	6.675	8.010	6.780	7.420	7.680
IQ-Range	1.180	0.320	0.430	1.375	1.140
Min	5.600	6.040	6.120	5.490	6.080
Max	8.800	8.260	7.320	8.770	10.01
p_L		0.161	0.268	0.398	0.265
p_J		0.111	0.696	0.374	0.191

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

170

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	6.648			7.758	7.272
SD	1.020			0.683	0.693
Median	6.550			7.580	7.050
IQ-Range	0.520			0.965	1.100
Min	5.300			7.160	6.620
Max	8.130			8.710	8.190
p_L				0.152	0.278
p_J					0.266
Creat (umol/l)					
week: 5 N	10	5	5	8	10
Mean	21.01	23.88	22.42	24.65	23.36
SD	2.757	2.683	3.167	3.125	2.335
Median	20.40	23.10	20.60	24.75	23.00
IQ-Range	4.300	3.500	4.700	5.400	0.800
Min	17.20	20.60	19.70	20.50	20.20
Max	25.50	27.20	26.70	29.20	27.70
p_L		0.158	0.611	0.083	0.068
p_J		0.058	0.189	0.024	0.056
week: 9 N	5			4	5
Mean	19.76			27.75	26.96
SD	1.315			6.994	2.819
Median	19.30			25.45 a	25.50 a
IQ-Range	2.200			9.400	4.800
Min	18.50			22.30	24.60
Max	21.40			37.80	30.50
p_L				0.043 *	0.033 *
p_J					0.004 +
Bili-tot (umol/l)					
week: 5 N	10	5	5	8	10
Mean	1.645	1.583	1.706	1.658	1.700
SD	0.355	0.317	0.336	0.419	0.313
Median	1.685	1.500	1.750	1.645	1.650
IQ-Range	0.460	0.290	0.340	0.590	0.570
Min	1.020	1.165	1.190	1.150	1.300
Max	2.300	2.000	2.050	2.360	2.220
p_L		0.914	0.841	0.999	0.991
p_J		0.903	0.644	0.869	0.766

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9	N	5			4	5
	Mean	1.964			1.866	1.916
	SD	0.418			0.703	0.383
	Median	2.050			1.780	1.750
	IQ-Range	0.610			1.188	0.460
	Min	1.530			1.255	1.550
	Max	2.510			2.650	2.480
	p_L				0.137	0.694
	p_J					0.953
Prot (g/l)						
week: 5	N	10	5	5	8	10
	Mean	66.67	67.35	65.39	64.96	65.88
	SD	1.585	2.709	1.565	1.481	2.493
	Median	66.44	66.08	65.82	64.99	66.00
	IQ-Range	1.780	3.380	1.800	2.250	3.440
	Min	64.46	64.87	62.97	62.69	60.92
	Max	69.92	71.33	66.79	67.13	69.10
	p_L		0.431	0.466	0.139	0.416
	p_J		1.000	0.303	0.033	0.200
week: 9	N	5			4	5
	Mean	68.20			67.60	65.68
	SD	2.811			1.410	1.254
	Median	68.11			67.83	65.90
	IQ-Range	1.620			1.910	0.830
	Min	64.64			65.69	63.62
	Max	72.38			69.05	66.88
	p_L				0.642	0.092
	p_J					0.053
Alb (g/l)						
week: 5	N	10	5	5	8	10
	Mean	35.60	36.01	34.67	35.10	35.46
	SD	0.788	1.510	0.940	1.547	1.244
	Median	35.53	35.13	34.67	34.96	35.33
	IQ-Range	1.030	2.380	0.710	2.025	2.140
	Min	34.72	34.59	33.67	32.56	33.79
	Max	37.31	37.85	36.14	37.39	37.41
	p_L		0.416	0.023 *	0.186	0.314
	p_J		0.806	0.145	0.160	0.535

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			4	5
	Mean	36.57			36.67	35.46
	SD	1.544			2.166	0.372
	Median	36.58			36.39	35.55
	IQ-Range	2.970			2.855	0.350
	Min	34.96			34.35	34.95
	Max	38.16			39.57	35.93
	p_L				0.867	0.152
	p_J					0.266
Glob (g/l)						
week:	5 N	10	5	5	8	10
	Mean	31.07	31.33	30.73	29.86	30.41
	SD	1.029	1.573	1.302	0.939	1.754
	Median	30.76	31.07	30.45	30.28	30.84
	IQ-Range	1.920	1.010	1.140	1.375	2.610
	Min	29.74	29.74	29.30	28.37	27.13
	Max	32.61	33.89	32.72	31.11	32.19
	p_L		0.982	0.638	0.130	0.597
	p_J		0.854	0.670	0.045	0.166
week:	9 N	5			4	5
	Mean	31.62			30.93	30.23
	SD	1.703			0.966	0.965
	Median	31.53			31.39	30.34
	IQ-Range	1.350			1.035	0.190
	Min	29.68			29.48	28.67
	Max	34.22			31.46	31.33
	p_L				0.236	0.204
	p_J					0.040
A/G (1)						
week:	5 N	10	5	5	8	10
	Mean	1.147	1.150	1.130	1.179	1.169
	SD	0.034	0.052	0.058	0.074	0.068
	Median	1.145	1.150	1.150	1.185	1.165
	IQ-Range	0.050	0.080	0.050	0.075	0.050
	Min	1.090	1.100	1.040	1.050	1.060
	Max	1.200	1.220	1.190	1.300	1.290
	p_L		0.558	0.885	0.128	0.671
	p_J		0.903	0.831	0.230	0.244

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	1.160			1.190	1.172
SD	0.055			0.104	0.033
Median	1.160			1.160	1.170
IQ-Range	0.060			0.130	0.020
Min	1.100			1.100	1.130
Max	1.240			1.340	1.220
p_L				0.949	0.371
p_J					0.598
Chol (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	2.209	2.246	2.216	2.088	2.268
SD	0.266	0.525	0.249	0.271	0.385
Median	2.215	2.040	2.240	2.145	2.235
IQ-Range	0.480	0.110	0.410	0.455	0.730
Min	1.800	1.940	1.920	1.680	1.810
Max	2.600	3.180	2.490	2.400	2.810
p_L		0.876	0.967	0.752	0.398
p_J		0.668	1.000	0.549	0.897
week: 9 N	5			4	5
Mean	2.324			1.795	2.000
SD	0.286			0.373	0.422
Median	2.150			1.750	1.890
IQ-Range	0.270			0.570	0.100
Min	2.130			1.410	1.580
Max	2.790			2.270	2.710
p_L				0.137	0.092
p_J					0.128
Na+ (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	144.4	143.8	144.4	145.0	144.2
SD	0.842	1.291	1.332	1.125	0.921
Median	144.5	143.6	144.2	145.3	144.1
IQ-Range	1.300	0.500	0.500	1.600	0.900
Min	143.3	142.1	142.7	143.5	142.9
Max	145.8	145.7	146.4	146.9	146.0
p_L		0.727	0.982	0.318	0.812
p_J		0.426	0.831	0.264	0.816

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	143.7			142.6	143.3
SD	1.585			0.265	1.054
Median	143.5			142.6	143.6
IQ-Range	0.600			0.400	1.700
Min	141.7			142.2	142.0
Max	146.1			142.8	144.4
p_L				0.129	0.995
p_J					0.770
K+ (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	3.328	3.458	3.524	3.354	3.460
SD	0.275	0.297	0.161	0.392	0.244
Median	3.250	3.400	3.550	3.245	3.455
IQ-Range	0.400	0.310	0.230	0.500	0.280
Min	2.860	3.020	3.360	2.910	3.040
Max	3.730	3.760	3.740	3.995	3.780
p_L		0.690	0.178	0.669	0.556
p_J		0.391	0.189	0.918	0.477
week: 9 N	5			4	5
Mean	3.096			3.183	3.042
SD	0.294			0.404	0.130
Median	3.170			3.195	3.040
IQ-Range	0.430			0.625	0.050
Min	2.800			2.700	2.880
Max	3.480			3.640	3.240
p_L				0.569	0.227
p_J					0.815
Ca++ (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	2.646	2.610	2.620	2.604	2.650
SD	0.071	0.071	0.070	0.104	0.065
Median	2.640	2.620	2.620	2.605	2.655
IQ-Range	0.120	0.090	0.060	0.110	0.110
Min	2.550	2.520	2.550	2.410	2.530
Max	2.770	2.700	2.730	2.750	2.730
p_L		0.654	0.760	0.696	0.855
p_J		0.358	0.374	0.331	0.846

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	2.602			2.585	2.546
SD	0.094			0.031	0.044
Median	2.600			2.595	2.550
IQ-Range	0.080			0.040	0.050
Min	2.490			2.540	2.500
Max	2.740			2.610	2.610
p_L				0.472	0.395
p_J					0.242
Cl- (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	100.3	100.5	101.9	101.5	100.7
SD	1.544	1.681	0.804	2.251	2.651
Median	100.4	100.4	102.0	101.3	100.9
IQ-Range	2.300	1.900	0.800	3.650	2.800
Min	97.70	98.10	100.6	98.80	94.60
Max	102.6	102.4	102.6	105.0	103.6
p_L		0.982	0.183	0.390	0.563
p_J		0.854	0.082	0.098	0.289
week: 9 N	5			4	5
Mean	102.5			103.1	102.3
SD	1.815			1.281	0.820
Median	101.9			103.2	102.0
IQ-Range	0.700			2.075	1.000
Min	100.9			101.6	101.5
Max	105.6			104.5	103.5
p_L				0.762	0.956
p_J					1.000
PO4-in (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	2.083	1.978	1.958	1.986	2.065
SD	0.151	0.205	0.146	0.321	0.117
Median	2.050	2.010	2.010	1.975	2.050
IQ-Range	0.290	0.230	0.180	0.605	0.170
Min	1.890	1.700	1.780	1.600	1.910
Max	2.300	2.230	2.140	2.430	2.250
p_L		0.610	0.501	0.175	0.454
p_J		0.327	0.201	0.341	1.000

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			4	5
Mean	1.258			1.378	1.264
SD	0.101			0.242	0.156
Median	1.230			1.390	1.240
IQ-Range	0.080			0.415	0.150
Min	1.160			1.130	1.080
Max	1.420			1.600	1.490
p_L				0.289	0.694
p_J					0.953
ASAT (GOT) (U/l)					
week: 5 N	10	5	5	8	10
Mean	67.96	66.62	64.90	72.85	70.42
SD	4.312	7.892	4.366	13.10	11.77
Median	68.60	65.80	67.40	71.60	65.55
IQ-Range	6.900	11.60	7.700	22.90	13.90
Min	59.50	56.60	60.00	57.40	57.50
Max	72.70	75.50	68.80	93.00	94.80
p_L		0.127	0.275	0.053	0.075
p_J		0.903	0.320	0.772	0.737
week: 9 N	5			4	5
Mean	62.94			63.90	64.40
SD	8.123			4.447	10.97
Median	63.40			63.05	65.50
IQ-Range	6.300			6.700	8.000
Min	50.20			59.70	48.00
Max	71.60			69.80	77.70
p_L				0.969	0.694
p_J					0.907
ALAT (GPT) (U/l)					
week: 5 N	10	5	5	8	10
Mean	24.70	27.66	25.34	24.23	26.50
SD	3.942	2.141	2.353	3.257	3.506
Median	24.75	27.20	25.40	24.55	25.25
IQ-Range	5.400	1.800	3.400	4.100	5.600
Min	19.80	25.90	22.30	20.60	23.00
Max	31.80	31.20	28.00	30.50	33.20
p_L		0.120	0.875	0.568	0.699
p_J		0.086	0.394	0.605	0.866

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (statistics) : females

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			4	5
	Mean	24.08			23.04	24.38
	SD	5.448			2.813	1.740
	Median	22.20			23.10	23.70
	IQ-Range	7.700			4.225	0.900 b
	Min	18.70			19.65	22.80
	Max	31.60			26.30	27.30
	p_L				0.502	0.034 *
	p_J					0.558
ALP (U/l)						
week:	5 N	10	5	5	8	10
	Mean	111.3	125.1	115.4	103.1	140.4
	SD	19.96	23.32	23.47	20.54	33.95
	Median	108.0	136.1	112.5	107.3	137.9
	IQ-Range	28.30	40.30	33.40	27.15	55.00
	Min	85.00	98.00	89.20	68.70	81.10
	Max	149.8	147.2	146.2	134.2	184.7
	p_L		0.445	0.903	0.811	0.105
	p_J		0.327	0.776	0.432	0.162
week:	9 N	5			4	5
	Mean	75.98			68.50	80.98
	SD	14.90			15.37	19.94
	Median	70.60			61.40	79.80
	IQ-Range	15.40			16.70	4.500
	Min	58.50			59.70	55.70
	Max	96.80			91.50	111.5
	p_L				0.762	0.870
	p_J					0.861

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.18. Urine analysis (means)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Urine analysis (means): males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Volume (ml)					
week: 5	5.200	4.700	5.960	5.589	3.470*
9	6.080			5.700	3.580*
Rel dens (1)					
week: 5	1.037	1.039	1.035	1.043	1.053*+
9	1.043			1.043	1.060
pH (1)					
week: 5	6.550	6.400	6.400	6.222	5.150*-
9	6.800			6.600	6.500
PRO (g/l)					
week: 5	0.600	0.650	0.750	0.583	0.550
9	0.350			0.550	0.450
GLU (mmol/l)					
week: 5	0.000	0.000	0.000	0.000	0.000
9	0.000			0.000	0.000
KET (mmol/l)					
week: 5	0.900	0.900	0.700	1.167	0.900
9	0.700			1.100	1.300
UBG (umol/l)					
week: 5	0.000	0.000	0.000	3.778	3.400
9	0.000			0.000	0.000

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
BIL ($\mu\text{mol/l}$)					
week: 5	3.400	6.800	3.400	5.667	11.90*
9	0.000			0.000	0.000
ERY (per μl)					
week: 5	10.50	13.00	10.00	13.33	10.00
9	6.000			67.00*	19.00
LEU (per μl)					
week: 5	77.50	100.0	70.00	41.67*	25.00*-
9	40.00			20.00	25.00

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

WILCOXON: * if $p_W < 0.05$

JONCKHEERE: +- if $p_J < 0.01$

Urine analysis (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Volume (ml)					
week: 5	3.190	2.480	3.260	2.263	2.350
9	4.440			2.375*	3.400
Rel dens (1)					
week: 5	1.039	1.051	1.041	1.052	1.048
9	1.040			1.058	1.039
pH (1)					
week: 5	5.950	5.800	6.000	5.563	5.000*-
9	6.400			6.000	6.200
PRO (g/l)					
week: 5	0.400	0.450	0.450	0.563	0.550
9	0.350			0.250	0.250
GLU (mmol/l)					
week: 5	0.000	0.000	0.000	0.000	0.000
9	0.000			0.000	0.000
KET (mmol/l)					
week: 5	0.700	0.900	0.700	0.688	0.700
9	0.600			0.750	0.400
UBG (umol/l)					
week: 5	3.400	6.800	6.800	10.63	15.30*+
9	0.000			0.000	0.000

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (means) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
BIL (umol/l)					
week: 5	1.700	3.400	10.20*	6.375	10.20*
9	0.000			0.000	0.000
ERY (per ul)					
week: 5	11.50	10.00	10.00	8.750	9.000
9	10.00			21.25	6.000
LEU (per ul)					
week: 5	25.00	25.00	25.00	25.00	22.50
9	0.000			6.250	10.00

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No statistical tests performed

Urine analysis (incidence) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Color (choice)					
week: 5	0/10	0/5	0/5	0/9	0/10
9	0/5			0/5	0/5

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No statistical tests performed

Urine analysis (incidence) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Color (choice)					
week: 5	0/10	0/5	0/5	0/8	0/10
9	0/5			0/4	0/5

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.19. Urine analysis (statistics)Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Urine analysis (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Volume (ml)					
week: 5 N	10	5	5	9	10
Mean	5.200	4.700	5.960	5.589	3.470
SD	1.891	1.012	1.101	1.847	0.763
Median	5.300	4.500	6.300	5.800	3.450
Min	2.400	3.800	4.100	3.200	2.400
Max	8.200	6.400	7.000	9.000	5.000
p_W		0.759	0.391	0.624	0.034 *
p_J		0.759	0.434	0.492	0.033
week: 9 N	5	5	5	5	5
Mean	6.080	6.080	5.700	5.700	3.580
SD	1.529	1.529	2.046	2.046	0.683
Median	5.600	5.600	5.500	5.500	3.700
Min	4.300	4.300	4.000	4.000	2.700
Max	8.000	8.000	9.100	9.100	4.400
p_W			0.602	0.602	0.016 *
p_J			0.602	0.602	0.011
Rel dens (1)					
week: 5 N	10	5	5	9	10
Mean	1.037	1.039	1.035	1.043	1.053
SD	0.007	0.008	0.006	0.009	0.014
Median	1.036	1.041	1.033	1.044	1.050
Min	1.029	1.030	1.030	1.028	1.032
Max	1.046	1.049	1.045	1.056	1.075
p_W		0.759	0.758	0.190	0.007 *
p_J		0.759	0.887	0.188	0.003 +

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : males

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	5			5	5
	Mean	1.043			1.043	1.060
	SD	0.013			0.013	0.018
	Median	1.046			1.041	1.058
	Min	1.031			1.029	1.043
	Max	1.062			1.064	1.084
	p_W				0.753	0.249
	p_J				0.754	0.224
pH	(1)					
week:	5 N	10	5	5	9	10
	Mean	6.550	6.400	6.400	6.222	5.150
	SD	0.158	0.224	0.224	0.565	0.474
	Median	6.500	6.500	6.500	6.500	5.000
	Min	6.500	6.000	6.000	5.000	5.000
	Max	7.000	6.500	6.500	7.000	6.500
	p_W		0.147	0.147	0.082	0.000 *
	p_J		0.391	0.320	0.121	0.000 -
week:	9 N	5			5	5
	Mean	6.800			6.600	6.500
	SD	0.274			0.224	0.354
	Median	7.000			6.500	6.500
	Min	6.500			6.500	6.000
	Max	7.000			7.000	7.000
	p_W				0.221	0.166
	p_J				0.296	0.170
PRO	(g/l)					
week:	5 N	10	5	5	9	10
	Mean	0.600	0.650	0.750	0.583	0.550
	SD	0.242	0.224	0.000	0.250	0.258
	Median	0.750	0.750	0.750	0.750	0.750
	Min	0.250	0.250	0.750	0.250	0.250
	Max	0.750	0.750	0.750	0.750	0.750
	p_W		0.690	0.186	0.879	0.648
	p_J		0.759	0.374	0.984	0.576

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	0.350			0.550	0.450
SD	0.224			0.274	0.274
Median	0.250			0.750	0.250
Min	0.250			0.250	0.250
Max	0.750			0.750	0.750
p_W				0.221	0.513
p_J				0.296	0.597
GLU (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	0.000	0.000	0.000	0.000	0.000
SD	0.000	0.000	0.000	0.000	0.000
Median	0.000	0.000	0.000	0.000	0.000
Min	0.000	0.000	0.000	0.000	0.000
Max	0.000	0.000	0.000	0.000	0.000
p_W		1.000	1.000	1.000	1.000
p_J		1.000	1.000	1.000	1.000
week: 9 N	5			5	5
Mean	0.000			0.000	0.000
SD	0.000			0.000	0.000
Median	0.000			0.000	0.000
Min	0.000			0.000	0.000
Max	0.000			0.000	0.000
p_W				1.000	1.000
p_J				1.000	1.000
KET (mmol/l)					
week: 5 N	10	5	5	9	10
Mean	0.900	0.900	0.700	1.167	0.900
SD	0.516	0.548	0.447	0.500	0.516
Median	0.500	0.500	0.500	1.500	0.500
Min	0.500	0.500	0.500	0.500	0.500
Max	1.500	1.500	1.500	1.500	1.500
p_W		1.000	0.454	0.258	1.000
p_J		1.000	0.594	0.409	0.728

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	0.700			1.100	1.300
SD	0.447			0.548	0.447
Median	0.500			1.500	1.500
Min	0.500			0.500	0.500
Max	1.500			1.500	1.500
p_W				0.221	0.072
p_J				0.296	0.113
UBG (umol/l)					
week: 5 N	10	5	5	9	10
Mean	0.000	0.000	0.000	3.778	3.400
SD	0.000	0.000	0.000	7.496	7.168
Median	0.000	0.000	0.000	0.000	0.000
Min	0.000	0.000	0.000	0.000	0.000
Max	0.000	0.000	0.000	17.00	17.00
p_W		1.000	1.000	0.125	0.146
p_J		1.000	1.000	0.432	0.332
week: 9 N	5			5	5
Mean	0.000			0.000	0.000
SD	0.000			0.000	0.000
Median	0.000			0.000	0.000
Min	0.000			0.000	0.000
Max	0.000			0.000	0.000
p_W				1.000	1.000
p_J				1.000	1.000
BIL (umol/l)					
week: 5 N	10	5	5	9	10
Mean	3.400	6.800	3.400	5.667	11.90
SD	7.168	9.311	7.603	8.500	8.212
Median	0.000	0.000	0.000	0.000	17.00
Min	0.000	0.000	0.000	0.000	0.000
Max	17.00	17.00	17.00	17.00	17.00
p_W		0.425	1.000	0.521	0.028 *
p_J		0.540	0.859	0.694	0.075

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	0.000			0.000	0.000
SD	0.000			0.000	0.000
Median	0.000			0.000	0.000
Min	0.000			0.000	0.000
Max	0.000			0.000	0.000
p_W				1.000	1.000
p_J				1.000	1.000
ERY (per ul)					
week: 5 N	10	5	5	9	10
Mean	10.50	13.00	10.00	13.33	10.00
SD	5.986	6.708	0.000	6.614	0.000
Median	10.00	10.00	10.00	10.00	10.00
Min	0.000	10.00	10.00	10.00	10.00
Max	25.00	25.00	10.00	25.00	10.00
p_W		0.430	1.000	0.301	1.000
p_J		0.582	0.887	0.517	0.970
week: 9 N	5			5	5
Mean	6.000			67.00	19.00
SD	5.477			102.5	19.49
Median	10.00			25.00	10.00
Min	0.000			10.00	0.000
Max	10.00			250.0	50.00
p_W				0.016 *	0.214
p_J				0.022	0.224
LEU (per ul)					
week: 5 N	10	5	5	9	10
Mean	77.50	100.0	70.00	41.67	25.00
SD	36.23	0.000	41.08	33.07	0.000
Median	100.0	100.0	100.0	25.00	25.00
Min	25.00	100.0	25.00	25.00	25.00
Max	100.0	100.0	100.0	100.0	25.00
p_W		0.186	0.708	0.043 *	0.001 *
p_J		0.358	1.000	0.062	0.001 -

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	5			5	5
Mean	40.00			20.00	25.00
SD	33.54			11.18	0.000
Median	25.00			25.00	25.00
Min	25.00			0.000	25.00
Max	100.0			25.00	25.00
P_W				0.180	0.317
P_J				0.347	0.634

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Urine analysis (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Volume (ml)					
week: 5 N	10	5	5	8	10
Mean	3.190	2.480	3.260	2.263	2.350
SD	0.942	1.033	1.518	0.896	0.913
Median	3.400	2.000	3.400	2.300	2.300
Min	1.500	1.800	1.800	1.100	0.900
Max	4.800	4.300	5.500	3.600	4.200
p _W		0.177	1.000	0.055	0.064
p _J		0.178	0.522	0.066	0.046
week: 9 N	5			4	5
Mean	4.440			2.375	3.400
SD	1.365			0.802	1.042
Median	3.900			2.650	3.100
Min	3.500			1.200	2.200
Max	6.800			3.000	5.000
p _W				0.014 *	0.175
p _J					0.242
Rel dens (1)					
week: 5 N	10	5	5	8	10
Mean	1.039	1.051	1.041	1.052	1.048
SD	0.008	0.016	0.012	0.023	0.015
Median	1.041	1.046	1.041	1.047	1.049
Min	1.021	1.034	1.028	1.021	1.021
Max	1.048	1.075	1.060	1.088	1.072
p _W		0.194	0.902	0.212	0.075
p _J		0.198	0.776	0.311	0.137
week: 9 N	5			4	5
Mean	1.040			1.058	1.039
SD	0.013			0.013	0.003
Median	1.041			1.058	1.039
Min	1.026			1.046	1.036
Max	1.060			1.070	1.043
p _W				0.050	0.917
p _J					0.770

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : females

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
pH (1)	week: 5 N	10	5	5	8	10
	Mean	5.950	5.800	6.000	5.563	5.000
	SD	0.550	0.758	0.707	0.776	0.000
	Median	6.000	6.000	6.000	5.000	5.000
	Min	5.000	5.000	5.000	5.000	5.000
	Max	6.500	6.500	7.000	6.500	5.000
	p_W		0.845	0.947	0.370	0.001 *
	p_J		0.854	0.943	0.432	0.005 -
	week: 9 N	5			4	5
	Mean	6.400			6.000	6.200
	SD	0.548			0.000	0.447
	Median	6.000			6.000	6.000
	Min	6.000			6.000	6.000
	Max	7.000			6.000	7.000
p_W				0.176	0.513	
p_J					0.598	
PRO (g/l)	week: 5 N	10	5	5	8	10
	Mean	0.400	0.450	0.450	0.563	0.550
	SD	0.242	0.274	0.274	0.259	0.258
	Median	0.250	0.250	0.250	0.750	0.750
	Min	0.250	0.250	0.250	0.250	0.250
	Max	0.750	0.750	0.750	0.750	0.750
	p_W		0.708	0.708	0.180	0.189
	p_J		0.759	0.722	0.264	0.187
	week: 9 N	5			4	5
	Mean	0.350			0.250	0.250
	SD	0.224			0.000	0.000
	Median	0.250			0.250	0.250
	Min	0.250			0.250	0.250
	Max	0.750			0.250	0.250
p_W				0.371	0.317	
p_J					0.598	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
GLU (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	0.000	0.000	0.000	0.000	0.000
SD	0.000	0.000	0.000	0.000	0.000
Median	0.000	0.000	0.000	0.000	0.000
Min	0.000	0.000	0.000	0.000	0.000
Max	0.000	0.000	0.000	0.000	0.000
p_W		1.000	1.000	1.000	1.000
p_J		1.000	1.000	1.000	1.000
week: 9 N	5			4	5
Mean	0.000			0.000	0.000
SD	0.000			0.000	0.000
Median	0.000			0.000	0.000
Min	0.000			0.000	0.000
Max	0.000			0.000	0.000
p_W				1.000	1.000
p_J				1.000	1.000
KET (mmol/l)					
week: 5 N	10	5	5	8	10
Mean	0.700	0.900	0.700	0.688	0.700
SD	0.422	0.548	0.447	0.530	0.422
Median	0.500	0.500	0.500	0.500	0.500
Min	0.500	0.500	0.500	0.000	0.500
Max	1.500	1.500	1.500	1.500	1.500
p_W		0.425	1.000	0.821	1.000
p_J		0.540	0.859	0.836	0.836
week: 9 N	5			4	5
Mean	0.600			0.750	0.400
SD	0.548			0.500	0.224
Median	0.500			0.500	0.500
Min	0.000			0.500	0.000
Max	1.500			1.500	0.500
p_W				0.558	0.606
p_J					0.639

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
UBG (umol/l)					
week: 5 N	10	5	5	8	10
Mean	3.400	6.800	6.800	10.63	15.30
SD	7.168	9.311	9.311	8.798	5.376
Median	0.000	0.000	0.000	17.00	17.00
Min	0.000	0.000	0.000	0.000	0.000
Max	17.00	17.00	17.00	17.00	17.00
p_W		0.425	0.425	0.074	0.002 *
p_J		0.540	0.477	0.137	0.006 +
week: 9 N	5			4	5
Mean	0.000			0.000	0.000
SD	0.000			0.000	0.000
Median	0.000			0.000	0.000
Min	0.000			0.000	0.000
Max	0.000			0.000	0.000
p_W				1.000	1.000
p_J					1.000
BIL (umol/l)					
week: 5 N	10	5	5	8	10
Mean	1.700	3.400	10.20	6.375	10.20
SD	5.376	7.603	9.311	8.798	8.779
Median	0.000	0.000	17.00	0.000	17.00
Min	0.000	0.000	0.000	0.000	0.000
Max	17.00	17.00	17.00	17.00	17.00
p_W		0.604	0.046 *	0.175	0.022 *
p_J		0.759	0.155	0.215	0.056
week: 9 N	5			4	5
Mean	0.000			0.000	0.000
SD	0.000			0.000	0.000
Median	0.000			0.000	0.000
Min	0.000			0.000	0.000
Max	0.000			0.000	0.000
p_W				1.000	1.000
p_J					1.000

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (statistics) : females

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
ERY					
(per ul)					
week: 5 N	10	5	5	8	10
Mean	11.50	10.00	10.00	8.750	9.000
SD	4.743	0.000	0.000	3.536	3.162
Median	10.00	10.00	10.00	10.00	10.00
Min	10.00	10.00	10.00	0.000	0.000
Max	25.00	10.00	10.00	10.00	10.00
p_W		0.480	0.480	0.167	0.168
p_J		0.759	0.722	0.444	0.408
week: 9 N	5			4	5
Mean	10.00			21.25	6.000
SD	0.000			21.75	5.477
Median	10.00			17.50	10.00
Min	10.00			0.000	0.000
Max	10.00			50.00	10.00
p_W				0.467	0.134
p_J					0.412
LEU					
(per ul)					
week: 5 N	10	5	5	8	10
Mean	25.00	25.00	25.00	25.00	22.50
SD	0.000	0.000	0.000	0.000	7.906
Median	25.00	25.00	25.00	25.00	25.00
Min	25.00	25.00	25.00	25.00	0.000
Max	25.00	25.00	25.00	25.00	25.00
p_W		1.000	1.000	1.000	0.317
p_J		1.000	1.000	1.000	0.717
week: 9 N	5			4	5
Mean	0.000			6.250	10.00
SD	0.000			12.50	13.69
Median	0.000			0.000	0.000
Min	0.000			0.000	0.000
Max	0.000			25.00	25.00
p_W				0.264	0.134
p_J					0.292

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.20. Organ weights and ratios (means)

8.20.1. Organ weights (means): 1. sacrifice

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 4 200	group 5 1000
Body (g)	327.9	317.6	341.2	336.2	313.1
Brain (g)	2.192	2.167	2.151	2.218	2.151
Heart (g)	1.119	1.120	1.201	1.169	1.183
Liver (g)	14.91	15.38	17.29*+	14.84	14.61
Kidney (both) (g)	2.459	2.492	2.651	2.500	2.337
Adrenal (both) (mg)	75.22	83.08	73.76	74.20	77.82
Thymus (mg)	754.2	711.1	796.5	857.7	616.3
Testis (both) (g)	3.558	3.279	3.393	3.646	3.683
Spleen (g)	0.644	0.687	0.681	0.659	0.621
Epididymis (g)	1.145	1.096	1.166	1.199	1.151

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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 4 200	group 5 1000
Body (g)	211.3	212.9	213.6	212.0	212.4
Brain (g)	2.079	2.013	2.096	2.040	2.017
Heart (g)	0.859	0.859	0.848	0.842	0.856
Liver (g)	9.402	9.767	9.338	9.377	9.645
Kidney (both) (g)	1.828	1.819	1.935	1.857	1.754
Adrenal (both) (mg)	103.6	85.54*	91.94	91.40	85.38
Thymus (mg)	543.6	471.7	516.8	511.3	532.2
Ovary (both) (mg)	172.2	173.5	176.0	185.5	184.5
Spleen (g)	0.456	0.504	0.513	0.541	0.496

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.20.2. Organ to body weight ratios (means): 1. sacrifice

Statistical tests and flags used:WILCOXON: * if $p_W < 0.05$ JONCKHEERE: +- if $p_J < 0.01$

Organ to body weight ratios (means): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Brain (o/oo)	6.683	6.844	6.327	6.635	6.889
Heart (o/oo)	3.417	3.536	3.528	3.476	3.780*
Liver (o/oo)	45.48	48.49	50.85*+	43.98	46.61
Kidney (both) (o/oo)	7.499	7.864	7.785	7.434	7.477
Adrenal (both) (o/oo)	0.230	0.262	0.217	0.222	0.251
Thymus (o/oo)	2.313	2.242	2.327	2.554	1.978
Testis (both) (o/oo)	10.84	10.35	9.991	10.90	11.78
Spleen (o/oo)	1.964	2.159	2.016	1.970	1.979
Epididymis (o/oo)	3.491	3.451	3.416	3.569	3.688

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

198

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

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

Organ to body weight ratios (means): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Brain (o/oo)	9.847	9.451	9.841	9.682	9.517
Heart (o/oo)	4.062	4.040	3.972	3.960	4.037
Liver (o/oo)	44.48	45.85	43.80	44.17	45.57
Kidney (both) (o/oo)	8.676	8.548	9.110	8.825	8.280
Adrenal (both) (o/oo)	0.492	0.402*	0.433	0.433	0.405
Thymus (o/oo)	2.592	2.208	2.421	2.409	2.504
Ovary (both) (o/oo)	0.813	0.817	0.821	0.881	0.869
Spleen (o/oo)	2.153	2.363	2.411	2.556	2.343

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.20.3. Organ weights (means): 2. sacrifice (recovery)

Statistical tests and flags used:WILCOXON: * if $p_W < 0.05$ JONCKHEERE: +- if $p_J < 0.01$

Organ weights (means): males week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Body (g)	360.5			374.6	387.0
Brain (g)	2.225			2.278	2.237
Heart (g)	1.312			1.299	1.317
Liver (g)	15.42			17.11*	16.02
Kidney (both) (g)	2.749			2.894	2.748
Adrenal (both) (mg)	83.82			84.32	81.62
Thymus (mg)	645.8			566.3	587.1
Testis (both) (g)	3.777			4.001	4.001
Spleen (g)	0.661			0.681	0.657
Epididymis (g)	1.486			1.585	1.568

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:WILCOXON: * if $p_W < 0.05$ JONCKHEERE: +- if $p_J < 0.01$

Organ weights (means): females week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Body (g)	237.8			248.1	240.0
Brain (g)	2.168			2.163	2.094
Heart (g)	0.972			1.034	0.941
Liver (g)	9.998			10.45	9.386
Kidney (both) (g)	2.034			1.920	1.867
Adrenal (both) (mg)	102.8			108.8	104.7
Thymus (mg)	456.5			451.1	407.3
Ovary (both) (mg)	193.1			177.4	168.6
Spleen (g)	0.486			0.584	0.525

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.20.4. Organ to body weight ratios (means):
2. sacrifice (recovery)Statistical tests and flags used:WILCOXON: * if $p_W < 0.05$ JONCKHEERE: +- if $p_J < 0.01$

Organ to body weight ratios (means): males week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Brain (o/oo)	6.182			6.094	5.809
Heart (o/oo)	3.645			3.459	3.419
Liver (o/oo)	42.74			45.73	41.46
Kidney (both) (o/oo)	7.644			7.748	7.119
Adrenal (both) (o/oo)	0.233			0.226	0.212
Thymus (o/oo)	1.777			1.522	1.526
Testis (both) (o/oo)	10.47			10.72	10.39
Spleen (o/oo)	1.832			1.817	1.692
Epididymis (o/oo)	4.117			4.242	4.076

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Organ to body weight ratios (means): females week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Brain (o/oo)	9.175			8.776	8.744
Heart (o/oo)	4.098			4.165	3.925
Liver (o/oo)	42.00			41.93	39.05
Kidney (both) (o/oo)	8.563			7.766	7.751
Adrenal (both) (o/oo)	0.435			0.438	0.438
Thymus (o/oo)	1.923			1.862	1.690
Ovary (both) (o/oo)	0.818			0.723	0.704
Spleen (o/oo)	2.037			2.369	2.183

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.21. Organ weights and ratios (statistics)

8.21.1. Organ weights (statistics): 1. sacrifice

Statistical tests and flags used:WILCOXON: * if p_W < 0.05JONCKHEERE: +- if p_J < 0.01Organ weights (statistics): males week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Body (g)	N	5	5	5	4	5
	Mean	327.9	317.6	341.2	336.2	313.1
	SD	11.08	15.38	27.73	25.51	19.81
	Median	327.5	313.4	339.9	348.5	324.6
	Min	316.9	303.6	314.0	297.9	281.9
	Max	345.2	343.9	376.7	349.9	327.1
	p _W		0.076	0.754	0.221	0.175
	p _J		0.076	0.958	0.490	0.648
Brain (g)	N	5	5	5	4	5
	Mean	2.192	2.167	2.151	2.218	2.151
	SD	0.123	0.086	0.110	0.133	0.067
	Median	2.197	2.178	2.162	2.195	2.128
	Min	2.015	2.021	1.971	2.101	2.080
	Max	2.306	2.234	2.262	2.380	2.237
	p _W		0.754	0.602	1.000	0.465
	p _J		0.754	0.492	0.856	0.509
Heart (g)	N	5	5	5	4	5
	Mean	1.119	1.120	1.201	1.169	1.183
	SD	0.022	0.074	0.073	0.102	0.102
	Median	1.124	1.103	1.244	1.185	1.162
	Min	1.086	1.054	1.080	1.033	1.072
	Max	1.143	1.244	1.249	1.273	1.321
	p _W		0.347	0.117	0.221	0.465
	p _J		0.347	0.316	0.260	0.223

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): males week 5

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Liver (g)	N	5	5	5	4	5
	Mean	14.91	15.38	17.29	14.84	14.61
	SD	0.894	0.918	0.782	2.063	1.761
	Median	14.54	15.14	17.35	15.65	13.92
	Min	14.09	14.30	16.01	11.78	12.58
	Max	16.40	16.48	18.01	16.29	16.93
	p_W		0.347	0.016 *	0.624	0.465
	p_J		0.347	0.005 +	0.157	1.000
Kidney (both) (g)	N	5	5	5	4	5
	Mean	2.459	2.492	2.651	2.500	2.337
	SD	0.108	0.231	0.235	0.224	0.210
	Median	2.514	2.479	2.659	2.559	2.286
	Min	2.325	2.208	2.414	2.194	2.090
	Max	2.559	2.764	2.992	2.690	2.565
	p_W		0.917	0.175	0.624	0.465
	p_J		0.917	0.267	0.537	0.509
Adrenal (both) (mg)	N	5	5	5	4	5
	Mean	75.22	83.08	73.76	74.20	77.82
	SD	3.374	10.21	5.060	2.894	14.34
	Median	75.20	83.20	74.80	73.80	85.20
	Min	70.80	68.80	67.90	71.60	59.70
	Max	78.50	94.20	79.50	77.60	90.60
	p_W		0.249	0.600	0.623	0.600
	p_J		0.251	0.634	0.404	0.684
Thymus (mg)	N	5	5	5	4	5
	Mean	754.2	711.1	796.5	857.7	616.3
	SD	148.7	46.37	202.8	121.0	115.9
	Median	808.7	716.3	742.2	810.4	625.2
	Min	510.4	634.7	541.8	775.8	478.6
	Max	900.2	748.5	1037	1034	741.2
	p_W		0.251	0.754	0.462	0.117
	p_J		0.251	0.792	0.327	0.334

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Testis (both) (g)					
N	5	5	5	4	5
Mean	3.558	3.279	3.393	3.646	3.683
SD	0.338	0.320	0.183	0.074	0.258
Median	3.419	3.309	3.442	3.644	3.525
Min	3.222	2.745	3.105	3.557	3.488
Max	3.947	3.556	3.567	3.739	4.086
p_W		0.347	0.754	0.624	0.347
p_J		0.347	0.792	0.179	0.054
Spleen (g)					
N	5	5	5	4	5
Mean	0.644	0.687	0.681	0.659	0.621
SD	0.066	0.084	0.111	0.045	0.084
Median	0.643	0.660	0.666	0.652	0.639
Min	0.570	0.607	0.568	0.614	0.530
Max	0.727	0.822	0.846	0.717	0.711
p_W		0.465	0.754	0.806	0.602
p_J		0.465	0.634	0.744	0.684
Epididymis (g)					
N	5	5	5	4	5
Mean	1.145	1.096	1.166	1.199	1.151
SD	0.076	0.101	0.124	0.084	0.040
Median	1.160	1.118	1.186	1.225	1.156
Min	1.044	0.934	1.001	1.077	1.100
Max	1.221	1.211	1.326	1.269	1.193
p_W		0.465	0.602	0.142	0.917
p_J		0.465	0.712	0.204	0.446

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Organ weights (statistics): females week 5

Dose (mg/kg) group 1 group 2 group 3 group 4 group 5
 0 10 50 200 1000

Dose (mg/kg)		group 1	group 2	group 3	group 4	group 5
Body (g)	N	5	5	5	4	5
	Mean	211.3	212.9	213.6	212.0	212.4
	SD	11.50	7.038	15.54	21.03	12.44
	Median	207.2	214.0	206.5	206.7	218.9
	Min	197.2	201.3	199.6	192.7	195.0
	Max	225.6	219.8	237.7	241.9	224.3
	p _W		0.917	0.917	0.806	0.754
	p _J		0.917	0.958	0.744	0.839
Brain (g)	N	5	5	5	4	5
	Mean	2.079	2.013	2.096	2.040	2.017
	SD	0.084	0.125	0.108	0.050	0.037
	Median	2.111	1.975	2.076	2.036	2.018
	Min	1.932	1.866	1.995	1.991	1.978
	Max	2.132	2.162	2.234	2.098	2.055
	p _W		0.602	0.917	0.221	0.117
	p _J		0.602	0.634	0.913	0.388
Heart (g)	N	5	5	5	4	5
	Mean	0.859	0.859	0.848	0.842	0.856
	SD	0.080	0.016	0.054	0.122	0.036
	Median	0.855	0.866	0.838	0.833	0.838
	Min	0.766	0.835	0.789	0.703	0.823
	Max	0.965	0.877	0.917	0.999	0.904
	p _W		0.917	0.917	0.806	0.917
	p _J		0.917	0.874	0.637	0.799
Liver (g)	N	5	5	5	4	5
	Mean	9.402	9.767	9.338	9.377	9.645
	SD	0.832	0.706	0.797	1.124	0.252
	Median	9.311	10.04	9.676	9.300	9.648
	Min	8.671	8.542	8.277	8.118	9.299
	Max	10.81	10.25	10.22	10.79	9.919
	p _W		0.465	0.917	1.000	0.251
	p _J		0.465	0.874	0.690	0.959

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): females week 5

Dose (mg/kg)	week 5					
	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000	
Kidney (both) (g)	N	5	5	4	5	
	Mean	1.828	1.819	1.935	1.857	1.754
	SD	0.145	0.099	0.126	0.228	0.101
	Median	1.836	1.829	1.949	1.842	1.800
	Min	1.611	1.713	1.750	1.621	1.631
	Max	2.011	1.967	2.105	2.123	1.855
	p_W		0.754	0.251	0.806	0.465
	p_J		0.754	0.267	0.446	0.648
Adrenal (both) (mg)	N	5	5	4	5	
	Mean	103.6	85.54	91.94	91.40	85.38
	SD	16.80	5.854	9.502	8.599	12.29
	Median	101.6	84.70	90.60	93.75	82.20
	Min	85.80	79.30	81.90	79.60	71.10
	Max	130.0	93.30	105.3	98.50	103.3
	p_W		0.028*	0.175	0.221	0.076
	p_J		0.028	0.245	0.383	0.141
Thymus (mg)	N	5	5	4	5	
	Mean	543.6	471.7	516.8	511.3	532.2
	SD	87.55	154.2	73.78	81.81	94.39
	Median	514.2	415.2	497.4	515.2	553.0
	Min	466.3	356.3	462.8	427.3	377.6
	Max	667.4	737.7	645.0	587.4	634.1
	p_W		0.117	0.602	0.327	0.917
	p_J		0.117	0.712	0.690	0.879
Ovary (both) (mg)	N	5	5	4	5	
	Mean	172.2	173.5	176.0	185.5	184.5
	SD	29.99	16.80	33.14	29.15	31.18
	Median	173.0	178.3	183.3	185.5	195.7
	Min	139.1	148.8	121.1	152.5	129.2
	Max	206.0	192.5	211.2	218.4	203.2
	p_W		0.917	0.754	0.462	0.754
	p_J		0.917	0.561	0.364	0.187

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
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Spleen (g)		5	5	5	4	5
N		5	5	5	4	5
Mean		0.456	0.504	0.513	0.541	0.496
SD		0.066	0.083	0.027	0.064	0.045
Median		0.430	0.527	0.502	0.568	0.491
Min		0.399	0.409	0.492	0.446	0.446
Max		0.566	0.590	0.560	0.583	0.547
p_W			0.347	0.117	0.086	0.251
p_J			0.347	0.267	0.064	0.298

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.21.2. Organ to body weight ratios (statistics):
1. sacrifice

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Organ to body weight ratios (statistics): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Brain (o/oo) N	5	5	5	4	5
Mean	6.683	6.844	6.327	6.635	6.889
SD	0.279	0.565	0.441	0.760	0.406
Median	6.680	6.978	6.259	6.451	6.825
Min	6.358	5.876	5.739	6.005	6.435
Max	7.040	7.359	6.856	7.634	7.550
p_W		0.251	0.117	0.624	0.602
p_J		0.251	0.267	0.327	0.839
Heart (o/oo) N	5	5	5	4	5
Mean	3.417	3.536	3.528	3.476	3.780
SD	0.157	0.314	0.185	0.129	0.226
Median	3.460	3.496	3.449	3.463	3.818
Min	3.146	3.142	3.316	3.332	3.518
Max	3.538	3.971	3.769	3.647	4.040
p_W		0.754	0.602	0.806	0.016 *
p_J		0.754	0.712	0.856	0.060
Liver (o/oo) N	5	5	5	4	5
Mean	45.48	48.49	50.85	43.98	46.61
SD	2.741	2.945	3.366	3.068	3.788
Median	45.46	47.32	50.84	44.90	45.09
Min	42.11	45.33	47.31	39.54	42.56
Max	49.67	52.90	55.25	46.56	52.15
p_W		0.117	0.028 *	0.624	0.754
p_J		0.117	0.010 +	0.799	0.799

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (statistics): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Kidney (both)					
(o/oo) N	5	5	5	4	5
Mean	7.499	7.864	7.785	7.434	7.477
SD	0.293	0.851	0.634	0.249	0.625
Median	7.414	7.455	7.690	7.465	7.819
Min	7.150	7.087	7.058	7.120	6.388
Max	7.860	8.809	8.802	7.687	7.843
p_W		0.754	0.602	0.624	0.602
p_J		0.754	0.634	0.799	0.879
Adrenal (both)					
(o/oo) N	5	5	5	4	5
Mean	0.230	0.262	0.217	0.222	0.251
SD	0.015	0.035	0.018	0.023	0.056
Median	0.235	0.265	0.211	0.215	0.279
Min	0.212	0.227	0.200	0.205	0.183
Max	0.248	0.302	0.246	0.254	0.302
p_W		0.175	0.175	0.462	0.602
p_J		0.175	0.267	0.137	0.446
Thymus					
(o/oo) N	5	5	5	4	5
Mean	2.313	2.242	2.327	2.554	1.978
SD	0.515	0.161	0.536	0.318	0.421
Median	2.449	2.271	2.210	2.511	1.911
Min	1.479	2.061	1.726	2.230	1.571
Max	2.841	2.403	3.050	2.964	2.540
p_W		0.347	0.917	0.624	0.347
p_J		0.347	0.561	0.690	0.388
Testis (both)					
(o/oo) N	5	5	5	4	5
Mean	10.84	10.35	9.991	10.90	11.78
SD	0.845	1.190	0.906	0.936	0.696
Median	10.79	10.49	9.862	10.58	11.70
Min	9.755	8.760	9.138	10.17	10.77
Max	11.88	11.51	11.36	12.26	12.49
p_W		0.465	0.117	1.000	0.117
p_J		0.465	0.126	0.637	0.128

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

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Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (statistics): males week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Spleen (o/oo)					
N	5	5	5	4	5
Mean	1.964	2.159	2.016	1.970	1.979
SD	0.196	0.166	0.419	0.219	0.177
Median	1.963	2.107	2.121	1.937	1.953
Min	1.790	1.950	1.507	1.765	1.738
Max	2.273	2.390	2.490	2.242	2.190
p_W		0.175	0.754	1.000	0.917
p_J		0.175	0.428	0.971	0.722
Epididymis (o/oo)					
N	5	5	5	4	5
Mean	3.491	3.451	3.416	3.569	3.688
SD	0.214	0.279	0.175	0.074	0.246
Median	3.536	3.521	3.484	3.567	3.648
Min	3.161	2.981	3.180	3.493	3.388
Max	3.685	3.681	3.605	3.649	3.982
p_W		0.754	0.465	1.000	0.465
p_J		0.754	0.369	0.971	0.310

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Test No.: 963128

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Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Organ to body weight ratios (statistics): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Brain (o/oo)					
N	5	5	5	4	5
Mean	9.847	9.451	9.841	9.682	9.517
SD	0.314	0.346	0.633	0.793	0.434
Median	9.795	9.285	9.782	9.927	9.378
Min	9.445	9.063	9.174	8.541	8.999
Max	10.19	9.835	10.82	10.33	10.14
p _W		0.175	0.602	1.000	0.175
p _J		0.175	0.634	0.913	0.477
Heart (o/oo)					
N	5	5	5	4	5
Mean	4.062	4.040	3.972	3.960	4.037
SD	0.218	0.116	0.143	0.229	0.175
Median	4.125	4.004	3.908	4.027	4.115
Min	3.698	3.927	3.857	3.649	3.781
Max	4.278	4.233	4.199	4.136	4.220
p _W		0.347	0.347	0.462	0.754
p _J		0.347	0.126	0.179	0.446
Liver (o/oo)					
N	5	5	5	4	5
Mean	44.48	45.85	43.80	44.17	45.57
SD	2.840	2.271	3.706	1.676	3.390
Median	42.96	47.12	42.39	44.21	44.78
Min	42.05	42.44	40.59	42.12	42.48
Max	47.90	47.88	48.92	46.14	50.87
p _W		0.602	0.602	1.000	0.465
p _J		0.602	0.561	0.446	1.000
Kidney (both) (o/oo)					
N	5	5	5	4	5
Mean	8.676	8.548	9.110	8.825	8.280
SD	0.917	0.409	0.989	1.389	0.663
Median	8.347	8.599	9.442	8.917	8.321
Min	7.776	7.935	7.359	7.113	7.410
Max	10.20	9.083	9.774	10.35	9.231
p _W		0.754	0.465	0.624	0.465
p _J		0.754	0.187	0.327	0.799

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (statistics): females week 5

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Adrenal (both)					
(o/oo) N	5	5	5	4	5
Mean	0.492	0.402	0.433	0.433	0.405
SD	0.096	0.028	0.063	0.052	0.078
Median	0.461	0.402	0.439	0.424	0.404
Min	0.416	0.366	0.356	0.382	0.323
Max	0.659	0.436	0.528	0.503	0.530
p_W		0.028 *	0.175	0.221	0.076
p_J		0.028	0.187	0.327	0.128
Thymus					
(o/oo) N	5	5	5	4	5
Mean	2.592	2.208	2.421	2.409	2.504
SD	0.538	0.685	0.308	0.285	0.412
Median	2.333	1.952	2.369	2.299	2.526
Min	2.067	1.770	2.128	2.217	1.854
Max	3.384	3.407	2.929	2.820	2.885
p_W		0.175	0.917	0.624	0.917
p_J		0.175	0.958	0.799	0.446
Ovary (both)					
(o/oo) N	5	5	5	4	5
Mean	0.813	0.817	0.821	0.881	0.869
SD	0.128	0.095	0.122	0.160	0.148
Median	0.785	0.811	0.874	0.874	0.894
Min	0.671	0.695	0.607	0.710	0.634
Max	0.999	0.957	0.899	1.065	1.042
p_W		0.917	0.754	0.462	0.465
p_J		0.917	0.634	0.404	0.243
Spleen					
(o/oo) N	5	5	5	4	5
Mean	2.153	2.363	2.411	2.556	2.343
SD	0.233	0.353	0.226	0.251	0.291
Median	2.053	2.435	2.413	2.556	2.246
Min	2.022	1.913	2.106	2.314	1.989
Max	2.568	2.775	2.711	2.798	2.751
p_W		0.251	0.076	0.050	0.347
p_J		0.251	0.126	0.032	0.187

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.21.3. Organ weights (statistics): 2. sacrifice (recovery)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Organ weights (statistics): males week 9

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	200	1000

Body (g)	N	5	5	5
	Mean	360.5	374.6	387.0
	SD	23.06	24.80	27.99
	Median	361.8	365.3	385.8
	Min	333.2	354.3	362.2
	Max	384.4	416.7	430.5
	p_W		0.602	0.076
	p_J		0.602	0.101
Brain (g)	N	5	5	5
	Mean	2.225	2.278	2.237
	SD	0.134	0.052	0.102
	Median	2.231	2.274	2.183
	Min	2.080	2.209	2.142
	Max	2.428	2.355	2.354
	p_W		0.251	0.754
	p_J		0.251	0.792
Heart (g)	N	5	5	5
	Mean	1.312	1.299	1.317
	SD	0.157	0.159	0.058
	Median	1.272	1.227	1.345
	Min	1.165	1.135	1.244
	Max	1.539	1.515	1.382
	p_W		0.917	0.917
	p_J		0.917	0.792

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): males week 9

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Liver (g)	N	5			5	5
	Mean	15.42			17.11	16.02
	SD	1.352			1.877	1.530
	Median	16.07			16.87	16.42
	Min	13.62			14.39	13.51
	Max	16.61			19.57	17.34
	p_W				0.047 *	0.602
	p_J				0.047	0.428
Kidney (both) (g)	N	5			5	5
	Mean	2.749			2.894	2.748
	SD	0.208			0.293	0.173
	Median	2.782			2.795	2.856
	Min	2.501			2.645	2.471
	Max	3.025			3.386	2.873
	p_W				0.465	0.754
	p_J				0.465	0.792
Adrenal (both) (mg)	N	5			5	5
	Mean	83.82			84.32	81.62
	SD	8.716			11.44	10.30
	Median	86.10			83.20	83.20
	Min	71.60			72.40	68.90
	Max	93.30			103.1	96.40
	p_W				0.917	0.602
	p_J				0.917	0.673
Thymus (mg)	N	5			5	5
	Mean	645.8			566.3	587.1
	SD	197.5			81.70	77.95
	Median	553.2			552.4	617.2
	Min	450.3			478.3	450.9
	Max	933.6			692.9	646.5
	p_W				0.602	0.917
	p_J				0.602	0.874

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): males week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Testis (both)					
(g) N	5			5	5
Mean	3.777			4.001	4.001
SD	0.483			0.112	0.258
Median	3.669			4.004	4.081
Min	3.341			3.840	3.669
Max	4.603			4.157	4.279
p_W				0.117	0.251
p_J				0.117	0.126
Spleen					
(g) N	5			5	5
Mean	0.661			0.681	0.657
SD	0.064			0.089	0.089
Median	0.661			0.654	0.618
Min	0.567			0.581	0.575
Max	0.728			0.800	0.799
p_W				0.754	0.754
p_J				0.754	0.712
Epididymis					
(g) N	5			5	5
Mean	1.486			1.585	1.568
SD	0.150			0.106	0.089
Median	1.475			1.574	1.549
Min	1.317			1.472	1.500
Max	1.711			1.736	1.722
p_W				0.251	0.175
p_J				0.251	0.267

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

JONCKHEERE: +- if p_J < 0.01

Organ weights (statistics): females week 9

Dose (mg/kg)		group 1	group 2	group 3	group 4	group 5
		0	10	50	200	1000
Body (g)	N	5			4	5
	Mean	237.8			248.1	240.0
	SD	23.89			23.16	17.53
	Median	232.7			250.1	236.6
	Min	216.0			221.2	227.2
	Max	272.2			271.1	270.3
	p_W				0.462	0.754
	p_J					0.770
Brain (g)	N	5			4	5
	Mean	2.168			2.163	2.094
	SD	0.106			0.036	0.096
	Median	2.202			2.171	2.062
	Min	1.992			2.116	1.996
	Max	2.269			2.196	2.243
	p_W				0.327	0.347
	p_J					0.114
Heart (g)	N	5			4	5
	Mean	0.972			1.034	0.941
	SD	0.094			0.174	0.117
	Median	1.003			0.995	0.936
	Min	0.835			0.868	0.776
	Max	1.054			1.275	1.095
	p_W				0.806	0.602
	p_J					0.598
Liver (g)	N	5			4	5
	Mean	9.998			10.45	9.386
	SD	1.170			2.025	1.148
	Median	9.311			10.17	9.509
	Min	8.912			8.292	7.653
	Max	11.53			13.18	10.86
	p_W				0.806	0.754
	p_J					0.598

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): females week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Kidney (both) (g)	N	5		4	5
	Mean	2.034		1.920	1.867
	SD	0.270		0.244	0.297
	Median	2.082		1.891	1.874
	Min	1.615		1.673	1.463
	Max	2.318		2.227	2.294
	p_W			0.624	0.251
	p_J				0.380
Adrenal (both) (mg)	N	5		4	5
	Mean	102.8		108.8	104.7
	SD	11.56		10.48	15.48
	Median	103.6		107.6	102.7
	Min	86.80		97.70	82.40
	Max	118.9		122.2	123.0
	p_W			0.462	0.917
	p_J				0.770
Thymus (mg)	N	5		4	5
	Mean	456.5		451.1	407.3
	SD	47.19		116.5	81.83
	Median	462.1		457.0	425.4
	Min	378.2		336.6	281.4
	Max	505.0		553.8	500.6
	p_W			1.000	0.251
	p_J				0.380
Ovary (both) (mg)	N	5		4	5
	Mean	193.1		177.4	168.6
	SD	54.05		17.83	26.62
	Median	205.1		174.8	171.1
	Min	126.5		159.6	136.6
	Max	269.3		200.4	208.3
	p_W			0.624	0.602
	p_J				0.447

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (statistics): females week 9

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Spleen (g)	N	5			4	5
	Mean	0.486			0.584	0.525
	SD	0.099			0.046	0.061
	Median	0.466			0.586	0.501
	Min	0.358			0.526	0.473
	Max	0.624			0.639	0.620
	p_W				0.142	0.347
	p_J					0.598

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.21.4. Organ to body weight ratios (statistics):
2. sacrifice (recovery)

Statistical tests and flags used:

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

Organ to body weight ratios (statistics): males week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Brain (o/oo) N	5			5	5
Mean	6.182			6.094	5.809
SD	0.374			0.282	0.558
Median	6.242			6.117	5.961
Min	5.583			5.651	5.072
Max	6.604			6.398	6.500
p _W				0.602	0.175
p _J				0.602	0.154
Heart (o/oo) N	5			5	5
Mean	3.645			3.459	3.419
SD	0.433			0.243	0.317
Median	3.644			3.395	3.225
Min	3.099			3.144	3.126
Max	4.252			3.762	3.814
p _W				0.347	0.465
p _J				0.347	0.316
Liver (o/oo) N	5			5	5
Mean	42.74			45.73	41.46
SD	1.901			4.824	3.690
Median	42.11			46.74	40.29
Min	40.88			39.41	37.24
Max	45.91			52.07	47.13
p _W				0.175	0.347
p _J				0.175	0.634

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (statistics): males week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Kidney (both)					
(o/oo) N	5			5	5
Mean	7.644			7.748	7.119
SD	0.661			0.896	0.514
Median	7.776			7.541	6.821
Min	6.550			6.707	6.674
Max	8.336			9.007	7.889
p_W				0.917	0.347
p_J				0.917	0.267
Adrenal (both)					
(o/oo) N	5			5	5
Mean	0.233			0.226	0.212
SD	0.024			0.036	0.035
Median	0.226			0.223	0.195
Min	0.215			0.193	0.179
Max	0.273			0.286	0.266
p_W				0.602	0.251
p_J				0.602	0.224
Thymus					
(o/oo) N	5			5	5
Mean	1.777			1.522	1.526
SD	0.466			0.270	0.253
Median	1.555			1.559	1.554
Min	1.351			1.148	1.146
Max	2.429			1.897	1.785
p_W				0.602	0.465
p_J				0.602	0.428
Testis (both)					
(o/oo) N	5			5	5
Mean	10.47			10.72	10.39
SD	1.086			0.781	1.081
Median	10.73			10.63	9.840
Min	9.233			9.613	9.323
Max	11.98			11.73	11.81
p_W				0.754	0.917
p_J				0.754	0.958

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (statistics): males week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Spleen (o/oo) N	5			5	5
Mean	1.832			1.817	1.692
SD	0.134			0.195	0.111
Median	1.908			1.784	1.672
Min	1.660			1.610	1.588
Max	1.959			2.129	1.856
p_W				0.602	0.117
p_J				0.602	0.101
Epididymis (o/oo) N	5			5	5
Mean	4.117			4.242	4.076
SD	0.220			0.344	0.450
Median	4.076			4.247	3.938
Min	3.857			3.916	3.599
Max	4.451			4.752	4.746
p_W				0.602	0.602
p_J				0.602	0.712

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

223

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Statistical tests and flags used:

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

Organ to body weight ratios (statistics): females week 9

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	200	1000
Brain (o/oo) N	5			4	5
Mean	9.175			8.776	8.744
SD	0.816			0.857	0.436
Median	9.172			8.559	8.588
Min	7.955			8.061	8.298
Max	10.19			9.924	9.319
p _W				0.462	0.347
p _J					0.520
Heart (o/oo) N	5			4	5
Mean	4.098			4.165	3.925
SD	0.318			0.554	0.453
Median	3.949			4.131	3.947
Min	3.867			3.554	3.414
Max	4.618			4.843	4.626
p _W				0.806	0.602
p _J					0.682
Liver (o/oo) N	5			4	5
Mean	42.00			41.93	39.05
SD	1.475			5.219	3.114
Median	42.37			40.81	40.20
Min	40.01			37.48	33.69
Max	43.69			48.61	41.59
p _W				0.806	0.076
p _J					0.178
Kidney (both) (o/oo) N	5			4	5
Mean	8.563			7.766	7.751
SD	0.945			0.954	0.819
Median	9.052			8.145	7.899
Min	7.435			6.351	6.439
Max	9.446			8.424	8.487
p _W				0.327	0.251
p _J					0.266

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

224

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (statistics): females week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Adrenal (both)					
(o/oo) N	5			4	5
Mean	0.435			0.438	0.438
SD	0.059			0.012	0.069
Median	0.402			0.441	0.449
Min	0.381			0.422	0.363
Max	0.511			0.451	0.519
p_W				0.624	0.917
p_J					0.770
Thymus					
(o/oo) N	5			4	5
Mean	1.923			1.862	1.690
SD	0.148			0.641	0.274
Median	1.895			1.852	1.852
Min	1.741			1.242	1.239
Max	2.136			2.503	1.879
p_W				1.000	0.117
p_J					0.266
Ovary (both)					
(o/oo) N	5			4	5
Mean	0.818			0.723	0.704
SD	0.245			0.129	0.110
Median	0.817			0.689	0.674
Min	0.585			0.606	0.601
Max	1.157			0.906	0.880
p_W				0.806	0.754
p_J					0.682
Spleen					
(o/oo) N	5			4	5
Mean	2.037			2.369	2.183
SD	0.290			0.269	0.127
Median	2.121			2.432	2.192
Min	1.538			1.997	2.028
Max	2.293			2.614	2.317
p_W				0.142	0.347
p_J					0.520

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.22. Summary tables: Pathology

8.22.1. Summary tables of macropathological findings

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EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

- M = MALE ANIMAL
- F = FEMALE ANIMAL
- K0 = TERMINAL SACRIFICE GROUP
- R1...R9 = RECOVERY / POST-TREATMENT GROUPS 1...9
- + = INTERCURRENT DEATH/SACRIFICED MORIBUND

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MACROSCOPIC PATHOLOGY
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INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

ORGAN/FINDING	DOSE GROUP: 1		5	
	SEX: M	F	M	F
	ANIM. EXAM.:		5	5
TESTES				
- SMALL				
EPIDIDYMIDES				
- SMALL				
ADRENAL GLANDS				
- SMALL				
BODY SURFACES				
- MASS				
THORACIC CAVITY				
- CONTENTS FLUID				
- CONTENTS HAEMORRHAGIC				
- FIBRINOUS ADHESION				
DIAPHRAGM				
- PERFORATION				

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INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1, INCL. +

ORGAN/FINDING	DOSE GROUP: 1		2		3		4	
	SEX: M F		M F		M F		M F	
	ANIM. EXAM.: 5 5						5 5	

LUNG								
- FIBRINOUS ADHESION								1
THYMUS								
- REDDISH								
THORACIC CAVITY								
- CONTENTS FLUID								1

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INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1, INCL. +

ORGAN/FINDING	DOSE GROUP:		SEX:		ANIM. EXAM.:	
	1	5	M	F	M	F
LUNG						
- FIBRINOUS ADHESION						
THYMUS						
- REDDISH						1
THORACIC CAVITY						
- CONTENTS FLUID						
END OF REPORT SECTION						
LAST PAGE OF REPORT						

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Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

8.22.2. Summary tables of micropathological findings

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STATUS AT NECROPSY: R1, INCL. + 239

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EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

- M = MALE ANIMAL
- F = FEMALE ANIMAL
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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

ORGAN/FINDING	SEX :	DOSE GROUP:	1	2	3	4	5	MALE
		NO. ANIMALS:	5	5	5	5	5	
LIVER	NO. EXAM.:		5	5	5	5	5	
- INFILT. LYMPHOHIST			1	2	2	1	2	
- CHANGE FATTY						1		
- CONGESTION						1		
SPLEEN	NO. EXAM.:		5	5	5	5	5	
- EXMED. HEMATOPOIESIS			3	2	3	2	2	
- HYPERPLAS. REACT. CHR.							1	
- CONGESTION						1		
LUNG	NO. EXAM.:		5	5	5	5	5	
- FOAM CELLS			1					
- GRANULOMA						1		
- CONGESTION						1		
PLEURA	NO. EXAM.:		5	5	5	5	5	
- INFL. FIBRINOUS							1	
KIDNEYS	NO. EXAM.:		5	5	5	5	5	
- PROLIF. BASOPH. TUB.			1		1			
- ATROPHY TUBULAR			1				1	
- INFL. CHRONIC			1	1	1			
- CAST TUBULAR			1					
- LESION TUBULAR CHRO.							1	
- CONGESTION						1		
HEART	NO. EXAM.:		5	5	5	5	5	
- INFILT. INFLAM. CELL			2		1	1	2	
- INFL. WITH FIBROSIS				1				
EPICARD./PERICARDIUM	NO. EXAM.:		5	5	5	5	5	
- INFL. FIBRINOUS							1	
SM. INT. PEYER'S PAT	NO. EXAM.:		5	5	5	5	5	
- MINERALIZATION			1	2	1	3	1	

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

ORGAN/FINDING	SEX :	MALE				
	DOSE GROUP:	1	2	3	4	5
	NO. ANIMALS:	5	5	5	5	5
THYMUS	NO. EXAM.:	5	5	5	5	5
- PHAGOCYTTIC CELLS		1	1			
TESTES	NO. EXAM.:	5	5	5	5	5
- ATROPHY TUBULAR			1			1
- GIANT CELLS SPERMAT.						1
EPIDIDYIMIDES	NO. EXAM.:	5	5	5	5	5
- DEBRIS CELLULAR			1			
- FIBROSIS			1			
URINARY BLADDER	NO. EXAM.:	5	5	5	5	5
- EDEMA INFLAMMATORY						1
- PRECIPITATE		2				
ADRENAL GLANDS	NO. EXAM.:	5	5	5	5	5
- CHANGE FATTY CORT.			2		1	
SKIN/SUBCUTIS	NO. EXAM.:		1			
- MALFORMATION			1			

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

ORGAN/FINDING	SEX :	FEMALE				
	DOSE GROUP:	1	2	3	4	5
	NO. ANIMALS:	5	5	5	5	5
LIVER	NO. EXAM.:	5	5	5	5	5
- INFILT. LYMPHOHIST.		1	2		3	2
- NECROSIS				1		
SPLEEN	NO. EXAM.:	5	5	5	5	5
- EXMED. HEMATOPOIESIS		1	1	1		2
- HEMOSIDEROSIS			1			
- ATROPHY WHITE PULP					1	
- CONGESTION						1
LUNG	NO. EXAM.:	5	5	5	5	5
- FOAM CELLS			1			1
- CONGESTION					1	
PLEURA	NO. EXAM.:	5	5	5	5	5
- THICKENING FIBROUS					1	
- INFL. FIBRINOUS					1	
KIDNEYS	NO. EXAM.:	5	5	5	5	5
- MINERALIZ. CORTICOMED		5	5	4	4	5
- PROLIF. BASOPH. TUB.			1	1	2	1
- ATROPHY TUBULAR		3	2	4	1	2
- CAST TUBULAR			1			1
- CONGESTION					1	
EPICARD./PERICARDIUM	NO. EXAM.:	5	5	5	5	5
- INFL. WITH FIBROSIS					1	
SM. INT. PEYER'S PAT	NO. EXAM.:	5	5	5	5	5
- MINERALIZATION		1	2	3	3	2
THYMUS	NO. EXAM.:	5	5	5	5	5
- PHAGOCYTTIC CELLS			1			1
- ATROPHY					1	
THYROID GLAND	NO. EXAM.:	5	5	5	5	5
- CYST DEVELOPMENTAL			1			

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

ORGAN/FINDING	SEX : FEMALE					
	DOSE GROUP:	1	2	3	4	5
	NO. ANIMALS:	5	5	5	5	5
PITUITARY GLAND	NO. EXAM.:	5	5	5	5	5
- CYST DEVELOPMENTAL				1		

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PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 239
P963128

TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1, INCL. +

ORGAN/FINDING	SEX :						FEMALE
	DOSE GROUP:	1	2	3	4	5	
	NO. ANIMALS:	5			5	5	
LIVER	NO. EXAM.:				1		
- CHANGE FATTY					1		
- CONGESTION					1		
.....							
SPLEEN	NO. EXAM.:				1		
- ATROPHY WHITE PULP					1		
- CONGESTION					1		
.....							
LUNG	NO. EXAM.:				1		
- CONGESTION					1		
.....							
PLEURA	NO. EXAM.:				1		
- INFL. FIBRINOUS					1		
.....							
KIDNEYS	NO. EXAM.:				1		
- MINERALIZ. CORTICOMED					1		
- ATROPHY TUBULAR					1		
- CONGESTION					1		
.....							
EPICARD./PERICARDIUM	NO. EXAM.:				1		
- INFL. FIBRINOUS					1		
.....							
SM. INT. PEYER'S PAT	NO. EXAM.:				1		
- MINERALIZATION					1		
.....							
THYMUS	NO. EXAM.:				1	1	
- HEMORRHAGE						1	
.....							
ADRENAL GLANDS	NO. EXAM.:				1		
- CONGESTION					1		
- CHANGE FATTY CORT.					1		
.....							

END OF REPORT SECTION
LAST PAGE OF REPORT

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

Test No. 963128

CGA 108906 tech.

(Intermediate of CGA 48988)

FINAL REPORT

Study Director: Dr. rer. nat. 5.1.2.3.W6

Testing Facility: Novartis Crop Protection AG
(successor in business of Sandoz
Ltd. and Ciba-Geigy Ltd.)
Toxicology/Experimental Toxicology
4332 Stein / Switzerland

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

Study completed: June 6, 1997

Sponsor: Novartis Crop Protection
Human Safety Assessment
4002 Basel / Switzerland

This report contains: 555 pages

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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9. APPENDIX A: INDIVIDUAL DATA

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In the appendices, the absence of a value due to technical problems is indicated - n.d.= not determined.

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9.1. In-life observations (individuals)

- : clinical sign observed until scheduled sacrifice
 * : clinical sign observed until early death
 l, r : left, right, resp.

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		
06	skin lesion	neck	25 30
07	no findings noted		
08	no findings noted		
09	hair loss	forelimbs	52 -
10	skin lesion	neck	25 30

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

No.	Finding	start day	end day
11	no findings noted		
12	no findings noted		
13	mass, 1-1cm diam	abdominal, 1	10 -
14	no findings noted		
15	eye, exudate	right	28 -

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

No.	Finding	start day	end day
16	no findings noted		
17	no findings noted		
18	no findings noted		
19	no findings noted		
20	no findings noted		

Antemortem findings (individuals) : males group 4 : 200 mg/kg

No.	Finding	start day	end day
21	no findings noted		
22	no findings noted		
23	no findings noted		
24	no findings noted		
25	no findings noted		24*
26	no findings noted		
27	no findings noted		
28	no findings noted		
29	no findings noted		
30	no findings noted		

Antemortem findings (individuals) : males group 5 : 1000 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		
36	no findings noted		
37	no findings noted		
38	no findings noted		
39	no findings noted		

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Antemortem findings (individuals): males group 5 : 1000 mg/kg

No.	Finding	start day	end day
40	no findings noted		

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

No.	Finding	start day	end day
41	no findings noted		
42	no findings noted		
43	no findings noted		
44	no findings noted		
45	no findings noted		
46	no findings noted		
47	no findings noted		
48	no findings noted		
49	no findings noted		
50	no findings noted		

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

No.	Finding	start day	end day
51	no findings noted		
52	no findings noted		
53	no findings noted		
54	no findings noted		
55	no findings noted		

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

No.	Finding	start day	end day
56	no findings noted		
57	no findings noted		
58	no findings noted		
59	no findings noted		
60	no findings noted		

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Antemortem findings (individuals) : females group 4 : 200 mg/kg

No.	Finding	start day	end day
61	hypoactivity	27	28*
61	piloerection	27	28*
62	no findings noted		
63	no findings noted		
64	no findings noted		
65	no findings noted		
66	no findings noted		
67	no findings noted		
68	no findings noted		28*
69	hair loss forelimbs	44	
70	no findings noted		

Antemortem findings (individuals) : females group 5 : 1000 mg/kg

No.	Finding	start day	end day
71	no findings noted		
72	no findings noted		
73	no findings noted		
74	no findings noted		
75	no findings noted		
76	no findings noted		
77	no findings noted		
78	hair loss forelimbs	44	-
79	no findings noted		
80	no findings noted		

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9.2. Functional Observational Battery (individuals)

Observations (individual values):

males

group 1
0 mg/kg

Note that individual signs or functions are presented only for weeks with corresponding findings

animal number	1	2	3	4	5	6	7	8	9	10
CNS activity (-4,+7)^a										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										
CNS excitation (-4,+27)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										
Autonomic functions (-3,+13)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										
Sensorimotor (-12,0)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										

^a range of scores

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animal number	1	2	3	4	5	6	7	8	9	10
Physiological functions (0,+19)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Non-specific signs (0,+9)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	1	0	0	0	1
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
skin lesion (0,+1)										
week 4						1				1

skin lesion (0,+1)
week 4

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Observations (individual values):

males

group 2
10 mg/kg

animal number	11	12	13	14	15
CNS activity (-4,+7)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
CNS excitation (-4,+27)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Autonomic functions (-3,+13)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Sensorimotor (-12,0)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Physiological functions (0,+19)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Non-specific signs (0,+9)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	1	0	0
week 3	0	0	1	0	0
week 4	0	0	1	0	0
mass (0,+1)					
week 2	.	.	1	.	.
week 3	.	.	1	.	.
week 4	.	.	1	.	.

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Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Observations (individual values):

males

group 3
50 mg/kg

animal number	16	17	18	19	20
CNS activity (-4,+7)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
CNS excitation (-4,+27)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Autonomic functions (-3,+13)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Sensorimotor (-12,0)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Physiological functions (0,+19)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Non-specific signs (0,+9)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0

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animal number	21	22	23	24	25	26	27	28	29	30
Physiological functions (0,+19)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Non-specific signs (0,+9)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0

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28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

256

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Observations (individual values):

males

group 5
1000 mg/kg

animal number	31	32	33	34	35	36	37	38	39	40
CNS activity (-4,+7)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	-1	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										
activity (-2,+2) week 2		-1								
CNS excitation (-4,+27)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										
Autonomic functions (-3,+13)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										
Sensorimotor (-12,0)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5						0	0	0	0	0
week 6						0	0	0	0	0
week 7						0	0	0	0	0
week 8						0	0	0	0	0

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

animal number	31	32	33	34	35	36	37	38	39	40
Physiological functions (0,+19)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Non-specific signs (0,+9)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0

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28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

258

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Observations (individual values):

females

group 1
0 mg/kg

animal number	41	42	43	44	45	46	47	48	49	50
CNS activity (-4,+7)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	1	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
activity (-2,+2) week 7									1	
CNS excitation (-4,+27)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Autonomic functions (-3,+13)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Sensorimotor (-12,0)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5						0	0	0	0	0
week 6						0	0	0	0	0
week 7						0	0	0	0	0
week 8						0	0	0	0	0

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Observations (individual values):

females

group 2
10 mg/kg

animal number	51	52	53	54	55
CNS activity (-4,+7)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
CNS excitation (-4,+27)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Autonomic functions (-3,+13)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Sensorimotor (-12,0)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Physiological functions (0,+19)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0
Non-specific signs (0,+9)					
week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Observations (individual values):

females

group 3
50 mg/kg

animal number 56 57 58 59 60

CNS activity (-4,+7)

week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	1	0	0
week 3	0	1	0	1	0
week 4	0	0	0	0	0

activity (-2,+2)

week 2			1		
week 3		1		1	

CNS excitation (-4,+27)

week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0

Autonomic functions (-3,+13)

week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0

Sensorimotor (-12,0)

week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0

Physiological functions (0,+19)

week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0

Non-specific signs (0,+9)

week -1	0	0	0	0	0
week 1	0	0	0	0	0
week 2	0	0	0	0	0
week 3	0	0	0	0	0
week 4	0	0	0	0	0

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

animal number	61	62	63	64	65	66	67	68	69	70
Physiological functions (0,+19)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Non-specific signs (0,+9)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0

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28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

264

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Observations (individual values):

females

group 5
1000 mg/kg

animal number	71	72	73	74	75	76	77	78	79	80
CNS activity (-4,+7)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	1	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
activity (-2,+2) week 6								1		
CNS excitation (-4,+27)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Autonomic functions (-3,+13)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5	0	0	0	0	0	0	0	0	0	0
week 6	0	0	0	0	0	0	0	0	0	0
week 7	0	0	0	0	0	0	0	0	0	0
week 8	0	0	0	0	0	0	0	0	0	0
Sensorimotor (-12,0)										
week -1	0	0	0	0	0	0	0	0	0	0
week 1	0	0	0	0	0	0	0	0	0	0
week 2	0	0	0	0	0	0	0	0	0	0
week 3	0	0	0	0	0	0	0	0	0	0
week 4	0	0	0	0	0	0	0	0	0	0
week 5						0	0	0	0	0
week 6						0	0	0	0	0
week 7						0	0	0	0	0
week 8						0	0	0	0	0

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Functional measurements

Abbreviations used: GSF grip strength forepaws (g)
 GSH grip strength hindpaws (g)
 LFS landing foot splay (cm)
 TMP body temperature, rectal (° C)

Measurements (individual values): males group 1
 0 mg/kg

Parameter	time	1	2	3	4	5	6	7	8	9	10
GSF	4	1110	1315	1075	1020	1210	1465	1070	1355	1225	1325
	8	2113	1763	1713	1650	2225
GSH	4	715	835	715	565	705	485	640	615	535	580
	8	1600	1563	1550	1500	1738
LFS	4	9.50	12.50	7.75	9.00	11.50	10.50	9.25	11.75	9.00	11.75
	8	12.25	9.75	10.50	12.50	11.75
TMP	4	38.80	38.60	39.00	38.70	38.50	38.80	38.90	38.80	38.30	38.60
	8	38.80	39.30	39.00	39.10	38.80

Measurements (individual values): males group 2
 10 mg/kg

Parameter	time	11	12	13	14	15
GSF	4	960	915	1075	1290	1140
GSH	4	500	605	610	575	535
LFS	4	9.75	10.50	11.75	11.00	10.00
TMP	4	38.80	38.80	38.60	38.70	38.60

Measurements (individual values): males group 3
 50 mg/kg

Parameter	time	16	17	18	19	20
GSF	4	1185	1025	1105	1145	1440
GSH	4	585	650	680	485	805
LFS	4	10.25	9.25	9.75	10.25	10.00
TMP	4	38.60	38.90	38.50	38.60	38.80

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

267

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements (individual values): males group 4
200 mg/kg

Parameter	time	21	22	23	24	25	26	27	28	29	30
GSF	4	1055	1715	1405	1280	1015	1145	1510	1155	1200	1570
	8	1900	2338	2288	2075	1663
GSH	4	585	885	550	745	415	510	560	695	575	585
	8	1525	1888	1425	1450	1325
LFS	4	9.50	8.75	6.00	12.50	11.00	8.50	11.25	9.50	9.75	10.75
	8	10.25	10.50	9.75	11.50	12.25
TMP	4	38.50	38.60	38.80	38.80	.	38.70	38.70	38.80	38.50	38.60
	8	38.80	39.30	39.10	38.80	39.00

Measurements (individual values): males group 5
1000 mg/kg

Parameter	time	31	32	33	34	35	36	37	38	39	40
GSF	4	1430	1165	1320	1310	1405	1305	1140	1455	1235	1280
	8	1913	2113	1963	1738	1688
GSH	4	610	665	575	585	675	520	540	720	800	505
	8	1763	1725	1575	1625	1313
LFS	4	7.25	9.75	11.25	11.00	10.75	12.00	10.50	14.25	10.00	7.25
	8	12.25	12.50	14.25	14.00	7.50
TMP	4	38.40	38.80	38.50	38.10	39.00	38.70	38.80	38.70	38.40	38.50
	8	39.10	39.20	39.00	38.80	38.90

Measurements (individual values): females group 1
0 mg/kg

Parameter	time	41	42	43	44	45	46	47	48	49	50
GSF	4	1190	1160	975	1155	1320	1135	1210	1085	1110	1180
	8	1863	1625	1513	1888	2063
GSH	4	815	620	525	545	710	420	845	425	530	550
	8	1338	1375	1200	1263	1238
LFS	4	10.00	10.00	8.75	11.00	12.00	10.25	7.25	10.25	12.00	10.25
	8	9.00	10.25	12.00	12.25	11.25
TMP	4	39.30	39.40	39.10	39.30	39.40	39.00	39.60	39.20	39.50	39.20
	8	39.20	39.80	39.80	39.70	39.30

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

268

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Measurements (individual values): females group 2
10 mg/kg

Parameter	time	51	52	53	54	55
GSF	4	1060	1035	1200	1025	1100
GSF	8
GSH	4	510	605	595	490	460
GSH	8
LFS	4	9.00	11.75	9.50	8.25	10.75
LFS	8
TMP	4	39.10	39.00	39.50	39.20	39.00
TMP	8

Measurements (individual values): females group 3
50 mg/kg

Parameter	time	56	57	58	59	60
GSF	4	1210	1000	925	1055	1005
GSF	8
GSH	4	505	565	485	700	610
GSH	8
LFS	4	8.25	7.00	8.75	10.25	7.50
LFS	8
TMP	4	39.10	39.30	39.40	39.20	39.10
TMP	8

Measurements (individual values): females group 4
200 mg/kg

Parameter	time	61	62	63	64	65	66	67	68	69	70
GSF	4	1120	1020	1050	1225	1090	1275	1085	1085	1280	1105
GSF	8	1700	1400	.	1413	1175
GSH	4	455	520	455	550	515	690	575	605	455	700
GSH	8	1325	1650	.	1175	1363
LFS	4	6.50	10.50	9.25	12.50	13.25	11.50	8.00	7.75	9.25	9.25
LFS	8	11.50	8.50	.	10.25	8.50
TMP	4	39.00	39.40	39.30	39.40	39.00	39.20	39.40	39.10	39.00	39.40
TMP	8	39.50	39.50	.	39.50	38.90

Measurements (individual values): females group 5
1000 mg/kg

Parameter	time	71	72	73	74	75	76	77	78	79	80
GSF	4	1105	985	950	1105	1195	1095	1190	1200	1040	1265
GSF	8	1600	1813	1450	1263	1688
GSH	4	685	435	445	545	460	650	490	510	515	505
GSH	8	1425	1738	1325	1200	1263
LFS	4	7.50	7.00	9.75	8.00	10.25	12.25	11.00	7.25	13.00	10.75
LFS	8	9.75	12.00	9.75	9.00	11.00
TMP	4	39.10	39.30	39.20	39.00	39.30	39.00	39.30	39.10	39.10	39.30
TMP	8	39.30	39.80	39.80	39.90	39.60

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.3. Motor activity (individuals)Total distance (individual): males group 1
(cm) 0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
1	4	769	739	591	396	297	162	548	358	111	203	4174
2	4	1176	904	683	477	370	233	139	236	218	55	4491
3	4	1071	668	706	944	721	424	510	673	12	294	6023
4	4	1125	1280	609	749	459	251	111	452	160	325	5521
5	4	1051	665	584	266	33	256	396	30	0	2	3283
6	4	1026	703	645	528	127	287	332	457	167	436	4708
8	8	883	805	810	721	612	381	292	477	609	190	5780
7	4	1102	779	612	314	601	601	505	358	640	215	5727
8	8	1297	624	170	210	261	86	322	185	314	2	3471
8	4	637	556	581	551	297	340	160	238	297	10	3667
8	8	1018	632	861	459	307	86	228	33	505	38	4167
9	4	1158	563	772	787	398	403	203	482	254	114	5134
8	8	655	538	515	147	274	15	38	388	165	5	2740
10	4	556	210	279	109	63	147	12	2	7	142	1527
8	8	490	15	322	83	190	0	10	2	71	12	1195

Total distance (individual): males group 2
(cm) 10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
11	4	883	1033	1155	772	789	822	594	419	264	439	7170
12	4	1016	871	416	340	568	251	63	292	175	292	4284
13	4	1074	1145	883	566	957	363	152	137	208	17	5502
14	4	1178	1038	822	568	800	518	490	248	492	342	6496
15	4	1016	619	680	508	604	408	248	424	325	2	4834

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Total distance (individual): males
(cm)

group 3
50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
16	4	769	998	650	736	535	533	172	365	10	2	4770
17	4	1328	1470	1066	721	632	574	472	662	690	543	8158
18	4	1295	1191	990	855	434	629	414	289	279	449	6825
19	4	675	617	574	307	86	266	177	106	177	40	3025
20	4	1353	1196	609	294	279	518	20	124	342	5	4740

Total distance (individual): males
(cm)

group 4
200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
21	4	1071	1036	695	726	513	589	520	248	195	434	6027
22	4	538	132	515	195	17	259	0	144	386	215	2401
23	4	1516	1465	916	706	713	467	330	835	472	439	7859
24	4	1140	843	817	551	355	487	528	378	99	78	5276
26	4	1125	680	472	246	304	391	137	182	81	226	3844
	8	1135	845	436	378	365	58	5	340	457	480	4499
27	4	1275	1219	1018	581	208	734	335	342	980	509	7281
	8	1254	1379	741	789	1158	594	815	568	584	342	8224
28	4	802	675	480	487	271	289	284	386	424	12	4110
	8	942	802	332	266	292	411	2	325	137	205	3714
29	4	1127	779	957	612	568	558	411	449	337	426	6224
	8	386	292	355	27	17	563	152	2	0	0	1794
30	4	967	927	678	307	619	535	254	231	137	55	4710
	8	391	180	50	71	2	63	2	0	12	99	870

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

271

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Total distance (individual): males group 5
(cm) 1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
31	4	904	520	309	269	114	568	251	132	403	190	3660
32	4	972	685	363	167	304	172	0	0	12	30	2705
33	4	1353	1290	734	698	137	421	279	170	256	182	5520
34	4	939	591	205	137	63	25	10	76	7	0	2053
35	4	975	713	937	871	396	434	342	292	345	180	5485
36	4	1361	830	474	525	210	271	375	370	180	246	4842
	8	426	408	17	66	20	60	553	375	0	104	2029
37	4	1214	1051	726	678	350	241	68	568	20	12	4928
	8	1196	835	759	363	391	386	132	401	114	213	4790
38	4	1221	1183	586	386	309	457	429	261	73	467	5372
	8	1917	777	830	497	12	322	0	0	144	403	4902
39	4	1005	810	777	637	680	769	495	553	322	538	6586
	8	909	314	680	480	401	370	134	193	106	137	3724
40	4	1737	1313	1356	764	614	668	347	266	220	182	7267
	8	528	45	190	58	2	27	0	12	563	45	1470

No. of movements (individual): males group 1
(counts) 0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
1	4	53	52	36	36	30	20	37	31	19	33	347
2	4	48	39	41	29	26	22	11	27	23	10	276
3	4	49	47	42	41	35	45	26	39	4	22	350
4	4	37	42	41	41	33	30	28	39	22	29	342
5	4	44	43	45	26	16	23	25	8	0	1	231
6	4	40	43	38	42	20	27	30	38	22	36	336
	8	34	40	45	47	36	33	29	36	34	23	357
7	4	46	44	48	36	40	37	36	32	45	27	391
	8	34	33	17	20	19	10	20	10	21	2	186
8	4	50	47	52	43	34	31	18	25	32	4	336
	8	38	24	32	19	29	13	17	6	32	7	217
9	4	42	43	38	42	35	22	17	42	17	17	315
	8	37	35	32	15	28	7	11	27	22	4	218
10	4	53	26	27	15	8	22	3	3	2	10	169
	8	34	4	28	17	14	0	7	2	12	9	127

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No. of movements (individual): males
(counts)group 2
10 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
11 4	41	44	40	38	34	43	43	34	23	31	371
12 4	46	38	47	40	47	21	13	37	23	38	350
13 4	42	44	42	39	33	33	20	18	18	10	299
14 4	46	41	43	37	42	37	33	22	33	23	357
15 4	45	43	42	35	40	28	22	35	13	2	305

No. of movements (individual): males
(counts)group 3
50 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
16 4	45	40	41	41	42	30	14	35	7	1	296
17 4	41	38	44	39	29	39	34	39	42	34	379
18 4	36	43	45	52	35	34	39	22	23	35	364
19 4	53	46	45	34	13	30	21	12	18	6	278
20 4	45	43	38	24	24	37	9	9	21	4	254

No. of movements (individual): males
(counts)group 4
200 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
21 4	36	46	44	41	34	30	36	23	30	30	350
22 4	44	16	45	19	10	25	0	15	35	25	234
23 4	46	37	47	36	47	29	25	36	39	27	369
24 4	46	34	35	34	22	37	35	21	12	21	297
26 4	43	42	39	33	32	40	24	17	15	24	309
8	38	42	28	37	31	13	3	18	31	39	280
27 4	43	43	38	39	28	42	25	28	36	19	341
8	40	31	24	24	28	27	36	34	33	24	301
28 4	47	52	39	38	38	26	30	24	30	6	330
8	32	47	18	21	34	19	2	33	12	17	235
29 4	37	38	47	48	28	41	31	43	21	31	365
8	30	25	22	8	6	33	16	2	0	0	142
30 4	45	44	36	35	36	32	20	21	13	4	286
8	13	14	8	7	1	7	1	0	4	5	60

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No. of movements (individual): males
(counts)

group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
31	4	43	45	39	26	28	35	39	20	31	20	326
32	4	47	41	34	26	34	14	0	1	9	18	224
33	4	36	38	38	40	21	28	23	15	26	15	280
34	4	44	35	23	21	4	8	4	18	4	1	162
35	4	49	37	45	36	27	34	26	26	32	21	333
36	4	40	42	35	29	27	22	39	26	16	19	295
	8	25	13	2	9	3	2	43	15	0	17	129
37	4	43	44	40	31	30	34	4	41	10	7	284
	8	30	25	30	22	20	19	14	15	10	13	198
38	4	38	39	41	26	26	35	33	26	16	32	312
	8	34	29	34	23	8	13	1	1	10	17	170
39	4	49	41	45	37	42	41	35	37	28	16	371
	8	47	22	44	36	38	41	15	21	10	12	286
40	4	38	34	34	37	38	29	26	36	2	12	286
	8	40	11	17	11	2	9	0	4	27	12	133

Movement time (individual): males
(sec)

group 1
0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
1	4	70	64	62	31	31	16	47	37	13	21	392
2	4	91	72	51	37	29	15	10	21	13	5	344
3	4	78	59	58	82	66	42	40	54	1	21	501
4	4	106	102	60	64	40	24	10	43	15	35	499
5	4	102	71	56	25	4	21	38	5	0	0	322
6	4	90	64	63	59	14	30	28	48	18	55	469
	8	81	67	72	68	59	37	32	49	50	20	535
7	4	91	69	46	30	53	42	37	33	47	23	471
	8	98	47	18	23	20	10	24	16	28	0	284
8	4	61	49	46	43	26	27	12	22	22	1	309
	8	75	39	50	30	30	7	18	2	35	6	292
9	4	76	51	63	59	37	33	17	48	20	9	413
	8	50	46	42	14	27	3	3	28	17	0	230
10	4	46	21	22	14	11	15	2	0	1	19	151
	8	41	1	30	9	16	0	1	0	8	1	107

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Movement time (individual): males
(sec)group 2
10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
11	4	90	92	101	72	59	71	50	36	20	33	624
12	4	88	86	38	32	51	25	7	29	14	21	391
13	4	96	91	70	43	78	32	17	13	17	1	458
14	4	89	95	61	40	61	32	32	20	38	22	490
15	4	89	56	66	49	47	34	25	30	18	0	414

Movement time (individual): males
(sec)group 3
50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
16	4	69	83	57	55	50	50	16	37	2	0	419
17	4	100	114	82	53	47	32	38	57	61	47	631
18	4	111	93	77	60	36	48	32	22	20	29	528
19	4	64	63	50	35	6	22	16	5	17	3	281
20	4	99	91	43	30	20	41	2	8	30	0	364

Movement time (individual): males
(sec)group 4
200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
21	4	98	82	60	56	33	51	43	19	15	38	495
22	4	50	20	47	16	2	25	0	12	41	18	231
23	4	106	105	73	67	67	44	24	68	41	35	630
24	4	84	60	52	36	24	30	47	31	11	8	383
26	4	80	60	40	23	25	41	12	20	10	22	333
	8	78	58	36	31	29	5	0	24	38	41	340
27	4	106	91	81	48	18	56	29	29	79	36	573
	8	69	82	47	54	73	43	55	53	54	34	564
28	4	75	66	49	46	23	25	24	37	38	0	383
	8	80	66	31	30	32	25	1	27	14	20	326
29	4	104	70	70	55	49	46	34	39	21	29	517
	8	32	22	22	4	4	51	14	1	0	0	150
30	4	80	78	56	24	50	41	21	13	8	5	376
	8	32	15	6	4	1	6	0	0	1	7	72

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Movement time (individual): males
(sec)

group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
31	4	66	55	28	27	11	46	28	11	38	15	325
32	4	86	71	31	18	33	20	0	0	1	4	264
33	4	109	94	63	55	9	31	28	16	25	14	444
34	4	91	52	13	17	5	3	1	6	0	0	188
35	4	75	58	83	71	33	31	24	18	37	15	445
36	4	101	70	38	41	23	30	36	24	17	17	397
	8	26	26	2	4	2	6	52	32	0	14	164
37	4	100	68	50	52	32	24	3	45	2	1	377
	8	83	58	44	25	26	25	11	32	6	14	324
38	4	97	100	62	35	30	37	37	18	10	41	467
	8	113	47	50	41	1	19	0	0	10	36	317
39	4	85	72	67	47	73	55	52	43	23	47	564
	8	76	26	58	50	41	30	14	18	7	11	331
40	4	120	98	103	68	51	59	27	31	2	18	577
	8	48	5	17	8	0	4	0	1	44	6	133

Vertical activity (individual): males
(counts)

group 1
0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
1	4	186	136	64	45	54	27	39	28	20	37	636
2	4	185	129	87	23	110	55	44	42	7	12	694
3	4	163	145	178	115	67	123	106	56	15	132	1100
4	4	181	135	161	83	76	39	83	44	16	77	895
5	4	189	146	122	77	84	116	44	35	0	2	815
6	4	108	142	120	92	28	19	153	59	63	138	922
	8	107	129	96	81	78	62	78	16	147	63	857
7	4	121	139	65	101	107	120	101	122	79	55	1010
	8	77	42	17	58	77	12	2	29	64	0	378
8	4	116	178	140	64	62	76	40	89	124	25	914
	8	120	144	89	25	21	14	22	0	94	8	537
9	4	191	170	87	114	64	42	43	49	89	67	916
	8	55	77	31	7	58	13	18	66	24	5	354
10	4	171	109	70	22	16	28	0	0	0	25	441
	8	64	3	43	19	38	0	0	0	10	6	183

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical activity (individual): males group 5
 (counts) 1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
31	4	150	158	49	62	63	114	29	28	68	84	805
32	4	137	129	55	16	52	18	0	0	0	0	407
33	4	123	121	182	83	14	36	51	14	45	13	682
34	4	83	127	49	17	6	4	0	5	0	0	291
35	4	245	191	96	114	68	75	88	77	57	134	1145
36	4	167	115	101	121	88	48	114	37	27	88	906
	8	47	21	0	37	8	0	25	9	0	13	160
37	4	137	210	158	78	51	64	27	119	6	17	867
	8	119	74	62	75	11	25	14	26	31	41	478
38	4	150	199	128	105	79	82	20	83	40	89	975
	8	163	59	77	36	6	16	0	0	15	60	432
39	4	187	178	119	120	53	118	15	96	78	87	1051
	8	124	25	84	80	32	43	38	17	13	0	456
40	4	163	197	183	79	241	97	110	129	135	102	1436
	8	83	0	32	10	0	16	0	11	68	33	253

No. of rearings (individual): males group 1
 (counts) 0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
1	4	28	19	11	8	8	5	8	4	4	6	101
2	4	25	21	13	3	11	6	5	8	2	2	96
3	4	25	20	24	18	10	19	14	9	3	16	158
4	4	27	22	18	15	11	5	10	8	5	12	133
5	4	28	24	17	13	11	13	7	6	0	1	120
6	4	16	20	17	8	4	4	16	6	7	16	114
	8	16	12	12	12	9	6	9	3	13	11	103
7	4	22	23	12	13	16	18	11	17	12	9	153
	8	15	8	3	9	9	2	1	3	10	0	60
8	4	19	25	19	12	10	11	7	13	19	6	141
	8	20	19	15	5	3	4	5	0	13	2	86
9	4	17	21	11	19	8	7	6	7	11	9	116
	8	10	11	4	1	9	1	1	9	5	1	52
10	4	24	18	10	3	4	5	0	0	0	4	68
	8	10	1	6	4	4	0	0	0	1	1	27

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No. of rearings (individual): males group 5
(counts) 1000 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
31 4	27	24	13	13	13	19	6	6	13	11	145
32 4	24	18	13	3	10	3	0	0	0	0	71
33 4	19	13	21	9	3	5	5	3	4	4	86
34 4	16	22	7	4	1	1	0	2	0	0	53
35 4	33	25	18	17	9	14	9	14	9	13	161
36 4	27	16	16	19	10	13	15	7	5	12	140
8	11	3	0	5	1	0	4	3	0	2	29
37 4	20	22	20	11	7	9	4	16	1	3	113
8	18	12	8	8	2	5	1	3	3	5	65
38 4	19	23	22	14	13	14	3	13	4	8	133
8	21	12	8	5	1	3	0	0	1	7	58
39 4	24	22	18	13	8	16	3	14	9	11	138
8	16	4	9	11	6	7	3	4	2	0	62
40 4	24	26	22	12	22	12	14	16	11	13	172
8	17	0	4	2	0	2	0	3	9	4	41

Vertical time (individual): males group 1
(sec) 0 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
1 4	55	52	29	19	29	9	20	14	15	35	277
2 4	49	41	39	7	51	29	54	29	3	7	309
3 4	47	60	65	48	27	56	60	29	4	65	461
4 4	52	36	58	36	32	18	47	21	6	31	337
5 4	52	54	52	46	89	70	26	28	0	1	418
6 4	36	43	45	32	8	4	77	22	30	59	356
8	34	50	52	35	26	42	47	7	61	26	380
7 4	43	48	26	43	50	55	53	62	39	37	456
8	29	16	7	27	31	5	1	16	37	0	169
8 4	41	73	58	25	23	38	19	34	66	24	401
8	34	57	37	11	21	5	10	0	47	1	223
9 4	69	67	45	42	31	18	25	24	57	33	411
8	23	30	17	5	36	10	16	49	13	2	201
10 4	50	44	48	6	7	10	0	0	0	15	180
8	20	2	22	11	21	0	0	0	4	1	81

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical time (individual): males
(sec)

group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
31	4	41	57	17	20	26	52	9	16	47	59	344
32	4	37	41	23	8	23	6	0	0	0	0	138
33	4	48	49	85	59	10	20	37	18	30	4	360
34	4	24	45	20	4	2	2	0	1	0	0	98
35	4	74	85	34	42	30	59	46	57	38	85	550
36	4	44	40	41	41	37	17	57	21	10	52	360
	8	19	14	0	17	3	0	11	4	0	11	79
37	4	42	66	71	28	17	25	14	42	2	5	312
	8	32	20	31	22	2	15	5	9	9	22	167
38	4	52	61	65	54	58	49	15	50	43	45	492
	8	55	29	34	13	4	7	0	0	10	25	177
39	4	65	72	55	62	24	60	6	62	57	52	515
	8	55	9	47	32	17	23	35	9	5	0	232
40	4	44	64	67	31	94	50	63	70	141	117	741
	8	21	0	12	4	0	11	0	14	29	17	108

Center time (individual): males
(sec)

group 1
0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
1	4	40	36	19	34	22	17	36	40	37	18	299
2	4	53	19	26	9	9	4	1	6	2	1	130
3	4	57	51	30	55	67	83	33	45	0	38	459
4	4	77	79	117	83	48	33	66	119	22	75	719
5	4	48	38	26	10	0	2	14	0	0	0	138
6	4	70	73	61	85	106	91	39	61	132	91	809
	8	57	58	32	47	33	45	36	30	45	28	411
7	4	36	83	94	44	63	53	48	43	34	71	569
	8	37	12	10	12	22	2	24	2	16	0	137
8	4	67	41	47	24	29	20	16	106	48	0	398
	8	64	15	18	3	10	5	10	1	25	10	161
9	4	24	27	12	26	15	36	28	38	22	18	246
	8	36	30	23	30	20	9	12	17	13	0	190
10	4	17	18	18	3	0	3	0	0	0	4	63
	8	24	5	16	0	6	0	0	0	4	2	57

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Center time (individual): males
(sec)

group 2
10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
11	4	65	91	52	44	33	78	25	22	3	38	451
12	4	63	94	56	86	87	74	1	21	30	96	608
13	4	52	63	26	83	23	11	20	7	15	0	300
14	4	58	69	49	64	67	67	39	78	75	31	597
15	4	35	34	39	17	27	15	0	4	4	0	175

Center time (individual): males
(sec)

group 3
50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
16	4	42	50	30	42	24	40	1	17	0	0	246
17	4	105	99	102	70	108	123	57	50	101	111	926
18	4	37	65	36	26	92	56	21	20	4	47	404
19	4	44	61	70	67	27	58	38	25	8	1	399
20	4	74	94	51	22	20	33	4	6	10	1	315

Center time (individual): males
(sec)

group 4
200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
21	4	54	57	25	11	14	15	30	9	3	12	230
22	4	23	2	32	4	0	20	0	1	17	11	110
23	4	52	44	40	24	24	26	19	57	44	39	369
24	4	61	33	31	89	106	54	54	48	17	2	495
26	4	46	40	30	54	55	45	27	32	29	102	460
	8	59	26	21	14	17	6	0	7	52	36	238
27	4	82	95	77	106	68	104	94	62	88	33	809
	8	79	47	45	27	58	60	117	85	91	49	658
28	4	48	33	27	14	36	38	19	40	13	0	268
	8	22	41	12	15	17	3	0	12	5	14	141
29	4	52	43	35	46	46	47	17	35	20	56	397
	8	21	21	10	3	0	18	2	0	0	0	75
30	4	53	39	12	24	38	44	32	40	54	7	343
	8	53	4	1	0	0	4	0	7	10	5	84

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Center time (individual): males
(sec)

group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
31	4	58	17	13	12	2	22	25	6	25	42	222
32	4	38	30	8	15	9	9	0	0	0	0	109
33	4	37	49	67	63	37	20	18	1	31	20	343
34	4	54	46	9	15	2	1	0	1	0	0	128
35	4	41	55	57	63	55	20	6	61	29	60	447
36	4	68	43	67	59	53	22	23	11	5	33	384
	8	11	1	0	1	0	1	7	6	0	6	33
37	4	60	84	40	65	19	37	2	72	0	3	382
	8	20	32	17	10	6	12	8	12	1	10	128
38	4	43	73	53	40	52	58	75	13	4	29	440
	8	51	18	5	13	0	4	0	0	8	24	123
39	4	32	41	42	37	45	34	62	19	60	37	409
	8	43	34	45	36	78	68	32	29	2	30	397
40	4	46	75	57	82	45	57	67	77	1	29	536
	8	26	7	15	1	0	5	0	7	12	6	79

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28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

284

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Total distance (individual): females group 1
(cm) 0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
41	4	1529	1198	901	970	673	960	271	441	246	541	7730
42	4	1343	1275	1003	347	967	279	360	777	1173	276	7800
43	4	1021	858	429	325	58	231	464	167	170	5	3728
44	4	1061	909	693	485	127	492	452	294	309	170	4992
45	4	1109	1343	896	878	622	637	629	220	650	579	7563
46	4	1229	1054	795	795	360	386	317	302	157	264	5659
	8	421	436	0	0	0	10	0	0	0	0	867
47	4	1257	929	929	693	652	505	655	353	535	335	6843
	8	1041	627	474	431	317	157	563	0	185	121	3916
48	4	1341	960	1028	447	525	342	538	548	510	426	6665
	8	1031	673	632	210	764	317	142	7	467	25	4268
49	4	1363	977	655	525	342	444	228	254	304	152	5244
	8	673	650	403	538	17	86	205	76	223	0	2871
50	4	1757	1546	1099	982	1097	579	833	889	1016	528	10326
	8	1577	1234	736	505	698	718	596	485	452	88	7089

Total distance (individual): females group 2
(cm) 10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
51	4	1610	975	784	627	711	467	127	223	355	25	5904
52	4	1092	896	586	553	81	330	121	508	264	0	4431
53	4	1719	1884	1877	1584	1534	1376	1932	916	815	1036	14673
54	4	1315	899	878	995	388	490	480	543	330	345	6663
55	4	698	556	662	302	624	429	469	76	81	127	4024

Total distance (individual): females group 3
(cm) 50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
56	4	1239	607	556	256	215	317	20	5	2	2	3219
57	4	1506	982	769	647	419	520	383	99	185	274	5784
58	4	1371	1513	1249	1242	713	624	574	548	756	574	9164
59	4	1280	777	871	548	187	464	525	632	431	553	6268
60	4	1064	840	695	914	497	360	472	579	325	530	6276

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

285

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Total distance (individual): females group 4
(cm) 200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
61	4	1153	929	657	391	322	383	246	299	403	182	4965
62	4	1226	883	279	121	673	365	185	299	195	378	4604
63	4	1051	922	812	601	261	444	269	383	231	93	5067
64	4	1356	1424	1277	1132	1054	784	584	739	335	949	9634
65	4	1320	1191	1089	462	622	825	528	472	317	312	7138
66	4	820	1023	787	474	492	604	495	93	40	337	5165
	8	1170	751	596	238	335	571	622	266	1071	279	5899
67	4	1031	1066	1366	952	952	645	774	487	513	784	8570
	8	17	2	2	22	0	25	0	0	7	0	75
68	4	2435	2194	2153	2313	1620	1615	1099	1264	1358	899	16950
69	4	1209	756	568	243	375	271	345	220	172	121	4280
	8	1071	444	566	353	533	55	0	213	165	12	3412
70	4	1041	1071	718	398	469	386	226	322	558	101	5290
	8	1150	868	896	256	561	335	289	502	129	68	5054

Total distance (individual): females group 5
(cm) 1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
71	4	1163	1076	906	454	657	609	462	561	828	535	7251
72	4	680	477	340	259	375	309	5	251	53	7	2756
73	4	1173	957	810	769	815	256	586	563	269	500	6698
74	4	975	525	203	190	401	195	243	510	160	5	3407
75	4	1234	767	467	381	345	502	406	228	233	172	4735
76	4	1252	795	805	309	284	574	208	304	302	294	5127
	8	914	497	15	116	30	406	142	7	5	0	2132
77	4	1127	977	703	937	444	767	312	739	340	599	6945
	8	838	388	114	711	12	497	43	320	20	12	2955
78	4	1457	815	685	398	111	391	436	20	5	17	4335
	8	777	266	154	147	73	116	35	210	284	10	2072
79	4	1531	1181	1584	1170	1412	967	830	1021	673	995	11364
	8	1661	1724	1160	1173	977	703	744	990	614	363	10109
80	4	1595	1005	703	530	855	342	175	261	236	406	6108
	8	1414	835	640	492	327	307	106	198	160	205	4684

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

286

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No. of movements (individual): females
(counts)

group 1
0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
41	4	37	49	43	47	36	47	21	25	21	32	358
42	4	41	38	38	28	35	21	14	36	42	14	307
43	4	40	31	28	29	10	10	24	18	18	4	212
44	4	42	47	39	43	14	30	40	25	25	17	322
45	4	46	42	46	39	41	44	31	15	34	23	361
46	4	44	50	42	41	28	43	33	23	19	12	335
	8	25	33	0	0	0	3	0	0	0	0	61
47	4	53	41	44	41	37	36	45	27	29	27	380
	8	47	38	37	27	36	13	32	0	28	16	274
48	4	44	41	46	30	39	35	32	38	29	26	360
	8	39	35	41	24	37	21	7	7	24	7	242
49	4	45	41	43	37	24	24	22	21	17	14	288
	8	39	37	31	33	6	8	30	15	14	0	213
50	4	39	36	44	50	39	34	49	40	37	33	401
	8	48	40	44	33	44	40	37	32	33	22	373

No. of movements (individual): females
(counts)

group 2
10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
51	4	43	52	44	43	45	34	23	23	27	8	342
52	4	50	47	40	44	17	25	13	46	20	2	304
53	4	43	38	43	40	37	39	38	35	33	39	385
54	4	40	34	32	44	22	34	27	29	25	32	319
55	4	49	48	39	33	37	31	32	11	14	11	305

No. of movements (individual): females
(counts)

group 3
50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
56	4	36	41	33	33	18	24	8	3	1	3	200
57	4	38	43	47	42	29	28	27	14	19	13	300
58	4	39	36	38	46	49	44	35	39	40	45	411
59	4	44	45	38	37	16	37	35	35	33	31	351
60	4	45	46	37	39	32	30	38	33	30	25	355

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

287

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No. of movements (individual): females group 4
(counts) 200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
61	4	41	44	25	34	25	27	22	22	33	25	298
62	4	41	44	26	10	37	31	17	20	10	16	252
63	4	41	47	41	43	18	44	26	32	18	12	322
64	4	42	39	40	45	43	39	28	36	19	37	368
65	4	44	41	38	34	36	31	28	33	30	19	334
66	4	47	44	38	33	30	32	33	15	8	24	304
66	8	38	31	35	18	23	26	40	19	32	21	283
67	4	51	40	43	42	30	34	32	32	21	30	355
67	8	2	1	3	4	1	9	0	0	2	0	22
68	4	21	38	31	31	35	39	36	36	37	35	339
69	4	43	46	36	16	35	32	22	21	12	12	275
69	8	42	30	37	26	34	8	1	27	15	5	225
70	4	42	35	41	30	41	32	33	32	41	14	341
70	8	40	48	37	21	40	21	22	29	20	7	285

No. of movements (individual): females group 5
(counts) 1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
71	4	45	41	45	39	37	37	47	32	33	33	389
72	4	50	41	40	31	42	26	3	17	7	3	260
73	4	44	44	45	41	41	13	36	36	28	28	356
74	4	47	42	34	26	36	21	22	37	14	3	282
75	4	43	42	36	34	22	26	29	19	20	9	280
76	4	48	54	39	28	33	35	13	19	30	27	326
76	8	34	35	8	8	9	21	12	4	5	0	136
77	4	48	54	39	46	32	37	26	34	25	32	373
77	8	30	18	7	36	11	21	9	25	7	9	173
78	4	43	47	39	32	15	27	32	8	4	13	260
78	8	30	16	18	13	10	13	11	16	20	4	151
79	4	39	43	35	42	38	41	33	41	34	34	380
79	8	40	43	40	40	44	36	39	42	40	31	395
80	4	42	44	45	39	45	31	19	21	26	27	339
80	8	39	37	35	37	27	34	10	23	15	27	284

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

288

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Movement time (individual): females
(sec)group 1
0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
41	4	104	71	68	70	45	64	23	38	21	34	538
42	4	98	90	80	21	64	23	28	52	69	23	548
43	4	95	71	37	28	5	22	44	15	13	0	330
44	4	94	85	47	42	9	37	30	21	19	9	393
45	4	79	91	72	68	49	46	41	12	49	36	543
46	4	102	81	60	69	30	32	31	21	10	20	456
	8	29	40	0	0	0	3	0	0	0	0	72
47	4	86	84	79	51	37	32	40	18	39	16	482
	8	76	45	42	41	25	11	42	0	16	10	308
48	4	83	70	71	35	38	21	39	39	37	34	467
	8	66	46	51	10	52	22	9	0	28	5	289
49	4	97	68	48	44	28	36	16	17	15	10	379
	8	47	40	27	38	3	9	19	6	18	0	207
50	4	107	116	88	72	75	49	66	61	59	32	725
	8	87	81	55	47	48	43	47	34	31	5	478

Movement time (individual): females
(sec)group 2
10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
51	4	108	90	68	52	59	41	10	24	30	3	485
52	4	80	70	57	51	7	35	9	36	24	0	369
53	4	101	114	105	102	101	86	105	54	47	61	876
54	4	96	70	62	60	25	28	34	37	23	24	459
55	4	73	54	51	21	50	29	37	8	6	10	339

Movement time (individual): females
(sec)group 3
50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
56	4	90	49	33	16	13	25	2	0	0	0	228
57	4	109	87	65	54	30	46	38	8	15	14	466
58	4	102	107	96	94	55	48	43	41	49	41	676
59	4	85	57	67	38	15	34	35	49	26	37	443
60	4	71	62	54	62	42	23	32	43	22	34	445

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

289

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Movement time (individual): females
(sec)group 4
200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
61	4	85	74	54	38	22	38	33	22	37	16	419
62	4	80	73	22	10	52	26	13	14	10	26	326
63	4	85	73	68	52	24	37	25	33	21	6	424
64	4	95	103	79	81	65	53	41	53	18	56	644
65	4	96	81	75	24	36	58	41	38	28	29	506
66	4	56	77	60	39	39	49	36	8	4	24	392
	8	76	55	41	18	25	32	36	22	80	21	406
67	4	78	81	87	68	50	39	42	31	30	48	554
	8	1	0	0	3	0	2	0	0	1	0	7
68	4	143	104	126	121	94	101	63	72	78	55	957
69	4	88	58	41	22	28	24	20	15	12	8	316
	8	64	41	37	26	37	2	0	14	11	2	234
70	4	76	73	53	34	35	38	16	27	38	4	394
	8	74	64	54	15	48	27	18	30	8	5	343

Movement time (individual): females
(sec)group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
71	4	83	87	74	45	48	40	44	47	63	34	565
72	4	49	40	27	32	37	26	1	25	2	2	241
73	4	80	62	57	53	55	16	35	36	23	31	448
74	4	87	49	21	15	33	15	21	34	11	1	287
75	4	94	58	35	31	20	33	29	15	15	12	342
76	4	82	61	68	20	28	46	21	23	24	29	402
	8	63	33	2	8	4	26	9	1	0	0	146
77	4	81	73	54	75	34	59	24	46	28	39	513
	8	50	22	9	45	0	29	4	24	2	1	186
78	4	96	64	62	28	7	28	41	3	0	1	330
	8	54	27	14	10	6	14	4	21	19	1	170
79	4	104	74	105	66	79	54	45	64	40	48	679
	8	93	85	69	67	51	48	53	61	35	26	588
80	4	117	89	50	42	67	30	15	16	23	29	478
	8	97	64	52	42	26	34	5	16	14	12	362

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

290

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical activity (individual): females group 1
(counts) 0 mg/kg

Rat Study no	week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
41	4	208	143	148	166	187	99	75	171	44	106	1347
42	4	189	129	102	52	87	18	44	121	140	64	946
43	4	122	97	78	32	103	57	52	12	17	0	570
44	4	164	171	120	117	125	164	134	117	115	52	1279
45	4	235	148	135	252	114	97	65	43	68	46	1203
46	4	144	209	178	130	142	87	66	12	37	86	1091
	8	55	32	0	0	0	0	0	0	0	0	87
47	4	317	198	298	157	165	100	165	130	99	160	1789
	8	189	208	156	82	39	29	146	1	85	57	992
48	4	147	154	172	222	200	153	177	128	74	97	1524
	8	86	65	110	65	114	42	15	8	36	12	553
49	4	161	170	139	83	26	21	58	65	60	55	838
	8	114	54	84	32	0	5	7	5	15	0	316
50	4	262	249	255	341	191	267	202	211	235	143	2356
	8	160	199	133	148	116	106	109	36	6	17	1030

Vertical activity (individual): females group 2
(counts) 10 mg/kg

Rat Study no	week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
51	4	244	127	156	207	153	123	159	159	147	126	1601
52	4	255	178	179	155	30	63	37	232	80	59	1268
53	4	254	283	228	192	282	126	161	83	85	102	1796
54	4	135	209	182	112	81	113	66	43	65	118	1124
55	4	162	139	179	207	65	72	51	0	10	40	925

Vertical activity (individual): females group 3
(counts) 50 mg/kg

Rat Study no	week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
56	4	114	85	71	99	29	58	11	0	0	0	467
57	4	199	137	102	161	126	69	67	8	101	37	1007
58	4	231	166	163	253	124	122	114	259	156	126	1714
59	4	163	204	114	173	128	136	127	71	52	72	1240
60	4	176	144	123	101	87	77	109	92	147	95	1151

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

291

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical activity (individual): females
(counts)group 4
200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
61	4	180	138	84	49	75	35	31	38	68	55	753
62	4	140	156	27	72	55	35	38	4	0	39	566
63	4	121	143	188	86	137	91	74	59	25	96	1020
64	4	172	278	203	151	193	60	22	40	49	191	1359
65	4	197	246	138	199	186	121	58	80	78	56	1359
66	4	123	171	163	84	139	129	131	50	21	125	1136
	8	201	130	111	89	86	120	139	40	82	32	1030
67	4	133	174	130	157	199	101	105	82	93	87	1261
	8	0	0	6	0	0	0	0	0	0	0	6
68	4	238	226	318	211	227	313	230	183	170	122	2238
69	4	137	154	100	46	65	33	28	59	51	59	732
	8	142	98	67	54	79	11	4	22	27	0	504
70	4	252	128	188	161	138	94	106	75	97	31	1270
	8	144	105	125	73	100	35	18	72	42	8	722

Vertical activity (individual): females
(counts)group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
71	4	192	190	127	54	115	107	56	66	71	153	1131
72	4	148	139	124	57	56	60	0	38	18	6	646
73	4	234	146	205	192	184	208	172	126	89	85	1641
74	4	176	132	77	62	93	44	31	52	31	9	707
75	4	182	149	73	41	65	137	100	45	55	32	879
76	4	194	157	110	124	38	91	14	64	50	52	894
	8	87	84	9	11	7	28	10	0	0	0	236
77	4	191	201	230	98	130	133	101	218	65	104	1471
	8	84	55	13	143	34	41	0	49	0	0	419
78	4	131	83	108	107	88	64	62	37	53	37	770
	8	61	29	24	11	15	29	23	33	24	0	249
79	4	221	303	200	280	186	215	118	64	105	136	1828
	8	213	177	89	136	128	61	60	114	57	60	1095
80	4	175	130	187	129	78	84	65	60	54	115	1077
	8	184	83	125	53	44	34	48	60	40	23	694

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

292

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No. of rearings (individual): females group 1
(counts) 0 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
41 4	29	20	20	19	21	15	9	16	5	12	166
42 4	26	20	19	6	12	2	7	16	16	8	132
43 4	18	16	11	6	9	10	9	2	4	0	85
44 4	25	26	22	10	19	18	14	12	12	8	166
45 4	31	20	21	30	19	20	17	7	12	9	186
46 4	25	28	24	22	17	12	10	4	5	8	155
8	9	8	0	0	0	0	0	0	0	0	17
47 4	33	32	23	16	14	15	22	17	14	20	206
8	27	20	22	15	8	5	12	1	12	6	128
48 4	21	17	19	19	18	11	18	19	12	10	164
8	16	16	15	10	14	9	3	1	7	2	93
49 4	27	18	18	13	4	4	6	7	10	6	113
8	18	9	7	6	0	2	2	0	4	0	48
50 4	31	27	25	20	19	16	19	24	22	22	225
8	30	27	25	18	17	18	16	8	2	4	165

No. of rearings (individual): females group 2
(counts) 10 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
51 4	34	21	18	28	25	20	18	26	18	17	225
52 4	29	18	21	16	4	9	5	19	9	10	140
53 4	24	24	25	23	26	23	26	19	16	15	221
54 4	23	19	22	16	10	9	9	12	10	15	145
55 4	23	19	19	10	7	10	6	0	1	5	100

No. of rearings (individual): females group 3
(counts) 50 mg/kg

Rat Study no week	S a m p l i n g i n t e r v a l										Session total
	1	2	3	4	5	6	7	8	9	10	
56 4	22	12	8	8	4	7	1	0	0	0	62
57 4	31	17	9	17	11	10	11	1	8	7	122
58 4	29	24	20	20	20	15	16	13	24	17	198
59 4	16	19	8	13	9	18	15	11	6	12	127
60 4	20	19	14	20	14	11	16	10	13	16	153

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

No. of rearings (individual): females
(counts)

group 4
200 mg/kg

Rat Study no	week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
61	4	27	21	10	8	10	4	3	5	9	9	106
62	4	27	25	4	6	9	6	5	2	0	5	89
63	4	20	17	24	15	11	12	10	9	5	11	134
64	4	18	22	19	24	20	9	6	9	11	21	159
65	4	22	25	15	21	18	13	10	10	10	5	149
66	4	19	21	19	11	20	14	18	6	5	19	152
	8	25	20	16	13	9	17	17	6	16	7	146
67	4	22	23	20	18	21	11	11	12	9	10	157
	8	1	0	1	0	0	0	0	0	0	0	2
68	4	40	36	37	29	24	14	18	16	21	18	253
69	4	20	22	17	7	10	6	4	10	8	9	113
	8	25	12	11	7	15	2	1	4	4	0	81
70	4	27	20	17	17	13	11	10	10	15	6	146
	8	25	14	17	8	12	6	2	11	2	1	98

No. of rearings (individual): females
(counts)

group 5
1000 mg/kg

Rat Study no	week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
71	4	25	23	18	12	16	16	12	11	15	16	164
72	4	20	23	18	9	8	9	0	6	4	2	99
73	4	20	17	14	22	12	13	18	14	12	9	151
74	4	27	14	14	8	11	7	7	9	6	2	105
75	4	27	20	11	7	9	16	14	11	12	4	131
76	4	27	24	15	16	4	14	4	13	9	7	133
	8	16	13	2	2	1	6	2	0	0	0	42
77	4	27	28	24	17	15	17	13	21	8	14	184
	8	16	10	1	21	6	7	0	7	0	0	68
78	4	23	15	17	14	15	10	11	6	10	9	130
	8	11	5	5	2	4	6	3	5	3	0	44
79	4	18	18	22	22	20	17	20	12	15	14	178
	8	29	20	14	18	20	11	9	15	9	8	153
80	4	28	16	17	18	17	13	9	11	9	12	150
	8	32	14	14	9	7	9	6	7	5	5	108

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

294

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical time (individual): females
(sec)

group 1
0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
41	4	63	63	53	80	98	44	72	125	33	80	711
42	4	56	61	40	26	52	10	26	74	87	34	466
43	4	49	39	41	17	79	39	34	11	12	0	321
44	4	65	63	42	48	49	95	84	63	76	26	611
45	4	84	52	65	115	55	56	31	21	31	20	530
46	4	55	68	81	64	94	65	33	6	28	54	548
8		25	20	0	0	0	0	0	0	0	0	45
47	4	93	55	93	71	73	55	80	57	53	100	730
8		69	93	71	31	15	7	64	0	38	20	408
48	4	49	59	70	94	92	109	121	76	46	76	792
8		43	30	54	31	64	28	11	3	25	6	295
49	4	50	74	64	45	22	11	87	51	52	34	490
8		52	28	66	16	0	5	3	4	26	0	200
50	4	63	71	69	107	87	112	90	94	90	80	863
8		46	63	46	60	58	41	63	16	3	12	408

Vertical time (individual): females
(sec)

group 2
10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
51	4	64	44	53	89	57	63	85	73	91	85	704
52	4	74	65	69	66	14	43	16	100	47	46	540
53	4	79	104	103	73	121	48	77	35	40	40	720
54	4	60	110	99	57	55	79	49	59	40	82	690
55	4	75	64	93	152	53	66	32	0	8	40	583

Vertical time (individual): females
(sec)

group 3
50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
56	4	36	43	40	43	22	35	5	0	0	0	224
57	4	59	65	60	94	80	34	58	4	87	25	566
58	4	59	39	56	97	51	54	42	109	68	66	641
59	4	59	98	58	94	82	62	70	42	36	40	641
60	4	84	64	67	68	83	60	94	55	104	62	741

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

295

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Vertical time (individual): females
(sec)group 4
200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
61	4	58	59	46	49	82	17	26	33	45	61	476
62	4	40	46	12	34	27	21	25	1	0	24	230
63	4	39	63	84	42	77	40	46	37	18	66	512
64	4	57	86	85	65	73	40	7	21	19	102	555
65	4	67	95	68	113	127	85	49	58	65	65	792
66	4	49	60	81	54	98	85	79	38	16	68	628
	8	98	84	85	48	65	90	89	30	53	18	660
67	4	44	66	52	75	125	79	65	62	56	64	688
	8	0	0	4	0	0	0	0	0	0	0	4
68	4	55	71	85	67	82	130	130	101	87	75	883
69	4	56	66	44	19	38	17	11	31	22	24	328
	8	51	29	30	33	27	13	2	12	14	0	211
70	4	93	63	93	102	90	84	66	60	49	14	714
	8	80	52	72	50	50	21	11	62	49	9	456

Vertical time (individual): females
(sec)group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
71	4	78	81	68	32	72	108	27	66	48	92	672
72	4	63	69	66	53	40	54	0	18	5	1	369
73	4	89	69	106	96	113	141	99	90	92	79	974
74	4	46	71	36	34	40	26	16	31	16	4	320
75	4	56	65	31	15	46	77	54	40	39	19	442
76	4	57	54	46	60	18	41	4	32	27	37	376
	8	38	33	3	4	1	15	4	0	0	0	98
77	4	55	57	81	44	66	65	67	109	60	69	673
	8	31	20	4	68	30	11	0	21	0	0	185
78	4	54	38	51	63	61	48	46	61	57	26	505
	8	20	16	15	4	8	15	5	12	23	0	118
79	4	77	116	68	132	74	107	71	46	64	74	829
	8	82	90	49	74	52	34	31	77	43	37	569
80	4	63	53	103	68	48	44	31	54	70	107	641
	8	60	39	78	37	30	25	26	44	31	22	392

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

296

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Center time (individual): females
(sec)

group 1
0 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
41	4	55	51	50	69	90	50	38	64	26	45	538
42	4	44	53	62	26	39	16	24	95	43	43	445
43	4	31	46	32	80	7	10	35	29	67	75	412
44	4	23	14	4	42	0	10	30	11	39	20	193
45	4	58	65	48	82	41	32	53	11	34	24	448
46	4	28	41	38	77	31	9	16	6	5	9	260
46	8	9	21	0	0	0	0	0	0	0	0	30
47	4	59	51	70	32	52	35	51	36	70	15	471
47	8	60	52	25	20	24	8	28	0	24	14	255
48	4	27	37	42	15	28	17	16	51	19	45	297
48	8	14	4	15	1	19	12	2	1	22	2	92
49	4	25	26	10	31	12	8	4	13	4	22	155
49	8	8	17	32	7	0	7	12	0	38	0	121
50	4	35	37	22	17	13	33	28	15	51	25	276
50	8	37	17	12	13	3	17	12	12	3	1	127

Center time (individual): females
(sec)

group 2
10 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
51	4	49	36	35	27	64	18	2	7	33	13	284
52	4	18	33	38	59	11	44	7	30	20	0	260
53	4	44	33	43	43	54	29	39	59	28	29	401
54	4	46	88	96	51	55	112	56	40	57	40	641
55	4	31	26	32	23	31	44	39	65	0	76	367

Center time (individual): females
(sec)

group 3
50 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
56	4	27	9	5	13	4	4	0	0	0	0	62
57	4	52	22	36	47	6	34	33	0	48	19	297
58	4	54	24	32	56	69	76	45	20	27	70	473
59	4	60	60	24	84	89	65	60	53	35	11	541
60	4	59	35	40	44	70	46	65	42	67	64	532

28-DAY SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

297

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Center time (individual): females
(sec)group 4
200 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
61	4	41	58	76	55	82	40	41	15	44	36	488
62	4	77	118	150	118	37	46	24	32	1	3	606
63	4	39	36	77	17	102	47	75	64	109	87	653
64	4	39	88	64	88	78	54	98	83	108	56	756
65	4	14	33	35	73	10	51	16	14	8	31	285
66	4	36	76	50	52	74	44	101	138	67	112	650
	8	83	51	51	133	70	66	64	66	58	129	771
67	4	42	46	31	29	53	33	23	19	4	23	303
	8	0	0	0	0	0	0	0	0	0	0	0
68	4	42	26	52	52	40	87	76	46	32	54	507
69	4	49	42	18	7	10	13	5	6	2	23	175
	8	16	26	19	5	6	18	0	8	3	0	101
70	4	25	21	33	18	33	31	11	7	34	4	217
	8	31	12	40	12	32	44	26	13	4	17	231

Center time (individual): females
(sec)group 5
1000 mg/kg

Rat no	Study week	S a m p l i n g i n t e r v a l										Session total
		1	2	3	4	5	6	7	8	9	10	
71	4	29	84	49	46	63	67	65	44	30	28	505
72	4	18	36	8	21	61	25	0	26	0	0	195
73	4	57	56	61	69	79	121	30	81	82	105	741
74	4	35	37	22	11	18	5	12	21	19	0	180
75	4	41	54	43	6	14	56	17	38	10	3	282
76	4	21	9	19	2	4	10	0	5	4	9	83
	8	24	31	0	1	3	12	1	0	0	0	72
77	4	40	52	64	45	43	39	15	15	34	23	370
	8	34	22	2	34	24	19	0	7	0	0	142
78	4	43	29	49	68	107	25	64	4	0	0	389
	8	33	6	5	17	10	24	22	6	16	0	139
79	4	62	77	79	103	63	107	93	51	56	79	770
	8	66	62	49	40	34	31	25	59	24	68	458
80	4	22	48	31	32	43	58	24	22	37	34	351
	8	36	23	30	29	13	16	13	19	15	5	199

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.4. Mortality (individuals)

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

Animal number	cage	date of death	study week	study day	necropsy	type of death
1	1	8 Jan 97	5	30	yes	Sacrifice 1
2	2	8 Jan 97	5	30	yes	Sacrifice 1
3	3	8 Jan 97	5	30	yes	Sacrifice 1
4	4	8 Jan 97	5	30	yes	Sacrifice 1
5	5	8 Jan 97	5	30	yes	Sacrifice 1
6	6	5 Feb 97	9	58	yes	Sacrifice 2
7	7	5 Feb 97	9	58	yes	Sacrifice 2
8	8	5 Feb 97	9	58	yes	Sacrifice 2
9	9	5 Feb 97	9	58	yes	Sacrifice 2
10	10	5 Feb 97	9	58	yes	Sacrifice 2

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

Animal number	cage	date of death	study week	study day	necropsy	type of death
11	11	8 Jan 97	5	30	yes	Sacrifice 1
12	12	8 Jan 97	5	30	yes	Sacrifice 1
13	13	8 Jan 97	5	30	yes	Sacrifice 1
14	14	8 Jan 97	5	30	yes	Sacrifice 1
15	15	8 Jan 97	5	30	yes	Sacrifice 1

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

299

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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

Animal number	cage	date of death	study week	study day	necropsy	type of death
16	16	8 Jan 97	5	30	yes	Sacrifice 1
17	17	8 Jan 97	5	30	yes	Sacrifice 1
18	18	8 Jan 97	5	30	yes	Sacrifice 1
19	19	8 Jan 97	5	30	yes	Sacrifice 1
20	20	8 Jan 97	5	30	yes	Sacrifice 1

Mortality (individuals) : males group 4 : 200 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
21	21	8 Jan 97	5	30	yes	Sacrifice 1
22	22	8 Jan 97	5	30	yes	Sacrifice 1
23	23	8 Jan 97	5	30	yes	Sacrifice 1
24	24	8 Jan 97	5	30	yes	Sacrifice 1
25	25	2 Jan 97	4	24	yes	Found dead
26	26	5 Feb 97	9	58	yes	Sacrifice 2
27	27	5 Feb 97	9	58	yes	Sacrifice 2
28	28	5 Feb 97	9	58	yes	Sacrifice 2
29	29	5 Feb 97	9	58	yes	Sacrifice 2
30	30	5 Feb 97	9	58	yes	Sacrifice 2

Mortality (individuals) : males group 5 : 1000 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
31	31	8 Jan 97	5	30	yes	Sacrifice 1
32	32	8 Jan 97	5	30	yes	Sacrifice 1
33	33	8 Jan 97	5	30	yes	Sacrifice 1
34	34	8 Jan 97	5	30	yes	Sacrifice 1
35	35	8 Jan 97	5	30	yes	Sacrifice 1
36	36	5 Feb 97	9	58	yes	Sacrifice 2
37	37	5 Feb 97	9	58	yes	Sacrifice 2
38	38	5 Feb 97	9	58	yes	Sacrifice 2
39	39	5 Feb 97	9	58	yes	Sacrifice 2
40	40	5 Feb 97	9	58	yes	Sacrifice 2

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

300

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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

Animal number	cage	date of death	study week	study day	necropsy	type of death
41	41	8 Jan 97	5	30	yes	Sacrifice 1
42	42	8 Jan 97	5	30	yes	Sacrifice 1
43	43	8 Jan 97	5	30	yes	Sacrifice 1
44	44	8 Jan 97	5	30	yes	Sacrifice 1
45	45	8 Jan 97	5	30	yes	Sacrifice 1
46	46	5 Feb 97	9	58	yes	Sacrifice 2
47	47	5 Feb 97	9	58	yes	Sacrifice 2
48	48	5 Feb 97	9	58	yes	Sacrifice 2
49	49	5 Feb 97	9	58	yes	Sacrifice 2
50	50	5 Feb 97	9	58	yes	Sacrifice 2

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

Animal number	cage	date of death	study week	study day	necropsy	type of death
51	51	8 Jan 97	5	30	yes	Sacrifice 1
52	52	8 Jan 97	5	30	yes	Sacrifice 1
53	53	8 Jan 97	5	30	yes	Sacrifice 1
54	54	8 Jan 97	5	30	yes	Sacrifice 1
55	55	8 Jan 97	5	30	yes	Sacrifice 1

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

Animal number	cage	date of death	study week	study day	necropsy	type of death
56	56	8 Jan 97	5	30	yes	Sacrifice 1
57	57	8 Jan 97	5	30	yes	Sacrifice 1
58	58	8 Jan 97	5	30	yes	Sacrifice 1
59	59	8 Jan 97	5	30	yes	Sacrifice 1
60	60	8 Jan 97	5	30	yes	Sacrifice 1

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Mortality (individuals) : females group 4 : 200 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
61	61	6 Jan 97	4	28	yes	Found dead
62	62	8 Jan 97	5	30	yes	Sacrifice 1
63	63	8 Jan 97	5	30	yes	Sacrifice 1
64	64	8 Jan 97	5	30	yes	Sacrifice 1
65	65	8 Jan 97	5	30	yes	Sacrifice 1
66	66	5 Feb 97	9	58	yes	Sacrifice 2
67	67	5 Feb 97	9	58	yes	Sacrifice 2
68	68	6 Jan 97	4	28	yes	Found dead
69	69	5 Feb 97	9	58	yes	Sacrifice 2
70	70	5 Feb 97	9	58	yes	Sacrifice 2

Mortality (individuals) : females group 5 : 1000 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
71	71	8 Jan 97	5	30	yes	Sacrifice 1
72	72	8 Jan 97	5	30	yes	Sacrifice 1
73	73	8 Jan 97	5	30	yes	Sacrifice 1
74	74	8 Jan 97	5	30	yes	Sacrifice 1
75	75	8 Jan 97	5	30	yes	Sacrifice 1
76	76	5 Feb 97	9	58	yes	Sacrifice 2
77	77	5 Feb 97	9	58	yes	Sacrifice 2
78	78	5 Feb 97	9	58	yes	Sacrifice 2
79	79	5 Feb 97	9	58	yes	Sacrifice 2
80	80	5 Feb 97	9	58	yes	Sacrifice 2

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.5. Body weight (individuals)Body weight (individuals) : males group 1 : 0 mg/kg
(g/animal)

	Animal no									
	1	2	3	4	5	6	7	8	9	10
week: -1	163.7	160.7	166.1	176.4	169.4	162.4	168.7	162.3	172.4	166.6
1	216.4	205.6	215.1	225.5	223.0	211.4	225.2	205.5	227.8	212.1
2	264.0	253.7	257.3	269.9	276.0	251.4	271.6	251.7	268.9	254.5
3	298.4	292.6	291.8	303.2	308.5	273.7	305.9	287.7	293.6	286.2
4	325.5	325.1	322.4	326.5	351.3	293.6	328.5	313.0	319.5	304.6
recovery										
week: 5					303.0	339.9	333.3	325.2	322.2	
6					324.1	356.7	364.0	347.9	331.5	
7					337.0	377.7	381.8	362.1	345.4	
8					349.9	392.2	391.1	370.8	348.0	

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

	Animal no				
	11	12	13	14	15
week: -1	168.6	169.3	170.3	170.4	159.7
1	219.6	224.8	212.6	220.8	197.3
2	264.6	277.4	255.0	258.5	248.1
3	298.6	317.5	286.4	287.6	283.8
4	322.9	345.8	321.0	304.5	308.2

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

303

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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

	Animal no				
	16	17	18	19	20
week: -1	153.3	175.8	163.1	158.1	178.5
1	204.2	225.8	213.2	205.8	237.3
2	251.6	278.2	256.1	250.3	290.8
3	295.3	317.1	286.5	286.4	338.9
4	333.1	357.5	308.8	310.9	372.5

Body weight (individuals) : males group 4 : 200 mg/kg
(g/animal)

	Animal no									
	21	22	23	24	25	26	27	28	29	30
week: -1	170.5	174.4	160.9	170.5	155.3	168.7	180.9	169.3	155.7	167.3
1	222.5	229.9	209.6	223.7	198.8	216.0	239.6	213.9	201.7	215.1
2	267.8	276.5	248.3	276.8	231.6	265.2	287.7	251.0	250.7	254.3
3	315.4	324.2	283.8	316.0	250.7	300.5	323.7	284.7	276.1	284.9
4	353.9	353.4	309.0	347.9	n.d.	328.6	349.1	312.9	303.3	311.3
recovery										
week: 5					347.2	363.1	323.6	312.6	322.0	
6					367.0	383.6	343.0	327.7	340.9	
7					387.1	412.0	363.3	341.6	360.5	
8					385.6	418.6	371.6	355.7	367.4	

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

304

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Body weight (individuals) : males group 5 : 1000 mg/kg
(g/animal)

	Animal no									
	31	32	33	34	35	36	37	38	39	40
week: -1	171.7	184.9	158.0	158.4	174.3	167.0	170.6	167.6	165.1	184.9
1	225.1	244.5	207.1	211.4	228.1	222.4	223.8	215.8	213.3	244.3
2	270.5	283.0	249.1	256.2	276.9	270.4	268.0	264.8	256.4	286.6
3	301.0	307.5	275.1	284.2	306.2	312.8	301.6	297.8	288.7	320.9
4	336.0	335.8	302.6	313.2	336.7	336.5	330.8	325.4	308.1	353.7
recovery										
week: 5					347.1	331.2	339.2	318.0	368.6	
6					354.7	348.2	357.5	343.2	395.6	
7					390.5	363.7	381.3	359.2	425.4	
8					390.2	377.0	389.4	374.7	439.0	

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

305

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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

	Animal no									
	41	42	43	44	45	46	47	48	49	50
week: -1	137.2	143.6	129.4	137.4	152.0	153.3	142.9	129.9	147.6	137.9
1	156.5	175.1	144.1	152.6	183.1	180.4	158.4	145.3	169.3	160.2
2	176.2	193.5	166.2	179.0	197.4	201.2	175.4	172.7	182.8	173.8
3	195.7	197.7	180.8	193.8	210.8	214.1	198.7	183.6	209.9	192.9
4	220.5	232.0	197.1	216.2	231.3	246.7	214.6	202.3	223.4	196.4
recovery										
week: 5					250.6	215.5	208.4	228.5	203.8	
6					258.1	221.1	214.1	237.3	215.0	
7					266.7	237.1	227.0	245.6	223.7	
8					278.7	250.6	231.5	263.5	226.4	

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

	Animal no				
	51	52	53	54	55
week: -1	148.6	138.2	142.5	144.7	129.8
1	167.3	160.8	153.6	167.3	163.7
2	184.2	189.9	163.6	183.0	182.9
3	192.4	203.4	195.0	192.1	196.8
4	213.8	228.9	202.8	212.6	222.5

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

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

	Animal no				
	56	57	58	59	60
week: -1	139.9	140.1	152.3	139.2	149.9
1	151.4	159.5	168.6	154.8	164.4
2	178.3	175.6	199.8	172.5	186.7
3	194.4	200.7	222.2	191.7	202.5
4	212.3	217.2	248.3	202.6	214.7

Body weight (individuals) : females group 4 : 200 mg/kg
(g/animal)

	Animal no									
	61	62	63	64	65	66	67	68	69	70
week: -1	130.0	141.9	148.0	142.3	136.6	143.7	156.0	138.2	150.0	144.2
1	148.3	158.9	162.8	169.0	158.0	172.0	183.8	160.1	168.6	164.5
2	167.7	179.0	180.0	191.2	171.1	190.3	203.1	183.4	181.9	181.3
3	181.8	202.3	198.3	207.3	195.5	206.0	206.7	194.4	201.4	194.6
4	202.0	212.9	212.6	246.4	215.1	238.9	238.1	218.0	216.1	208.2
recovery										
week: 5					253.3	258.5			221.2	207.0
6					254.6	268.2			233.2	213.0
7					278.9	272.7			235.9	227.6
8					283.2	270.7			243.9	230.1

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

307

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Body weight (individuals) : females group 5 : 1000 mg/kg
(g/animal)

	Animal no	71	72	73	74	75	76	77	78	79	80
week: -1		151.9	130.4	140.4	142.7	145.4	144.7	142.0	149.4	133.2	146.9
1		171.5	145.4	157.0	166.0	168.0	163.4	160.6	175.8	153.6	163.3
2		199.7	161.1	176.5	198.8	194.6	185.1	183.1	194.4	173.4	176.3
3		216.6	183.4	190.2	220.4	208.7	193.7	201.6	208.8	181.2	201.9
4		233.4	200.4	205.0	238.5	222.2	217.1	228.8	223.5	203.1	213.3
recovery											
week: 5						211.4	249.0	219.9	211.4	222.0	
6						220.8	252.3	230.4	221.7	231.1	
7						230.0	259.9	238.7	224.3	235.7	
8						239.4	273.5	245.1	241.7	247.1	

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.6. Food consumption (individuals)Food consumption (individuals) : males
(g/animal/week)

group 1 : 0 mg/kg

	Cage no									
	1	2	3	4	5	6	7	8	9	10
week: -1	174.8	163.7	176.8	186.1	187.3	192.3	198.9	168.3	191.8	174.7
1	193.8	184.6	191.7	178.2	203.5	212.7	207.2	186.2	212.6	180.9
2	208.1	197.6	216.7	179.8	210.2	204.9	220.4	198.7	210.1	187.7
3	207.5	194.4	209.0	191.0	211.6	182.0	206.0	206.6	197.3	185.1
4	199.6	182.5	209.1	185.5	201.1	179.7	195.2	183.1	194.1	172.4
recovery										
week: 5					185.5	180.4	186.6	168.5	164.5	
6					190.4	209.4	208.9	184.3	175.7	
7					172.9	183.6	184.5	170.0	167.6	
8					172.7	185.6	190.8	177.0	162.4	

Food consumption (individuals) : males
(g/animal/week)

group 2 : 10 mg/kg

	Cage no				
	11	12	13	14	15
week: -1	180.7	181.6	180.1	181.4	162.0
1	198.9	205.0	185.2	189.5	193.0
2	214.0	210.6	202.5	200.3	211.7
3	204.8	207.3	197.9	196.8	203.7
4	199.0	181.7	190.8	188.0	185.5

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

309

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (individuals) : males
(g/animal/week)

group 3 : 50 mg/kg

	16	17	18	19	Cage no 20
week: -1	174.0	192.8	174.7	164.4	207.2
1	195.3	211.6	199.1	170.2	226.1
2	218.7	235.3	202.3	195.1	235.8
3	233.8	230.8	198.8	201.1	246.5
4	219.3	230.2	189.5	193.6	235.6

Food consumption (individuals) : males
(g/animal/week)

group 4 : 200 mg/kg

	21	22	23	24	25	26	27	28	29	30
week: -1	175.6	192.1	172.3	180.7	156.8	187.1	202.1	171.5	161.4	159.2
1	200.5	211.4	179.4	199.9	175.7	197.0	218.6	171.7	177.7	173.6
2	214.0	231.9	189.0	219.3	171.5	209.8	217.1	186.0	195.4	186.3
3	213.8	218.3	191.5	212.6	170.2	220.3	214.7	180.4	186.6	183.1
4	220.2	210.0	175.7	212.6	1.400	207.3	213.9	178.9	170.0	170.6
recovery										
week: 5					190.1	191.0	169.1	158.9	165.0	
6					217.8	199.5	189.7	176.8	181.8	
7					186.6	196.7	173.8	167.9	165.6	
8					182.4	200.9	165.4	175.5	161.9	

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (individuals) : males
(g/animal/week)

group 5 : 1000 mg/kg

	Cage no									
	31	32	33	34	35	36	37	38	39	40
week: -1	200.0	205.5	167.7	171.7	192.7	193.2	178.0	178.8	175.4	205.9
1	217.6	213.6	182.5	193.1	205.6	211.1	200.6	196.3	186.1	212.3
2	221.9	215.6	197.1	201.6	209.8	234.4	213.7	199.2	211.6	219.8
3	221.2	216.5	189.4	193.2	195.6	229.1	208.6	207.7	202.2	215.5
4	207.0	216.2	186.1	196.6	194.7	209.4	199.7	205.6	182.8	203.9
recovery										
week: 5					195.1	174.8	180.4	161.8	204.5	
6					219.2	190.6	202.5	187.2	211.2	
7					198.3	182.0	186.9	198.5	211.1	
8					179.7	179.0	186.6	159.8	208.4	

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

311

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (individuals) : females
(g/animal/week)

group 1 : 0 mg/kg

	Cage no									
	41	42	43	44	45	46	47	48	49	50
week: -1	131.7	155.3	141.6	134.9	147.9	154.3	159.2	129.0	163.4	147.3
1	135.0	149.7	127.4	133.8	152.5	160.5	167.5	131.6	168.2	141.2
2	147.0	168.4	136.4	142.2	153.2	171.1	167.4	135.9	175.5	151.7
3	148.5	173.8	136.4	142.3	166.2	174.1	169.2	150.1	169.8	165.3
4	136.4	167.0	127.6	135.7	147.0	160.2	155.3	133.1	155.9	144.8
recovery										
week: 5					138.5	137.0	119.1	150.7	126.5	
6					166.8	157.7	133.7	165.5	149.9	
7					152.1	152.4	122.8	154.3	132.8	
8					140.7	140.2	125.8	155.5	126.4	

Food consumption (individuals) : females
(g/animal/week)

group 2 : 10 mg/kg

	Cage no				
	51	52	53	54	55
week: -1	135.6	137.2	138.4	129.6	140.8
1	147.1	143.5	154.0	138.5	149.0
2	140.8	198.8	132.7	119.4	148.2
3	136.0	152.0	166.8	151.1	160.7
4	134.4	147.1	173.3	143.0	149.9

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Food consumption (individuals) : females
(g/animal/week)

group 3 : 50 mg/kg

	56	57	58	59	Cage no 60
week: -1	137.8	134.6	159.0	131.5	140.6
1	150.1	149.1	171.3	137.0	137.6
2	144.0	124.5	174.3	143.0	148.6
3	152.7	157.6	171.3	146.5	151.5
4	141.2	157.7	171.4	137.9	143.0

Food consumption (individuals) : females
(g/animal/week)

group 4 : 200 mg/kg

	61	62	63	64	Cage no 65	66	67	68	69	70
week: -1	124.7	148.5	136.6	145.1	126.2	146.4	140.3	150.2	150.3	132.1
1	129.9	148.8	130.2	150.0	138.1	145.6	140.8	150.4	141.8	141.6
2	145.4	156.2	136.2	177.0	141.2	164.3	154.6	172.4	151.7	126.9
3	147.4	159.0	138.6	186.1	147.8	164.3	142.1	169.6	143.5	144.2
4	96.02	158.3	114.6	187.7	135.7	150.3	149.7	104.8	129.0	121.3
recovery										
week: 5					151.3	148.5			121.9	117.7
6					153.0	157.2			139.2	130.2
7					150.0	139.0			120.8	130.4
8					157.3	126.7			114.0	125.3

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.7. Water consumption (individuals)

Water consumption (individuals) : males
(g/animal/week)

group 1 : 0 mg/kg

	Cage no									
	1	2	3	4	5	6	7	8	9	10
week: -1	190.4	182.7	261.1	200.2	288.4	198.8	198.8	202.3	216.3	196.0
1	182.0	195.3	245.7	174.3	279.3	198.1	210.0	207.9	203.0	179.2
2	191.8	231.7	255.5	206.5	303.1	203.7	231.0	220.5	212.8	175.0
3	191.1	192.5	261.1	177.8	358.4	168.7	256.2	215.6	180.6	186.9
4	182.7	215.6	252.0	165.2	315.0	175.7	228.9	207.9	186.2	194.6
recovery										
week: 5					222.6	226.1	254.1	196.7	205.1	205.1
6					212.8	225.4	246.4	205.1	138.6	138.6
7					165.2	244.3	300.3	195.3	161.0	161.0
8					201.6	235.2	307.3	226.1	198.8	198.8

Water consumption (individuals) : males
(g/animal/week)

group 2 : 10 mg/kg

	Cage no				
	11	12	13	14	15
week: -1	201.6	195.3	197.4	198.1	218.4
1	203.7	217.0	269.5	214.9	207.9
2	206.5	210.0	247.1	235.2	253.4
3	184.8	201.6	241.5	249.9	234.5
4	153.3	197.4	266.0	253.4	185.5

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (individuals) : males
(g/animal/week)

group 3 : 50 mg/kg

	16	17	18	19	Cage no 20
week: -1	186.9	229.6	210.0	208.6	293.3
1	200.9	228.2	222.6	191.1	275.1
2	231.0	243.6	263.2	238.0	344.4
3	200.9	254.1	217.0	250.6	400.4
4	237.3	242.2	189.7	223.3	387.1

Water consumption (individuals) : males
(g/animal/week)

group 4 : 200 mg/kg

	21	22	23	24	Cage no 25	26	27	28	29	30
week: -1	208.6	213.5	184.8	191.8	201.6	214.9	207.9	186.2	194.6	194.6
1	220.5	216.3	187.6	200.2	189.7	230.3	219.1	159.6	205.8	181.3
2	220.5	239.4	224.0	221.9	205.1	252.7	224.7	191.8	213.5	214.9
3	212.1	245.7	175.7	176.4	196.0	224.7	237.3	169.4	166.6	223.3
4	204.4	220.5	175.7	194.6	94.50	194.6	206.5	154.7	194.6	185.5
recovery										
week: 5					229.6	254.1	213.5	219.1	186.2	
6					240.8	210.7	206.5	205.1	204.4	
7					245.7	228.2	189.7	192.5	176.4	
8					361.2	217.7	196.7	192.5	196.7	

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

316

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (individuals) : males
(g/animal/week)

group 5 : 1000 mg/kg

	Cage no									
	31	32	33	34	35	36	37	38	39	40
week: -1	220.5	241.5	219.1	209.3	200.9	201.6	231.7	206.5	191.1	216.3
1	235.9	245.7	200.9	230.3	235.2	227.5	247.8	231.7	191.8	245.7
2	237.3	268.1	232.4	290.5	242.9	257.6	265.3	320.6	266.0	256.2
3	225.4	274.4	193.2	249.9	218.4	221.9	251.3	276.5	238.7	214.2
4	245.0	252.7	186.2	287.7	195.3	219.8	237.3	258.3	218.4	198.1
recovery										
week: 5					245.7	233.8	265.3	232.4	254.1	
6					261.8	191.1	274.4	173.6	231.7	
7					241.5	202.3	331.1	234.5	330.4	
8					254.8	270.2	217.7	216.3	260.4	

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

317

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (individuals) : females
(g/animal/week)

group 1 : 0 mg/kg

	Cage no										
	41	42	43	44	45	46	47	48	49	50	
week: -1	182.7	195.3	164.5	180.6	159.6	166.6	154.7	168.7	232.4	189.7	
1	179.2	203.7	158.9	181.3	175.0	186.9	134.4	184.1	231.0	178.5	
2	205.1	169.4	165.9	139.3	203.0	127.4	155.4	196.0	226.8	193.2	
3	175.7	256.9	134.4	191.1	194.6	186.9	134.4	149.1	186.9	222.6	
4	137.2	215.6	106.4	179.9	113.4	167.3	117.6	211.4	184.1	180.6	
recovery											
week: 5					200.2	150.5	200.2	231.0	184.8		
6					227.5	165.9	189.0	200.9	209.3		
7					168.7	135.1	235.9	262.5	207.2		
8					135.8	148.4	224.0	228.9	249.9		

Water consumption (individuals) : females
(g/animal/week)

group 2 : 10 mg/kg

	Cage no					
	51	52	53	54	55	
week: -1	184.8	231.0	191.1	143.5	163.1	
1	231.7	140.7	147.0	140.7	184.8	
2	200.9	167.3	185.5	129.5	177.1	
3	172.2	140.7	204.4	153.3	197.4	
4	181.3	140.0	165.2	107.1	181.3	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (individuals) : females
(g/animal/week)

group 3 : 50 mg/kg

	56	57	58	59	Cage no 60
week: -1	184.1	180.6	196.7	167.3	207.9
1	175.7	147.0	163.1	154.7	178.5
2	173.6	263.2	200.9	179.2	203.7
3	129.5	253.4	130.2	170.1	147.0
4	164.5	256.2	215.6	156.8	172.2

Water consumption (individuals) : females
(g/animal/week)

group 4 : 200 mg/kg

	61	62	63	64	Cage no 65	66	67	68	69	70
week: -1	174.3	194.6	168.0	205.1	181.3	220.5	195.3	233.8	196.7	165.2
1	175.0	123.2	106.4	212.8	163.1	242.2	205.1	261.8	183.4	180.6
2	182.7	213.5	159.6	200.9	220.5	143.5	143.5	242.9	172.9	181.3
3	167.3	183.4	132.3	236.6	208.6	268.8	190.4	305.9	133.7	151.9
4	142.1	187.6	123.2	255.5	162.4	248.5	160.3	252.0	136.5	142.1
recovery										
week: 5					247.1	224.7			169.4	178.5
6					245.0	211.4			143.5	159.6
7					189.7	168.7			157.5	180.6
8					264.6	180.6			142.8	174.3

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

319

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Water consumption (individuals) : females
(g/animal/week)

group 5 : 1000 mg/kg

	Cage no									
	71	72	73	74	75	76	77	78	79	80
week: -1	189.0	126.0	193.2	182.0	161.0	186.2	200.9	172.2	184.1	177.1
1	188.3	123.2	185.5	182.0	174.3	182.0	238.7	202.3	198.1	181.3
2	239.4	181.3	165.2	205.1	215.6	224.7	194.6	203.0	156.1	170.8
3	170.1	173.6	165.9	145.6	191.8	214.2	233.8	203.7	177.1	200.2
4	161.7	145.6	149.1	172.9	135.1	226.1	249.2	168.0	174.3	188.3
recovery										
week: 5					203.7	260.4	200.2	182.7	198.8	
6					186.2	249.9	221.9	185.5	148.4	
7					198.1	226.8	178.5	205.1	144.2	
8					293.3	308.7	216.3	184.1	162.4	

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.8. Hematology (individuals)

Hematology (individuals): males

group 1
0 mg/kg

		Animal no									
		1	2	3	4	5	6	7	8	9	10
RBC (T/l)											
week:	5	8.250	7.590	8.130	8.250	7.710	8.360	8.250	8.000	8.620	8.350
	9						9.150	8.880	8.670	9.480	9.290
Hb (mmol/l)											
week:	5	9.900	9.200	10.20	9.500	9.200	9.500	9.500	9.300	10.10	9.800
	9						9.600	9.400	9.600	10.30	9.700
Hct (l)											
week:	5	0.481	0.446	0.495	0.460	0.451	0.473	0.463	0.463	0.492	0.474
	9						0.476	0.477	0.467	0.515	0.483
MCV (fl)											
week:	5	58.30	58.70	60.90	55.80	58.40	56.60	56.10	57.90	57.10	56.70
	9						52.00	53.70	53.90	54.30	52.00
RDW (l)											
week:	5	0.119	0.124	0.116	0.130	0.122	0.113	0.110	0.121	0.112	0.117
	9						0.155	0.121	0.128	0.148	0.149
MCH (fmol)											
week:	5	1.210	1.220	1.260	1.150	1.190	1.140	1.150	1.170	1.170	1.170
	9						1.050	1.060	1.100	1.080	1.040
MCHC (mmol/l)											
week:	5	20.68	20.71	20.61	20.63	20.31	20.17	20.53	20.16	20.55	20.59
	9						20.12	19.79	20.46	19.96	20.06

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

321

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 1
0 mg/kg

		Animal no									
		1	2	3	4	5	6	7	8	9	10
HDW	(mmol/l)										
week:	5	1.810	1.920	1.370	2.070	2.090	1.560	1.440	1.650	1.500	1.570
	9					1.590	1.430	1.590	1.440	1.510	
WBC	(G/l)										
week:	5	13.22	10.19	11.34	11.24	8.770	8.870	9.110	10.65	11.32	11.14
	9					8.640	8.130	11.94	9.910	7.990	
Neut	(1)										
week:	5	0.093	0.103	0.080	0.077	0.151	0.085	0.088	0.123	0.042	0.079
	9					0.101	0.106	0.138	0.056	0.083	
Eos	(1)										
week:	5	0.014	0.007	0.005	0.008	0.010	0.009	0.003	0.007	0.009	0.005
	9					0.013	0.006	0.009	0.025	0.006	
Baso	(1)										
week:	5	0.007	0.005	0.007	0.006	0.004	0.006	0.005	0.006	0.006	0.006
	9					0.005	0.005	0.008	0.006	0.003	
Lympho	(1)										
week:	5	0.818	0.837	0.870	0.861	0.787	0.842	0.852	0.820	0.887	0.871
	9					0.827	0.828	0.760	0.848	0.867	
Mono	(1)										
week:	5	0.037	0.032	0.026	0.033	0.028	0.039	0.030	0.029	0.027	0.020
	9					0.033	0.037	0.049	0.031	0.022	
Luc	(1)										
week:	5	0.030	0.016	0.012	0.016	0.020	0.019	0.021	0.016	0.028	0.019
	9					0.021	0.018	0.036	0.033	0.019	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 1
0 mg/kg

		Animal no										
		1	2	3	4	5	6	7	8	9	10	
Neut (G/l)	week:	5	1.240	1.050	0.910	0.860	1.320	0.750	0.800	1.310	0.480	0.880
		9					0.880	0.860	1.640	0.560	0.660	
Eos (G/l)	week:	5	0.190	0.070	0.050	0.090	0.090	0.080	0.030	0.070	0.110	0.060
		9					0.110	0.050	0.110	0.250	0.050	
Baso (G/l)	week:	5	0.100	0.050	0.080	0.070	0.030	0.060	0.050	0.060	0.060	0.060
		9					0.050	0.040	0.090	0.060	0.030	
Lympho (G/l)	week:	5	10.81	8.530	9.860	9.680	6.910	7.470	7.760	8.740	10.04	9.710
		9					7.140	6.730	9.080	8.400	6.930	
Mono (G/l)	week:	5	0.490	0.320	0.300	0.370	0.240	0.350	0.280	0.310	0.310	0.230
		9					0.280	0.300	0.580	0.310	0.180	
Luc (G/l)	week:	5	0.400	0.160	0.140	0.170	0.180	0.170	0.190	0.170	0.320	0.210
		9					0.180	0.150	0.430	0.330	0.150	
Plt (G/l)	week:	5	1078	1191	826.0	1174	1032	1136	1060	1139	1020	1154
		9					1092	963.0	1011	968.0	1039	
PT (rel. 1)	week:	5	0.754	0.764	0.772	0.704	0.767	0.679	0.692	0.730	0.770	0.670
		9					0.851	0.798	0.872	0.819	0.777	

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 2
10 mg/kg

		Animal no				
		11	12	13	14	15
RBC (T/l) week:	5	8.390	7.980	7.850	8.470	8.190
Hb (mmol/l) week:	5	9.800	9.500	9.500	9.800	9.900
Hct (l) week:	5	0.474	0.460	0.450	0.477	0.496
MCV (fl) week:	5	56.40	57.70	57.30	56.40	60.60
RDW (l) week:	5	0.112	0.128	0.125	0.115	0.107
MCH (fmol) week:	5	1.170	1.190	1.210	1.160	1.210
MCHC (mmol/l) week:	5	20.76	20.62	21.03	20.59	20.02
HDW (mmol/l) week:	5	1.470	2.130	2.150	1.470	1.330
WBC (G/l) week:	5	11.65	16.01	10.90	13.81	8.750
Neut (l) week:	5	0.060	0.070	0.149	0.105	0.090

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

325

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 2
10 mg/kg

		11	12	13	14	15
		Animal no				
Luc (G/l) week:	5	0.200	0.240	0.230	0.310	0.230
Plt (G/l) week:	5	1043	1180	1239	1053	1014
PT (rel. 1) week:	5	0.798	0.788	0.676	0.742	0.713

Hematology (individuals): males

group 3
50 mg/kg

		16	17	18	19	20
		Animal no				
RBC (T/l) week:	5	8.200	8.280	8.350	8.630	7.580
Hb (mmol/l) week:	5	9.700	9.700	9.700	10.10	9.700
Hct (1) week:	5	0.468	0.473	0.468	0.495	0.472
MCV (fl) week:	5	57.00	57.10	56.00	57.40	62.20
RDW (1) week:	5	0.117	0.110	0.119	0.110	0.113

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

326

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 3

50 mg/kg

		Animal no				
		16	17	18	19	20
MCH (fmol)						
week:	5	1.180	1.170	1.160	1.170	1.270
MCHC (mmol/l)						
week:	5	20.64	20.41	20.74	20.43	20.47
HDW (mmol/l)						
week:	5	1.530	1.560	1.820	1.410	1.460
WBC (G/l)						
week:	5	15.21	11.77	12.89	11.58	11.98
Neut (1)						
week:	5	0.071	0.071	0.079	0.101	0.073
Eos (1)						
week:	5	0.004	0.008	0.008	0.012	0.006
Baso (1)						
week:	5	0.007	0.006	0.007	0.007	0.005
Lympho (1)						
week:	5	0.854	0.865	0.819	0.818	0.872
Mono (1)						
week:	5	0.044	0.035	0.049	0.045	0.027
Luc (1)						
week:	5	0.020	0.015	0.038	0.018	0.017

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

327

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 3
50 mg/kg

		Animal no				
		16	17	18	19	20
Neut (G/l)						
week:	5	1.080	0.830	1.020	1.170	0.870
Eos (G/l)						
week:	5	0.060	0.090	0.110	0.140	0.070
Baso (G/l)						
week:	5	0.100	0.080	0.090	0.080	0.060
Lympho (G/l)						
week:	5	12.99	10.17	10.55	9.470	10.45
Mono (G/l)						
week:	5	0.660	0.410	0.630	0.520	0.320
Luc (G/l)						
week:	5	0.300	0.180	0.480	0.200	0.210
Plt (G/l)						
week:	5	1050	1058	1248	1151	1159
PT (rel. 1)						
week:	5	0.787	0.682	0.732	0.833	0.815

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

328

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 4
200 mg/kg

		Animal no									
		21	22	23	24	26	27	28	29	30	
RBC (T/l)											
week:	5	7.990	8.250	8.100	8.020	7.560	7.980	8.390	8.490	7.910	
	9					8.220	8.780	9.220	8.990	8.430	
Hb (mmol/l)											
week:	5	9.600	9.900	9.400	9.400	9.400	9.500	9.800	10.00	9.700	
	9					9.300	9.700	10.10	9.800	9.600	
Hct (l)											
week:	5	0.468	0.478	0.457	0.465	0.455	0.467	0.478	0.487	0.466	
	9					0.461	0.480	0.494	0.483	0.469	
MCV (fl)											
week:	5	58.60	58.00	56.40	57.90	60.10	58.50	57.00	57.40	58.90	
	9					56.10	54.70	53.50	53.70	55.60	
RDW (l)											
week:	5	0.110	0.113	0.113	0.115	0.129	0.117	0.109	0.114	0.115	
	9					0.135	0.128	0.145	0.128	0.128	
MCH (fmol)											
week:	5	1.200	1.210	1.160	1.170	1.240	1.190	1.170	1.180	1.220	
	9					1.130	1.100	1.100	1.100	1.140	
MCHC (mmol/l)											
week:	5	20.49	20.79	20.55	20.20	20.67	20.26	20.58	20.51	20.73	
	9					20.12	20.16	20.53	20.41	20.54	
HDW (mmol/l)											
week:	5	1.370	1.370	1.990	1.610	2.140	1.540	1.500	1.480	1.860	
	9					1.990	1.520	1.470	1.580	1.810	

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

329

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 4
200 mg/kg

		Animal no									
		21	22	23	24	26	27	28	29	30	
WBC											
(G/l)											
week:	5	11.10	12.97	13.91	13.40	11.32	7.880	12.17	10.93	10.31	
	9					11.86	8.770	9.200	13.84	12.03	
Neut											
(1)											
week:	5	0.065	0.084	0.081	0.076	0.085	0.084	0.088	0.086	0.118	
	9					0.087	0.142	0.128	0.201	0.114	
Eos											
(1)											
week:	5	0.007	0.007	0.006	0.011	0.008	0.004	0.011	0.006	0.009	
	9					0.009	0.008	0.015	0.011	0.013	
Baso											
(1)											
week:	5	0.005	0.005	0.005	0.007	0.005	0.005	0.007	0.006	0.004	
	9					0.005	0.005	0.007	0.006	0.006	
Lympho											
(1)											
week:	5	0.881	0.848	0.853	0.844	0.853	0.856	0.854	0.847	0.802	
	9					0.841	0.759	0.805	0.708	0.811	
Mono											
(1)											
week:	5	0.021	0.035	0.040	0.047	0.028	0.032	0.027	0.037	0.042	
	9					0.032	0.062	0.032	0.048	0.034	
Luc											
(1)											
week:	5	0.021	0.021	0.015	0.016	0.020	0.019	0.014	0.020	0.026	
	9					0.026	0.023	0.014	0.026	0.021	
Neut											
(G/l)											
week:	5	0.720	1.080	1.130	1.020	0.970	0.660	1.070	0.940	1.210	
	9					1.030	1.240	1.180	2.780	1.370	

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

330

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 4
200 mg/kg

		Animal no									
		21	22	23	24	26	27	28	29	30	
Eos (G/l)	week:	5	0.080	0.090	0.080	0.140	0.100	0.030	0.130	0.070	0.090
		9					0.110	0.070	0.130	0.150	0.160
Baso (G/l)	week:	5	0.050	0.070	0.070	0.090	0.050	0.040	0.090	0.060	0.040
		9					0.060	0.040	0.060	0.090	0.070
Lympho (G/l)	week:	5	9.780	11.00	11.87	11.31	9.660	6.750	10.39	9.250	8.260
		9					9.980	6.660	7.400	9.790	9.750
Mono (G/l)	week:	5	0.230	0.460	0.550	0.620	0.320	0.260	0.330	0.400	0.430
		9					0.380	0.550	0.290	0.660	0.410
Luc (G/l)	week:	5	0.230	0.280	0.210	0.210	0.230	0.150	0.170	0.210	0.270
		9					0.310	0.210	0.130	0.360	0.260
Plt (G/l)	week:	5	1066	1020	1170	1276	1208	973.0	1120	1026	1113
		9					1122	964.0	1064	1072	1124
PT (rel. 1)	week:	5	0.809	0.673	0.764	0.630	0.864	0.718	0.722	0.715	0.807
		9					0.964	0.922	0.839	0.839	0.839

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

331

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 5
1000 mg/kg

		Animal no									
		31	32	33	34	35	36	37	38	39	40
RBC (T/l)											
week:	5	8.580	8.150	8.230	8.020	8.450	8.080	7.750	7.940	7.730	7.780
	9					8.950	8.680	8.860	8.430	8.700	
Hb (mmol/l)											
week:	5	10.00	9.600	10.00	9.600	10.00	9.900	9.400	9.700	9.200	9.300
	9					9.900	9.700	9.900	9.400	9.900	
Hct (l)											
week:	5	0.478	0.472	0.511	0.482	0.491	0.480	0.455	0.468	0.452	0.456
	9					0.483	0.475	0.494	0.467	0.500	
MCV (fl)											
week:	5	55.70	57.90	62.10	60.10	58.10	59.40	58.70	59.00	58.50	58.60
	9					53.90	54.70	55.70	55.40	57.50	
RDW (l)											
week:	5	0.164	0.110	0.106	0.110	0.116	0.113	0.125	0.116	0.118	0.126
	9					0.121	0.137	0.123	0.124	0.136	
MCH (fmol)											
week:	5	1.160	1.180	1.220	1.200	1.180	1.230	1.210	1.220	1.180	1.200
	9					1.100	1.120	1.120	1.110	1.140	
MCHC (mmol/l)											
week:	5	20.88	20.33	19.63	19.93	20.36	20.64	20.67	20.74	20.25	20.45
	9					20.48	20.47	20.15	20.05	19.85	
HDW (mmol/l)											
week:	5	1.410	1.410	1.400	1.470	1.430	1.370	1.950	1.430	1.940	2.210
	9					1.520	1.810	1.450	1.730	1.910	

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

332

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 5
1000 mg/kg

		Animal no											
		31	32	33	34	35	36	37	38	39	40		
WBC (G/l)													
week:	5	7.660	13.00	16.69	9.910	12.62	9.870	12.08	12.41	11.30	13.66		
	9						8.930	11.85	9.660	8.990	13.32		
Neut (1)													
week:	5	0.073	0.058	0.066	0.187	0.096	0.111	0.096	0.069	0.112	0.094		
	9						0.130	0.085	0.085	0.118	0.089		
Eos (1)													
week:	5	0.008	0.007	0.005	0.006	0.010	0.009	0.007	0.015	0.007	0.012		
	9						0.009	0.009	0.010	0.007	0.012		
Baso (1)													
week:	5	0.004	0.006	0.008	0.006	0.006	0.004	0.005	0.007	0.006	0.006		
	9						0.005	0.005	0.004	0.004	0.008		
Lympho (1)													
week:	5	0.831	0.871	0.865	0.728	0.825	0.830	0.834	0.848	0.820	0.841		
	9						0.789	0.832	0.847	0.814	0.835		
Mono (1)													
week:	5	0.054	0.038	0.034	0.040	0.048	0.030	0.042	0.043	0.035	0.032		
	9						0.036	0.050	0.038	0.034	0.039		
Luc (1)													
week:	5	0.030	0.021	0.023	0.033	0.015	0.017	0.016	0.019	0.020	0.015		
	9						0.032	0.020	0.016	0.022	0.017		
Neut (G/l)													
week:	5	0.560	0.750	1.100	1.850	1.220	1.100	1.160	0.860	1.270	1.280		
	9						1.160	1.010	0.820	1.060	1.190		

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): males

group 5
1000 mg/kg

		Animal no										
		31	32	33	34	35	36	37	38	39	40	
Eos (G/l)	week:	5	0.060	0.090	0.080	0.060	0.120	0.090	0.080	0.180	0.070	0.170
		9					0.080	0.100	0.100	0.070	0.160	
Baso (G/l)	week:	5	0.030	0.070	0.130	0.060	0.070	0.040	0.060	0.080	0.070	0.080
		9					0.040	0.050	0.040	0.040	0.100	
Lympho (G/l)	week:	5	6.360	11.32	14.43	7.220	10.41	8.190	10.08	10.52	9.270	11.48
		9					7.050	9.860	8.180	7.320	11.12	
Mono (G/l)	week:	5	0.410	0.500	0.570	0.400	0.610	0.300	0.500	0.530	0.390	0.440
		9					0.320	0.600	0.370	0.310	0.520	
Luc (G/l)	week:	5	0.230	0.280	0.380	0.330	0.190	0.160	0.190	0.230	0.220	0.210
		9					0.290	0.230	0.150	0.200	0.230	
Plt (G/l)	week:	5	984.0	1094	965.0	938.0	1049	1050	1158	1082	1104	1133
		9					1007	1031	962.0	1109	1058	
PT (rel. 1)	week:	5	0.676	0.829	0.689	0.702	0.753	0.754	0.718	0.843	0.702	0.873
		9					0.837	0.799	0.853	0.850	0.913	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 1
0 mg/kg

		Animal no									
		41	42	43	44	45	46	47	48	49	50
RBC											
(T/l)											
week:	5	7.800	8.270	8.230	8.250	8.520	7.830	8.050	8.000	7.860	7.520
	9						8.540	8.500	8.470	8.490	7.940
Hb											
(mmol/l)											
week:	5	9.500	9.600	9.400	9.500	10.20	9.500	9.000	9.400	9.000	9.100
	9						10.00	9.200	9.600	9.400	9.400
Hct											
(l)											
week:	5	0.449	0.455	0.449	0.461	0.486	0.458	0.455	0.450	0.431	0.426
	9						0.501	0.451	0.475	0.464	0.450
MCV											
(fl)											
week:	5	57.60	55.00	54.50	56.00	57.10	58.40	56.50	56.20	54.80	56.70
	9						58.70	53.00	56.10	54.60	56.70
RDW											
(l)											
week:	5	0.119	0.107	0.111	0.165	0.134	0.115	0.108	0.119	0.120	0.127
	9						0.113	0.142	0.123	0.124	0.129
MCH											
(fmol)											
week:	5	1.210	1.160	1.140	1.160	1.200	1.210	1.120	1.180	1.140	1.210
	9						1.170	1.080	1.130	1.110	1.190
MCHC											
(mmol/l)											
week:	5	21.07	21.05	20.85	20.64	20.93	20.76	19.90	20.94	20.80	21.28
	9						20.00	20.43	20.09	20.24	20.93
HDW											
(mmol/l)											
week:	5	1.990	1.290	1.260	1.180	1.340	1.670	1.440	1.410	1.450	1.960
	9						1.480	1.240	1.220	1.250	1.560

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

335

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 1
0 mg/kg

		Animal no									
		41	42	43	44	45	46	47	48	49	50
WBC (G/l) week:	5	10.37	5.780	9.770	4.870	8.750	13.14	6.920	7.980	5.900	6.230
	9						7.340	4.720	5.990	5.880	5.500
Neut (1) week:	5	0.068	0.213	0.054	0.059	0.041	0.042	0.154	0.079	0.169	0.103
	9						0.098	0.177	0.095	0.144	0.087
Eos (1) week:	5	0.008	0.010	0.008	0.008	0.009	0.008	0.004	0.009	0.011	0.007
	9						0.014	0.011	0.013	0.022	0.019
Baso (1) week:	5	0.006	0.004	0.005	0.003	0.006	0.005	0.004	0.005	0.003	0.002
	9						0.006	0.003	0.005	0.004	0.003
Lympho (1) week:	5	0.875	0.733	0.883	0.892	0.888	0.901	0.796	0.868	0.770	0.843
	9						0.836	0.746	0.834	0.759	0.820
Mono (1) week:	5	0.028	0.029	0.029	0.022	0.035	0.029	0.027	0.025	0.034	0.031
	9						0.032	0.045	0.033	0.051	0.050
Luc (1) week:	5	0.015	0.012	0.020	0.017	0.021	0.015	0.014	0.015	0.013	0.013
	9						0.015	0.019	0.019	0.020	0.021
Neut (G/l) week:	5	0.710	1.230	0.530	0.280	0.360	0.550	1.070	0.630	1.000	0.640
	9						0.720	0.830	0.570	0.850	0.480

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 1
0 mg/kg

		Animal no									
		41	42	43	44	45	46	47	48	49	50
Eos (G/l) week:	5	0.080	0.060	0.080	0.040	0.080	0.100	0.030	0.070	0.060	0.050
	9						0.100	0.050	0.080	0.130	0.100
Baso (G/l) week:	5	0.060	0.020	0.050	0.010	0.050	0.060	0.030	0.040	0.020	0.010
	9						0.040	0.010	0.030	0.020	0.020
Lympho (G/l) week:	5	9.080	4.240	8.620	4.340	7.770	11.83	5.510	6.920	4.540	5.250
	9						6.140	3.520	5.000	4.470	4.510
Mono (G/l) week:	5	0.290	0.170	0.290	0.110	0.300	0.390	0.180	0.200	0.200	0.190
	9						0.230	0.210	0.200	0.300	0.270
Luc (G/l) week:	5	0.150	0.070	0.200	0.080	0.180	0.200	0.100	0.120	0.080	0.080
	9						0.110	0.090	0.120	0.110	0.110
Plt (G/l) week:	5	1122	1165	1121	1047	1147	1070	1065	1032	1181	1035
	9						999.0	1032	986.0	1144	1030
PT (rel. 1) week:	5	0.984	1.015	0.925	0.950	0.974	1.032	1.095	0.944	0.989	0.974
	9						1.031	1.093	0.974	0.995	0.974

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

337

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 2
10 mg/kg

		51	52	53	54	55
		Animal no				
RBC (T/l)						
week:	5	8.150	7.410	8.290	8.080	7.420
Hb (mmol/l)						
week:	5	9.100	9.200	9.300	9.500	9.400
Hct (l)						
week:	5	0.461	0.451	0.449	0.452	0.443
MCV (fl)						
week:	5	56.60	60.80	54.10	56.00	59.80
RDW (l)						
week:	5	0.119	0.122	0.114	0.115	0.106
MCH (fmol)						
week:	5	1.120	1.240	1.120	1.170	1.260
MCHC (mmol/l)						
week:	5	19.83	20.44	20.77	20.95	21.12
HDW (mmol/l)						
week:	5	1.390	1.720	1.430	1.340	1.260
WBC (G/l)						
week:	5	8.430	11.28	7.170	10.76	9.890
Neut (l)						
week:	5	0.081	0.085	0.160	0.116	0.083

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

338

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 2
10 mg/kg

		Animal no				
		51	52	53	54	55
Eos (1) week:	5	0.009	0.008	0.008	0.014	0.006
Baso (1) week:	5	0.004	0.004	0.004	0.004	0.003
Lympho (1) week:	5	0.864	0.863	0.756	0.818	0.873
Mono (1) week:	5	0.024	0.027	0.052	0.034	0.024
Luc (1) week:	5	0.018	0.013	0.019	0.015	0.012
Neut (G/l) week:	5	0.680	0.960	1.150	1.250	0.820
Eos (G/l) week:	5	0.080	0.090	0.060	0.150	0.050
Baso (G/l) week:	5	0.030	0.050	0.030	0.040	0.030
Lympho (G/l) week:	5	7.280	9.730	5.420	8.800	8.630
Mono (G/l) week:	5	0.200	0.300	0.370	0.370	0.240

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

339

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 2
10 mg/kg

		51	52	53	54	55	Animal no
Luc (G/l) week:	5	0.150	0.150	0.140	0.160	0.120	
Plt (G/l) week:	5	1074	1071	1001	1075	1169	
PT (rel. 1) week:	5	0.955	1.014	1.000	0.947	0.953	

Hematology (individuals): females

group 3
50 mg/kg

		56	57	58	59	60	Animal no
RBC (T/l) week:	5	8.140	7.840	8.040	7.870	8.640	
Hb (mmol/l) week:	5	9.400	9.300	9.500	9.400	10.00	
Hct (l) week:	5	0.452	0.450	0.457	0.453	0.477	
MCV (fl) week:	5	55.60	57.40	56.80	57.50	55.20	
RDW (l) week:	5	0.130	0.129	0.130	0.138	0.117	

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

340

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 3
50 mg/kg

		56	57	58	59	Animal no 60
MCH (fmol)						
week:	5	1.160	1.180	1.180	1.190	1.160
MCHC (mmol/l)						
week:	5	20.83	20.55	20.79	20.71	21.05
HDW (mmol/l)						
week:	5	1.260	1.230	1.270	1.320	1.530
WBC (G/l)						
week:	5	11.08	8.210	7.290	7.440	9.870
Neut (1)						
week:	5	0.060	0.095	0.106	0.050	0.058
Eos (1)						
week:	5	0.022	0.004	0.011	0.007	0.010
Baso (1)						
week:	5	0.005	0.004	0.005	0.004	0.006
Lympho (1)						
week:	5	0.860	0.855	0.822	0.892	0.887
Mono (1)						
week:	5	0.027	0.026	0.042	0.035	0.026
Luc (1)						
week:	5	0.026	0.016	0.015	0.012	0.015

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

341

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 3
50 mg/kg

		56	57	58	59	60
		Animal no				
		56	57	58	59	60
Neut (G/l)						
week:	5	0.670	0.780	0.770	0.370	0.570
Eos (G/l)						
week:	5	0.240	0.030	0.080	0.050	0.090
Baso (G/l)						
week:	5	0.060	0.040	0.040	0.030	0.060
Lympho (G/l)						
week:	5	9.530	7.010	5.990	6.640	8.750
Mono (G/l)						
week:	5	0.300	0.220	0.300	0.260	0.250
Luc (G/l)						
week:	5	0.280	0.130	0.110	0.090	0.140
Plt (G/l)						
week:	5	1227	1071	982.0	1067	1050
PT (rel. 1)						
week:	5	0.967	0.954	1.046	0.928	0.925

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

342

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
RBC (T/l)									
week:	5	8.010	8.340	7.860	7.730	7.380	7.900	8.010	7.970
	9					7.850	8.310	8.150	8.320
Hb (mmol/l)									
week:	5	9.100	10.00	9.500	9.600	9.200	9.600	9.100	9.300
	9					9.300	9.700	9.200	9.800
Hct (l)									
week:	5	0.444	0.482	0.462	0.463	0.437	0.460	0.434	0.444
	9					0.458	0.471	0.433	0.473
MCV (fl)									
week:	5	55.50	57.80	58.80	59.90	59.10	58.20	54.20	55.70
	9					58.30	56.60	53.20	56.90
RDW (l)									
week:	5	0.168	0.130	0.112	0.108	0.125	0.133	0.125	0.137
	9					0.125	0.116	0.176	0.138
MCH (fmol)									
week:	5	1.130	1.200	1.210	1.240	1.240	1.220	1.140	1.170
	9					1.190	1.170	1.130	1.170
MCHC (mmol/l)									
week:	5	20.44	20.77	20.61	20.64	20.98	20.99	21.00	20.99
	9					20.38	20.63	21.30	20.63
HDW (mmol/l)									
week:	5	1.320	1.430	1.230	1.270	1.830	1.330	1.210	1.760
	9					1.690	1.200	1.130	1.410

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
WBC (G/l)									
week:	5	4.850	11.02	10.04	11.24	7.530	7.890	11.84	10.43
	9					4.950	6.470	6.580	7.780
Neut (1)									
week:	5	0.129	0.026	0.050	0.060	0.054	0.188	0.061	0.059
	9					0.061	0.078	0.060	0.090
Eos (1)									
week:	5	0.007	0.005	0.010	0.008	0.012	0.018	0.004	0.008
	9					0.029	0.022	0.008	0.010
Baso (1)									
week:	5	0.003	0.007	0.007	0.006	0.006	0.005	0.005	0.005
	9					0.004	0.003	0.004	0.004
Lympho (1)									
week:	5	0.813	0.898	0.893	0.877	0.888	0.750	0.880	0.877
	9					0.864	0.851	0.874	0.826
Mono (1)									
week:	5	0.031	0.046	0.024	0.031	0.025	0.024	0.030	0.037
	9					0.025	0.029	0.032	0.051
Luc (1)									
week:	5	0.016	0.018	0.016	0.018	0.016	0.015	0.021	0.014
	9					0.019	0.017	0.023	0.020
Neut (G/l)									
week:	5	0.630	0.280	0.500	0.680	0.410	1.490	0.720	0.610
	9					0.300	0.500	0.400	0.700

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

344

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
Eos (G/l)									
week:	5	0.040	0.060	0.100	0.090	0.090	0.140	0.050	0.090
	9					0.140	0.140	0.050	0.080
Baso (G/l)									
week:	5	0.020	0.080	0.070	0.070	0.040	0.040	0.060	0.050
	9					0.020	0.020	0.020	0.030
Lympho (G/l)									
week:	5	3.940	9.890	8.960	9.860	6.690	5.920	10.42	9.150
	9					4.280	5.510	5.750	6.420
Mono (G/l)									
week:	5	0.150	0.510	0.250	0.350	0.190	0.190	0.350	0.380
	9					0.120	0.190	0.210	0.390
Luc (G/l)									
week:	5	0.080	0.200	0.160	0.200	0.120	0.110	0.250	0.140
	9					0.090	0.110	0.150	0.150
Plt (G/l)									
week:	5	1003	1191	998.0	1127	1203	568.0	988.0	1106
	9					1113	1212	1006	988.0
PT (rel. 1)									
week:	5	0.888	0.896	0.950	0.938	1.032	0.860	0.880	0.918
	9					1.072	0.853	0.906	0.937

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

345

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 5
1000 mg/kg

		Animal no									
		71	72	73	74	75	76	77	78	79	80
RBC	(T/l)										
week:	5	8.560	7.730	7.670	7.930	8.210	7.950	7.760	8.160	8.140	8.060
	9					8.450	8.200		8.360	8.690	8.400
Hb	(mmol/l)										
week:	5	10.00	9.300	9.200	9.600	9.600	9.200	9.600	9.600	9.300	9.200
	9					9.700	10.00	9.700	9.900	9.500	
Hct	(l)										
week:	5	0.476	0.439	0.437	0.463	0.453	0.445	0.472	0.458	0.445	0.451
	9					0.478	0.478	0.464	0.474	0.465	
MCV	(fl)										
week:	5	55.60	56.70	57.00	58.40	55.20	56.00	60.80	56.00	54.70	56.00
	9					56.50	58.30	55.50	54.50	55.30	
RDW	(l)										
week:	5	0.131	0.110	0.130	0.133	0.129	0.115	0.119	0.131	0.107	0.134
	9					0.150	0.117	0.115	0.133	0.123	
MCH	(fmol)										
week:	5	1.170	1.200	1.200	1.220	1.170	1.150	1.230	1.170	1.140	1.140
	9					1.150	1.220	1.160	1.130	1.140	
MCHC	(mmol/l)										
week:	5	21.02	21.16	20.96	20.79	21.17	20.60	20.30	20.96	20.87	20.29
	9					20.35	20.91	20.85	20.80	20.52	
HDW	(mmol/l)										
week:	5	1.370	1.380	1.430	1.340	1.350	1.640	1.650	1.230	1.170	1.260
	9					1.420	1.450	1.170	1.090	1.170	

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

346

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females group 5
1000 mg/kg

		Animal no									
		71	72	73	74	75	76	77	78	79	80
WBC (G/l)	week: 5	11.63	9.120	6.600	10.23	8.350	8.930	7.180	9.570	6.180	9.520
	9					6.010	5.950	6.470	3.900	5.250	
Neut (1)	week: 5	0.036	0.126	0.083	0.077	0.059	0.067	0.141	0.044	0.061	0.085
	9					0.082	0.137	0.070	0.079	0.122	
Eos (1)	week: 5	0.009	0.007	0.016	0.022	0.012	0.010	0.007	0.015	0.010	0.006
	9					0.017	0.010	0.023	0.014	0.009	
Baso (1)	week: 5	0.007	0.005	0.005	0.006	0.006	0.004	0.008	0.006	0.007	0.005
	9					0.002	0.004	0.005	0.003	0.003	
Lympho (1)	week: 5	0.900	0.819	0.853	0.842	0.871	0.883	0.776	0.884	0.875	0.811
	9					0.852	0.773	0.842	0.848	0.801	
Mono (1)	week: 5	0.032	0.028	0.031	0.035	0.035	0.021	0.044	0.035	0.034	0.050
	9					0.029	0.047	0.045	0.036	0.048	
Luc (1)	week: 5	0.017	0.015	0.013	0.018	0.017	0.016	0.023	0.017	0.014	0.042
	9					0.018	0.028	0.015	0.020	0.017	
Neut (G/l)	week: 5	0.420	1.150	0.540	0.790	0.490	0.590	1.010	0.420	0.380	0.810
	9					0.490	0.820	0.450	0.310	0.640	

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

347

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Hematology (individuals): females

group 5
1000 mg/kg

		Animal no										
		71	72	73	74	75	76	77	78	79	80	
Eos (G/l)	week:	5	0.100	0.060	0.100	0.220	0.100	0.090	0.050	0.150	0.060	0.060
		9					0.100	0.060	0.150	0.050	0.050	
Baso (G/l)	week:	5	0.080	0.050	0.030	0.060	0.050	0.030	0.060	0.060	0.040	0.040
		9					0.010	0.030	0.030	0.010	0.020	
Lympho (G/l)	week:	5	10.47	7.470	5.630	8.610	7.270	7.880	5.570	8.460	5.410	7.720
		9					5.110	4.600	5.450	3.310	4.210	
Mono (G/l)	week:	5	0.370	0.250	0.200	0.360	0.290	0.180	0.320	0.330	0.210	0.480
		9					0.180	0.280	0.290	0.140	0.250	
Luc (G/l)	week:	5	0.200	0.140	0.090	0.180	0.140	0.140	0.170	0.160	0.080	0.400
		9					0.110	0.170	0.100	0.080	0.090	
Plt (G/l)	week:	5	1071	1127	1100	1285	1137	1197	1089	956.0	1009	1073
		9					1082	1012	951.0	993.0	990.0	
PT (rel. 1)	week:	5	0.958	0.978	0.954	0.997	0.887	0.746	0.951	0.931	0.915	0.832
		9					0.982	0.910	0.851	0.957	0.898	

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.9. Blood chemistry (individuals)Blood chemistry (individuals): males group 1
0 mg/kg

	Animal no									
	1	2	3	4	5	6	7	8	9	10
Gluc (mmol/l)										
week: 5	7.510	7.290	8.840	6.900	10.07	7.560	8.580	7.490	7.510	7.330
9						7.730	7.480	7.970	6.790	7.460
Urea (mmol/l)										
week: 5	4.870	4.670	5.990	6.690	4.200	6.350	4.690	5.330	6.500	7.330
9						6.380	4.410	6.550	7.600	7.140
Creat (umol/l)										
week: 5	17.70	17.80	18.90	18.80	19.90	17.00	13.30	19.20	16.60	17.40
9						18.20	14.20	20.30	20.60	16.30
Bili-tot (umol/l)										
week: 5	1.310	1.200	1.880	1.710	1.320	1.030	1.080	1.260	2.080	1.010
9						1.195	1.430	1.640	2.080	1.480
Prot (g/l)										
week: 5	71.50	65.04	65.59	66.56	66.81	63.73	69.39	66.43	65.83	67.10
9						66.81	66.98	68.26	66.67	68.16
Alb (g/l)										
week: 5	35.00	33.63	33.23	34.85	35.41	33.53	36.15	34.95	34.37	34.57
9						34.49	35.39	34.34	34.14	34.95
Glob (g/l)										
week: 5	36.50	31.41	32.36	31.71	31.40	30.20	33.24	31.48	31.46	32.53
9						32.32	31.59	33.92	32.53	33.21

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

349

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 1
0 mg/kg

		Animal no									
		1	2	3	4	5	6	7	8	9	10
A/G	(1)										
week:	5	0.960	1.070	1.030	1.100	1.130	1.110	1.090	1.110	1.090	1.060
	9					1.070	1.120	1.010	1.050	1.050	
Chol	(mmol/l)										
week:	5	1.770	1.650	1.790	1.400	2.190	1.550	1.780	1.720	1.680	1.700
	9					1.640	1.470	1.670	1.780	1.720	
Na+	(mmol/l)										
week:	5	145.2	142.9	143.4	147.3	146.1	142.5	142.3	147.3	143.3	142.3
	9					144.1	143.4	144.6	145.1	143.0	
K+	(mmol/l)										
week:	5	3.270	3.340	3.270	3.390	3.370	3.510	3.930	3.350	3.710	3.780
	9					3.590	3.300	3.150	3.590	3.630	
Ca++	(mmol/l)										
week:	5	2.720	2.590	2.530	2.670	2.590	2.540	2.670	2.690	2.680	2.660
	9					2.570	2.620	2.630	2.610	2.620	
Cl-	(mmol/l)										
week:	5	95.60	98.90	99.70	98.70	99.50	98.20	100.4	96.50	100.8	101.0
	9					102.8	101.0	103.6	100.2	101.7	
PO4-in	(mmol/l)										
week:	5	2.510	2.080	2.220	2.470	1.950	2.220	1.750	2.660	2.270	1.950
	9					1.740	1.570	1.670	2.000	1.540	
ASAT (GOT)	(U/l)										
week:	5	62.80	53.20	73.20	73.30	73.40	76.30	58.30	72.10	81.20	56.90
	9					81.40	70.90	81.70	91.90	54.80	

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

350

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 1

0 mg/kg

		Animal no									
		1	2	3	4	5	6	7	8	9	10
ALAT (GPT)											
(U/l)											
week:	5	36.30	26.30	32.80	29.60	37.30	33.90	30.60	38.90	39.70	25.40
	9					45.40	36.90	47.50	44.10	24.30	
ALP											
(U/l)											
week:	5	142.6	130.8	173.4	142.9	205.1	148.5	199.7	160.8	207.0	135.1
	9					123.3	136.8	126.2	148.6	96.50	

Blood chemistry (individuals): males

group 2

10 mg/kg

		Animal no				
		11	12	13	14	15
Gluc						
(mmol/l)						
week:	5	8.200	7.810	7.700	7.740	8.600
Urea						
(mmol/l)						
week:	5	7.750	7.040	5.840	7.850	5.360
Creat						
(umol/l)						
week:	5	16.30	21.90	18.60	18.60	18.30
Bili-tot						
(umol/l)						
week:	5	1.050	0.950	0.950	0.970	1.290
Prot						
(g/l)						
week:	5	66.95	68.31	69.24	64.01	65.82

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

351

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 2
10 mg/kg

		11	12	13	14	15
		Animal no				
Alb (g/l)						
week:	5	34.85	34.10	35.53	33.93	34.31
Glob. (g/l)						
week:	5	32.10	34.21	33.71	30.08	31.51
A/G (1)						
week:	5	1.090	1.000	1.050	1.130	1.090
Chol (mmol/l)						
week:	5	1.900	1.990	2.370	1.290	1.870
Na+ (mmol/l)						
week:	5	144.9	141.9	142.7	143.0	143.0
K+ (mmol/l)						
week:	5	3.810	3.990	3.830	3.320	3.630
Ca++ (mmol/l)						
week:	5	2.710	2.730	2.650	2.600	2.680
Cl- (mmol/l)						
week:	5	100.0	95.60	100.2	99.00	100.0
PO4-in (mmol/l)						
week:	5	2.120	2.200	2.000	2.140	1.870
ASAT (GOT) (U/l)						
week:	5	74.60	64.00	57.40	72.00	66.70

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

352

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 2
10 mg/kg

		11	12	13	14	15
		Animal no				
ALAT (GPT) (U/l)						
week:	5	31.20	22.70	29.50	30.60	31.40
ALP (U/l)						
week:	5	218.3	175.7	105.7	140.7	158.2

Blood chemistry (individuals): males

group 3
50 mg/kg

		16	17	18	19	20
		Animal no				
Gluc (mmol/l)						
week:	5	8.860	8.310	8.520	7.970	8.540
Urea (mmol/l)						
week:	5	4.300	6.840	4.780	7.340	5.120
Creat (umol/l)						
week:	5	15.90	19.90	17.00	19.50	20.00
Bili-tot (umol/l)						
week:	5	1.350	0.850	1.290	1.160	1.660
Prot (g/l)						
week:	5	66.65	67.53	68.62	69.69	67.72
Alb (g/l)						
week:	5	34.26	34.25	34.84	35.72	34.58

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

353

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 3
50 mg/kg

		16	17	18	19	20
		Animal no				
Glob (g/l)						
week:	5	32.39	33.28	33.78	33.97	33.14
A/G (l)						
week:	5	1.060	1.030	1.030	1.050	1.040
Chol (mmol/l)						
week:	5	2.150	1.900	1.630	1.980	1.880
Na+ (mmol/l)						
week:	5	143.8	143.0	143.6	145.1	143.1
K+ (mmol/l)						
week:	5	3.620	3.740	3.650	3.910	3.730
Ca++ (mmol/l)						
week:	5	2.760	2.690	2.620	2.750	2.710
Cl- (mmol/l)						
week:	5	99.90	101.0	101.8	98.50	98.80
PO4-in (mmol/l)						
week:	5	2.250	1.880	1.740	2.220	2.140
ASAT (GOT) (U/l)						
week:	5	67.40	61.50	68.00	70.40	59.00
ALAT (GPT) (U/l)						
week:	5	33.20	27.60	30.00	28.60	27.30

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

354

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 3
50 mg/kg

		16	17	18	19	20	Animal no				
ALP (U/l) week:	5	212.9	149.2	168.7	144.4	144.4					

Blood chemistry (individuals): males

group 4
200 mg/kg

		21	22	23	24	26	27	28	29	30	Animal no	
Gluc (mmol/l) week:	5	7.410	8.790	6.440	7.710	8.800	8.410	7.620	8.240	7.300		
	9					9.080	8.280	7.730	7.800	7.650		
Urea (mmol/l) week:	5	6.440	5.100	6.550	6.100	5.980	5.530	5.670	6.700	6.800		
	9					7.010	5.580	5.300	6.540	7.130		
Creat (umol/l) week:	5	18.90	17.80	19.10	16.30	16.40	22.20	19.70	19.10	22.70		
	9					20.40	21.10	19.30	18.30	20.70		
Bili-tot (umol/l) week:	5	1.050	1.330	1.510	1.630	2.110	1.060	1.320	1.400	1.420		
	9					2.450	1.860	1.325	1.830	1.550		
Prot (g/l) week:	5	65.81	67.08	66.89	69.75	65.39	68.89	67.71	66.73	67.84		
	9					63.97	69.31	68.75	65.95	63.32		

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

355

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 4
200 mg/kg

		Animal no									
		21	22	23	24	26	27	28	29	30	
Alb	(g/l)										
week:	5	34.03	34.41	34.20	35.60	33.39	35.47	35.05	34.28	35.22	
	9					33.15	36.04	35.61	33.33	33.22	
Glob	(g/l)										
week:	5	31.78	32.67	32.69	34.15	32.00	33.42	32.66	32.45	32.62	
	9					30.82	33.27	33.14	32.62	30.10	
A/G	(l)										
week:	5	1.070	1.050	1.050	1.040	1.040	1.060	1.070	1.060	1.080	
	9					1.080	1.080	1.070	1.020	1.100	
Chol	(mmol/l)										
week:	5	2.050	1.800	1.710	1.620	1.800	2.140	1.870	1.760	1.880	
	9					2.450	1.980	1.700	1.670	1.690	
Na+	(mmol/l)										
week:	5	142.2	144.4	144.4	144.8	144.2	146.8	145.9	144.6	146.5	
	9					142.4	144.4	144.5	144.3	144.3	
K+	(mmol/l)										
week:	5	3.870	3.880	3.560	3.640	3.560	3.280	3.410	3.740	3.580	
	9					3.400	3.360	3.750	3.630	3.490	
Ca++	(mmol/l)										
week:	5	2.640	2.750	2.670	2.690	2.690	2.610	2.620	2.610	2.650	
	9					2.660	2.620	2.620	2.620	2.580	
Cl-	(mmol/l)										
week:	5	99.20	97.80	98.00	97.40	99.50	98.80	100.7	96.50	99.00	
	9					102.6	101.3	103.4	100.9	100.6	

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

356

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 4
200 mg/kg

		Animal no									
		21	22	23	24	26	27	28	29	30	
PO4-in (mmol/l)	week: 5	1.820	2.360	2.070	2.410	2.100	1.970	1.990	2.310	2.000	
	9					1.820	1.490	1.560	1.880	1.740	
ASAT (GOT) (U/l)	week: 5	63.30	64.30	85.00	55.70	71.30	57.40	67.50	55.00	60.20	
	9					108.1	82.80	63.00	77.00	80.20	
ALAT (GPT) (U/l)	week: 5	33.30	29.30	31.90	30.70	22.00	25.80	30.70	23.40	31.40	
	9					37.90	28.40	26.00	26.40	30.90	
ALP (U/l)	week: 5	138.7	172.9	140.7	162.6	157.4	149.7	122.6	138.4	169.0	
	9					118.3	121.7	95.00	125.2	123.5	

Blood chemistry (individuals): males

group 5
1000 mg/kg

		Animal no									
		31	32	33	34	35	36	37	38	39	40
Gluc (mmol/l)	week: 5	8.900	9.670	8.660	10.22	9.550	8.340	9.070	8.200	8.210	8.290
	9						6.800	8.260	7.600	8.340	8.430
Urea (mmol/l)	week: 5	5.000	6.970	7.420	6.750	5.570	5.880	6.300	6.320	5.010	6.550
	9						7.770	6.580	6.840	4.660	6.780

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

357

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 5
1000 mg/kg

		Animal no									
		31	32	33	34	35	36	37	38	39	40
Creat ($\mu\text{mol/l}$)	week: 5	17.20	18.30	20.20	22.70	23.10	18.80	22.80	19.50	15.00	20.90
	9					18.80	19.80	18.70	15.60	22.00	
Bili-tot ($\mu\text{mol/l}$)	week: 5	1.090	1.300	1.980	1.620	1.100	1.580	1.210	1.350	1.670	1.560
	9					1.600	2.010	1.980	2.040	1.620	
Prot (g/l)	week: 5	66.73	65.03	65.26	62.42	69.81	68.56	64.23	67.65	68.95	67.43
	9					68.84	65.18	67.45	67.84	69.69	
Alb (g/l)	week: 5	34.59	33.41	34.76	33.12	36.46	35.67	33.60	34.65	35.77	34.26
	9					35.20	34.05	35.05	36.42	34.98	
Glob (g/l)	week: 5	32.14	31.62	30.50	29.30	33.35	32.89	30.63	33.00	33.18	33.17
	9					33.64	31.13	32.40	31.42	34.71	
A/G (1)	week: 5	1.080	1.060	1.140	1.130	1.090	1.080	1.100	1.050	1.080	1.030
	9					1.050	1.090	1.080	1.160	1.010	
Chol (mmol/l)	week: 5	1.660	2.110	1.500	1.750	1.650	2.040	1.720	1.650	2.110	2.280
	9					1.880	1.640	1.530	1.970	2.350	
Na ⁺ (mmol/l)	week: 5	142.9	142.5	145.2	143.3	142.8	143.7	142.6	143.7	144.8	144.4
	9					144.2	144.3	145.0	144.4	145.7	

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

358

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): males

group 5
1000 mg/kg

		31	32	33	34	35	36	37	38	39	40
	Animal no										
K+	(mmol/l)										
week:	5	3.930	3.830	4.555	3.680	4.080	4.080	3.530	3.980	3.990	3.750
	9					3.610	3.530	3.690	3.790	3.500	
Ca++	(mmol/l)										
week:	5	2.670	2.730	2.890	2.620	2.760	2.710	2.550	2.620	2.800	2.610
	9					2.620	2.530	2.590	2.710	2.720	
Cl-	(mmol/l)										
week:	5	100.8	95.60	95.00	99.50	98.60	96.40	98.10	97.10	99.00	98.30
	9						100.0	97.50	100.7	100.8	98.10
PO4-in	(mmol/l)										
week:	5	1.930	2.620	3.040	2.310	2.280	2.080	2.300	2.060	2.210	2.140
	9						1.500	2.020	1.810	1.820	1.970
ASAT (GOT)	(U/l)										
week:	5	62.20	60.70	120.6	79.20	94.50	66.70	62.60	62.80	59.70	71.80
	9						66.10	88.90	73.30	84.30	68.30
ALAT (GPT)	(U/l)										
week:	5	33.60	31.60	87.00	47.80	45.20	32.70	28.00	33.30	29.10	29.60
	9						34.90	46.80	37.30	29.60	29.90
AlP	(U/l)										
week:	5	223.6	187.3	245.1	146.2	198.5	202.6	171.8	162.1	142.4	198.7
	9						118.8	146.0	117.8	117.6	131.1

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 1
0 mg/kg

	Animal no										
	41	42	43	44	45	46	47	48	49	50	
Gluc (mmol/l)											
week:	5	6.300	8.320	6.700	7.720	6.100	8.590	8.810	7.580	7.770	7.150
	9					8.120	8.640	7.560	7.100	6.810	
Urea (mmol/l)											
week:	5	7.350	6.220	6.430	7.380	8.800	6.170	5.600	6.920	5.740	7.300
	9					8.130	5.300	6.370	6.550	6.890	
Creat (umol/l)											
week:	5	25.50	22.40	17.20	20.50	23.10	20.30	19.50	18.80	18.30	24.50
	9						20.90	18.50	18.70	19.30	21.40
Bili-tot (umol/l)											
week:	5	1.020	1.380	1.440	1.800	1.900	1.850	1.390	1.670	1.700	2.300
	9						2.510	1.530	1.560	2.170	2.050
Prot (g/l)											
week:	5	68.24	69.92	65.68	66.83	66.76	67.46	66.11	64.46	66.09	65.12
	9						72.38	68.11	68.74	67.12	64.64
Alb (g/l)											
week:	5	36.00	37.31	34.98	36.01	35.10	35.25	35.80	34.72	36.01	34.83
	9						38.16	36.58	38.07	35.10	34.96
Glob (g/l)											
week:	5	32.24	32.61	30.70	30.82	31.66	32.21	30.31	29.74	30.08	30.29
	9						34.22	31.53	30.67	32.02	29.68
A/G (1)											
week:	5	1.120	1.140	1.140	1.170	1.110	1.090	1.180	1.170	1.200	1.150
	9						1.120	1.160	1.240	1.100	1.180

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

360

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 1
0 mg/kg

		Animal no									
		41	42	43	44	45	46	47	48	49	50
Chol (mmol/l)	week: 5	2.550	2.420	1.940	1.920	1.800	2.600	2.220	2.230	2.200	2.210
	9						2.790	2.130	2.140	2.410	2.150
Na+ (mmol/l)	week: 5	144.7	144.4	143.3	143.4	145.3	144.8	145.8	143.5	144.5	143.8
	9						146.1	143.5	143.8	143.2	141.7
K+ (mmol/l)	week: 5	3.580	3.070	3.640	3.490	3.730	3.240	2.860	3.180	3.230	3.260
	9						2.800	2.800	3.230	3.480	3.170
Ca++ (mmol/l)	week: 5	2.770	2.590	2.580	2.590	2.670	2.710	2.650	2.720	2.630	2.550
	9						2.740	2.550	2.600	2.630	2.490
Cl- (mmol/l)	week: 5	99.80	100.7	100.0	99.20	98.70	101.2	101.5	97.70	102.0	102.6
	9						102.4	101.7	105.6	101.9	100.9
PO4-in (mmol/l)	week: 5	2.250	1.990	2.000	1.890	2.300	1.920	2.250	2.100	2.170	1.960
	9						1.420	1.230	1.160	1.280	1.200
ASAT (GOT) (U/l)	week: 5	72.70	72.40	64.80	68.00	71.70	68.30	70.20	59.50	63.10	68.90
	9						63.40	67.90	50.20	61.60	71.60
ALAT (GPT) (U/l)	week: 5	26.30	24.20	25.10	20.90	29.60	31.80	24.80	19.80	24.70	19.80
	9						27.80	22.20	20.10	31.60	18.70

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 1

0 mg/kg

		Animal no									
		41	42	43	44	45	46	47	48	49	50
AlP (U/l)	week: 5	103.5	112.5	92.40	85.00	126.7	149.8	99.40	112.7	98.40	132.4
	9					96.80	70.60	58.50	69.30	84.70	

Blood chemistry (individuals): females

group 2

10 mg/kg

		Animal no				
		51	52	53	54	55
Gluc (mmol/l)	week: 5	6.270	9.530	8.590	7.930	7.390
Urea (mmol/l)	week: 5	7.830	8.260	6.040	8.150	8.010
Creat (umol/l)	week: 5	27.20	23.10	20.60	22.50	26.00
Bili-tot (umol/l)	week: 5	1.770	1.500	2.000	1.165	1.480
Prot (g/l)	week: 5	71.33	66.08	68.92	65.54	64.87
Alb (g/l)	week: 5	37.44	34.59	37.85	35.06	35.13

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

362

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 2
10 mg/kg

		Animal no				
		51	52	53	54	55
Glob (g/l)						
week:	5	33.89	31.49	31.07	30.48	29.74
A/G (1)						
week:	5	1.100	1.100	1.220	1.150	1.180
Chol (mmol/l)						
week:	5	1.940	3.180	2.040	1.980	2.090
Na+ (mmol/l)						
week:	5	145.7	143.5	143.6	144.0	142.1
K+ (mmol/l)						
week:	5	3.760	3.400	3.020	3.710	3.400
Ca++ (mmol/l)						
week:	5	2.700	2.650	2.560	2.620	2.520
Cl- (mmol/l)						
week:	5	102.4	101.7	98.10	100.4	99.80
PO4-in (mmol/l)						
week:	5	2.090	2.010	2.230	1.860	1.700
ASAT (GOT) (U/l)						
week:	5	75.50	61.80	73.40	65.80	56.60
ALAT (GPT) (U/l)						
week:	5	31.20	27.20	25.90	27.90	26.10

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

363

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 2
10 mg/kg

		51	52	53	54	55	Animal no
ALP (U/l) week:	5	98.00	147.2	136.1	101.9	142.2	

Blood chemistry (individuals): females

group 3
50 mg/kg

		56	57	58	59	60	Animal no
Gluc (mmol/l) week:	5	7.080	7.910	7.470	7.420	7.030	
Urea (mmol/l) week:	5	6.560	6.780	6.120	7.320	6.990	
Creat (umol/l) week:	5	19.70	20.20	24.90	26.70	20.60	
Bili-tot (umol/l) week:	5	1.940	1.190	1.600	1.750	2.050	
Prot (g/l) week:	5	62.97	65.82	66.79	64.79	66.59	
Alb (g/l) week:	5	33.67	34.67	34.07	34.78	36.14	
Glob (g/l) week:	5	29.30	31.15	32.72	30.01	30.45	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 3
50 mg/kg

		Animal no				
		56	57	58	59	60
A/G (l)						
week:	5	1.150	1.110	1.040	1.160	1.190
Chol (mmol/l)						
week:	5	2.420	2.240	2.490	2.010	1.920
Na+ (mmol/l)						
week:	5	144.0	142.7	144.2	144.5	146.4
K+ (mmol/l)						
week:	5	3.740	3.600	3.360	3.370	3.550
Ca++ (mmol/l)						
week:	5	2.630	2.570	2.620	2.550	2.730
Cl- (mmol/l)						
week:	5	100.6	102.5	101.7	102.0	102.6
PO4-in (mmol/l)						
week:	5	2.010	1.780	1.840	2.020	2.140
ASAT (GOT) (U/l)						
week:	5	68.80	67.40	68.00	60.30	60.00
ALAT (GPT) (U/l)						
week:	5	28.00	27.20	22.30	23.80	25.40
AlP (U/l)						
week:	5	97.80	146.2	89.20	112.5	131.2

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

365

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
Gluc (mmol/l)	week: 5	6.790	5.980	6.690	7.040	6.260	5.630	7.350	6.250
	9					8.690	5.830	6.810	7.850
Urea (mmol/l)	week: 5	6.230	7.480	8.160	7.360	6.840	7.660	5.490	8.770
	9					7.160	8.710	7.390	7.770
Creat (umol/l)	week: 5	22.20	27.80	26.60	21.40	25.00	29.20	20.50	24.50
	9					27.10	37.80	22.30	23.80
Bili-tot (umol/l)	week: 5	1.150	1.150	1.620	1.490	2.090	1.730	2.360	1.670
	9					2.270	1.255	1.290	2.650
Prot (g/l)	week: 5	62.69	63.67	65.38	64.00	64.60	65.91	67.13	66.26
	9					67.60	65.69	68.06	69.05
Alb (g/l)	week: 5	34.32	32.56	35.09	34.83	34.11	35.61	36.87	37.39
	9					36.14	34.35	36.63	39.57
Glob (g/l)	week: 5	28.37	31.11	30.29	29.17	30.49	30.30	30.26	28.87
	9					31.46	31.34	31.43	29.48
A/G (1)	week: 5	1.210	1.050	1.160	1.190	1.120	1.180	1.220	1.300
	9					1.150	1.100	1.170	1.340

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

366

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
Chol (mmol/l)	week: 5	2.400	2.370	1.960	2.250	2.210	2.080	1.680	1.750
	9					2.270	1.410	1.890	1.610
Na+ (mmol/l)	week: 5	145.6	146.9	144.1	143.5	145.1	143.9	145.5	145.6
	9					142.8	142.2	142.5	142.7
K+ (mmol/l)	week: 5	2.910	3.310	3.060	3.995	3.190	3.910	3.300	3.160
	9					3.040	3.350	3.640	2.700
Ca++ (mmol/l)	week: 5	2.410	2.630	2.550	2.610	2.710	2.750	2.570	2.600
	9					2.590	2.540	2.600	2.610
Cl- (mmol/l)	week: 5	102.6	99.30	99.90	98.80	102.1	100.4	105.0	103.9
	9					104.5	102.5	103.8	101.6
PO4-in (mmol/l)	week: 5	1.600	2.240	2.020	2.430	1.930	2.320	1.700	1.650
	9					1.210	1.600	1.130	1.570
ASAT (GOT) (U/l)	week: 5	73.70	93.00	63.80	82.70	69.50	84.80	57.90	57.40
	9					59.70	69.80	64.70	61.40
ALAT (GPT) (U/l)	week: 5	24.60	26.20	30.50	24.50	20.70	24.70	22.00	20.60
	9					19.65	22.20	26.30	24.00

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

367

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 4
200 mg/kg

		Animal no									
		62	63	64	65	66	67	69	70		
AlP (U/l)	week: 5	107.5	68.70	107.0	134.2	87.00	118.8	89.60	112.1		
	9					59.70	62.20	60.60	91.50		

Blood chemistry (individuals): females

group 5
1000 mg/kg

		Animal no									
		71	72	73	74	75	76	77	78	79	80
Gluc (mmol/l)	week: 5	7.340	6.510	6.720	7.100	6.170	6.120	6.310	6.500	8.120	9.570
	9						6.010	7.110	6.040	6.760	8.760
Urea (mmol/l)	week: 5	6.080	7.730	7.650	6.760	8.310	7.710	7.900	10.01	6.200	6.810
	9						7.050	7.800	8.190	6.620	6.700
Creat (umol/l)	week: 5	20.80	23.00	20.20	22.80	23.00	23.00	23.50	27.70	22.70	26.90
	9						24.60	30.50	29.50	24.70	25.50
Bili-tot (umol/l)	week: 5	1.610	1.690	1.300	1.380	1.610	1.970	1.400	2.110	2.220	1.710
	9						2.130	1.550	2.480	1.750	1.670
Prot (g/l)	week: 5	66.13	64.39	69.10	67.83	68.66	65.87	65.20	67.09	60.92	63.59
	9						66.42	65.90	65.59	63.62	66.88

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

368

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 5

1000 mg/kg

		Animal no										
		71	72	73	74	75	76	77	78	79	80	
Alb (g/l)	week:	5	34.08	36.29	36.91	36.30	37.41	35.45	35.20	35.05	33.79	34.16
	9						35.93	35.60	35.25	34.95	35.55	
Glob (g/l)	week:	5	32.05	28.10	32.19	31.53	31.25	30.42	30.00	32.04	27.13	29.43
	9						30.49	30.30	30.34	28.67	31.33	
A/G (1)	week:	5	1.060	1.290	1.150	1.150	1.200	1.170	1.170	1.090	1.250	1.160
	9						1.180	1.170	1.160	1.220	1.130	
Chol (mmol/l)	week:	5	2.710	1.990	2.410	2.690	1.810	2.810	2.060	2.420	1.960	1.820
	9						2.710	1.890	1.860	1.960	1.580	
Na+ (mmol/l)	week:	5	143.6	143.9	144.3	146.0	144.5	142.9	144.4	143.9	143.3	145.3
	9						142.4	144.4	143.6	142.0	144.1	
K+ (mmol/l)	week:	5	3.780	3.440	3.090	3.390	3.040	3.470	3.610	3.670	3.680	3.430
	9						3.050	2.880	3.240	3.040	3.000	
Ca++ (mmol/l)	week:	5	2.600	2.530	2.710	2.730	2.690	2.650	2.650	2.660	2.570	2.710
	9						2.610	2.560	2.510	2.500	2.550	
Cl- (mmol/l)	week:	5	103.5	102.5	100.2	99.70	101.3	99.00	94.60	100.4	103.6	102.1
	9						101.5	102.0	103.5	101.7	102.7	

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

369

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Blood chemistry (individuals): females

group 5
1000 mg/kg

		71	72	73	74	75	76	77	78	79	80
	Animal no										
PO4-in (mmol/l)											
week:	5	1.910	1.950	2.080	2.040	2.250	1.950	2.040	2.120	2.060	2.250
	9					1.080	1.240	1.490	1.330	1.180	
ASAT (GOT) (U/l)											
week:	5	67.50	94.80	63.60	61.30	63.40	57.50	74.60	75.80	83.80	61.90
	9					48.00	65.50	69.40	77.70	61.40	
ALAT (GPT) (U/l)											
week:	5	23.00	23.20	23.60	25.20	30.60	25.30	29.20	33.20	27.60	24.10
	9					22.80	23.70	24.50	27.30	23.60	
ALP (U/l)											
week:	5	117.8	183.3	117.9	156.1	184.7	131.6	144.1	81.10	114.9	172.8
	9					79.80	76.70	55.70	81.20	111.5	

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.10. Urine analysis (individuals)

Urine analysis (individuals): males

group 1
0 mg/kg

	Animal no									
	1	2	3	4	5	6	7	8	9	10
Volume (ml)										
week: 5	6.800	7.100	5.200	3.300	8.200	2.400	5.400	3.800	3.600	6.200
9						4.300	8.000	7.300	5.600	5.200
Rel dens (1)										
week: 5	1.029	1.031	1.036	1.044	1.029	1.045	1.036	1.044	1.046	1.032
9						1.062	1.031	1.032	1.046	1.046
pH (1)										
week: 5	6.500	6.500	6.500	6.500	7.000	6.500	6.500	6.500	6.500	6.500
9						6.500	7.000	7.000	6.500	7.000
PRO (g/l)										
week: 5	0.250	0.250	0.750	0.750	0.250	0.750	0.750	0.750	0.750	0.750
9						0.750	0.250	0.250	0.250	0.250
GLU (mmol/l)										
week: 5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
9						0.000	0.000	0.000	0.000	0.000
KET (mmol/l)										
week: 5	0.500	0.500	1.500	1.500	0.500	1.500	0.500	1.500	0.500	0.500
9						0.500	0.500	0.500	0.500	1.500
UBG (umol/l)										
week: 5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
9						0.000	0.000	0.000	0.000	0.000

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

371

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males

group 1
0 mg/kg

		Animal no									
		1	2	3	4	5	6	7	8	9	10
BIL	(umol/l)										
week:	5	0.000	0.000	17.00	0.000	0.000	0.000	0.000	17.00	0.000	0.000
	9					0.000	0.000	0.000	0.000	0.000	0.000
ERY	(per ul)										
week:	5	10.00	0.000	10.00	25.00	10.00	10.00	10.00	10.00	10.00	10.00
	9					10.00	0.000	10.00	10.00	0.000	
LEU	(per ul)										
week:	5	100.0	25.00	100.0	100.0	25.00	100.0	100.0	100.0	100.0	25.00
	9					100.0	25.00	25.00	25.00	25.00	25.00

Urine analysis (individuals): males

group 2
10 mg/kg

		Animal no				
		11	12	13	14	15
Volume	(ml)					
week:	5	4.100	3.800	6.400	4.500	4.700
Rel dens	(1)					
week:	5	1.042	1.041	1.030	1.049	1.032
pH	(1)					
week:	5	6.500	6.000	6.500	6.500	6.500
PRO	(g/l)					
week:	5	0.750	0.750	0.750	0.750	0.250

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

372

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males

group 2
10 mg/kg

		11	12	13	14	15	Animal no
GLU (mmol/l)							
week:	5	0.000	0.000	0.000	0.000	0.000	
KET (mmol/l)							
week:	5	1.500	0.500	0.500	1.500	0.500	
UBG (umol/l)							
week:	5	0.000	0.000	0.000	0.000	0.000	
BIL (umol/l)							
week:	5	17.00	0.000	0.000	0.000	17.00	
ERY (per ul)							
week:	5	25.00	10.00	10.00	10.00	10.00	
LEU (per ul)							
week:	5	100.0	100.0	100.0	100.0	100.0	

Urine analysis (individuals): males

group 3
50 mg/kg

		16	17	18	19	20	Animal no
Volume (ml)							
week:	5	6.000	6.400	7.000	4.100	6.300	
Rel dens (1)							
week:	5	1.045	1.035	1.030	1.033	1.033	

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

373

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males

group 3
50 mg/kg

		16	17	18	19	20
		Animal no				
pH						
(1)						
week:	5	6.500	6.500	6.500	6.000	6.500
PRO						
(g/l)						
week:	5	0.750	0.750	0.750	0.750	0.750
GLU						
(mmol/l)						
week:	5	0.000	0.000	0.000	0.000	0.000
KET						
(mmol/l)						
week:	5	0.500	1.500	0.500	0.500	0.500
UBG						
(umol/l)						
week:	5	0.000	0.000	0.000	0.000	0.000
BIL						
(umol/l)						
week:	5	0.000	0.000	0.000	0.000	17.00
ERY						
(per ul)						
week:	5	10.00	10.00	10.00	10.00	10.00
LEU						
(per ul)						
week:	5	25.00	100.0	100.0	25.00	100.0

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males

group 4
200 mg/kg

		21	22	23	24	26	27	28	29	30
	Animal no									
Volume (ml)										
week:	5	5.800	6.900	3.200	4.100	9.000	7.000	4.100	5.900	4.300
	9					9.100	5.500	5.700	4.000	4.200
Rel dens (1)										
week:	5	1.049	1.028	1.056	1.048	1.035	1.035	1.044	1.042	1.049
	9					1.029	1.045	1.037	1.041	1.064
pH (1)										
week:	5	6.000	6.500	6.000	6.500	5.000	7.000	6.500	6.500	6.000
	9					6.500	6.500	7.000	6.500	6.500
PRO (g/l)										
week:	5	0.750	0.250	0.750	0.750	0.250	0.250	0.750	0.750	0.750
	9					0.250	0.750	0.250	0.750	0.750
GLU (mmol/l)										
week:	5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	9					0.000	0.000	0.000	0.000	0.000
KET (mmol/l)										
week:	5	1.500	0.500	1.500	1.500	1.500	0.500	1.500	0.500	1.500
	9					1.500	0.500	0.500	1.500	1.500
UBG (umol/l)										
week:	5	0.000	0.000	17.00	0.000	0.000	0.000	0.000	0.000	17.00
	9					0.000	0.000	0.000	0.000	0.000
BIL (umol/l)										
week:	5	0.000	0.000	17.00	0.000	17.00	0.000	0.000	0.000	17.00
	9					0.000	0.000	0.000	0.000	0.000

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

375

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males

group 4
200 mg/kg

		Animal no									
		21	22	23	24	26	27	28	29	30	
ERY (per ul)	week: 5	10.00	10.00	10.00	25.00	25.00	10.00	10.00	10.00	10.00	
	9					25.00	25.00	25.00	250.0	10.00	
LEU (per ul)	week: 5	25.00	25.00	25.00	100.0	25.00	100.0	25.00	25.00	25.00	
	9					0.000	25.00	25.00	25.00	25.00	

Urine analysis (individuals): males

group 5
1000 mg/kg

		Animal no									
		31	32	33	34	35	36	37	38	39	40
Volume (ml)	week: 5	5.000	3.500	3.300	4.200	2.600	2.400	3.400	3.700	3.700	2.900
	9						2.700	4.000	3.100	3.700	4.400
Rel dens (1)	week: 5	1.039	1.047	1.051	1.048	1.062	1.032	1.066	1.043	1.069	1.075
	9						1.084	1.043	1.072	1.058	1.044
pH (1)	week: 5	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	6.500
	9						6.000	7.000	6.500	6.500	6.500
PRO (g/l)	week: 5	0.250	0.750	0.250	0.250	0.750	0.750	0.750	0.750	0.750	0.250
	9						0.750	0.250	0.250	0.750	0.250

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

376

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males

group 5
1000 mg/kg

		Animal no									
		31	32	33	34	35	36	37	38	39	40
GLU	(mmol/l)										
week:	5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	9					0.000	0.000	0.000	0.000	0.000	0.000
KET	(mmol/l)										
week:	5	0.500	1.500	1.500	0.500	0.500	1.500	0.500	0.500	0.500	1.500
	9					1.500	0.500	1.500	1.500	1.500	1.500
UBG	(umol/l)										
week:	5	0.000	0.000	0.000	0.000	0.000	0.000	17.00	0.000	17.00	0.000
	9						0.000	0.000	0.000	0.000	0.000
BIL	(umol/l)										
week:	5	17.00	17.00	17.00	17.00	0.000	0.000	17.00	17.00	17.00	0.000
	9						0.000	0.000	0.000	0.000	0.000
ERY	(per ul)										
week:	5	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
	9						10.00	10.00	50.00	0.000	25.00
LEU	(per ul)										
week:	5	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
	9						25.00	25.00	25.00	25.00	25.00

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

377

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 1
0 mg/kg

		Animal no									
		41	42	43	44	45	46	47	48	49	50
Volume (ml)	week: 5	2.100	3.300	1.500	3.600	3.500	4.800	3.500	3.200	3.900	2.500
	9					3.600	3.900	3.500	4.400	6.800	
Rel dens (1)	week: 5	1.048	1.034	1.021	1.039	1.048	1.034	1.038	1.042	1.046	1.042
	9					1.041	1.033	1.042	1.060	1.026	
pH (1)	week: 5	6.000	6.500	5.000	6.000	5.000	6.000	6.500	6.000	6.000	6.500
	9						6.000	7.000	6.000	6.000	7.000
PRO (g/l)	week: 5	0.250	0.750	0.750	0.250	0.250	0.250	0.250	0.250	0.750	0.250
	9						0.250	0.250	0.250	0.750	0.250
GLU (mmol/l)	week: 5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	9						0.000	0.000	0.000	0.000	0.000
KET (mmol/l)	week: 5	1.500	0.500	0.500	0.500	0.500	0.500	0.500	1.500	0.500	0.500
	9						0.500	0.500	0.500	1.500	0.000
UBG (umol/l)	week: 5	0.000	0.000	17.00	0.000	0.000	0.000	0.000	0.000	0.000	17.00
	9						0.000	0.000	0.000	0.000	0.000
BIL (umol/l)	week: 5	0.000	17.00	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	9						0.000	0.000	0.000	0.000	0.000

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 1
0 mg/kg

		41	42	43	44	45	46	47	48	49	50
		Animal no									
ERY (per ul)											
week:	5	10.00	25.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
	9					10.00	10.00	10.00	10.00	10.00	10.00
LEU (per ul)											
week:	5	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
	9					0.000	0.000	0.000	0.000	0.000	0.000

Urine analysis (individuals): females

group 2
10 mg/kg

		51	52	53	54	55
		Animal no				
Volume (ml)						
week:	5	2.000	2.000	4.300	1.800	2.300
Rel dens (1)						
week:	5	1.046	1.034	1.042	1.075	1.058
pH (1)						
week:	5	6.000	6.500	6.500	5.000	5.000
PRO (g/l)						
week:	5	0.250	0.250	0.250	0.750	0.750
GLU (mmol/l)						
week:	5	0.000	0.000	0.000	0.000	0.000

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

379

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 2
10 mg/kg

		51	52	53	54	55	Animal no
KET (mmol/l) week: 5		0.500	1.500	0.500	1.500	0.500	
UBG (umol/l) week: 5		0.000	17.00	0.000	17.00	0.000	
BIL (umol/l) week: 5		0.000	17.00	0.000	0.000	0.000	
ERY (per ul) week: 5		10.00	10.00	10.00	10.00	10.00	
LEU (per ul) week: 5		25.00	25.00	25.00	25.00	25.00	

Urine analysis (individuals): females

group 3
50 mg/kg

		56	57	58	59	60	Animal no
Volume (ml) week: 5		1.900	5.500	3.400	1.800	3.700	
Rel dens (1) week: 5		1.060	1.028	1.041	1.033	1.043	
pH (1) week: 5		5.000	7.000	6.000	6.000	6.000	

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

380

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 3
50 mg/kg

		56	57	58	59	60	Animal no
PRO (g/l) week:	5	0.750	0.250	0.250	0.250	0.750	
GLU (mmol/l) week:	5	0.000	0.000	0.000	0.000	0.000	
KET (mmol/l) week:	5	0.500	0.500	0.500	1.500	0.500	
UBG (umol/l) week:	5	17.00	0.000	0.000	17.00	0.000	
BIL (umol/l) week:	5	17.00	0.000	17.00	0.000	17.00	
ERY (per ul) week:	5	10.00	10.00	10.00	10.00	10.00	
LEU (per ul) week:	5	25.00	25.00	25.00	25.00	25.00	

Urine analysis (individuals): females

group 4
200 mg/kg

		62	63	64	65	66	67	69	70	Animal no
Volume (ml) week:	5	2.900	1.100	3.600	1.800	2.900	2.800	1.500	1.500	
	9					2.700	3.000	2.600	1.200	

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
Rel dens	(1)								
week:	5	1.039	1.088	1.038	1.047	1.050	1.046	1.021	1.085
	9					1.048	1.046	1.070	1.068
pH	(1)								
week:	5	6.500	5.000	5.000	5.000	5.000	5.000	6.500	6.500
	9					6.000	6.000	6.000	6.000
PRO	(g/l)								
week:	5	0.750	0.750	0.250	0.750	0.250	0.250	0.750	0.750
	9					0.250	0.250	0.250	0.250
GLU	(mmol/l)								
week:	5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	9					0.000	0.000	0.000	0.000
KET	(mmol/l)								
week:	5	0.500	1.500	0.000	0.500	0.500	0.500	0.500	1.500
	9					0.500	0.500	1.500	0.500
UBG	(umol/l)								
week:	5	17.00	17.00	0.000	17.00	0.000	0.000	17.00	17.00
	9					0.000	0.000	0.000	0.000
BIL	(umol/l)								
week:	5	17.00	0.000	0.000	17.00	0.000	0.000	0.000	17.00
	9					0.000	0.000	0.000	0.000
ERY	(per ul)								
week:	5	10.00	10.00	10.00	10.00	0.000	10.00	10.00	10.00
	9					50.00	25.00	10.00	0.000

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

382

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
LEU (per ul) week:	5	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
	9					0.000	0.000	0.000	25.00

Urine analysis (individuals): females

group 5
1000 mg/kg

		Animal no									
		71	72	73	74	75	76	77	78	79	80
Volume (ml) week:	5	4.200	2.300	2.700	1.600	2.300	3.200	2.600	1.900	1.800	0.900
	9						5.000	2.200	3.700	3.100	3.000
Rel dens (1) week:	5	1.048	1.050	1.065	1.021	1.031	1.049	1.054	1.047	1.040	1.072
	9						1.036	1.039	1.039	1.043	1.037
pH (1) week:	5	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000
	9						6.000	6.000	6.000	6.000	7.000
PRO (g/l) week:	5	0.250	0.750	0.750	0.750	0.750	0.750	0.250	0.250	0.750	0.250
	9						0.250	0.250	0.250	0.250	0.250
GLU (mmol/l) week:	5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	9						0.000	0.000	0.000	0.000	0.000

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 5
1000 mg/kg

		Animal no									
		71	72	73	74	75	76	77	78	79	80
KET	(mmol/l)										
week:	5	0.500	0.500	0.500	1.500	1.500	0.500	0.500	0.500	0.500	0.500
	9					0.500	0.500	0.000	0.500	0.500	
UBG	(umol/l)										
week:	5	0.000	17.00	17.00	17.00	17.00	17.00	17.00	17.00	17.00	17.00
	9					0.000	0.000	0.000	0.000	0.000	
BIL	(umol/l)										
week:	5	0.000	0.000	17.00	17.00	17.00	0.000	17.00	0.000	17.00	
	9					0.000	0.000	0.000	0.000	0.000	
ERY	(per ul)										
week:	5	0.000	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
	9					0.000	10.00	10.00	10.00	10.00	0.000
LEU	(per ul)										
week:	5	25.00	25.00	25.00	25.00	0.000	25.00	25.00	25.00	25.00	25.00
	9					0.000	0.000	25.00	0.000	25.00	

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males group 1
0 mg/kg

		Animal no									
		1	2	3	4	5	6	7	8	9	10
Color (choice) week:	5	N	N	N	N	N	N	N	N	N	N
	9					N	N	N	N	N	N

Urine analysis (individuals): males group 2
10 mg/kg

		Animal no				
		11	12	13	14	15
Color (choice) week:	5	N	N	N	N	N

Urine analysis (individuals): males group 3
50 mg/kg

		Animal no				
		16	17	18	19	20
Color (choice) week:	5	N	N	N	N	N

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

385

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): males

group 4
200 mg/kg

		Animal no									
		21	22	23	24	26	27	28	29	30	
Color (choice)											
week:	5	N	N	N	N	N	N	N	N	N	
	9					N	N	N	N	N	

Urine analysis (individuals): males

group 5
1000 mg/kg

		Animal no									
		31	32	33	34	35	36	37	38	39	40
Color (choice)											
week:	5	N	N	N	N	N	N	N	N	N	N
	9						N	N	N	N	N

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

386

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females group 1
0 mg/kg

		41	42	43	44	45	46	47	48	49	50
Color (choice) week:	5	N	N	N	N	N	N	N	N	N	N
	9					N	N	N	N	N	N

Urine analysis (individuals): females group 2
10 mg/kg

		51	52	53	54	55
Color (choice) week:	5	N	N	N	N	N

Urine analysis (individuals): females group 3
50 mg/kg

		56	57	58	59	60
Color (choice) week:	5	N	N	N	N	N

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Urine analysis (individuals): females

group 4
200 mg/kg

		Animal no							
		62	63	64	65	66	67	69	70
Color (choice) week:	5	N	N	N	N	N	N	N	N
	9	N	N	N	N	N	N	N	N

Urine analysis (individuals): females

group 5
1000 mg/kg

		Animal no									
		71	72	73	74	75	76	77	78	79	80
Color (choice) week:	5	N	N	N	N	N	N	N	N	N	N
	9	N	N	N	N	N	N	N	N	N	N

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.11. Organ weights and ratios (individuals)

9.11.1. Organ weights (individuals): 1. sacrifice

Organ weights (individuals): males

group 1: 0 mg/kg week 5

	Animal no				
	1	2	3	4	5
Body (g)	330.3	327.5	316.9	319.8	345.2
Brain (g)	2.137	2.306	2.015	2.197	2.306
Heart (g)	1.143	1.124	1.112	1.132	1.086
Liver (g)	16.40	14.97	14.09	14.54	14.54
Kidney (both) (g)	2.361	2.534	2.325	2.514	2.559
Adrenal (both) (mg)	78.50	70.80	78.50	75.20	73.10
Thymus (mg)	808.7	732.7	900.2	819.2	510.4
Testis (both) (g)	3.222	3.891	3.419	3.310	3.947
Spleen (g)	0.591	0.643	0.570	0.727	0.689
Epididymis (g)	1.044	1.207	1.160	1.091	1.221

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

389

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : males

group 2 : 10 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Body (g)	315.4	343.9	313.4	303.6	311.5
Brain (g)	2.227	2.021	2.178	2.234	2.173
Heart (g)	1.103	1.080	1.244	1.120	1.054
Liver (g)	14.30	16.18	14.83	15.14	16.48
Kidney (both) (g)	2.764	2.479	2.336	2.674	2.208
Adrenal (both) (mg)	91.10	78.10	83.20	68.80	94.20
Thymus (mg)	716.3	708.6	747.6	634.7	748.5
Testis (both) (g)	3.309	3.288	2.745	3.495	3.556
Spleen (g)	0.709	0.822	0.660	0.638	0.607
Epididymis (g)	1.085	1.211	0.934	1.118	1.132

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

390

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Body (g)	339.9	360.6	314.8	314.0	376.7
Brain (g)	2.262	2.208	1.971	2.153	2.162
Heart (g)	1.247	1.244	1.187	1.080	1.249
Liver (g)	18.01	17.26	16.01	17.35	17.82
Kidney (both) (g)	2.992	2.740	2.449	2.414	2.659
Adrenal (both) (mg)	67.90	74.80	77.40	69.20	79.50
Thymus (mg)	1037	966.5	695.7	541.8	742.2
Testis (both) (g)	3.515	3.336	3.105	3.567	3.442
Spleen (g)	0.846	0.599	0.724	0.666	0.568
Epididymis (g)	1.225	1.186	1.001	1.094	1.326

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

391

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : males

group 4 : 200 mg/kg

week 5

	Animal no			
	21	22	23	24
Body (g)	349.0	347.9	297.9	349.9
Brain (g)	2.380	2.116	2.274	2.101
Heart (g)	1.273	1.159	1.033	1.210
Liver (g)	15.56	15.73	11.78	16.29
Kidney (both) (g)	2.641	2.477	2.194	2.690
Adrenal (both) (mg)	72.00	77.60	75.60	71.60
Thymus (mg)	1034	775.8	782.7	838.0
Testis (both) (g)	3.739	3.634	3.653	3.557
Spleen (g)	0.636	0.614	0.668	0.717
Epididymis (g)	1.228	1.269	1.077	1.222

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

392

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals): males

group 5 : 1000 mg/kg week 5

	Animal no				
	31	32	33	34	35
Body (g)	324.6	327.1	281.9	304.7	327.1
Brain (g)	2.205	2.237	2.128	2.080	2.105
Heart (g)	1.162	1.321	1.111	1.072	1.249
Liver (g)	16.93	15.90	12.58	13.74	13.92
Kidney (both) (g)	2.542	2.565	2.204	2.286	2.090
Adrenal (both) (mg)	90.60	59.70	85.20	88.50	65.10
Thymus (mg)	520.4	741.2	716.0	478.6	625.2
Testis (both) (g)	3.799	4.086	3.488	3.516	3.525
Spleen (g)	0.711	0.639	0.538	0.530	0.689
Epididymis (g)	1.100	1.193	1.122	1.185	1.156

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

393

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : females

group 1 : 0 mg/kg

week 5

	Animal no				
	41	42	43	44	45
Body (g)	207.2	225.6	197.2	206.2	220.4
Brain (g)	2.111	2.131	1.932	2.090	2.132
Heart (g)	0.766	0.965	0.801	0.855	0.909
Liver (g)	8.902	10.81	9.311	8.671	9.320
Kidney (both) (g)	1.611	1.883	2.011	1.800	1.836
Adrenal (both) (mg)	93.60	107.0	130.0	85.80	101.6
Thymus (mg)	599.7	466.3	667.4	470.5	514.2
Ovary (both) (mg)	139.1	197.4	145.3	206.0	173.0
Spleen (g)	0.421	0.463	0.399	0.430	0.566

Organ weights (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no				
	51	52	53	54	55
Body (g)	201.3	219.8	214.0	212.7	216.5
Brain (g)	1.866	2.162	1.939	1.975	2.122

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no				
	51	52	53	54	55
Heart (g)	0.852	0.877	0.866	0.835	0.867
Liver (g)	8.542	9.809	10.25	10.04	10.20
Kidney (both) (g)	1.713	1.744	1.843	1.829	1.967
Adrenal (both) (mg)	80.90	84.70	93.30	89.50	79.30
Thymus (mg)	356.3	466.1	383.0	415.2	737.7
Ovary (both) (mg)	192.5	178.3	148.8	165.8	182.2
Spleen (g)	0.423	0.569	0.409	0.590	0.527

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	56	57	58	59	60
Body (g)	199.6	220.2	237.7	203.9	206.5
Brain (g)	1.996	2.076	2.181	1.995	2.234
Heart (g)	0.838	0.887	0.917	0.789	0.807
Liver (g)	9.765	10.22	9.676	8.277	8.751

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

395

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	56	57	58	59	60
Kidney (both) (g)	1.951	2.105	1.750	1.921	1.949
Adrenal (both) (mg)	105.3	97.20	84.70	81.90	90.60
Thymus (mg)	472.9	645.0	505.8	497.4	462.8
Ovary (both) (mg)	121.1	184.2	211.2	183.3	180.4
Spleen (g)	0.502	0.508	0.501	0.492	0.560

Organ weights (individuals) : females

group 4 : 200 mg/kg

week 5

	Animal no			
	62	63	64	65
Body (g)	205.1	192.7	241.9	208.3
Brain (g)	2.006	1.991	2.066	2.098
Heart (g)	0.848	0.703	0.999	0.817
Liver (g)	8.988	8.118	10.79	9.611
Kidney (both) (g)	2.123	1.621	1.721	1.963
Adrenal (both) (mg)	90.50	97.00	98.50	79.60

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : females

group 4 : 200 mg/kg week 5

	Animal no			
	62	63	64	65
Thymus (mg)	455.2	427.3	575.2	587.4
Ovary (both) (mg)	218.4	152.5	171.7	199.2
Spleen (g)	0.563	0.446	0.572	0.583

Organ weights (individuals) : females

group 5 : 1000 mg/kg week 5

	Animal no				
	71	72	73	74	75
Body (g)	218.9	195.0	203.7	224.3	220.0
Brain (g)	2.053	1.978	1.981	2.018	2.055
Heart (g)	0.904	0.823	0.838	0.884	0.832
Liver (g)	9.299	9.919	9.510	9.648	9.849
Kidney (both) (g)	1.821	1.800	1.631	1.662	1.855
Adrenal (both) (mg)	79.30	103.3	82.20	91.00	71.10
Thymus (mg)	553.0	562.5	377.6	634.1	533.6
Ovary (both) (mg)	195.7	203.2	129.2	193.0	201.3

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

397

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : females

group 5 : 1000 mg/kg week 5

	71	72	73	74	75	Animal no
Spleen (g)	0.547	0.537	0.458	0.446	0.491	

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.11.2. Organ to body weight ratios (individuals):
1. sacrifice

Organ to body weight ratios (individuals) : males

group 1 : 0 mg/kg week 5

	Animal no				
	1	2	3	4	5
Brain (o/oo)	6.471	7.040	6.358	6.868	6.680
Heart (o/oo)	3.460	3.433	3.509	3.538	3.146
Liver (o/oo)	49.67	45.72	44.45	45.46	42.11
Kidney (both) (o/oo)	7.150	7.736	7.335	7.860	7.414
Adrenal (both) (o/oo)	0.238	0.216	0.248	0.235	0.212
Thymus (o/oo)	2.449	2.237	2.841	2.561	1.479
Testis (both) (o/oo)	9.755	11.88	10.79	10.35	11.43
Spleen (o/oo)	1.790	1.963	1.797	2.273	1.995
Epididymis (o/oo)	3.161	3.685	3.660	3.412	3.536

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : males

group 2 : 10 mg/kg week 5

	Animal no				
	11	12	13	14	15
Brain (o/oo)	7.060	5.876	6.949	7.359	6.978
Heart (o/oo)	3.496	3.142	3.971	3.690	3.384
Liver (o/oo)	45.33	47.06	47.32	49.86	52.90
Kidney (both) (o/oo)	8.762	7.209	7.455	8.809	7.087
Adrenal (both) (o/oo)	0.289	0.227	0.265	0.227	0.302
Thymus (o/oo)	2.271	2.061	2.386	2.091	2.403
Testis (both) (o/oo)	10.49	9.561	8.760	11.51	11.42
Spleen (o/oo)	2.246	2.390	2.107	2.101	1.950
Epididymis (o/oo)	3.439	3.521	2.981	3.681	3.633

Organ to body weight ratios (individuals) : males

group 3 : 50 mg/kg week 5

	Animal no				
	16	17	18	19	20
Brain (o/oo)	6.654	6.124	6.259	6.856	5.739
Heart (o/oo)	3.668	3.449	3.769	3.439	3.316

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

400

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : males

group 3 : 50 mg/kg week 5

	Animal no				
	16	17	18	19	20
Liver (o/oo)	52.97	47.86	50.84	55.25	47.31
Kidney (both) (o/oo)	8.802	7.599	7.779	7.690	7.058
Adrenal (both) (o/oo)	0.200	0.207	0.246	0.220	0.211
Thymus (o/oo)	3.050	2.680	2.210	1.726	1.970
Testis (both) (o/oo)	10.34	9.252	9.862	11.36	9.138
Spleen (o/oo)	2.490	1.660	2.300	2.121	1.507
Epididymis (o/oo)	3.605	3.289	3.180	3.484	3.519

Organ to body weight ratios (individuals) : males

group 4 : 200 mg/kg week 5

	Animal no			
	21	22	23	24
Brain (o/oo)	6.819	6.083	7.634	6.005
Heart (o/oo)	3.647	3.332	3.466	3.459
Liver (o/oo)	44.60	45.21	39.54	46.56
Kidney (both) (o/oo)	7.567	7.120	7.363	7.687

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : males

group 4 : 200 mg/kg week 5

	Animal no			
	21	22	23	24
Adrenal (both) (o/oo)	0.206	0.223	0.254	0.205
Thymus (o/oo)	2.964	2.230	2.627	2.395
Testis (both) (o/oo)	10.71	10.45	12.26	10.17
Spleen (o/oo)	1.823	1.765	2.242	2.051
Epididymis (o/oo)	3.519	3.649	3.614	3.493

Organ to body weight ratios (individuals) : males

group 5 : 1000 mg/kg week 5

	Animal no				
	31	32	33	34	35
Brain (o/oo)	6.794	6.840	7.550	6.825	6.435
Heart (o/oo)	3.579	4.040	3.942	3.518	3.818
Liver (o/oo)	52.15	48.61	44.62	45.09	42.56
Kidney (both) (o/oo)	7.831	7.843	7.819	7.503	6.388
Adrenal (both) (o/oo)	0.279	0.183	0.302	0.290	0.199
Thymus (o/oo)	1.603	2.266	2.540	1.571	1.911

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

402

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : males

group 5 : 1000 mg/kg week 5

	Animal no				
	31	32	33	34	35
Testis (both) (o/oo)	11.70	12.49	12.37	11.54	10.77
Spleen (o/oo)	2.190	1.953	1.909	1.738	2.107
Epididymis (o/oo)	3.388	3.648	3.982	3.888	3.533

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

403

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : females

group 1 : 0 mg/kg

week 5

	Animal no				
	41	42	43	44	45
Brain (o/oo)	10.19	9.445	9.795	10.14	9.673
Heart (o/oo)	3.698	4.278	4.062	4.146	4.125
Liver (o/oo)	42.96	47.90	47.22	42.05	42.28
Kidney (both) (o/oo)	7.776	8.347	10.20	8.728	8.327
Adrenal (both) (o/oo)	0.452	0.474	0.659	0.416	0.461
Thymus (o/oo)	2.894	2.067	3.384	2.282	2.333
Ovary (both) (o/oo)	0.671	0.875	0.737	0.999	0.785
Spleen (o/oo)	2.033	2.053	2.022	2.086	2.568

Organ to body weight ratios (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no				
	51	52	53	54	55
Brain (o/oo)	9.272	9.835	9.063	9.285	9.800
Heart (o/oo)	4.233	3.990	4.046	3.927	4.004
Liver (o/oo)	42.44	44.62	47.88	47.18	47.12

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

404

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : females

group 2 : 10 mg/kg week 5

	Animal no				
	51	52	53	54	55
Kidney (both) (o/oo)	8.512	7.935	8.613	8.599	9.083
Adrenal (both) (o/oo)	0.402	0.385	0.436	0.421	0.366
Thymus (o/oo)	1.770	2.120	1.790	1.952	3.407
Ovary (both) (o/oo)	0.957	0.811	0.695	0.780	0.842
Spleen (o/oo)	2.101	2.590	1.913	2.775	2.435

Organ to body weight ratios (individuals) : females

group 3 : 50 mg/kg week 5

	Animal no				
	56	57	58	59	60
Brain (o/oo)	10.00	9.426	9.174	9.782	10.82
Heart (o/oo)	4.199	4.028	3.857	3.870	3.908
Liver (o/oo)	48.92	46.41	40.70	40.59	42.39
Kidney (both) (o/oo)	9.774	9.559	7.359	9.418	9.442
Adrenal (both) (o/oo)	0.528	0.441	0.356	0.402	0.439
Thymus (o/oo)	2.369	2.929	2.128	2.439	2.242

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

405

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	56	57	58	59	60
Ovary (both) (o/oo)	0.607	0.836	0.888	0.899	0.874
Spleen (o/oo)	2.514	2.309	2.106	2.413	2.711

Organ to body weight ratios (individuals) : females

group 4 : 200 mg/kg

week 5

	Animal no			
	62	63	64	65
Brain (o/oo)	9.782	10.33	8.541	10.07
Heart (o/oo)	4.136	3.649	4.131	3.923
Liver (o/oo)	43.82	42.12	44.60	46.14
Kidney (both) (o/oo)	10.35	8.411	7.113	9.423
Adrenal (both) (o/oo)	0.441	0.503	0.407	0.382
Thymus (o/oo)	2.219	2.217	2.378	2.820
Ovary (both) (o/oo)	1.065	0.791	0.710	0.956
Spleen (o/oo)	2.746	2.314	2.366	2.798

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

406

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : females

group 5 : 1000 mg/kg

week 5

	Animal no				
	71	72	73	74	75
Brain (o/oo)	9.378	10.14	9.724	8.999	9.342
Heart (o/oo)	4.129	4.220	4.115	3.941	3.781
Liver (o/oo)	42.48	50.87	46.69	43.03	44.78
Kidney (both) (o/oo)	8.321	9.231	8.008	7.410	8.432
Adrenal (both) (o/oo)	0.362	0.530	0.404	0.406	0.323
Thymus (o/oo)	2.526	2.885	1.854	2.828	2.426
Ovary (both) (o/oo)	0.894	1.042	0.634	0.861	0.915
Spleen (o/oo)	2.499	2.751	2.246	1.989	2.231

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.11.3. Organ weights (individuals): 2. sacrifice (recovery)

Organ weights (individuals) : males

group 1 : 0 mg/kg

week 9

	Animal no				
	6	7	8	9	10
Body (g)	333.2	384.4	381.7	361.8	341.5
Brain (g)	2.080	2.428	2.131	2.231	2.255
Heart (g)	1.272	1.401	1.183	1.539	1.165
Liver (g)	13.62	16.45	16.07	16.61	14.35
Kidney (both) (g)	2.591	3.025	2.501	2.782	2.847
Adrenal (both) (mg)	71.60	89.50	86.10	78.60	93.30
Thymus (mg)	450.3	933.6	553.2	760.9	531.0
Testis (both) (g)	3.574	4.603	3.669	3.341	3.697
Spleen (g)	0.638	0.661	0.728	0.709	0.567
Epididymis (g)	1.393	1.711	1.535	1.475	1.317

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

408

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : males

group 4 : 200 mg/kg

week 9

	Animal no				
	26	27	28	29	30
Body (g)	375.9	416.7	365.3	354.3	361.0
Brain (g)	2.274	2.355	2.285	2.267	2.209
Heart (g)	1.414	1.515	1.227	1.203	1.135
Liver (g)	19.57	17.84	14.39	16.86	16.87
Kidney (both) (g)	3.386	2.795	2.645	2.920	2.723
Adrenal (both) (mg)	72.40	83.80	83.20	79.10	103.1
Thymus (mg)	588.8	478.3	692.9	552.4	519.1
Testis (both) (g)	3.998	4.006	3.840	4.157	4.004
Spleen (g)	0.800	0.743	0.627	0.654	0.581
Epididymis (g)	1.472	1.641	1.736	1.505	1.574

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

409

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : males

group 5 : 1000 mg/kg

week 9

	Animal no				
	36	37	38	39	40
Body (g)	385.8	362.8	393.6	362.2	430.5
Brain (g)	2.341	2.163	2.142	2.354	2.183
Heart (g)	1.244	1.345	1.268	1.382	1.346
Liver (g)	16.42	13.51	15.78	17.07	17.34
Kidney (both) (g)	2.856	2.471	2.685	2.857	2.873
Adrenal (both) (mg)	68.90	83.20	75.60	96.40	84.00
Thymus (mg)	599.6	621.2	450.9	646.5	617.2
Testis (both) (g)	3.796	4.081	3.669	4.279	4.178
Spleen (g)	0.618	0.607	0.687	0.575	0.799
Epididymis (g)	1.519	1.722	1.500	1.553	1.549

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

410

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : females

group 1 : 0 mg/kg

week 9

	Animal no				
	46	47	48	49	50
Body (g)	272.2	232.7	216.0	251.0	217.2
Brain (g)	2.165	2.214	2.202	2.269	1.992
Heart (g)	1.054	0.919	0.835	1.050	1.003
Liver (g)	11.53	9.311	9.267	10.97	8.912
Kidney (both) (g)	2.082	2.199	1.955	2.318	1.615
Adrenal (both) (mg)	103.6	118.9	86.80	99.30	105.3
Thymus (mg)	505.0	462.1	461.3	475.7	378.2
Ovary (both) (mg)	159.2	269.3	126.5	205.1	205.4
Spleen (g)	0.624	0.358	0.466	0.532	0.451

Organ weights (individuals) : females

group 4 : 200 mg/kg

week 9

	Animal no			
	66	67	69	70
Body (g)	271.1	263.3	236.9	221.2
Brain (g)	2.186	2.156	2.116	2.196

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

411

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ weights (individuals) : females

group 4 : 200 mg/kg

week 9

	Animal no			
	66	67	69	70
Heart (g)	0.964	1.275	1.027	0.868
Liver (g)	13.18	10.03	10.31	8.292
Kidney (both) (g)	2.227	1.673	1.996	1.787
Adrenal (both) (mg)	122.2	111.0	104.1	97.70
Thymus (mg)	336.6	364.8	549.2	553.8
Ovary (both) (mg)	181.6	159.6	167.9	200.4
Spleen (g)	0.639	0.526	0.594	0.578

Organ weights (individuals) : females

group 5 : 1000 mg/kg

week 9

	Animal no				
	76	77	78	79	80
Body (g)	228.7	270.3	227.2	237.2	236.6
Brain (g)	2.131	2.243	2.062	2.037	1.996
Heart (g)	0.907	0.992	0.776	0.936	1.095
Liver (g)	9.509	10.86	7.653	9.620	9.284

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

9.11.4. Organ to body weight ratios (individuals):
2. sacrifice (recovery)

Organ to body weight ratios (individuals) : males

group 1 : 0 mg/kg week 9

	Animal no				
	6	7	8	9	10
Brain (o/oo)	6.242	6.316	5.583	6.165	6.604
Heart (o/oo)	3.817	3.644	3.099	4.252	3.412
Liver (o/oo)	40.88	42.81	42.11	45.91	42.01
Kidney (both) (o/oo)	7.776	7.871	6.550	7.688	8.336
Adrenal (both) (o/oo)	0.215	0.233	0.226	0.217	0.273
Thymus (o/oo)	1.351	2.429	1.449	2.103	1.555
Testis (both) (o/oo)	10.73	11.98	9.613	9.233	10.82
Spleen (o/oo)	1.915	1.719	1.908	1.959	1.660
Epididymis (o/oo)	4.180	4.451	4.021	4.076	3.857

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

414

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : males

group 4 : 200 mg/kg week 9

	Animal no				
	26	27	28	29	30
Brain (o/oo)	6.049	5.651	6.256	6.398	6.117
Heart (o/oo)	3.762	3.636	3.360	3.395	3.144
Liver (o/oo)	52.07	42.82	39.41	47.60	46.74
Kidney (both) (o/oo)	9.007	6.707	7.242	8.241	7.541
Adrenal (both) (o/oo)	0.193	0.201	0.228	0.223	0.286
Thymus (o/oo)	1.566	1.148	1.897	1.559	1.438
Testis (both) (o/oo)	10.63	9.613	10.51	11.73	11.09
Spleen (o/oo)	2.129	1.784	1.716	1.845	1.610
Epididymis (o/oo)	3.916	3.937	4.752	4.247	4.359

Organ to body weight ratios (individuals) : males

group 5 : 1000 mg/kg week 9

	Animal no				
	36	37	38	39	40
Brain (o/oo)	6.068	5.961	5.443	6.500	5.072
Heart (o/oo)	3.225	3.706	3.221	3.814	3.126

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

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : males

group 5 : 1000 mg/kg week 9

	Animal no				
	36	37	38	39	40
Liver (o/oo)	42.55	37.24	40.10	47.13	40.29
Kidney (both) (o/oo)	7.404	6.809	6.821	7.889	6.674
Adrenal (both) (o/oo)	0.179	0.229	0.192	0.266	0.195
Thymus (o/oo)	1.554	1.712	1.146	1.785	1.434
Testis (both) (o/oo)	9.840	11.25	9.323	11.81	9.706
Spleen (o/oo)	1.601	1.672	1.745	1.588	1.856
Epididymis (o/oo)	3.938	4.746	3.810	4.287	3.599

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

416

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : females

group 1 : 0 mg/kg week 9

	Animal no				
	46	47	48	49	50
Brain (o/oo)	7.955	9.513	10.19	9.039	9.172
Heart (o/oo)	3.873	3.949	3.867	4.185	4.618
Liver (o/oo)	42.37	40.01	42.90	43.69	41.04
Kidney (both) (o/oo)	7.650	9.446	9.052	9.233	7.435
Adrenal (both) (o/oo)	0.381	0.511	0.402	0.396	0.485
Thymus (o/oo)	1.855	1.985	2.136	1.895	1.741
Ovary (both) (o/oo)	0.585	1.157	0.586	0.817	0.946
Spleen (o/oo)	2.293	1.538	2.155	2.121	2.079

Organ to body weight ratios (individuals) : females

group 4 : 200 mg/kg week 9

	Animal no			
	66	67	69	70
Brain (o/oo)	8.061	8.186	8.933	9.924
Heart (o/oo)	3.554	4.843	4.336	3.925
Liver (o/oo)	48.61	38.09	43.53	37.48

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

417

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : females

group 4 : 200 mg/kg

week 9

	Animal no			
	66	67	69	70
Kidney (both) (o/oo)	8.213	6.351	8.424	8.078
Adrenal (both) (o/oo)	0.451	0.422	0.439	0.442
Thymus (o/oo)	1.242	1.385	2.318	2.503
Ovary (both) (o/oo)	0.670	0.606	0.709	0.906
Spleen (o/oo)	2.355	1.997	2.508	2.614

Organ to body weight ratios (individuals) : females

group 5 : 1000 mg/kg

week 9

	Animal no				
	76	77	78	79	80
Brain (o/oo)	9.319	8.298	9.079	8.588	8.436
Heart (o/oo)	3.969	3.671	3.414	3.947	4.626
Liver (o/oo)	41.59	40.20	33.69	40.56	39.23
Kidney (both) (o/oo)	8.355	8.487	6.439	7.899	7.574
Adrenal (both) (o/oo)	0.449	0.371	0.363	0.519	0.486
Thymus (o/oo)	1.860	1.852	1.239	1.622	1.879

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

418

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

Organ to body weight ratios (individuals) : females

group 5 : 1000 mg/kg week 9

	Animal no				
	76	77	78	79	80
Ovary (both) (o/oo)	0.674	0.633	0.601	0.729	0.880
Spleen (o/oo)	2.192	2.293	2.084	2.317	2.028

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9.12. Macroscopical and microscopical findings (individuals):

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EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

- M = MALE ANIMAL
- F = FEMALE ANIMAL
- KO = TERMINAL SACRIFICE GROUP
- R1...R9 = RECOVERY / POST-TREATMENT GROUPS 1...9
- +1 = FOUND DEAD

CODES AND SYMBOLS USED AT FINDING LEVEL:

- GRADE 1 = MINIMAL / VERY FEW / VERY SMALL
- GRADE 2 = SLIGHT / FEW / SMALL
- GRADE 3 = MODERATE / MODERATE NUMBER / MODERATE SIZE
- GRADE 4 = MARKED / MANY / LARGE
- P = FINDING PRESENT, SEVERITY NOT SCORED

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ANIMAL HEADING DATA
DOSE GROUP : 1, Control

ANIMAL NUMBER	SEX M/F	DEFINED STATE	AND FINAL NECROPSY	TEST DAYS	FIRST DAY	AND LAST DAY UNDER TEST	DATE OF NECROPSY
1	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
2	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
3	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
4	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
5	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
6	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
7	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
8	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
9	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
10	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
41	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
42	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
43	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
44	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
45	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
46	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
47	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
48	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
49	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
50	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 1, Control MALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 1

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:
-FOAM CELLS, GRADE 2
KIDNEYS:
-CHRONIC INFLAMMATION, UNILATERAL, GRADE 2
SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
LARGE INTESTINE PEYER'S PATCHES:
TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION
URINARY BLADDER:
-PRECIPITATE, GRADE 3
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 2

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

CONT./FF. ANIMAL NO. : 2

* MICROSCOPIC FINDINGS

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

KIDNEYS:

-TUBULAR ATROPHY, UNILATERAL, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 3

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2

KIDNEYS:

-BASOPHILIC TUBULAR PROLIFERATION, UNILATERAL, GRADE 2

-TUBULAR CAST, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 4

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2
HEART:
-INFLAMMATORY CELL INFILTRATION, GRADE 2
THYMUS:
-PHAGOCYTTIC CELLS, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 5

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 3
HEART:
-INFLAMMATORY CELL INFILTRATION, GRADE 2
URINARY BLADDER:
-PRECIPITATE, GRADE 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

CONT./FF. ANIMAL NO. : 5

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1 * ANIMAL NO. : 6
DAYS ON TEST : 58

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
ADRENAL GLANDS:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: R1 * ANIMAL NO. : 7
DAYS ON TEST : 58

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

CONT./FF. ANIMAL NO. : 7
.....

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 8
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 9
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

CONT./FF. ANIMAL NO. : 9

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1

DAYS ON TEST : 58 * ANIMAL NO. : 10

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 41

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-TUBULAR ATROPHY, UNILATERAL, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 42

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 43

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 1
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
-TUBULAR ATROPHY, GRADE 2
LARGE INTESTINE PEYER'S PATCHES:
TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 44

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 1
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

CONT./FF. ANIMAL NO. : 44

LARGE INTESTINE PEYER'S PATCHES:
TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 45

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-TUBULAR ATROPHY, UNILATERAL, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 46

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

CONT./FF. ANIMAL NO. : 46

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1

DAYS ON TEST : 58 * ANIMAL NO. : 47

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1

DAYS ON TEST : 58 * ANIMAL NO. : 48

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

CONT./FF. ANIMAL NO. : 48

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 49

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 50

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

CONT./FF. ANIMAL NO. : 50

* MICROSCOPIC FINDINGS

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TEST SYSTEM : RAT, 28 DAYS, ORAL
SPONSOR : Crop Protection Sector

PATHOL. NO.: 10035 PSC
DATE : 04-JUN-97
PATHDATA SYSTEM V3.6B

ANIMAL HEADING DATA

DOSE GROUP : 2, 10 mg/kg

ANIMAL NUMBER	SEX M/F	DEFINED STATE	AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY
11	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
12	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
13	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
14	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
15	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
51	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
52	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
53	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
54	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
55	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 2, 10 mg/kg MALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 11

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2
SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
ADRENAL GLANDS:
-CORTICAL FATTY CHANGE, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 12

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

HEART:
-INFLAMMATION WITH FIBROSIS, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 2, 10 mg/kg MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 30 * ANIMAL NO. : 13

* NECROPSY FINDINGS

TESTES:

01: SMALL LE B.

EPIDIDYMIDES:

01: SMALL LE C.

BODY SURFACES:

01: ABDOMINAL WALL MASS <1 ONE LE A.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

LUNG:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PLEURA:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

-CHRONIC INFLAMMATION, UNILATERAL, GRADE 2

RENAL PELVES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

EPICARDIUM/PERICARDIUM:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SMALL INTESTINE:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SMALL INTESTINE PEYER'S PATCHES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 2, 10 mg/kg MALE

CONT./FF. ANIMAL NO. : 13

THYMUS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LARGE INTESTINE:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LARGE INTESTINE PEYER'S PATCHES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

TESTES:

-TUBULAR ATROPHY, UNILATERAL, GRADE 3

THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.

EPIDIDYMIDES:

-CELLULAR DEBRIS, UNILATERAL, GRADE 3

-FIBROSIS, UNILATERAL, GRADE 3

THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.

PROSTATE GLAND:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

URINARY BLADDER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ADRENAL MEDULLAS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

THYROID GLAND:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PARATHYROID GLAND:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

TRACHEA:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

MESENTERIC LYMPH NODE:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

AXILLARY LYMPH NODES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PITUITARY GLAND:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

BRAIN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 2, 10 mg/kg MALE

CONT./FF. ANIMAL NO. : 13

PERIPHER. NERVE(S):

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SPINAL CORD:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

BONE MARROW:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

FEMUR:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

JOINT:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

BODY SURFACES:

ORGAN NOT EXAMINED

FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER: SKIN/SUBCUTIS.

SKIN/SUBCUTIS:

-MALFORMATION

HERNIA

THIS FINDING CORRESPONDS WITH NECROPSY OBSERVATION NO: 01
IN THE BODY SURFACES.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 14

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 2, 10 mg/kg MALE

CONT./FF ANIMAL NO. : 14

* MICROSCOPIC FINDINGS

LIVER:
-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2
SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
THYMUS:
-PHAGOCYtic CELLS, GRADE 2
ADRENAL GLANDS:
-CORTICAL FATTY CHANGE, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 15

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 2, 10 mg/kg FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 51

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-FOAM CELLS, GRADE 2

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2

-BASOPHILIC TUBULAR PROLIFERATION, UNILATERAL, GRADE 1

-TUBULAR CAST, UNILATERAL, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 52

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2

THYROID GLAND:

-DEVELOPMENTAL CYST

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 2, 10 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 52

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 53

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 1
-TUBULAR ATROPHY, UNILATERAL, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 54

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 2, 10 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 54

* MICROSCOPIC FINDINGS

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 2

THYMUS:

-PHAGOCYtic CELLS, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO

DAYS ON TEST

30

* ANIMAL NO. : 55

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2

SPLEEN:

-HEMOSIDEROSIS, GRADE 2

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2

-TUBULAR ATROPHY, UNILATERAL, GRADE 1

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 2

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TEST ARTICLE : CGA 108906 tech.
TEST SYSTEM : RAT, 28 DAYS, ORAL
SPONSOR : Crop Protection Sector

PATHOL. NO.: 10035 PSC
DATE : 04-JUN-97
PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 2, 10 mg/kg

FEMALE

CONT./FF. ANIMAL NO. : 55

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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INDIVIDUAL ANIMAL DATA

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

ANIMAL HEADING DATA

DOSE GROUP : 3, 50 mg/kg

ANIMAL NUMBER	SEX M/F	DEFINED STATE	AND FINAL OF NECROPSY	TEST DAYS	FIRST DAY	AND LAST DAY UNDER TEST	DATE OF NECROPSY
16	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
17	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
18	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
19	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
20	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
56	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
57	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
58	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
59	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
60	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 3, 50 mg/kg MALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 16

* NECROPSY FINDINGS

ADRENAL GLANDS:
01: SMALL RI A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

LIVER:
-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2
SPLEEN:
-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2
ADRENAL GLANDS:
ONLY ONE OF PAIRED ORGANS EXAMINED/PRESENT
MACR. CHANGE CONSIDERED BY PATHOLOGIST
ADRENAL MEDULLAS:
ONLY ONE OF PAIRED ORGANS EXAMINED/PRESENT
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 17

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEST ARTICLE : CGA 108906 tech.

PATHOL. NO.: 10035 PSC

TEST SYSTEM : RAT, 28 DAYS, ORAL

DATE : 04-JUN-97

SPONSOR : Crop Protection Sector

PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 3, 50 mg/kg

MALE

CONT./FF. ANIMAL NO. : 17

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 18

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-BASOPHILIC TUBULAR PROLIFERATION, UNILATERAL, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 3, 50 mg/kg MALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 19

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

KIDNEYS:

-CHRONIC INFLAMMATION, UNILATERAL, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 20

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

HEART:

-INFLAMMATORY CELL INFILTRATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 3, 50 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 30 * ANIMAL NO. : 56

* NECROPSY FINDINGS

DIAPHRAGM:
01: PERFORATION A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-BASOPHILIC TUBULAR PROLIFERATION, UNILATERAL, GRADE 1
DIAPHRAGM:
NOTHING ABNORMAL DISCOVERED CORRESPONDING WITH THE NECROPSY
OBSERVATION NO.01.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 30 * ANIMAL NO. : 57

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
-TUBULAR ATROPHY, UNILATERAL, GRADE 2

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 3, 50 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 57

SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
PITUITARY GLAND:
-DEVELOPMENTAL CYST
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 58

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
LIVER:
-NECROSIS, GRADE 2
SPLEEN:
-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-TUBULAR ATROPHY, UNILATERAL, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 3, 50 mg/kg FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 59

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 3

-TUBULAR ATROPHY, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 60

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR ATROPHY, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

ANIMAL HEADING DATA

DOSE GROUP : 4, 200 mg/kg

ANIMAL NUMBER	SEX M/F	DEFINED STATE	AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	AND LAST DAY UNDER TEST	DATE OF NECROPSY
21	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
22	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
23	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
24	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
25	M	KO	+1	24	10-DEC-96	02-JAN-97	02-JAN-97
26	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
27	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
28	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
29	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
30	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
61	F	KO	+1	28	10-DEC-96	06-JAN-97	06-JAN-97
62	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
63	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
64	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
65	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
66	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
67	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
68	F	R1	+1	28	10-DEC-96	06-JAN-97	06-JAN-97
69	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
70	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97

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TEST ARTICLE : CGA 108906 tech.	PATHOL. NO. : 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL	DATE : 04-JUN-97
SPONSOR : Crop Protection Sector	PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 4, 200 mg/kg MALE

* STATE AT NECROPSY: KO	
DAYS ON TEST : 30	* ANIMAL NO. : 21

.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SMALL INTESTINE PEYER'S PATCHES:
 -MINERALIZATION, GRADE 2
 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO	
DAYS ON TEST : 30	* ANIMAL NO. : 22

.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
 -CORTICAL FATTY CHANGE, UNILATERAL, GRADE 2
 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 4, 200 mg/kg MALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 23

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

LUNG:

-GRANULOMA, GRADE 2

HEART:

-INFLAMMATORY CELL INFILTRATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 24

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 2

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 4, 200 mg/kg MALE

CONT./FF ANIMAL NO. : 24

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO/+1
DAYS ON TEST : 24 * ANIMAL NO. : 25

* NECROPSY FINDINGS

THORACIC CAVITY:
01: CONTENTS FLUID
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

LIVER:

- FATTY CHANGE, GRADE 2
- CONGESTION, GRADE 3

SPLEEN:

- CONGESTION, GRADE 3

LUNG:

- CONGESTION, GRADE 3

PLEURA:

- FIBRINOUS INFLAMMATION, GRADE 2
THIS FINDING CORRESPONDS WITH NECROPSY OBSERVATION NO: 01
IN THE THORACIC CAVITY.

KIDNEYS:

- CONGESTION, GRADE 3

EPICARDIUM/PERICARDIUM:

- FIBRINOUS INFLAMMATION, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

- MINERALIZATION, GRADE 2

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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 4, 200 mg/kg MALE

CONT./FF. ANIMAL NO. : 25

THORACIC CAVITY:

FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER: PLEURA.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 26

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 27

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

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TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 4, 200 mg/kg MALE

CONT./FF ANIMAL NO. : 27

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 28

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 29

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

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TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 4, 200 mg/kg MALE

CONT./FF. ANIMAL NO. : 29

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1

DAYS ON TEST : 58 * ANIMAL NO. : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 4, 200 mg/kg FEMALE

* STATE AT NECROPSY: KO/+1
DAYS ON TEST : 28 * ANIMAL NO. : 61

* NECROPSY FINDINGS

THORACIC CAVITY:

01: CONTENTS HAEMORRHAGIC
FIBRINOUS ADHESION A.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

SPLEEN:

-ATROPHY OF WHITE PULP, GRADE 2

LUNG:

-CONGESTION, GRADE 3

PLEURA:

-FIBRINOUS INFLAMMATION, GRADE 3

THIS FINDING CORRESPONDS WITH NECROPSY OBSERVATION NO: 01
IN THE THORACIC CAVITY.

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2

-BASOPHILIC TUBULAR PROLIFERATION, UNILATERAL, GRADE 1

-CONGESTION, GRADE 3

THYMUS:

-ATROPHY, GRADE 2

THORACIC CAVITY:

FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER: PLEURA.

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 4, 200 mg/kg FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 62

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-TUBULAR ATROPHY, UNILATERAL, GRADE 1
SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 63

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 1
PLEURA:
-FIBROUS THICKENING, GRADE 2

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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 4, 200 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 63

KIDNEYS:

- CORTICOMEDULLARY MINERALIZATION, GRADE 2
- EPICARDIUM/PERICARDIUM:
 - INFLAMMATION WITH FIBROSIS, GRADE 2
- ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 64

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

- LYMPHOHISTIOCYTIC INFILTRATION, GRADE 1

KIDNEYS:

- BASOPHILIC TUBULAR PROLIFERATION, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

- MINERALIZATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 4, 200 mg/kg FEMALE

* STATE AT NECROPSY: KO * ANIMAL NO. : 65
DAYS ON TEST : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1 * ANIMAL NO. : 66
DAYS ON TEST : 58

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 4, 200 mg/kg FEMALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 67

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1/+1
DAYS ON TEST : 28 * ANIMAL NO. : 68

* NECROPSY FINDINGS

LUNG:

01: FIBRINOUS ADHESION A.

THORACIC CAVITY:

01: CONTENTS FLUID

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

LIVER:

-FATTY CHANGE, GRADE 2

-CONGESTION, GRADE 3

SPLEEN:

-ATROPHY OF WHITE PULP, GRADE 2

-CONGESTION, GRADE 2

LUNG:

FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER: PLEURA.

-CONGESTION, GRADE 4

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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 4, 200 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 68

PLEURA:

-FIBRINOUS INFLAMMATION, GRADE 4
with marked foreign bodies
THIS FINDING CORRESPONDS WITH NECROPSY OBSERVATION NO: 01
IN THE LUNG.

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-TUBULAR ATROPHY, UNILATERAL, GRADE 1
-CONGESTION, GRADE 3

EPICARDIUM/PERICARDIUM:

-FIBRINOUS INFLAMMATION, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 3

LARGE INTESTINE PEYER'S PATCHES:

TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION

ADRENAL GLANDS:

-CONGESTION, GRADE 3
-CORTICAL FATTY CHANGE, GRADE 2

THORACIC CAVITY:

FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER: PLEURA.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1

DAYS ON TEST : 58

* ANIMAL NO. : 69

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 4, 200 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 69

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1

DAYS ON TEST : 58 * ANIMAL NO. : 70

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

ANIMAL HEADING DATA

DOSE GROUP : 5, 1000 mg/kg

ANIMAL NUMBER	SEX M/F	DEFINED STATE	AND FINAL NECROPSY	TEST DAYS	FIRST DAY	AND LAST UNDER TEST	DATE OF NECROPSY
31	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
32	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
33	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
34	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
35	M	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
36	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
37	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
38	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
39	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
40	M	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
71	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
72	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
73	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
74	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
75	F	KO	KO	30	10-DEC-96	08-JAN-97	08-JAN-97
76	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
77	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
78	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
79	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97
80	F	R1	R1	58	10-DEC-96	05-FEB-97	05-FEB-97

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 5, 1000 mg/kg MALE

* STATE AT NECROPSY: KO * ANIMAL NO. : 31
DAYS ON TEST : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-CHRONIC REACTIVE HYPERPLASIA, GRADE 2
KIDNEYS:
-TUBULAR ATROPHY, UNILATERAL, GRADE 2
HEART:
-INFLAMMATORY CELL INFILTRATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO * ANIMAL NO. : 32
DAYS ON TEST : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CHRONIC TUBULAR LESION, UNILATERAL, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 5, 1000 mg/kg MALE

* STATE AT NECROPSY: KO * ANIMAL NO. : 33
DAYS ON TEST : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2
URINARY BLADDER:
-INFLAMMATORY EDEMA, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO * ANIMAL NO. : 34
DAYS ON TEST : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2
HEART:
-INFLAMMATORY CELL INFILTRATION, GRADE 2
TESTES:
-TUBULAR ATROPHY, UNILATERAL, GRADE 2
-SPERMATIC GIANT CELLS, UNILATERAL, GRADE 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 5, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 34

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 35

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 2

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 2

SMALL INTESTINE PEYER'S PATCHES:

-MINERALIZATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 5, 1000 mg/kg MALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 36

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 37

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 5, 1000 mg/kg MALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 38

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 39

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 472
P963128

TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 5, 1000 mg/kg MALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 40

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 474
P963128

TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 5, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 72

SMALL INTESTINE PEYER'S PATCHES:
-MINERALIZATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 73

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 74

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 475
P963128

TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 5, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 74

* MICROSCOPIC FINDINGS

LIVER:

-LYMPHOHISTIOCYTIC INFILTRATION, GRADE 1

SPLEEN:

-EXTRAMEDULLARY HEMATOPOIESIS, GRADE 1
-CONGESTION, GRADE 3

LUNG:

-FOAM CELLS, GRADE 2

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-TUBULAR ATROPHY, GRADE 2
-TUBULAR CAST, UNILATERAL, GRADE 1

THYMUS:

-PHAGOCYTIC CELLS, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 75

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 2
-BASOPHILIC TUBULAR PROLIFERATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT

PAGE : 477

INDIVIDUAL ANIMAL DATA

P963128

TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 5, 1000 mg/kg FEMALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 78

* NECROPSY FINDINGS

THYMUS:
O1: REDDISH A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

THYMUS:
-HEMORRHAGE, GRADE 1
THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: O1.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 79

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 478
P963128

TEST ARTICLE : CGA 108906 tech. PATHOL. NO.: 10035 PSC
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 04-JUN-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 5, 1000 mg/kg FEMALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 80

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

END OF REPORT SECTION
LAST PAGE OF REPORT

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

10. APPENDIX B: ANALYTICAL RESULTS

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**Study Title:**

DETERMINATION OF CONCENTRATION OF CGA 108906 TECH.
(INTERMEDIATE OF CGA 48988) IN DISTILLED WATER WITH
0.5% CMC AND 0.1% TWEEN 80

**ANALYTICAL REPORT TO NOVARTIS CROP PROTECTION STUDY NO. 963128:
28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)**

Authors:

Mr. 5.1.2.6 W
Mrs. [REDACTED]

Completion Date:

April 18, 1997

Performing Laboratory:

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

Study Project No.:

NOVARTIS CROP PROTECTION STUDY NO. 963128
RCC PROJECT 641531

Sponsor:

Novartis Crop Protection AG
CH-4002 Basle

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE

NOVARTIS CROP PROTECTION STUDY NO.: 963128
RCC PROJECT NO.: 641531
TEST ARTICLE: CGA 108906 Tech. (Intermediate of CGA 48988)
PRINCIPAL INVESTIGATOR ANALYTICS: Mr. 5.1.2.e Woo
TITLE: Determination of Concentration of CGA 108906 Tech. (Intermediate of CGA 48988) in Distilled Water with 0.5% CMC and 0.1% Tween 80

This study was conducted in compliance with Good Laboratory Practice Regulations and meets the requirements as listed below.

- The OECD Principles of Good Laboratory Practice, Paris/France, 1981.
- Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986.

Principal Investigator Analytics:

Mr. 5.1.2.e Woo

Date: April 28, 1997

QUALITY ASSURANCE UNIT

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

STATEMENT

NOVARTIS CROP PROTECTION STUDY NO.: 963128

RCC PROJECT NO.: 641531

TEST ARTICLE: CGA 108906 Tech. (Intermediate of CGA 48988)

PRINCIPAL INVESTIGATOR ANALYTICS: Mr. [REDACTED]

TITLE: Determination of Concentration of CGA 108906 Tech. (Intermediate of CGA 48988) in Distilled Water with 0.5% CMC and 0.1% Tween 80

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

Dates of QAU Inspections/Audits		Dates of Reports to the Principal Investigator Analytics and the Management	
January 07, 1997	Analytical work	January 09, 1997	
April 16/17, 1997	Final analytical report	April 17, 1997	

Manager, Quality Assurance Unit:

Mrs. [REDACTED]

5.1.2.e Woo

Date:

April 18, 1997

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GENERAL INFORMATION

GENERAL

Title: Determination of Concentration of CGA 108906 Tech. (Intermediate of CGA 48988) in Distilled Water with 0.5% CMC and 0.1% Tween 80

Novartis Crop Protection Study Title: 28 Days Subacute, Oral Toxicity Study in Rats (Gavage)

RCC Project No.: 641531

Novartis Crop Protection Study No.: 963128

Sponsor: Novartis Crop Protection AG
Crop Protection Division
4002 Basle / Switzerland

Study Director: Dr. **5.1.2.e Woo**
Novartis Crop Protection AG
Toxicology / Experimental Toxicology
4332 Stein / Switzerland

Test Article: CGA 108906 Tech. (Intermediate of CGA 48988)

Testing Facility: RCC UMWELTCHEMIE AG
CH-4452 Itingen / Switzerland

PROJECT STAFF

Principal Investigator Analytics: Mr. **5.1.2.e Woo**

SCHEDULE

Dates of Analyses: See Section 2.2

Completion Date: April 18, 1997 /ufa

ARCHIVING

R C C, CH-4452 Itingen

Raw data, copy of protocol, analytical report and test article reference sample for at least 10 years.

SIGNATURE PAGE

PRINCIPAL INVESTIGATOR ANALYTICS:

Mr. [Redacted]

Date: April 18, 1997

MANAGING DIRECTOR:

Mr. [Redacted]

Date: April 18, 1997

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ABSTRACT

This chemical analysis determined the concentrations of CGA 108906 Tech. (Intermediate of CGA 48988) in distilled water with 0.5% CMC and 0.1% Tween 80.

Pretest:

The mean concentrations of the homogeneity samples were found to be 93.5%, 99.6%, and 97.8% of the nominal concentrations for dose group 2 (1 mg/ml), for dose group 3 (10 mg/ml), and for dose group 4 (100 mg/ml), respectively. The individual concentrations varied in the range from -4% to +3% of the mean concentrations. Therefore, the test article was found to be homogenous.

Test:

The overall mean concentrations of the samples taken during administration were found to be 104.5%, 98.8%, 98.2%, and 98.2% of the nominal concentrations for dose group 2 (1 mg/ml), for dose group 3 (5 mg/ml), for dose group 4 (20 mg/ml) and for dose group 5 (100 mg/ml), respectively.

CGA 108906 Tech. (Intermediate of CGA 48988) was found to be stable in the vehicle at room temperature over a period of four hours.

2 MATERIALS AND METHODS

2.1 TEST ARTICLE

Company code no.: CGA 108906 Tech.
Batch number: KI-5240/3
Purity: 99%
Description: Solid
Date of receipt: October 23, 1996
Storage conditions: Room temperature
Stability: October 1999

2.2 SAMPLES

Pretest:

- Shipment no.: 01
- Prepared by sponsor on: 29-OCT-96
- Sampled by sponsor on: 29-OCT-96
- Received at RCC on: 30-OCT-96
- Date of analysis: 12/13-NOV-96

Test:

- Shipment no.:	01	02
- Prepared by sponsor on:	11-DEC-96	18-DEC-96
- Sampled by sponsor on:	11-DEC-96	18-DEC-96
- Received at RCC on:	13-DEC-96	19-DEC-96
- Date of analysis:	07-JAN-97	07-JAN-97

- Shipment no.:	03	04
- Prepared by sponsor on:	25-DEC-96	01-JAN-97
- Sampled by sponsor on:	25-DEC-96	01-JAN-97
- Received at RCC on:	03-JAN-97	03-JAN-97
- Date of analysis:	07-JAN-97	07-JAN-97

2.3 SAMPLE PREPARATION AND STORAGE

Test article/vehicle mixtures were prepared and collected by the sponsor. Afterwards, the samples were deepfrozen by the sponsor until shipment to RCC Umweltchemie AG. All samples were shipped to the analytical laboratories of RCC Umweltchemie AG, Itingen/Switzerland under deepfrozen conditions in a cool box and were kept deepfrozen until sample work-up and analysis by HPLC.

2.4 ANALYTICAL PROCEDURE

2.4.1 Standard Solutions

Stock solutions of the test substance (see Section 2.1) in acetonitrile/0.2% phosphoric acid (1+1 v/v or 2+8 v/v) with a concentration of 200 µg/ml were prepared as follows: 20-mg portions of test article were weighed into 100-ml volumetric flasks and dissolved in about 70 ml acetonitrile/0.2% phosphoric acid (1+1 v/v or 2+8 v/v) by means of an ultrasonic bath. Afterwards, the volumetric flasks were filled to volume with acetonitrile/0.2% phosphoric acid (2+8 v/v). Next, various standard solutions were prepared by respective dilution of these stock solutions with acetonitrile/0.2% phosphoric acid (2+8 v/v) to yield concentrations in the range from 5 µg/ml to 50 µg/ml. These standard solutions were used to calibrate the HPLC.

2.4.2 Analysis of Samples

The delivered samples (cf. Section 2.2) (about 2 g*, weighed to the fourth decimal place) were mixed with 5 ml of 0.2% phosphoric acid by means of an ultrasonic bath. Afterwards, the sample solutions were quantitatively transferred to 100-ml volumetric flasks with 45-ml portions of 0.2% phosphoric acid. The volumetric flasks were then filled to the mark with acetonitrile. Depending on the dose group, the latter sample solutions were further diluted with acetonitrile/0.2% phosphoric acid (2+8 v/v) to yield concentrations within the calibration range. Finally, a 20-µl aliquot was quantified by HPLC.

* In the case of group 1 (untreated samples), a 2.0-g portion was taken from the sample volume (ca. 20 ml) delivered by the sponsor

2.4.3 High Performance Liquid Chromatographic Determination

Operating Conditions

Apparatus: Merck L-6200 pump
Merck L-4200 UV-VIS-detector
Merck D-2500 integrator
Merck AS 2000A sampling unit

Column: Lichrospher 100 RP-8; 5 μ m; 125 x 4 mm (i.d.)

Temperature: Room temperature

Eluent: Acetonitrile/0.2% phosphoric acid (2+8 v/v)

Flow: 1.0 ml/min

Wavelength: 220 nm

Injection volume: 10 μ l

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2.4.4 Evaluation of Results

Injected samples were quantified by the sum of peak areas of the test article in counts with reference to the calibration curve. The latter was obtained by correlation of the sum of peak areas of the test substance with their corresponding concentrations of test substance ($\mu\text{g/ml}$), using the following equation 1:

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

where

Y = sum of peak areas of injected sample in counts
in injected sample

a = y-axis intercept

b = slope

X = $\mu\text{g/ml}$ CGA 108906 Tech. (Intermediate of CGA 48988)

The concentration of CGA 108906 Tech. (Intermediate of CGA 48988) was calculated from the following equation 2:

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

where

C = Concentration of CGA 108906 Tech. (Intermediate of CGA 48988) (mg/ml)

X = $\mu\text{g/ml}$ of injected sample calculated by equation 1

V = Final volume (100 ml)

D = Dilution factor

Q = Density of the test article/vehicle mixtures (g/ml)

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

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

3 RESULTS

This chemical analysis determined the concentrations of CGA 108906 Tech. (Intermediate of CGA 48988) in distilled water with 0.5% CMC and 0.1% Tween 80.

Pretest:

The mean concentrations of the homogeneity samples were found to be 93.5%, 99.6%, and 97.8% of the nominal concentrations for dose group 2 (1 mg/ml), for dose group 3 (10 mg/ml), and for dose group 4 (100 mg/ml), respectively. The individual concentrations varied in the range from -4% to +3% of the mean concentrations. Therefore, the test article was found to be homogenous.

Test:

The overall mean concentrations of the samples taken during administration were found to be 104.5%, 98.8%, 98.2%, and 98.2% of the nominal concentrations for dose group 2 (1 mg/ml), for dose group 3 (5 mg/ml), for dose group 4 (20 mg/ml) and for dose group 5 (100 mg/ml), respectively.

CGA 108906 Tech. (Intermediate of CGA 48988) was found to be stable in the vehicle at room temperature over a period of four hours.

An example of a calibration curve of CGA 108906 Tech. (Intermediate of CGA 48988) is listed in Table 1. Detailed results of concentration, homogeneity, and stability of test article in vehicle are presented in Tables 2 to 4. Typical chromatograms of standard solutions and test samples are shown in Figures 1 and 2.

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

Table 1: Calibration Curve

Date of Analysis: 07-JAN-1997

Standard Concentration (µg/ml) (X)	Sum of Peak Area (Counts) (Y)	
	before samples	after samples
5	41995	41508
10	81734	86007
20	160890	167635
50	414032	422188

$$Y = -731 + 8364 \cdot X \quad (R^2 = 1.000)$$

where

Y = Sum of peak areas of injected sample (in counts)

X = µg/ml CGA 108906 Tech. (Intermediate of 48988) in injected sample

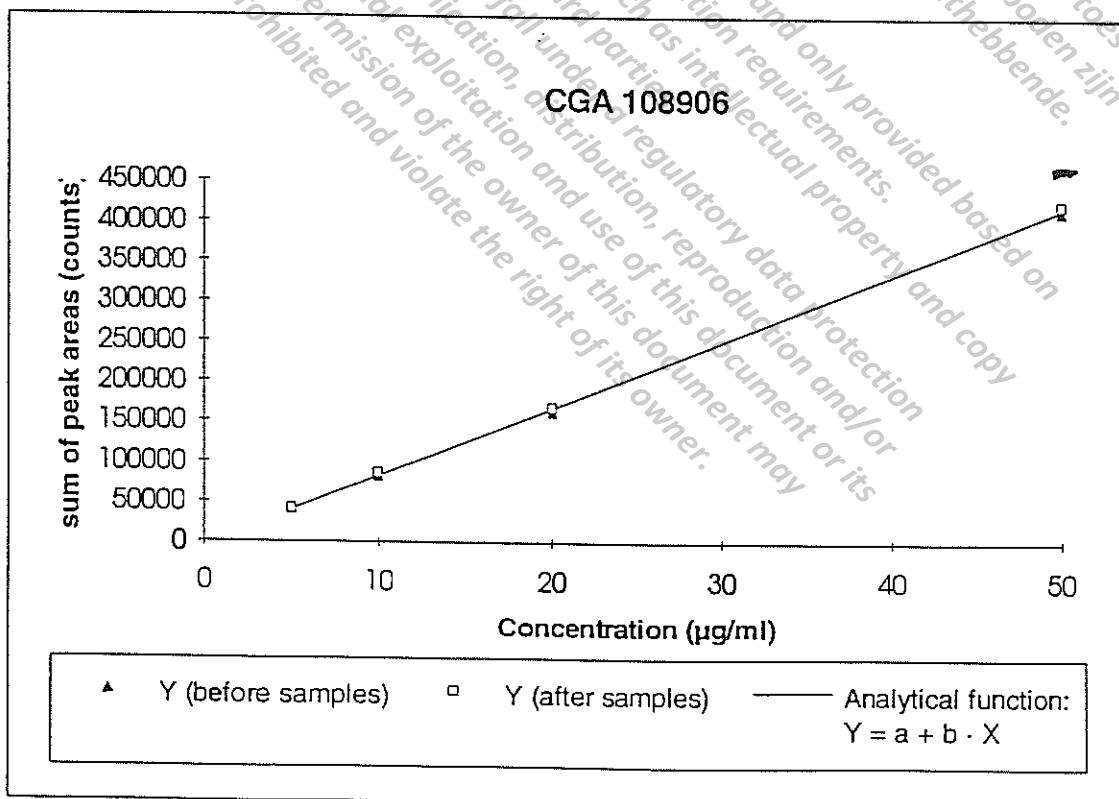


Table 2: Concentration, Homogeneity, and Stability of Test Article in Vehicle

Dose Group	Nominal Conc. (mg/ml)	Labelling	T M B	Storage Time (h) ¹	Date of Analysis	Concentration Found			
						(mg/ml)	% of Nom.	Mean % of Nom.	± Dev. in % of Mean
PRETEST (Date of Preparation: October 29, 1996)									
1	0	1S	-	0	13-NOV-96	0.000	---	---	---
2	1	2A	T	0	12-NOV-96	0.893	89.3	93.5	-4 / +3
		2B	M	0	12-NOV-96	0.961	96.1		
		2C	B	0	12-NOV-96	0.950	95.0		
		2S		4	12-NOV-96	1.061	106.1		
3	10	3A	T	0	12-NOV-96	9.888	98.9	99.6	-2 / +3
		3B	M	0	12-NOV-96	10.27	102.7		
		3C	B	0	12-NOV-96	9.732	97.3		
		3S		4	12-NOV-96	9.872	98.7		
4	100	4A	T	0	12-NOV-96	98.84	98.8	97.8	-1 / +1
		4B	M	0	12-NOV-96	96.48	96.5		
		4C	B	0	12-NOV-96	98.22	98.2		
		4S		4	12-NOV-96	97.11	97.1		

T/M/B: Top / Middle / Bottom (segment of mixing container)

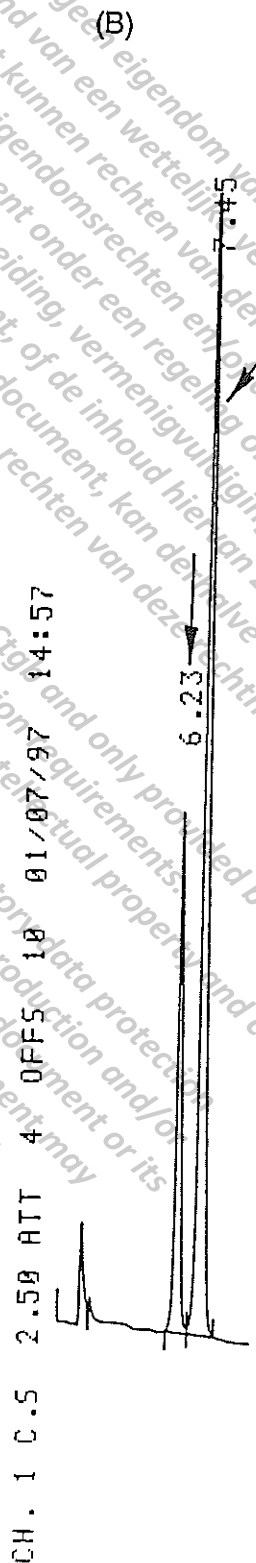
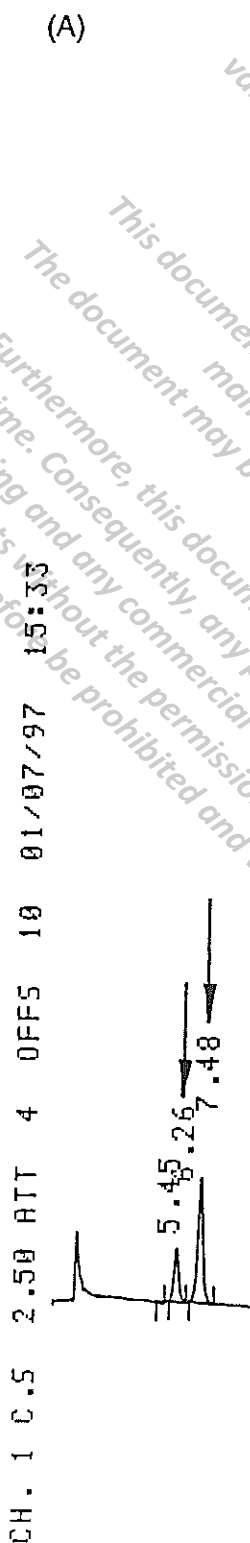
¹ Stability test under actual conditions of administration

Table 3: Concentration of Test Article in Vehicle

Dose Group	Nominal Conc. (mg/ml)	Labelling	Date of Analysis	Concentration Found	
				(mg/ml)	% of Norm.
(Date of Preparation: December 11, 1996)					
1	0	1S	07-JAN-97	0.000	—
2	1	2S	07-JAN-97	1.015	101.5
3	5	3S	07-JAN-97	4.914	98.3
4	20	4S	07-JAN-97	20.05	100.2
5	100	5S	07-JAN-97	96.00	96.0
(Date of Preparation: December 18, 1996)					
1	0	1S	07-JAN-97	0.000	—
2	1	2S	07-JAN-97	1.151	115.1
3	5	3S	07-JAN-97	4.951	99.0
4	20	4S	07-JAN-97	19.50	97.5
5	100	5S	07-JAN-97	97.58	97.6
(Date of Preparation: December 25, 1996)					
1	0	1S	07-JAN-97	0.000	—
2	1	2S	07-JAN-97	1.013	101.3
3	5	3S	07-JAN-97	5.001	100.0
4	20	4S	07-JAN-97	19.53	97.7
5	100	5S	07-JAN-97	100.1	100.1
(Date of Preparation: January 01, 1997)					
1	0	1S	07-JAN-97	0.000	—
2	1	2S	07-JAN-97	1.001	100.1
3	5	3S	07-JAN-97	4.886	97.7
4	20	4S	07-JAN-97	19.50	97.5
5	100	5S	07-JAN-97	99.06	99.1

Figure 1: Typical Chromatograms of Standard Solutions

- (A) Standard solution 5 µg/ml, before samples
- (B) Standard solution 50 µg/ml, before samples



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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

11. APPENDIX C: REFERENCE VALUES

11.1. Scoring criteria used in FOB

HOME CAGE

recumbency

Scores: -1 animal lies on abdomen or on side and is unable to stand on feet
0 normal posture

paddling movements

Scores: -1 paddling movements of hindlimbs and/or forelimbs with animal flaccid and recumbent
0 absent

diarrhea

Scores: 0 absent
1 feces soft but still formed as boli
2 feces very soft, do not keep form

urination

Scores: 0 normal
1 frequent micturition and/or bedding of homecage wet

OPEN FIELD

activity

Scores: -2 low: animal barely moves, or maintains abnormal position for prolonged time
-1 reduced: animal somewhat dull, moves less or slower
0 normal: animal alert and explores environment
1 increased: animal moves faster with only short pauses
2 high: animal restless, excited, sudden darting or freezing, bouts of running separated by only short pauses

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Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

posture/gait

- Scores:
- 2 animal lies with extended extremities or crawling with abdomen sliding on floor
 - 1 animal moves with abdomen close to floor
 - 0 normal posture or gait
 - 1 hunchback posture or tiptoe gait with abdomen elevated more than normal
 - 2 pronounced hunchback posture or stiff tiptoe gait with elevated abdomen and difficulties walking

gait abnormality

- Scores:
- 0 normal gait
 - 1 gait slightly abnormal but animal has no difficulty to walk
 - 2 gait disturbed with animal having difficulties walking, may tumble or fall

paralysis

- Scores:
- 0 absent
 - 1 leg dragged when walking, may be splayed or correctly placed when not moving; resistance when leg is bent passively (=paresis)
 - 2 leg dragged when walking, remains extended when not moving, no resistance upon passive bending

spasms

- Scores:
- 0 absent
 - 1 tonic contractions of single muscles or muscle groups

fasciculations

- Scores:
- 0 absent
 - 1 twitching of single muscles or muscle groups; often of jaw, face or neck

forelimb clonus

- Scores:
- 0 absent
 - 1 involuntary movements of forelimbs, often accompanied by clonic movements of jaw, face or neck; animal may rise on hindlegs, but does not fall

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Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

convulsion, clonic

alternating contraction and relaxation of muscles

Scores: 0 absent

1 clonic convulsion of whole body; animal falls when standing on hindfeet or pops in air

convulsion, clonic-tonic

Scores: 0 absent

1 clonic convulsion followed by a tonic convulsion

convulsion, tonic

prolonged contraction of majority of muscles

Scores: 0 absent

1 tonic convulsion of hindlimbs only
2 convulsion of forelimbs and hindlimbs; often accompanied by asphyxia, post-ictal depression or death

stereotypies

Scores: 0 absent

1 repetitive sniffing, licking, grooming etc., behavior appears mechanical, not goal directed
2 compulsive sniffing, licking, grooming etc.

Straub tail

Scores: 0 absent

1 tail slightly elevated also when not walking
2 tail elevated or bent over back

bizarre behavior

Scores: 0 absent

1 animal shows strange behavior as e.g. circling, backward moving, self mutilation etc.

palpebral closure

Scores: 0 eyelids wide open

1 eyelids drooping, about 1/3 closed

2 eyelids almost shut, more than 2/3 closed

piloerection

Scores: 0 absent

1 neck fur raised

2 fur on whole back raised

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

fur unkempt

Scores: 0 normal
1 fur unkempt with hairs sticking together

dyspnea

Scores: 0 absent
1 impaired, irregular or slow respiration
2 labored respiration or asphyxia, animal gasping or breathing through mouth

MANIPULATIVE**ease of removal**

Scores: 0 easy, animal quiet, can be picked up easily
1 animal tries to escape repeatedly and/or assumes defensive posture
2 difficult, animal aggressive, rattles, escapes repeatedly, jumps out of cage and/or bites

ease of handling

Scores: 0 easy, animal quiet
1 slight resistance to handling, animal tense, freezes or rattles
2 difficult, animal tries to escape, rattles, vocalizes or bites

vocalization

Scores: 0 absent
1 vocalization during handling or when undisturbed
2 prolonged vocalization

muscle tone

Scores: -2 animal flaccid when held, unable to stand on feet, muscles soft when squeezed
-1 animal slightly flaccid, can lift abdomen when walking, locomotion not impaired
0 normal
1 animal stiffer, locomotion not impaired
2 animal stiff when held, hindlimbs splayed, some muscles may mark off, locomotion impaired

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

tremor

Scores: 0 absent
1 fine trembling, does not impair locomotion
2 coarse, rough trembling that impairs locomotion

abdomen distended

Scores: 0 absent
1 abdomen slightly distended, soft on touch
2 abdomen distended, hard on touch

emaciated

Scores: 0 absent
1 animal skinny, bony

dehydrated

Scores: 0 absent
1 skinfold disappears only slowly

lacrimation

Scores: 0 absent
1 accumulation of clear fluid in eyes, fur around eyes slightly wet
2 clear fluid from eyes leaks out of eyes, fur around eyes wet

chromodacryorrhea

Scores: 0 absent
1 discharge of red fluid from eyes, fur around eyes wet

rhinorrhea

Scores: 0 absent
1 no visible discharge of clear fluid from nose, fur around nose may be wet
2 discharge of clear fluid from nose, fur around nose wet

chromorhinorrhea

Scores: 0 absent
1 discharge of red fluid from nose, fur around nose wet

salivation

Scores: 0 absent
1 wet fur on chin and/or frequent swallowing
2 discharge of clear fluid from mouth, fur on chin wet

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

eye prominence

Scores: -1 enophthalmus
0 normal
1 exophthalmus

respiratory sounds

Scores: 0 absent
1 sounds produced during inspiration or expiration

skin cold to touch

Scores: 1 animal feels cold to touch
0 normal skin temperature

eye, crust

Scores: 0 fur around eyes clean
1 some dark, dry stain on fur around eyes
2 fur around eyes stained dark

nose, crust

Scores: 0 fur around nose clean
1 patchy, dark, dry stain on fur around nose
2 fur around nose stained dark

pale

Scores: 0 bald skin and mucous membranes with faint red color
1 bald skin and mucous membranes pale

cyanosis

Scores: 0 bald skin and mucous membranes with faint red color
1 bald skin and mucous membranes blueish discolored

hair loss

Scores: 0 fur normal
1 thinning or total loss of hairs at some areas of body
2 thinning or total loss of hairs on entire body surface

skin lesion

Scores: 0 skin normal
1 superficial skin lesion not affecting
subcutaneous structures

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

scab

Scores: 0 normal
1 skin lesion or wound covered by scab

wound

Scores: 0 normal
1 lesion of skin and underlying tissue(s)

crust

Scores: 0 normal
1 dry stain (other than blood or plasma) on skin

swelling

Scores: 0 normal
1 soft, not clearly demarcated swelling on body surface

mass

Scores: 0 normal
1 clearly demarcated, palpable mass below skin

discharge

Scores: 0 normal
1 discharge of liquid from body orifice, lesion or wound

SENSORIMOTOR RESPONSES**approach response**

Scores -1 animal does not respond to object in front of nose
0 animal approaches object and curiously follows it when pulled back
1 animal freezes, startles or escapes when noticing object

touch response

Scores -1 no response even after heavy touching animal
0 animal orients toward side being touched, retracts ears or interrupts ongoing behavior
1 exaggerated response upon being touched

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

click response

- Scores
- 2 no response induced by cracking sound
 - 1 animal responds with barely visible movement to cracking sound
 - 0 animal reacts to cracking sound with visible movement of body and/or head
 - 1 animal reacts to cracking sound with heavy body movement but does not jump or run
 - 2 animal reacts with exaggerated startle response, jumps and/or runs away

tail pinch

- Scores
- 1 no response upon pinching tail
 - 0 upon pinching tail animal startles, tries to escape, vocalizes or turns around
 - 1 exaggerated response upon pinching tail

righting response

- Scores
- 0 animal tries to keep head in horizontal position when rotated or bent head over
 - 1 head position not corrected during above maneuvers

visual placing

- Scores
- 0 animal tries to grab grid when approaching it and before it touches grid with whiskers or nose
 - 1 animal grabs grid only after touching grid with whiskers or nose

hearing response

- Scores
- 0 Preyer's reflex induced by tone stimulus (10 kHz, 80 db, 30 msec)
 - 1 absence of Preyer's reflex

pupillary reflex

- Scores
- 0 pupil constricts when light touches eye
 - 1 pupil does not constrict

pupil size

- Scores
- 1 small pupils in absence of pupillary reflex (miosis)
 - 0 pupil normal in size
 - 1 pupils large (mydriasis)

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

11.2 Assignment of signs and functions to functional domains

FUNCTIONAL DOMAIN	CLINICAL SIGN	SCORE	SUM SCORE	
CNS activity	activity	±2		
	recumbency	-1		
	paddling movements	-1		
	stereotypies	+2		
	Straub tail	+2		
	bizarre behavior	+1	-4/+7	
CNS excitation	posture/gait	±2		
	muscle tone	±2		
	spasms	+1		
	tremor	+2		
	fasciculations	+1		
	clonic convulsions	+2/3/4		
	tonic convulsions	+3/4		
	ease of removal	+2		
	ease of handling	+2		
	vocalization	+2		
	approach response	+1		
	touch response	+1		
	tail pinch	+1		
click response	+2	-4/+27		
Autonomic function	lacrimation	+2		
	chromodacryorrhea	+1		
	rhinorrhea	+2		
	chromorhinorrhea	+1		
	salivation	+2		
	eye prominence	±1		
	pupillary reflex	-1		
	pupil size	±1		
	diarrhea	+2		
	urination	+1	-3/+13	
Sensorimotor functions	gait abnormal	-2		
	paralysis	-2		
	approach response	-1		
	touch response	-1		
	click response	-2		
	tail pinch	-1		
	righting response	-1		
	visual placing	-1		
hearing response	-1	-12/0		
Physiological functions	dyspnea	+2		
	respiratory sounds	+1		
	fur unkempt	+1		
	piloerection	+2		
	abdomen distended	+2		
	dehydrated	+1		
	emaciated	+1		
	pale	+1		
	cyanosis	+1		
	skin cold to touch	+1		
	palpebral closure	+2		
	crust eye	+2		
	crust nose	+2	0/+19	
	Non-specific signs	skin lesion	+1	
		scab	+1	
hair loss		+2		
wound		+1		
crust		+1		
swelling		+1		
mass		+1		
discharge		+1	0/+9	

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

11.3. Units used in hematology

Parameter	SI Unit	Conventional Unit	Conversion Factor
Red Blood Cell Parameters			
Erythrocyte Count	$T/l = 10^{12}/l$	$10^6/\mu l$	1
Hemoglobin	mmol/l	g/100 ml	1.611
Hematocrit	l	%	100
Mean Corpuscular Volume	fl	μm^3	1
Red Cell Volume Distribution Width	l	%	100
Mean Corpuscular Hemoglobin	fmol	pg	16.11
Mean Corpuscular Hemoglobin Concentration	mmol/l	g/100 ml (%)	1.611
Hemoglobin Concentration Distribution Width	mmol/l	g/100 ml	1.611
White Blood Cell Parameters			
Leukocyte Count	$G/l = 10^9/l$	Number/ μl	1000
Differential Leukocyte Count	relative absolute	relative absolute	rel. abs
Neutrophils	1 G/l	% Number/ μl	100 1000
Eosinophils	1 G/l	% Number/ μl	100 1000
Basophils	1 G/l	% Number/ μl	100 1000
Lymphocytes	1 G/l	% Number/ μl	100 1000
Monocytes	1 G/l	% Number/ μl	100 1000
Large Unstained Cells	1 G/l	% Number/ μl	100 1000
Blood Platelets			
Thrombocyte Count	$G/l = 10^9/l$	Number/ μl	1000

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

11.4. Reference values: HematologyHEMATOLOGY REFERENCE VALUES
UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks Period : 08.04.91 - 18.02.97

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	729	7.320	7.850	8.450
Hb	M0002	mmol/l	729	9.000	9.600	10.20
Hct	M0002	l	729	0.426	0.454	0.484
MCV	M0002	fl	729	54.30	57.80	61.70
RDW	M0002	l	729	0.106	0.119	0.145
MCH	M0002	fmol	729	1.150	1.220	1.290
MCHC	M0002	mmol/l	729	20.10	20.99	22.00
HDW	M0002	mmol/l	729	1.295	1.540	2.130
Reti	M0002	l	89	0.016	0.029	0.044
	M0003	l	80	0.040	0.054	0.078
WBC	M0002	G/l	729	8.570	13.06	20.07
Neut	M0002	l	729	0.050	0.080	0.147
Eos	M0002	l	729	0.003	0.007	0.015
Baso	M0002	l	729	0.002	0.005	0.009
Lympho	M0002	l	729	0.765	0.849	0.895
Mono	M0002	l	729	0.019	0.034	0.058
Luc	M0002	l	729	0.009	0.022	0.042
Neut	M0002	G/l	356	0.650	1.125	2.100
Eos	M0002	G/l	356	0.040	0.090	0.200
Baso	M0002	G/l	356	0.030	0.080	0.155
Lympho	M0002	G/l	356	7.360	11.33	17.34
Mono	M0002	G/l	356	0.240	0.480	0.960
Luc	M0002	G/l	356	0.110	0.320	0.710
Plt	M0002	G/l	729	824.0	1010	1170
PT(CS)	M0001	sec	493	30.00	37.54	51.82
PT	M0001	rel. l	63	0.699	0.804	0.923
MetHb	M0001	l	332	0.005	0.007	0.010
Heinz B	M0001	l	10	0.000	0.000	0.000

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

HEMATOLOGY REFERENCE VALUES
UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks

Period : 06.05.91 - 17.12.96

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	148	7.820	8.323	8.860
Hb	M0002	mmol/l	148	8.900	9.600	10.10
Hct	M0002	l	148	0.422	0.450	0.481
MCV	M0002	fl	148	51.20	54.45	57.80
RDW	M0002	l	148	0.119	0.132	0.154
MCH	M0002	fmol	148	1.090	1.150	1.220
MCHC	M0002	mmol/l	148	20.15	21.17	22.09
HDW	M0002	mmol/l	148	1.420	1.650	2.060
Reti	M0002	l	10	0.014	0.021	0.038
	M0003	l	20	0.015	0.046	0.059
WBC	M0002	G/l	148	7.940	11.59	17.92
Neut	M0002	l	148	0.065	0.103	0.168
Eos	M0002	l	148	0.005	0.010	0.017
Baso	M0002	l	148	0.002	0.004	0.007
Lympho	M0002	l	148	0.737	0.825	0.872
Mono	M0002	l	148	0.021	0.036	0.063
Luc	M0002	l	148	0.013	0.024	0.041
Neut	M0002	G/l	73	0.710	1.210	1.760
Eos	M0002	G/l	73	0.060	0.100	0.220
Baso	M0002	G/l	73	0.030	0.060	0.110
Lympho	M0002	G/l	73	6.780	10.07	15.40
Mono	M0002	G/l	73	0.280	0.450	0.890
Luc	M0002	G/l	73	0.170	0.310	0.590
Plt	M0002	G/l	148	792.0	942.5	1097
PT(CS)	M0001	sec	129	28.31	36.00	49.39
PT	M0001	rel. l	19	0.720	0.800	0.939
MetHb	M0001	l	119	0.006	0.007	0.012

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

HEMATOLOGY REFERENCE VALUES
UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks

Period : 08.04.91 - 18.02.97

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	585	7.170	7.700	8.310
Hb	M0002	mmol/l	585	8.800	9.400	10.00
Hct	M0002	l	585	0.409	0.439	0.468
MCV	M0002	fl	585	53.80	57.10	60.30
RDW	M0002	l	585	0.104	0.119	0.149
MCH	M0002	fmol	585	1.150	1.220	1.290
MCHC	M0002	mmol/l	585	20.47	21.35	22.35
HDW	M0002	mmol/l	585	1.230	1.420	1.920
Reti	M0001	l	10	0.011	0.030	0.035
	M0002	l	85	0.014	0.026	0.054
	M0003	l	108	0.033	0.047	0.068
WBC	M0002	G/l	585	4.910	8.460	13.01
Neut	M0002	l	585	0.043	0.083	0.167
Eos	M0002	l	585	0.005	0.010	0.020
Baso	M0002	l	585	0.001	0.003	0.006
Lympho	M0002	l	585	0.762	0.846	0.903
Mono	M0002	l	585	0.017	0.032	0.057
Luc	M0002	l	585	0.008	0.019	0.037
Neut	M0002	G/l	333	0.360	0.680	1.310
Eos	M0002	G/l	333	0.050	0.090	0.190
Baso	M0002	G/l	333	0.010	0.030	0.080
Lympho	M0002	G/l	333	3.880	7.220	11.27
Mono	M0002	G/l	333	0.120	0.300	0.600
Luc	M0002	G/l	333	0.060	0.170	0.390
Plt	M0002	G/l	585	872.0	1048	1229
PT(CS)	M0001	sec	510	23.85	30.19	37.04
PT	M0001	rel. l	59	0.867	0.967	1.063
MetHb	M0001	l	328	0.005	0.007	0.010
Heinz B	M0001	l	10	0.000	0.000	0.000

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

HEMATOLOGY REFERENCE VALUES
UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 06.05.91 - 17.12.96

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	147	7.400	7.910	8.490
Hb	M0002	mmol/l	147	8.900	9.400	10.00
Hct	M0002	l	147	0.415	0.443	0.472
MCV	M0002	fl	147	53.15	55.90	59.20
RDW	M0002	l	147	0.112	0.123	0.147
MCH	M0002	fmol	147	1.130	1.190	1.260
MCHC	M0002	mmol/l	147	20.46	21.29	22.23
HDW	M0002	mmol/l	147	1.190	1.330	1.700
Reti	M0003	l	20	0.014	0.036	0.054
WBC	M0002	G/l	147	3.960	6.800	10.89
Neut	M0002	l	147	0.056	0.093	0.174
Eos	M0002	l	147	0.007	0.012	0.023
Baso	M0002	l	147	0.001	0.003	0.005
Lympho	M0002	l	147	0.737	0.829	0.879
Mono	M0002	l	147	0.021	0.035	0.056
Luc	M0002	l	147	0.009	0.021	0.048
Neut	M0002	G/l	75	0.360	0.680	1.030
Eos	M0002	G/l	75	0.050	0.090	0.160
Baso	M0002	G/l	75	0.010	0.020	0.070
Lympho	M0002	G/l	75	3.300	5.860	10.18
Mono	M0002	G/l	75	0.110	0.270	0.460
Luc	M0002	G/l	75	0.070	0.160	0.320
Plt	M0002	G/l	147	731.5	967.0	1154
PT(CS)	M0001	sec	128	24.52	29.44	36.43
PT	M0001	rel. l	20	0.834	0.929	0.987
MetHb	M0001	l	118	0.005	0.007	0.012

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

11.5. Reference values: Blood chemistryBLOOD CHEMISTRY REFERENCE VALUES
UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks Period : 08.04.91 - 18.02.97

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	730	5.440	7.190	9.170
Urea	M0001	mmol/l	730	4.500	6.075	8.030
Creat	M0001	umol/l	467	41.10	61.00	79.00
	M0002	umol/l	58	13.40	18.00	22.10
Creat-e	M0001	umol/l	45	45.90	52.50	66.60
Bili-tot	M0001	umol/l	570	1.525	2.320	3.160
Prot	M0001	g/l	730	60.61	64.98	69.80
Alb	M0001	g/l	560	33.60	36.66	38.90
Glob	M0001	g/l	560	24.65	27.98	33.25
A/G	M0001	l	560	1.010	1.320	1.490
Chol	M0001	mmol/l	730	1.410	1.820	2.350
Trigly	M0001	mmol/l	297	0.430	0.780	1.490
Phos-Lip	M0001	mmol/l	5	1.270	1.510	1.790
Na+	M0001	mmol/l	730	141.0	143.4	146.4
K+	M0001	mmol/l	730	3.050	3.540	4.020
Ca++	M0001	mmol/l	560	2.550	2.690	2.840
Cl-	M0001	mmol/l	560	94.67	98.20	101.7
PO4-in	M0001	mmol/l	560	1.850	2.150	2.530
ASAT (GOT)	M0001	U/l	647	45.40	55.90	71.50
	M0002	U/l	83	54.30	68.20	87.40
ALAT (GPT)	M0001	U/l	647	22.40	34.40	52.40
	M0002	U/l	83	24.30	31.40	42.00
ALP	M0001	U/l	730	109.3	169.5	208.7
GGT	M0001	U/l	497	0.000	0.000	2.200
ChE-P1	M0001	U/l	30	180.0	307.0	506.0
ChE-RBC	M0002	U/l	5	1677	1764	1834
ChE-Br	M0002	U/g	5	3.111	3.324	3.680
T4	M0001	nmol/l	48	40.00	47.83	56.97
T3	M0001	nmol/l	48	1.340	1.650	1.930

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

BLOOD CHEMISTRY REFERENCE VALUES
 UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks

Period : 06.05.91 - 17.12.96

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	148	6.050	7.585	9.700
Urea	M0001	mmol/l	148	4.920	6.400	8.180
Creat	M0001	umol/l	114	45.30	62.80	82.20
	M0002	umol/l	19	14.70	18.80	23.70
Creat-e	M0001	umol/l	15	50.80	61.60	71.90
Bili-tot	M0001	umol/l	148	1.470	2.390	3.040
Prot	M0001	g/l	148	62.22	66.34	71.38
Alb	M0001	g/l	148	33.56	37.01	38.67
Glob	M0001	g/l	148	25.74	29.35	35.72
A/G	M0001	l	148	0.950	1.250	1.430
Chol	M0001	mmol/l	148	1.400	1.760	2.330
Trigly	M0001	mmol/l	119	0.540	0.880	1.670
Na+	M0001	mmol/l	148	141.1	143.3	147.8
K+	M0001	mmol/l	148	3.020	3.485	3.950
Ca++	M0001	mmol/l	148	2.530	2.660	2.800
Cl-	M0001	mmol/l	148	96.10	98.80	102.4
PO4-in	M0001	mmol/l	148	1.420	1.780	2.030
ASAT (GOT)	M0001	U/l	129	45.40	56.50	86.40
	M0002	U/l	19	54.70	72.10	114.3
ALAT (GPT)	M0001	U/l	129	21.80	34.40	50.80
	M0002	U/l	19	24.90	30.50	63.35
ALP	M0001	U/l	148	82.20	121.0	184.7
GGT	M0001	U/l	134	0.000	0.000	2.300
ChE-Pl	M0001	U/l	10	234.0	355.0	749.5
ChE-RBC	M0002	U/l	5	1081	1423	1493
ChE-Br	M0002	U/g	5	3.268	3.373	3.630
T4	M0001	nmol/l	8	40.41	45.54	53.20
T3	M0001	nmol/l	8	1.540	1.745	2.120

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

BLOOD CHEMISTRY REFERENCE VALUES
UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks

Period : 08.04.91 - 18.02.97

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	585	4.910	6.190	7.890
Urea	M0001	mmol/l	585	4.860	6.890	8.750
Creat	M0001	umol/l	476	40.40	59.40	80.30
	M0002	umol/l	59	15.70	21.10	27.80
Creat-e	M0001	umol/l	45	43.70	53.20	63.80
Bili-tot	M0001	umol/l	570	1.730	2.570	3.650
Prot	M0001	g/l	585	59.84	64.49	70.32
Alb	M0001	g/l	570	34.62	37.32	39.96
Glob	M0001	g/l	570	23.55	27.17	32.26
A/G	M0001	l	570	1.110	1.380	1.590
Chol	M0001	mmol/l	585	1.510	2.040	2.640
Trigly	M0001	mmol/l	292	0.370	0.560	1.080
Na+	M0001	mmol/l	585	139.0	142.6	146.9
K+	M0001	mmol/l	585	2.720	3.240	3.760
Ca++	M0001	mmol/l	570	2.480	2.620	2.770
Cl-	M0001	mmol/l	570	95.90	99.80	104.0
PO4-in	M0001	mmol/l	570	1.390	1.790	2.220
ASAT (GOT)	M0001	U/l	546	45.40	56.40	70.90
	M0002	U/l	59	58.50	70.80	92.05
ALAT (GPT)	M0001	U/l	546	18.50	29.00	46.00
	M0002	U/l	59	18.50	25.50	33.20
AlP	M0001	U/l	605	74.40	114.3	198.3
GGT	M0001	U/l	366	0.000	0.000	2.400
ChE-Pl	M0001	U/l	25	657.0	1246	2120
ChE-RBC	M0002	U/l	5	1752	1892	2047
ChE-Br	M0002	U/g	5	3.768	3.923	4.267
T4	M0001	nmol/l	15	37.22	42.92	54.55
T3	M0001	nmol/l	15	1.640	1.910	2.360

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

BLOOD CHEMISTRY REFERENCE VALUES
UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 06.05.91 - 17.12.96

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	148	5.460	7.095	8.790
Urea	M0001	mmol/l	148	5.260	7.190	9.700
Creat	M0001	umol/l	113	45.30	59.40	87.00
	M0002	umol/l	20	17.30	22.65	26.00
Creat-e	M0001	umol/l	15	47.30	58.80	76.10
Bili-tot	M0001	umol/l	148	1.500	2.565	3.595
Prot	M0001	g/l	148	61.49	67.19	72.28
Alb	M0001	g/l	148	35.10	38.01	41.36
Glob	M0001	g/l	148	24.35	28.41	33.48
A/G	M0001	l	148	1.100	1.350	1.590
Chol	M0001	mmol/l	148	1.390	1.945	2.650
Trigly	M0001	mmol/l	118	0.430	0.640	1.220
Na+	M0001	mmol/l	148	139.7	142.5	146.8
K+	M0001	mmol/l	148	2.690	3.020	3.560
Ca++	M0001	mmol/l	148	2.460	2.580	2.690
Cl-	M0001	mmol/l	148	97.20	100.7	104.8
PO4-in	M0001	mmol/l	148	1.030	1.325	1.720
ASAT (GOT)	M0001	U/l	138	44.80	55.80	78.30
	M0002	U/l	20	54.20	74.10	88.00
ALAT (GPT)	M0001	U/l	138	20.20	29.60	47.60
	M0002	U/l	20	19.10	24.10	33.30
AlP	M0001	U/l	158	52.40	78.55	123.3
GGT	M0001	U/l	133	0.000	0.000	2.500
ChE-Pl	M0001	U/l	10	1198	1439	2156
ChE-RBC	M0002	U/l	5	878.0	1288	1961
ChE-Br	M0002	U/g	5	3.704	3.810	4.095

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

11.6. Reference values: Urine analysisURINE ANALYSIS REFERENCE VALUES
UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks Period : 17.12.91 - 18.02.97

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	296	2.900	5.800	10.60
Rel dens	M0001	1	228	1.031	1.042	1.061
	M0002	1	68	1.029	1.039	1.064
pH	M0001	1	208	6.000	6.500	7.000
	M0002	1	68	6.000	6.500	7.000
PRO	M0001	g/l	68	0.250	0.250	0.750
GLU	M0001	mmol/l	68	0.000	0.000	0.000
KET	M0001	mmol/l	68	0.000	0.500	1.500
UBG	M0001	umol/l	68	0.000	0.000	0.000
BIL	M0001	umol/l	68	0.000	0.000	17.00
ERY	M0001	per ul	68	0.000	10.00	25.00
LEU	M0001	per ul	10	25.00	25.00	500.0

URINE ANALYSIS REFERENCE VALUES
UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 14.01.92 - 17.12.96

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	88	3.000	5.500	10.40
Rel dens	M0001	1	69	1.025	1.042	1.065
	M0002	1	19	1.018	1.048	1.080
pH	M0001	1	59	6.000	6.500	7.000
	M0002	1	19	6.000	6.500	7.000
PRO	M0001	g/l	19	0.000	0.750	0.750
GLU	M0001	mmol/l	19	0.000	0.000	0.000
KET	M0001	mmol/l	19	0.000	0.500	1.500
UBG	M0001	umol/l	19	0.000	0.000	17.00
BIL	M0001	umol/l	19	0.000	0.000	17.00
ERY	M0001	per ul	19	0.000	10.00	250.0

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

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Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

URINE ANALYSIS REFERENCE VALUES
UNTREATED FEMALE RATS Tif: RAIF (SPF)

Age : 9 - 12 weeks

Period : 17.12.91 - 18.02.97

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	298	1.400	3.700	7.400
Rel dens	M0001	1	229	1.030	1.042	1.064
	M0002	1	69	1.030	1.043	1.084
pH	M0001	1	209	6.000	6.500	6.500
	M0002	1	69	5.000	6.000	6.500
PRO	M0001	g/l	69	0.250	0.250	0.750
GLU	M0001	mmol/l	69	0.000	0.000	0.000
KET	M0001	mmol/l	69	0.000	0.500	0.500
UBG	M0001	umol/l	69	0.000	0.000	17.00
BIL	M0001	umol/l	69	0.000	0.000	17.00
ERY	M0001	per ul	69	0.000	10.00	10.00
LEU	M0001	per ul	9	0.000	25.00	25.00

URINE ANALYSIS REFERENCE VALUES
UNTREATED FEMALE RATS Tif: RAIF (SPF)

Age : 13 - 16 weeks

Period : 14.01.92 - 17.12.96

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	90	1.500	3.850	6.900
Rel dens	M0001	1	70	1.028	1.039	1.072
	M0002	1	20	1.039	1.056	1.080
pH	M0001	1	60	6.000	6.500	7.000
	M0002	1	20	5.000	6.000	7.000
PRO	M0001	g/l	20	0.250	0.750	0.750
GLU	M0001	mmol/l	20	0.000	0.000	0.000
KET	M0001	mmol/l	20	0.000	0.500	1.500
UBG	M0001	umol/l	20	0.000	0.000	17.00
BIL	M0001	umol/l	20	0.000	0.000	17.00
ERY	M0001	per ul	20	0.000	10.00	10.00

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

11.7. Reference values: Organ weights

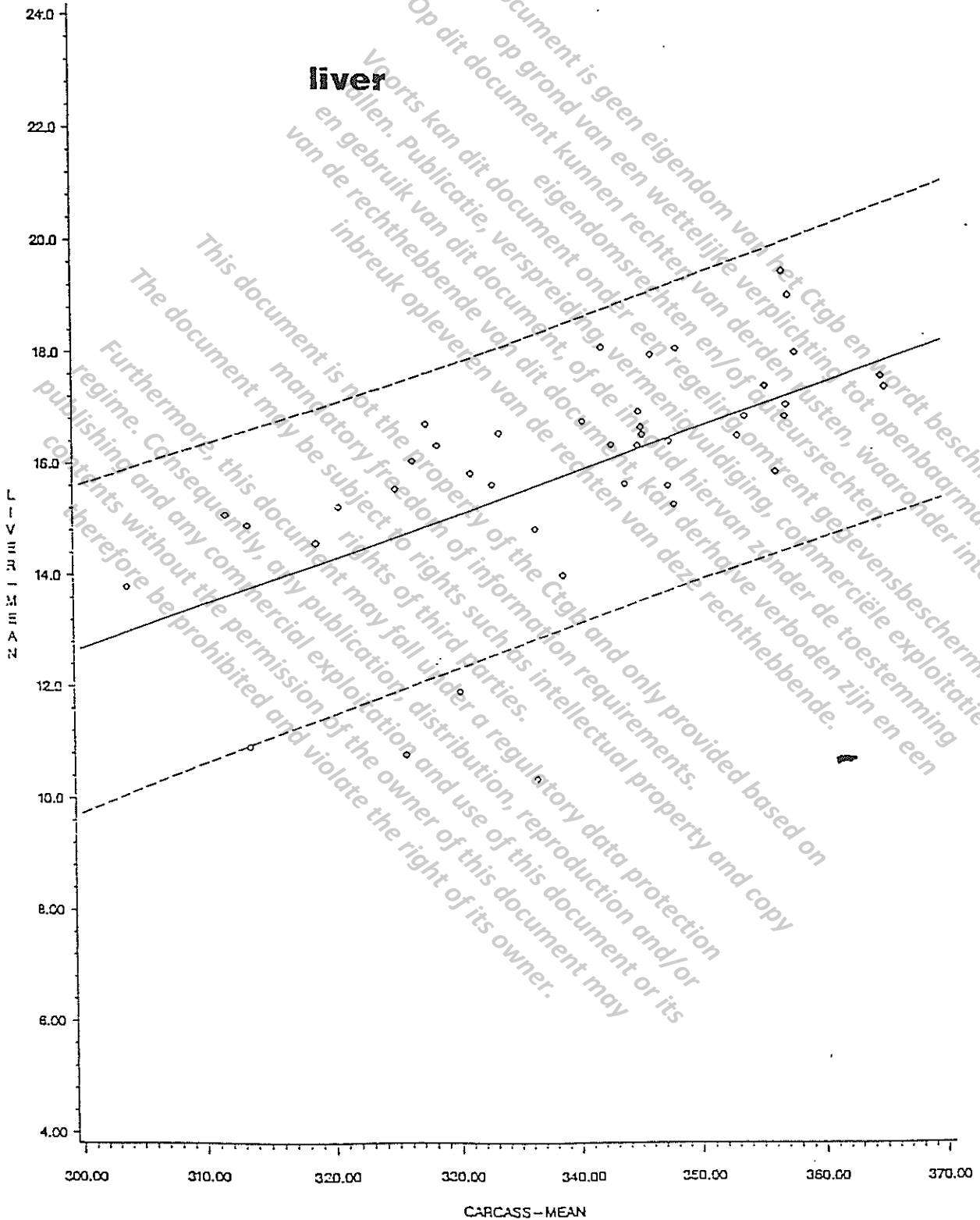
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UNTREATED MALE RATS, GAVAGE, WEEK 5

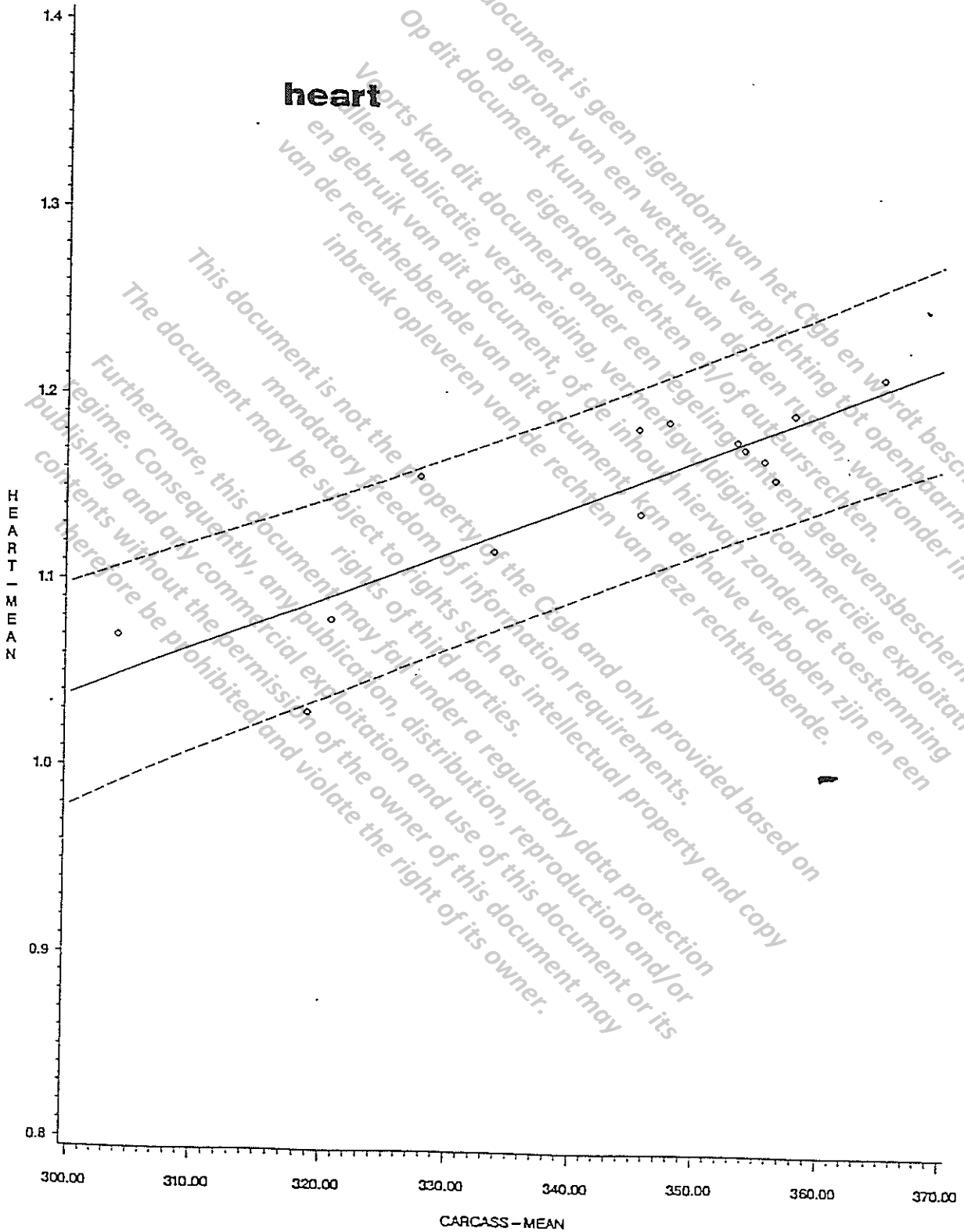


ORGAN WEIGHT VS. BODY WEIGHT (43 STUDIES)
with 80% confidence limits

Test No.: 963128

Test Article: CGA 108906 tech. (Intermediate of CGA 48988)

UNTREATED MALE RATS, GAVAGE, WEEK 5



ORGAN WEIGHT VS. BODY WEIGHT (43 STUDIES) with 90% confidence limits

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12. APPENDIX D: STUDY PROTOCOL

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

Test No. 963128

CGA 108906 tech.

(Intermediate of CGA 48988)

FINAL PROTOCOL

Study Director: Dr. rer. nat. 5.1.2.e Wco

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

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

Protocol proposed: November 14, 1996

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

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Responsible for
Neurotoxicology

Dr. sc. nat. W. Classen

512.e Woo

date: November 15, 1996

For the Sponsor

Dr. 512.e Woo

512.e Woo
date: November 18, 1996

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1. PURPOSE

The present study is designed to determine the oral toxicity of the test article in rats upon daily administration by gavage for 28 consecutive days, to estimate a no-observed-adverse-effect level of exposure (NOAEL), and for observation of reversibility, persistence of, or delayed occurrence of toxic effects after a 4-week recovery period.

2. GENERAL

Sponsor

CIBA-GEIGY Limited,
Crop Protection Division (VB 66815)
4002 Basle / Switzerland

Testing facility

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

Proposed dates

Starting date of acclimatization: December 3, 1996
Starting date of administration: December 10, 1996
Date of completion, experimental group I: January 8, 1997
Starting date of recovery period: January 7, 1997
Recovery end date: (experimental group II): February 5, 1997
Submission of the final report for audit: April 25, 1997
Submission of the final report: May 25, 1997

Personnel and responsible scientists

Study director: Dr. rer. nat. [redacted] 5123 WGG
Longterm Toxicology

Technical assistant: [redacted]
Longterm Toxicology

Supervisor: [redacted]
Longterm Toxicology

Responsible for laboratory investigations: Dr. med. vet. [redacted] 18 WGG
Clinical Laboratory

Assistant, laboratory investigations: [redacted]
Clinical Laboratory

Responsible for neurotoxicology: Dr. sc. nat. [redacted]
Neurotoxicology

Responsible for pathology services: Dr. med. vet. [redacted]
Macropathology

Responsible for pathology: Dr. med. vet. [redacted]
FVH Pathology
Toxicological Pathology

Study pathologist: Dr. med. [redacted] 18 WGG
Toxicological Pathology

Responsible for analytics: [redacted] R C C
Umweltchemie AG
4452 Itingen / Switzerland

Responsible for statistics: [redacted], dipl.stat.
Mathematical Applications

Good laboratory practice

The study will be 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 will be subjected to periodic internal quality assurance evaluation.

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

Basis of the study

This study will be carried out according to:

- The OECD Guideline for testing of chemicals, No. 407, "Repeated Dose 28-day Oral Toxicity Study in Rodents: 28-day or 14-day Study", adopted July 27, 1995.
- 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).

Alteration of design

In the normal case no alterations will be made to this protocol without prior consent of the sponsor. However, when difficulties in contacting the sponsor are encountered, Short/Long-term Toxicology reserves the right to act independently should this be necessary; whereupon the sponsor is informed as soon as possible.

3. METHODS

3.1. Test system

3.1.1. Experimental animals

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

Rationale for selection of species

Albino rats are selected as a standard rodent species.

Age

The initial age will be approximately 5 weeks at the beginning of the acclimatization period and no more than 9 weeks at initiation of dosing. Females will be nulliparous and non-pregnant.

Body weight

At the beginning of the acclimatization period, individual weight variation will not exceed +20 % of the mean value for each sex.

Identification

The animal number is identical with the cage number and is tattooed on the tail root.

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3.1.2. Husbandry

Conditions

The experiment will be carried out under specified pathogen free (SPF) standard laboratory conditions. The animals will be housed individually in macrolon cages type 3 with wire mesh tops and soft wood bedding (Societe Parisienne des Sciures Pantin).

An air-conditioned room with 16-20 air-changes per hour, maintained at a temperature of $22 \pm 2^{\circ}\text{C}$, relative humidity (%) of 55 ± 10 and 12 hours light per day will be used.

Neither insecticides nor chemicals are applied in the animal room with the exception of disinfectant: BRADOPHENtm.

Diet

Pelleted, certified standard diet (NAFAG No.8900 FOR GLP) will be fed ad libitum (except as noted under Laboratory Investigations). All batches of the diet will be assayed for nutritive ingredients and contaminant level by the manufacturer and will not be used unless consistency with EPA standards for contaminants will be proved. Analytical results are archived at Short/Long-term Toxicology, 4332 Stein / Switzerland.

Water

Tap water ad libitum, drinking water quality according to the specifications of the "Schweizerisches Lebensmittelbuch" (Ed. 1972 / Appendix B). Results of the routine chemical examination at source (Grundwasserfassung Stein) as conducted periodically by the water authority (Baudepartement des Kantons Aargau, Abteilung Gewaesserschutz) and at supply point by the Analytical Laboratories of the Pharmaceuticals Division, CIBA-GEIGY Limited are archived at Short/Long-term Toxicology, 4332 Stein / Switzerland.

3.2. Test article

Company code No.: CGA 108906 tech.
Batch No.: KI-5240/3
Purity: 99 %
Description: solid
Date of receipt: October 23, 1996
Storage conditions: room temperature
Stability: October 1999

Analytical pretests

Pretest analyses of the test article in the vehicle were performed prior to the start of the study at the analytical laboratories of 4452 Itingen / Switzerland.

The results of the analyses are filed in the archives of Short/Long-term Toxicology, CIBA-GEIGY Limited, 4332 Stein, Switzerland.

Homogeneous distribution of the test article in the vehicle was recorded. The content of the test article in the vehicle was in agreement with the nominal concentrations. CGA 108906 tech. was stable in the vehicle over a period of 4 hours at room temperature.

Estimated quantity of test article needed

300 g

Safety precautions

All personnel which may be exposed to the test material during weighing, dissolving or applying of the test substance will wear dust masks, protective glasses and disposable plastic gloves.

3.3. Study conduct

3.3.1. Design

Number of animals

80 (total)

5 males, 5 females per dose group (experimental group I); additionally, 5 males, 5 females will be used at the control, the high intermediate, and high dose level for recovery evaluation (experimental group II).

Distribution

Animal No. (=cage no.)	Group 1 Control	Group 2 10mg/kg	Group 3 50mg/kg	Group 4 200mg/kg	Group 5 1000mg/kg
MALES I	1- 5	11- 15	16- 20	21- 25	31- 35
MALES II	6- 10			26- 30	36- 40
FEMALES I	41- 45	51- 55	56- 60	61- 65	71- 75
FEMALES II	46- 50			66- 70	76- 80

I EXPERIMENTAL GROUP I

5 animals per sex and group for evaluation of toxicity, including laboratory investigations

II EXPERIMENTAL GROUP II

5 animals per sex and group for reversibility evaluation after 4 weeks of recovery, including laboratory investigations

Control of bias

Computer controlled data processing (Tandem, Non Stop-System). Number and identification of animals, number and type of organs, weight-range of animals and organs are controlled by a procedure established according to this protocol before entry of corresponding parameters. The initiation program for weighings includes a calibration procedure of balances.

3.3.2. Acclimatization

During the acclimatization period, the animals will be assigned to the dose groups. In order to set up a fully randomized experiment, they will be assigned to these groups by means of computer-generated random numbers.

Duration of the acclimatization period

7 days at least.

3.3.3. Treatment

The treatment will be performed on a main group (experimental group I) and a recovery group (experimental group II) of animals. The surviving animals of experimental group I will be sacrificed at the end of the treatment period, those of experimental group II will be sacrificed at the end of the recovery period.

Duration of treatment period

4 weeks

Route of administration

Orally by gavage (rubber catheter).

Rationale for route of administration

Ingestion is a probable route for human exposure.

Frequency of administration

1 dose per day, 7 times per week.

Vehicle

As a standard procedure, distilled water containing 0.5% carboxymethylcellulose and 0.1% Tween 80, will be used.

Volume applied

10 ml/kg body weight.

Administered quantities of the test article suspension will be adjusted daily to individual body weights.

Preparation of suspension

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

Control analyses

Control analyses of the test article concentrations in the vehicle will be performed once per experimental week (total 4 times). For this purpose samples of suspensions administered at each dose level will be collected after administration, immediately deep frozen and sent to the analytical laboratories of RCC Umweltchemie AG, 4452 Itingen / Switzerland.

Control animals

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

3.3.4. Recovery

The recovery group (experimental group II) will be kept on control diet for a consecutive recovery phase before sacrifice of the remaining animals.

Duration of the recovery period

4 weeks

3.3.5. Dose levels

0, 10, 50, 200 and 1000 mg/kg body weight per day.

Rationale for dose level selection

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

Project no. 943085
Short/Long-term Toxicology, CIBA-GEIGY Limited, Stein
Acute Oral Toxicity in the Rat
LD50 > 2000 mg/kg body weight

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The following dose levels were selected:

- | | |
|------------------------|--|
| 10 mg/kg bw. per day | this dose is expected to cause no observable effects |
| 50 mg/kg bw. per day | this dose is expected to cause no or minimal observable effects |
| 200 mg/kg bw. per day | this dose is expected to cause slight effects, if any |
| 1000 mg/kg bw. per day | this dose is expected to cause observable effects, but no or few fatalities to permit a meaningful evaluation of the study. According to the guidelines on which this study is based, this dose represents the limit dose which needs not be exceeded. |

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3.4. Study evaluation

3.4.1. Standard animal observations

The observations will be made during both the treatment and the recovery phases of the test.

Mortality

Mortality and morbidity will be checked twice daily (a.m. and p.m.).

General clinical observations

Clinical signs (cage-side observation) will be assessed and reported daily.

Detailed clinical observations

Clinical signs will be fully assessed once weekly. In order to make experimenters unaware of the animal's treatment, rats will be randomized and the cage labels covered with the corresponding random number.

Observations include, but are not limited to, signs of general appearance, alertness when undisturbed, reactivity to handling, changes in skin, fur, eyes, mucous membranes, occurrence of secretions or excretions, autonomic signs, postural and gait abnormalities, and abnormal behavior.

Body weight weekly (midweek)

Food consumption weekly

Food consumption ratios

weekly, according to the following formula:

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

unit: g food/kg body weight per day

Water consumption weekly

3.4.2. Neurotoxicologic examinations

Functional observational battery (FOB)

Observations and functional measurements included in the FOB will be conducted on all animals toward the end of the treatment and recovery periods (recovery animals only). FOB will be conducted in the morning on all animals which do not otherwise reveal signs of toxicity to an extent that would significantly interfere with the functional test performance.

For the conduct of the FOB, animals will be randomized and the cage labels covered with the corresponding FOB number in order to make experimenters unaware to the animals' treatment.

Animals will be observed in the homecage, during handling, and in an standard arena. Observations conducted cover the functional domains of CNS activity, CNS excitation and sensorimotor, autonomic, and physiologic functions and include the following signs:

recumbency	salivation
posture/gait	lacrimation
gait abnormalities	chromodacryorrhea
paddling movements	rhinorrhea
muscle tone	chromorhinorrhea
fasciculations	piloerection
spasms	palpebral closure
tremor	eye prominence
convulsions	fecal consistency
ease of removal	urination
ease of handling	respiratory abnormalities
vocalisation	unkempt fur
Straub tail	emaciation
stereotypies	dehydration
click response	distended abdomen
paralysis	pupil size

Functional examinations include tests for

- sensorimotor functions (approach, touch, vision, audition, pain, vestibular)
- autonomic functions (pupillary reflex, body temperature)

- sensorimotor coordination (grip strength, landing foot splay)

Motor activity

Motor activity will be measured on all animals toward the end of the treatment and recovery periods (recovery animals only).

Motor activity will be assessed shortly after the conduct of the FOB using an automated openfield device (DIGISCAN, Omnitech Electronics, Columbus, Ohio, USA). This device has been shown to detect increases as well as decreases in locomotor activity.¹ The test boxes (40 x 40 x 35 cm) are made of transparent plexiglass. Horizontal activity is monitored by 16 infrared beams per side that cross the box at 3 cm above the floor. To register vertical activity a single row of 16 photobeams is mounted at an approximate height of 2/3 of the rats' body length.

Motor activity will be recorded over 30 minutes and stored on an IBM-PC at 3-minute intervals. Activity measurements will be performed between 8 a.m. and 3 p.m. in an air conditioned (22±2°C, 55% rh (range 30 to 70%)), illuminated room (about 50 lux in test box) with background noise (about 45 db) provided by the PC's fan. Animals will be allocated to the different runs and test boxes by means of a latin square design so that treatment groups will be balanced across test boxes and time. Males and females will be tested on separate days. The following parameters will be evaluated:

Horizontal activity: distance (in cm)
movement time (in sec)
number of movements (counts)

Vertical activity: vertical activity (counts)
movement time (in sec)
number of movements (counts)

Other parameters: time in central quadrant (in sec)

<1> FitzGerald RE, Berres M, and Schaeppi U. Validation of a photobeam system for assessment of motor activity in rats. Toxicology 49: 433-439, 1988

3.4.3. Laboratory investigations

Laboratory investigations (hematology, clinical chemistry, urine analysis) will be performed on all surviving animals of each sex and group at the end of the treatment and the recovery periods. Food will be removed overnight prior to blood collection. Ether anesthesia will be used to restrain the animals during retroorbital blood collection.

Urine for analysis will be collected overnight. The animals will be housed individually in special metabolism cages.

Hematology

erythrocyte count
hemoglobin
hematocrit
mean corpuscular volume
red cell volume distribution width
mean corpuscular hemoglobin
mean corpuscular hemoglobin concentration
hemoglobin concentration distribution width
reticulocytes (if signs of anemia are present)
leukocyte count
differential leukocyte count (absolute and relative)
thrombocyte count
prothrombin time

Clinical chemistry

glucose
urea
creatinine
total bilirubin
total protein
albumin
globulin
albumin/globulin ratio
cholesterol
sodium
potassium
calcium
chloride
phosphorus inorganic
aspartate aminotransferase
alanine aminotransferase
alkaline phosphatase

Urine analysis

urine color
volume
relative density
pH-value
protein
glucose
ketones
urobilinogen
bilirubin
erythrocytes
leukocytes

Proposed dates

at the end of the application period: January 7, 1997,
for the animals of the experimental groups I and II.
at the end of the recovery period: February 4, 1997,
for the animals of the experimental group II.

3.4.4. Pathology

Necropsies

Any animal showing signs of severe debility or intoxication, particularly if death appears imminent, will be sacrificed in order to prevent loss of tissues through autolysis. All animals killed in extremis as well as animals surviving at the time of scheduled sacrifice will be exsanguinated under ether anesthesia and subjected to detailed macroscopical examination. A full spectrum of tissue samples will be preserved for histopathological evaluation. Where at all feasible the animals found dead will be similarly submitted to macroscopical examination and tissue sampling.

Organ weights

At scheduled necropsy, the following weights will be recorded from all surviving animals (as soon as possible after dissection to avoid drying):

body (exsanguinated)
brain
heart
liver

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kidneys
adrenals
thymus
ovaries/testes
epididymides
spleen

Organ samples

From all animals, appropriate samples of organs and tissues listed below will be preserved in neutral buffered 4% formalin:

skin
mammary area
spleen
mesenteric lymph node
axillary lymph node
sternum
femur with joint
bone marrow (femur)
skeletal muscle
trachea
lung
heart
aorta
submandibular salivary gland, both
liver
pancreas
esophagus
stomach
small intestine (duodenum, jejunum, ileum)
large intestine (cecum, colon, rectum)
Peyer's patches (small and large intestine)
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 (sciatic nerve)
brain (incl. medulla, pons, cerebral and cerebellar cortex)
spinal cord
eye with optic nerve, both
orbital gland, both
extraorbital lacrimal gland, both

Zymbal gland, both
muzzle
tongue
any tissue with gross lesions

Proposed date for necropsy and sampling

at the end of the application period: January 8, 1997,
for the animals of the experimental group I.

at the end of the recovery period: February 5, 1997,
for the animals of the experimental group II.

Histopathological evaluation

Histopathological examination of all animals of the control and all treated groups (experimental group I) will be performed on the organs/tissues listed below:

spleen
mesenteric lymph node
axillary lymph node
femur with joint
bone marrow (femur)
trachea
lung
heart
liver
stomach
small intestine (duodenum, ileum, jejunum)
large intestine (cecum, colon, rectum)
Peyer's patches (small and large intestine)
kidney, both
urinary bladder
testis, both
epididymis, both
prostate
uterus
ovary, both
pituitary gland
adrenal gland, both
thyroid with parathyroid gland
thymus
peripheral nerve (sciatic nerve)
brain (incl. medulla, pons, cerebral and cerebellar cortex)
spinal cord
any organ with gross lesions

Any organs and tissues showing changes attributable to treatment will be examined also in the satellite recovery groups (experimental group II).

Further, any target organ revealed in laboratory tests, by clinical observations, or at necropsy will be examined in experimental groups I and II.

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3.4.5. Statistical analysis

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

Each treated group will be compared to the control group either by Lepage's <2> or 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 <3>. The Lepage test is a combination of Wilcoxon and Ansari-Bradley statistics, i.e. a combined test for location and dispersion. The Lepage test has a good power against the more general alternative that the distributions differ not only in location but also in dispersion. The Jonckheere test is sensitive to monotone dose-related effects.

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

Whenever feasible, further statistical analyses will be conducted using appropriate methods which will be specified in the report.

References

- <1> 5.1.2.e Woo, Nonparametrics: Statistical Methods Based on Ranks. Holden-Day (1975): pp. 5-31, 95, 232-238
- <2> 5.1.2.e Woo, Biometrika (1971) 58: pp. 213-217
- <3> 5.1.2.e Woo, Biometrika (1954) 41: pp. 133-145

4. REPORTING

Content of the final report

At the termination of the study, a report will be prepared showing fully the design of the experiment and the results obtained.

Name and address of the facility performing the study and the dates on which the study was initiated and completed.

Objectives and procedures stated in the approved protocol, including any changes in the original protocol in the form of an amendment.

Statistical methods employed for analysing the data.

The test and control articles identified by name or code numbers, strength, purity and composition or other appropriate characteristics.

Stability of the test article under the conditions of administration.

A description of the methods used.

The final report will include the number of animals used, sex, body weight range, source of supply, species, strain, age and procedure used for identification.

A description of the dosage, dosage regimen, route of administration and duration.

A description of all circumstances that may have affected the quality or integrity of the data.

The name and signature of the study director, the names of other scientists or professionals and the names of all supervisory personnel, involved in the study.

A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

The signed and dated reports of each of the individual scientists or other professionals involved in the study.

The statement prepared and signed by the quality assurance unit.

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The locations where all specimens, raw data, and the final report are to be stored.

A summary and assessment will be included setting out the dose levels, the main toxic signs, neurological findings, the mortality, effects on body weight, food consumption, food consumption ratios, water consumption, significant changes in hematology, clinical chemistry, and urine analysis, organ weights, organ/body weight ratios, gross pathology and histopathology.

The report will contain tables showing group means and individual values for the following:

- body weight
- food consumption
- food consumption ratios
- water consumption
- neurology
- laboratory investigations
- organ weights and ratios
- gross pathology
- histopathology

In all cases figures for male and female animals will be shown separately.

Body weight, food consumption, food consumption ratios and water consumption will be presented graphically.

Archives

Archives are located at CIBA-GEIGY Limited, Werk Stein WST 460, 4332 Stein / Switzerland. Raw data, protocol and report, specimens and raw data of laboratory investigations will be stored at this location.

Raw data of the histopathological examination and specimens (wet tissues, tissue blocks or histological slides) will be stored in the Archives of Short/Long-term Toxicology (Pathology), CIBA-GEIGY Limited, 4002 Basle / Switzerland.

Raw data of the analytical determinations, analytical report, and duplicate of protocol pertaining to the chemical analyses will be stored in the archives of RCC Research and Consulting Company Limited, 4452 Itingen / Switzerland.

Distribution

Archive

Dr. 5.1.2.e Woo
Mr.
Dr.
Dr.
Mr.
Dr.
Mr.
Dr.
Mrs.
Mrs.
QAU
Mr.
Dr.

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(RCC)

Sponsor)

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