

Annex	II	
Point addressed	5.8.1	Short-term toxicity - oral 28-day studies

1.2	Title	28 days subacute, oral toxicity study in rats (gavage)
1.3	Report and/or project N° Ciba File N° (Desire)	963103 62826 / I1
1.4	Lab. Report N°	963103
1.5	Cross reference to original study / report	5.8.1 / 07
1.6	Authors	Report: Summary:
1.7	Date of report	May 21, 1997
1.8	Published / owner	Unpublished / Novartis Crop Protection AG
2.1	Testing facility	Novartis Crop Protection AG, Toxicology/Experimental Toxicology, Stein, Switzerland
2.2	Dates of experimental work	October 22 - December 18, 1996
3.	Objectives	Assessment of toxicological profile of CGA 62826 in rats upon administration by oral gavage for 4 weeks.
4.1	Test substance	CGA 62826 technical grade (metabolite of CGA 48988 and of CGA 329351)
4.2	Specification	Batch No. RV-1592/4, Purity 100%
4.3	Storage stability	Reanalysis date: August 1999
4.4	Stability in vehicle	Confirmed. The test article was found to be stable in the vehicle at room temperature for at least four hours
4.5	Homogeneity in vehicle	Confirmed.
4.6	Validity	Not applicable.
5	Vehicle / solvent	Aqueous solution of 0.5% carboxymethylcellulose and 0.1% Tween 80.
6	Physical form	Solid.
7.1	Test method	According to Council Directive 92/69/EEC B.7, OECD Guideline 407.
7.2	Justification	Not applicable
7.3	Copy of method	Not applicable
8	Choice of method	Standard procedure for intended purpose.
9	Deviations from EC-Directive 92/69 B.7	None. According to the latest version of OECD Guideline 407, the study was extended by neurotoxicological investigations.
10.1	Certified laboratory	Yes
10.2	Certifying authority	Swiss Federal Department of the Interior
10.3	GLP	Yes
10.4	Justification	Not applicable
11.1	GEP	Not applicable

11.2 Type of facility (official or officially recognised) Not applicable

11.3 Justification Not applicable

12 Test system

Animal species: Rat, Tif RAIf (SPF), Sprague-Dawley derived
Source: Ciba-Geigy Ltd. Animal Production, 4332 Stein, Switzerland
Dose levels: 0, 10, 50, 200 and 1000 mg/kg
Group size: 5 males and 5 females
plus 5 males and 5 females in control and high dose groups for four week recovery
Age/weight: Young adult (5 weeks),
144.3-199.0 g (males) and 117.5-150.6 g (females)
Administration: Oral by gavage
Study duration: 28 days (plus 4 week recovery)
General study Design: Daily treatment (10 ml/kg), 7 days per week for 4 weeks.
Mortality: Twice daily
Clinical signs: Daily
Body weight: Recorded weekly (body weights were determined daily for accurate dosing but not recorded).
Food consumption: Weekly
Water consumption: Weekly
Detailed clinical observations: Pretest and once weekly thereafter, in home cage and in an open field.
Functional observational battery (FOB): Observations at week 4 and 8 (recovery groups) included but were not restricted to the following signs:
recumbency salivation
posture/gait lacrimation
gait abnormalities chromodacryorrhea
padding 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 at week 4 and 8 (recovery groups) included 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: Horizontal activity, vertical activity and time in central quadrant were assessed at week 4 and 8 (recovery groups) in an automated openfield device.

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Laboratory: Hematology, blood biochemistry and urinalysis were carried out on all surviving individuals from all dose groups at the end of the treatment and at the end of the recovery period.

Hematology: The following parameters were investigated:

Red blood cells

- ✓ Erythrocyte count (RBC)
- ✓ Hemoglobin (Hb)
- ✓ Hematocrit (Hct)
- ✓ Mean corp. volume (MCV)
- ✓ Mean corp. hemoglobin (MCH)
- ✓ Mean corp. Hb. conc. (MCHC)
- ✓ Red cell vol. distr. width (RDW)
- ✓ Hb conc. distr. width (HDW)

White blood cells

- Total leukocyte count
- ✓ Neutrophils (differential)
- ✓ Eosinophils (differential)
- ✓ Basophils (differential)
- ✓ Lymphocytes (differential)
- Plasma cells
- ✓ Large unstained cells (diff.)
- ✓ Monocytes (differential)

Clotting Potential

- ✓ Prothrombine time
- Partial thromboplastin time
- Thrombocyte count
- Thrombin time

Clinical chemistry: The following parameters were investigated:

Electrolytes

- Calcium
- ✓ Chloride
- ✓ Phosphorus (inorganic)
- Potassium
- ✓ Sodium

Metabolites and Proteins

- ✓ Albumin
- ✓ A/G ratio
- ✓ Bilirubin (total)
- Cholesterol
- ✓ Creatinine
- ✓ Globulin
- Glucose
- ✓ Protein (total)
- Protein (electrophoresis)
- ✓ Urea

Enzymes:

- ✓ Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- ✓ Alkaline phosphatase (ALP)
- Lactate dehydrogenase

Urinalysis: The following parameters were investigated:

Quantitative parameters:

- ✓ Urine volume
- Relative density

Semiquantitative parameters:

- ✓ pH-value
- ✓ Bilirubin
- Protein
- ✓ Urobilinogen
- ✓ Erythrocytes
- Colour
- ✓ Ketones
- Glucose
- Leukocytes

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Pathology: The following organs were collected (column C) and weighed (W) from all individuals. No histopathological examination (H) was done.

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13 Findings

Mortality: No mortality occurred which could be attributed to treatment.

Clinical signs: No behavioural changes or clinical signs which could be attributed to treatment were observed.

Body weight: Body weight development was not influenced by treatment.

Food consumption: No effects on food consumption was observed.

Water consumption: Water consumption was not affected by treatment.

Functional observational battery: Clinical observations and functional measurements did not reveal any relevant changes throughout treatment and recovery periods.

Motor activity: No treatment related effects were seen in any of the measured parameters.

Hematology: No treatment related effects on the hematological profile were noted.

Clinical chemistry: Treatment had no effect on blood chemistry.

Urine analysis: No indication for a treatment-related effect was found.

Organ weights: Minimally increased liver to body weight ratios were found in males at 1000 mg/kg and females at 50 and 1000 mg/kg. This findings were reversible within the following four weeks.

Macropathology: Macroscopical examination at necropsy did not reveal any treatment related changes.

Micropathology: Minimal hypertrophy of liver hepatocytes was increased in males (≥ 200 mg/kg) and females (≥ 50 mg/kg) at the end of treatment. This effect disappeared within the recovery period.

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NOAEL: Due to the reversibility and the weakness of the few described findings no toxicological importance was attributed to them. Therefore, under the conditions of this test the NOAEL was 1000 mg/kg body weight for both sexes.

14 Statistics For each time point and parameter, a univariate statistical analysis was conducted. Non-parametric methods were applied. Each treated group was compared to vehicle controls by Wilcoxon's or Lepage's¹ two-sample test and tested for increasing or decreasing trends from control up to the respective dose group by Jonckheere's test² for ordered alternatives.

15 References (published) none

16 Unpublished data none

CP 2.31 / TH / 14.08.1997

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¹ Lepage, Y., 1971, *Biometrika* 58, 212-217
² Jonckheere, A.R., 1954, *Biometrika*, 41, 133-145

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

Test No. 963103

CGA 62826 tech. (Metabolite of CGA 48988)

FINAL REPORT

Author: Dr. phil.- nat. 5126 Weo

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 (adopted July 95)
EEC 92/69 B.7.

Final Report issued: May 21, 1997

Sponsor: Novartis Crop Protection AG
4002 Basel / Switzerland

This report contains: 532 pages

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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.
- Japan Ministry of Agriculture, Forestry and Fisheries, NohSan, Notification No. 3850, Agricultural Production Bureau, August 10, 1984.

Study Director: Dr. phil. - nat. [redacted]

date: May 21, 1997

For the Facility Management: PD Dr. med. vet. [redacted]
FVH Fundamental Medicine

date: May 16, 1997

For the Sponsor:

5.1.2.e Woo [redacted]

date: May 22, 1997

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0.4. Signatures

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

Dr. phil.-nat.
Study Director

date: May 21, 1997

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For the Facility Management

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0.5. Quality Assurance Statement

Quality Assurance Statement

Novartis Crop Protection AG, GLP Quality Assurance, R & D Services, CH-4002 Basel
(Successor in business of Ciba-Geigy Ltd. and Sandoz Ltd.)

Study 963103
Test Substance CGA 62826 tech.
Study Title 28 Days Subacute, Oral Toxicity Study in Rats (Gavage)
Study Director Dr. 5.1.2.e Woo
QA-Inspector 5.1.2.e Woo

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

Activity	Performed	Reported
Facility Based Inspection	March 13, 1996	March 19, 1996
Protocol Audit	September 26, 1996	September 26, 1996
Facility Based Inspection	October 03, 1996	October 09, 1996
Study Based Inspection	October 22, 1996	October 22, 1996
Study Based Inspection	November 20, 1996	November 20, 1996
Final Report Audit	May 13, 1997	May 13, 1997

May 21, 1997

Date
Form. QSSTAT12

5.1.2.e Woo

Inspector Quality Assurance

0.6. Table of contents

	Page
VOLUME 1 OF 2	
0.1 Reserved Page for Proprietary Information or Statement of No Data Confidentiality Claims.....	2
0.2 Certification of Good Laboratory Practices.....	3
0.3 Reserved Page for Flagging Statements.....	4
0.4 Signatures.....	5
0.5 Quality Assurance Statement.....	6
0.6 Table of contents.....	7
1 Summary and conclusion.....	11
2 Introduction.....	14
Purpose.....	14
Good laboratory practice.....	14
Basis of the study.....	14
Sponsor.....	14
Testing facility.....	15
Study dates.....	15
Personnel and responsible scientists.....	16
Archiving and distribution.....	17
2.1 Deviations.....	18
3 Materials and methods.....	19
3.1 Test article.....	19
Pretest analytics.....	19
3.2 Test system.....	20
3.2.1 Experimental animals.....	20
3.2.2 Husbandry.....	20
3.2.3 Identification.....	20
3.3 Procedures.....	21
3.3.1 Study schedule.....	21
3.3.2 Animal number and distribution.....	21
3.3.3 Acclimatization.....	22
3.3.4 Treatment.....	22
3.3.5 Dose levels.....	23
3.3.6 Rationale for dose selection.....	23
3.4 Test article administration and dist.....	24
Route of administration.....	24
Frequency of administration.....	24
Preparation of suspension.....	24
Vehicle.....	24
Volume of suspension applied.....	24
Control analyses.....	24
Control animals.....	24
3.4.1 Diet.....	25
3.4.2 Water.....	25
3.5 Observations and records.....	25
3.5.1 Standard animal observations.....	26
3.6 Neurotoxicologic examinations.....	26
3.6.1 Detailed clinical observations.....	27

3.6.2	Functional observational battery (FOB).....	27
3.6.3	Motor activity.....	29
3.7	Laboratory investigations.....	30
3.7.1	Parameters and methods used in hematology....	31
3.7.2	Parameters and methods used in blood chemistry.....	32
3.7.3	Parameters and methods used in urinalysis....	34
3.8	Pathology.....	35
3.8.1	Macroscopical examination.....	35
3.8.2	Microscopical examination.....	36
3.8.3	Acquisition and presentation of pathology data.....	37
3.9	Statistical analysis.....	39
4	Results.....	41
4.1	Analytical results.....	41
	Pretest analytics.....	41
	Test analytics.....	42
4.2	In-life observations.....	42
4.2.1	Clinical signs.....	42
4.2.2	Functional observational battery (FOB).....	42
4.2.3	Motor activity.....	42
4.2.4	Mortality.....	43
4.2.5	Body weight.....	43
4.2.6	Food consumption.....	43
4.2.7	Food consumption ratios.....	43
4.2.8	Water consumption.....	44
4.2.9	Hematology.....	44
4.2.10	Blood chemistry.....	45
4.2.11	Urine analysis.....	45
4.3	Organ weights and ratios.....	46
4.4	Pathology.....	47
4.4.1	Macroscopical findings.....	47
4.4.2	Microscopical findings.....	47
5	Discussion.....	48
6	References.....	50
7	Figures.....	51
7.1	Functional observational battery (Measurements)...	52
7.2	Motor activity.....	54
7.2.1	Mean session totals males.....	54
7.2.2	Mean session totals females.....	55
7.2.3	Motor activity (within-session time course) males.....	56
7.2.4	Motor activity (within-session time course) females.....	58
7.3	Body weight.....	60
7.4	Food consumption.....	62
7.5	Food consumption ratios.....	64
7.6	Water consumption.....	66

8	Tables (means, statistics).....	68
8.1	Analytical results.....	69
	Pretest analytics.....	69
	Test analytics.....	69
8.2	Clinical signs.....	70
8.3	Functional observational battery (means).....	71
8.4	Functional observational battery (statistics).....	76
8.5	Motor activity (means).....	83
8.6	Motor activity (statistics).....	88
8.7	Summary of animal fate.....	97
8.8	Body weight (means).....	98
8.9	Body weight (statistics).....	99
8.10	Food consumption (means).....	105
8.11	Food consumption (statistics).....	106
8.12	Food consumption ratios (means).....	112
8.13	Water consumption (means).....	113
8.14	Water consumption (statistics).....	114
8.15	Hematology (means).....	120
8.16	Hematology (statistics).....	126
8.17	Blood chemistry (means).....	150
8.18	Blood chemistry (statistics).....	155
8.19	Urine analysis (means).....	174
8.20	Urine analysis (statistics).....	180
8.21	Organ weights and ratios (means).....	190
	8.21.1 Organ weights (means).....	190
	8.21.2 Organ to body weight ratios (means).....	192
	8.21.3 Organ weights (means): 2. sacrifice.....	194
	8.21.4 Organ to body weight ratios (means): 2. sacrifice.....	195
8.22	Organ weights and ratios (statistics).....	198
	8.22.1 Organ weights (statistics).....	198
	8.22.2 Organ to body weight ratios (statistics).....	204
	8.22.3 Organ weights (statistics): 2. sacrifice.....	209
	8.22.4 Organ to body weight ratios (statistics): 2. sacrifice.....	214
9	Appendix A: Individual data.....	216
9.1	Clinical signs (individuals).....	219
9.2	Functional observational battery (individuals).....	223
9.3	Motor activity (individuals).....	240
9.4	Mortality (individuals).....	263
9.5	Body weight (individuals).....	272
9.6	Food consumption (individuals).....	273
9.7	Water consumption (individuals).....	284
9.8	Hematology (individuals).....	290
9.9	Blood chemistry (individuals).....	318
9.10	Urine analysis (individuals).....	339
9.11	Organ weights and ratios (individuals).....	353
	9.11.1 Organ weights (individuals).....	353
	9.11.2 Organ to body weight ratios (individuals).....	365
	9.11.3 Organ weights (individuals): 2. sacrifice.....	374
	9.11.4 Organ to body weight ratios (individuals): 2. sacrifice.....	378

Page

VOLUME 2 OF 2 OF SUBMISSION

10 Appendix B: Analytical report..... 386

11 Appendix C: Reference values..... 406

11.1 Scoring criteria used in FOB..... 406

11.2 Assignment of signs and functions to functional domains..... 414

11.3 Units used in hematology..... 415

11.4 Reference values: Hematology..... 416

11.5 Reference values: Blood chemistry..... 420

11.6 Reference values: Urine analysis..... 424

11.7 Reference values: Organ weights..... 426

12 Appendix D: Pathology report..... 434

13 Appendix E: Study protocol and amendment..... 499

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1. SUMMARY AND CONCLUSION

This study in rats was designed to determine the oral toxicity of CGA 62826 tech. (Metabolite of CGA 48988) when administered by gavage over a period of 28 consecutive days, to estimate a no-observed-adverse-effect level of exposure (NOAEL), and to evaluate reversibility, persistence of, or delayed occurrence of potential toxic effects after a 4-week recovery period.

The test article CGA 62826 tech. (Batch no. RV-1592/4, Purity 100 %), suspended in vehicle (0.5% CMC/0.1% Tween 80), was administered by gavage at daily doses of 0, 10, 50, 200, and 1000 mg/kg body weight to a total of 70 albino rats, 5 animals per sex and dose group (experimental group I). At the control and high dose level, additionally 5 animals per sex were used for recovery evaluation (experimental group II). 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.

Test article analytics

The test article was homogeneously distributed in the vehicle and was stable at the targeted concentrations. Weekly analyses of test article suspensions used in the study confirmed the intended doses.

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

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

Throughout the entire study period neither daily clinical observations, weekly detailed clinical observations, nor functional measurements performed at week 4 and 8 did reveal any change of toxicological relevance. At week 4 and 8 motor activity measurements, no significant changes were observed in any of the parameters assessed.

Mortality

No treatment-related death occurred during the study.

Body weight

The body weight development of treated male and female groups was not influenced by treatment.

Food consumption

There were no relevant differences in mean food consumption between treated groups and controls.

Food consumption ratios

Similar mean food consumption ratios were obtained for treated and control groups.

Water consumption

The mean water consumption of all treated groups was similar to that of the respective control groups.

Hematology

The treatment had no effect on the hematological profile of male and female rats.

Blood chemistry

The treatment had no effect on blood chemistry parameters investigated.

Urine analysis

The treatment did not influence the urine parameters investigated.

Organ weights

At treatment end, relative liver weights of males treated at 1000 mg/kg were minimally increased. Equally, a tendency to increased liver weights was also noted for female groups 3 and 5 (50 and 1000 mg/kg). These changes were reversible within the recovery period.

Pathology

No treatment-related changes were observed at necropsy.

On microscopical examination, minimal hypertrophy of liver hepatocytes was found at increased incidences in male groups 4 and 5 (200 and 1000 mg/kg) and in female groups 3, 4 and 5 (50, 200, and 1000 mg/kg). This treatment-related effect disappeared within the scheduled recovery period.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Conclusion

Under the conditions of this test, treatment with CGA 62826 tech. (Metabolite of CGA 48988) was well tolerated without any signs of overt toxicity. There was no indication of a neurotoxic potential of the test article. Minimal changes to the liver (hypertrophy of liver hepatocytes, increases in liver weights) indicated a weak hepatotropic effect of the treatment. However, considering the complete reversibility of these changes after a 4-week recovery period, treatment with CGA 62826 tech. did not result in adverse effects.

It can be inferred from the observations made during the above study, that the "no-observed-adverse-effect level" (NOAEL) is defined as 1000 mg/kg body weight per day for animals of both sexes.

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2. INTRODUCTION

Purpose

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

Good laboratory practice

The 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 of the study

This study was 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).

Sponsor

Novartis Crop Protection
4002 Basel / Switzerland

Testing facility

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

Novartis Crop Protection
Toxicology/Experimental Toxicology
4332 Stein / Switzerland

Laboratory investigations were performed at:

Novartis Crop Protection
Toxicology/Toxicology Services
4332 Stein / Switzerland

Tissue processing and slide preparation from animals of experimental group I was contracted to the following laboratory:

ProPath (UK) LTD.
Willow Court
Netherwood Road
Hereford HR2 6JU
England

Tissue processing and slide preparation from animals of experimental group II was performed at:

Novartis Crop Protection
Toxicology/Toxicology Services
4002 Basel / Switzerland

Histopathological examination was performed at:

Novartis Crop Protection
Toxicology/Toxicologic Pathology
4002 Basel / Switzerland

Analytical examinations were performed at:

RCC Umweltchemie AG
4452 Itingen / Switzerland

Study dates

Study initiation: September 16, 1996 (protocol date)

Completion date: December 18, 1996 (sacrifice 2, recovery group)

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Personnel and responsible scientists

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

Study director: Dr. phil.-nat. [redacted]
Longterm Toxicology

Technical assistant: [redacted]
Longterm Toxicology

Supervisor: [redacted]
Longterm Toxicology

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

Laboratory investigations: Dr. med. vet. [redacted]
FVH Clinical Chemistry
Toxicology Services

Laboratory assistant: [redacted]
Clinical Laboratory

Necropsy and Pathology services: Dr. med. vet. [redacted]
Pathology Services
Dr. med. vet. [redacted]
FVH Clinical Chemistry
Toxicology Services
(as from January 1, 1997)

Tissue processing and slide preparation: Mr. [redacted] F.I.M.L.S.
ProPath (UK) LTD.

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

Study pathologist: Dr. med. vet. [redacted]
B.V.M.S., M.R.C.V.S., FTA Pathology
Toxicologic Pathology

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

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 Toxicology Services
(WST Facility)

Novartis Crop Protection for Toxicologic Pathology
4002 Basel / Switzerland Toxicology Services
(Basel Facility)

ProPath (UK) LTD. for ProPath (UK) LTD.
Hereford HR2 6JU
England

RCC Umweltchemie AG for RCC Umweltchemie AG
4452 Itingen / Switzerland

Archiving 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 will be stored at this location.

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

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

This report was distributed to:

Dr. **5.1.2.e Woo** (Sponsor)

Archive

2.1. Deviations

Amended

Protocol Amendment No. 1 dated October 23, 1996:

detailed the contracting of the tissue processing and slide preparation (animals of experimental group I) to:

ProPath (UK) LTD.
Willow Court
Netherwood Road
Hereford HR2 6JU
England

Not amended

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 requirements of Good Laboratory Practice.

Dr. med. vet. 5.1.2.e Woo, responsible for laboratory investigations, necropsy and pathology services, left the company as per December 31, 1996. Her responsibilities were assumed by Dr. med. vet. 5.1.2.e Woo, responsible for Toxicology Services.

Effective as of January 31, 1997, the responsibility for Facility Management was transferred to Dr. med. vet. 5.1.2.e Woo. PD Dr. med. vet. 5.1.2.e Woo was appointed Experimental Toxicology Test Unit Manager.

The animals were delivered 4 days earlier than proposed in the protocol. Therefore, the duration of the acclimatization period was prolonged to 11 days.

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

At week 8, motor activity was measured on the same day in males and females and not on different days as proposed in the protocol.

The above mentioned deviations are considered to have no impact on the validity of the study. There were no known circumstances that could have affected the quality and/or integrity of the data.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

3. MATERIALS AND METHODS

3.1. Test article

Company code No.: CGA 62826 tech.

Batch No.: RV-1592/4

Description: solid

Purity: 100 %

Date of receipt: August 20, 1996

Stability: August 1999

Storage conditions: below 10°C

Pretest analytics

Prior to the start of the study, samples of the vehicle containing the test article at concentrations of 1, 5, 30 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 these analyses (RCC Project 636827) are given in Section 4. "RESULTS" and in Appendix B, respectively.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

Delivery of animals: October 10, 1996

Number of animals
delivered: 40 males, 40 females

Initial body weight:
(range at week -1) 144.3 - 199.0 g in males
117.5 - 150.6 g in females

Initial age: approx. 5 weeks

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 sterilized granulated soft wood bedding (Societe Parisienne des Sciures Pantin). Cages were allocated to racks by sex and group and changed at 1-week intervals.

The animal room was air conditioned:

Temperature: $22 \pm 2^{\circ}\text{C}$
Relative humidity (%): 55 ± 10
Ventilation: 16 - 20 air changes/hour
Light cycle: 12 hours light per day

Neither insecticides nor chemicals were applied in the animal room with the exception of disinfectant: BRADOPHENtm.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

3.2.3. Identification

The animal number was tattooed on the tail root for individual identification. The animal number was identical with the cage number.

3.3. Procedures

A written protocol dated September 16, 1996, was prepared prior to the initiation of this study. A copy of this protocol is included in Appendix E of this report.

Procedures were performed according to Toxicology "Standard Operating Procedures".

3.3.1. Study schedule

Study initiation: September 16, 1996 (protocol date)
Start of acclimatization: October 11, 1996
Treatment start: October 22, 1996
Laboratory investigations: November 19, 1996
Date of sacrifice 1: November 20, 1996 (exp. group I)
Recovery start: November 19, 1996
Laboratory investigations: December 17, 1996 (exp. group II)
Date of sacrifice 2
(experimental end date): December 18, 1996 (exp. group II)

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

3.3.2. Animal number and distribution

Number of animals: 70 (total)
5 males, 5 females per dose group, additionally 5 males and 5 females at the control and high dose level, respectively.

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

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

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

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.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

3.3.4. Treatment

The treatment (daily oral gavage) was performed over a period of 28 days on a main group (experimental group I) and a recovery group (experimental group II) of animals. The surviving animals of experimental group I were sacrificed at the end of the treatment period, those of experimental group II were sacrificed at the end of the recovery period.

3.3.5. Dose levels

0, 10, 50, 200 and 1000 mg/kg body weight.

3.3.6. Rationale for dose selection

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

Project no. 963100

Short/Long-term Toxicology, CIBA-GEIGY Limited, Stein

Acute Oral Toxicity in the Rat

LD50 > 2000 mg/kg body weight.

3.4. Test article administration and diet

Route of administration

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

Frequency of administration

The test article was administered as 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

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

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 (RCC Project 636827) are given in Section 4. "RESULTS" and in Appendix B, respectively.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Control animals

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

3.4.1. Diet

Pelleted, certified standard diet (Nafag No. 8900 FOR GLP) was provided ad libitum (except as noted under Laboratory Investigations). All batches of diet were assayed for composition and contaminant levels by the manufacturer. Analytical results are available at Longterm Toxicology, 4332 Stein / Switzerland. None of the contaminants reported in the analysis profile was considered likely to have affected the conduct or purpose of the study.

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, Toxicology/Experimental Toxicology, as well as the results of inhouse chemical analysis by the analytical laboratories of Novartis Pharma AG, 4002 Basel / Switzerland. There were no contaminants present at concentrations considered likely to have affected the conduct or purpose of the study.

3.5. Observations and records

3.5.1. Standard animal observations

The following observations and recordings were made during both the treatment and the recovery phases of the study:

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.

Clinical signs

In order to detect changes in state of health or behavior, or any reaction to treatment, examination was carried out daily (cage-side observation). All clinical signs 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.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

3.6. Neurotoxicologic examinations

3.6.1. 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.

3.6.2. 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
vocalization	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)
- **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.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

3.6.3. 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 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. 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)

3.7.1. 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

3.7.2. Parameters and methods used in blood chemistry

Parameter	Method of analysis (Method code) <1> Instrument	Abbreviation	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

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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3.7.3. 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

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

3.8. Pathology

3.8.1. 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 with peripheral nerve (sciatic nerve)
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 intestine)
Peyer's patches (large intestine)
kidney, both
urinary bladder
prostate
seminal vesicle

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

testis, both
epididymis, both
uterus
vagina
ovary, both
pituitary gland
adrenal gland, both
thyroid with parathyroid gland
thymus
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.

3.8.2. Microscopical examination

After the fixation, organ samples listed below were taken from all animals of experimental group I, 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
bone marrow (femur)
trachea
lung
heart
liver
stomach
small intestine (duodenum, ileum, jejunum)
large intestine (cecum, colon, rectum)
Peyer's patches (small intestine)
Peyer's patches (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

Male control animal no. 10, originally scheduled for reversibility evaluation (Experimental group II), was found dead on experimental day 5. It was therefore subsequently treated as an animal of experimental group I. The organs and tissues of this animal were taken, processed and examined according to the above mentioned procedure.

After accomplishing the microscopical examination of experimental group I and identifying the liver as a target organ for the treatment-related finding "hepatocytic hypertrophy", liver samples were taken from all animals of experimental group II, processed and examined as mentioned above.

3.8.3. Acquisition and presentation of pathology data

At necropsy, data collected were entered on-line into the data base of a TANDEM-Computer-System using the GUTOX software specially designed for the testing facility and were additionally simultaneously written by hand on the animal raw data sheets archived later on at the testing facility.

All histopathological data were recorded on-line on the DEC/VAX-Microcomputer using the Pathdata-System V3.6B.

The pathology report was written and archived on the above mentioned TANDEM-Computer-System.

At the histopathological examination, all macroscopical lesions identified at necropsy were explicitly correlated to their corresponding microscopical changes using the built-in correlation function of the Pathdata-Reporting-System.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

Grade "1" = minimal / very few / very small: Includes a histopathological change that is inconspicuous or barely a noticeable feature of the tissue.

Grade "2" = slight / few / small: Includes a histopathological change that is a noticeable but not prominent feature of the tissue.

Grade "3" = moderate / moderate number / moderate size: Includes a histopathological change that is a prominent but not dominant feature of the tissue.

Grade "4" = marked / many / large: Includes a histopathological change that is a dominant but not overwhelming feature of the tissue.

Grade "P" = finding present, severity not scored.

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3.9. 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, 1992). Raw and multiplicity-adjusted p-values based on bootstrap resampling were given.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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). 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). 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

4. RESULTS

Figures and Tables (mean values and their statistics, where performed) are given in Sections 7. "FIGURES" and 8. "TABLES", respectively. Individual data and Reference values are given in the Appendices A (Section 9) and C (Section 11), respectively. Pathology data (summary tables, individuals) are given in Appendix D (Section 12).

4.1. Analytical results

Detailed analytical results are given in the original analytical report (RCC Project 636827) which is included in Appendix B of this report. Summarized results thereof are given below.

Acceptability criteria

(According to Standard Operation Procedure at Toxicology/Experimental Toxicology)

Content: An analytical result of test article content 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 container no sample differs from the mean value by more than 20 %.

Stability: The test article in the 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.

Pretest analytics

(Section 8.1; Appendix B)

Prior to the beginning of the study, suspensions containing the test article at concentrations of 1, 5, 30 and 100 mg/ml were analyzed for determination of content, homogeneity and stability.

The results of these analyses (RCC Project 636827) showed that the contents of CGA 62826 tech. in the vehicle were in agreement with the nominal concentrations and that the samples were homogeneous and stable for 4 hours at room temperature.

Test analytics

(Section 8.1; Appendix B)

The mean concentrations of CGA 62826 tech. in the vehicle were found to 108.5%, 107.5%, 111.3% and 111.3% 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.

4.2. In-life observations

4.2.1. Clinical signs

(Sections 8.2; 9.1)

Daily cage-side observations revealed no relevant clinical signs and no changes in behavior were noted.

4.2.2. Functional observational battery (FOB)

(Sections 7.1; 8.3 and 8.4; 9.2; Appendix C)

Observations and functional measurements conducted as part of the detailed clinical observations or FOB were all unremarkable with non-specific signs such as skin lesions being observed with comparable frequency in animals of most dose groups.

Due to the isolated occurrence, the slightly hunched posture and reduced ease of removal from the home-cage observed at week 4 in a control male and a group 3 female, respectively, were considered as incidental.

4.2.3. Motor activity

(Sections 7.2; 8.5 and 8.6; 9.3)

Motor activity measurements conducted in treated and control groups at week 4 and week 8 were all comparable. Statistical analysis did not indicate any relevant difference across groups.

4.2.4. Mortality

(Sections 8.7; 9.4)

No treatment-related death occurred during the study.

Two males of the control group (nos. 2 and 10) and one female of group 2 (no. 47, 10 mg/kg) were found dead at study day 5. However, in absence of dose-dependency and of in-life or postmortem observations indicating a test article related effect, no toxicological relevance was attributed to these deaths.

4.2.5. Body weight

(Sections 7.3; 8.8 and 8.9; 9.5)

The body weight development of treated male and female groups was not influenced by treatment.

Minimally lower mean body weights in male groups 2 and 3 (10 and 50 mg/kg) were mainly due to light-weighted animals (nos. 14 and 20) in the respective groups.

4.2.6. Food consumption

(Sections 7.4; 8.10 and 8.11; 9.6)

There were no relevant differences in mean food consumption between treated groups and controls.

No experimental relevance was attributed to the minimally increased diet intake noted for female groups 3 and 4 (50 and 200 mg/kg), particularly as there was no dose-relationship.

4.2.7. Food consumption ratios

(Sections 7.5; 8.12)

Essentially comparable mean food consumption ratios were obtained for control and treated male and female groups.

4.2.8. Water consumption

(Sections 7.6; 8.13 and 8.14; 9.7)

The mean water consumption of treated male and female groups was considered to be comparable to that of the respective control groups.

As large variations in water consumption were recorded already before treatment start, no toxicological relevance was attributed to higher mean water consumption recorded for the high dose male group (1000 mg/kg).

4.2.9. Hematology

(Sections 8.15 and 8.16; 9.8; Appendix C)

Treatment had no effect on the hematological profile of male and female rats.

The mean value for hemoglobin in females of group 5 (1000 mg/kg) attained a level of statistical significance ($p < 0.05$) from the control value. However, the difference was considered of insufficient magnitude to be of toxicological relevance. No significant difference for hemoglobin was obtained for group 5 females at the end of the recovery period.

Other statistical changes were considered not to be related to the treatment as they did not form a dose-response relationship, or the magnitude of the changes was too small. These include: slightly lower mean red cell volume distribution width (RDW) for group 5 males at the end of the recovery period; higher absolute neutrophil count for group 3 males at week 5; slightly lower relative eosinophil count for group 5 females at week 5, and slightly lower platelet count for group 2 females at week 5.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

4.2.10. Blood chemistry

(Sections 8.17 and 8.18; 9.9; Appendix C)

Treatment had no effect on blood chemistry profile of male and female rats.

Some statistically significant differences between the means were recorded although these changes were considered not to be toxicologically relevant as they did not form a dose-response relationship, or the magnitude of the changes was too small, or the changes were in the opposite direction to those considered to be toxicologically relevant. At week 5, these changes included higher urea and lower sodium values and changes to globulin levels for males of groups 2 and 3 (10 and 50 mg/kg); lower bilirubin, sodium and chloride values for males of group 5 (1000 mg/kg), and a lower protein value for males of group 5 (1000 mg/kg) at the end of the recovery period. In females, at week 5, these changes included: higher albumin and lower potassium values for group 2 (10 mg/kg); higher sodium values for groups 3 and 4 (50 and 200 mg/kg) and lower calcium values for group 3 (50 mg/kg).

4.2.11. Urine analysis

(Sections 8.19 and 8.20; 9.10; Appendix C)

The qualitative and quantitative tests performed gave no indication of a treatment-related effect.

Some statistically significant differences between the means were recorded although these changes were considered not to be toxicologically relevant as the magnitude of the changes was too small, and/or the changes were in the opposite direction to those considered to be toxicologically relevant. At week 5, these findings included a lower erythrocyte content for males of group 5 (1000 mg/kg), and slightly more acidic urine excreted by females of group 5 (1000 mg/kg) with lower ketone and urobilinogen values.

4.3. Organ weights and ratios

(Sections 8.21 and 8.22; 9.11; Appendix C)

Although within the historical control range, minimally increased mean liver to body weight ratio (statistically significant) was recorded for male group 5 (1000 mg/kg). Equally, a tendency to increased liver weights was noted for female groups 3 and 5 (50 and 1000 mg/kg). After the 4-week recovery period, liver weights of group 5 animals were comparable to the respective controls.

Additionally, a few statistically significant differences in relative organ weights were found. However, in absence of dose-relationship and histopathological correlates, no experimental relevance was attributed to these findings (thymus, male group 3; testis, male group 2; spleen, female group 5).

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4.4. Pathology

The tabulated summaries of the gross pathological and histopathological examinations and the detailed findings for individual animals are presented in the Pathology Report given in Appendix D.

4.4.1. Macroscopical findings

No treatment-related changes were observed at necropsy.

The few findings recorded occurred with no dose-relation and were comparable to those occurring spontaneously in our colony of rats. Thus, no experimental relevance is attributed to these findings.

4.4.2. Microscopical findings

Minimal hypertrophy of liver hepatocytes was found to be increased in male groups 4 and 5 (200 and 1000 mg/kg) and in female groups 3, 4 and 5 (50, 200, and 1000 mg/kg) at the end of the treatment (experimental group I), respectively. This treatment-related effect disappeared within the scheduled recovery period (experimental group II).

The incidences of this lesion were as follows:

	affected / examined males	affected / examined females
Experimental group I :		
Dose group:		
1 (0 mg/kg)	1/6	1/5
2 (10 mg/kg)	1/5	1/5
3 (50 mg/kg)	1/5	3/5
4 (200 mg/kg)	3/5	2/5
5 (1000 mg/kg)	4/5	3/5
Experimental group II:		
Dose group:		
1 (0 mg/kg)	2/4	1/5
5 (1000 mg/kg)	2/5	1/5

Additionally, some other microscopical changes were found in this study. They commonly occur in our colony of rats, and, neither their incidences nor their distribution and morphological appearance gave any indication of a treatment-related association.

5. DISCUSSION

Oral administration of CGA 62826 tech. (Metabolite of CGA 48988) to rats by daily gavage at dose levels up to 1000 mg/kg body weight was well tolerated without effect on mortality, clinical signs, functional observational battery, motor activity and histopathology of the nervous system, body weight, and food and water consumption. Equally, the treatment had no effect on hematology, blood chemistry or urinalysis parameters.

As substantiated by minimal and reversible hypertrophy of liver hepatocytes in males treated at 200 and 1000 mg/kg and in females treated at 50, 200 and 1000 mg/kg, correlated with minimal and reversible liver weight increases (male group 5; female groups 3 and 5), the test article was shown to exhibit a weak hepatotropic effect.

Taking into account the minimal extent of effects observed as well as their complete reversibility, no toxicological importance is attributed to these findings. Therefore, for both sexes a dose level of 1000 mg/kg body weight per day is considered to represent the "no-observed-adverse-effect level" (NOAEL) for CGA 62826 tech. when administered by daily gavage for 28 days.

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

CONCLUSION

Oral administration of CGA 62826 tech. by daily gavage for 4 weeks to Sprague-Dawley derived rats resulted in:

- No effect on mortality;
- No effect on appearance and behavior;
- No effect on in-life and postmortem neurotoxicologic examinations;
- No effect on body weight development, diet and water consumption;
- No effect on laboratory investigations (hematology, blood chemistry, urine analysis);
- Reversibly increased relative liver weights in male group 5 (1000 mg/kg) and a tendency to increased liver weights in females of groups 3 and 5 (50 and 1000 mg/kg); and
- Minimal and reversible hypertrophy of liver hepatocytes in males at 200 and 1000 mg/kg and in females at 50, 200 and 1000 mg/kg.

Based on the results of this study, the "no-observed-adverse-effect level" (NOAEL) is defined as 1000 mg/kg body weight per day for animals of both sexes.

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7. FIGURES

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

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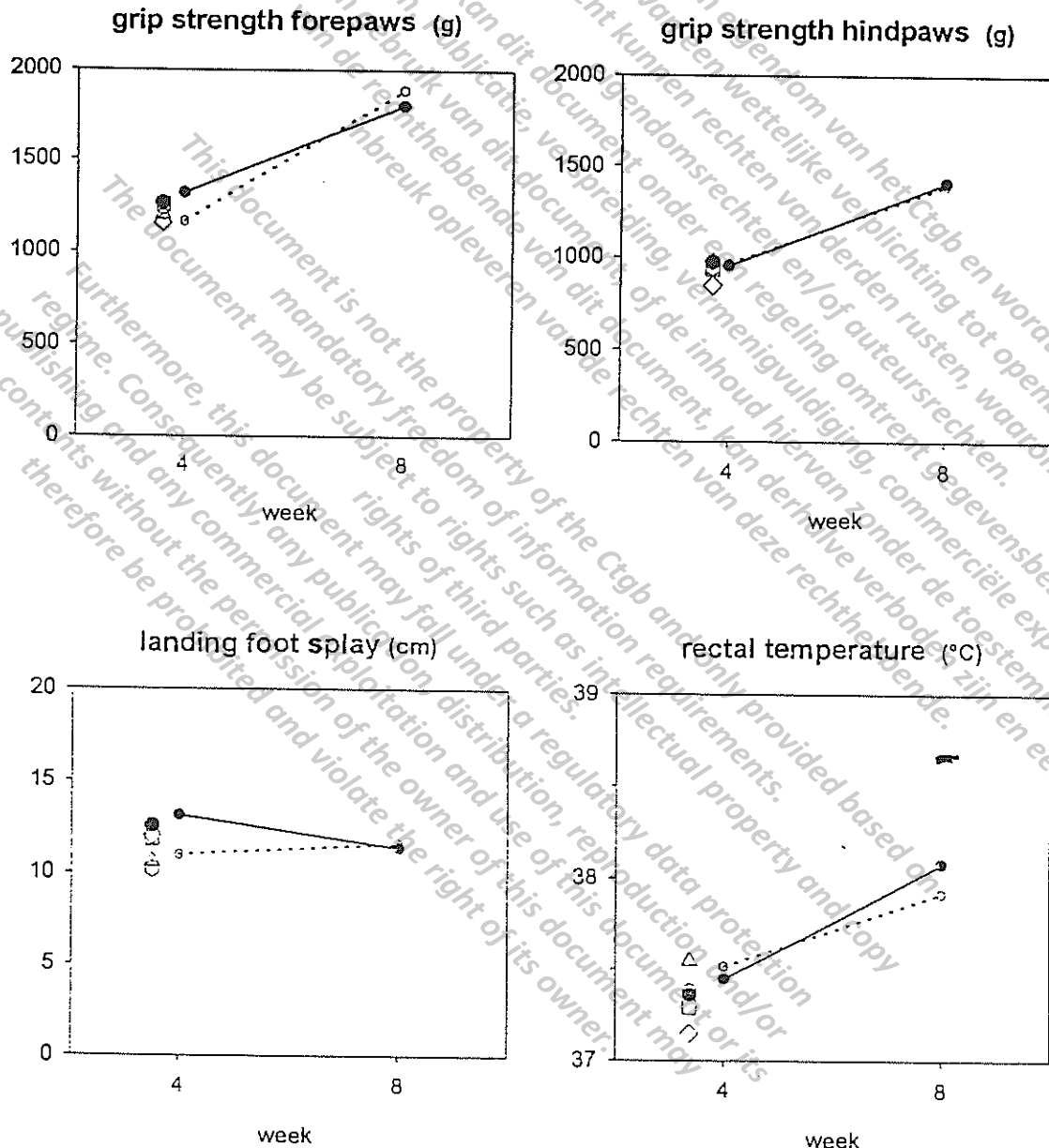
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7.1. Functional Observational Battery (Measurements)

Group means for functional measurements measured at each of the time points.



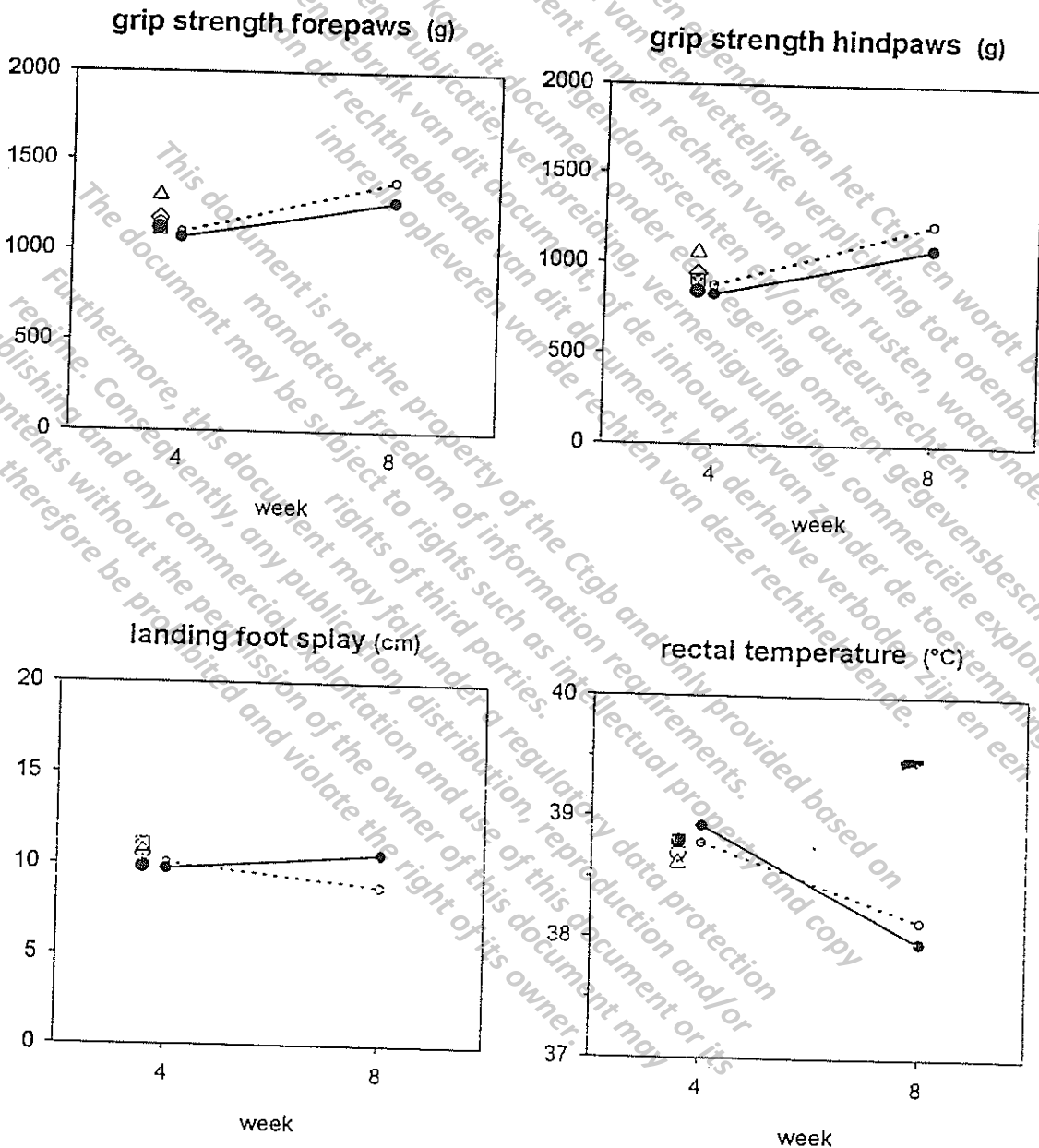
males

- control
- ▲····▲ CGA 62926 10 mg/kg
- ◇····◇ CGA 62826 50 mg/kg
- CGA 62826 200 mg/kg
- CGA 62826 1000 mg/kg

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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



females

- control
- △····△ CGA 62826 10 mg/kg
- ◇····◇ CGA 62826 50 mg/kg
- CGA 62826 200 mg/kg
- CGA 62826 1000 mg/kg

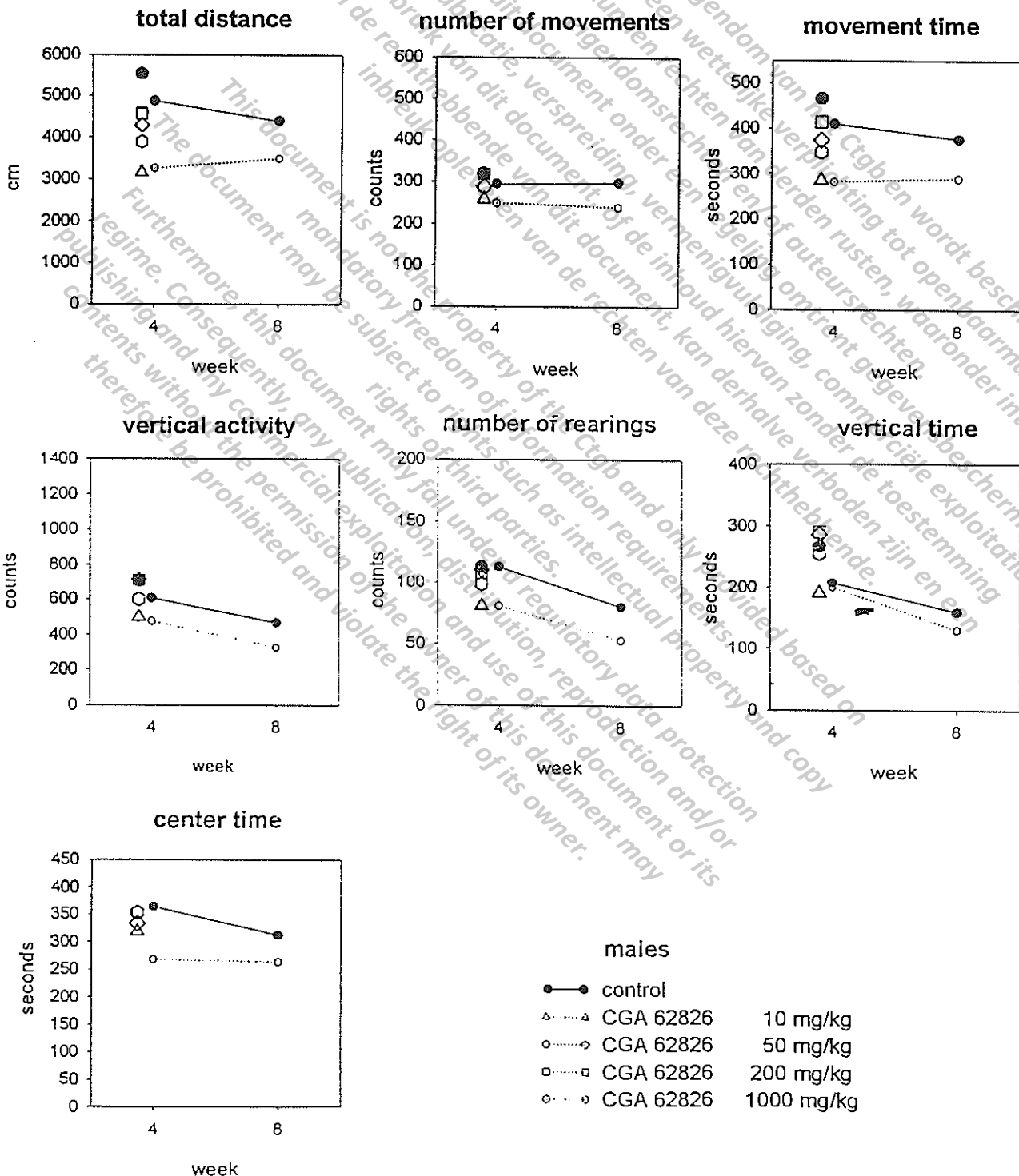
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7.2. Motor activity

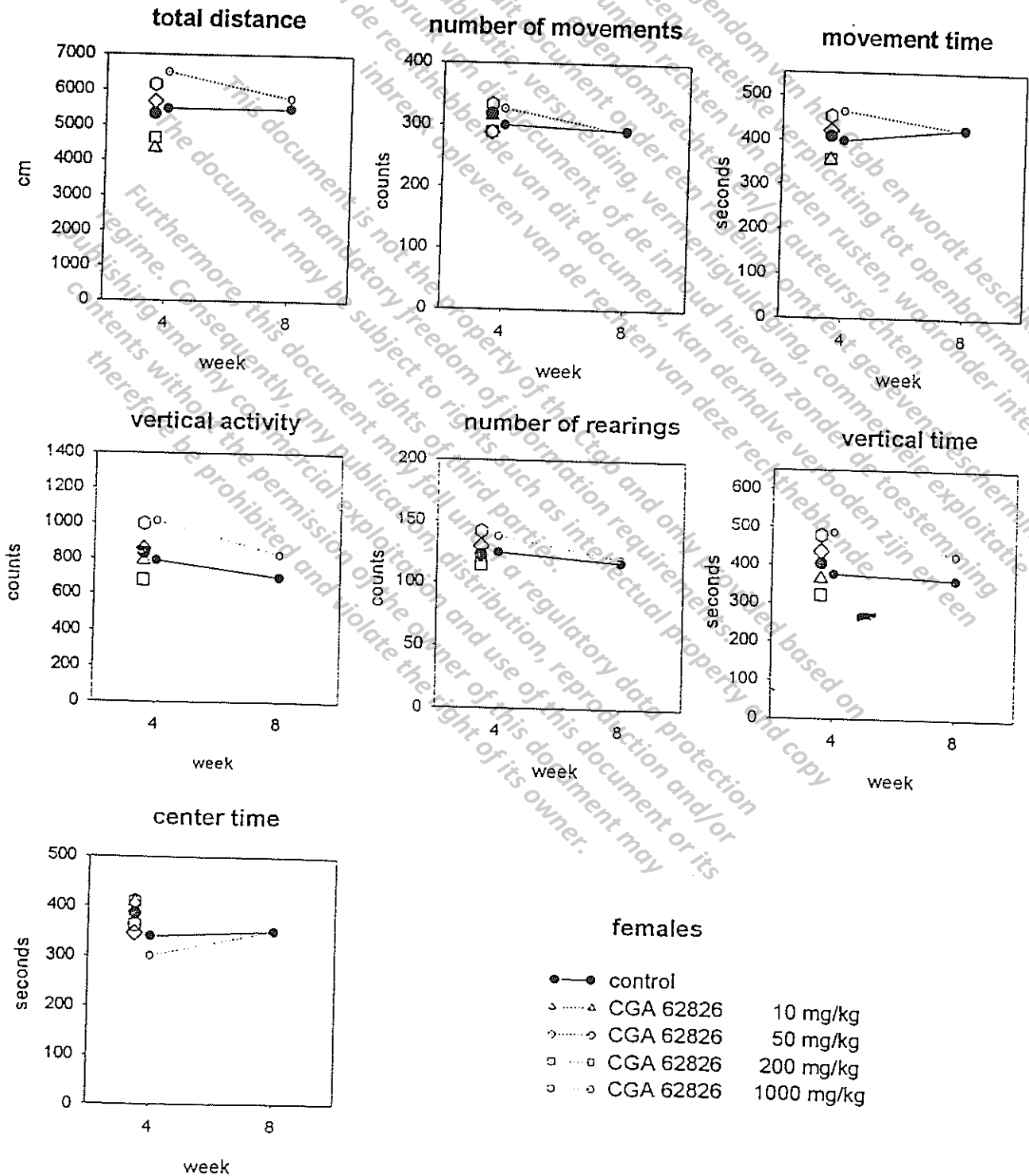
7.2.1. Mean session totals males

Group means of session totals for horizontal and vertical motor activity parameters and for center time for each of the time points measured



7.2.2. Mean session totals females

explanations see legend Figure 7.2.1



females

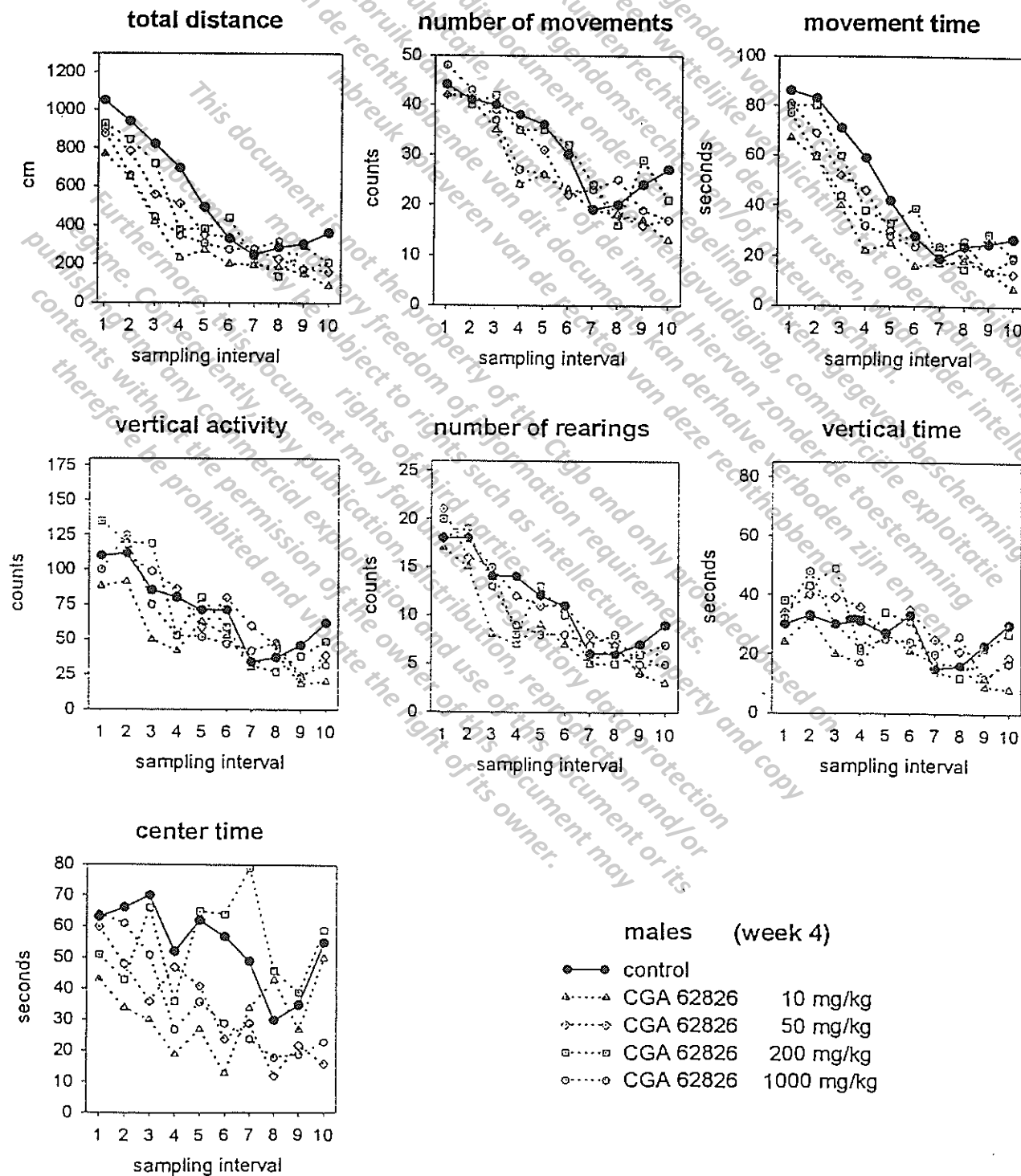
- control
- △—△ CGA 62826 10 mg/kg
- CGA 62826 50 mg/kg
- CGA 62826 200 mg/kg
- ◇—◇ CGA 62826 1000 mg/kg

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

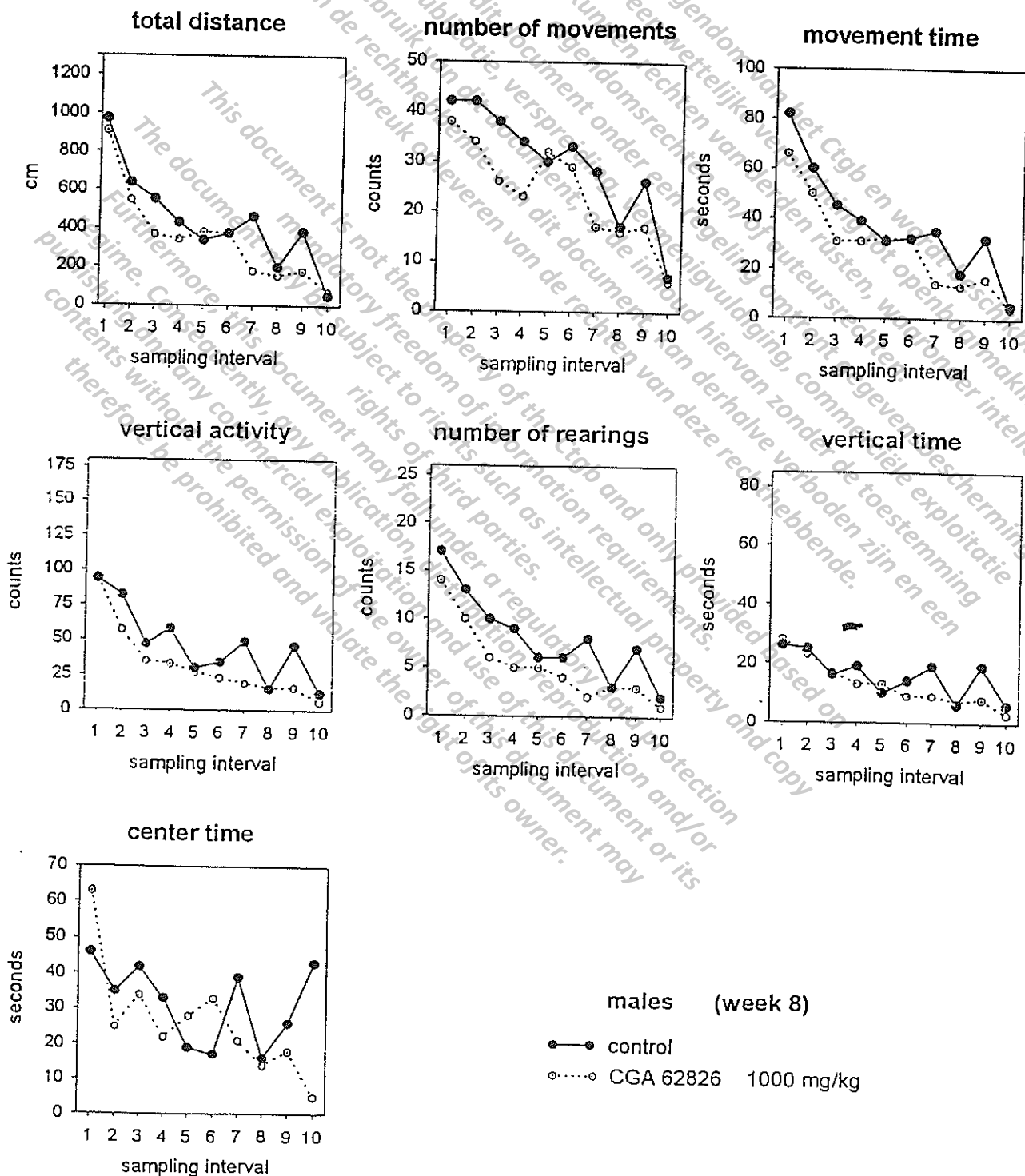
Group means for horizontal and vertical motor activity parameters and for center time for each of the 10 sampling intervals of a session.



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

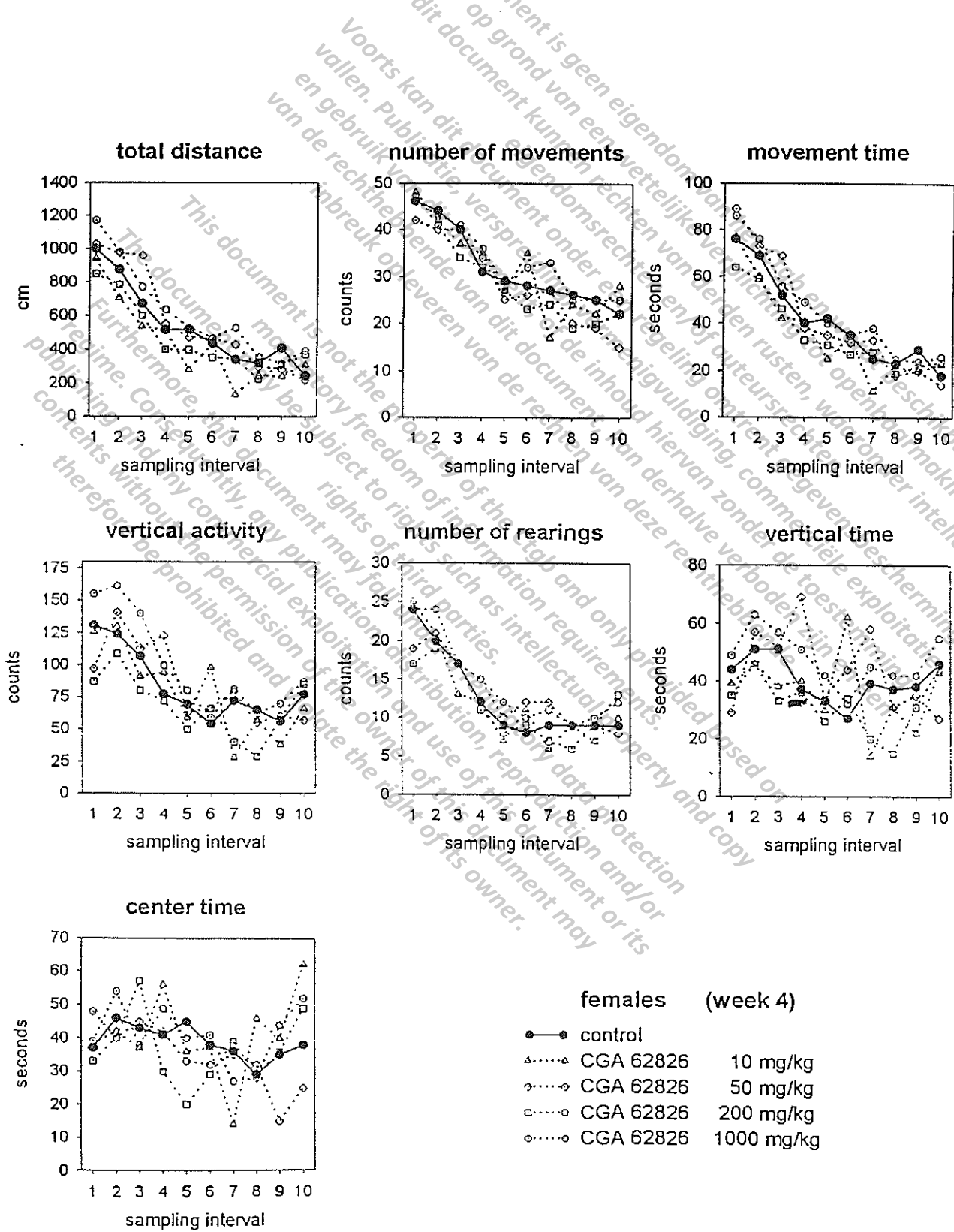


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7.2.4. Motor activity (within-session time course) females

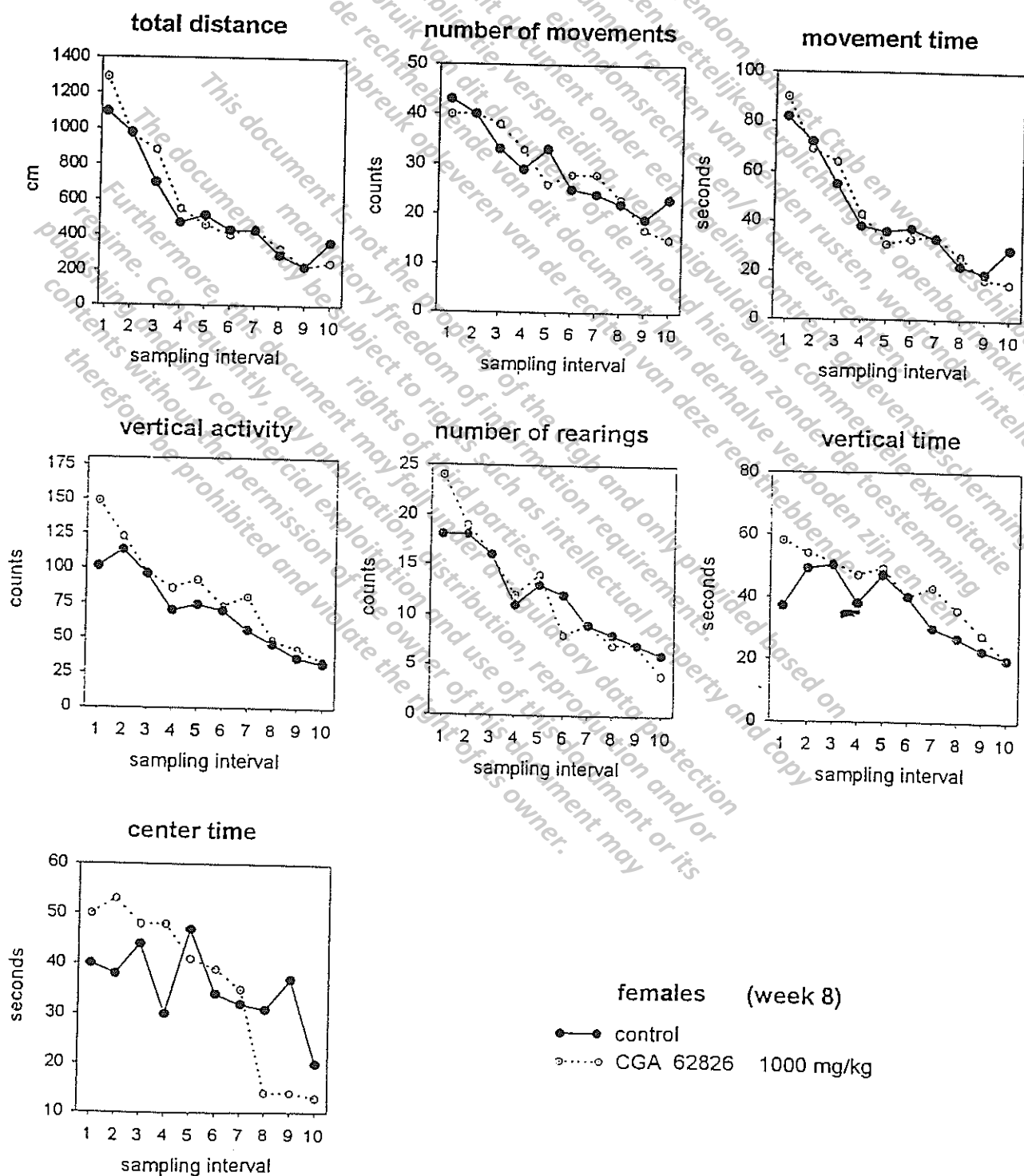
explanations see legend Figure 8.4.3



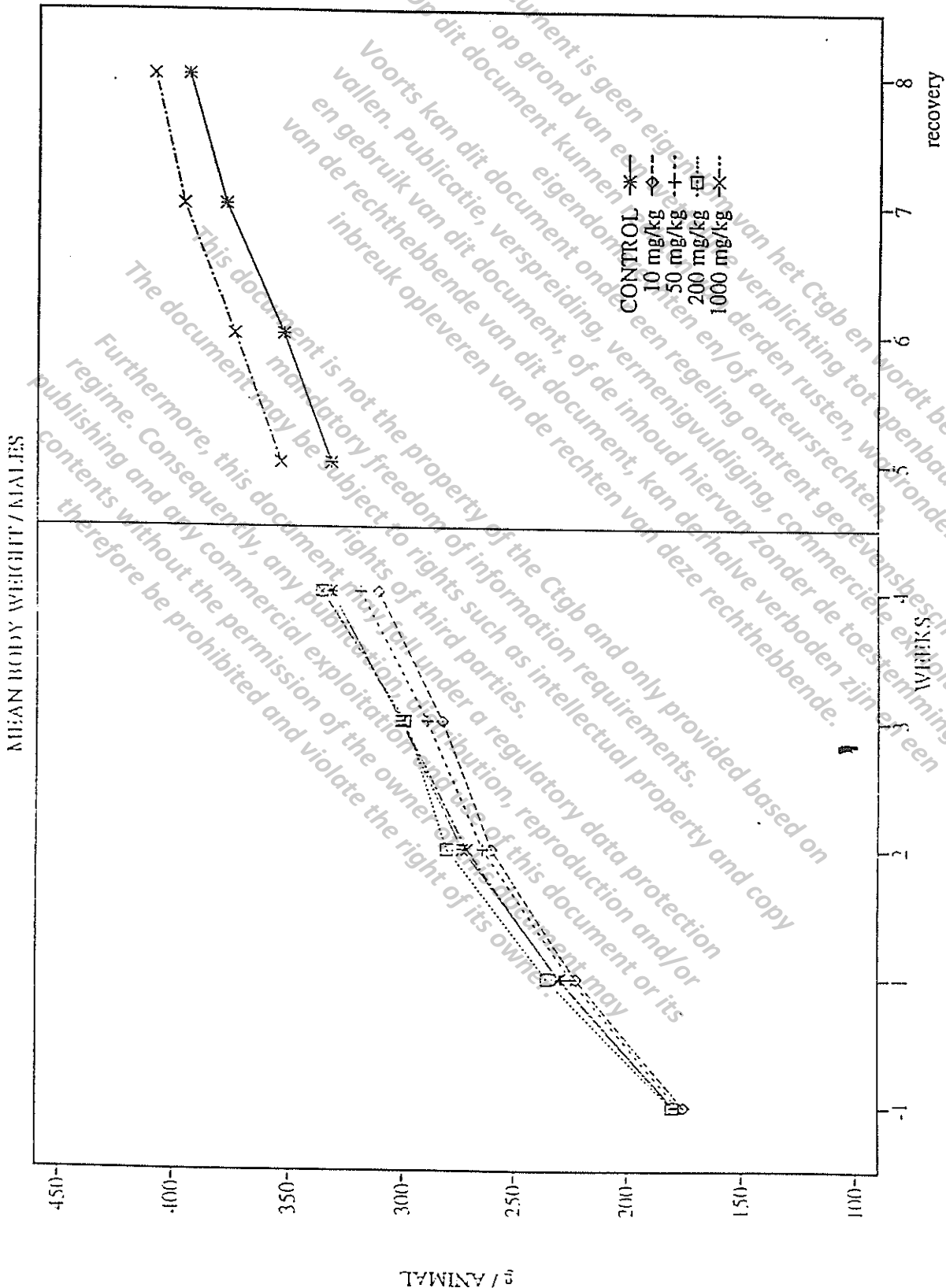
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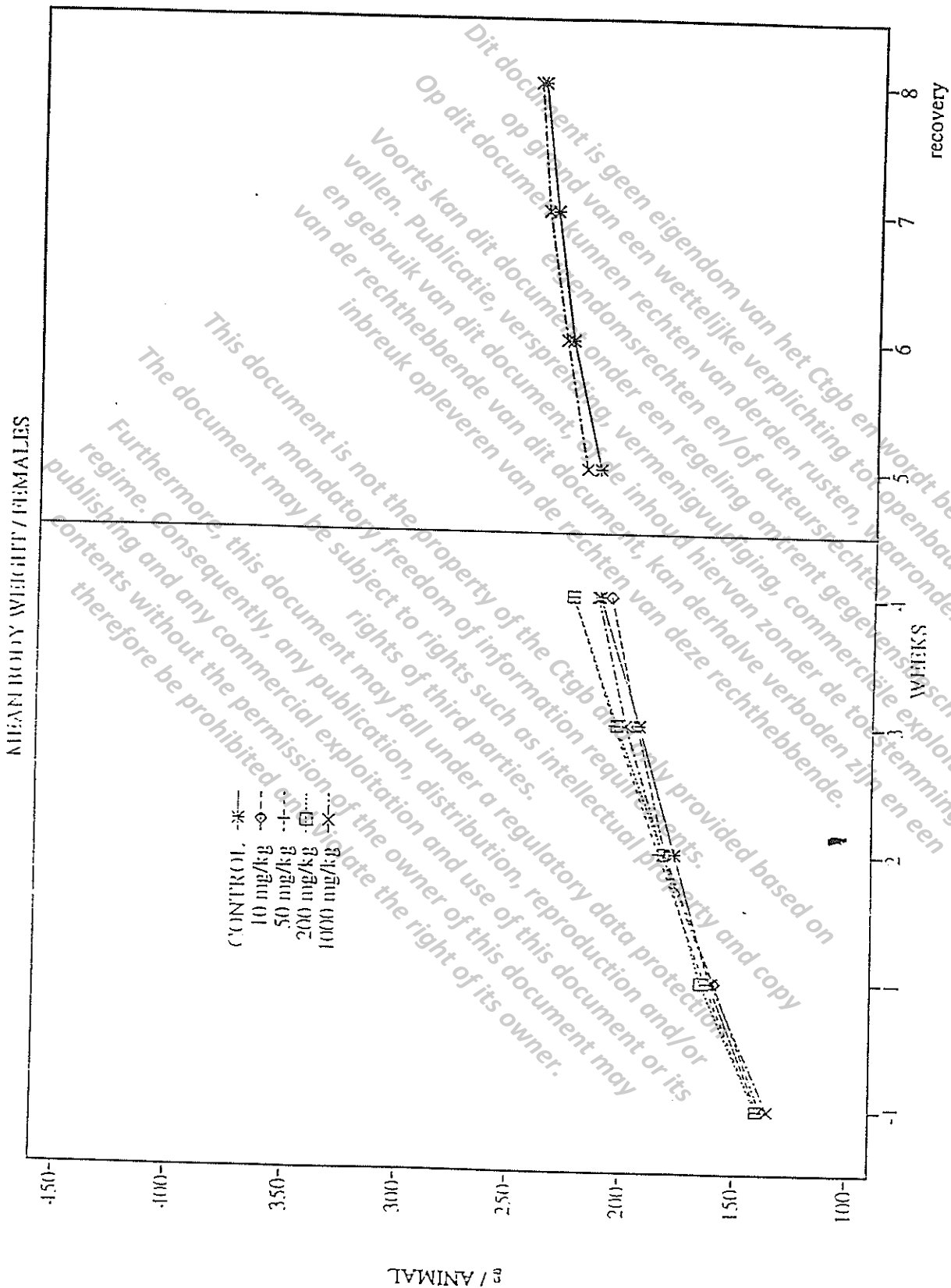
Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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



7.3. Body weight

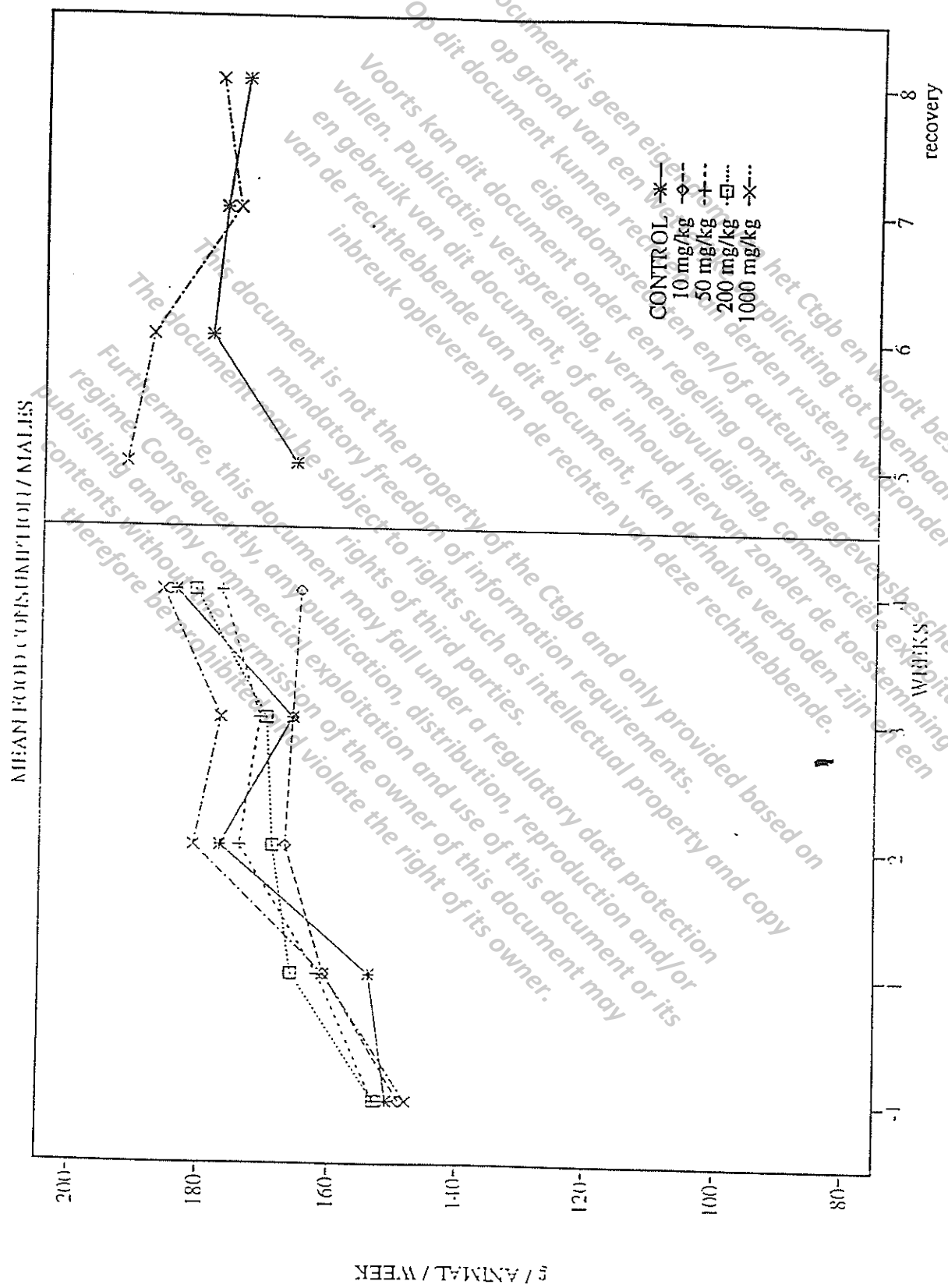




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7.4. Food consumption



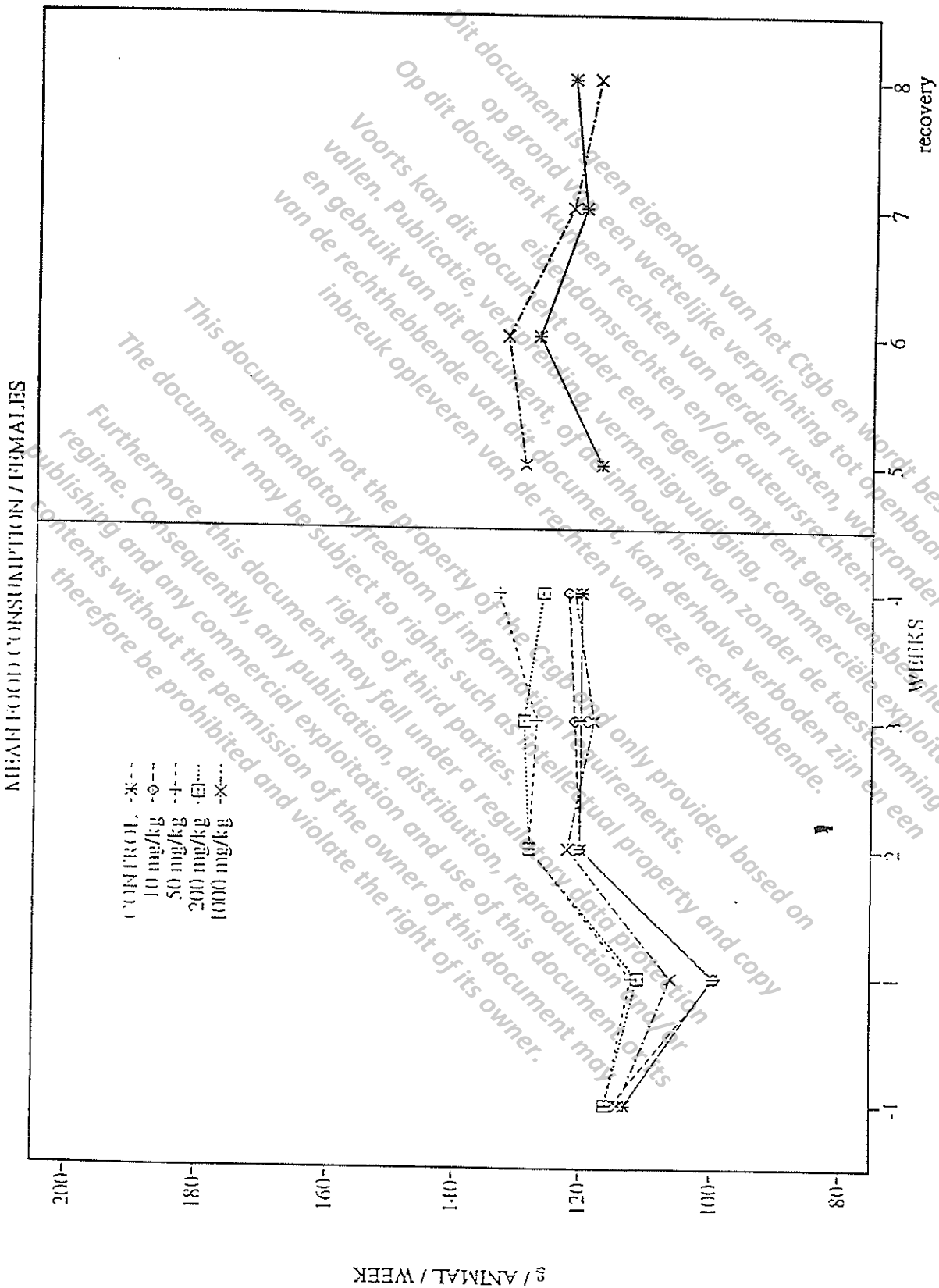
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28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)



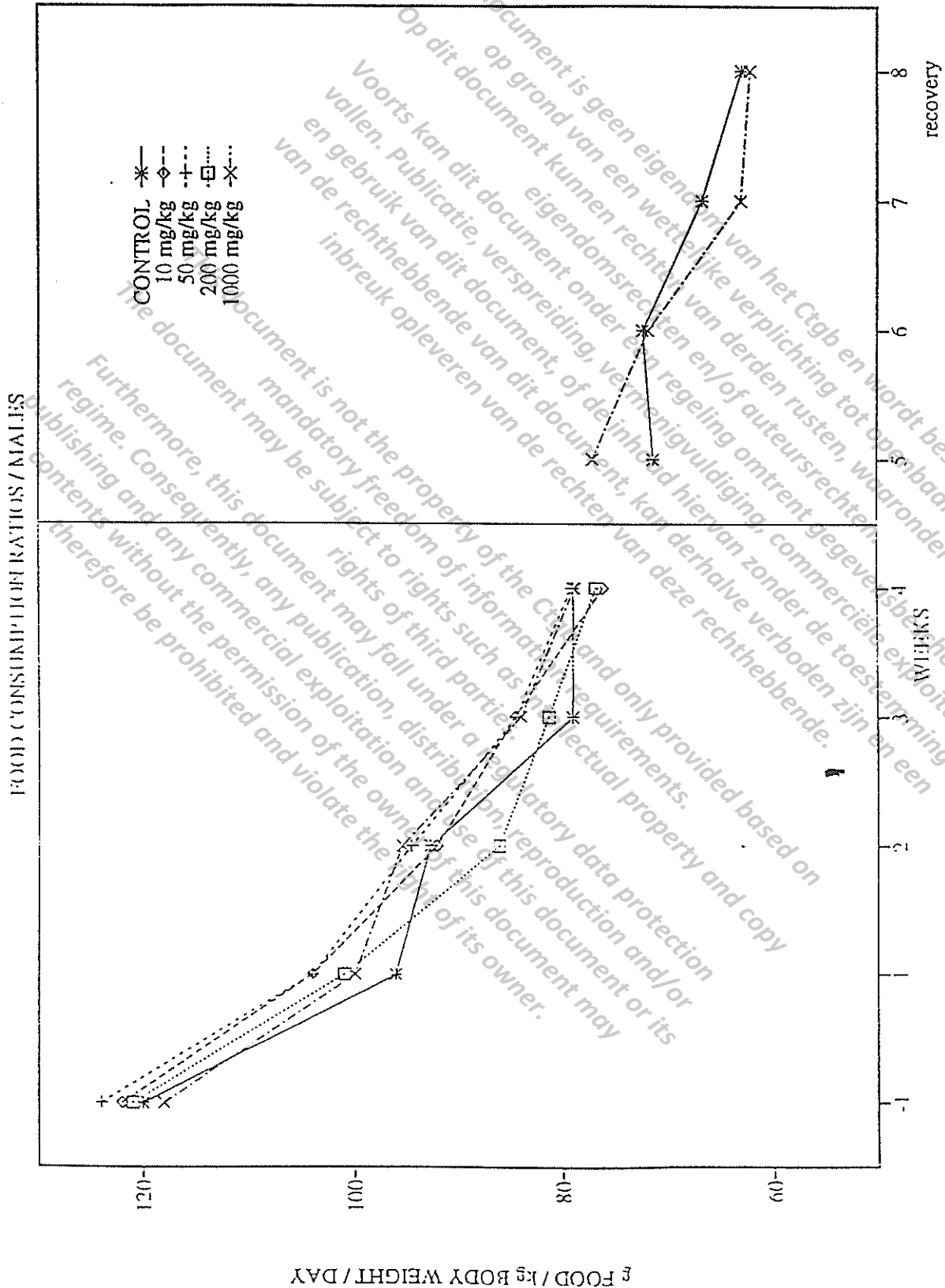
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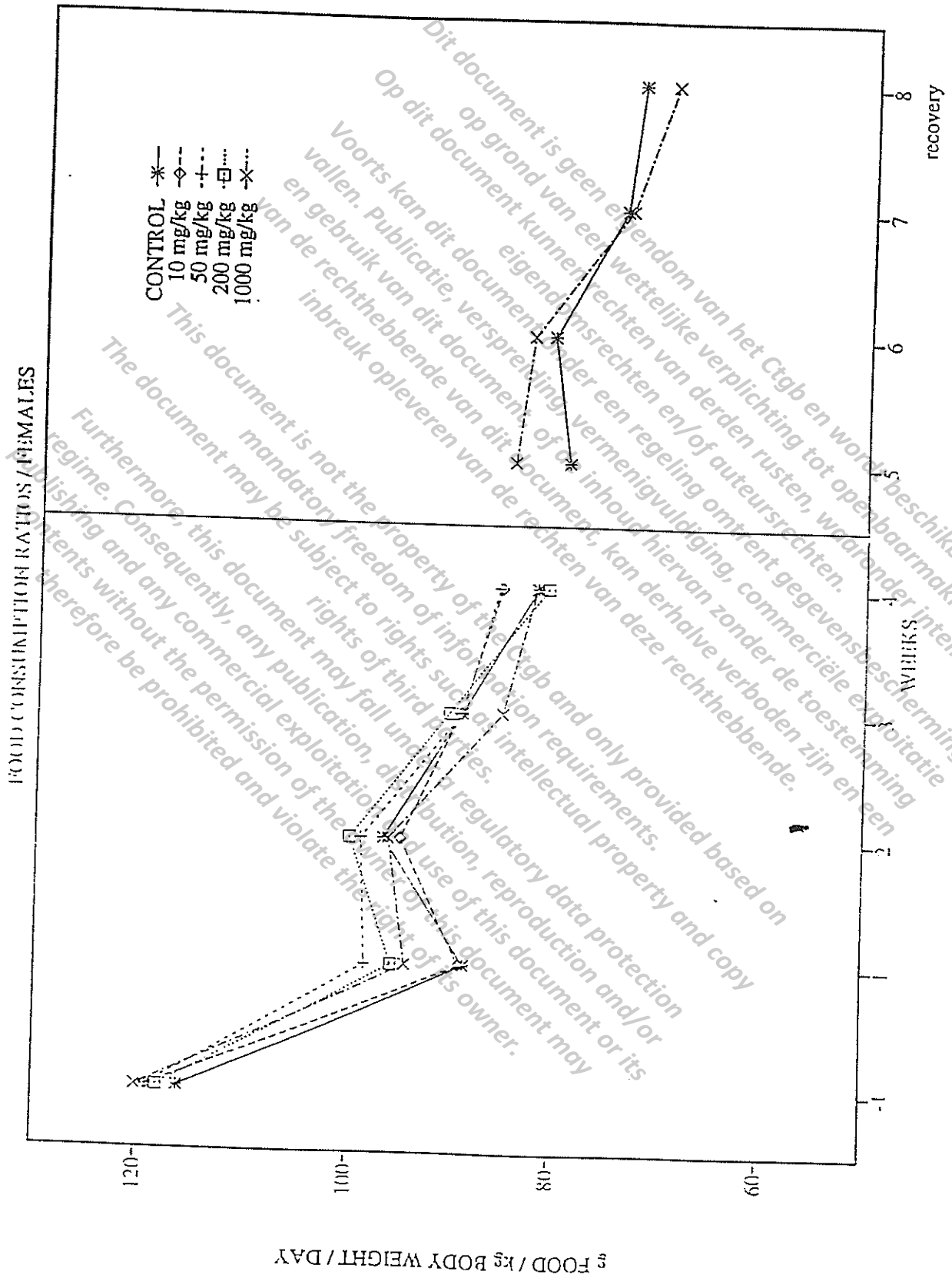
7.5. Food consumption ratios



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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)



FOOD CONSUMPTION RATIOS / FEMALES

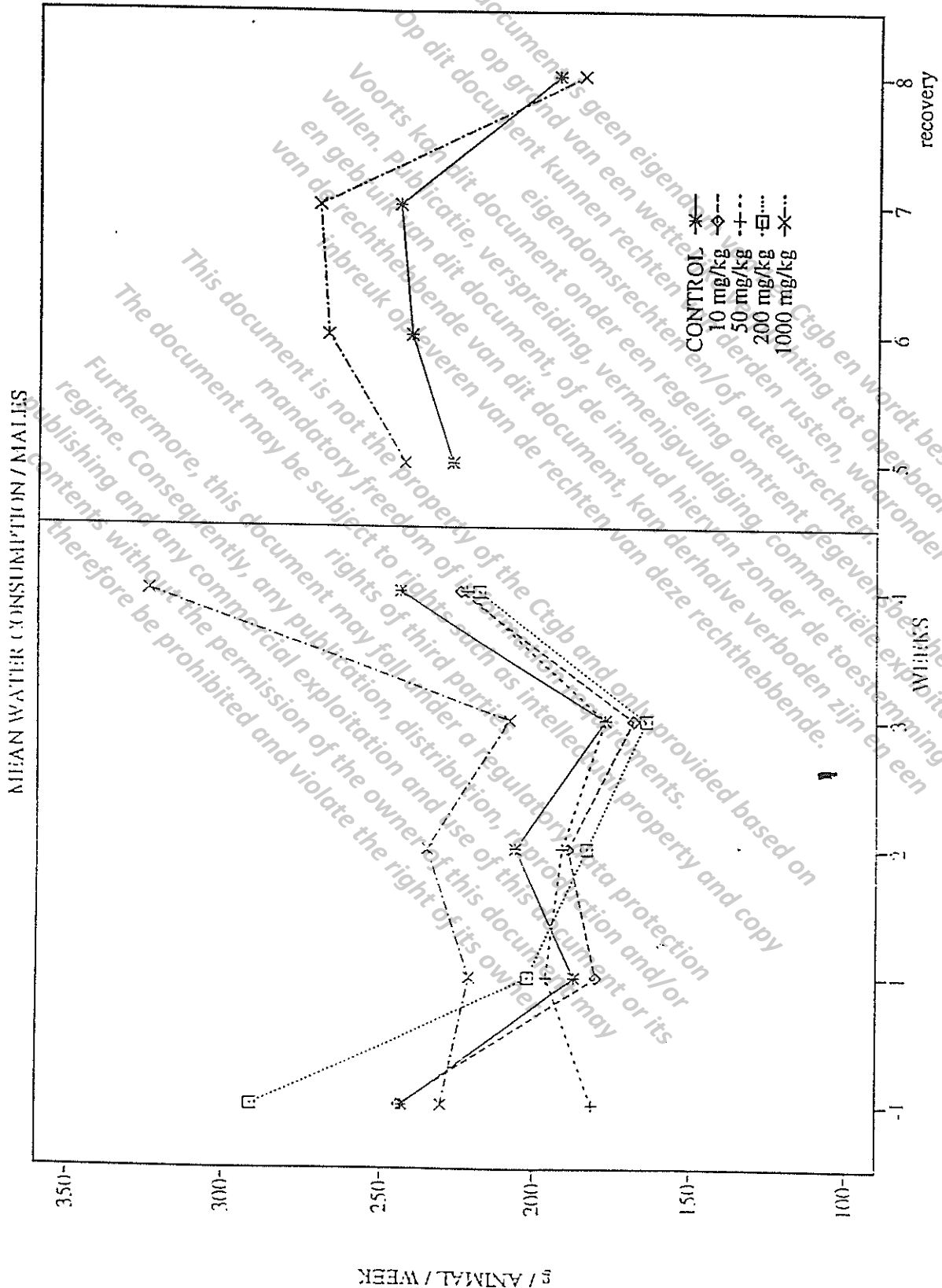
recovery

FOOD / kg BODY WEIGHT / DAY

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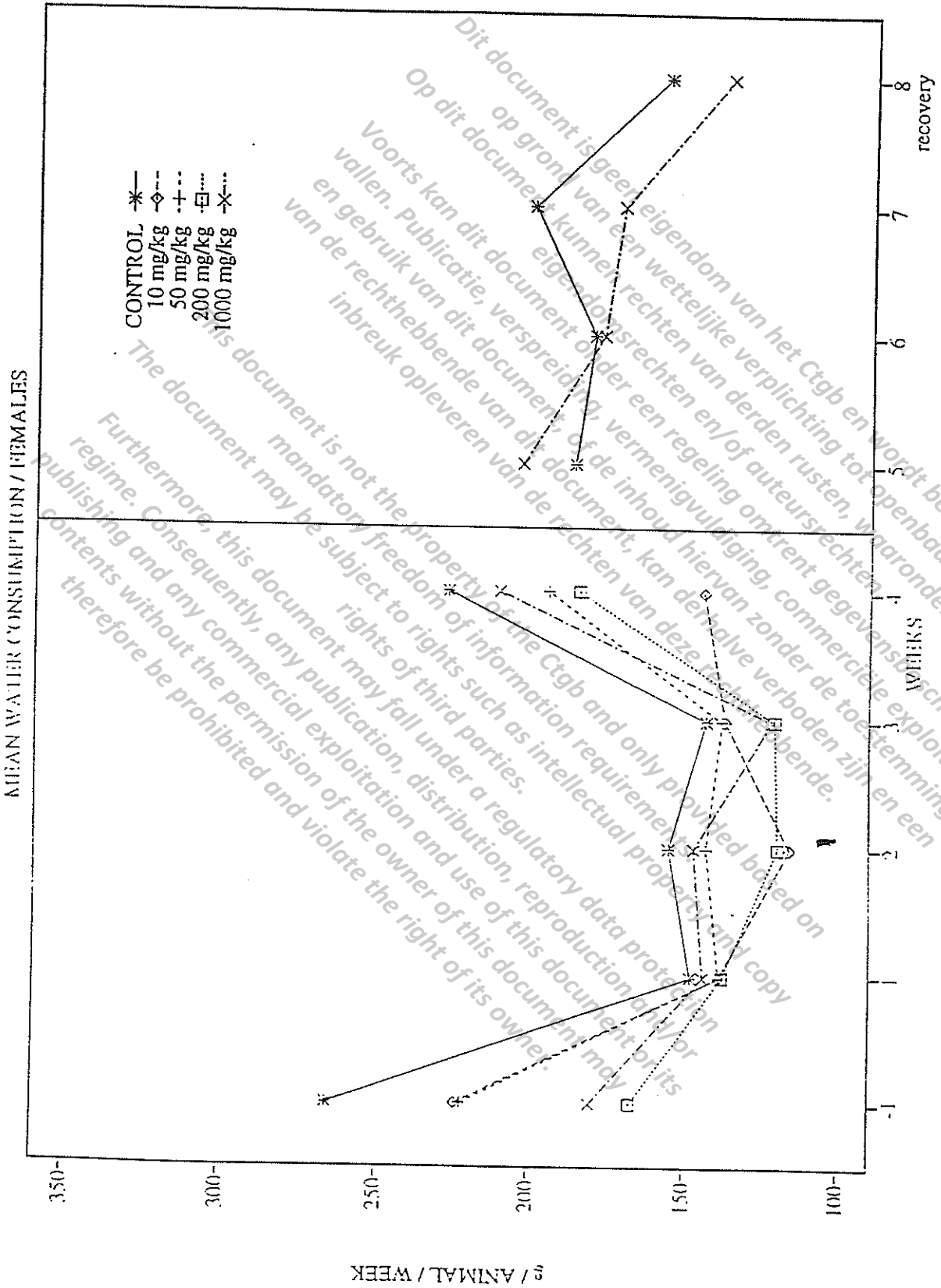
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7.6. Water consumption



Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)



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8. TABLES (MEANS, STATISTICS)

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8.1. Analytical results

Pretest analytics

CGA 62826 tech.

HOMOGENEITY AND STABILITY

	GROUP 2	GROUP 3	GROUP 4	GROUP 5
NOMINAL (mg/ml)	1	5	30	100
ANALYTICAL (mg/ml)				
pretest: A	1.024	5.093	29.64	99.1
B	1.009	5.084	30.01	100.8
C	1.072	5.092	29.90	99.7
S	1.039	5.071	30.87	100.2

- A: Top of mixing container
- B: Middle of mixing container
- C: Bottom of mixing container
- S: Stability over 4 hours

Test analytics

CGA 62826 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	1.090	5.238	22.11	110.8
2	1.141	5.298	23.09	117.5
3	0.986	5.509	22.40	108.0
4	1.124	5.455	21.42	108.7
MEAN 1 - 4	1.085	5.375	22.26	111.3
MEAN (%)	108.5	107.5	111.3	111.3

8.2. Clinical signs

Identical observations occurring repeatedly in the same animal are counted only once.

INCIDENCES OF IN-LIFE OBSERVATIONS

OBSERVATIONS	males					females				
	1	2	3	4	5	1	2	3	4	5
Group:										
Hunched posture	1	-	-	-	-	-	-	-	-	-
Piloerection	1	-	-	-	-	1	-	-	-	-
Skin lesion	3	2	2	-	1	1	1	2	-	-
No findings	6	3	3	5	9	9	4	3	5	10

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	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
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

^a range of scores

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	.2	.2	0	0
week 2	0	.2	.2	0	0
week 3	.1	.2	.4	0	0
week 4	.5	.2	.2	0	.1
week 5	.3				.2
week 6	.3				.2
week 7	0				0
week 8	0				0

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	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
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

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	.1	0	0	0	0
week 3	.1	.3	.2	0	0
week 4	.1	.3	.4	0	0
week 5	.2				0
week 6	.2				0
week 7	.2				0
week 8	.2				0

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	1250	1190	1145	1245	1228
	4 rec.	1319	.	.	.	1165
	8 rec.	1806	.	.	.	1890
GSH	4	972	975	850	935	945
	4 rec.	956	.	.	.	970
	8 rec.	1413	.	.	.	1395
LFS	4	12.75	10.80	12.20	12.05	10.40
	4 rec.	13.13	.	.	.	11.00
	8 rec.	11.38	.	.	.	11.60
TMP	4	37.35	37.54	37.14	37.28	37.37
	4 rec.	37.45	.	.	.	37.52
	8 rec.	38.08	.	.	.	37.92

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	1110	1288	1165	1105	1128
	4 rec.	1070	.	.	.	1100
	8 rec.	1270	.	.	.	1385
GSH	4	843	1056	940	900	885
	4 rec.	830	.	.	.	880
	8 rec.	1080	.	.	.	1220
LFS	4	9.93	10.63	10.55	11.00	10.88
	4 rec.	9.75	.	.	.	10.05
	8 rec.	10.55	.	.	.	8.80
TMP	4	38.78	38.60	38.68	38.78	38.68
	4 rec.	38.92	.	.	.	38.78
	8 rec.	37.96	.	.	.	38.14

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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)

Test	1	5
group 5 vs 1	-1	1

Abbreviations used:

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

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Measurements males week 4

Seed: 51841

MULTITEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
GSF	Mean	1250.000	1190.000	1145.000	1245.000	1227.500
	Std Dev	121.7433	120.6752	133.9310	218.2315	135.6312
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.4744	0.9997		
	group 3 vs 1		0.2149	0.9616		
	group 4 vs 1		0.9522	1.0000		
	group 5 vs 1		0.7462	1.0000		
	trend 1 to 4		0.8223	1.0000		
	trend 1 to 5		0.9522	1.0000		
GSH	Mean	971.8750	975.0000	850.0000	935.0000	945.0000
	Std Dev	61.8718	121.1920	88.3883	67.5463	77.9957
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.9474	1.0000		
	group 3 vs 1		0.0148	0.2163		
	group 4 vs 1		0.4387	0.9994		
	group 5 vs 1		0.4970	0.9997		
	trend 1 to 4		0.1278	0.8487		
	trend 1 to 5		0.3265	0.9953		
LFS	Mean	12.7500	10.8000	12.2000	12.0500	10.4000
	Std Dev	1.5698	1.3158	1.9875	2.2178	1.9692
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.0732	0.6618		
	group 3 vs 1		0.6037	1.0000		
	group 4 vs 1		0.5095	0.9997		
	group 5 vs 1		0.0117	0.1760		
	trend 1 to 4		0.8360	1.0000		
	trend 1 to 5		0.1108	0.8045		
TMP	Mean	37.3500	37.5400	37.1400	37.2800	37.3700
	Std Dev	0.3251	0.2302	0.2191	0.4658	0.3199
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.3119	0.9937		
	group 3 vs 1		0.2647	0.9837		
	group 4 vs 1		0.7073	1.0000		
	group 5 vs 1		0.8973	1.0000		
	trend 1 to 4		0.3102	0.9936		
	trend 1 to 5		0.5558	1.0000		

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Measurements males week 4 (recovery)

Seed: 51850

MULTITEST TABLES

Variable	Statistic	1	Class	5
GSF	Mean	1318.750	1165.000	
	Std Dev	134.4355	120.6752	
	N	4.0000	5.0000	

Contrast	Raw_p	Boot_p
group 5 vs 1	0.1135	0.3254

Variable	Statistic	1	Class	5
GSH	Mean	956.2500	970.0000	
	Std Dev	65.7489	77.8621	
	N	4.0000	5.0000	

Contrast	Raw_p	Boot_p
group 5 vs 1	0.7863	0.9952

Variable	Statistic	1	Class	5
LFS	Mean	13.1250	11.0000	
	Std Dev	3.9242	1.3919	
	N	4.0000	5.0000	

Contrast	Raw_p	Boot_p
group 5 vs 1	0.0349	0.1184

Variable	Statistic	1	Class	5
TMP	Mean	37.4500	37.5200	
	Std Dev	0.3317	0.2864	
	N	4.0000	5.0000	

Contrast	Raw_p	Boot_p
group 5 vs 1	0.7436	0.9891

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Measurements males week 8 (recovery)

Seed: 51852

MULTTEST TABLES

Variable	Statistic	1	Class	5
GSF	Mean	1806.250	1890.000	
	Std Dev	74.6520	139.8660	
	N	4.0000	5.0000	
Contrast		Raw_p	Boot_p	
group 5 vs 1		0.3193	0.7322	
GSH	Mean	1412.500	1395.000	
	Std Dev	166.4582	67.0820	
	N	4.0000	5.0000	
Contrast		Raw_p	Boot_p	
group 5 vs 1		0.8344	0.9986	
LFS	Mean	11.3750	11.6000	
	Std Dev	0.7773	2.3425	
	N	4.0000	5.0000	
Contrast		Raw_p	Boot_p	
group 5 vs 1		0.8607	0.9991	
TMP	Mean	38.0750	37.9200	
	Std Dev	0.4272	0.4324	
	N	4.0000	5.0000	
Contrast		Raw_p	Boot_p	
group 5 vs 1		0.6078	0.9638	

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Measurements females week 4

Seed: 52264

MULTTEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
GSF	Mean	1110.000	1287.500	1165.000	1105.000	1127.500
	Std Dev	115.5903	136.1678	109.8294	73.7394	109.5762
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.0110		0.1667	
	group 3 vs 1		0.3709		0.9980	
	group 4 vs 1		0.9347		1.0000	
	group 5 vs 1		0.7257		1.0000	
	trend 1 to 4		0.4887		1.0000	
	trend 1 to 5		0.2421		0.9783	
GSH	Mean	842.5000	1056.250	940.0000	900.0000	885.0000
	Std Dev	102.7740	269.5482	109.8294	131.1011	95.8877
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.0110		0.1665	
	group 3 vs 1		0.1911		0.9490	
	group 4 vs 1		0.4362		0.9996	
	group 5 vs 1		0.4805		0.9999	
	trend 1 to 4		0.8133		1.0000	
	trend 1 to 5		0.6354		1.0000	
LFS	Mean	9.8250	10.6250	10.5500	11.0000	10.8750
	Std Dev	1.6876	1.7017	0.9421	1.6202	1.6040
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.3963		0.9990	
	group 3 vs 1		0.4062		0.9992	
	group 4 vs 1		0.1824		0.9406	
	group 5 vs 1		0.1457		0.8903	
	trend 1 to 4		0.2257		0.9712	
	trend 1 to 5		0.1693		0.9255	
TMP	Mean	38.7800	38.6000	38.6800	38.7800	38.6800
	Std Dev	0.4367	0.5099	0.4025	0.3768	0.2974
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.4465		0.9997	
	group 3 vs 1		0.6468		1.0000	
	group 4 vs 1		1.0000		1.0000	
	group 5 vs 1		0.5750		1.0000	
	trend 1 to 4		0.9099		1.0000	
	trend 1 to 5		0.9641		1.0000	

Measurements females week 4 (recovery)

Seed: 52272

MULTTEST TABLES

Variable	Statistic	Class 1	Class 5
GSF	Mean	1070.000	1100.000
	Std Dev	140.7569	113.1923
	N	5.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.7200	0.9930	
GSH	Mean	830.0000	880.0000
	Std Dev	62.2495	112.3610
	N	5.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.4094	0.8751	
LES	Mean	9.7500	10.0500
	Std Dev	2.0463	1.6621
	N	5.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.8056	0.9982	
TMP	Mean	38.9200	38.7800
	Std Dev	0.4658	0.3114
	N	5.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.5917	0.9693	

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Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Measurements

males

week 8 (recovery)

Seed:

52274

MULTTEST TABLES

Variable	Statistic	Class	
		1	5
GSF	Mean	1270.000	1385.000
	Std Dev	190.7223	139.8660
	N	5.0000	5.0000
Contrast		Raw_p	Boot_p
group 5 vs 1		0.3086	0.7145
GSH	Mean	1080.000	1220.000
	Std Dev	116.4581	165.2649
	N	5.0000	5.0000
Contrast		Raw_p	Boot_p
group 5 vs 1		0.1601	0.4492
LFS	Mean	10.5500	8.8000
	Std Dev	3.0383	1.3158
	N	5.0000	5.0000
Contrast		Raw_p	Boot_p
group 5 vs 1		0.2712	0.6561
TMP	Mean	37.9600	38.1400
	Std Dev	0.3209	0.3647
	N	5.0000	5.0000
Contrast		Raw_p	Boot_p
group 5 vs 1		0.4314	0.8512

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Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	8	1049	939	819	693	492	332	247	286	304	364	5526
	2	5	767	644	419	231	272	203	193	184	149	90	3152 *
	3	5	899	782	558	511	352	341	278	228	177	160	4287
	4	5	928	844	717	378	381	439	224	136	296	208	4552
	5	10	876	657	443	349	309	278	280	321	167	212	3891
	1 rec.	4	1008	793	755	627	441	267	207	242	165	362	4865
	5 rec.	5	910	618	352	281	213	209	158	291	122	106	3261
8	1	4	970	635	551	430	339	374	462	198	383	50	4389
	5	5	908	546	367	342	381	376	178	154	178	70	3500

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	8	44	41	40	38	36	30	19	20	24	27	319
	2	5	42	41	35	24	26	23	19	18	17	13	258
	3	5	42	42	39	35	31	22	24	18	16	17	287
	4	5	44	40	42	35	35	32	24	16	29	21	318
	5	10	48	43	37	27	26	22	23	25	19	17	286
	1 rec.	4	43	44	39	38	33	27	16	17	15	23	294
	5 rec.	5	47	44	33	24	19	17	17	23	14	9	249
8	1	4	42	42	38	34	36	33	28	17	26	7	297
	5	5	38	34	26	23	32	29	17	16	17	6	239

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	8	86	83	71	59	42	28	19	24	25	27	465
	2	5	67	59	40	22	25	16	17	18	14	7	285 *
	3	5	81	69	52	46	30	26	23	20	14	13	374
	4	5	80	80	60	38	33	39	20	15	29	20	414
	5	10	77	60	44	32	28	24	24	26	14	19	347
	1 rec.	4	78	76	67	53	40	20	15	21	13	27	410
	5 rec.	5	75	55	34	26	17	18	14	22	11	10	282
8	1	4	82	60	45	39	31	32	35	18	32	5	376
	5	5	66	50	31	31	32	32	14	13	16	4	289

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	8	110	112	85	80	71	71	34	37	46	62	707
	2	5	88	91	50	42	63	53	30	41	18	20	497
	3	5	111	110	99	86	59	80	60	46	22	39	712
	4	5	135	119	119	53	80	59	31	27	38	49	709
	5	10	100	125	75	53	52	47	42	48	24	32	598
	1 rec.	4	106	107	75	68	55	83	27	27	24	33	605
	5 rec.	5	105	108	51	51	39	48	20	26	17	11	475
8	1	4	94	82	47	58	30	34	49	15	46	12	466
	5	5	94	57	35	33	27	23	19	16	16	6	326

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	8	18	18	14	14	12	11	6	6	7	9	114
	2	5	17	15	8	7	9	7	5	7	4	3	82
	3	5	21	16	15	12	11	11	8	7	4	7	112
	4	5	20	18	15	8	13	10	5	5	6	7	109
	5	10	18	19	13	9	8	8	7	8	5	5	100
	1 rec.	4	21	18	14	14	11	14	5	6	5	6	113
	5 rec.	5	19	17	9	7	7	8	4	5	3	2	81
8	1	4	17	13	10	9	6	6	8	3	7	2	80
	5	5	14	10	6	5	5	4	2	3	3	1	53

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	8	30	33	30	31	27	33	15	16	23	30	267
	2	5	24	32	20	17	27	21	17	16	9	8	190
	3	5	34	40	39	36	25	35	25	21	11	19	286
	4	5	38	43	49	21	34	31	14	12	22	27	290
	5	10	32	48	30	22	25	24	20	26	12	17	255
	1 rec.	4	27	31	27	24	18	37	10	10	10	13	207
	5 rec.	5	32	39	22	20	21	25	10	15	10	6	200
8	1	4	26	25	16	19	10	14	19	6	19	6	159
	5	5	28	23	17	13	13	9	9	7	8	3	130

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	8	63	66	70	52	62	57	49	30	35	55	538
	2	5	43	34	30	19	27	13	34	43	27	50	
	3	5	60	48	36	47	41	24	29	12	22	16	
	4	5	51	43	66	36	65	64	79	46	39	59	
	5	10	64	61	51	27	36	29	24	18	19	23	
1 rec.	4	61	54	64	33	42	33	29	21	18	11	364	
5 rec.	5	65	59	41	15	20	32	17	7	8	6	269	
8	1	4	46	35	42	33	19	17	39	16	26	43	313
	5	5	63	25	34	22	28	33	21	14	18	5	264

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	998	875	669	515	519	435	340	320	409	244	5322
	2	4	941	704	536	514	281	433	132	245	240	309	
	3	5	1028	974	961	552	473	465	430	297	282	216	
	4	5	849	785	599	400	398	354	344	224	309	371	
	5	10	1171	983	772	636	529	470	527	356	319	393	
1 rec.	5	1123	966	711	434	495	409	308	333	468	227	5472	
5 rec.	5	1270	1055	726	644	571	570	533	360	366	407	6503	
8	1	5	1093	975	699	470	512	428	427	288	223	362	5475
	5	5	1289	962	882	551	460	403	442	326	221	245	5780

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	46	44	40	31	29	28	27	26	25	22	318
	2	4	48	42	37	35	27	35	17	24	22	28	
	3	5	42	40	40	34	25	26	27	20	19	15	
	4	5	47	41	34	32	27	23	24	19	20	22	
	5	10	46	43	41	36	28	32	33	25	25	25	
1 rec.	5	45	45	41	24	25	24	21	26	26	22	300	
5 rec.	5	44	40	39	35	27	36	29	27	26	24	327	
8	1	5	43	40	33	29	33	25	24	22	19	23	292
	5	5	40	40	38	33	26	28	28	23	17	15	289

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	76	69	52	40	42	35	25	23	29	18	408
	2	4	77	60	42	41	25	35	11	22	20	23	355
	3	5	89	73	69	38	35	32	33	18	20	14	421
	4	5	64	59	46	33	31	27	28	19	22	24	355
	5	10	86	76	56	49	40	35	38	25	24	26	454
	1 rec.	5	82	71	53	33	36	31	23	24	31	16	398
5 rec.	5	91	83	52	46	42	42	33	23	26	26	465	
	5	5	82	72	55	38	36	37	33	22	19	29	425
8	1	5	90	69	64	43	31	33	34	26	17	15	421
	5	5	82	72	55	38	36	37	33	22	19	29	425

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	131	124	107	77	69	54	72	65	56	77	832
	2	4	126	130	91	94	59	98	28	57	38	66	787
	3	5	97	141	113	123	63	66	79	55	60	57	855
	4	5	87	109	80	72	50	66	40	29	58	85	676
	5	10	155	161	140	100	80	59	81	62	70	87	996
	1 rec.	5	135	115	107	65	62	60	77	53	57	59	789
5 rec.	5	171	155	152	95	68	67	90	63	74	78	1014	
	5	5	101	113	96	70	74	70	56	46	36	32	695
8	1	5	149	123	97	86	92	73	80	49	42	34	826
	5	5	101	113	96	70	74	70	56	46	36	32	695

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	24	20	17	12	9	8	9	9	9	9	124
	2	4	25	21	13	12	7	11	6	9	7	10	121
	3	5	19	21	17	15	10	12	12	9	9	8	131
	4	5	17	19	17	11	9	9	7	6	9	13	116
	5	10	24	24	17	15	12	10	11	9	10	12	143
	1 rec.	5	25	19	19	10	8	8	10	9	9	8	125
5 rec.	5	25	22	15	13	12	11	10	8	11	10	138	
	5	5	18	18	16	11	13	12	9	8	7	6	117
8	1	5	24	19	16	12	14	9	9	7	7	4	120
	5	5	18	18	16	11	13	12	9	8	7	6	117

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	44	51	51	37	33	27	39	37	38	46	403
	2	4	39	46	38	40	30	62	14	31	22	43	363
	3	5	29	57	52	69	34	44	58	31	35	27	435
	4	5	35	46	33	36	26	34	20	15	31	44	320
	5	10	49	63	57	51	42	32	45	42	42	55	478
	5 rec.	5	43	49	47	31	30	29	43	31	35	37	375
8	1	5	37	49	50	38	47	40	30	27	23	20	361
	5	5	58	54	51	47	49	40	43	36	28	20	426

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	37	46	43	41	45	38	36	29	35	38	387
	2	4	38	42	37	56	36	37	14	46	40	62	408
	3	5	48	40	45	42	33	32	35	32	15	25	347
	4	5	33	40	57	30	20	29	39	29	36	49	362
	5	10	39	54	38	49	40	41	27	28	44	52	412
8	1 rec.	5	36	45	45	37	40	29	37	25	27	21	342
	5 rec.	5	34	41	35	37	31	32	25	16	25	29	303
8	1	5	40	38	44	30	47	34	32	31	37	20	353
	5	5	50	53	48	48	41	39	35	14	14	13	354

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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

	Class				
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)

	Class	
Contrast	1	5
group 5 vs 1	-1	1

Abbreviations used:

- TD total distance (cm)
- NM number of movements (counts)
- MT movement time (sec)
- VA vertical activity (counts)
- VM number of rearings (counts)
- VT vertical time (sec)
- CT center time (sec)

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Motor activity males week 4

Seed: 32041

MULTTEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
TD_AUC	Mean	5526.250	3152.000	4286.600	4551.600	3890.900
	Std Dev	1304.943	924.8867	1152.754	754.7584	986.9006
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.0005		0.0122	
	group 3 vs 1		0.0505		0.5133	
	group 4 vs 1		0.1193		0.8062	
	group 5 vs 1		0.0031		0.0603	
	trend 1 to 4		0.3643		0.9974	
	trend 1 to 5		0.1342		0.8437	
NM_AUC	Mean	319.3750	258.2000	287.0000	318.0000	286.1000
	Std Dev	44.0323	70.6413	43.2897	15.7639	56.6519
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.0419		0.4569	
	group 3 vs 1		0.2687		0.9815	
	group 4 vs 1		0.9621		1.0000	
	group 5 vs 1		0.1743		0.9154	
	trend 1 to 4		0.7900		1.0000	
	trend 1 to 5		0.9072		1.0000	
MT_AUC	Mean	465.3750	285.0000	373.8000	414.4000	347.4000
	Std Dev	95.3953	67.7643	95.5913	55.6534	89.5051
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.0009		0.0212	
	group 3 vs 1		0.0697		0.6249	
	group 4 vs 1		0.3028		0.9907	
	group 5 vs 1		0.0068		0.1141	
	trend 1 to 4		0.6828		1.0000	
	trend 1 to 5		0.2819		0.9857	
VA_AUC	Mean	707.0000	496.6000	711.8000	708.8000	597.8000
	Std Dev	173.3477	152.7377	302.7015	105.5566	209.2801
	N	8.0000	5.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p		Boot_p	
	group 2 vs 1		0.0742		0.6473	
	group 3 vs 1		0.9666		1.0000	
	group 4 vs 1		0.9875		1.0000	
	group 5 vs 1		0.2571		0.9780	
	trend 1 to 4		0.5481		0.9998	
	trend 1 to 5		0.9784		1.0000	

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Motor activity males week 4 (recovery)

Seed: 32057

MULTTEST TABLES

Variable	Statistic	Class	
		1	5
TD_AUC	Mean	4865.250	3261.000
	Std Dev	1390.332	392.9383
	N	4.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.0411	0.1468	
NM_AUC	Mean	293.5000	248.8000
	Std Dev	38.9059	19.6138
	N	4.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.0582	0.1987	
MT_AUC	Mean	409.7500	282.0000
	Std Dev	35.7958	18.3984
	N	4.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.0133	0.0562	
VA_AUC	Mean	604.5000	475.4000
	Std Dev	93.3613	142.8051
	N	4.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.1548	0.4841	
VM_AUC	Mean	112.5000	81.4000
	Std Dev	6.6081	17.3436
	N	4.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.0121	0.0507	
VT_AUC	Mean	207.2500	200.0000
	Std Dev	51.7518	92.3688
	N	4.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.3932	0.9998	
CT_AUC	Mean	364.2500	268.8000
	Std Dev	185.9559	127.2780
	N	4.0000	5.0000
Contrast	Raw_p	Boot_p	
group 5 vs 1	0.3896	0.8484	

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Motor activity males week 8 (recovery)

Seed: 32059

MULTITEST TABLES

Variable	Statistic	1	Class	5
TD_AUC	Mean	4389.000		3500.000
	Std Dev	1976.776		1166.846
	N	4.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1	0.4254		0.7761	
NM_AUC	Mean	297.2500		238.8000
	Std Dev	61.8459		61.7997
	N	4.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1	0.2015		0.4593	
MT_AUC	Mean	375.7500		289.0000
	Std Dev	148.4012		103.5664
	N	4.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1	0.3345		0.6633	
VA_AUC	Mean	465.7500		326.0000
	Std Dev	109.5822		158.3777
	N	4.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1	0.1792		0.4188	
VM_AUC	Mean	80.0000		53.0000
	Std Dev	20.8487		23.9270
	N	4.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1	0.1189		0.3021	
VT_AUC	Mean	159.0000		130.4000
	Std Dev	27.8927		78.2707
	N	4.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1	0.5133		0.8635	
CT_AUC	Mean	312.5000		263.6000
	Std Dev	136.2314		119.2237
	N	4.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1	0.5833		0.9189	

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Motor activity

females

week 4

Seed:

54135

MULTTEST TABLES

Variable	Statistic	Class				
		1	2	3	4	5
TD_AUC	Mean	5322.000	4334.500	5677.800	4634.000	6155.500
	Std Dev	989.2061	591.8967	1947.029	2463.614	1951.272
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.3336	0.9965		
	group 3 vs 1		0.7048	1.0000		
	group 4 vs 1		0.4653	1.0000		
	group 5 vs 1		0.2813	0.9903		
	trend 1 to 4		0.8126	1.0000		
	trend 1 to 5		0.3087	0.9949		
NM_AUC	Mean	318.3000	313.7500	288.2000	289.4000	333.1000
	Std Dev	33.2200	8.5000	45.9967	90.5334	48.3217
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.8787	1.0000		
	group 3 vs 1		0.2805	0.9903		
	group 4 vs 1		0.2997	0.9935		
	group 5 vs 1		0.5130	1.0000		
	trend 1 to 4		0.2157	0.9686		
	trend 1 to 5		0.9258	1.0000		
MT_AUC	Mean	407.8000	355.0000	420.8000	354.6000	453.9000
	Std Dev	65.1559	42.8797	112.6863	179.7673	117.5268
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.4219	0.9996		
	group 3 vs 1		0.9300	1.0000		
	group 4 vs 1		0.3826	0.9988		
	group 5 vs 1		0.3545	0.9979		
	trend 1 to 4		0.6332	1.0000		
	trend 1 to 5		0.4596	1.0000		
VA_AUC	Mean	831.9000	786.7500	855.2000	676.4000	995.6000
	Std Dev	226.0096	220.2777	292.1638	301.7537	395.1450
	N	10.0000	4.0000	5.0000	5.0000	10.0000
	Contrast		Raw_p	Boot_p		
	group 2 vs 1		0.8048	1.0000		
	group 3 vs 1		0.8904	1.0000		
	group 4 vs 1		0.3612	0.9980		
	group 5 vs 1		0.2414	0.9800		
	trend 1 to 4		0.4695	1.0000		
	trend 1 to 5		0.5308	1.0000		

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

VM_AUC	Mean	124.0000	120.5000	131.4000	115.6000	142.9000
	Std Dev	23.3047	4.4347	49.6216	50.8163	34.0635
	N	10.0000	4.0000	5.0000	5.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.8670	1.0000
group 3 vs 1	0.7025	1.0000
group 4 vs 1	0.6647	1.0000
group 5 vs 1	0.2373	0.9784
trend 1 to 4	0.8197	1.0000
trend 1 to 5	0.4076	0.9995

VT_AUC	Mean	403.1000	363.2500	435.4000	320.4000	477.8000
	Std Dev	111.3388	89.5372	168.9121	139.9582	164.6686
	N	10.0000	4.0000	5.0000	5.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.6351	1.0000
group 3 vs 1	0.6777	1.0000
group 4 vs 1	0.2913	0.9919
group 5 vs 1	0.2440	0.9810
trend 1 to 4	0.4859	1.0000
trend 1 to 5	0.5028	1.0000

CT_AUC	Mean	387.2000	408.2500	346.8000	361.8000	411.8000
	Std Dev	108.0245	50.7371	132.0992	195.1710	225.1626
	N	10.0000	4.0000	5.0000	5.0000	10.0000

Contrast	Raw_p	Boot_p
group 2 vs 1	0.8314	1.0000
group 3 vs 1	0.6593	1.0000
group 4 vs 1	0.7814	1.0000
group 5 vs 1	0.7421	1.0000
trend 1 to 4	0.6430	1.0000
trend 1 to 5	0.9883	1.0000

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Motor activity females week 4 (recovery)

Seed: 54149

MULTTEST TABLES

Variable	Statistic	Class 1	Class 5
TD_AUC	Mean	5472.400	6503.200
	Std Dev	1159.235	2291.336
	N	5.0000	5.0000
Contrast	Raw_p		Boot_p
group 5 vs 1		0.3956	0.7902
NM_AUC	Mean	299.6000	326.6000
	Std Dev	31.3656	58.4534
	N	5.0000	5.0000
Contrast	Raw_p		Boot_p
group 5 vs 1		0.3894	0.7812
MT_AUC	Mean	398.4000	464.8000
	Std Dev	70.9845	144.2314
	N	5.0000	5.0000
Contrast	Raw_p		Boot_p
group 5 vs 1		0.3827	0.7735
VA_AUC	Mean	789.4000	1014.000
	Std Dev	265.0487	543.9779
	N	5.0000	5.0000
Contrast	Raw_p		Boot_p
group 5 vs 1		0.4306	0.8315
VM_AUC	Mean	125.0000	137.6000
	Std Dev	33.1964	43.9124
	N	5.0000	5.0000
Contrast	Raw_p		Boot_p
group 5 vs 1		0.6226	0.9648
VT_AUC	Mean	375.2000	485.6000
	Std Dev	121.9455	221.2957
	N	5.0000	5.0000
Contrast	Raw_p		Boot_p
group 5 vs 1		0.3572	0.7421
CT_AUC	Mean	342.0000	303.4000
	Std Dev	115.0891	131.8780
	N	5.0000	5.0000
Contrast	Raw_p		Boot_p
group 5 vs 1		0.6352	0.9696

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Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Motor activity females week 8 (recovery)

Seed: 54151

MULTTEST TABLES

Variable	Statistic	1	Class	5
TD_AUC	Mean	5475.400		5779.800
	Std Dev	1695.687		1358.749
	N	5.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1		0.7621		0.9884
NM_AUC	Mean	291.6000		288.8000
	Std Dev	64.3995		49.5853
	N	5.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1		0.9405		0.9993
MT_AUC	Mean	424.6000		421.2000
	Std Dev	116.4766		103.1004
	N	5.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1		0.9622		0.9993
VA_AUC	Mean	694.8000		825.8000
	Std Dev	247.2927		453.6747
	N	5.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1		0.5863		0.9156
VM_AUC	Mean	116.6000		120.2000
	Std Dev	38.0959		51.8768
	N	5.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1		0.9036		0.9993
VT_AUC	Mean	360.8000		426.2000
	Std Dev	114.3468		223.7615
	N	5.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1		0.5766		0.9078
CT_AUC	Mean	352.8000		354.0000
	Std Dev	181.0434		155.0016
	N	5.0000		5.0000
Contrast	Raw_p		Boot_p	
group 5 vs 1		0.9913		0.9993

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

8.7. Summary of animal fate

SUMMARY OF ANIMAL FATE					
Number of Rats	Dose level (mg/kg)				
	0	10	50	200	1000
MALES					
Initiation	10	5	5	5	10
Found dead	2	0	0	0	0
Moribund sacrifice	0	0	0	0	0
Accidental death	0	0	0	0	0
% Survival at termination	80	100	100	100	100
FEMALES					
Initiation	10	5	5	5	10
Found dead	0	1	0	0	0
Moribund sacrifice	0	0	0	0	0
Accidental death	0	0	0	0	0
% Survival at termination	100	80	100	100	100

8.8. 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	179.4	175.3	176.5	179.8	179.2
1	228.6	221.6	224.1	234.7	229.6
2	273.3	260.5	263.5	279.9	270.6
3	300.7	282.4	288.5	299.4	300.4
4	332.4	311.3	319.3	335.8	336.1
recovery					
week: 5	332.2				354.0
6	353.4				373.6
7	377.8				396.2
8	393.9				409.4

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	138.9	138.1	139.9	140.3	135.2
1	160.7	159.4	162.9	165.0	159.7
2	177.2	181.0	184.4	182.3	181.8
3	192.6	194.2	203.6	203.5	198.9
4	210.6	206.0	223.1	222.5	212.4
recovery					
week: 5	212.1				218.2
6	224.7				228.0
7	233.2				237.4
8	240.2				242.4*

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

8.9. 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 < 0.01Body 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	5	10
Mean	179.4	175.3	176.5	179.8	179.2
SD	10.01	19.21	16.32	9.460	12.73
Median	179.5	180.6	177.5	177.7	179.1
IQ-Range	10.43	18.76	15.16	10.90	18.60
Min	163.8	144.3	150.4	166.8	155.6
Max	197.6	191.7	191.2	190.7	199.0
p _L		0.845	0.949	0.958	0.952
p _J		0.903	0.972	0.941	0.803
week: 1 N	10	5	5	5	10
Mean	228.6	221.6	224.1	234.7	229.6
SD	13.34	22.51	18.35	14.32	14.93
Median	225.6	229.0	224.4	239.5	229.9
IQ-Range	22.14	19.33	24.10	9.657	25.13
Min	211.5	186.0	197.8	210.5	201.1
Max	253.3	244.0	242.5	246.5	249.3
p _L		0.796	0.796	0.724	0.944
p _J		0.713	0.696	0.641	0.568
week: 2 N	8	5	5	5	10
Mean	273.3	260.5	263.5	279.9	270.6
SD	16.99	24.77	22.81	16.70	19.89
Median	269.6	270.2	265.0	283.5	273.5
IQ-Range	21.57	25.23	16.49	2.900	35.16
Min	243.7	222.1	230.6	252.5	240.5
Max	296.4	284.0	292.8	298.1	294.8
p _L		0.842	0.421	0.679	0.763
p _J		0.558	0.391	0.640	0.690

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

100

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	8	5	5	5	10
Mean	300.7	282.4	288.5	299.4	300.4
SD	18.56	26.13	32.12	15.63	24.67
Median	295.1	293.4	286.9	296.4	306.3
IQ-Range	19.19	32.14	20.37	30.73	41.83
Min	278.1	243.6	244.2	284.3	263.5
Max	336.4	306.5	332.7	315.7	328.8
p_L		0.730	0.365	0.957	0.274
p_J		0.558	0.437	0.804	0.774
week: 4 N	8	5	5	5	10
Mean	332.4	311.3	319.3	335.8	336.1
SD	23.32	26.43	36.12	21.16	29.17
Median	331.1	325.2	313.9	329.0	336.5
IQ-Range	15.29	34.83	15.30	34.87	52.40
Min	305.1	275.7	269.5	312.0	295.9
Max	383.9	338.1	370.2	359.1	378.6
p_L		0.574	0.574	0.866	0.274
p_J		0.306	0.270	0.762	0.737
recovery					
week: 5 N	4				5
Mean	332.2				354.0
SD	10.15				37.98
Median	331.9				369.4
IQ-Range	12.45				64.31
Min	320.1				305.8
Max	344.9				387.8
p_L					0.133
p_J					
week: 6 N	4				5
Mean	353.4				373.6
SD	8.910				44.64
Median	354.9				390.1
IQ-Range	12.21				73.21
Min	341.3				316.9
Max	362.5				416.0
p_L					0.056
p_J					

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

101

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	377.8				396.2
SD	13.32				46.21
Median	376.8				412.7
IQ-Range	18.57				76.77
Min	362.8				340.1
Max	394.9				442.7
p_L					0.056
p_J					
week: 8 N	4				5
Mean	393.9				409.4
SD	15.53				50.11
Median	391.0				415.9
IQ-Range	22.56				89.11
Min	378.9				357.0
Max	414.9				466.2
p_L					0.056
p_J					

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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

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

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	200	1000
week: -1 N	10	5	5	5	10
Mean	138.9	138.1	139.9	140.3	135.2
SD	6.978	7.572	7.957	13.11	7.090
Median	139.3	138.1	142.7	143.8	135.3
IQ-Range	10.49	9.129	11.60	4.457	9.143
Min	125.5	127.8	128.8	117.5	122.7
Max	147.7	147.1	147.4	150.6	144.5
p _L		0.914	0.921	0.589	0.633
p _J		0.903	0.804	0.447	0.491
week: 1 N	10	5	5	5	10
Mean	160.7	159.4	162.9	165.0	159.7
SD	10.32	12.74	9.587	14.22	8.082
Median	160.1	162.2	163.3	172.0	159.3
IQ-Range	16.43	9.071	9.386	15.61	14.89
Min	146.5	141.4	152.0	142.6	147.7
Max	178.7	176.0	177.0	176.4	171.2
p _L		0.958	0.861	0.549	0.659
p _J		0.806	0.749	0.447	0.988
week: 2 N	10	4	5	5	10
Mean	177.2	181.0	184.4	182.3	181.8
SD	10.52	15.00	9.528	21.77	10.26
Median	176.6	179.3	181.6	187.6	179.9
IQ-Range	17.86	23.29	10.50	12.93	16.27
Min	163.3	165.6	174.4	147.9	168.0
Max	192.8	199.9	198.5	206.6	196.7
p _L		0.878	0.383	0.397	0.655
p _J		0.671	0.245	0.199	0.366
week: 3 N	10	4	5	5	10
Mean	192.6	194.2	203.6	203.5	198.9
SD	11.12	17.00	9.928	24.41	13.44
Median	189.9	191.5	205.1	210.1	195.6
IQ-Range	19.06	23.35	5.243	16.03	23.02
Min	177.9	176.7	190.1	164.7	183.2
Max	209.2	217.1	217.5	229.8	222.2
p _L		0.850	0.184	0.123	0.520
p _J		1.000	0.121	0.063	0.203

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	10
Mean	210.6	206.0	223.1	222.5	212.4
SD	12.47	19.03	6.386	30.41	12.78
Median	211.0	204.3	221.9	229.6	213.0
IQ-Range	20.76	28.24	0.985	28.24	21.87
Min	193.5	185.4	215.5	176.9	194.4
Max	228.4	230.3	233.2	256.6	231.5
p_L		0.634	0.227	0.096	0.975
p_J		0.671	0.188	0.089	0.471
recovery					
week: 5 N	5				5
Mean	212.1				218.2
SD	13.02				14.04
Median	213.7				219.1
IQ-Range	23.19				21.96
Min	197.9				201.9
Max	226.4				234.9
p_L					0.643
p_J					0.347
week: 6 N	5				5
Mean	224.7				228.0
SD	9.903				16.02
Median	229.0				229.0
IQ-Range	15.33				26.17
Min	213.3				212.0
Max	235.6				248.3
p_L					0.236
p_J					0.917
week: 7 N	5				5
Mean	233.2				237.4
SD	13.78				16.80
Median	239.1				244.8
IQ-Range	20.59				28.17
Min	215.2				217.9
Max	246.9				254.2
p_L					0.341
p_J					0.465

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	200	1000
week: 8 N		5			5
Mean		240.2			242.4
SD		9.447			18.35
Median		246.2			249.4
IQ-Range		10.00			28.54 b
Min		225.3			222.2
Max		246.9			263.7
p_L					0.034 *
p_J					0.602

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Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

8.10. 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	151.1	149.1	153.2	152.8	147.7
1	153.8	160.7	161.8	165.6	161.4
2	177.2	167.4	174.4*	169.1	180.7
3	165.7	166.0	170.6	170.3	176.8
4	183.6	165.0	176.5	180.5	185.7
recovery					
week: 5	166.2				191.7
6	179.3				187.9
7	176.7				174.8
8	173.7				178.4

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	112.6	115.0	116.0	116.2	113.6
1	99.63	99.31	112.2	111.1	105.5*
2	120.0	120.1	127.5	128.2	122.4
3	119.9	120.7	126.7	128.8	118.1
4	120.4	122.1	133.3*	125.9	121.4
recovery					
week: 5	117.2				128.9
6	126.5				132.1
7	120.4				122.2
8	122.0				117.6

8.11. 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	5	10
Mean	151.1	149.1	153.2	152.8	147.7
SD	11.00	6.111	12.69	11.86	8.581
Median	151.7	148.9	154.1	149.0	151.2
IQ-Range	14.20	11.50	22.00	14.30	14.70
Min	135.9	142.7	140.2	137.2	131.8
Max	171.2	155.6	168.3	166.5	158.1
p_L		0.861	0.638	0.932	0.863
p_J		0.713	0.915	0.768	0.639
week: 1 N	10	5	5	5	10
Mean	153.8	160.7	161.8	165.6	161.4
SD	25.36	8.806	12.30	13.37	12.98
Median	159.9	161.4	164.8	167.7	163.0
IQ-Range	15.70	7.600	6.100	6.100	23.40
Min	91.70	149.5	142.9	142.8	145.2
Max	182.8	173.1	176.6	176.8	182.2
p_L		0.958	0.875	0.343	0.862
p_J		0.806	0.546	0.147	0.348
week: 2 N	8	5	5	5	10
Mean	177.2	167.4	174.4	169.1	180.7
SD	9.658	8.386	18.03	15.56	15.49
Median	178.1	168.1	164.0	179.0	177.3
IQ-Range	13.00	9.700	28.80 b	16.70	23.30
Min	166.2	159.5	159.9	144.5	166.7
Max	195.6	179.9	198.2	180.0	213.6
p_L		0.342	0.028 *	0.742	0.608
p_J		0.143	0.347	0.393	0.513

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	8	5	5	5	10
Mean	165.7	166.0	170.6	170.3	176.8
SD	26.66	7.181	19.78	6.585	18.70
Median	165.4	169.7	161.4	172.7	177.1
IQ-Range	16.65	10.60	22.00	0.900	27.90
Min	108.9	156.3	148.9	158.6	150.5
Max	201.9	172.5	198.2	174.7	208.7
p_L		0.859	0.452	0.323	0.563
p_J		0.661	0.653	0.847	0.299
week: 4 N	8	5	5	5	10
Mean	183.6	165.0	176.5	180.5	185.7
SD	17.97	2.679	19.03	15.41	23.20
Median	183.9	165.7	171.4	171.7	179.8
IQ-Range	20.36	1.517	13.77	12.60	28.00
Min	151.6	160.4	157.2	170.1	156.2
Max	208.1	167.0	207.1	206.3	225.6
p_L		0.085	0.679	0.742	0.775
p_J		0.028	0.205	0.762	0.482
recovery					
week: 5 N	4				5
Mean	166.2				191.7
SD	15.64				26.57
Median	167.3				195.8
IQ-Range	19.66				43.52
Min	146.0				158.8
Max	184.1				219.6
p_L					0.310
p_J					
week: 6 N	4				5
Mean	179.3				187.9
SD	14.74				20.90
Median	177.1				186.2
IQ-Range	23.35				28.30
Min	165.1				162.9
Max	197.8				214.7
p_L					0.505
p_J					

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

Dose(mg/kg)		group 1	group 2	group 3	group 4	group 5
		0	10	50	200	1000
week: 7	N	4				5
	Mean	176.7				174.8
	SD	16.03				17.31
	Median	179.3				176.1
	IQ-Range	22.95				19.10
	Min	155.3				153.6
	Max	193.0				198.4
	p_L					0.969
week: 8	N	4				5
	Mean	173.7				178.4
	SD	10.11				22.30
	Median	170.8				180.5
	IQ-Range	13.77				38.73
	Min	165.2				154.8
	Max	188.1				204.3
	p_L					0.169
p_J						

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

109

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	5	10
Mean	112.6	115.0	116.0	116.2	113.6
SD	9.312	8.064	6.129	13.61	6.811
Median	112.2	111.4	117.7	120.2	115.0
IQ-Range	9.500	11.10	10.90	12.40	10.40
Min	97.70	107.9	108.8	94.90	101.2
Max	130.7	126.6	122.0	129.9	122.1
p_L		0.958	0.611	0.475	0.859
p_J		0.806	0.414	0.269	0.598
week: 1 N	10	5	5	5	10
Mean	99.63	99.31	112.2	111.1	105.5
SD	8.621	14.57	7.111	17.63	5.302
Median	96.15	103.3	110.2	110.7	105.0
IQ-Range	9.700	13.30	6.600	16.70	9.200
Min	91.20	75.43	103.0	85.60	97.20
Max	115.3	111.3	121.7	132.1	114.2
p_L		0.893	0.087	0.123	0.039*
p_J		0.668	0.047	0.024	0.104
week: 2 N	10	4	5	5	10
Mean	120.0	120.1	127.5	128.2	122.4
SD	8.958	6.714	3.691	17.16	8.521
Median	118.5	117.0	127.1	128.6	123.0
IQ-Range	14.30	7.100	4.700	18.10	14.30
Min	110.0	116.1	122.9	106.2	110.8
Max	137.6	130.1	132.2	151.2	136.3
p_L		0.517	0.121	0.238	0.758
p_J		0.888	0.104	0.084	0.366
week: 3 N	10	4	5	5	10
Mean	119.9	120.7	126.7	128.8	118.1
SD	6.350	7.938	3.836	20.71	7.067
Median	120.0	122.6	125.1	124.1	119.8
IQ-Range	9.000	10.70	4.200	29.70	6.400
Min	108.0	109.6	123.7	103.8	103.8
Max	129.3	128.1	132.8	153.6	131.4
p_L		0.914	0.119	0.253	0.884
p_J		0.671	0.075	0.122	0.679

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

110

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	10
Mean	120.4	122.1	133.3	125.9	121.4
SD	8.334	10.22	4.039	19.79	11.20
Median	119.5	117.7	134.1 a	121.7	120.1
IQ-Range	7.000	11.67	3.500	9.450	19.48
Min	105.9	115.6	126.7	101.2	108.7
Max	135.3	137.3	136.9	155.8	140.5
p_L		0.990	0.031 *	0.826	0.246
p_J		0.888	0.053	0.165	0.890
recovery					
week: 5 N	5				5
Mean	117.2				128.9
SD	8.638				16.01
Median	121.9				133.4
IQ-Range	12.37				29.87
Min	105.2				110.6
Max	124.7				143.9
p_L					0.230
p_J					0.251
week: 6 N	5				5
Mean	126.5				132.1
SD	5.499				14.14
Median	126.3				137.9
IQ-Range	4.100				24.40
Min	117.8				115.1
Max	132.1				145.4
p_L					0.081
p_J					0.465
week: 7 N	5				5
Mean	120.4				122.2
SD	5.402				11.57
Median	119.7				120.3
IQ-Range	5.200				20.90
Min	112.4				109.8
Max	126.3				134.8
p_L					0.424
p_J					0.754

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

Dose (mg/kg)	group 1	group 2	group 3	group 4	group 5
	0	10	50	200	1000
week: 8 N	5				5
Mean	122.0				117.6
SD	14.07				10.82
Median	124.1				116.7
IQ-Range	15.75				6.417
Min	105.2				105.2
Max	141.3				134.5
p _L					0.514
p _J					0.676

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8.12. Food consumption ratios (means)

No statistical tests performed

Food 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	120.3	122.5	124.2	121.3	117.9
1	96.11	104.2	103.6	100.7	100.5
2	92.76	92.24	94.56	86.21	95.47
3	78.95	84.56	84.50	81.33	84.03
4	78.91	76.15	79.07	76.76	78.76
recovery					
week: 5	71.36				77.15
6	72.44				71.94
7	66.83				63.15
8	62.99				62.24

No statistical tests performed

Food 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	115.7	119.3	118.7	118.2	120.0
1	88.51	89.04	98.42	95.78	94.44
2	96.74	94.98	98.88	100.4	96.21
3	89.04	89.06	88.98	90.29	84.95
4	81.73	85.24	85.46	80.74	81.79
recovery					
week: 5	78.93				84.18
6	80.56				82.65
7	74.00				73.48
8	72.57				69.36

8.13. 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	243.5	244.2	181.0	291.2	229.6
1	186.6	179.6	195.9	202.0	221.3 +
2	206.3	189.0	191.4	183.4	235.1
3	176.8	167.9	177.2	163.9	208.2
4	243.5	224.1	222.5	218.1	323.6
recovery					
week: 5	226.6				242.8
6	240.8				267.8
7	244.8				271.2
8	193.4				184.7

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	266.1	224.1	222.0	166.9	180.1
1	148.1	138.9	138.6	138.3	143.7
2	155.1	116.0	142.9*	120.5	146.8
3	142.7	136.9	137.6	120.5	122.3
4	227.4	143.5*	194.3	183.5	210.1
recovery					
week: 5	186.1				203.0
6	179.9				176.8
7	200.5				170.8
8	156.5				137.5

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

8.14. 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	5	10
Mean	243.5	244.2	181.0	291.2	229.6
SD	95.21	75.38	9.228	171.2	100.4
Median	207.9	250.6	179.2	203.7	193.2
IQ-Range	63.00	105.0	14.00	172.9	68.60
Min	168.7	163.8	171.5	149.8	130.9
Max	497.0	345.8	193.2	562.8	469.0
p_L		0.303	0.096	0.303	0.434
p_J		0.903	0.136	0.461	0.387
week: 1 N	10	5	5	5	10
Mean	186.6	179.6	195.9	202.0	221.3
SD	26.77	10.01	29.38	24.28	27.54
Median	181.0	184.8	196.0	206.5	226.1
IQ-Range	24.50	22.60	28.70	12.60	46.20
Min	156.1	164.5	161.7	160.3	176.4
Max	248.5	167.6	238.7	220.5	252.7
p_L		0.430	0.713	0.161	0.064
p_J		0.759	0.546	0.122	0.002 +
week: 2 N	8	5	5	5	10
Mean	206.3	189.0	191.4	183.4	235.1
SD	26.99	26.67	21.74	34.71	35.24
Median	193.2	188.3	196.7	200.2	240.8
IQ-Range	29.05	30.10	23.80	60.90	35.00
Min	186.2	163.8	163.1	144.9	180.6
Max	262.5	229.6	219.1	217.0	312.9
p_L		0.421	0.730	0.646	0.152
p_J		0.306	0.414	0.409	0.043

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	8	5	5	5	10
Mean	176.8	167.9	177.2	163.9	208.2
SD	37.03	14.19	55.87	20.19	24.19
Median	169.8	169.4	163.8	167.3	212.1
IQ-Range	57.40	21.70	1.400	21.00	35.70
Min	130.9	149.8	121.8	132.3	176.4
Max	235.9	183.4	271.6	182.7	251.3
p_L		0.323	0.821	0.463	0.080
p_J		0.884	0.838	0.826	0.018
week: 4 N	8	5	5	5	10
Mean	243.5	224.1	222.5	218.1	323.6
SD	55.37	84.93	28.01	53.26	93.85
Median	241.5	194.6	208.6	196.0	315.0
IQ-Range	31.50	75.60	42.70	18.90	178.5
Min	178.5	158.2	193.9	175.0	199.5
Max	366.8	364.7	256.9	310.1	455.0
p_L		0.284	0.770	0.297	0.110
p_J		0.213	0.595	0.393	0.082
recovery					
week: 5 N	4				5
Mean	226.6				242.8
SD	26.60				22.24
Median	225.4				245.0
IQ-Range	45.85				30.80
Min	203.0				213.5
Max	252.7				268.1
p_L					0.536
p_J					
week: 6 N	4				5
Mean	240.8				267.8
SD	48.12				35.52
Median	234.2				282.8
IQ-Range	76.30				7.700
Min	193.9				205.1
Max	301.0				291.9
p_L					0.456
p_J					

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

116

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
	Mean	244.8				271.2
	SD	54.73				93.02
	Median	232.8				247.8
	IQ-Range	71.75				94.50
	Min	192.5				161.7
	Max	321.3				403.9
	p_L					0.642
	p_J					
week: 8	N	4				5
	Mean	193.4				184.7
	SD	58.45				39.14
	Median	198.1				180.6
	IQ-Range	76.65				33.60
	Min	117.6				142.1
	Max	259.7				245.0
	p_L					0.769
	p_J					

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

117

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	group 2	group 3	group 4	group 5
	0	10	50	200	1000
week: -1 N	10	5	5	5	10
Mean	266.1	224.1	222.0	166.9	180.1
SD	153.6	68.80	70.99	40.64	24.36
Median	199.2	189.0	207.2	157.5	179.9
IQ-Range	98.00	100.1	13.30	58.10	35.00
Min	149.8	149.8	149.8	119.0	149.8
Max	580.3	306.6	340.9	217.0	227.5
p_L		0.863	0.663	0.243	0.130
p_J		0.759	0.972	0.248	0.107
week: 1 N	10	5	5	5	10
Mean	148.1	138.9	138.6	138.3	143.7
SD	27.28	4.304	19.43	15.84	22.68
Median	149.5	140.0	128.8	141.4	144.2
IQ-Range	46.20	7.000	23.80	25.20	31.50
Min	105.7	133.7	121.1	121.1	105.0
Max	189.0	143.5	167.3	157.5	177.8
p_L		0.054	0.591	0.401	0.647
p_J		0.624	0.394	0.364	0.714
week: 2 N	10	4	5	5	10
Mean	155.1	116.0	142.9	120.5	146.8
SD	51.15	26.87	14.96	19.80	33.79
Median	141.4	116.6	137.2	123.9	146.3
IQ-Range	69.30	42.35	9.100 b	7.000	63.00
Min	106.4	84.70	132.3	89.95	100.8
Max	261.8	146.3	168.7	144.9	189.7
p_L		0.367	0.033 *	0.266	0.891
p_J		0.157	0.877	0.359	0.988
week: 3 N	10	4	5	5	10
Mean	142.7	136.9	137.6	120.5	122.3
SD	25.88	18.97	30.84	32.44	21.88
Median	135.5	138.6	130.2	112.0	128.5
IQ-Range	27.30	23.10	36.40	11.20	26.60
Min	94.50	112.0	104.3	83.30	81.20
Max	180.6	158.2	182.0	172.2	143.5
p_L		0.767	0.377	0.096	0.220
p_J		0.944	0.727	0.157	0.092

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	4	5	5	10
Mean	227.4	143.5	194.3	183.5	210.1
SD	83.83	13.71	85.65	60.58	56.25
Median	196.0	146.7	151.2	181.3	192.2
IQ-Range	140.0	21.00	111.3	28.00	76.30
Min	147.7	125.3	126.0	114.1	149.8
Max	399.0	155.4	322.7	279.3	339.5
p_L		0.020 *	0.166	0.638	0.189
p_J		0.011	0.053	0.182	0.771
recovery					
week: 5 N	5				5
Mean	186.1				203.0
SD	27.57				48.68
Median	176.4				207.9
IQ-Range	35.70				64.40
Min	157.5				137.9
Max	224.7				259.0
p_L					0.341
p_J					0.465
week: 6 N	5				5
Mean	179.9				176.8
SD	21.51				31.83
Median	169.4				178.5
IQ-Range	30.80				23.80
Min	156.8				126.7
Max	206.5				210.7
p_L					0.870
p_J					0.754
week: 7 N	5				5
Mean	200.5				170.8
SD	32.29				32.12
Median	188.3				184.1
IQ-Range	51.80				39.20
Min	170.8				123.2
Max	242.9				200.9
p_L					0.643
p_J					0.347

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	156.5				137.5
SD	30.99				28.09
Median	152.6				146.3
IQ-Range	32.20				31.50
Min	118.3				101.5
Max	199.5				172.9
p_L					0.643
p_J					0.347

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8.15. 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	7.911	8.182	8.072	8.364	8.044
9	8.588				8.598
Hb (mmol/l)					
week: 5	9.438	9.700	9.510	9.900	9.350
9	9.850				9.640
Hct (l)					
week: 5	0.463	0.476	0.472	0.484	0.462
9	0.493				0.479
MCV (fl)					
week: 5	58.54	58.14	58.49	57.88	57.53
9	57.38				55.66
RDW (l)					
week: 5	0.122	0.126	0.119	0.113	0.116
9	0.132				0.126*
MCH (fmol)					
week: 5	1.191	1.184	1.177	1.188	1.163
9	1.145				1.120
MCHC (mmol/l)					
week: 5	20.36	20.39	20.16	20.51	20.23
9	19.98				20.14

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	1.548	1.448	1.594	1.540	1.548
9	1.533				1.496
WBC (G/l)					
week: 5	13.90	13.01	15.72	13.39	15.13
9	12.31				15.00
Neut (1)					
week: 5	0.095	0.078	0.145	0.080	0.091
9	0.085				0.091
Eos (1)					
week: 5	0.009	0.011	0.010	0.012	0.011
9	0.008				0.012
Baso (1)					
week: 5	0.007	0.006	0.007	0.006	0.007
9	0.006				0.007
Lympho (1)					
week: 5	0.836	0.849	0.782	0.841	0.836
9	0.849				0.830
Mono (1)					
week: 5	0.031	0.032	0.030	0.038	0.032
9	0.034				0.035
Luc (1)					
week: 5	0.023	0.024	0.026	0.023	0.023
9	0.019				0.025

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Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	1.289	0.986	2.477*	1.072	1.360
9	1.055				1.366
Eos (G/l)					
week: 5	0.119	0.134	0.161	0.170	0.166
9	0.103				0.188
Baso (G/l)					
week: 5	0.101	0.088	0.114	0.086	0.110
9	0.078				0.100
Lympho (G/l)					
week: 5	11.65	11.09	12.06	11.23	12.67
9	10.43				12.44
Mono (G/l)					
week: 5	0.420	0.410	0.497	0.514	0.482
9	0.413				0.508
Luc (G/l)					
week: 5	0.318	0.300	0.406	0.312	0.348
9	0.235				0.394
Plt (G/l)					
week: 5	1103	1056	1062	1152	1135
9	945.3				982.2
PT (rel. 1)					
week: 5	0.757	0.733	0.794	0.714	0.685
9	0.847				0.797

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Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	8.095	7.793	7.832	7.704	7.780
9	8.462				8.166
Hb (mmol/l)					
week: 5	9.490	9.225	9.200	9.140	9.050*
9	9.760				9.500
Hct (l)					
week: 5	0.454	0.446	0.440	0.445	0.440
9	0.472				0.460
MCV (fl)					
week: 5	56.06	57.15	56.20	57.76	56.63
9	55.80				56.38
RDW (l)					
week: 5	0.120	0.125	0.124	0.123	0.116
9	0.119				0.124
MCH (fmol)					
week: 5	1.170	1.183	1.176	1.188	1.164
9	1.154				1.167
MCHC (mmol/l)					
week: 5	20.89	20.68	20.94	20.53	20.55
9	20.68				20.68

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	1.351	1.545	1.320	1.386	1.446
9	1.190				1.284
WBC (G/l)					
week: 5	7.979	6.180	7.534	7.562	9.191
9	9.212				7.519
Neut (1)					
week: 5	0.115	0.136	0.137	0.126	0.135
9	0.118				0.108
Eos (1)					
week: 5	0.013	0.011	0.008	0.013	0.008*
9	0.011				0.010
Baso (1)					
week: 5	0.005	0.004	0.004	0.004	0.007
9	0.005				0.004
Lympho (1)					
week: 5	0.819	0.792	0.791	0.803	0.798
9	0.820				0.818
Mono (1)					
week: 5	0.030	0.036	0.038	0.033	0.032
9	0.031				0.039
Luc (1)					
week: 5	0.018	0.022	0.021	0.021	0.021
9	0.016				0.020

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	0.966	0.795	1.018	0.962	1.163
9	1.094				0.804
Eos (G/l)					
week: 5	0.101	0.063	0.062	0.104	0.074
9	0.096				0.073
Baso (G/l)					
week: 5	0.044	0.025	0.030	0.032	0.064
9	0.050				0.029
Lympho (G/l)					
week: 5	6.488	4.930	5.962	6.052	7.416
9	7.532				6.169
Mono (G/l)					
week: 5	0.238	0.228	0.290	0.254	0.286
9	0.288				0.283
Luc (G/l)					
week: 5	0.140	0.140	0.164	0.164	0.189
9	0.154				0.155
Plt (G/l)					
week: 5	1213	1113 *	1160	1187	1196
9	1047				983.7
PT (rel. 1)					
week: 5	0.993	0.976	0.967	1.007	0.995
9	0.900				0.916

8.16. 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	8	5	5	5	10
Mean	7.911	8.182	8.072	8.364	8.044
SD	0.267	0.216	0.206	0.335	0.247
Median	7.945	8.220	7.950	8.380	8.005
IQ-Range	0.495	0.280	0.210	0.190	0.230
Min	7.570	7.870	7.920	7.970	7.660
Max	8.260	8.400	8.400	8.880	8.500
p _L		0.224	0.626	0.087	0.452
p _J		0.092	0.270	0.030	0.398
week: 9 N	4				5
Mean	8.588				8.598
SD	0.199				0.356
Median	8.545				8.730
IQ-Range	0.305				0.140
Min	8.410				7.990
Max	8.850				8.910
p _L					0.809
p _J					
Hb (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	9.438	9.700	9.510	9.900	9.350
SD	0.302	0.339	0.213	0.274	0.190
Median	9.400	9.700	9.550	9.900	9.300
IQ-Range	0.400	0.300	0.300	0.300	0.300
Min	9.000	9.300	9.200	9.500	9.100
Max	9.900	10.20	9.700	10.20	9.700
p _L		0.433	0.776	0.083	0.670
p _J		0.213	0.540	0.042	0.492

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	4				5
Mean	9.850				9.640
SD	0.173				0.365
Median	9.800				9.600
IQ-Range	0.200				0.200
Min	9.700				9.100
Max	10.10				10.10
p_L					0.233
p_J					
Hct (1)					
week: 5 N	8	5	5	5	10
Mean	0.463	0.476	0.472	0.484	0.462
SD	0.019	0.018	0.009	0.019	0.006
Median	0.462	0.477	0.476	0.473	0.462
IQ-Range	0.034	0.016	0.008	0.033	0.008
Min	0.439	0.452	0.457	0.467	0.451
Max	0.492	0.500	0.479	0.505	0.473
p_L		0.396	0.326	0.178	0.113
p_J		0.188	0.270	0.098	0.503
week: 9 N	4				5
Mean	0.493				0.479
SD	0.011				0.016
Median	0.496				0.485
IQ-Range	0.016				0.011
Min	0.478				0.451
Max	0.501				0.492
p_L					0.204
p_J					
MCV (fl)					
week: 5 N	8	5	5	5	10
Mean	58.54	58.14	58.49	57.88	57.53
SD	2.106	2.616	1.854	1.757	1.258
Median	59.00	59.10	59.10	56.90	57.45
IQ-Range	3.400	3.500	2.900	2.500	2.000
Min	55.30	55.00	56.10	56.20	55.70
Max	61.20	61.30	60.35	60.20	59.20
p_L		0.772	0.979	0.861	0.151
p_J		0.826	1.000	0.762	0.257

Hematology (statistics) : males

Dose (mg/kg)		group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week:	9 N	4				5
	Mean	57.38				55.66
	SD	1.723				1.379
	Median	57.30				55.70
	IQ-Range	2.750				0.900
	Min	55.50				53.50
	Max	59.40				57.20
	p_L					0.294
	p_J					
RDW (1)						
week:	5 N	8	5	5	5	10
	Mean	0.122	0.126	0.119	0.113	0.116
	SD	0.013	0.021	0.007	0.007	0.004
	Median	0.119	0.116	0.117	0.111	0.116
	IQ-Range	0.018	0.020	0.008	0.002	0.008
	Min	0.108	0.107	0.113	0.108	0.110
	Max	0.142	0.160	0.130	0.125	0.121
	p_L		0.703	0.935	0.405	0.666
	p_J		0.884	0.838	0.160	0.444
week:	9 N	4				5
	Mean	0.132				0.126
	SD	0.013				0.001
	Median	0.129				0.126
	IQ-Range	0.019				0.002 b
	Min	0.120				0.125
	Max	0.149				0.128
	p_L					0.044 *
	p_J					
MCH (fmol)						
week:	5 N	8	5	5	5	10
	Mean	1.191	1.184	1.177	1.188	1.163
	SD	0.028	0.047	0.028	0.041	0.022
	Median	1.190	1.200	1.160	1.170	1.165
	IQ-Range	0.045	0.070	0.045	0.050	0.040
	Min	1.150	1.130	1.150	1.150	1.130
	Max	1.230	1.240	1.210	1.250	1.190
	p_L		0.503	0.506	0.466	0.152
	p_J		0.770	0.462	0.680	0.094

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129

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Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	4				5
Mean	1.145				1.120
SD	0.031				0.034
Median	1.155				1.120
IQ-Range	0.040				0.030
Min	1.100				1.080
Max	1.170				1.170
p_L					0.613
p_J					
MCHC (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	20.36	20.39	20.16	20.51	20.23
SD	0.362	0.150	0.503	0.382	0.212
Median	20.32	20.40	20.32	20.42	20.20
IQ-Range	0.335	0.210	0.585	0.530	0.390
Min	19.98	20.23	19.37	20.08	19.94
Max	21.15	20.59	20.57	21.01	20.52
p_L		0.693	0.514	0.730	0.794
p_J		0.558	0.967	0.563	0.576
week: 9 N	4				5
Mean	19.98				20.14
SD	0.476				0.244
Median	20.05				20.17
IQ-Range	0.710				0.140
Min	19.36				19.77
Max	20.47				20.44
p_L					0.579
p_J					
HDW (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	1.548	1.448	1.594	1.540	1.548
SD	0.139	0.136	0.229	0.306	0.131
Median	1.525	1.490	1.490	1.450	1.525
IQ-Range	0.130	0.220	0.160	0.060	0.120
Min	1.380	1.280	1.390	1.330	1.350
Max	1.830	1.590	1.970	2.080	1.850
p_L		0.362	0.701	0.416	1.000
p_J		0.380	0.806	0.409	0.886

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Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	4				5
Mean	1.533				1.496
SD	0.109				0.097
Median	1.515				1.480
IQ-Range	0.145				0.100
Min	1.420				1.410
Max	1.680				1.650
p_L					0.678
p_J					
WBC (G/l)					
week: 5 N	8	5	5	5	10
Mean	13.90	13.01	15.72	13.39	15.13
SD	2.702	2.526	3.136	2.147	2.564
Median	13.97	12.85	14.79	12.84	15.52
IQ-Range	4.310	3.190	1.520	3.400	2.960
Min	9.920	10.43	12.80	10.95	10.96
Max	17.29	16.66	20.99	15.90	19.41
p_L		0.693	0.329	0.597	0.777
p_J		0.558	0.487	0.912	0.278
week: 9 N	4				5
Mean	12.31				15.00
SD	1.425				2.099
Median	12.50				14.13
IQ-Range	2.245				3.740
Min	10.52				13.17
Max	13.72				17.55
p_L					0.127
p_J					
Neut (1)					
week: 5 N	8	5	5	5	10
Mean	0.095	0.078	0.145	0.080	0.091
SD	0.020	0.019	0.095	0.011	0.029
Median	0.098	0.084	0.120	0.082	0.092
IQ-Range	0.023	0.019	0.107	0.014	0.046
Min	0.064	0.050	0.062	0.065	0.049
Max	0.127	0.099	0.293	0.094	0.142
p_L		0.341	0.104	0.164	0.429
p_J		0.143	0.967	0.441	0.666

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

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Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	4				5
Mean	0.085				0.091
SD	0.017				0.018
Median	0.081				0.087
IQ-Range	0.022				0.018
Min	0.068				0.065
Max	0.109				0.112
p_L					0.761
p_J					
Eos (1)					
week: 5 N	8	5	5	5	10
Mean	0.009	0.011	0.010	0.012	0.011
SD	0.003	0.002	0.004	0.006	0.003
Median	0.009	0.010	0.009	0.015	0.011
IQ-Range	0.006	0.003	0.005	0.010	0.004
Min	0.005	0.008	0.006	0.005	0.006
Max	0.013	0.014	0.015	0.018	0.015
p_L		0.382	0.720	0.090	0.254
p_J		0.306	0.414	0.215	0.151
week: 9 N	4				5
Mean	0.008				0.012
SD	0.003				0.004
Median	0.007				0.011
IQ-Range	0.004				0.003
Min	0.006				0.007
Max	0.013				0.018
p_L					0.195
p_J					
Baso (1)					
week: 5 N	8	5	5	5	10
Mean	0.007	0.006	0.007	0.006	0.007
SD	0.002	0.002	0.001	0.001	0.001
Median	0.008	0.005	0.008	0.007	0.008
IQ-Range	0.001	0.002	0.001	0.001	0.002
Min	0.003	0.005	0.005	0.005	0.005
Max	0.009	0.009	0.008	0.007	0.009
p_L		0.396	0.833	0.116	0.855
p_J		0.272	0.683	0.247	0.762

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	0.006				0.007
SD	0.001				0.001
Median	0.006				0.006
IQ-Range	0.001				0.000
Min	0.005				0.006
Max	0.007				0.009
p_L					0.677
p_J					
Lympho (1)					
week: 5 N	8	5	5	5	10
Mean	0.836	0.849	0.782	0.841	0.836
SD	0.030	0.036	0.102	0.017	0.036
Median	0.837	0.855	0.817	0.849	0.848
IQ-Range	0.036	0.027	0.093	0.006	0.058
Min	0.782	0.792	0.622	0.811	0.768
Max	0.875	0.887	0.882	0.852	0.882
p_L		0.679	0.161	0.722	0.616
p_J		0.380	0.624	0.956	0.823
week: 9 N	4				5
Mean	0.849				0.830
SD	0.025				0.032
Median	0.857				0.836
IQ-Range	0.034				0.049
Min	0.813				0.788
Max	0.868				0.864
p_L					0.565
p_J					
Mono (1)					
week: 5 N	8	5	5	5	10
Mean	0.031	0.032	0.030	0.038	0.032
SD	0.009	0.012	0.011	0.006	0.007
Median	0.029	0.027	0.033	0.036	0.032
IQ-Range	0.012	0.006	0.012	0.009	0.010
Min	0.020	0.024	0.015	0.032	0.023
Max	0.045	0.053	0.043	0.045	0.045
p_L		0.922	0.619	0.138	0.939
p_J		0.942	1.000	0.177	0.523

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	0.034				0.035
SD	0.004				0.009
Median	0.036				0.030
IQ-Range	0.005				0.012
Min	0.027				0.027
Max	0.036				0.048
p_L					0.490
p_J					
Luc (1)					
week: 5 N	8	5	5	5	10
Mean	0.023	0.024	0.026	0.023	0.023
SD	0.004	0.008	0.008	0.003	0.007
Median	0.022	0.021	0.023	0.023	0.021
IQ-Range	0.006	0.006	0.007	0.002	0.007
Min	0.019	0.018	0.018	0.020	0.016
Max	0.031	0.037	0.038	0.028	0.038
p_L		0.665	0.808	0.319	0.391
p_J		0.770	0.744	0.700	0.555
week: 9 N	4				5
Mean	0.019				0.025
SD	0.003				0.012
Median	0.018				0.022
IQ-Range	0.004				0.009
Min	0.017				0.015
Max	0.024				0.045
p_L					0.471
p_J					
Neut (G/l)					
week: 5 N	8	5	5	5	10
Mean	1.289	0.986	2.477	1.072	1.360
SD	0.258	0.133	2.160	0.244	0.446
Median	1.230	0.990	1.710	1.030	1.285
IQ-Range	0.455	0.210	1.660 b	0.250	0.610
Min	0.990	0.840	0.920	0.830	0.750
Max	1.690	1.150	6.135	1.450	2.290
p_L		0.137	0.013 *	0.263	0.728
p_J		0.048	0.806	0.308	0.911

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	4				5
Mean	1.055				1.366
SD	0.301				0.365
Median	1.035				1.140
IQ-Range	0.450				0.340
Min	0.720				1.110
Max	1.430				1.960
p_L					0.290
p_J					
Eos (G/l)					
week: 5 N	8	5	5	5	10
Mean	0.119	0.134	0.161	0.170	0.166
SD	0.051	0.038	0.082	0.101	0.043
Median	0.110	0.130	0.130	0.200	0.155
IQ-Range	0.085	0.050	0.130	0.160	0.080
Min	0.060	0.100	0.070	0.060	0.100
Max	0.200	0.190	0.255	0.290	0.220
p_L		0.492	0.588	0.069	0.096
p_J		0.464	0.270	0.259	0.088
week: 9 N	4				5
Mean	0.103				0.188
SD	0.053				0.080
Median	0.085				0.180
IQ-Range	0.065				0.050
Min	0.060				0.110
Max	0.180				0.320
p_L					0.134
p_J					
Baso (G/l)					
week: 5 N	8	5	5	5	10
Mean	0.101	0.088	0.114	0.086	0.110
SD	0.038	0.044	0.038	0.027	0.032
Median	0.105	0.070	0.110	0.070	0.120
IQ-Range	0.055	0.040	0.040	0.040	0.040
Min	0.030	0.050	0.070	0.060	0.060
Max	0.140	0.160	0.170	0.120	0.150
p_L		0.539	0.903	0.449	0.844
p_J		0.464	0.806	0.601	0.655

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

135

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	0.078				0.100
SD	0.015				0.037
Median	0.070				0.080
IQ-Range	0.015				0.030
Min	0.070				0.070
Max	0.100				0.160
p_L					0.344
p_J					
Lympho (G/l)					
week: 5 N	8	5	5	5	10
Mean	11.65	11.09	12.06	11.23	12.67
SD	2.500	2.535	1.025	1.664	2.328
Median	11.66	10.80	11.65	10.90	12.55
IQ-Range	4.230	3.360	1.760	2.300	2.960
Min	8.330	8.670	11.05	9.330	8.970
Max	15.13	14.78	13.26	13.40	16.68
p_L		0.859	0.058	0.297	0.553
p_J		0.661	0.775	0.934	0.315
week: 9 N	4				5
Mean	10.43				12.44
SD	1.058				1.677
Median	10.46				11.39
IQ-Range	1.505				2.570
Min	9.130				11.05
Max	11.68				14.65
p_L					0.137
p_J					
Mono (G/l)					
week: 5 N	8	5	5	5	10
Mean	0.420	0.410	0.497	0.514	0.482
SD	0.101	0.111	0.262	0.135	0.137
Median	0.450	0.400	0.490	0.550	0.475
IQ-Range	0.145	0.020	0.220	0.160	0.200
Min	0.230	0.270	0.200	0.350	0.260
Max	0.520	0.580	0.895	0.690	0.730
p_L		0.786	0.224	0.134	0.680
p_J		0.770	0.902	0.335	0.315

Hematology (statistics) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
week: 9 N	4				5
Mean	0.413				0.508
SD	0.076				0.115
Median	0.425				0.520
IQ-Range	0.125				0.060
Min	0.320				0.350
Max	0.480				0.670
p_L					0.318
p_J					
Luc (G/l)					
week: 5 N	8	5	5	5	10
Mean	0.318	0.300	0.406	0.312	0.348
SD	0.070	0.074	0.141	0.086	0.124
Median	0.340	0.300	0.420	0.290	0.320
IQ-Range	0.095	0.060	0.170	0.130	0.140
Min	0.200	0.210	0.230	0.230	0.180
Max	0.410	0.410	0.590	0.430	0.590
p_L		0.779	0.117	0.609	0.653
p_J		0.608	0.368	0.741	0.702
week: 9 N	4				5
Mean	0.235				0.394
SD	0.060				0.238
Median	0.230				0.370
IQ-Range	0.090				0.160
Min	0.170				0.190
Max	0.310				0.790
p_L					0.313
p_J					
Plt (G/l)					
week: 5 N	8	5	5	5	10
Mean	1103	1056	1062	1152	1135
SD	144.9	108.8	93.21	72.02	113.3
Median	1054	1104	1045	1136	1174
IQ-Range	197.0	84.00	46.00	62.00	146.0
Min	879.0	877.0	973.0	1074	950.0
Max	1325	1150	1218	1263	1284
p_L		0.859	0.842	0.069	0.510
p_J		0.661	0.487	0.457	0.231

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

137

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	945.3				982.2
SD	127.8				137.1
Median	932.5				1023
IQ-Range	167.5				40.00
Min	803.0				740.0
Max	1113				1068
p_L					0.769
p_J					
PT (rel. 1)					
week: 5 N	8	5	5	5	10
Mean	0.757	0.733	0.794	0.714	0.685
SD	0.067	0.028	0.096	0.076	0.127
Median	0.764	0.727	0.783	0.711	0.704
IQ-Range	0.093	0.022	0.089	0.122	0.209
Min	0.633	0.708	0.701	0.619	0.447
Max	0.835	0.778	0.946	0.793	0.863
p_L		0.329	0.866	0.432	0.300
p_J		0.380	0.935	0.457	0.125
week: 9 N	4				5
Mean	0.847				0.797
SD	0.005				0.029
Median	0.849				0.798
IQ-Range	0.008				0.020
Min	0.840				0.764
Max	0.852				0.842
p_L					0.088
p_J					

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	10
	Mean	8.095	7.793	7.832	7.704	7.780
	SD	0.314	0.337	0.188	0.519	0.353
	Median	8.000	7.915	7.840	7.870	7.910
	IQ-Range	0.340	0.425	0.320	0.310	0.480
	Min	7.660	7.300	7.640	6.820	7.200
	Max	8.660	8.040	8.060	8.120	8.190
	p _L		0.504	0.240	0.436	0.280
	p _J		0.258	0.096	0.110	0.114
week: 9	N	5				5
	Mean	8.462				8.166
	SD	0.154				0.470
	Median	8.470				8.310
	IQ-Range	0.110				0.490
	Min	8.220				7.450
	Max	8.630				8.640
	p _L					0.449
	p _J					0.347
Hb (mmol/l)						
week: 5	N	10	4	5	5	10
	Mean	9.490	9.225	9.200	9.140	9.050
	SD	0.314	0.411	0.200	0.691	0.299
	Median	9.450	9.250	9.100	9.600	9.050 a
	IQ-Range	0.200	0.550	0.200	1.000	0.300
	Min	8.900	8.700	9.000	8.200	8.600
	Max	10.10	9.700	9.500	9.700	9.500
	p _L		0.172	0.181	0.395	0.038 *
	p _J		0.179	0.048	0.182	0.015

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				5
	Mean	9.760				9.500
	SD	0.152				0.406
	Median	9.800				9.500
	IQ-Range	0.000				0.300
	Min	9.500				8.900
	Max	9.900				10.00
	p_L					0.234
	p_J					0.210
Hct (1)						
week:	5 N	10	4	5	5	10
	Mean	0.454	0.446	0.440	0.445	0.440
	SD	0.013	0.021	0.006	0.036	0.013
	Median	0.452	0.451	0.441	0.447	0.442
	IQ-Range	0.014	0.031	0.005	0.052	0.008
	Min	0.440	0.417	0.431	0.396	0.415
	Max	0.478	0.463	0.446	0.480	0.460
	p_L		0.499	0.127	0.195	0.167
	p_J		0.777	0.096	0.295	0.101
week:	9 N	5				5
	Mean	0.472				0.460
	SD	0.008				0.025
	Median	0.477				0.455
	IQ-Range	0.013				0.019
	Min	0.464				0.427
	Max	0.479				0.493
	p_L					0.219
	p_J					0.251
MCV (f1)						
week:	5 N	10	4	5	5	10
	Mean	56.06	57.15	56.20	57.76	56.63
	SD	1.251	1.182	1.089	1.749	1.417
	Median	55.55	57.30	56.00	58.10	56.55
	IQ-Range	1.200	1.700	0.900	2.200	2.700
	Min	55.00	55.60	55.30	55.20	54.50
	Max	58.90	58.40	58.00	59.50	58.60
	p_L		0.297	0.424	0.095	0.488
	p_J		0.120	0.333	0.067	0.203

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				5
Mean	55.80				56.38
SD	0.636				1.028
Median	55.80				56.90
IQ-Range	0.900				1.100
Min	54.90				54.80
Max	56.40				57.30
p_L					0.224
p_J					0.251
RDW (1)					
week: 5 N	10	4	5	5	10
Mean	0.120	0.125	0.124	0.123	0.116
SD	0.010	0.004	0.014	0.018	0.007
Median	0.119	0.125	0.126	0.131	0.114
IQ-Range	0.016	0.008	0.024	0.026	0.007
Min	0.105	0.121	0.107	0.103	0.110
Max	0.132	0.129	0.137	0.145	0.132
p_L		0.192	0.426	0.085	0.512
p_J		0.572	0.510	0.547	0.408
week: 9 N	5				5
Mean	0.119				0.124
SD	0.003				0.006
Median	0.118				0.121
IQ-Range	0.005				0.004
Min	0.115				0.119
Max	0.123				0.135
p_L					0.277
p_J					0.144
MCH (fmol)					
week: 5 N	10	4	5	5	10
Mean	1.170	1.183	1.176	1.188	1.164
SD	0.025	0.025	0.017	0.039	0.024
Median	1.170	1.185	1.180	1.200	1.160
IQ-Range	0.030	0.035	0.020	0.000	0.030
Min	1.130	1.150	1.150	1.120	1.120
Max	1.220	1.210	1.190	1.220	1.200
p_L		0.587	0.746	0.084	0.909
p_J		0.358	0.416	0.089	0.976

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

Test No.: 963103

141

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	1.154				1.167
SD	0.005				0.030
Median	1.150				1.160
IQ-Range	0.010				0.045
Min	1.150				1.130
Max	1.160				1.200
p_L					0.148
p_J					0.531
MCHC (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	20.89	20.68	20.94	20.53	20.55
SD	0.368	0.292	0.370	0.565	0.390
Median	20.87	20.76	21.14	20.23	20.59
IQ-Range	0.460	0.400	0.470	0.420	0.470
Min	20.09	20.26	20.38	20.09	19.89
Max	21.42	20.92	21.22	21.47	21.25
p_L		0.505	0.585	0.091	0.100
p_J		0.258	0.969	0.239	0.043
week: 9 N	5				5
Mean	20.68				20.68
SD	0.294				0.266
Median	20.62				20.63
IQ-Range	0.210				0.225
Min	20.43				20.31
Max	21.17				21.02
p_L					0.995
p_J					0.917
HDW (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	1.351	1.545	1.320	1.386	1.446
SD	0.123	0.303	0.074	0.175	0.130
Median	1.310	1.555	1.310	1.300	1.418
IQ-Range	0.090	0.520	0.030	0.260	0.260
Min	1.240	1.240	1.240	1.240	1.280
Max	1.660	1.830	1.440	1.630	1.620
p_L		0.281	0.878	0.485	0.160
p_J		0.358	0.938	0.875	0.220

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				5
Mean	1.190				1.284
SD	0.060				0.145
Median	1.210				1.220
IQ-Range	0.070				0.210
Min	1.110				1.160
Max	1.260				1.490
p_L					0.564
p_J					0.296
WBC (G/l)					
week: 5 N	10	4	5	5	10
Mean	7.979	6.180	7.534	7.562	9.191
SD	2.701	1.029	2.640	1.322	2.035
Median	7.395	6.590	6.250	7.270	9.150
IQ-Range	5.010	1.340	2.460	2.180	3.370
Min	4.220	4.680	4.920	6.020	6.250
Max	11.81	6.860	11.58	9.000	12.19
p_L		0.142	0.958	0.525	0.162
p_J		0.322	0.535	0.979	0.073
week: 9 N	5				5
Mean	9.212				7.519
SD	3.236				2.368
Median	7.530				6.330
IQ-Range	5.480				2.480
Min	6.220				5.745
Max	13.05				11.32
p_L					0.472
p_J					0.251
Neut (1)					
week: 5 N	10	4	5	5	10
Mean	0.115	0.136	0.137	0.126	0.135
SD	0.064	0.066	0.044	0.033	0.106
Median	0.086	0.117	0.136	0.119	0.087
IQ-Range	0.031	0.095	0.027	0.037	0.088
Min	0.067	0.080	0.081	0.092	0.053
Max	0.264	0.228	0.201	0.176	0.389
p_L		0.659	0.461	0.106	0.183
p_J		0.480	0.245	0.165	0.915

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
	Mean	0.118				0.108
	SD	0.036				0.052
	Median	0.121				0.099
	IQ-Range	0.049				0.067
	Min	0.077				0.063
	Max	0.164				0.187
	p_L					0.603
	p_J					0.602
Eos (1)						
week: 5	N	10	4	5	5	10
	Mean	0.013	0.011	0.008	0.013	0.008
	SD	0.003	0.004	0.002	0.005	0.003
	Median	0.014	0.011	0.008	0.014	0.008 a
	IQ-Range	0.002	0.006	0.000	0.003	0.003
	Min	0.007	0.006	0.007	0.006	0.003
	Max	0.017	0.015	0.011	0.020	0.015
	p_L		0.315	0.052	0.525	0.028 *
	p_J		0.289	0.016	0.359	0.021
week: 9	N	5				5
	Mean	0.011				0.010
	SD	0.003				0.004
	Median	0.011				0.009
	IQ-Range	0.005				0.001
	Min	0.007				0.006
	Max	0.014				0.017
	p_L					0.869
	p_J					0.602
Baso (1)						
week: 5	N	10	4	5	5	10
	Mean	0.005	0.004	0.004	0.004	0.007
	SD	0.001	0.001	0.002	0.001	0.002
	Median	0.006	0.004	0.004	0.004	0.006
	IQ-Range	0.002	0.001	0.002	0.002	0.002
	Min	0.003	0.003	0.002	0.003	0.004
	Max	0.007	0.005	0.006	0.006	0.011
	p_L		0.187	0.274	0.308	0.319
	p_J		0.090	0.058	0.067	0.250

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				5
Mean	0.005				0.004
SD	0.001				0.002
Median	0.004				0.005
IQ-Range	0.002				0.003
Min	0.003				0.002
Max	0.006				0.006
p_L					0.781
p_J					0.602
Lympho (1)					
week: 5 N	10	4	5	5	10
Mean	0.819	0.792	0.791	0.803	0.798
SD	0.068	0.068	0.038	0.039	0.104
Median	0.848	0.797	0.781	0.817	0.846
IQ-Range	0.030	0.111	0.031	0.004	0.107
Min	0.663	0.712	0.745	0.734	0.566
Max	0.885	0.863	0.846	0.827	0.875
p_L		0.818	0.228	0.120	0.306
p_J		0.572	0.201	0.143	0.878
week: 9 N	5				5
Mean	0.820				0.818
SD	0.039				0.053
Median	0.824				0.844
IQ-Range	0.048				0.071
Min	0.763				0.747
Max	0.860				0.871
p_L					0.812
p_J					1.000
Mono (1)					
week: 5 N	10	4	5	5	10
Mean	0.030	0.036	0.038	0.033	0.032
SD	0.010	0.009	0.006	0.007	0.011
Median	0.030	0.034	0.039	0.035	0.029
IQ-Range	0.010	0.015	0.002	0.006	0.020
Min	0.015	0.028	0.028	0.022	0.020
Max	0.047	0.048	0.044	0.041	0.052
p_L		0.584	0.277	0.762	0.890
p_J		0.322	0.096	0.307	0.927

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

145

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	0.031				0.039
SD	0.004				0.015
Median	0.030				0.035
IQ-Range	0.002				0.024
Min	0.028				0.022
Max	0.037				0.057
p_L					0.332
p_J					0.465
Luc (1)					
week: 5 N	10	4	5	5	10
Mean	0.018	0.022	0.021	0.021	0.021
SD	0.004	0.011	0.006	0.006	0.005
Median	0.018	0.018	0.020	0.021	0.021
IQ-Range	0.003	0.012	0.009	0.002	0.004
Min	0.011	0.015	0.015	0.013	0.013
Max	0.024	0.039	0.029	0.030	0.033
p_L		0.972	0.200	0.109	0.199
p_J		0.888	0.439	0.182	0.129
week: 9 N	5				5
Mean	0.016				0.020
SD	0.003				0.004
Median	0.014				0.019
IQ-Range	0.005				0.006
Min	0.012				0.017
Max	0.019				0.026
p_L					0.252
p_J					0.117
Neut (G/l)					
week: 5 N	10	4	5	5	10
Mean	0.966	0.795	1.018	0.962	1.163
SD	0.809	0.254	0.420	0.354	0.893
Median	0.660	0.780	1.040	0.870	0.880
IQ-Range	0.700	0.430	0.530	0.100	0.290
Min	0.360	0.550	0.510	0.620	0.540
Max	3.110	1.070	1.570	1.560	3.480
p_L		0.850	0.611	0.431	0.299
p_J		1.000	0.394	0.295	0.270

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				5
Mean	1.094				0.804
SD	0.600				0.455
Median	0.910				0.710
IQ-Range	0.090				0.260
Min	0.610				0.370
Max	2.140				1.560
p_L					0.364
p_J					0.175
Eos (G/l)					
week: 5 N	10	4	5	5	10
Mean	0.101	0.063	0.062	0.104	0.074
SD	0.032	0.021	0.019	0.053	0.027
Median	0.095	0.060	0.060	0.090	0.075
IQ-Range	0.040	0.025	0.020	0.050	0.030
Min	0.060	0.040	0.040	0.040	0.030
Max	0.150	0.090	0.090	0.180	0.115
p_L		0.121	0.080	0.632	0.201
p_J		0.048	0.013	0.271	0.188
week: 9 N	5				5
Mean	0.096				0.073
SD	0.027				0.018
Median	0.090				0.070
IQ-Range	0.020				0.020
Min	0.070				0.055
Max	0.140				0.100
p_L					0.306
p_J					0.144
Baso (G/l)					
week: 5 N	10	4	5	5	10
Mean	0.044	0.025	0.030	0.032	0.064
SD	0.022	0.010	0.020	0.013	0.034
Median	0.035	0.030	0.020	0.030	0.055
IQ-Range	0.040	0.010	0.020	0.020	0.040
Min	0.020	0.010	0.010	0.020	0.020
Max	0.080	0.030	0.060	0.050	0.140
p_L		0.279	0.327	0.614	0.315
p_J		0.179	0.131	0.239	0.154

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				5
Mean	0.050				0.029
SD	0.027				0.017
Median	0.030				0.030
IQ-Range	0.050				0.025
Min	0.030				0.010
Max	0.080				0.050
p_L					0.525
p_J					0.296
Lympho (G/l)					
week: 5 N	10	4	5	5	10
Mean	6.488	4.930	5.962	6.052	7.416
SD	2.142	1.111	2.085	0.968	2.253
Median	6.290	5.245	5.290	5.940	7.315
IQ-Range	3.000	1.310	2.380	1.060	4.435
Min	3.570	3.330	3.820	4.940	4.920
Max	10.46	5.900	9.040	7.440	10.66
p_L		0.191	0.932	0.260	0.610
p_J		0.258	0.535	0.937	0.250
week: 9 N	5				5
Mean	7.532				6.169
SD	2.577				2.140
Median	6.210				4.950
IQ-Range	4.100				1.300
Min	4.990				4.875
Max	10.64				9.860
p_L					0.278
p_J					0.175
Mono (G/l)					
week: 5 N	10	4	5	5	10
Mean	0.238	0.228	0.290	0.254	0.286
SD	0.115	0.082	0.130	0.088	0.092
Median	0.205	0.220	0.240	0.220	0.318
IQ-Range	0.130	0.125	0.190	0.120	0.170
Min	0.090	0.140	0.170	0.150	0.130
Max	0.470	0.330	0.470	0.360	0.390
p_L		1.000	0.718	0.635	0.637
p_J		1.000	0.535	0.513	0.263

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				5
	Mean	0.288				0.283
	SD	0.132				0.092
	Median	0.220				0.310
	IQ-Range	0.170				0.040
	Min	0.170				0.125
	Max	0.480				0.360
	p_L					0.442
	p_J					0.917
Luc (G/l)						
week: 5	N	10	4	5	5	10
	Mean	0.140	0.140	0.164	0.164	0.189
	SD	0.049	0.088	0.100	0.069	0.051
	Median	0.135	0.105	0.130	0.140	0.195
	IQ-Range	0.080	0.110	0.020	0.060	0.100
	Min	0.080	0.080	0.090	0.090	0.120
	Max	0.210	0.270	0.340	0.270	0.260
	p_L		0.810	0.505	0.762	0.122
	p_J		0.777	0.757	0.432	0.042
week: 9	N	5				5
	Mean	0.154				0.155
	SD	0.083				0.078
	Median	0.100				0.140
	IQ-Range	0.150				0.035
	Min	0.090				0.100
	Max	0.250				0.290
	p_L					0.213
	p_J					0.403
Plt (G/l)						
week: 5	N	10	4	5	5	10
	Mean	1213	1113	1160	1187	1196
	SD	74.13	121.3	82.13	58.28	191.2
	Median	1214	1075	1159	1160	1214
	IQ-Range	52.00	145.5	46.00	24.00	105.0
	Min	1102	1012	1033	1149	759.0
	Max	1349	1289	1256	1289	1526
	p_L		0.032 *	0.543	0.543	0.659
	p_J		0.090	0.163	0.295	0.963

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				5
Mean	1047				983.7
SD	137.5				175.1
Median	1125				1017
IQ-Range	85.00				47.50
Min	811.0				697.0
Max	1134				1174
p_L					0.588
p_J					0.347
PT (rel. 1)					
week: 5 N	10	4	5	5	10
Mean	0.993	0.976	0.967	1.007	0.995
SD	0.050	0.044	0.050	0.071	0.070
Median	0.998	0.978	0.988	1.037	0.990
IQ-Range	0.061	0.067	0.043	0.081	0.081
Min	0.894	0.922	0.891	0.908	0.889
Max	1.054	1.024	1.020	1.084	1.139
p_L		0.748	0.501	0.382	0.891
p_J		0.480	0.245	0.937	0.976
week: 9 N	5				5
Mean	0.900				0.916
SD	0.045				0.058
Median	0.912				0.941
IQ-Range	0.073				0.040
Min	0.852				0.820
Max	0.953				0.966
p_L					0.609
p_J					0.602

8.17. Blood chemistry (means)

Statistical tests and flags used:

LEPAGE: * if p_L < 0.05
 JONCKHEERE: +- 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	7.096	7.092	7.342	6.856	6.980
9	7.888				8.076
Urea (mmol/l)					
week: 5	5.481	6.766*+	6.880*+	5.928	5.953
9	5.980				6.468
Creat (umol/l)					
week: 5	20.26	21.26	20.82	20.44	20.08
9	20.33				21.96
Bili-tot (umol/l)					
week: 5	1.379	1.417	1.430	1.212	1.063*-
9	1.805				1.748
Prot (g/l)					
week: 5	66.61	65.67	67.27	67.15	65.74
9	70.40				68.02*
Alb (g/l)					
week: 5	33.84	33.62	34.10	34.47	33.69
9	34.61				33.99
Glob (g/l)					
week: 5	32.77	32.05*	33.17*	32.68	32.04
9	35.79				34.02

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

151

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	1.033	1.054*	1.032	1.056	1.054
9	0.965				1.000
Chol (mmol/l)					
week: 5	1.794	1.664	1.662	1.692	1.862
9	1.908				1.652
Na+ (mmol/l)					
week: 5	146.3	145.1*	142.6*-	144.9	144.5*
9	143.3				144.6
K+ (mmol/l)					
week: 5	3.715	4.003	4.036	4.095	4.057
9	3.388				3.458
Ca++ (mmol/l)					
week: 5	2.641	2.630	2.604	2.658	2.675
9	2.730				2.676
Cl- (mmol/l)					
week: 5	96.61	97.42	97.70	96.26	93.81*
9	99.38				93.36
PO4-in (mmol/l)					
week: 5	2.139	2.038	2.034	2.024	1.988
9	2.030				2.000
ASAT (GOT) (U/l)					
week: 5	67.36	65.58	64.76	71.24	62.24
9	73.03				83.28

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	29.29	30.86	35.44	32.84	28.00
9	36.21				38.78
ALP (U/l)					
week: 5	153.4	132.8	174.6	176.0	142.4
9	115.5				108.4

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

153

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	6.615	6.725	6.744	6.850	6.661
9	7.246				7.808
Urea (mmol/l)					
week: 5	6.855	6.720	6.112	7.518	8.401
9	8.726				7.894
Creat (umol/l)					
week: 5	22.68	23.70	22.40	25.46	24.63
9	23.66				23.46
Bili-tot (umol/l)					
week: 5	1.603	1.530	1.346	1.426	1.393
9	1.633				1.958
Prot (g/l)					
week: 5	68.09	68.54	66.97	66.77	66.91
9	67.76				68.64
Alb (g/l)					
week: 5	36.26	36.42*	35.19	35.53	35.93
9	35.37				36.16
Glob (g/l)					
week: 5	31.83	32.13	31.79	31.24	30.98
9	32.39				32.49

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	1.142	1.138	1.112	1.142	1.164
	9	1.092				1.114
Chol (mmol/l)						
week:	5	1.927	1.843	2.000	1.914	1.998
	9	1.716				2.024
Na+ (mmol/l)						
week:	5	143.3	144.0	144.9*	144.5*	143.6
	9	142.8				143.4
K+ (mmol/l)						
week:	5	3.653	3.295*	3.574	3.567	3.745
	9	3.158				3.284
Ca++ (mmol/l)						
week:	5	2.605	2.505	2.472*	2.501	2.578
	9	2.604				2.590
Cl- (mmol/l)						
week:	5	97.86	100.1	99.16	99.20	97.59
	9	101.6				102.5
PO4-in (mmol/l)						
week:	5	1.715	1.593	1.719	1.632	1.657
	9	1.486				1.220
ASAT (GOT) (U/l)						
week:	5	68.13	74.40	69.40	69.22	70.23
	9	76.68				66.20

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

155

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	26.82	25.83	24.64	24.56	24.19
9	29.08				26.02
ALP (U/l)					
week: 5	108.5	89.84	120.0	115.4	128.0
9	73.60				86.34

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8.18. 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 < 0.01

Blood 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	8	5	5	5	10
Mean	7.096	7.092	7.342	6.856	6.980
SD	0.710	0.440	0.834	0.528	0.629
Median	7.055	7.290	7.240	6.890	7.085
IQ-Range	1.060	0.310	0.620	0.520	1.110
Min	6.260	6.350	6.520	6.260	5.900
Max	8.340	7.430	8.690	7.630	7.650
p _L		0.788	0.842	0.716	0.984
p _J		0.770	0.540	0.741	0.823
week: 9 N	4				5
Mean	7.888				8.076
SD	0.579				0.506
Median	7.950				8.180
IQ-Range	0.965				0.230
Min	7.220				7.260
Max	8.430				8.630
p _L					0.579
p _J					
Urea (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	5.481	6.766	6.880	5.928	5.953
SD	0.733	0.425	0.911	0.622	1.075
Median	5.375	6.680 a	6.580 a	5.620	5.720
IQ-Range	1.105	0.320	0.220	0.630	1.590
Min	4.460	6.220	6.090	5.400	4.670
Max	6.570	7.370	8.450	6.910	8.250
p _L		0.027 *	0.044 *	0.329	0.689
p _J		0.008 +	0.008 +	0.236	0.936

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	4				5
Mean	5.980				6.468
SD	0.471				1.042
Median	5.920				6.270
IQ-Range	0.580				1.020
Min	5.470				5.410
Max	6.610				8.080
p_L					0.338
p_J					
Creat (umol/l)					
week: 5 N	8	5	5	5	10
Mean	20.26	21.26	20.82	20.44	20.08
SD	1.613	2.369	1.686	3.139	2.266
Median	20.70	20.40	21.20	19.70	19.90
IQ-Range	2.600	2.800	1.700	0.400	2.800
Min	18.00	18.30	18.40	17.50	17.50
Max	22.50	24.20	22.80	25.80	24.70
p_L		0.741	0.669	0.859	0.873
p_J		0.464	0.462	0.869	0.453
week: 9 N	4				5
Mean	20.33				21.96
SD	1.630				2.832
Median	21.00				20.80
IQ-Range	1.850				3.900
Min	17.90				18.60
Max	21.40				25.30
p_L					0.642
p_J					
Bili-tot (umol/l)					
week: 5 N	8	5	5	5	10
Mean	1.379	1.417	1.430	1.212	1.063
SD	0.228	0.158	0.482	0.097	0.135
Median	1.420	1.360	1.340	1.210	1.060 a
IQ-Range	0.300	0.275	0.240	0.040	0.180
Min	0.935	1.270	1.020	1.090	0.880
Max	1.640	1.610	2.250	1.360	1.280
p_L		0.869	0.842	0.155	0.013 *
p_J		0.826	0.683	0.093	0.000 -

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	4				5
	Mean	1.805				1.748
	SD	0.507				0.170
	Median	1.625				1.790
	IQ-Range	0.700				0.040
	Min	1.440				1.460
	Max	2.530				1.910
	p_L					0.769
	p_J					
Prot (g/l)						
week:	5 N	8	5	5	5	10
	Mean	66.61	65.67	67.27	67.15	65.74
	SD	1.265	3.683	1.744	1.130	1.852
	Median	66.25	64.18	66.69	67.48	66.00
	IQ-Range	1.550	3.040	2.950	1.090	1.640
	Min	64.73	62.06	65.42	65.58	62.79
	Max	68.83	71.51	69.26	68.54	69.66
	p_L		0.082	0.544	0.679	0.537
	p_J		0.306	0.838	0.457	0.503
week:	9 N	4				5
	Mean	70.40				68.02
	SD	1.000				1.288
	Median	70.01				68.11 a
	IQ-Range	1.220				0.555
	Min	69.69				65.95
	Max	71.87				69.45
	p_L					0.043 *
	p_J					
Alb (g/l)						
week:	5 N	8	5	5	5	10
	Mean	33.84	33.62	34.10	34.47	33.69
	SD	0.964	1.148	0.889	0.531	0.691
	Median	33.63	33.52	34.39	34.73	33.59
	IQ-Range	1.120	1.170	1.180	0.830	0.665
	Min	32.83	32.53	32.90	33.78	32.72
	Max	35.81	35.41	35.07	34.96	35.12
	p_L		0.544	0.730	0.176	0.924
	p_J		0.464	0.838	0.177	0.962

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	4				5
Mean	34.61				33.99
SD	1.025				1.016
Median	34.45				34.13
IQ-Range	1.715				1.955
Min	33.74				32.89
Max	35.79				34.98
p_L					0.536
p_J					
Glob (g/l)					
week: 5 N	8	5	5	5	10
Mean	32.77	32.05	33.17	32.68	32.04
SD	0.618	2.977	2.046	0.985	1.302
Median	32.82	30.66	31.94	32.76	32.15
IQ-Range	0.840	4.410 b	2.970 b	1.650	1.140
Min	31.90	29.33	31.62	31.57	30.07
Max	33.73	36.10	36.07	33.81	34.54
p_L		0.014 *	0.032 *	0.364	0.159
p_J		0.558	0.838	0.890	0.307
week: 9 N	4				5
Mean	35.79				34.02
SD	0.530				1.040
Median	36.02				33.88
IQ-Range	0.625				1.360
Min	35.00				33.06
Max	36.12				35.56
p_L					0.088
p_J					
A/G (1)					
week: 5 N	8	5	5	5	10
Mean	1.033	1.054	1.032	1.056	1.054
SD	0.030	0.083	0.080	0.035	0.033
Median	1.030	1.090	1.050	1.060	1.040
IQ-Range	0.045	0.140 b	0.090	0.030	0.060
Min	0.990	0.950	0.910	1.020	1.020
Max	1.080	1.130	1.110	1.110	1.110
p_L		0.014 *	0.205	0.536	0.448
p_J		0.558	0.744	0.509	0.444

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	0.965				1.000
SD	0.035				0.047
Median	0.965				1.010
IQ-Range	0.060				0.020
Min	0.930				0.930
Max	1.000				1.060
p_L					0.293
p_J					
Chol (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	1.794	1.664	1.662	1.692	1.862
SD	0.329	0.093	0.223	0.416	0.242
Median	1.705	1.690	1.670	1.540	1.820
IQ-Range	0.245	0.090	0.380	0.100	0.230
Min	1.430	1.520	1.390	1.430	1.540
Max	2.525	1.760	1.890	2.430	2.310
p_L		0.404	0.532	0.293	0.583
p_J		0.558	0.513	0.186	0.425
week: 9 N	4				5
Mean	1.908				1.652
SD	0.308				0.165
Median	1.870				1.640
IQ-Range	0.445				0.170
Min	1.580				1.420
Max	2.310				1.850
p_L					0.282
p_J					
Na+ (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	146.3	145.1	142.6	144.9	144.5
SD	1.092	3.106	0.915	1.670	2.458
Median	146.1	143.7	142.3 a	144.4	143.9
IQ-Range	1.600	1.000	0.400	1.500	1.400
Min	144.7	143.1	141.5	143.4	141.7
Max	147.8	150.6	144.0	147.6	149.9
p_L		0.016 *	0.007 *	0.115	0.016 *
p_J		0.079	0.001 -	0.026	0.071

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	4				5
Mean	143.3				144.6
SD	1.813				0.644
Median	143.3				144.4
IQ-Range	2.700				0.800
Min	141.2				143.8
Max	145.5				145.4
p_L					0.114
p_J					
K+ (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	3.715	4.003	4.036	4.095	4.057
SD	0.243	0.185	0.158	0.364	0.376
Median	3.700	4.040	4.030	4.010	3.940
IQ-Range	0.320	0.285	0.160	0.300	0.440
Min	3.260	3.760	3.860	3.820	3.660
Max	4.000	4.190	4.270	4.705	4.905
p_L		0.122	0.087	0.122	0.221
p_J		0.040	0.016	0.022	0.060
week: 9 N	4				5
Mean	3.388				3.458
SD	0.400				0.164
Median	3.330				3.470
IQ-Range	0.655				0.040
Min	3.020				3.210
Max	3.870				3.670
p_L					0.137
p_J					
Ca++ (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	2.641	2.630	2.604	2.658	2.675
SD	0.060	0.092	0.048	0.044	0.056
Median	2.655	2.640	2.630	2.660	2.680
IQ-Range	0.075	0.130	0.060	0.030	0.070
Min	2.560	2.500	2.530	2.600	2.590
Max	2.750	2.720	2.640	2.720	2.790
p_L		0.507	0.160	0.709	0.437
p_J		0.770	0.220	0.978	0.238

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

162

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	2.730				2.676
SD	0.074				0.038
Median	2.740				2.680
IQ-Range	0.120				0.040
Min	2.640				2.630
Max	2.800				2.730
p_L					0.282
p_J					
Cl- (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	96.61	97.42	97.70	96.26	93.81
SD	1.630	2.054	2.245	2.268	2.372
Median	96.30	96.60	97.00	95.60	93.05 a
IQ-Range	1.900	3.300	0.100	2.300	3.250
Min	93.60	95.30	95.80	93.90	90.75
Max	98.90	99.90	101.6	99.70	97.40
p_L		0.449	0.689	0.449	0.039 *
p_J		0.558	0.391	0.890	0.012
week: 9 N	4				5
Mean	99.38				99.36
SD	1.187				1.139
Median	99.20				99.70
IQ-Range	1.950				1.500
Min	98.30				97.90
Max	100.8				100.7
p_L					0.949
p_J					
PO4-in (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	2.139	2.038	2.034	2.024	1.988
SD	0.257	0.195	0.109	0.185	0.154
Median	2.075	2.110	2.010	2.040	1.990
IQ-Range	0.240	0.290	0.160	0.140	0.200
Min	1.870	1.770	1.920	1.750	1.710
Max	2.690	2.220	2.180	2.250	2.180
p_L		0.904	0.780	0.742	0.591
p_J		0.826	0.624	0.545	0.271

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	4				5
Mean	2.030				2.000
SD	0.165				0.089
Median	2.065				1.990
IQ-Range	0.250				0.070
Min	1.810				1.880
Max	2.180				2.120
p_L					0.456
p_J					
ASAT (GOT) (U/l)					
week: 5 N	8	5	5	5	10
Mean	67.36	65.58	64.76	71.24	68.24
SD	8.097	5.996	12.98	6.315	5.962
Median	67.80	67.80	69.70	71.80	68.90
IQ-Range	12.45	4.600	7.300	5.300	7.600
Min	56.50	56.20	43.00	61.90	56.30
Max	79.30	71.90	76.40	78.80	78.05
p_L		0.693	0.960	0.723	0.863
p_J		0.558	0.806	0.509	0.632
week: 9 N	4				5
Mean	73.03				63.28
SD	27.57				10.82
Median	60.30				62.80
IQ-Range	29.55				9.700
Min	57.20				66.10
Max	114.3				93.00
p_L					0.067
p_J					
ALAT (GPT) (U/l)					
week: 5 N	8	5	5	5	10
Mean	29.29	30.86	35.44	32.84	28.00
SD	4.654	4.795	5.184	4.857	3.199
Median	29.75	30.90	33.30	31.40	27.30
IQ-Range	5.700	4.400	6.300	8.300	2.200
Min	22.80	25.40	29.60	28.00	23.20
Max	37.60	38.00	42.40	38.70	33.70
p_L		0.589	0.106	0.574	0.520
p_J		0.380	0.025	0.073	0.555

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	4				5
Mean	36.21				38.78
SD	18.24				4.830
Median	28.30				38.40
IQ-Range	21.23				6.100
Min	24.90				32.60
Max	63.35				44.80
p_L					0.067
p_J					
ALP (U/l)					
week: 5 N	8	5	5	5	10
Mean	153.4	132.8	174.6	176.0	142.4
SD	33.59	15.70	37.00	39.96	19.87
Median	149.4	136.9	170.5	162.0	144.3
IQ-Range	45.20	18.30	30.80	40.70	34.70
Min	108.9	113.2	139.1	128.3	112.0
Max	210.0	153.0	234.0	231.4	171.0
p_L		0.310	0.559	0.574	0.672
p_J		0.272	0.462	0.168	0.949
week: 9 N	4				5
Mean	115.5				108.4
SD	24.38				14.42
Median	120.7				112.1
IQ-Range	36.00				9.900
Min	82.50				84.50
Max	137.9				121.6
p_L					0.456
p_J					

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

165

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	10
Mean	6.615	6.725	6.744	6.850	6.661
SD	0.632	0.647	0.652	1.155	0.547
Median	6.430	6.920	6.710	6.310	6.615
IQ-Range	1.060	0.870	0.800	1.350	0.920
Min	5.880	5.800	5.860	5.940	5.910
Max	7.820	7.260	7.510	8.650	7.620
p _L		0.923	0.886	0.431	0.747
p _J		0.777	0.699	0.773	0.854
week: 9 N	5				5
Mean	7.246				7.808
SD	0.972				1.733
Median	6.880				7.520
IQ-Range	0.680				0.940
Min	6.580				6.400
Max	8.910				10.76
p _L					0.609
p _J					0.602
Urea (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	6.855	6.720	6.112	7.518	8.401
SD	0.963	0.542	0.680	1.434	1.378
Median	6.805	6.725	5.930	7.210	8.320
IQ-Range	0.880	0.760	0.460	0.800	2.470
Min	5.360	6.060	5.600	6.170	6.700
Max	8.750	7.370	7.270	9.910	10.46
p _L		0.850	0.343	0.589	0.053
p _J		1.000	0.188	0.855	0.010

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	8.726				7.894
SD	0.572				0.914
Median	8.770				8.100
IQ-Range	0.840				1.390
Min	8.040				6.620
Max	9.420				8.720
p_L					0.268
p_J					0.117
Creat (umol/l)					
week: 5 N	10	4	5	5	10
Mean	22.68	23.70	22.40	25.46	24.63
SD	2.837	1.711	2.151	2.436	1.919
Median	22.45	23.35	21.90	25.10	24.25
IQ-Range	1.600	2.700	2.100	1.700	2.000
Min	18.40	22.20	20.00	22.80	22.30
Max	29.70	25.90	25.60	29.30	28.87
p_L		0.647	0.632	0.087	0.057
p_J		0.358	1.000	0.099	0.020
week: 9 N	5				5
Mean	23.66				23.46
SD	1.234				1.599
Median	23.30				24.20
IQ-Range	1.200				1.200
Min	22.30				20.90
Max	25.50				25.00
p_L					0.975
p_J					1.000
Bili-tot (umol/l)					
week: 5 N	10	4	5	5	10
Mean	1.603	1.530	1.346	1.426	1.393
SD	0.258	0.378	0.255	0.291	0.301
Median	1.635	1.460	1.360	1.350	1.405
IQ-Range	0.450	0.620	0.100	0.490	0.580
Min	1.190	1.210	0.960	1.110	0.960
Max	1.910	1.990	1.670	1.760	1.790
p_L		0.632	0.243	0.402	0.234
p_J		0.671	0.152	0.122	0.068

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				5
Mean	1.633				1.958
SD	0.215				0.181
Median	1.770				1.980
IQ-Range	0.240				0.210
Min	1.295				1.680
Max	1.780				2.120
p_L					0.096
p_J					0.047
Prot (g/l)					
week: 5 N	10	4	5	5	10
Mean	68.09	68.54	66.97	66.77	66.91
SD	1.978	1.961	2.035	3.100	2.504
Median	68.58	68.12	67.00	67.92	67.08
IQ-Range	2.740	3.145	2.810	2.880	3.640
Min	64.28	66.92	64.41	61.79	61.80
Max	70.37	71.02	69.43	69.53	69.69
p_L		0.961	0.638	0.638	0.520
p_J		0.777	0.486	0.359	0.226
week: 9 N	5				5
Mean	67.76				68.64
SD	2.640				2.360
Median	67.37				69.55
IQ-Range	3.980				2.410
Min	64.48				65.14
Max	70.73				71.15
p_L					0.609
p_J					0.602
Alb (g/l)					
week: 5 N	10	4	5	5	10
Mean	36.26	36.42	35.19	35.53	35.93
SD	1.250	0.323	1.061	1.867	1.553
Median	35.69	36.45	35.40	36.55	35.79
IQ-Range	2.140	0.545 b	1.040	3.210	2.780
Min	35.05	36.06	33.53	33.22	33.54
Max	38.38	36.71	36.23	37.07	37.97
p_L		0.032 *	0.543	0.706	0.665
p_J		0.572	0.296	0.432	0.702

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	35.37				36.16
SD	2.215				1.437
Median	35.25				36.48
IQ-Range	4.060				1.810
Min	33.10				34.46
Max	37.86				38.03
p_L					0.609
p_J					0.602
Glob (g/l)					
week: 5 N	10	4	5	5	10
Mean	31.83	32.13	31.79	31.24	30.98
SD	1.497	2.014	2.087	1.933	2.103
Median	32.10	31.70	32.19	32.19	30.99
IQ-Range	2.330	3.080	3.770	1.540	1.280
Min	29.23	30.31	29.54	28.00	27.31
Max	34.02	34.79	34.03	32.64	35.43
p_L		0.850	0.569	0.719	0.447
p_J		1.000	0.938	0.675	0.193
week: 9 N	5				5
Mean	32.39				32.49
SD	0.851				1.721
Median	32.23				33.02
IQ-Range	0.890				1.560
Min	31.20				30.14
Max	33.39				34.67
p_L					0.424
p_J					0.754
A/G (1)					
week: 5 N	10	4	5	5	10
Mean	1.142	1.138	1.112	1.142	1.164
SD	0.065	0.073	0.090	0.076	0.089
Median	1.150	1.150	1.130	1.140	1.190
IQ-Range	0.080	0.105	0.140	0.060	0.070
Min	1.040	1.040	1.000	1.020	0.950
Max	1.260	1.210	1.210	1.210	1.260
p_L		0.909	0.502	0.962	0.422
p_J		0.944	0.699	1.000	0.220

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				5
Mean	1.092				1.114
SD	0.063				0.072
Median	1.100				1.110
IQ-Range	0.050				0.110
Min	1.000				1.040
Max	1.170				1.210
p_L					0.870
p_J					0.754
Chol (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	1.927	1.843	2.000	1.914	1.998
SD	0.270	0.165	0.150	0.273	0.386
Median	1.965	1.790	1.970	1.950	1.885
IQ-Range	0.260	0.215	0.120	0.410	0.270
Min	1.480	1.710	1.880	1.560	1.560
Max	2.430	2.080	2.250	2.210	2.700
p_L		0.777	0.512	0.941	0.974
p_J		0.671	0.561	0.753	0.854
week: 9 N	5				5
Mean	1.716				2.024
SD	0.239				0.392
Median	1.770				2.080
IQ-Range	0.120				0.490
Min	1.340				1.520
Max	1.990				2.510
p_L					0.230
p_J					0.251
Na+ (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	143.3	144.0	144.9	144.5	143.6
SD	1.301	1.307	1.287	2.493	1.207
Median	143.3	144.0	145.0	144.6	143.9
IQ-Range	1.200	2.250	0.700	2.400	1.600
Min	140.0	142.8	142.9	142.0	141.6
Max	144.6	145.3	146.4	148.3	145.2
p_L		0.192	0.015 *	0.041 *	0.543
p_J		0.572	0.058	0.199	0.759

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

170

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	142.8				143.4
SD	1.203				1.309
Median	143.2				144.0
IQ-Range	1.600				0.800
Min	141.1				141.3
Max	144.0				144.7
p_L					0.452
p_J					0.296
K+ (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	3.653	3.295	3.574	3.567	3.745
SD	0.203	0.160	0.270	0.459	0.318
Median	3.655	3.305 a	3.460	3.370	3.675
IQ-Range	0.230	0.200	0.330	0.180	0.320
Min	3.370	3.090	3.300	3.220	3.340
Max	4.090	3.480	3.960	4.365	4.310
p_L		0.020 *	0.289	0.092	0.544
p_J		0.011	0.163	0.157	0.635
week: 9 N	5				5
Mean	3.158				3.284
SD	0.376				0.129
Median	3.110				3.290
IQ-Range	0.130				0.170
Min	2.770				3.110
Max	3.780				3.430
p_L					0.255
p_J					0.210
Ca++ (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	2.605	2.505	2.472	2.501	2.578
SD	0.056	0.133	0.076	0.107	0.061
Median	2.625	2.500	2.470 a	2.570	2.590
IQ-Range	0.100	0.230	0.100	0.175	0.100
Min	2.520	2.390	2.370	2.370	2.460
Max	2.680	2.630	2.560	2.590	2.660
p_L		0.349	0.038 *	0.118	0.505
p_J		0.157	0.012	0.015	0.462

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

171

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	2.604				2.590
SD	0.030				0.068
Median	2.600				2.570
IQ-Range	0.050				0.060
Min	2.570				2.510
Max	2.640				2.690
p_L					0.227
p_J					0.403
Cl- (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	97.86	100.1	99.16	99.20	97.59
SD	1.455	1.961	1.110	1.925	1.810
Median	97.90	99.35	99.40	99.50	97.70
IQ-Range	2.300	2.300	0.900	2.500	1.700
Min	95.40	98.70	97.40	96.60	94.80
Max	99.50	103.0	100.3	101.4	100.5
p_L		0.181	0.199	0.183	0.931
p_J		0.066	0.040	0.047	0.890
week: 9 N	5				5
Mean	101.6				102.5
SD	1.791				1.529
Median	101.5				103.0
IQ-Range	2.100				0.800
Min	99.70				99.80
Max	104.2				103.5
p_L					0.588
p_J					0.347
PO4-in (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	1.715	1.593	1.719	1.632	1.657
SD	0.232	0.167	0.312	0.095	0.121
Median	1.685	1.600	1.850	1.630	1.680
IQ-Range	0.290	0.255	0.220	0.070	0.110
Min	1.430	1.390	1.225	1.500	1.400
Max	2.170	1.780	2.040	1.760	1.840
p_L		0.519	0.635	0.203	0.425
p_J		0.322	0.938	0.637	0.759

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				5
Mean	1.486				1.220
SD	0.242				0.163
Median	1.610				1.130
IQ-Range	0.300				0.260
Min	1.140				1.080
Max	1.720				1.430
p_L					0.207
p_J					0.076
ASAT (GOT) (U/l)					
week: 5 N	10	4	5	5	10
Mean	68.13	74.40	69.40	69.22	70.23
SD	7.445	11.68	8.728	11.79	8.459
Median	70.30	75.75	66.10	70.50	71.15
IQ-Range	10.30	19.80	5.400	17.40	12.60
Min	55.90	61.60	63.10	55.90	54.70
Max	82.20	84.50	84.40	84.10	81.60
p_L		0.425	0.786	0.497	0.524
p_J		0.322	0.816	0.979	0.830
week: 9 N	5				5
Mean	76.68				66.20
SD	12.55				7.498
Median	75.70				64.80
IQ-Range	20.90				11.90
Min	62.00				57.20
Max	90.60				74.50
p_L					0.268
p_J					0.117
ALAT (GPT) (U/l)					
week: 5 N	10	4	5	5	10
Mean	26.82	25.83	24.64	24.56	24.19
SD	4.154	3.966	3.453	3.232	3.214
Median	27.75	26.75	22.80	25.10	24.00
IQ-Range	5.300	5.450	2.000	3.500	4.000
Min	20.10	20.30	22.40	20.20	18.25
Max	34.60	29.50	30.60	28.60	28.50
p_L		0.798	0.464	0.501	0.329
p_J		0.724	0.296	0.218	0.163

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
	Mean	29.08				26.02
	SD	7.541				5.164
	Median	25.50				27.20
	IQ-Range	6.800				3.900
	Min	23.40				18.10
	Max	41.50				31.90
	p_L					0.909
	p_J					0.917
ALP (U/l)						
week:	5 N	10	4	5	5	10
	Mean	108.5	89.84	120.0	115.4	128.0
	SD	20.01	13.45	19.80	40.92	28.16
	Median	112.6	94.30	117.5	110.6	130.5
	IQ-Range	25.80	18.83	12.20	62.60	47.10
	Min	75.70	70.75	95.60	71.60	83.60
	Max	134.5	100.0	149.8	168.2	165.3
	p_L		0.201	0.638	0.303	0.106
	p_J		0.090	0.816	0.773	0.101
week:	9 N	5				5
	Mean	73.60				86.34
	SD	14.30				21.56
	Median	75.80				92.00
	IQ-Range	11.40				7.800
	Min	54.40				49.30
	Max	93.00				104.8
	p_L					0.361
	p_J					0.251

8.19. 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	5.188	5.480	5.520	5.060	4.260
9	4.900				4.560
Rel dens (1)					
week: 5	1.036	1.033	1.041	1.039	1.043
9	1.040				1.041
pH (1)					
week: 5	6.188	6.500	6.500	6.500	5.850
9	6.625				6.500
PRO (g/l)					
week: 5	0.500	0.750	0.650	0.750	0.700
9	0.375				0.450
GLU (mmol/l)					
week: 5	0.000	0.000	0.000	0.000	0.000
9	0.000				0.000
KET (mmol/l)					
week: 5	0.563	0.500	0.600	0.900	0.650
9	0.750				0.700
UBG (umol/l)					
week: 5	0.000	0.000	0.000	0.000	0.000
9	0.000				0.000

Urine analysis (means) : males

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
BIL (umol/l)					
week: 5	2.125	10.20	6.800	3.400	3.400
9	0.000				0.000
ERY (per ul)					
week: 5	11.88	18.00	13.00	13.00	6.000*
9	7.500				6.000

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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	3.280	3.425	3.580	2.680	3.750
9	1.500				2.960
Rel dens (1)					
week: 5	1.038	1.044	1.039	1.048	1.042
9	1.064				1.050
pH (1)					
week: 5	5.850	6.375	6.200	5.800	5.150*
9	6.000				6.000
PRO (g/l)					
week: 5	0.350	0.625	0.450	0.650*	0.550
9	0.650				0.550
GLU (mmol/l)					
week: 5	0.000	0.000	0.000	0.000	0.000
9	0.000				0.000
KET (mmol/l)					
week: 5	0.600	0.750	0.500	0.400	0.300*
9	0.900				0.500
UBG (umol/l)					
week: 5	6.800	8.500	0.000	10.20	0.000*
9	10.20				6.800

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	5.100	8.500	6.800	3.400	5.100
9	3.400				0.000
ERY (per ul)					
week: 5	10.00	13.75	18.00	8.000	24.50
9	4.000				34.00

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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	0/8	0/5	0/5	0/5	0/10
9	0/4				0/5

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	0/4	0/5	0/5	0/10
9	0/5				0/5

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8.20. 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	8	5	5	5	10
Mean	5.188	5.480	5.520	5.060	4.260
SD	1.684	1.262	2.067	1.927	1.045
Median	4.850	5.500	4.900	5.100	4.250
Min	2.300	3.700	3.400	2.600	2.600
Max	7.500	6.900	8.700	7.700	6.000
p_W		0.714	0.941	1.000	0.181
p_J		0.714	0.935	0.912	0.155
week: 9 N	4				5
Mean	4.900				4.560
SD	1.252				1.064
Median	4.550				5.000
Min	3.800				3.100
Max	6.700				5.600
p_W					0.902
p_J					
Rel dens (1)					
week: 5 N	8	5	5	5	10
Mean	1.036	1.033	1.041	1.039	1.043
SD	0.007	0.004	0.013	0.008	0.012
Median	1.034	1.033	1.037	1.039	1.043
Min	1.029	1.028	1.032	1.027	1.027
Max	1.047	1.037	1.062	1.050	1.064
p_W		0.509	0.303	0.659	0.248
p_J		0.510	0.487	0.283	0.079

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	1.040				1.041
SD	0.008				0.016
Median	1.042				1.039
Min	1.030				1.026
Max	1.048				1.067
p_W					0.712
p_J					
pH (1)					
week: 5 N	8	5	5	5	10
Mean	6.188	6.500	6.500	6.500	5.850
SD	0.594	0.354	0.000	0.354	0.747
Median	6.250	6.500	6.500	6.500	6.250
Min	5.000	6.000	6.500	6.000	5.000
Max	7.000	7.000	6.500	7.000	6.500
p_W		0.309	0.207	0.309	0.449
p_J		0.341	0.252	0.259	0.444
week: 9 N	4				5
Mean	6.625				6.500
SD	0.250				0.354
Median	6.500				6.500
Min	6.500				6.000
Max	7.000				7.000
p_W					0.558
p_J					
PRO (g/l)					
week: 5 N	8	5	5	5	10
Mean	0.500	0.750	0.650	0.750	0.700
SD	0.267	0.000	0.224	0.000	0.158
Median	0.500	0.750	0.750	0.750	0.750
Min	0.250	0.750	0.250	0.750	0.250
Max	0.750	0.750	0.750	0.750	0.750
p_W		0.068	0.299	0.068	0.067
p_J		0.143	0.270	0.152	0.207

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4				5
Mean	0.375				0.450
SD	0.250				0.274
Median	0.250				0.250
Min	0.250				0.250
Max	0.750				0.750
p_W					0.655
p_J					
GLU (mmol/l)					
week: 5 N	8	5	5	5	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	4				5
Mean	0.000				0.000
SD	0.000				0.000
Median	0.000				0.000
Min	0.000				0.000
Max	0.000				0.000
p_W					1.000
p_J					
KET (mmol/l)					
week: 5 N	8	5	5	5	10
Mean	0.563	0.500	0.600	0.900	0.650
SD	0.417	0.000	0.548	0.548	0.474
Median	0.500	0.500	0.500	0.500	0.500
Min	0.000	0.500	0.000	0.500	0.000
Max	1.500	0.500	1.500	1.500	1.500
p_W		1.000	1.000	0.207	0.693
p_J		1.000	1.000	0.378	0.576

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	4				5
Mean	0.750				0.700
SD	0.500				0.758
Median	0.500				0.500
Min	0.500				0.000
Max	1.500				1.500
p_W					0.694
p_J					
UBG (umol/l)					
week: 5 N	8	5	5	5	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	4				5
Mean	0.000				0.000
SD	0.000				0.000
Median	0.000				0.000
Min	0.000				0.000
Max	0.000				0.000
p_W					1.000
p_J					
BIL (umol/l)					
week: 5 N	8	5	5	5	10
Mean	2.125	10.20	6.800	3.400	3.400
SD	6.010	9.311	9.311	7.603	7.168
Median	0.000	17.00	0.000	0.000	0.000
Min	0.000	0.000	0.000	0.000	0.000
Max	17.00	17.00	17.00	17.00	17.00
p_W		0.083	0.271	0.726	0.680
p_J		0.164	0.307	0.720	0.861

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	4				5
Mean	0.000				0.000
SD	0.000				0.000
Median	0.000				0.000
Min	0.000				0.000
Max	0.000				0.000
p_W					1.000
p_J					
ERY (per ul)					
week: 5 N	8	5	5	5	10
Mean	11.88	18.00	13.00	13.00	6.000
SD	5.303	17.89	6.708	6.708	5.164
Median	10.00	10.00	10.00	10.00	10.00
Min	10.00	10.00	10.00	10.00	0.000
Max	25.00	50.00	25.00	25.00	10.00
p_W		0.642	0.726	0.726	0.031 *
p_J		0.770	0.806	0.826	0.085
week: 9 N	4				5
Mean	7.500				6.000
SD	5.000				5.477
Median	10.00				10.00
Min	0.000				0.000
Max	10.00				10.00
p_W					0.655
p_J					

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	10
Mean	3.280	3.425	3.580	2.680	3.750
SD	0.752	0.932	0.856	1.047	1.665
Median	3.250	3.050	4.000	2.900	3.200
Min	2.500	2.800	2.400	1.200	2.100
Max	4.300	4.800	4.500	4.000	6.400
p _W		0.722	0.712	0.218	1.000
p _J		0.724	0.615	0.480	0.818
week: 9 N	5				5
Mean	1.500				2.960
SD	0.212				1.790
Median	1.500				2.300
Min	1.300				1.200
Max	1.800				5.800
p _W					0.116
p _J					0.117
Rel dens (1)					
week: 5 N	10	4	5	5	10
Mean	1.038	1.044	1.039	1.048	1.042
SD	0.009	0.007	0.004	0.018	0.013
Median	1.039	1.046	1.039	1.045	1.041
Min	1.015	1.034	1.034	1.029	1.022
Max	1.048	1.049	1.045	1.077	1.063
p _W		0.288	0.854	0.244	0.649
p _J		0.289	0.908	0.373	0.613
week: 9 N	5				5
Mean	1.064				1.050
SD	0.010				0.023
Median	1.064				1.038
Min	1.051				1.027
Max	1.077				1.084
p _W					0.249
p _J					0.251

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	4	5	5	10
	Mean	5.850	6.375	6.200	5.800	5.150
	SD	0.626	0.250	0.671	0.837	0.474
	Median	6.000	6.500	6.500	6.000	5.000
	Min	5.000	6.000	5.000	5.000	5.000
	Max	6.500	6.500	6.500	7.000	6.500
	p_W		0.111	0.167	0.796	0.016 *
	p_J		0.138	0.104	0.619	0.045
	week: 9 N	5				5
	Mean	6.000				6.000
	SD	0.707				0.707
	Median	6.000				6.000
	Min	5.000				5.000
	Max	7.000				7.000
p_W					1.000	
p_J					1.000	
PRO (g/l)	week: 5 N	10	4	5	5	10
	Mean	0.350	0.625	0.450	0.650	0.550
	SD	0.211	0.250	0.274	0.224	0.258
	Median	0.250	0.750	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		0.062	0.425	0.031 *	0.075
	p_J		0.120	0.333	0.084	0.125
	week: 9 N	5				5
	Mean	0.650				0.550
SD	0.224				0.274	
Median	0.750				0.750	
Min	0.250				0.250	
Max	0.750				0.750	
p_W					0.513	
p_J					0.602	

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	4	5	5	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
Mean	0.000				0.000
SD	0.000				0.000
Median	0.000				0.000
Min	0.000				0.000
Max	0.000				0.000
p_W					1.000
p_J					1.000
KET (mmol/l)					
week: 5 N	10	4	5	5	10
Mean	0.600	0.750	0.500	0.400	0.300
SD	0.316	0.500	0.000	0.224	0.258
Median	0.500	0.500	0.500	0.500	0.500
Min	0.500	0.500	0.500	0.000	0.000
Max	1.500	1.500	0.500	0.500	0.500
p_W		0.485	0.480	0.147	0.021 *
p_J		0.671	0.877	0.417	0.048
week: 9 N	5				5
Mean	0.900				0.500
SD	0.548				0.612
Median	0.500				0.500
Min	0.500				0.000
Max	1.500				1.500
p_W					0.212
p_J					0.251

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	4	5	5	10
Mean	6.800	8.500	0.000	10.20	0.000
SD	8.779	9.815	0.000	9.311	0.000
Median	0.000	8.500	0.000	17.00	0.000
Min	0.000	0.000	0.000	0.000	0.000
Max	17.00	17.00	0.000	17.00	0.000
p_W		0.742	0.111	0.480	0.029 *
p_J		0.777	0.314	0.979	0.173
week: 9 N	5				5
Mean	10.20				6.800
SD	9.311				9.311
Median	17.00				0.000
Min	0.000				0.000
Max	17.00				17.00
p_W					0.549
p_J					0.602
BIL (umol/l)					
week: 5 N	10	4	5	5	10
Mean	5.100	8.500	6.800	3.400	5.100
SD	8.212	9.815	9.311	7.603	8.212
Median	0.000	8.500	0.000	0.000	0.000
Min	0.000	0.000	0.000	0.000	0.000
Max	17.00	17.00	17.00	17.00	17.00
p_W		0.497	0.708	0.690	1.000
p_J		0.572	0.670	0.896	0.842
week: 9 N	5				5
Mean	3.400				0.000
SD	7.603				0.000
Median	0.000				0.000
Min	0.000				0.000
Max	17.00				0.000
p_W					0.317
p_J					0.602

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	4	5	5	10
Mean	10.00	13.75	18.00	8.000	24.50
SD	0.000	7.500	17.89	4.472	44.50
Median	10.00	10.00	10.00	10.00	10.00
Min	10.00	10.00	10.00	0.000	0.000
Max	10.00	25.00	50.00	10.00	150.0
p_W		0.114	0.157	0.157	0.543
p_J		0.480	0.439	0.855	0.902
week: 9 N	5				5
Mean	4.000				34.00
SD	5.477				65.04
Median	0.000				10.00
Min	0.000				0.000
Max	10.00				150.0
p_W					0.419
p_J					0.465

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8.21. Organ weights and ratios (means)

8.21.1. Organ weights (means)

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)	346.2	304.8*	312.2	329.9	321.7
Brain (g)	2.213	2.117	2.135	2.218	2.183
Heart (g)	1.224	1.107	1.099	1.226	1.057
Liver (g)	15.30	13.43	13.81	15.15	15.16
Kidney (both) (g)	2.400	2.288	2.361	2.314	2.334
Adrenal (both) (mg)	82.00	72.46	78.38	70.54	80.00
Thymus (mg)	839.4	645.9	568.0	787.7	746.4
Testis (both) (g)	3.410	3.269	3.424	3.416	3.474
Spleen (g)	0.576	0.585	0.584	0.658	0.592
Epididymis (g)	1.235	1.114	1.178	1.110	1.208

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

191

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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)	207.9	204.3	222.0	211.8	205.1
Brain (g)	2.055	1.995	2.168	2.019	2.046
Heart (g)	0.816	0.848	0.858	0.860	0.787
Liver (g)	8.934	8.519	10.14	8.789	9.338
Kidney (both) (g)	1.757	1.684	1.968	1.765	1.826
Adrenal (both) (mg)	98.54	93.90	99.54	85.30	92.08
Thymus (mg)	543.9	474.7	541.1	505.1	51.3
Ovary (both) (mg)	153.9	168.5	182.9	144.9	162.8
Spleen (g)	0.493	0.518	0.570	0.504	0.569

8.21.2. Organ to body weight ratios (means)

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)	6.409	6.982	6.926	6.750	6.835
Heart (o/oo)	3.533	3.642	3.534	3.722	3.279
Liver (o/oo)	44.15	44.02	44.34	45.94	47.12*
Kidney (both) (o/oo)	6.968	7.511	7.544	7.035	7.260
Adrenal (both) (o/oo)	0.237	0.238	0.251	0.214	0.248
Thymus (o/oo)	2.442	2.117	1.817*	2.405	2.314
Testis (both) (o/oo)	9.847	10.78*	11.03	10.39	10.84
Spleen (o/oo)	1.664	1.933	1.878	2.005	1.848
Epididymis (o/oo)	3.582	3.693	3.798	3.372	3.787

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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)	9.908	9.804	9.771	9.650	9.985
Heart (o/oo)	3.926	4.140	3.872	4.099	3.842
Liver (o/oo)	42.83	41.69	45.77	41.41	45.37
Kidney (both) (o/oo)	8.466	8.268	8.881	8.354	8.904
Adrenal (both) (o/oo)	0.478	0.461	0.450	0.409	0.449
Thymus (o/oo)	2.637	2.305	2.432	2.417	2.705
Ovary (both) (o/oo)	0.741	0.825	0.824	0.693	0.791
Spleen (o/oo)	2.365	2.542	2.574	2.417	2.778*

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8.21.3. Organ weights (means): 2. sacrifice

Statistical tests and flags used:
 WILCOXON: * if p_W < 0.05

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)	381.3				403.8
Brain (g)	2.202				2.216
Heart (g)	1.273				1.302
Liver (g)	15.35				16.27
Kidney (both) (g)	2.494				2.552
Adrenal (both) (mg)	77.20				22.28
Thymus (mg)	604.3				664.4
Testis (both) (g)	3.723				3.699
Spleen (g)	0.641				0.703
Epididymis (g)	1.529				1.505

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

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)	232.4				236.9
Brain (g)	2.122				2.103
Heart (g)	0.897				0.887
Liver (g)	9.526				9.880
Kidney (both) (g)	1.868				1.935
Adrenal (both) (mg)	92.54				97.64
Thymus (mg)	387.9				485.9
Ovary (both) (mg)	184.6				165.9
Spleen (g)	0.509				0.489

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Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

Statistical tests and flags used:
 WILCOXON: * if p_W < 0.05

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)		5.777			5.567
Heart (o/oo)		3.338			3.224
Liver (o/oo)		40.27			40.40
Kidney (both) (o/oo)		6.545			6.344
Adrenal (both) (o/oo)		0.202			0.184
Thymus (o/oo)		1.589			1.651
Testis (both) (o/oo)		9.765			9.237
Spleen (o/oo)		1.685			1.747
Epididymis (o/oo)		4.009			3.752

Statistical tests and flags used:
 WILCOXON: * if $p_W < 0.05$

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)	9.132				8.900
Heart (o/oo)	3.852				3.750
Liver (o/oo)	40.98				41.76
Kidney (both) (o/oo)	8.036				8.199
Adrenal (both) (o/oo)	0.398				0.413
Thymus (o/oo)	1.672				2.050
Ovary (both) (o/oo)	0.793				0.702
Spleen (o/oo)	2.185				2.071

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8.22. Organ weights and ratios (statistics)

8.22.1. Organ weights (statistics)

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

Organ weights (statistics): males week 5

Dose (mg/kg)		group 1	group 2	group 3	group 4	group 5
		0	10	50	200	1000
Body (g)	N	4	5	5	5	5
	Mean	346.2	304.8	312.2	329.9	321.7
	SD	27.16	27.07	38.80	20.59	25.40
	Median	333.6	321.6	310.9	321.4	312.3
	Min	330.7	270.9	255.8	310.2	298.9
	Max	386.8	329.1	364.0	356.5	351.7
	p_W		0.014 *	0.086	0.327	0.327
	p_J			0.053	0.327	0.361
Brain (g)	N	4	5	5	5	5
	Mean	2.213	2.117	2.135	2.218	2.183
	SD	0.107	0.131	0.092	0.106	0.120
	Median	2.242	2.096	2.116	2.162	2.138
	Min	2.060	1.982	2.047	2.128	2.050
	Max	2.308	2.325	2.238	2.357	2.357
	p_W		0.327	0.142	1.000	0.624
	p_J			0.380	0.690	0.648
Heart (g)	N	4	5	5	5	5
	Mean	1.224	1.107	1.099	1.226	1.057
	SD	0.149	0.105	0.112	0.079	0.115
	Median	1.221	1.135	1.067	1.177	1.017
	Min	1.076	0.945	0.991	1.162	0.946
	Max	1.379	1.201	1.289	1.342	1.208
	p_W		0.327	0.086	0.806	0.142
	p_J			0.178	0.744	0.416

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

199

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	5	5
	Mean	15.30	13.43	13.81	15.15	15.16
	SD	1.598	1.539	1.549	1.173	1.271
	Median	14.66	13.78	13.45	15.39	14.82
	Min	14.23	11.58	12.13	13.70	13.69
	Max	17.65	15.23	15.93	16.63	17.07
	p_W		0.221	0.221	1.000	1.000
	p_J			0.320	0.690	0.334
Kidney (both) (g)	N	4	5	5	5	5
	Mean	2.400	2.288	2.361	2.314	2.334
	SD	0.064	0.209	0.353	0.148	0.203
	Median	2.386	2.262	2.439	2.297	2.392
	Min	2.343	2.056	1.846	2.184	2.032
	Max	2.484	2.518	2.782	2.541	2.537
	p_W		0.624	0.806	0.327	0.806
	p_J			0.861	0.856	0.919
Adrenal (both) (mg)	N	4	5	5	5	5
	Mean	82.00	72.46	78.38	70.54	80.00
	SD	9.766	5.647	11.09	6.112	10.51
	Median	79.85	71.80	77.20	70.30	85.90
	Min	74.00	66.00	67.40	64.40	64.90
	Max	94.30	81.30	95.30	79.80	89.90
	p_W		0.050	0.624	0.050	0.806
	p_J			0.520	0.102	0.666
Thymus (mg)	N	4	5	5	5	5
	Mean	839.4	645.9	568.0	787.7	746.4
	SD	255.2	104.7	95.66	117.8	147.8
	Median	736.1	651.2	529.2	824.1	808.7
	Min	672.6	481.0	483.4	582.1	511.3
	Max	1213	755.6	722.2	883.2	884.7
	p_W		0.142	0.050	0.624	0.806
	p_J			0.030	0.856	0.402

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

200

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	5	5
Mean	3.410	3.269	3.424	3.416	3.474
SD	0.291	0.091	0.286	0.282	0.186
Median	3.291	3.258	3.538	3.493	3.549
Min	3.221	3.147	2.918	3.042	3.180
Max	3.838	3.380	3.601	3.754	3.649
p_W		0.624	0.624	1.000	0.624
p_J			0.380	0.490	0.243
Spleen					
(g) N	4	5	5	5	5
Mean	0.576	0.585	0.584	0.658	0.592
SD	0.075	0.037	0.084	0.087	0.081
Median	0.590	0.587	0.560	0.640	0.611
Min	0.485	0.528	0.507	0.563	0.477
Max	0.639	0.628	0.686	0.781	0.692
p_W		0.806	0.624	0.142	1.000
p_J			0.953	0.179	0.416
Epididymis					
(g) N	4	5	5	5	5
Mean	1.235	1.114	1.178	1.110	1.208
SD	0.120	0.112	0.070	0.150	0.095
Median	1.211	1.088	1.184	1.104	1.222
Min	1.115	1.009	1.077	0.912	1.102
Max	1.402	1.251	1.268	1.327	1.350
p_W		0.221	0.462	0.142	1.000
p_J			0.598	0.260	0.959

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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 0	group 2 10	group 3 50	group 4 200	group 5 1000
Body (g)	N	5	4	5	5	5
	Mean	207.9	204.3	222.0	211.8	205.1
	SD	15.17	16.26	6.110	29.58	10.73
	Median	201.6	205.6	224.2	216.7	203.7
	Min	191.3	183.2	212.2	168.5	190.9
	Max	225.2	222.8	227.7	250.8	217.6
	p_W		1.000	0.117	0.754	0.754
	p_J			0.069	0.327	0.839
Brain (g)	N	5	4	5	5	5
	Mean	2.055	1.995	2.168	2.019	2.046
	SD	0.114	0.062	0.117	0.083	0.119
	Median	2.069	1.997	2.181	2.050	2.007
	Min	1.913	1.917	1.986	1.890	1.953
	Max	2.181	2.068	2.306	2.095	2.242
	p_W		0.462	0.076	0.602	0.917
	p_J			0.143	0.856	0.919
Heart (g)	N	5	4	5	5	5
	Mean	0.816	0.848	0.858	0.860	0.787
	SD	0.069	0.114	0.041	0.071	0.043
	Median	0.802	0.890	0.883	0.885	0.801
	Min	0.726	0.681	0.795	0.745	0.718
	Max	0.915	0.932	0.888	0.930	0.833
	p_W		0.462	0.347	0.251	0.465
	p_J			0.520	0.364	0.477
Liver (g)	N	5	4	5	5	5
	Mean	8.934	8.519	10.14	8.789	9.338
	SD	1.318	0.770	0.684	1.479	1.619
	Median	8.392	8.498	10.17	8.563	9.042
	Min	7.773	7.703	9.050	6.624	8.016
	Max	10.75	9.378	10.86	10.42	12.05
	p_W		0.624	0.117	0.754	0.602
	p_J			0.089	0.490	0.648

Organ weights (statistics): females

week 5

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	5	5
	Mean	1.757	1.684	1.968	1.765	1.826
	SD	0.170	0.137	0.140	0.245	0.161
	Median	1.844	1.713	2.056	1.759	1.823
	Min	1.473	1.495	1.797	1.458	1.638
	Max	1.879	1.815	2.092	2.010	2.018
	p_W		0.327	0.175	0.917	0.754
	p_J			0.178	0.690	0.722
Adrenal (both) (mg)	N	5	4	5	5	5
	Mean	98.54	93.90	99.54	85.30	92.08
	SD	16.72	5.601	14.29	7.736	12.51
	Median	96.60	93.90	101.5	86.70	88.40
	Min	77.00	87.10	81.80	77.20	81.00
	Max	122.5	100.7	118.1	96.20	109.5
	p_W		0.624	0.917	0.175	0.602
	p_J			0.861	0.157	0.223
Thymus (mg)	N	5	4	5	5	5
	Mean	543.9	474.7	541.1	505.1	551.3
	SD	67.08	108.3	120.5	74.61	101.9
	Median	542.5	450.1	485.4	547.6	556.3
	Min	454.6	373.0	412.2	383.0	441.3
	Max	642.8	625.4	714.2	562.3	704.3
	p_W		0.221	0.754	0.754	0.754
	p_J			0.770	0.856	0.722
Ovary (both) (mg)	N	5	4	5	5	5
	Mean	153.9	168.5	182.9	144.9	162.8
	SD	18.01	29.21	27.68	13.75	28.27
	Median	151.8	171.3	185.9	137.5	165.1
	Min	132.1	130.4	143.9	135.8	119.2
	Max	180.7	201.1	210.2	168.4	191.9
	p_W		0.462	0.117	0.465	0.347
	p_J			0.089	0.856	1.000

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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
Spleen (g)	N	5	4	5	5	5
	Mean	0.493	0.518	0.570	0.504	0.569
	SD	0.093	0.086	0.059	0.045	0.038
	Median	0.479	0.509	0.554	0.496	0.552
	Min	0.369	0.423	0.495	0.454	0.539
	Max	0.630	0.630	0.655	0.577	0.634
	p_W		0.462	0.117	0.754	0.076
	p_J			0.089	0.690	0.187

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Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

8.22.2. Organ to body weight ratios (statistics)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05JONCKHEERE: +- 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	4	5	5	5	5
Mean	6.409	6.982	6.926	6.750	6.835
SD	0.383	0.638	0.899	0.616	0.823
Median	6.461	7.229	7.151	6.860	7.117
Min	5.967	6.022	5.622	6.064	5.828
Max	6.745	7.523	8.020	7.334	7.863
p _W		0.221	0.327	0.327	0.462
p _J			0.380	0.537	0.684
Heart (o/oo) N	4	5	5	5	5
Mean	3.533	3.642	3.534	3.722	3.279
SD	0.298	0.370	0.201	0.262	0.104
Median	3.472	3.487	3.477	3.743	3.256
Min	3.252	3.299	3.355	3.385	3.155
Max	3.936	4.242	3.873	4.105	3.435
p _W		0.624	1.000	0.221	0.142
p _J			0.953	0.292	0.223
Liver (o/oo) N	4	5	5	5	5
Mean	44.15	44.02	44.34	45.94	47.12
SD	1.414	2.272	2.441	2.143	1.577
Median	44.05	43.86	43.82	46.01	47.44
Min	42.84	41.32	40.92	43.58	45.19
Max	45.64	47.35	47.43	49.08	48.67
p _W		0.624	0.624	0.142	0.027 *
p _J			0.953	0.231	0.013

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	4	5	5	5	5
Mean	6.968	7.511	7.544	7.035	7.260
SD	0.617	0.283	0.318	0.620	0.434
Median	7.205	7.587	7.642	7.041	7.166
Min	6.058	7.017	7.197	6.298	6.797
Max	7.404	7.730	7.844	7.904	7.979
p_W		0.086	0.142	1.000	0.806
p_J			0.069	0.744	0.919
Adrenal (both)					
(o/oo) N	4	5	5	5	5
Mean	0.237	0.238	0.251	0.214	0.248
SD	0.015	0.014	0.020	0.010	0.022
Median	0.234	0.236	0.254	0.209	0.245
Min	0.224	0.223	0.220	0.203	0.217
Max	0.255	0.258	0.274	0.225	0.275
p_W		0.806	0.327	0.086	0.327
p_J			0.219	0.204	0.919
Thymus					
(o/oo) N	4	5	5	5	5
Mean	2.442	2.117	1.817	2.405	2.314
SD	0.817	0.278	0.158	0.434	0.400
Median	2.048	2.208	1.890	2.564	2.330
Min	2.004	1.717	1.637	1.633	1.711
Max	3.667	2.403	1.984	2.672	2.833
p_W		0.806	0.014 *	0.624	0.624
p_J			0.022	0.856	0.611
Testis (both)					
(o/oo) N	4	5	5	5	5
Mean	9.847	10.78	11.03	10.39	10.84
SD	0.200	0.788	0.749	1.133	0.955
Median	9.831	10.49	11.41	10.07	10.64
Min	9.638	10.03	9.808	9.048	9.688
Max	10.09	11.63	11.58	11.94	12.17
p_W		0.027 *	0.050	0.462	0.086
p_J			0.053	0.404	0.334

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

206

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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
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Spleen					
(o/oo) N	4	5	5	5	5
Mean	1.664	1.933	1.878	2.005	1.848
SD	0.182	0.217	0.238	0.329	0.276
Median	1.645	1.948	1.809	1.845	2.000
Min	1.461	1.604	1.630	1.679	1.528
Max	1.904	2.165	2.234	2.428	2.102
p_W		0.142	0.221	0.086	0.327
p_J			0.266	0.137	0.361
Epididymis					
(o/oo) N	4	5	5	5	5
Mean	3.582	3.693	3.798	3.372	3.787
SD	0.446	0.631	0.272	0.501	0.533
Median	3.503	3.756	3.755	3.096	4.075
Min	3.145	3.069	3.483	2.941	3.133
Max	4.177	4.618	4.211	4.127	4.324
p_W		1.000	0.221	0.221	0.806
p_J			0.520	0.364	0.919

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

207

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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 (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	4	5	5	5
Mean	9.908	9.804	9.771	9.650	9.985
SD	0.563	0.772	0.577	1.066	0.512
Median	9.764	9.507	9.873	9.575	10.26
Min	9.286	9.280	8.805	8.355	9.143
Max	10.80	10.92	10.28	11.22	10.37
p _W		0.624	0.754	0.465	0.602
p _J			0.861	0.690	0.684
Heart (o/oo)					
N	5	4	5	5	5
Mean	3.926	4.140	3.872	4.099	3.842
SD	0.238	0.344	0.270	0.391	0.186
Median	3.952	4.151	3.958	4.064	3.826
Min	3.601	3.716	3.491	3.566	3.595
Max	4.218	4.541	4.184	4.531	4.093
p _W		0.221	0.754	0.465	0.465
p _J			0.861	0.744	0.611
Liver (o/oo)					
N	5	4	5	5	5
Mean	42.83	41.69	45.77	41.41	45.37
SD	3.737	1.683	4.000	2.737	5.980
Median	43.87	42.07	45.85	41.54	42.99
Min	38.55	39.33	40.12	38.76	40.14
Max	47.74	43.31	51.20	45.71	55.38
p _W		0.462	0.175	0.602	0.602
p _J			0.219	0.744	0.648
Kidney (both) (o/oo)					
N	5	4	5	5	5
Mean	8.466	8.268	8.881	8.354	8.904
SD	0.766	0.786	0.809	0.592	0.691
Median	8.436	8.297	9.328	8.082	8.950
Min	7.307	7.289	7.968	7.777	7.948
Max	9.285	9.189	9.717	9.245	9.771
p _W		0.624	0.347	0.602	0.465
p _J			0.447	0.913	0.576

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	4	5	5	5
Mean	0.478	0.461	0.450	0.409	0.449
SD	0.100	0.035	0.073	0.066	0.060
Median	0.434	0.456	0.453	0.384	0.424
Min	0.382	0.425	0.363	0.355	0.399
Max	0.617	0.508	0.536	0.515	0.548
p_W		0.806	0.602	0.175	0.917
p_J			0.770	0.157	0.416
Thymus (o/oo) N	5	4	5	5	5
Mean	2.637	2.305	2.432	2.417	2.705
SD	0.445	0.351	0.497	0.445	0.607
Median	2.627	2.189	2.288	2.595	2.699
Min	2.041	2.036	1.872	1.759	2.197
Max	3.236	2.807	3.137	2.875	3.689
p_W		0.221	0.465	0.602	0.917
p_J			0.447	0.586	0.799
Ovary (both) (o/oo) N	5	4	5	5	5
Mean	0.741	0.825	0.824	0.693	0.791
SD	0.069	0.129	0.122	0.100	0.118
Median	0.761	0.876	0.829	0.662	0.810
Min	0.655	0.636	0.638	0.581	0.624
Max	0.803	0.914	0.954	0.816	0.914
p_W		0.221	0.251	0.465	0.347
p_J			0.219	0.537	0.879
Spleen (o/oo) N	5	4	5	5	5
Mean	2.365	2.542	2.574	2.417	2.778
SD	0.376	0.435	0.325	0.403	0.170
Median	2.492	2.525	2.517	2.417	2.824
Min	1.860	2.063	2.208	1.973	2.523
Max	2.827	3.057	3.086	2.948	2.966
p_W		0.624	0.465	0.917	0.047 *
p_J			0.447	0.913	0.155

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

8.22.3. Organ weights (statistics): 2. sacrifice

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

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	4			5
	Mean	381.3			403.8
	SD	14.81			57.18
	Median	376.4			416.3
	Min	369.6			339.0
	Max	402.9			461.5
	p_W				0.624
Brain (g)	N	4			5
	Mean	2.202			2.216
	SD	0.060			0.082
	Median	2.197			2.197
	Min	2.146			2.139
	Max	2.268			2.356
	p_W				1.000
Heart (g)	N	4			5
	Mean	1.273			1.302
	SD	0.082			0.223
	Median	1.270			1.335
	Min	1.184			1.072
	Max	1.369			1.635
	p_W				1.000
Liver (g)	N	4			5
	Mean	15.35			16.27
	SD	1.246			2.315
	Median	15.79			16.28
	Min	13.59			13.50
	Max	16.24			19.11
	p_W				0.462

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

210

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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
Kidney (both) (g)	N	4			5
	Mean	2.494			2.552
	SD	0.086			0.309
	Median	2.512			2.748
	Min	2.380			2.076
	Max	2.573			2.781
	p_W				0.462
Adrenal (both) (mg)	N	4			5
	Mean	77.20			72.28
	SD	6.037			9.906
	Median	78.10			70.00
	Min	69.10			60.10
	Max	83.50			87.40
	p_W				0.462
Thymus (mg)	N	4			5
	Mean	604.3			664.4
	SD	44.84			184.3
	Median	602.9			736.7
	Min	554.6			427.6
	Max	657.0			869.9
	p_W				0.624
Testis (both) (g)	N	4			5
	Mean	3.723			3.699
	SD	0.260			0.407
	Median	3.824			3.610
	Min	3.337			3.241
	Max	3.907			4.286
	p_W				0.806
Spleen (g)	N	4			5
	Mean	0.641			0.703
	SD	0.107			0.145
	Median	0.621			0.688
	Min	0.532			0.558
	Max.	0.789			0.945
p_W				0.327	

Organ weights (statistics): males week 9

Dose (mg/kg)	group 1 0	group 2 10	group 3 50	group 4 200	group 5 1000
Epididymis (g)					
N	4				5
Mean	1.529				1.505
SD	0.108				0.163
Median	1.552				1.487
Min	1.388				1.327
Max	1.624				1.756
p_w					0.624

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

212

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Statistical tests and flags used:

WILCOXON: * if p_W < 0.05

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				5
	Mean	232.4				236.9
	SD	6.250				16.30
	Median	233.5				241.6
	Min	221.7				219.3
	Max	237.6				254.3
	p _W					0.602
Brain (g)	N	5				5
	Mean	2.122				2.103
	SD	0.052				0.096
	Median	2.108				2.117
	Min	2.068				1.954
	Max	2.201				2.208
	p _W					0.917
Heart (g)	N	5				5
	Mean	0.897				0.887
	SD	0.091				0.050
	Median	0.909				0.876
	Min	0.749				0.827
	Max	0.991				0.946
	p _W					0.602
Liver (g)	N	5				5
	Mean	9.526				9.880
	SD	0.434				1.095
	Median	9.396				10.13
	Min	9.003				7.985
	Max	10.18				10.66
	p _W					0.251

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

213

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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			5
	Mean	1.868			1.935
	SD	0.197			0.170
	Median	1.940			1.965
	Min	1.647			1.760
	Max	2.052			2.152
	p_W				0.602
Adrenal (both) (mg)	N	5			5
	Mean	92.54			97.64
	SD	14.57			15.75
	Median	89.10			98.30
	Min	81.60			75.50
	Max	117.2			114.0
	p_W				0.602
Thymus (mg)	N	5			5
	Mean	387.9			485.9
	SD	53.60			139.9
	Median	404.0			441.2
	Min	307.8			361.4
	Max	439.1			719.4
	p_W				0.175
Ovary (both) (mg)	N	5			5
	Mean	184.6			165.9
	SD	41.73			24.00
	Median	171.7			166.5
	Min	153.3			135.2
	Max	255.9			191.4
	p_W				0.602
Spleen (g)	N	5			5
	Mean	0.509			0.489
	SD	0.084			0.045
	Median	0.521			0.491
	Min	0.391			0.444
	Max	0.593			0.542
	p_W				0.602

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

Statistical tests and flags used:
 WILCOXON: * if p_W < 0.05

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	4				5
Mean	5.777				5.567
SD	0.125				0.711
Median	5.781				5.246
Min	5.629				4.851
Max	5.917				6.506
p_W					0.624
Heart (o/oo) N	4				5
Mean	3.338				3.224
SD	0.131				0.270
Median	3.363				3.231
Min	3.161				2.893
Max	3.465				3.610
p_W					0.327
Liver (o/oo) N	4				5
Mean	40.27				40.40
SD	3.125				3.096
Median	40.44				41.66
Min	36.28				35.28
Max	43.92				43.05
p_W					1.000
Kidney (both) (o/oo) N	4				5
Mean	6.545				6.344
SD	0.246				0.410
Median	6.468				6.122
Min	6.353				5.954
Max	6.892				6.882
p_W					0.327

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

215

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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
Adrenal (both) (o/oo) N	4				5
Mean	0.202				0.184
SD	0.014				0.046
Median	0.201				0.168
Min	0.187				0.130
Max	0.221				0.250
p_W					0.462
Thymus (o/oo) N	4				5
Mean	1.589				1.651
SD	0.168				0.415
Median	1.601				1.667
Min	1.377				1.027
Max	1.778				2.110
p_W					0.624
Testis (both) (o/oo) N	4				5
Mean	9.765				9.237
SD	0.634				0.990
Median	9.896				9.369
Min	8.907				7.630
Max	10.36				10.34
p_W					0.327
Spleen (o/oo) N	4				5
Mean	1.685				1.747
SD	0.315				0.283
Median	1.593				1.654
Min	1.421				1.379
Max	2.134				2.086
p_W					1.000
Epididymis (o/oo) N	4				5
Mean	4.009				3.752
SD	0.220				0.309
Median	3.993				3.801
Min	3.756				3.284
Max	4.293				4.149
p_W					0.221

Statistical tests and flags used:
 WILCOXON: * if p_W < 0.05

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				5
Mean	9.132				8.900
SD	0.274				0.535
Median	9.016				8.684
Min	8.858				8.503
Max	9.428				9.825
p_W					0.175
Heart (o/oo) N	5				5
Mean	3.852				3.750
SD	0.316				0.106
Median	3.892				3.733
Min	3.377				3.624
Max	4.243				3.916
p_W					0.251
Liver (o/oo) N	5				5
Mean	40.98				41.76
SD	1.548				4.517
Median	40.61				41.52
Min	39.54				36.27
Max	43.59				48.62
p_W					0.754
Kidney (both) (o/oo) N	5				5
Mean	8.036				8.199
SD	0.784				0.912
Median	8.309				7.993
Min	6.931				6.946
Max	8.792				9.258
p_W					0.602

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

217

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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				5
Mean	0.398				0.413
SD	0.061				0.069
Median	0.382				0.395
Min	0.343				0.343
Max	0.502				0.520
p_W					0.602
Thymus					
(o/oo) N	5				5
Mean	1.672				2.050
SD	0.254				0.537
Median	1.730				2.004
Min	1.319				1.451
Max	1.981				2.829
p_W					0.251
Ovary (both)					
(o/oo) N	5				5
Mean	0.793				0.702
SD	0.174				0.096
Median	0.728				0.753
Min	0.657				0.543
Max	1.096				0.774
p_W					0.602
Spleen					
(o/oo) N	5				5
Mean	2.185				2.071
SD	0.333				0.238
Median	2.209				2.018
Min	1.765				1.840
Max	2.542				2.471
p_W					0.754

9. APPENDIX A: INDIVIDUAL DATA

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

9.1. Clinical signs (individuals)

- : clinical sign observed until scheduled sacrifice
- * : clinical sign observed until early death

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

No.	Finding	start day	end day
01	piloerection	24	29
02	no findings noted		5*
03	skin lesion neck	24	-
04	no findings noted		
05	no findings noted		
06	skin lesion neck	24	44
06	hunched posture	24	31
07	no findings noted		
08	skin lesion neck	15	31
09	no findings noted		
10	no findings noted		5*

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

No.	Finding	start day	end day
11	skin lesion neck	3	24
11	skin lesion back	15	24
12	skin lesion neck	15	28
13	no findings noted		
14	no findings noted		
15	no findings noted		

28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)
 Test No.: 963103
 Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

No.	Finding	start day	end day
16	no findings noted		
17	no findings noted		
18	skin lesion head	17	28
19	no findings noted		
20	skin lesion back	3	-
20	skin lesion abdomen	17	-
20	skin lesion neck	24	-

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		

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

No.	Finding	start day	end day
26	no findings noted		
27	no findings noted		
28	no findings noted		
29	no findings noted		
30	no findings noted		
31	skin lesion neck	24	44
32	no findings noted		
33	no findings noted		
34	no findings noted		
35	no findings noted		

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

No.	Finding	start day	end day
36	no findings noted		
37	no findings noted		
38	no findings noted		
39	no findings noted		
40	no findings noted		
41	skin lesion	neck	6
42	no findings noted		
43	no findings noted		
44	no findings noted		
45	no findings noted		

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

No.	Finding	start day	end day
46	no findings noted		
47	no findings noted		5*
48	no findings noted		
49	no findings noted		
50	skin lesion	neck	17 28

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

No.	Finding	start day	end day
51	no findings noted		
52	no findings noted		
53	no findings noted		
54	skin lesion	neck	25 -
55	skin lesion	neck	17 -

Antemortem findings (individuals) : females group 4 : 200 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		

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

No.	Finding	start day	end day
61	no findings noted		
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		
69	no findings noted		
70	no findings noted		

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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						1	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
posture/gait (-2,+2)										
week 4						1				
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	1	0	0	0	0	0	0	0	0	0
week 5										
week 6										
week 7										
week 8										
piloerection (0,+2)										
week 4						1				

^a range of scores

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

animal number	1	2	3	4	5	6	7	8	9	10
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	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
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	1	0	0	1	0	1	1	0
week 5	0	0	0	0	0	1	0	0	0	0
week 6	0	0	0	0	0	1	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 3								1		
week 4			1			1		1	1	
week 5						1				
week 6						1				

skin lesion (0,+1)

- week 3
- week 4
- week 5
- week 6

week 6

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Observations (individual values):

males

group 2
10 mg/kg

animal number	11	12	13	14	15
CNS activity (-4,+7)^a					
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	1	0	0	0	0
week 2	1	0	0	0	0
week 3	1	0	0	0	0
week 4	0	1	0	0	0
skin lesion (0,+1)					
week 1	1
week 2	1
week 3	1
week 4	.	1	.	.	.

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

226

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Observations (individual values):

males

group 3
50 mg/kg

animal number	16	17	18	19	20
CNS activity (-4,+7)^a					
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	1
week 2	0	0	0	0	1
week 3	0	0	1	0	1
week 4	0	0	0	0	1
skin lesion (0,+1)					
week 1	1
week 2	1
week 3	.	.	1	.	1
week 4	1

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

227

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Observations (individual values):

males

group 4
200 mg/kg

animal number 21 22 23 24 25

CNS activity (-4,+7)^a

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

animal number	26	27	28	29	30	31	32	33	34	35
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	0
week 5	0	0	0	0	0	1	0	0	0	0
week 6	0	0	0	0	0	1	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				
week 5						1				
week 6						1				

skin lesion (0,+1)
week 4
week 5
week 6

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 aard ook voortvloeiende uit het gebruik van de informatie van dit document.

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

animal number	36	37	38	39	40	41	42	43	44	45
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	1	0	0	0	0
week 3	0	0	0	0	0	1	0	0	0	0
week 4	0	0	0	0	0	1	0	0	0	0
week 5	0	0	0	0	0	1	0	0	0	0
week 6	0	0	0	0	0	1	0	0	0	0
week 7	0	0	0	0	0	1	0	0	0	0
week 8	0	0	0	0	0	1	0	0	0	0
skin lesion (0,+1)										
week 2						1				
week 3						1				
week 4						1				
week 5						1				
week 6						1				
week 7						1				
week 8						1				

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

232

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Observations (individual values):

females

group 2
10 mg/kg

animal number	46	47	48	49	50
CNS activity (-4,+7)^a					
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	1
week 4	0	0	0	0	1
skin lesion (0,+1)					
week 3					1
week 4					1

skin lesion (0,+1)

week 3

week 4

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Observations (individual values):

females

group 3
50 mg/kg

animal number 51 52 53 54 55

CNS activity (-4,+7)^a

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 1 0 0 0 0

ease of removal (0,+2)

week 4 1 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 1
 week 4 0 0 0 1 1

skin lesion (0,+1)

week 3 0 0 0 0 1
 week 4 0 0 0 1 1

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

234

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Observations (individual values):

females

group 4
200 mg/kg

animal number 56 57 58 59 60

CNS activity (-4,+7)^a

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Observations (individual values):

females group 5
1000 mg/kg

animal number	61	62	63	64	65	66	67	68	69	70
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	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
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	1	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
ease of removal (0,+2)										
week 4	1									
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	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)

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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)

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	1150	.	1275	1150	1150	1450	1150	1275	1400	.
	8	1700	1825	1825	1875	.
GSH	4	1050	.	1000	1000	900	950	900	1050	925	.
	8	1550	1425	1175	1500	.
LFS	4	12.50	.	15.25	11.50	10.25	12.00	13.00	13.25	14.25	.
	8	12.00	10.25	11.50	11.75	.
TMP	4	37.30	.	37.00	37.70	37.00	37.40	37.10	37.90	37.40	.
	8	37.80	37.80	38.70	38.00	.

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

Parameter	time	11	12	13	14	15
GSF	4	1325	1250	1200	1175	1000
GSH	4	850	1175	950	975	925
LFS	4	11.50	11.75	9.50	12.00	9.25
TMP	4	37.50	37.50	37.70	37.80	37.20

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

Parameter	time	16	17	18	19	20
GSF	4	1175	950	1150	1125	1325
GSH	4	800	825	775	850	1000
LFS	4	15.25	11.50	9.75	12.25	12.25
TMP	4	37.20	36.80	37.40	37.10	37.20

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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

Parameter	time	21	22	23	24	25
GSF	4	1500	1325	1100	950	1350
GSF	8
GSH	4	1000	950	925	825	975
GSH	8
LFS	4	13.50	13.75	13.25	8.50	11.25
LFS	8
TMP	4	37.60	36.90	36.80	37.90	37.20
TMP	8

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

Parameter	time	26	27	28	29	30	31	32	33	34	35
GSF	4	1175	1500	1200	1250	1325	1275	1075	1150	1025	1300
GSF	8	1975	1900	2000	1650
GSH	4	850	875	900	1050	925	950	925	1050	875	1050
GSH	8	1425	1300	1350	1450	1450
LFS	4	8.75	8.25	12.00	12.75	7.25	9.25	11.25	13.00	10.25	11.25
LFS	8	13.25	10.25	12.25	8.25	14.00
TMP	4	37.10	37.20	36.90	37.40	37.60	37.90	37.20	37.50	37.30	37.70
TMP	8	38.30	37.60	37.90	38.40	37.40

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

Parameter	time	36	37	38	39	40	41	42	43	44	45
GSF	4	1050	1150	1250	1100	1200	1200	1050	900	1225	975
GSF	8	1225	1275	975	1450	1425
GSH	4	950	1050	750	725	800	825	925	750	825	825
GSH	8	1250	1050	925	1100	1075
LFS	4	11.50	9.25	11.00	10.00	7.75	10.75	11.50	11.00	9.00	6.50
LFS	8	11.50	15.00	10.25	6.75	9.25
TMP	4	38.60	38.70	38.00	39.10	38.80	39.20	39.00	39.10	39.20	38.10
TMP	8	38.00	38.50	37.80	37.70	37.80

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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

Parameter	time	46	47	48	49	50
GSF	4	1350	.	1175	1175	1450
GSH	4	1000	.	850	925	1450
LFS	4	10.00	.	10.50	9.00	13.00
TMP	4	37.90	.	39.10	38.60	38.80

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

Parameter	time	51	52	53	54	55
GSF	4	1025	1325	1150	1125	1200
GSH	4	1050	1050	925	875	800
LFS	4	10.00	12.00	10.50	10.75	9.50
TMP	4	38.50	38.20	38.50	39.10	39.10

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

Parameter	time	56	57	58	59	60
GSF	4	1175	1175	1000	1075	1100
GSH	4	1050	1025	750	850	825
LFS	4	13.00	12.50	10.00	10.00	9.50
TMP	4	38.70	38.80	39.00	39.20	38.20

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

Parameter	time	61	62	63	64	65	66	67	68	69	70
GSF	4	1275	1200	1225	1025	1050	1075	1050	1025	1050	1300
	8	1350	1425	1325	1225	1600
GSH	4	925	775	1000	825	925	825	1025	925	725	900
	8	1075	1150	1225	1150	1500
LFS	4	12.00	13.00	12.50	10.50	10.50	11.50	7.25	10.50	10.00	11.00
	8	10.50	9.50	7.75	9.00	7.25
TMP	4	38.50	38.40	38.30	39.00	38.70	38.70	39.10	38.80	39.00	38.30
	8	37.80	38.00	38.30	37.90	38.70

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	881	919	746	802	861	538	398	502	358	398	6403
3	4	1071	1038	1023	581	510	444	350	492	594	317	6420
4	4	1348	1402	901	967	490	378	271	325	510	472	7064
5	4	1064	977	866	690	314	231	127	2	312	279	4862
6	4	601	845	1188	1046	627	431	441	543	375	701	6798
	8	769	690	858	769	548	480	904	609	751	12	6390
7	4	868	845	668	388	185	116	165	7	127	538	3907
	8	675	243	279	144	195	200	2	17	162	5	1922
8	4	1115	688	505	266	581	177	96	149	134	88	3799
	8	1064	774	414	292	276	408	347	17	127	30	3749
9	4	1447	795	657	807	370	342	124	269	25	121	4957
	8	1371	833	652	513	335	406	594	147	492	152	5495

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	548	548	480	320	215	259	236	307	129	60	3102
12	4	1087	551	762	35	386	396	292	5	91	33	3638
13	4	502	642	292	556	193	193	48	152	147	337	3062
14	4	317	447	238	190	226	167	139	5	2	0	1731
15	4	1381	1033	322	53	340	0	248	452	378	20	4227

Total distance (individual): males 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	
16	4	1277	726	393	579	238	347	17	386	15	162	4140
17	4	637	1010	797	746	459	744	533	73	487	73	5559
18	4	1031	990	802	591	594	355	347	289	132	30	5161
19	4	668	762	477	373	403	101	426	139	127	485	3961
20	4	881	424	322	266	66	160	68	251	124	50	2612

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	1257	1069	711	266	299	391	38	320	525	86	4962
22	4	863	721	556	228	340	109	317	55	431	2	3622
23	4	1021	982	919	640	337	462	210	220	91	434	5316
24	4	977	734	546	563	576	820	375	58	119	223	4991
25	4	523	716	855	193	355	411	180	25	312	297	3867

Total distance (individual): males
(cm)

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	
26	4	848	883	762	617	533	551	617	375	187	281	5654
27	4	993	441	543	20	299	15	10	350	45	381	3097
28	4	858	944	312	500	144	434	246	345	93	147	4023
29	4	703	533	502	647	518	619	716	398	480	193	5309
30	4	812	680	546	294	530	116	421	287	251	584	4521
31	4	1158	716	535	38	274	307	350	78	66	68	3590
	8	1178	866	520	589	759	347	378	261	304	2	5204
32	4	594	502	541	347	236	180	96	208	175	5	2884
	8	726	332	254	68	96	386	0	5	15	190	2072
33	4	1023	599	393	452	35	327	91	144	149	386	3589
	8	939	452	180	302	424	307	7	149	15	134	2909
34	4	1092	553	33	200	510	53	187	612	213	0	3453
	8	960	525	317	388	289	609	259	172	355	12	3886
35	4	683	718	269	370	10	180	68	411	7	73	2789
	8	736	553	566	363	337	233	246	185	200	10	3429

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

242

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	51	38	38	37	43	37	24	41	31	26	366
3	4	41	40	41	37	43	34	26	28	35	33	358
4	4	45	36	47	37	44	36	24	19	42	34	364
5	4	44	42	41	41	30	24	16	3	25	27	293
6	4	36	41	40	35	35	31	31	35	28	39	351
	8	39	45	52	36	39	35	42	40	35	5	368
7	4	46	49	33	41	25	20	8	2	15	39	278
	8	42	38	30	18	28	32	2	10	18	2	220
8	4	48	41	46	33	37	27	21	11	10	6	280
	8	43	39	30	43	26	37	33	7	22	5	285
9	4	42	44	36	43	34	28	5	18	6	9	265
	8	43	46	41	40	26	28	35	12	29	16	316

No. of movements (individual): males group 2
(counts) 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	47	53	53	45	36	38	30	36	18	22	378
12	4	43	29	35	11	27	30	25	6	13	9	228
13	4	41	39	28	38	22	20	10	13	23	30	264
14	4	41	43	32	23	23	24	12	4	1	0	203
15	4	40	42	26	3	21	1	18	32	29	6	218

No. of movements (individual): males group 3
(counts) 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	38	33	24	37	22	28	10	24	9	24	249
17	4	47	50	44	42	36	36	38	9	32	22	356
18	4	38	38	48	39	47	24	25	25	14	4	302
19	4	39	46	34	18	31	7	36	8	13	20	262
20	4	47	45	46	40	17	17	10	23	14	7	266

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

No. of movements (individual): males
(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	
21	4	38	33	46	24	32	34	9	26	41	9	292
22	4	49	38	43	38	33	19	38	13	49	3	323
23	4	44	44	40	38	35	30	25	22	15	40	333
24	4	48	46	33	38	48	38	29	11	7	28	326
25	4	43	40	46	37	29	37	17	8	32	27	316

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	
26	4	50	45	45	40	36	41	43	36	35	30	401
27	4	39	49	49	11	30	4	7	28	19	20	256
28	4	49	32	30	30	22	35	23	22	19	25	287
29	4	51	43	36	39	42	33	38	22	32	25	361
30	4	52	34	45	32	29	17	35	24	15	29	312
31	4	47	50	47	15	26	24	22	11	9	3	254
	8	41	43	38	38	40	34	24	20	20	2	300
32	4	54	44	42	36	24	15	17	27	18	2	279
	8	39	34	23	10	13	36	1	4	6	8	174
33	4	46	41	30	24	9	22	19	16	10	31	247
	8	36	19	19	19	33	21	4	8	5	8	172
34	4	41	34	15	18	34	11	17	33	25	0	228
	8	36	38	25	28	41	31	24	25	34	6	288
35	4	49	53	33	27	5	15	12	26	7	9	236
	8	37	36	25	19	35	23	32	24	22	7	260

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	90	92	73	73	65	48	36	46	31	28	582
3	4	97	84	78	48	42	41	30	35	44	20	519
4	4	101	104	76	79	38	37	20	28	45	39	567
5	4	86	84	74	64	27	20	8	0	27	26	416
6	4	52	84	91	85	55	26	32	46	22	44	537
	8	74	66	71	63	52	38	70	53	65	2	554
7	4	72	78	64	41	20	10	10	1	14	45	355
	8	69	23	33	17	18	19	0	3	13	1	196
8	4	90	70	56	22	58	22	9	15	12	8	362
	8	91	78	34	26	24	45	31	1	11	4	345
9	4	99	70	58	63	27	23	10	22	4	9	385
	8	93	71	40	49	29	27	37	13	37	12	408

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	64	53	59	32	20	18	25	36	13	7	327
12	4	91	51	65	5	37	37	23	0	10	3	322
13	4	44	55	26	48	14	14	3	12	14	24	254
14	4	35	50	26	18	25	12	13	1	0	0	180
15	4	100	88	25	5	27	0	19	42	35	1	342

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	103	61	30	51	15	30	2	36	1	11	340
17	4	64	72	73	60	43	57	41	9	40	6	465
18	4	97	89	77	54	55	23	28	32	11	3	469
19	4	64	75	50	36	30	5	37	7	12	38	354
20	4	76	49	29	29	7	13	7	18	8	5	241

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	105	98	57	34	23	34	5	36	49	8	449
22	4	83	77	54	27	37	13	32	6	45	0	374
23	4	92	89	78	57	35	34	16	24	11	36	472
24	4	75	68	43	52	47	78	31	4	11	29	438
25	4	44	70	70	20	24	36	15	3	29	28	339

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	
26	4	86	76	81	60	44	47	51	32	19	19	515
27	4	93	51	54	3	32	1	2	42	5	35	318
28	4	76	79	35	47	14	39	20	28	8	18	364
29	4	66	54	57	60	51	50	61	28	36	22	485
30	4	76	65	43	23	50	9	35	21	17	43	382
31	4	89	63	46	4	22	33	27	7	7	6	304
	8	78	88	43	55	62	31	29	20	26	0	431
32	4	60	48	62	40	21	12	9	21	19	1	293
	8	61	30	24	5	8	36	0	0	3	11	178
33	4	67	46	31	37	5	23	7	11	13	38	278
	8	59	28	16	21	38	21	0	13	3	7	206
34	4	95	49	4	17	36	5	18	41	15	0	280
	8	73	51	29	34	31	55	23	15	35	2	348
35	4	65	70	25	33	1	17	8	29	2	5	255
	8	61	52	42	38	20	17	18	19	14	1	282

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

246

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	56	78	68	93	51	49	21	70	17	70	573
3	4	123	115	70	136	66	77	80	48	32	146	893
4	4	145	153	133	57	150	44	43	57	118	99	999
5	4	134	121	112	81	79	66	22	13	101	44	773
6	4	32	60	84	108	68	99	78	36	55	48	668
	8	82	64	43	26	27	26	86	40	89	3	486
7	4	136	140	105	66	61	97	14	2	22	58	701
	8	89	63	42	28	21	18	0	12	30	3	306
8	4	104	116	70	35	37	92	10	43	19	0	526
	8	84	102	40	121	39	42	46	0	40	8	522
9	4	151	113	40	64	53	43	7	25	0	27	523
	8	119	97	63	56	33	51	62	9	24	35	549

Vertical activity (individual): males
(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	
11	4	81	116	77	71	71	56	37	71	25	49	654
12	4	114	88	75	31	112	125	44	40	7	40	646
13	4	63	92	4	55	31	65	31	29	11	40	421
14	4	54	74	51	43	50	17	9	0	0	0	298
15	4	127	85	42	11	53	0	30	64	49	3	464

Vertical activity (individual): males
(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	
16	4	164	159	50	99	95	163	4	52	0	58	844
17	4	83	91	209	133	111	87	145	62	48	59	1028
18	4	112	160	106	130	57	92	91	79	42	11	870
19	4	95	99	82	57	34	22	55	28	13	65	550
20	4	100	43	50	10	0	45	3	7	9	0	267

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Vertical activity (individual): males group 4
(counts) 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	137	120	139	31	106	45	6	52	46	50	732
22	4	139	100	127	36	66	33	47	18	67	0	633
23	4	94	134	103	80	84	102	39	42	24	49	751
24	4	228	144	149	69	54	93	53	17	22	20	849
25	4	77	95	75	48	89	21	12	5	33	124	579

Vertical activity (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	
26	4	103	143	103	106	43	72	101	48	34	67	820
27	4	96	125	102	32	70	14	5	62	11	87	604
28	4	77	105	29	17	18	29	79	46	17	4	421
29	4	102	198	126	87	94	75	30	60	64	40	876
30	4	95	140	134	30	100	46	110	130	31	64	880
31	4	119	128	114	37	77	122	21	26	38	0	682
	8	110	103	88	63	38	50	39	48	34	1	574
32	4	56	102	66	92	63	67	35	29	14	0	524
	8	95	44	51	9	10	10	0	0	4	17	240
33	4	146	116	36	46	14	21	8	3	6	41	437
	8	119	38	7	21	52	15	0	9	0	10	271
34	4	150	126	7	28	33	4	32	36	27	0	443
	8	115	66	22	52	26	31	33	23	2	2	379
35	4	56	67	33	51	6	24	3	37	0	14	291
	8	31	33	9	21	8	9	22	13	20	0	166

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

No. of rearings (individual): males 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	
1	4	9	13	10	16	10	8	4	9	4	12	95
3	4	19	20	11	16	12	15	11	11	6	18	139
4	4	20	21	16	10	17	6	5	6	12	13	126
5	4	15	20	16	11	10	4	5	2	13	7	103
6	4	7	13	17	16	13	15	13	8	10	9	121
	8	18	12	11	6	6	6	14	7	15	1	96
7	4	22	19	15	13	11	14	3	1	4	11	113
	8	16	12	6	4	3	2	0	2	4	1	50
8	4	27	22	15	9	7	16	3	8	4	0	111
	8	16	15	9	15	6	7	9	0	4	1	82
9	4	27	19	8	17	14	9	1	6	0	4	105
	8	18	13	13	11	8	7	10	2	4	6	92

No. of rearings (individual): males 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	
11	4	15	16	13	11	10	9	7	12	4	5	102
12	4	17	12	9	7	13	15	5	7	2	3	90
13	4	12	15	1	9	5	8	4	5	2	7	68
14	4	12	14	6	7	6	4	2	0	0	0	51
15	4	27	19	10	2	11	0	5	10	13	2	99

No. of rearings (individual): males 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	
16	4	28	24	12	14	15	19	1	10	0	9	132
17	4	17	17	24	17	19	16	18	9	11	11	159
18	4	23	19	17	14	11	10	13	11	5	3	126
19	4	19	12	12	13	8	3	7	5	3	10	92
20	4	18	9	10	2	0	7	1	2	2	0	51

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

249

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

No. of rearings (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	19	20	16	5	18	9	2	10	10	7	116
22 4	20	14	11	7	11	5	7	4	11	0	90
23 4	16	18	16	13	11	16	9	3	8	8	119
24 4	31	24	19	10	10	16	6	3	4	4	127
25 4	15	16	15	5	15	6	2	1	4	16	95

No. of rearings (individual): males
(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	
26 4	20	24	21	18	9	14	17	7	8	10	148
27 4	17	18	20	7	11	3	1	10	1	14	102
28 4	16	17	6	5	2	5	13	8	2	1	75
29 4	17	23	19	13	13	10	5	9	15	8	132
30 4	19	24	18	5	12	5	18	16	6	9	132
31 4	22	20	18	7	12	17	3	5	4	0	108
8	17	17	12	10	10	7	6	6	6	1	92
32 4	11	16	13	8	10	11	4	8	3	0	84
8	13	7	9	2	2	2	0	0	1	3	39
33 4	22	16	7	11	3	4	2	1	1	10	77
8	16	7	1	4	9	4	0	2	0	2	45
34 4	25	18	1	4	9	1	9	6	5	0	78
8	17	11	4	8	3	4	3	3	4	1	58
35 4	15	17	5	7	2	5	0	7	0	2	60
8	7	6	2	3	2	2	3	2	4	0	31

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Vertical time (individual): males group 1
(sec) 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	17	18	25	45	18	26	8	41	16	37	251
3	4	32	35	24	50	35	34	39	22	11	67	349
4	4	37	43	51	23	54	21	29	22	67	54	401
5	4	44	39	33	29	38	38	7	6	46	27	307
6	4	10	18	26	39	21	37	30	12	21	20	234
8	4	24	19	14	8	9	11	31	12	32	0	160
7	4	37	41	45	28	23	51	5	2	10	25	267
8	4	26	20	23	14	9	12	0	5	19	1	129
8	4	24	30	25	10	10	38	2	18	9	0	166
8	4	19	26	10	37	13	13	13	0	16	4	151
9	4	37	36	12	20	19	20	2	8	0	8	162
8	4	34	35	16	18	10	19	31	6	9	18	196

Vertical time (individual): males group 2
(sec) 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	18	35	25	27	26	28	24	31	9	21	244
12	4	35	35	37	17	48	48	31	15	5	3	274
13	4	20	39	1	18	14	25	16	12	8	15	169
14	4	17	28	24	19	28	5	2	0	0	0	123
15	4	30	22	14	3	18	0	10	20	22	1	140

Vertical time (individual): males group 3
(sec) 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	49	62	18	48	41	72	1	18	0	30	339
17	4	19	23	79	45	39	26	50	22	16	23	340
18	4	39	51	36	61	31	41	43	48	30	7	337
19	4	32	48	30	22	16	7	30	12	5	35	237
20	4	32	18	30	5	0	31	3	3	4	0	126

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Vertical 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	38	44	51	15	50	27	8	30	28	24	315
22	4	41	42	68	25	27	21	24	7	45	0	300
23	4	26	46	36	28	29	60	14	15	13	20	287
24	4	69	54	61	22	27	41	19	8	11	14	326
25	4	18	28	29	17	36	6	3	1	11	75	224

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	
26	4	36	49	41	50	23	31	49	25	17	39	360
27	4	30	71	45	26	28	9	4	41	4	48	306
28	4	28	44	13	9	13	14	40	23	15	1	200
29	4	32	69	45	28	42	38	8	35	23	18	339
30	4	31	50	45	10	36	19	51	57	15	34	348
31	4	41	49	57	12	36	58	11	12	29	0	305
8		34	42	47	22	29	24	21	25	19	0	263
32	4	21	36	31	44	41	50	29	25	8	0	285
8		28	19	21	4	6	4	0	0	5	9	96
33	4	46	52	12	15	5	11	2	2	1	24	170
8		32	14	4	8	14	4	0	3	0	5	84
34	4	36	39	3	13	20	2	9	21	10	0	153
8		32	25	11	21	10	11	16	1	10	1	138
35	4	15	17	9	17	2	6	1	16	0	4	87
8		15	14	3	9	5	4	9	6	6	0	71

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	43	85	58	79	116	92	112	46	54	83	768
3	4	81	68	75	81	83	57	49	54	71	165	784
4	4	49	83	89	44	76	46	28	32	55	104	606
5	4	83	75	81	82	52	128	86	22	30	46	685
6	4	31	38	55	45	52	78	59	66	60	12	496
	8	33	33	68	36	35	19	43	40	59	119	485
7	4	23	34	42	20	15	2	9	0	1	19	165
	8	41	28	33	23	17	9	0	0	5	0	156
8	4	94	96	133	22	94	42	36	7	12	11	547
	8	60	39	19	57	20	36	53	2	17	27	330
9	4	96	47	25	43	6	9	10	12	0	1	249
	8	49	38	46	16	2	4	58	20	21	25	279

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	53	20	28	49	18	3	12	15	26	51	275
12	4	40	32	27	0	54	46	90	41	20	0	350
13	4	40	49	26	35	13	2	5	19	34	37	260
14	4	16	26	9	6	8	5	30	0	0	0	100
15	4	64	45	61	5	42	8	32	139	53	160	609

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	82	42	22	65	108	25	1	13	0	19	377
17	4	50	62	53	59	33	55	94	17	93	28	544
18	4	55	17	61	33	29	34	2	13	8	0	252
19	4	48	64	14	34	34	4	45	1	3	24	271
20	4	66	54	29	43	0	1	3	16	4	10	226

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

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	59	72	118	63	112	64	172	139	73	162	1034
22	4	44	37	93	14	76	41	56	13	82	3	459
23	4	50	29	48	62	60	110	47	61	7	30	504
24	4	64	36	23	35	42	84	99	13	1	25	422
25	4	38	43	46	8	36	21	22	3	33	77	327

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	
26	4	53	71	63	91	53	29	41	19	13	101	534
27	4	117	77	95	0	82	0	0	56	15	31	473
28	4	42	39	45	21	48	29	13	18	64	7	326
29	4	36	21	37	45	29	55	45	18	32	32	350
30	4	70	109	70	34	48	13	58	39	29	34	504
31	4	70	61	102	8	45	95	28	4	6	15	434
	8	65	25	61	31	49	20	11	42	16	6	326
32	4	59	81	64	26	32	27	52	7	21	0	369
	8	58	9	22	1	6	21	0	0	1	8	126
33	4	97	72	11	19	0	9	0	1	6	12	227
	8	58	25	11	19	18	10	1	10	5	10	167
34	4	61	34	5	16	24	13	3	13	7	0	176
	8	67	38	22	13	13	48	37	11	30	0	279
35	4	38	46	21	6	0	17	0	9	0	1	138
	8	68	30	53	44	53	67	58	9	37	1	420

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

254

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Total distance (individual): females group 1
(cm) 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	
36 4	645	480	596	518	624	312	421	426	426	271	4719
37 4	863	878	505	553	490	444	238	203	637	111	4922
38 4	1267	1109	820	833	373	538	327	467	373	304	6411
39 4	962	678	777	609	693	833	538	162	137	307	5696
40 4	629	772	434	462	533	175	335	281	172	317	4110
41 4	1170	1130	795	408	541	731	347	546	548	441	6657
8	1470	1412	944	556	772	134	657	276	228	340	6789
42 4	980	1013	314	147	248	0	381	436	157	193	3869
8	812	251	312	96	447	596	213	17	0	325	3069
43 4	861	734	769	807	650	530	332	111	360	251	5405
8	911	1196	655	464	551	734	683	436	215	563	6408
44 4	1209	1003	840	274	436	104	2	462	457	129	4916
8	1109	797	645	416	373	210	284	345	129	2	4310
45 4	1394	949	835	535	599	678	477	109	820	119	6515
8	1163	1219	932	820	419	464	299	365	541	579	6801

Total distance (individual): females group 2
(cm) 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	
46 4	1092	698	601	515	134	596	175	162	215	581	4569
48 4	1165	883	734	703	248	271	96	302	195	439	5036
49 4	759	660	266	589	408	459	83	233	492	99	4048
50 4	749	576	543	248	332	406	172	284	58	317	3685

Total distance (individual): females group 3
(cm) 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	
51 4	1082	1389	1348	835	863	469	370	591	144	73	7164
52 4	840	863	731	414	515	152	289	40	279	444	4567
53 4	1407	1145	1353	896	490	972	546	320	604	508	8241
54 4	843	853	891	429	233	165	563	441	381	55	4854
55 4	967	619	480	187	266	568	383	93	0	0	3563

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Total distance (individual): females group 4
(cm) 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	
56	4	789	551	429	274	152	342	73	7	7	144	2768
57	4	1122	1313	957	510	957	701	977	601	601	574	8313
58	4	960	995	1026	477	619	457	246	340	457	360	5937
59	4	673	393	287	373	256	269	421	170	482	347	3671
60	4	703	675	297	365	7	0	5	0	0	429	2481

Total distance (individual): females group 5
(cm) 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	
61	4	1303	1216	1341	378	889	426	777	472	568	642	8512
62	4	1117	904	833	711	591	472	665	358	71	284	6006
63	4	980	652	619	350	396	421	363	619	299	276	4975
64	4	693	800	515	421	48	284	287	167	256	335	3806
65	4	1267	980	784	774	510	246	515	139	167	358	5740
66	4	1402	1181	878	1112	1155	1145	891	594	520	825	9703
	8	1551	1031	1282	436	774	482	248	180	203	784	6971
67	4	1313	1402	937	599	665	515	421	266	462	576	7156
	8	1066	873	795	662	474	287	236	698	472	170	5733
68	4	1277	1043	754	815	736	447	833	307	386	345	6943
	8	1150	947	695	657	502	635	566	472	167	177	5968
69	4	1143	817	655	472	205	548	312	398	434	55	5039
	8	1691	1107	1109	637	505	434	858	274	0	86	6701
70	4	1216	830	408	223	96	195	208	236	30	233	3675
	8	985	850	528	363	43	175	304	7	261	10	3526

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

No. of movements (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	
36	4	49	46	42	34	36	36	35	37	34	23	372
37	4	51	40	34	40	34	38	20	10	32	9	308
38	4	47	46	36	43	25	34	30	35	24	29	349
39	4	46	44	43	41	35	33	38	19	14	23	336
40	4	42	42	40	33	34	15	38	30	17	29	320
41	4	46	47	42	17	19	42	25	32	24	37	331
	8	45	42	37	34	34	11	24	24	26	19	296
42	4	50	46	39	14	17	0	31	35	17	26	275
	8	42	26	16	8	39	32	12	7	0	23	205
43	4	44	40	41	38	34	33	18	20	27	20	315
	8	42	41	40	42	33	39	41	30	20	39	367
44	4	44	45	43	19	27	6	2	31	28	13	258
	8	41	46	30	27	30	11	22	30	15	2	254
45	4	40	45	40	34	29	38	31	14	36	12	319
	8	43	44	44	36	29	30	23	21	32	34	336

No. of movements (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	
46	4	50	39	34	34	18	38	15	24	24	32	308
48	4	44	46	45	45	20	35	12	23	18	34	322
49	4	49	46	26	41	37	31	13	22	40	15	320
50	4	47	38	41	21	33	35	26	25	7	32	305

No. of movements (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	
51	4	43	37	43	42	35	29	20	29	13	12	303
52	4	42	42	41	30	35	17	29	10	17	32	295
53	4	36	43	39	42	29	35	25	10	26	16	301
54	4	49	45	38	35	14	16	38	44	38	15	332
55	4	40	35	38	23	14	32	22	5	0	1	210

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	
56	4	48	33	34	22	15	28	13	3	3	6	205
57	4	43	47	42	40	39	28	41	39	37	35	391
58	4	47	45	45	28	46	36	22	30	34	26	359
59	4	48	31	24	39	28	24	42	24	27	17	304
60	4	51	47	26	29	6	0	2	1	0	26	188

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	
61	4	41	52	44	50	38	34	40	34	36	38	407
62	4	56	47	43	42	31	30	38	27	7	20	341
63	4	46	34	35	29	36	28	44	27	37	20	336
64	4	49	47	50	32	9	31	37	18	24	21	318
65	4	49	45	43	32	30	14	30	11	15	27	296
66	4	40	43	46	47	41	43	35	41	33	36	405
	8	38	43	41	34	35	30	18	22	23	39	323
67	4	42	37	44	40	33	40	30	21	32	36	355
	8	45	40	40	31	26	25	29	41	33	12	322
68	4	44	43	38	40	30	23	31	24	21	21	315
	8	42	40	39	27	33	41	25	27	22	12	308
69	4	45	43	35	31	14	37	29	33	41	3	311
	8	35	37	38	41	32	28	44	22	1	9	287
70	4	48	36	31	18	16	35	19	17	4	23	247
	8	38	42	33	34	5	14	26	3	7	2	204

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

258

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Movement time (individual): females group 1
(sec) 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	
36	4	53	45	52	38	53	26	26	38	36	20	387
37	4	77	83	50	43	53	31	19	12	54	11	433
38	4	86	81	72	57	21	50	30	32	26	22	477
39	4	80	65	57	57	64	69	36	9	12	21	470
40	4	52	58	30	39	45	18	24	19	11	23	319
41	4	82	80	54	24	41	62	25	40	31	35	474
	8	95	92	70	43	52	10	47	18	14	18	459
42	4	79	81	26	11	13	0	32	26	13	11	292
	8	72	19	29	10	41	48	18	2	0	30	269
43	4	70	58	65	67	55	41	27	8	26	19	436
	8	71	95	57	47	36	68	60	31	20	52	537
44	4	84	75	69	21	33	6	0	36	33	9	366
	8	85	64	51	31	22	18	17	33	17	1	339
45	4	95	63	49	40	37	46	29	8	50	7	424
	8	87	90	70	59	30	42	23	28	45	45	519

Movement time (individual): females group 2
(sec) 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	
46	4	87	66	45	40	14	47	17	19	18	31	384
48	4	90	69	54	51	22	20	7	23	12	32	380
49	4	70	59	27	49	32	37	10	28	42	10	364
50	4	61	46	42	23	30	35	9	19	7	20	292

Movement time (individual): females group 3
(sec) 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	
51	4	91	92	83	52	53	34	26	36	12	3	487
52	4	78	69	55	31	38	14	25	3	22	33	368
53	4	121	82	99	60	38	65	40	16	31	27	579
54	4	72	66	69	31	18	12	42	29	35	6	379
55	4	84	54	41	16	24	37	30	5	0	0	291

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Movement time (individual): females group 4
(sec) 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	
56	4	57	40	34	14	14	31	8	2	1	10	211
57	4	83	90	76	39	69	60	76	52	43	37	625
58	4	70	78	68	49	48	31	21	24	35	26	450
59	4	46	32	25	30	23	15	36	16	31	19	273
60	4	62	57	29	35	2	0	0	0	0	29	214

Movement time (individual): females group 5
(sec) 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	
61	4	90	75	89	61	61	30	57	38	41	37	579
62	4	78	77	68	69	45	42	63	30	5	20	497
63	4	83	61	40	29	42	31	37	41	30	19	413
64	4	63	65	42	32	7	23	23	12	23	24	314
65	4	87	64	63	63	34	16	37	10	12	26	412
66	4	96	88	48	61	77	79	62	36	29	58	634
	8	108	65	77	37	47	40	14	12	13	51	464
67	4	103	106	76	54	59	46	25	23	35	34	561
	8	78	78	68	51	31	20	22	64	43	6	461
68	4	91	81	56	59	51	30	44	19	31	20	482
	8	90	69	56	50	33	55	41	31	15	16	456
69	4	78	75	50	37	14	40	19	25	31	5	374
	8	113	72	81	51	40	37	68	21	0	4	487
70	4	86	66	32	20	8	16	16	13	3	13	273
	8	59	63	37	27	2	13	23	1	13	0	238

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

260

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Vertical activity (individual): females
(counts)group 1
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	
36 4	104	158	117	84	81	69	64	44	67	59	847
37 4	116	139	101	100	56	62	46	11	67	9	707
38 4	121	106	88	81	24	56	59	137	69	107	848
39 4	124	68	105	76	119	41	59	35	37	90	754
40 4	173	190	128	108	105	11	104	157	32	208	1216
41 4	135	173	121	12	57	100	47	83	80	145	953
8	133	129	147	66	40	34	83	67	52	33	784
42 4	124	87	54	33	27	0	39	50	29	16	459
8	80	29	52	6	78	44	9	4	0	19	321
43 4	88	99	90	140	109	146	206	46	86	85	1095
8	96	133	86	89	107	95	121	96	33	80	936
44 4	119	92	124	16	68	8	18	65	36	29	575
8	87	107	82	57	63	67	36	31	43	6	579
45 4	210	123	146	123	47	48	77	20	52	19	865
8	110	165	114	132	81	112	33	32	51	24	854

Vertical activity (individual): females
(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	
46 4	101	112	44	71	18	85	34	74	77	32	698
48 4	187	185	147	214	25	137	26	73	17	105	1116
49 4	112	131	74	41	117	84	9	51	49	12	680
50 4	103	91	99	50	74	87	44	31	10	64	653

Vertical activity (individual): females
(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	
51 4	84	171	102	150	76	88	100	80	40	39	930
52 4	93	50	123	50	27	27	45	0	27	79	521
53 4	113	117	145	202	110	95	119	97	105	141	1243
54 4	103	196	115	139	67	45	70	82	129	27	972
55 4	92	170	82	75	37	77	61	16	0	0	610

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Vertical activity (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	
56	4	68	42	19	10	9	49	0	0	0	19	216
57	4	100	129	109	37	96	47	54	39	92	108	811
58	4	79	146	124	84	110	122	42	84	97	78	966
59	4	94	118	100	105	33	111	96	18	102	75	852
60	4	96	110	48	124	0	0	8	5	0	146	537

Vertical activity (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	
61	4	190	200	147	114	105	29	74	62	42	78	1041
62	4	142	114	68	58	108	7	59	71	20	80	727
63	4	99	122	41	138	70	42	28	47	81	66	734
64	4	106	141	199	100	38	117	126	84	138	151	1200
65	4	158	261	182	112	139	61	73	38	54	106	1184
66	4	245	205	389	212	140	153	155	178	137	117	1931
	8	164	255	138	101	133	174	178	116	102	102	1463
67	4	174	162	84	57	52	46	76	16	69	153	889
	8	114	59	72	100	47	32	19	49	56	42	590
68	4	112	123	117	67	115	32	92	8	41	26	733
	8	164	143	117	122	210	106	134	67	28	16	1107
69	4	142	190	128	119	33	76	96	82	121	14	1001
	8	150	104	116	85	72	46	49	12	0	8	642
70	4	193	94	44	23	2	28	31	32	0	79	516
	8	155	54	44	23	0	5	20	0	26	0	327

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

262

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

No. of rearings (individual): females
(counts)group 1
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	
36 4	20	23	17	11	8	11	7	4	10	9	120
37 4	18	24	16	15	9	9	8	2	11	1	113
38 4	25	15	10	14	5	7	9	18	11	10	124
39 4	22	13	15	11	17	8	8	6	6	11	117
40 4	27	26	13	16	13	2	4	16	7	17	141
41 4	21	27	21	4	8	14	7	18	11	19	150
8	20	20	25	16	10	4	11	12	11	5	134
42 4	29	15	13	5	5	0	6	9	2	4	88
8	17	5	7	1	12	8	4	1	0	4	59
43 4	23	15	15	23	13	15	22	6	13	10	155
8	17	24	13	12	17	17	15	15	7	12	149
44 4	20	15	22	4	7	2	1	8	7	4	90
8	16	17	15	8	9	14	6	5	6	1	97
45 4	32	25	23	14	8	10	13	4	10	3	142
8	19	24	19	20	15	16	9	7	9	6	144

No. of rearings (individual): females
(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	
46 4	21	23	8	9	3	11	7	5	15	14	116
48 4	28	18	12	19	2	6	4	15	3	11	118
49 4	24	23	15	9	14	13	4	8	10	2	122
50 4	25	19	18	10	10	15	9	6	0	14	126

No. of rearings (individual): females
(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	
51 4	11	19	13	15	14	14	12	11	4	4	117
52 4	22	9	21	9	5	6	8	0	5	14	99
53 4	26	23	25	25	17	19	22	20	19	21	217
54 4	15	28	13	17	3	6	9	12	18	2	128
55 4	21	24	11	11	5	13	9	2	0	0	96

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

No. of rearings (individual): females group 4
(counts) 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	
56	4	12	8	6	3	1	8	0	0	0	3	41
57	4	18	21	20	7	15	8	9	8	16	16	138
58	4	17	29	26	13	17	15	8	15	15	15	170
59	4	19	17	19	15	6	14	18	5	16	11	140
60	4	18	19	12	15	0	0	2	2	0	21	89

No. of rearings (individual): females 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	
61	4	30	36	26	19	14	7	12	9	8	13	174
62	4	27	24	13	8	14	2	9	14	4	11	126
63	4	19	23	10	21	10	6	7	9	15	16	136
64	4	21	29	25	20	5	19	14	16	10	17	176
65	4	24	19	16	14	15	9	11	5	6	10	129
66	4	22	19	12	25	18	20	18	15	18	17	184
	8	22	32	20	14	20	16	17	13	16	13	183
67	4	26	23	14	9	9	4	5	2	8	17	117
	8	19	12	13	16	10	6	4	8	12	3	103
68	4	25	23	20	13	21	7	10	2	5	6	132
	8	27	25	21	17	27	9	13	12	6	2	159
69	4	25	27	22	15	9	20	13	17	25	4	177
	8	28	16	17	13	11	9	8	3	0	0	105
70	4	25	18	7	4	1	5	6	5	0	7	78
	8	23	11	9	2	0	1	3	0	2	0	51

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Vertical time (individual): females group 1
(sec) 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	
36	4	39	64	64	44	42	33	38	35	44	33	436
37	4	37	50	40	45	29	34	29	7	43	4	318
38	4	43	53	57	37	14	32	35	75	76	70	492
39	4	39	27	46	36	48	14	22	18	30	59	339
40	4	64	71	71	54	48	6	49	84	13	110	570
41	4	45	58	50	3	21	37	29	38	32	66	379
	8	50	45	66	33	19	9	32	45	36	20	355
42	4	44	45	25	19	15	0	26	38	17	13	242
	8	35	17	26	2	55	31	7	4	0	17	194
43	4	23	30	32	60	56	73	106	23	56	68	527
	8	30	64	52	45	67	43	73	55	12	46	487
44	4	34	37	48	9	33	3	8	45	23	28	268
	8	31	46	43	26	52	53	19	17	28	8	323
45	4	70	73	81	65	24	33	48	11	46	9	460
	8	38	73	62	82	41	66	17	15	40	11	445

Vertical time (individual): females group 2
(sec) 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	
46	4	29	29	15	36	6	41	14	40	27	49	286
48	4	58	68	52	89	10	83	16	34	10	72	492
49	4	40	52	38	16	64	53	2	28	47	7	347
50	4	29	35	45	17	41	70	22	20	5	44	328

Vertical time (individual): females group 3
(sec) 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	
51	4	24	65	48	92	49	67	78	51	34	41	549
52	4	24	15	36	19	6	12	18	0	12	29	171
53	4	35	46	65	112	65	60	80	54	42	51	610
54	4	35	79	42	59	25	22	36	40	85	16	440
55	4	29	78	68	62	25	59	78	8	0	0	407

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	
56	4	35	27	12	7	5	37	0	0	0	14	137
57	4	31	45	35	16	44	22	18	16	51	56	334
58	4	40	57	49	44	67	63	29	47	62	43	501
59	4	33	53	48	58	15	50	46	11	41	37	392
60	4	35	49	19	57	0	0	7	1	0	70	238

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	
61	4	62	66	55	40	63	14	40	30	18	40	428
62	4	41	36	26	29	39	4	30	59	17	54	335
63	4	37	46	27	88	45	48	9	31	49	46	426
64	4	51	46	83	42	23	57	73	52	80	98	605
65	4	48	115	70	53	87	30	38	23	31	61	556
66	4	78	81	159	90	56	70	79	104	88	54	859
	8	51	99	62	48	67	83	102	100	70	65	747
67	4	36	57	24	27	27	16	33	7	32	92	341
	8	65	24	55	57	20	21	9	33	35	28	347
68	4	39	59	49	35	67	18	42	6	32	13	360
	8	60	58	55	64	94	62	68	43	19	6	529
69	4	40	69	54	90	14	39	71	62	72	8	519
	8	53	60	62	53	62	31	28	6	0	2	357
70	4	61	54	21	18	1	19	35	42	0	98	349
	8	61	27	20	14	0	3	8	0	18	0	151

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

266

Test No.: 963103

Test Article: CGA 62826 (Metabolite of CGA 48988)

Center time (individual): females group 1
(sec) 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
36	4	7	25	59	33	55	32	20	25	71	97	424
37	4	36	60	43	39	70	52	24	1	39	14	378
38	4	47	71	45	68	26	47	76	82	61	57	580
39	4	51	24	34	55	68	92	25	6	37	38	430
40	4	46	60	23	26	33	9	27	51	9	66	350
41	4	31	60	27	41	72	52	3	53	36	13	388
	8	63	37	53	37	18	37	36	22	14	20	337
42	4	54	48	41	16	51	0	25	44	37	58	374
	8	33	15	19	26	41	14	27	5	0	4	184
43	4	7	11	60	51	20	38	80	1	36	5	309
	8	24	59	62	50	45	81	54	83	116	60	634
44	4	35	21	63	2	12	4	0	18	7	3	165
	8	37	38	25	8	47	11	4	25	13	0	208
45	4	51	83	35	75	46	52	76	8	20	28	474
	8	43	43	62	30	83	25	38	19	44	14	401

Center time (individual): females group 2
(sec) 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
46	4	46	41	24	32	29	21	20	86	47	62	408
48	4	46	46	41	56	25	32	21	18	63	79	427
49	4	42	51	38	50	75	71	8	52	39	33	459
50	4	17	28	46	85	16	25	8	29	11	74	339

Center time (individual): females group 3
(sec) 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
51	4	50	37	50	70	58	91	22	76	15	37	506
52	4	46	24	20	8	11	2	2	2	1	55	171
53	4	68	46	51	42	46	39	20	6	44	23	385
54	4	36	58	67	64	24	15	84	39	17	9	413
55	4	40	33	36	24	26	13	49	38	0	0	259

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

Test No.: 963103

Test Article: CGA 62826 (Metabolite 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	
56	4	28	46	23	21	11	15	1	0	0	28	173
57	4	48	45	51	48	40	29	83	72	60	71	547
58	4	28	39	54	35	30	44	22	37	41	33	363
59	4	24	40	142	31	17	55	88	37	81	51	566
60	4	38	29	16	14	2	0	0	0	0	61	160

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	
61	4	36	65	38	59	42	48	56	45	38	69	496
62	4	78	92	52	72	127	118	27	103	160	120	949
63	4	32	53	15	78	15	26	16	36	46	51	368
64	4	26	55	33	29	1	42	8	8	34	28	264
65	4	49	73	67	68	62	16	40	8	37	104	524
66	4	41	44	59	66	44	35	44	33	36	16	418
	8	43	87	62	103	75	74	63	9	19	53	588
67	4	35	42	54	32	46	66	13	4	23	107	422
	8	67	26	36	43	18	16	24	20	27	12	289
68	4	23	21	14	8	41	3	8	2	2	8	130
	8	35	36	29	17	38	45	16	3	3	0	222
69	4	28	43	31	39	14	40	42	39	64	6	346
	8	55	65	50	60	73	45	49	36	0	0	433
70	4	41	53	15	42	10	16	16	0	0	8	201
	8	48	50	62	15	1	16	23	0	23	0	238

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	20 Nov 96	5	30	yes	Sacrifice 1
2	2	26 Oct 96	1	5	yes	Found dead
3	3	20 Nov 96	5	30	yes	Sacrifice 1
4	4	20 Nov 96	5	30	yes	Sacrifice 1
5	5	20 Nov 96	5	30	yes	Sacrifice 1
6	6	18 Dec 96	9	58	yes	Sacrifice 2
7	7	18 Dec 96	9	58	yes	Sacrifice 2
8	8	18 Dec 96	9	58	yes	Sacrifice 2
9	9	18 Dec 96	9	58	yes	Sacrifice 2
10	10	26 Oct 96	1	5	yes	Found dead

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

Animal number	cage	date of death	study week	study day	necropsy	type of death
11	11	20 Nov 96	5	30	yes	Sacrifice 1
12	12	20 Nov 96	5	30	yes	Sacrifice 1
13	13	20 Nov 96	5	30	yes	Sacrifice 1
14	14	20 Nov 96	5	30	yes	Sacrifice 1
15	15	20 Nov 96	5	30	yes	Sacrifice 1

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

269

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	20 Nov 96	5	30	yes	Sacrifice 1
17	17	20 Nov 96	5	30	yes	Sacrifice 1
18	18	20 Nov 96	5	30	yes	Sacrifice 1
19	19	20 Nov 96	5	30	yes	Sacrifice 1
20	20	20 Nov 96	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	20 Nov 96	5	30	yes	Sacrifice 1
22	22	20 Nov 96	5	30	yes	Sacrifice 1
23	23	20 Nov 96	5	30	yes	Sacrifice 1
24	24	20 Nov 96	5	30	yes	Sacrifice 1
25	25	20 Nov 96	5	30	yes	Sacrifice 1

Mortality (individuals) : males group 5 : 1000 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
26	26	20 Nov 96	5	30	yes	Sacrifice 1
27	27	20 Nov 96	5	30	yes	Sacrifice 1
28	28	20 Nov 96	5	30	yes	Sacrifice 1
29	29	20 Nov 96	5	30	yes	Sacrifice 1
30	30	20 Nov 96	5	30	yes	Sacrifice 1
31	31	18 Dec 96	9	58	yes	Sacrifice 2
32	32	18 Dec 96	9	58	yes	Sacrifice 2
33	33	18 Dec 96	9	58	yes	Sacrifice 2
34	34	18 Dec 96	9	58	yes	Sacrifice 2
35	35	18 Dec 96	9	58	yes	Sacrifice 2

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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
36	36	20 Nov 96	5	30	yes	Sacrifice 1
37	37	20 Nov 96	5	30	yes	Sacrifice 1
38	38	20 Nov 96	5	30	yes	Sacrifice 1
39	39	20 Nov 96	5	30	yes	Sacrifice 1
40	40	20 Nov 96	5	30	yes	Sacrifice 1
41	41	18 Dec 96	9	58	yes	Sacrifice 2
42	42	18 Dec 96	9	58	yes	Sacrifice 2
43	43	18 Dec 96	9	58	yes	Sacrifice 2
44	44	18 Dec 96	9	58	yes	Sacrifice 2
45	45	18 Dec 96	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
46	46	20 Nov 96	5	30	yes	Sacrifice 1
47	47	26 Oct 96	1	5	yes	Found dead
48	48	20 Nov 96	5	30	yes	Sacrifice 1
49	49	20 Nov 96	5	30	yes	Sacrifice 1
50	50	20 Nov 96	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
51	51	20 Nov 96	5	30	yes	Sacrifice 1
52	52	20 Nov 96	5	30	yes	Sacrifice 1
53	53	20 Nov 96	5	30	yes	Sacrifice 1
54	54	20 Nov 96	5	30	yes	Sacrifice 1
55	55	20 Nov 96	5	30	yes	Sacrifice 1

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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
56	56	20 Nov 96	5	30	yes	Sacrifice 1
57	57	20 Nov 96	5	30	yes	Sacrifice 1
58	58	20 Nov 96	5	30	yes	Sacrifice 1
59	59	20 Nov 96	5	30	yes	Sacrifice 1
60	60	20 Nov 96	5	30	yes	Sacrifice 1

Mortality (individuals) : females group 5 : 1000 mg/kg

Animal number	cage	date of death	study week	study day	necropsy	type of death
61	61	20 Nov 96	5	30	yes	Sacrifice 1
62	62	20 Nov 96	5	30	yes	Sacrifice 1
63	63	20 Nov 96	5	30	yes	Sacrifice 1
64	64	20 Nov 96	5	30	yes	Sacrifice 1
65	65	20 Nov 96	5	30	yes	Sacrifice 1
66	66	18 Dec 96	9	58	yes	Sacrifice 2
67	67	18 Dec 96	9	58	yes	Sacrifice 2
68	68	18 Dec 96	9	58	yes	Sacrifice 2
69	69	18 Dec 96	9	58	yes	Sacrifice 2
70	70	18 Dec 96	9	58	yes	Sacrifice 2

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

272

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

9.5. Body weight (individuals)

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

group 1 : 0 mg/kg

	Animal no									
	1	2	3	4	5	6	7	8	9	10
week: -1	173.8	174.7	182.4	197.6	168.5	190.0	163.8	177.3	181.8	184.3
1	217.2	218.5	239.9	253.3	217.8	240.5	211.5	227.9	223.4	235.9
2	267.3		292.8	296.4	265.1	282.4	243.7	272.0	266.9	
3	289.0		336.4	319.4	300.2	293.3	278.1	292.3	297.0	
4	335.7		383.9	331.7	333.7	305.1	313.9	324.9	330.4	
recovery										
week: 5					331.9	320.1	331.8	344.9		
6					356.5	341.3	353.2	362.5		
7					379.3	362.8	374.2	394.9		
8					395.5	378.9	386.4	414.9		

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

group 2 : 10 mg/kg

	Animal no				
	11	12	13	14	15
week: -1	189.3	191.7	180.6	144.3	170.5
1	234.0	244.0	229.0	186.0	214.7
2	275.7	284.0	270.2	222.1	250.4
3	300.2	306.5	293.4	243.6	268.1
4	338.1	326.2	325.2	275.7	291.4

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

273

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 3 : 50 mg/kg

	16	17	18	19	20
	Animal no				
week: -1	191.2	189.3	177.5	174.1	150.4
1	239.9	242.5	224.4	215.8	197.8
2	265.0	292.8	272.8	256.3	230.6
3	286.9	332.7	299.7	279.3	244.2
4	313.9	370.2	329.1	313.8	269.5

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

group 4 : 200 mg/kg

	21	22	23	24	25
	Animal no				
week: -1	177.7	190.7	176.4	166.8	187.3
1	233.7	243.4	239.5	210.5	246.5
2	284.2	281.3	283.5	252.5	298.1
3	315.7	296.4	315.7	285.0	284.3
4	359.1	329.0	357.0	322.1	312.0

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

group 5 : 1000 mg/kg

	26	27	28	29	30	31	32	33	34	35
	Animal no									
week: -1	199.0	190.4	179.0	167.9	171.8	155.6	179.2	192.4	182.3	174.8
1	249.3	245.6	225.8	217.6	217.2	201.1	237.3	242.8	231.9	227.8
2	294.8	293.6	257.5	251.0	249.5	240.5	286.1	285.7	268.6	278.4
3	319.7	319.8	277.9	280.8	275.1	263.5	328.8	319.1	293.4	325.5
4	347.2	351.3	306.6	322.0	304.4	295.9	370.4	359.0	325.9	378.6

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

275

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 1 : 0 mg/kg

	Animal no									
	36	37	38	39	40	41	42	43	44	45
week: -1	125.5	147.7	136.8	143.8	141.0	143.8	146.6	133.4	137.6	133.2
1	152.2	178.7	155.0	172.4	157.7	162.6	168.7	146.5	163.4	150.3
2	163.3	192.8	178.9	190.6	171.8	180.9	186.3	164.4	174.4	168.4
3	178.6	203.8	190.9	204.7	188.9	199.5	209.2	177.9	187.3	184.8
4	203.8	228.4	206.4	225.1	200.2	221.0	217.1	193.5	215.6	195.3
recovery										
week: 5					222.8	226.4	197.9	213.7	199.6	
6					229.0	235.6	215.2	230.5	213.3	
7					239.1	242.7	215.2	246.9	222.1	
8					246.2	246.9	225.3	246.3	236.3	

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

group 2 : 10 mg/kg

	Animal no				
	46	47	48	49	50
week: -1	147.1	138.1	127.8	134.1	143.2
1	163.1	154.0	141.4	162.2	176.0
2	173.1		165.6	185.4	199.9
3	188.4		176.7	194.7	217.1
4	198.5		185.4	210.1	230.3

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

276

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 3 : 50 mg/kg

	51	52	53	54	55
week: -1	146.0	147.4	128.8	134.4	142.7
1	163.3	177.0	156.4	152.0	165.8
2	178.5	198.5	181.6	174.4	189.0
3	205.2	217.5	200.0	190.1	205.1
4	215.5	233.2	221.9	221.9	222.9

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

group 4 : 200 mg/kg

	56	57	58	59	60
week: -1	142.5	150.6	117.5	146.9	143.8
1	159.1	176.4	142.6	172.0	174.8
2	178.3	206.6	147.9	191.2	187.6
3	198.4	229.8	164.7	214.4	210.1
4	210.7	256.6	176.9	229.6	238.9

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

group 5 : 1000 mg/kg

	61	62	63	64	65	66	67	68	69	70
week: -1	144.5	133.5	139.9	122.7	138.9	133.6	137.0	144.2	127.1	130.8
1	171.2	158.3	160.4	147.7	164.6	152.8	168.5	167.6	155.1	151.0
2	196.7	178.0	181.7	168.0	189.9	174.4	188.8	195.4	173.6	171.7
3	213.1	192.7	198.5	187.7	206.2	185.4	210.7	222.2	189.1	183.2
4	223.2	214.2	211.8	199.1	224.3	201.4	222.4	231.5	201.3	194.4

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 5 : 1000 mg/kg

	Animal no	61	62	63	64	65	66	67	68	69	70
recovery											
week:	5					219.1	228.5	234.9	206.6	201.9	
	6					229.0	238.5	248.3	212.0	212.3	
	7					244.8	249.1	254.2	217.9	220.9	
	8					249.4	252.6	263.7	222.2	224.1	

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Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	135.9	136.6	159.0	171.2	146.1	152.0	144.8	161.8	151.9	151.4
1	159.9	91.70	166.8	182.8	159.8	158.0	151.1	161.8	172.7	133.7
2	167.5		195.6	181.1	181.7	169.3	166.2	178.1	178.0	
3	161.6		201.9	108.9	174.9	166.3	164.4	163.9	183.9	
4	179.3		208.1	204.5	181.7	151.6	186.7	171.2	186.2	
recovery										
week: 5					167.9	146.0	166.7	184.1		
6					165.1	170.1	184.1	197.8		
7					155.3	175.2	183.4	193.0		
8					168.5	173.1	165.2	188.1		

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

group 2 : 10 mg/kg

	Cage no				
	11	12	13	14	15
week: -1	154.9	155.6	143.4	142.7	148.9
1	163.6	173.1	161.4	156.0	149.5
2	179.9	168.1	169.5	159.8	159.5
3	171.1	172.5	160.5	169.7	156.3
4	165.3	166.8	167.0	165.7	160.4

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

279

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 3 : 50 mg/kg

	16	17	18	19	Cage no 20
week: -1	162.7	168.3	154.1	140.7	140.2
1	159.4	176.6	164.8	142.9	165.5
2	160.5	198.2	189.3	164.0	159.9
3	161.4	198.2	183.3	161.3	148.9
4	171.4	207.1	180.4	166.6	157.2

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

group 4 : 200 mg/kg

	21	22	23	24	Cage no 25
week: -1	149.0	162.7	148.4	137.2	166.5
1	167.4	167.7	173.5	142.8	176.8
2	179.0	162.7	179.4	144.5	180.0
3	173.1	172.2	174.7	172.7	158.6
4	183.5	171.7	206.3	170.9	170.1

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

group 5 : 1000 mg/kg

	26	27	28	29	Cage no		32	33	34	35
					30	31				
week: -1	154.9	158.1	143.3	139.8	139.4	131.8	153.0	151.9	154.5	150.4
1	167.4	175.0	147.1	151.6	148.2	145.2	160.2	165.8	171.6	182.2
2	180.2	191.0	167.6	167.7	166.7	167.8	195.7	181.9	174.3	213.6
3	171.6	186.0	150.5	176.3	155.2	158.1	197.5	185.7	177.9	208.7
4	173.6	195.7	158.8	185.4	156.2	171.7	215.5	199.7	174.3	225.6

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

group 5 : 1000 mg/kg

		Cage no									
		26	27	28	29	30	31	32	33	34	35
recovery											
week:	5					158.8	219.6	195.8	170.3	213.9	
	6					162.9	214.7	186.2	173.7	202.0	
	7					153.6	198.4	176.1	163.3	182.4	
	8					154.8	204.3	180.5	156.9	195.7	

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

281

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 1 : 0 mg/kg

	Cage no									
	36	37	38	39	40	41	42	43	44	45
week: -1	108.3	130.7	112.0	121.8	103.6	117.6	112.3	108.1	113.6	97.70
1	94.40	113.3	94.70	115.3	100.9	91.20	103.3	92.00	97.60	93.60
2	113.7	137.6	128.0	128.5	110.0	118.6	121.1	110.2	118.4	114.1
3	116.8	125.0	126.4	129.3	114.4	119.9	120.0	108.0	123.0	116.0
4	115.7	122.7	117.0	135.3	120.1	131.1	114.8	105.9	122.7	119.0
recovery										
week: 5					123.2	121.9	110.8	124.7	105.2	
6					130.2	117.8	126.1	132.1	126.3	
7					119.2	112.4	119.7	124.4	126.3	
8					127.6	105.2	111.9	141.3	124.1	

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

group 2 : 10 mg/kg

	Cage no				
	46	47	48	49	50
week: -1	107.9	108.9	111.4	126.6	120.0
1	111.3	75.43	96.60	103.3	109.9
2	116.9		117.1	116.1	130.1
3	128.1		109.6	121.1	124.0
4	137.3		115.6	116.9	118.5

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 3 : 50 mg/kg

	51	52	53	54	55
week: -1	110.3	122.0	117.7	108.8	121.2
1	116.4	121.7	110.2	103.0	109.8
2	130.0	132.2	125.3	122.9	127.1
3	128.0	132.8	125.1	123.7	123.8
4	136.2	126.7	134.1	132.7	136.9

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

group 4 : 200 mg/kg

	56	57	58	59	60
week: -1	111.8	129.9	94.90	120.2	124.2
1	105.3	132.1	85.60	110.7	122.0
2	118.4	151.2	106.2	128.6	136.5
3	116.5	153.6	103.8	124.1	146.2
4	120.6	155.8	101.2	121.7	130.1

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

group 5 : 1000 mg/kg

	61	62	63	64	65	66	67	68	69	70
week: -1	122.1	108.9	115.9	105.2	111.9	116.6	120.6	119.3	114.0	101.2
1	110.7	106.0	97.20	100.9	106.5	102.9	114.2	111.3	101.5	103.9
2	124.5	123.1	111.9	110.8	132.4	122.9	127.7	136.3	121.3	113.4
3	120.1	114.6	121.0	116.0	120.2	119.4	121.4	131.4	113.4	103.8
4	108.7	123.7	111.4	110.7	131.3	140.5	130.0	130.2	110.7	116.6

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

283

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 5 : 1000 mg/kg

	61	62	63	64	Cage no 65	66	67	68	69	70
recovery										
week: 5					143.9	133.4	143.3	113.4	110.6	
6					145.4	137.9	143.2	115.1	118.8	
7					134.8	120.3	133.4	112.5	109.8	
8					134.5	116.7	118.9	105.2	112.5	

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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	168.7	196.0	274.4	497.0	247.1	207.2	208.6	193.2	256.2	186.2
1	184.8	156.1	193.9	197.4	156.8	248.5	172.9	176.4	202.3	177.1
2	231.0		192.5	191.1	186.2	193.9	205.8	187.6	262.5	
3	191.1		177.1	130.9	142.8	235.9	162.4	154.0	220.5	
4	239.4		226.1	243.6	202.3	243.6	366.8	178.5	247.8	
recovery										
week: 5					252.7	203.0	204.4	246.4		
6					256.9	211.4	193.9	301.0		
7					240.1	225.4	192.5	321.3		
8					192.5	203.7	117.6	259.7		

Water consumption (individuals) : males
 (g/animal/week) group 2 : 10 mg/kg

	Cage no				
	11	12	13	14	15
week: -1	345.8	250.6	163.8	282.8	177.8
1	184.8	187.6	174.3	164.5	186.9
2	229.6	188.3	166.6	163.8	196.7
3	179.2	157.5	169.4	149.8	183.4
4	194.6	158.2	364.7	163.8	239.4

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

285

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 3 : 50 mg/kg

	16	17	18	19	Cage no 20
week: -1	193.2	179.2	173.6	187.6	171.5
1	238.7	196.0	177.1	161.7	205.8
2	219.1	200.9	177.1	163.1	196.7
3	271.6	121.8	163.8	165.2	163.8
4	256.9	208.6	205.1	193.9	247.8

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

group 4 : 200 mg/kg

	21	22	23	24	Cage no 25
week: -1	562.8	183.4	356.3	149.8	203.7
1	205.1	206.5	220.5	160.3	217.7
2	207.9	200.2	217.0	144.9	147.0
3	167.3	158.2	179.2	132.3	182.7
4	214.2	195.3	310.1	175.0	196.0

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

group 5 : 1000 mg/kg

	26	27	28	29	30	31	32	33	34	35
week: -1	469.0	200.2	165.2	130.9	243.6	206.5	175.0	184.8	186.2	334.6
1	214.9	240.8	184.1	176.4	197.4	252.7	227.5	243.6	224.7	251.3
2	241.5	249.9	219.1	210.7	180.6	312.9	244.3	245.7	206.5	240.1
3	177.8	251.3	176.4	188.3	191.8	222.6	215.6	225.4	208.6	224.0
4	207.2	289.8	199.5	389.2	228.2	430.5	455.0	318.5	406.7	311.5

recovery

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

286

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 5 : 1000 mg/kg

		26	27	28	29	30	31	32	33	34	35
week:	5					228.2	259.0	245.0	213.5	268.1	
	6					283.5	291.9	282.8	205.1	275.8	
	7					318.5	224.0	247.8	161.7	403.9	
	8					142.1	180.6	194.6	161.0	245.0	

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 1 : 0 mg/kg

	36	37	38	39	Cage no		42	43	44	45
					40	41				
week: -1	194.6	240.1	149.8	517.3	259.0	161.0	199.5	580.3	198.8	160.3
1	189.0	172.2	126.0	165.2	117.6	142.1	133.7	172.9	156.8	105.7
2	184.1	261.8	119.7	159.6	114.8	111.3	123.2	159.6	210.7	106.4
3	134.4	136.5	149.1	127.4	94.50	134.4	158.2	180.6	180.6	130.9
4	147.7	252.7	302.4	177.8	158.9	399.0	158.2	298.9	214.2	164.5
recovery										
week: 5					157.5		176.4	203.7	224.7	168.0
6					168.0		169.4	198.8	206.5	156.8
7					170.8		174.3	242.9	188.3	226.1
8					140.0		118.3	199.5	172.2	152.6

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

group 2 : 10 mg/kg

	46	47	48	Cage no	
				49	50
week: -1	306.6	287.7	187.6	189.0	149.8
1	133.7	143.5	142.1	140.0	135.1
2	84.70		128.1	146.3	105.0
3	112.0		138.6	158.2	138.6
4	140.7		152.6	125.3	155.4

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

group 3 : 50 mg/kg

	51	52	53	54	Cage no 55
week: -1	207.2	149.8	199.5	340.9	212.8
1	126.0	149.8	121.1	128.8	167.3
2	142.8	137.2	133.7	132.3	168.7
3	117.6	154.0	104.3	130.2	182.0
4	151.2	126.0	130.2	322.7	241.5

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

group 4 : 200 mg/kg

	56	57	58	59	Cage no 60
week: -1	199.5	217.0	119.0	157.5	141.4
1	141.4	157.5	148.4	121.1	123.2
2	118.3	123.9	125.3	89.95	144.9
3	112.0	172.2	83.30	123.2	112.0
4	157.5	185.5	279.3	181.3	114.1

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

group 5 : 1000 mg/kg

	61	62	63	64	Cage no		67	68	69	70
					65	66				
week: -1	193.9	158.9	156.1	164.5	200.9	189.7	227.5	170.1	149.8	189.7
1	128.1	121.1	139.3	133.7	149.1	177.8	159.6	152.6	105.0	170.8
2	122.5	136.5	100.8	112.7	170.1	189.7	156.1	176.4	113.4	189.7
3	140.0	113.4	127.4	128.8	81.20	128.1	130.9	142.1	87.50	143.5
4	339.5	190.4	256.2	199.5	170.8	247.1	182.7	193.9	149.8	170.8

recovery

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

289

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

group 5 : 1000 mg/kg

		Cage no									
		61	62	63	64	65	66	67	68	69	70
week:	5					207.9	259.0	237.3		137.9	172.9
	6					196.0	210.7	178.5		126.7	172.2
	7					153.3	184.1	200.9		123.2	192.5
	8					146.3	172.9	149.1		101.5	117.6

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9.8. Hematology (individuals)

Hematology (individuals): males

group 1
 0 mg/kg

		Animal no							
		1	3	4	5	6	7	8	9
RBC (T/l)									
week:	5	7.950	7.570	8.210	7.940	8.070	8.260	7.670	7.620
	9					8.460	8.630	8.850	8.410
Hb (mmol/l)									
week:	5	9.300	9.300	9.500	9.800	9.500	9.900	9.000	9.200
	9					9.800	10.10	9.800	9.700
Hct (l)									
week:	5	0.439	0.463	0.461	0.482	0.475	0.492	0.439	0.451
	9					0.478	0.501	0.492	0.500
MCV (fl)									
week:	5	55.30	61.20	56.20	60.80	58.90	59.50	57.30	59.10
	9					56.50	58.10	55.50	59.40
RDW (l)									
week:	5	0.142	0.115	0.141	0.111	0.118	0.120	0.119	0.108
	9					0.149	0.124	0.134	0.120
MCH (fmol)									
week:	5	1.170	1.220	1.150	1.230	1.180	1.200	1.170	1.210
	9					1.160	1.170	1.100	1.150
MCHC (mmol/l)									
week:	5	21.15	19.98	20.49	20.27	20.09	20.14	20.37	20.41
	9					20.47	20.20	19.89	19.36

Hematology (individuals): males

group 1
 0 mg/kg

		Animal no								
		1	3	4	5	6	7	8	9	
HDW										
(mmol/l)										
week:	5	1.500	1.540	1.650	1.380	1.510	1.830	1.540	1.430	
	9					1.530	1.680	1.500	1.420	
WBC										
(G/l)										
week:	5	16.77	17.29	12.00	15.45	15.56	11.71	9.920	12.49	
	9					13.14	10.52	11.85	13.72	
Neut										
(1)										
week:	5	0.101	0.071	0.127	0.064	0.098	0.091	0.107	0.098	
	9					0.109	0.068	0.080	0.082	
Eos										
(1)										
week:	5	0.011	0.006	0.012	0.005	0.013	0.010	0.007	0.005	
	9					0.013	0.006	0.007	0.006	
Baso										
(1)										
week:	5	0.008	0.008	0.007	0.008	0.009	0.008	0.003	0.007	
	9					0.005	0.006	0.006	0.007	
Lympho										
(1)										
week:	5	0.833	0.875	0.782	0.873	0.822	0.821	0.840	0.842	
	9					0.813	0.868	0.863	0.851	
Mono										
(1)										
week:	5	0.028	0.020	0.042	0.027	0.032	0.045	0.024	0.029	
	9					0.036	0.036	0.027	0.035	
Luc										
(1)										
week:	5	0.020	0.020	0.031	0.023	0.027	0.025	0.020	0.019	
	9					0.024	0.017	0.018	0.018	

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): males

group 1
0 mg/kg

	Animal no								
	1	3	4	5	6	7	8	9	
Neut (G/l)									
week:	5	1.690	1.230	1.520	0.990	1.520	1.070	1.060	1.230
	9				1.430	0.720	0.940		1.130
Eos (G/l)									
week:	5	0.180	0.100	0.140	0.080	0.200	0.120	0.070	0.060
	9				0.180	0.060	0.080		0.090
Baso (G/l)									
week:	5	0.130	0.140	0.080	0.120	0.140	0.090	0.030	0.080
	9				0.070	0.070	0.070		0.100
Lympho (G/l)									
week:	5	13.96	15.13	9.380	13.49	12.79	9.610	8.330	10.52
	9				10.69	9.130	10.23		11.68
Mono (G/l)									
week:	5	0.480	0.350	0.500	0.420	0.500	0.520	0.230	0.360
	9				0.470	0.380	0.320		0.480
Luc (G/l)									
week:	5	0.330	0.350	0.370	0.350	0.410	0.290	0.200	0.240
	9				0.310	0.170	0.210		0.250
Plt (G/l)									
week:	5	1325	1248	1059	1046	1049	1012	879.0	1204
	9					920.0	945.0	803.0	1113
PT (rel. 1)									
week:	5	0.633	0.725	0.777	0.832	0.835	0.751	0.713	0.793
	9					0.840	0.850	0.847	0.852

Hematology (individuals): males

group 2
 10 mg/kg

		Animal no				
		11	12	13	14	15
RBC (T/l) week:	5	7.870	8.400	8.070	8.350	8.220
Hb (mmol/l) week:	5	9.800	10.20	9.700	9.500	9.300
Hct (l) week:	5	0.483	0.500	0.477	0.467	0.452
MCV (fl) week:	5	61.30	59.40	59.10	55.90	55.00
RDW (l) week:	5	0.107	0.133	0.113	0.160	0.116
MCH (fmol) week:	5	1.240	1.210	1.200	1.140	1.130
MCHC (mmol/l) week:	5	20.25	20.40	20.23	20.46	20.59
HDW (mmol/l) week:	5	1.280	1.550	1.490	1.330	1.590
WBC (G/l) week:	5	12.85	16.66	14.14	10.43	10.95
Neut (l) week:	5	0.089	0.050	0.070	0.084	0.099

Hematology (individuals): males

group 2
 10 mg/kg

		Animal no				
		11	12	13	14	15
Eos (1) week:	5	0.008	0.012	0.009	0.010	0.014
Baso (1) week:	5	0.005	0.009	0.007	0.005	0.005
Lympho (1) week:	5	0.841	0.887	0.868	0.855	0.792
Mono (1) week:	5	0.032	0.024	0.027	0.026	0.053
Luc (1) week:	5	0.025	0.018	0.019	0.021	0.037
Neut (G/l) week:	5	1.150	0.840	0.990	0.870	1.080
Eos (G/l) week:	5	0.100	0.190	0.130	0.100	0.150
Baso (G/l) week:	5	0.070	0.160	0.100	0.050	0.060
Lympho (G/l) week:	5	10.80	14.78	12.27	8.910	8.670
Mono (G/l) week:	5	0.410	0.400	0.390	0.270	0.580

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

295

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): males

group 2
10 mg/kg

		11	12	13	14	15
		Animal no				
Luc (G/l)						
week:	5	0.320	0.300	0.260	0.210	0.410
Plt (G/l)						
week:	5	1116	1150	1104	877.0	1032
PT (rel. 1)						
week:	5	0.736	0.727	0.708	0.714	0.778

Hematology (individuals): males

group 3
50 mg/kg

		16	17	18	19	20
		Animal no				
RBC (T/l)						
week:	5	8.150	8.400	7.940	7.950	7.920
Hb (mmol/l)						
week:	5	9.400	9.700	9.200	9.700	9.550
Hct (l)						
week:	5	0.457	0.479	0.476	0.470	0.478
MCV (fl)						
week:	5	56.10	57.00	59.90	59.10	60.35
RDW (l)						
week:	5	0.117	0.130	0.113	0.113	0.121

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

296

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): males

group 3
50 mg/kg

		Animal no				
		16	17	18	19	20
MCH						
(fmol)						
week:	5	1.150	1.160	1.160	1.210	1.205
MCHC						
(mmol/l)						
week:	5	20.57	20.32	19.37	20.56	19.98
HDW						
(mmol/l)						
week:	5	1.390	1.970	1.480	1.490	1.640
WBC						
(G/l)						
week:	5	14.79	15.77	14.25	12.80	20.99
Neut						
(1)						
week:	5	0.179	0.062	0.120	0.072	0.293
Eos						
(1)						
week:	5	0.007	0.015	0.009	0.006	0.013
Baso						
(1)						
week:	5	0.005	0.008	0.008	0.007	0.008
Lympho						
(1)						
week:	5	0.748	0.841	0.817	0.882	0.622
Mono						
(1)						
week:	5	0.033	0.036	0.024	0.015	0.043
Luc						
(1)						
week:	5	0.028	0.038	0.021	0.018	0.023

Hematology (individuals): males

group 3
 50 mg/kg

		16	17	18	19	Animal no 20
Neut (G/l) week: 5	2.640	0.980	1.710	0.920	6.135	
Eos (G/l) week: 5	0.110	0.240	0.130	0.070	0.255	
Baso (G/l) week: 5	0.070	0.130	0.110	0.090	0.170	
Lympho (G/l) week: 5	11.05	13.26	11.65	11.29	13.05	
Mono (G/l) week: 5	0.490	0.560	0.340	0.200	0.895	
Luc (G/l) week: 5	0.420	0.590	0.310	0.230	0.480	
Plt (G/l) week: 5	1045	973.0	1061	1015	1218	
PT (rel. 1) week: 5	0.701	0.814	0.783	0.725	0.946	

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

298

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): males

group 4
200 mg/kg

		21	22	23	24	25
		Animal no				
RBC (T/l) week:	5	8.390	8.880	8.380	7.970	8.200
Hb (mmol/l) week:	5	10.10	10.20	9.800	9.900	9.500
Hct (l) week:	5	0.505	0.504	0.471	0.473	0.467
MCV (fl) week:	5	60.20	56.80	56.20	59.30	56.90
RDW (l) week:	5	0.110	0.111	0.108	0.112	0.125
MCH (fmol) week:	5	1.210	1.150	1.170	1.250	1.160
MCHC (mmol/l) week:	5	20.08	20.26	20.79	21.01	20.42
HDW (mmol/l) week:	5	1.330	1.450	1.450	1.390	2.080
WBC (G/l) week:	5	10.95	15.90	12.84	11.92	15.32
Neut (l) week:	5	0.082	0.072	0.065	0.086	0.094

Hematology (individuals): males

group 4
 200 mg/kg

		Animal no				
		21	22	23	24	25
Eos (1) week:	5	0.006	0.018	0.016	0.005	0.015
Baso (1) week:	5	0.007	0.007	0.006	0.005	0.007
Lympho (1) week:	5	0.852	0.843	0.849	0.849	0.811
Mono (1) week:	5	0.032	0.036	0.043	0.034	0.045
Luc (1) week:	5	0.021	0.023	0.023	0.020	0.028
Neut (G/l) week:	5	0.900	1.150	0.830	1.030	1.450
Eos (G/l) week:	5	0.070	0.290	0.200	0.060	0.230
Baso (G/l) week:	5	0.070	0.120	0.070	0.060	0.110
Lympho (G/l) week:	5	9.330	13.40	10.90	10.12	12.42
Mono (G/l) week:	5	0.350	0.570	0.550	0.410	0.690

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

300

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): males

group 4
200 mg/kg

		Animal no				
		21	22	23	24	25
Luc (G/l)						
week:	5	0.230	0.370	0.290	0.240	0.430
Plt (G/l)						
week:	5	1112	1174	1136	1074	1263
PT (rel. 1)						
week:	5	0.793	0.662	0.619	0.784	0.711

Hematology (individuals): males

group 5
1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
RBC (T/l)											
week:	5	7.870	8.500	8.110	7.990	8.060	7.660	7.880	8.390	8.020	7.960
	9						8.610	7.990	8.910	8.730	8.750
Hb (mmol/l)											
week:	5	9.300	9.700	9.500	9.500	9.200	9.100	9.300	9.500	9.200	9.200
	9						10.10	9.100	9.600	9.800	9.600
Hct (l)											
week:	5	0.464	0.473	0.461	0.462	0.461	0.451	0.467	0.467	0.459	0.459
	9						0.492	0.451	0.477	0.485	0.488
MCV (fl)											
week:	5	59.00	55.70	56.90	57.80	57.20	58.90	59.20	55.70	57.20	57.70
	9						57.20	56.40	53.50	55.50	55.70

Hematology (individuals): males

group 5
 1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
RDW	(1)										
week:	5	0.110	0.114	0.117	0.115	0.113	0.121	0.113	0.118	0.121	0.121
	9						0.126	0.125	0.128	0.125	0.127
MCH	(fmol)										
week:	5	1.190	1.140	1.170	1.180	1.140	1.190	1.180	1.130	1.150	1.160
	9						1.170	1.130	1.080	1.120	1.100
MCHC	(mmol/l)										
week:	5	20.08	20.50	20.52	20.47	19.94	20.27	20.00	20.29	20.10	20.13
	9						20.44	20.09	20.17	20.23	19.77
HDW	(mmol/l)										
week:	5	1.530	1.470	1.490	1.480	1.570	1.600	1.350	1.520	1.850	1.620
	9						1.480	1.410	1.420	1.650	1.520
WBC	(G/l)										
week:	5	19.41	16.89	15.24	10.96	11.49	17.07	13.93	15.80	16.11	14.42
	9						16.95	13.17	17.55	14.13	13.21
Neut	(1)										
week:	5	0.078	0.059	0.049	0.112	0.087	0.066	0.096	0.102	0.142	0.120
	9						0.065	0.087	0.112	0.105	0.087
Eos	(1)										
week:	5	0.011	0.011	0.011	0.013	0.013	0.013	0.009	0.009	0.006	0.015
	9						0.011	0.011	0.018	0.007	0.014
Baso	(1)										
week:	5	0.007	0.007	0.006	0.005	0.005	0.008	0.008	0.009	0.008	0.008
	9						0.009	0.006	0.006	0.006	0.006

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): males

group 5
1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
Lympho (1)											
week:	5	0.859	0.863	0.882	0.818	0.854	0.867	0.842	0.804	0.768	0.805
	9						0.864	0.855	0.788	0.806	0.836
Mono (1)											
week:	5	0.026	0.036	0.030	0.035	0.023	0.028	0.023	0.038	0.045	0.033
	9						0.028	0.027	0.030	0.048	0.040
Luc (1)											
week:	5	0.018	0.025	0.022	0.016	0.018	0.018	0.022	0.038	0.030	0.020
	9						0.022	0.015	0.045	0.027	0.018
Neut (G/l)											
week:	5	1.510	1.000	0.750	1.230	1.010	1.120	1.340	1.620	2.290	1.730
	9						1.110	1.140	1.960	1.480	1.140
Eos (G/l)											
week:	5	0.220	0.180	0.160	0.150	0.150	0.220	0.120	0.140	0.100	0.220
	9						0.190	0.140	0.320	0.110	0.180
Baso (G/l)											
week:	5	0.140	0.130	0.090	0.060	0.060	0.130	0.100	0.150	0.130	0.110
	9						0.160	0.070	0.110	0.080	0.080
Lympho (G/l)											
week:	5	16.68	14.57	13.44	8.970	9.810	14.80	11.73	12.71	12.38	11.61
	9						14.65	11.26	13.83	11.39	11.05
Mono (G/l)											
week:	5	0.510	0.600	0.460	0.390	0.260	0.480	0.330	0.590	0.730	0.470
	9						0.470	0.350	0.530	0.670	0.520

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

303

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): males

group 5
1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
Luc (G/l)	week: 5	0.360	0.420	0.330	0.180	0.210	0.310	0.310	0.590	0.490	0.280
	9					0.370	0.190	0.790	0.390	0.230	
Plt (G/l)	week: 5	1200	1102	1168	1054	969.0	1249	1284	1179	950.0	1195
	9					1068	1020	1023	740.0	1060	
PT (rel. 1)	week: 5	0.653	0.863	0.569	0.793	0.447	0.771	0.778	0.688	0.566	0.720
	9					0.842	0.764	0.798	0.781	0.801	

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

		Animal no									
		36	37	38	39	40	41	42	43	44	45
RBC (T/l)											
week:	5	7.860	7.660	7.950	7.960	7.870	8.210	8.660	8.040	8.550	8.190
	9						8.550	8.630	8.220	8.440	8.470
Hb (mmol/l)											
week:	5	9.300	9.400	9.500	9.400	8.900	9.500	10.10	9.400	9.800	9.600
	9						9.800	9.900	9.500	9.800	9.800
Hct (l)											
week:	5	0.444	0.451	0.457	0.440	0.441	0.458	0.478	0.444	0.471	0.452
	9						0.477	0.479	0.464	0.464	0.477
MCV (fl)											
week:	5	56.40	58.90	57.50	55.30	56.00	55.80	55.30	55.20	55.00	55.20
	9						55.80	55.50	56.40	54.90	56.40
RDW (l)											
week:	5	0.131	0.115	0.130	0.132	0.127	0.114	0.105	0.123	0.115	0.107
	9						0.121	0.116	0.115	0.123	0.118
MCH (fmol)											
week:	5	1.180	1.220	1.190	1.180	1.130	1.150	1.160	1.170	1.150	1.170
	9						1.150	1.150	1.160	1.160	1.150
MCHC (mmol/l)											
week:	5	20.86	20.76	20.75	21.42	20.09	20.70	21.04	21.21	20.88	21.21
	9						20.62	20.69	20.48	21.17	20.43
HDW (mmol/l)											
week:	5	1.270	1.660	1.280	1.310	1.280	1.440	1.240	1.310	1.370	1.350
	9						1.260	1.150	1.110	1.220	1.210

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

305

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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

		Animal no									
		36	37	38	39	40	41	42	43	44	45
WBC (G/l) week:	5	5.670	11.81	7.120	6.040	6.240	11.78	11.05	7.670	8.190	4.220
	9						13.05	12.37	6.890	7.530	6.220
Neut (1) week:	5	0.082	0.067	0.087	0.087	0.197	0.264	0.113	0.085	0.082	0.085
	9						0.164	0.077	0.089	0.121	0.138
Eos (1) week:	5	0.014	0.007	0.017	0.010	0.015	0.012	0.014	0.012	0.014	0.014
	9						0.011	0.007	0.014	0.009	0.014
Baso (1) week:	5	0.006	0.006	0.004	0.007	0.003	0.006	0.006	0.006	0.004	0.005
	9						0.006	0.006	0.004	0.003	0.004
Lympho (1) week:	5	0.849	0.885	0.853	0.862	0.731	0.663	0.823	0.849	0.829	0.846
	9						0.763	0.860	0.850	0.824	0.802
Mono (1) week:	5	0.031	0.017	0.028	0.015	0.037	0.040	0.027	0.028	0.047	0.031
	9						0.037	0.030	0.028	0.030	0.028
Luc (1) week:	5	0.019	0.018	0.011	0.018	0.016	0.014	0.016	0.020	0.024	0.019
	9						0.019	0.019	0.014	0.012	0.014
Neut (G/l) week:	5	0.460	0.790	0.620	0.530	1.230	3.110	1.240	0.650	0.670	0.360
	9						2.140	0.950	0.610	0.910	0.860

Hematology (individuals): females

group 1
 0 mg/kg

		Animal no									
		36	37	38	39	40	41	42	43	44	45
Eos (G/l) week:	5	0.080	0.090	0.120	0.060	0.100	0.150	0.150	0.090	0.110	0.060
	9					0.140	0.090	0.100	0.070	0.080	
Baso (G/l) week:	5	0.030	0.080	0.030	0.040	0.020	0.070	0.070	0.050	0.030	0.020
	9					0.080	0.080	0.030	0.030	0.030	
Lympho (G/l) week:	5	4.810	10.46	6.070	5.210	4.560	7.810	9.100	6.510	6.780	3.570
	9						9.960	10.64	5.860	6.210	4.990
Mono (G/l) week:	5	0.170	0.200	0.200	0.090	0.230	0.470	0.300	0.210	0.380	0.130
	9						0.480	0.370	0.200	0.220	0.170
Luc (G/l) week:	5	0.110	0.210	0.080	0.110	0.100	0.170	0.180	0.160	0.200	0.080
	9						0.250	0.240	0.100	0.090	0.090
Plt (G/l) week:	5	1194	1216	1245	1193	1102	1349	1292	1213	1110	1214
	9						1126	1125	1041	811.0	1134
PT (rel. 1) week:	5	0.942	1.050	0.894	1.005	0.991	1.054	1.017	1.027	0.966	0.981
	9						0.912	0.852	0.953	0.855	0.928

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

307

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): females

group 2
10 mg/kg

		Animal no			
		46	48	49	50
RBC (T/l) week: 5		7.860	7.970	8.040	7.300
Hb (mmol/l) week: 5		9.300	9.200	9.700	8.700
Hct (l) week: 5		0.459	0.443	0.463	0.417
MCV (fl) week: 5		58.40	55.60	57.60	57.00
RDW (l) week: 5		0.121	0.129	0.128	0.121
MCH (fmol) week: 5		1.180	1.150	1.210	1.190
MCHC (mmol/l) week: 5		20.26	20.69	20.92	20.83
HDW (mmol/l) week: 5		1.830	1.330	1.240	1.780
WBC (G/l) week: 5		6.840	4.680	6.340	6.860
Neut (l) week: 5		0.080	0.228	0.096	0.138

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

308

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): females

group 2
10 mg/kg

		Animal no			
		46	48	49	50
Eos (1) week:	5	0.006	0.012	0.015	0.009
Baso (1) week:	5	0.005	0.003	0.004	0.004
Lympho (1) week:	5	0.863	0.712	0.832	0.761
Mono (1) week:	5	0.028	0.029	0.039	0.048
Luc (1) week:	5	0.018	0.017	0.015	0.039
Neut (G/l) week:	5	0.550	1.070	0.610	0.950
Eos (G/l) week:	5	0.040	0.060	0.090	0.060
Baso (G/l) week:	5	0.030	0.010	0.030	0.030
Lympho (G/l) week:	5	5.900	3.330	5.270	5.220
Mono (G/l) week:	5	0.190	0.140	0.250	0.330

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

		46	48	49	50	Animal no
Luc (G/l) week:	5	0.120	0.080	0.090	0.270	
Plt (G/l) week:	5	1082	1068	1289	1012	
PT (rel. 1) week:	5	1.024	0.962	0.994	0.922	

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

		51	52	53	54	55	Animal no
RBC (T/l) week:	5	7.970	8.060	7.640	7.840	7.650	
Hb (mmol/l) week:	5	9.100	9.500	9.000	9.300	9.100	
Hct (l) week:	5	0.441	0.446	0.444	0.439	0.431	
MCV (fl) week:	5	55.30	55.40	58.00	56.00	56.30	
RDW (l) week:	5	0.107	0.126	0.112	0.136	0.137	

Hematology (individuals): females

group 3
 50 mg/kg

		Animal no				
		51	52	53	54	55
MCH						
(fmol)						
week:	5	1.150	1.170	1.180	1.190	1.190
MCHC						
(mmol/l)						
week:	5	20.75	21.22	20.38	21.22	21.14
HDW						
(mmol/l)						
week:	5	1.290	1.320	1.310	1.240	1.440
WBC						
(G/l)						
week:	5	4.920	6.250	8.690	11.58	6.230
Neut						
(1)						
week:	5	0.147	0.081	0.120	0.136	0.201
Eos						
(1)						
week:	5	0.008	0.011	0.007	0.008	0.008
Baso						
(1)						
week:	5	0.003	0.004	0.005	0.006	0.002
Lympho						
(1)						
week:	5	0.777	0.846	0.808	0.781	0.745
Mono						
(1)						
week:	5	0.039	0.039	0.044	0.041	0.028
Luc						
(1)						
week:	5	0.025	0.020	0.016	0.029	0.015

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): females

group 3
50 mg/kg

		Animal no				
		51	52	53	54	55
Neut (G/l) week: 5		0.720	0.510	1.040	1.570	1.250
Eos (G/l) week: 5		0.040	0.070	0.060	0.090	0.050
Baso (G/l) week: 5		0.020	0.020	0.040	0.060	0.010
Lympho (G/l) week: 5		3.820	5.290	7.020	9.040	4.640
Mono (G/l) week: 5		0.190	0.240	0.380	0.470	0.170
Luc (G/l) week: 5		0.120	0.130	0.140	0.340	0.090
Plt (G/l) week: 5		1154	1256	1033	1159	1200
PT (rel. 1) week: 5		0.990	0.891	0.988	0.947	1.020

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

312

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): females

group 4
200 mg/kg

		56	57	58	59	60
		Animal no				
RBC (T/l) week:	5	7.870	8.120	7.700	8.010	6.820
Hb (mmol/l) week:	5	9.600	9.700	8.600	9.600	8.200
Hct (l) week:	5	0.447	0.480	0.425	0.477	0.396
MCV (fl) week:	5	56.90	59.10	55.20	59.50	58.10
RDW (l) week:	5	0.131	0.105	0.145	0.103	0.131
MCH (fmol) week:	5	1.220	1.200	1.120	1.200	1.200
MCHC (mmol/l) week:	5	21.47	20.23	20.22	20.09	20.64
HDW (mmol/l) week:	5	1.240	1.300	1.630	1.250	1.510
WBC (G/l) week:	5	6.670	6.020	7.270	8.850	9.000
Neut (l) week:	5	0.140	0.103	0.119	0.176	0.092

Hematology (individuals): females

group 4
 200 mg/kg

		56	57	58	59	60
		Animal no				
Eos (1) week:	5	0.006	0.015	0.012	0.014	0.020
Baso (1) week:	5	0.003	0.006	0.003	0.005	0.004
Lympho (1) week:	5	0.816	0.820	0.817	0.734	0.827
Mono (1) week:	5	0.022	0.035	0.030	0.041	0.036
Luc (1) week:	5	0.013	0.022	0.020	0.030	0.021
Neut (G/1) week:	5	0.930	0.620	0.870	1.560	0.830
Eos (G/1) week:	5	0.040	0.090	0.080	0.130	0.180
Baso (G/1) week:	5	0.020	0.040	0.020	0.050	0.030
Lympho (G/1) week:	5	5.440	4.940	5.940	6.500	7.440
Mono (G/1) week:	5	0.150	0.210	0.220	0.360	0.330

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Hematology (individuals): females group 4
200 mg/kg

		Animal no				
		56	57	58	59	60
Luc (G/l) week:	5	0.090	0.130	0.140	0.270	0.190
Plt (G/l) week:	5	1156	1149	1180	1289	1160
PT (rel. 1) week:	5	1.044	1.037	0.963	0.908	1.084

Hematology (individuals): females group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
RBC (T/l) week:	5	7.200	7.970	7.490	7.910	8.190	7.960	7.260	8.175	7.910	7.730
	9						8.310	7.450	8.460	8.640	7.970
Hb (mmol/l) week:	5	8.600	8.900	8.900	9.100	9.500	9.100	8.700	9.500	9.200	9.000
	9						9.400	8.900	9.700	10.00	9.500
Hct (l) week:	5	0.415	0.443	0.439	0.460	0.453	0.441	0.422	0.446	0.446	0.438
	9						0.455	0.427	0.473	0.493	0.454
MCV (fl) week:	5	57.60	55.60	58.60	58.10	55.30	55.40	58.10	54.50	56.40	56.70
	9						54.80	57.30	55.90	57.00	56.90

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

315

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): females

group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
RDW	(1)										
week:	5	0.112	0.132	0.118	0.113	0.120	0.110	0.114	0.113	0.110	0.119
	9					0.120	0.135	0.124	0.121	0.119	
MCH	(fmol)										
week:	5	1.190	1.120	1.190	1.160	1.160	1.140	1.200	1.160	1.160	1.160
	9					1.130	1.195	1.150	1.160	1.200	
MCHC	(mmol/l)										
week:	5	20.70	20.19	20.23	19.89	20.97	20.61	20.56	21.25	20.64	20.49
	9					20.63	20.83	20.60	20.31	21.02	
HDW	(mmol/l)										
week:	5	1.430	1.310	1.620	1.280	1.470	1.360	1.610	1.405	1.350	1.620
	9					1.170	1.380	1.220	1.160	1.490	
WBC	(G/l)										
week:	5	8.950	9.350	11.59	12.19	10.13	6.880	6.250	7.680	11.05	7.840
	9					6.330	5.745	5.860	8.340	11.32	
Neut	(1)										
week:	5	0.389	0.090	0.083	0.057	0.053	0.133	0.157	0.243	0.069	0.076
	9					0.130	0.099	0.063	0.187	0.063	
Eos	(1)										
week:	5	0.007	0.010	0.007	0.007	0.003	0.009	0.010	0.015	0.010	0.006
	9					0.009	0.009	0.017	0.010	0.006	
Baso	(1)										
week:	5	0.006	0.007	0.006	0.011	0.009	0.006	0.004	0.006	0.007	0.005
	9					0.002	0.003	0.006	0.005	0.005	

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

316

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): females

group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
Lympho (1)											
week:	5	0.566	0.831	0.860	0.874	0.875	0.767	0.788	0.673	0.869	0.875
	9						0.779	0.850	0.844	0.747	0.871
Mono (1)											
week:	5	0.020	0.042	0.025	0.030	0.034	0.052	0.020	0.044	0.028	0.022
	9						0.057	0.022	0.053	0.035	0.029
Luc (1)											
week:	5	0.013	0.020	0.019	0.021	0.026	0.033	0.021	0.022	0.018	0.016
	9						0.023	0.019	0.017	0.017	0.026
Neut (G/l)											
week:	5	3.480	0.840	0.960	0.690	0.540	0.920	0.980	1.860	0.760	0.600
	9						0.820	0.560	0.370	1.560	0.710
Eos (G/l)											
week:	5	0.060	0.090	0.080	0.080	0.030	0.070	0.060	0.115	0.110	0.040
	9						0.060	0.055	0.100	0.080	0.070
Baso (G/l)											
week:	5	0.050	0.060	0.070	0.140	0.090	0.040	0.020	0.045	0.080	0.040
	9						0.010	0.015	0.030	0.040	0.050
Lympho (G/l)											
week:	5	5.070	7.770	9.970	10.66	8.860	5.280	4.920	5.165	9.600	6.860
	9						4.930	4.875	4.950	6.230	9.860
Mono (G/l)											
week:	5	0.180	0.390	0.290	0.370	0.340	0.350	0.130	0.335	0.300	0.170
	9						0.360	0.125	0.310	0.290	0.330

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

317

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Hematology (individuals): females

group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
Luc (G/l)	week: 5	0.120	0.190	0.210	0.250	0.260	0.230	0.130	0.165	0.200	0.130
	9						0.140	0.105	0.100	0.140	0.290
Plt (G/l)	week: 5	1526	1169	1224	1256	1151	1204	1239	759.0	1313	1116
	9						1039	991.5	1174	697.0	1017
PT (rel. 1)	week: 5	1.139	1.017	0.985	0.928	0.947	0.968	1.050	1.028	0.995	0.889
	9						0.906	0.946	0.941	0.966	0.820

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9.9. Blood chemistry (individuals)

Blood chemistry (individuals): males group 1
0 mg/kg

		Animal no								
		1	3	4	5	6	7	8	9	
Gluc (mmol/l)	week: 5	6.390	6.580	6.970	6.260	7.140	7.320	7.770	8.340	
	9					7.220	8.310	8.430	7.590	
Urea (mmol/l)	week: 5	6.290	5.850	5.030	5.080	6.570	5.670	4.900	4.460	
	9					5.930	6.610	5.470	5.910	
Creat (umol/l)	week: 5	19.20	21.50	21.20	18.00	22.50	18.30	21.10	20.30	
	9					21.40	17.90	20.90	21.10	
Bili-tot (umol/l)	week: 5	1.585	0.935	1.640	1.525	1.270	1.430	1.410	1.240	
	9					1.440	1.780	1.470	2.530	
Prot (g/l)	week: 5	66.20	67.41	66.29	65.87	67.57	68.83	66.01	64.73	
	9					69.69	70.14	71.87	69.88	
Alb (g/l)	week: 5	33.58	33.68	33.02	33.28	34.55	35.81	33.99	32.83	
	9					33.74	35.14	35.79	33.76	
Glob (g/l)	week: 5	32.62	33.73	33.27	32.59	33.02	33.02	32.02	31.90	
	9					35.95	35.00	36.08	36.12	

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

319

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): males

group 1
0 mg/kg

		Animal no							
		1	3	4	5	6	7	8	9
A/G	(1)								
week:	5	1.030	1.000	0.990	1.020	1.050	1.080	1.060	1.030
	9					0.940	1.000	0.990	0.930
Chol	(mmol/l)								
week:	5	1.580	1.730	1.670	1.430	1.870	2.525	1.680	1.870
	9					1.580	2.310	1.790	1.950
Na+	(mmol/l)								
week:	5	146.0	146.1	147.7	147.8	146.6	145.9	145.2	144.7
	9					141.2	143.8	142.7	145.5
K+	(mmol/l)								
week:	5	3.540	3.970	3.260	3.720	3.670	4.000	3.680	3.880
	9					3.870	3.020	3.560	3.100
Ca++	(mmol/l)								
week:	5	2.670	2.660	2.590	2.560	2.650	2.660	2.750	2.590
	9					2.780	2.700	2.800	2.640
Cl-	(mmol/l)								
week:	5	93.60	95.90	98.00	98.90	96.30	96.10	97.80	96.30
	9					99.90	98.30	100.8	98.50
PO4-in	(mmol/l)								
week:	5	2.690	2.260	1.900	1.870	2.060	2.070	2.180	2.080
	9					2.130	2.180	1.810	2.000
ASAT (GOT)	(U/l)								
week:	5	69.50	66.10	71.50	56.50	79.30	64.60	56.70	74.70
	9					61.30	59.30	57.20	114.3

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

320

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): males

group 1
0 mg/kg

		Animal no								
		1	3	4	5	6	7	8	9	
ALAT (GPT) (U/l)										
week:	5	32.10	27.20	29.20	22.80	30.80	30.30	24.30	37.60	
	9					24.90	30.30	26.30	63.35	
ALP (U/l)										
week:	5	160.2	128.2	159.1	131.5	108.9	189.9	139.7	210.0	
	9					82.50	129.0	112.4	137.9	

Blood chemistry (individuals): males

group 2
10 mg/kg

		Animal no				
		11	12	13	14	15
Gluc (mmol/l)						
week:	5	7.290	7.430	6.350	7.350	7.040
Urea (mmol/l)						
week:	5	6.940	6.220	6.680	6.620	7.370
Creat (umol/l)						
week:	5	20.30	20.40	24.20	18.30	23.10
Bili-tot (umol/l)						
week:	5	1.560	1.270	1.285	1.360	1.610
Prot (g/l)						
week:	5	66.81	71.51	64.18	62.06	63.77

Blood chemistry (individuals): males

group 2
 10 mg/kg

		Animal no				
		11	12	13	14	15
Alb (g/l) week:	5	32.53	35.41	33.52	32.73	33.90
Glob (g/l) week:	5	34.28	36.10	30.66	29.33	29.87
A/G (1) week:	5	0.950	0.980	1.090	1.120	1.130
Chol (mmol/l) week:	5	1.760	1.630	1.720	1.520	1.690
Na+ (mmol/l) week:	5	143.1	144.5	150.6	143.7	143.5
K+ (mmol/l) week:	5	3.760	4.190	4.155	4.040	3.870
Ca++ (mmol/l) week:	5	2.640	2.720	2.710	2.580	2.500
Cl- (mmol/l) week:	5	96.00	95.30	99.90	96.60	99.30
PO4-in (mmol/l) week:	5	2.110	2.190	2.220	1.900	1.770
ASAT (GOT) (U/l) week:	5	71.90	67.80	56.20	68.30	63.70

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

322

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): males

group 2
10 mg/kg

		Animal no				
		11	12	13	14	15
ALAT (GPT)						
(U/l)						
week:	5	38.00	27.80	25.40	30.90	32.20
ALP						
(U/l)						
week:	5	121.4	136.9	113.2	139.7	153.0

Blood chemistry (individuals): males

group 3
50 mg/kg

		Animal no				
		16	17	18	19	20
Gluc						
(mmol/l)						
week:	5	6.820	6.520	7.440	8.690	7.240
Urea						
(mmol/l)						
week:	5	6.750	6.090	6.580	6.530	8.450
Creat						
(umol/l)						
week:	5	20.00	21.20	18.40	21.70	22.80
Bili-tot						
(umol/l)						
week:	5	1.390	2.250	1.150	1.340	1.020
Prot						
(g/l)						
week:	5	66.69	66.02	69.26	65.42	68.97
Alb						
(g/l)						
week:	5	35.07	34.39	34.66	33.48	32.90

Blood chemistry (individuals): males

group 3
 50 mg/kg

		Animal no				
		16	17	18	19	20
Glob (g/l)						
week:	5	31.62	31.63	34.60	31.94	36.07
A/G (l)						
week:	5	1.110	1.090	1.000	1.050	0.910
Chol (mmol/l)						
week:	5	1.490	1.870	1.670	1.390	1.890
Na+ (mmol/l)						
week:	5	142.3	141.5	142.7	144.0	142.3
K+ (mmol/l)						
week:	5	4.030	4.090	4.270	3.860	3.930
Ca++ (mmol/l)						
week:	5	2.640	2.580	2.630	2.530	2.640
Cl- (mmol/l)						
week:	5	97.00	97.10	97.00	101.6	95.80
PO4-in (mmol/l)						
week:	5	2.010	2.110	1.950	1.920	2.180
ASAT (GOT) (U/l)						
week:	5	71.00	76.40	43.00	69.70	63.70
ALAT (GPT) (U/l)						
week:	5	39.10	32.80	42.40	29.60	33.30

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

324

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): males

group 3
50 mg/kg

		16	17	18	19	20	Animal no
ALP (U/l) week:	5	180.1	234.0	149.3	170.5	139.1	

Blood chemistry (individuals): males

group 4
200 mg/kg

		21	22	23	24	25	Animal no
Gluc (mmol/l) week:	5	7.010	6.890	7.630	6.490	6.260	
Urea (mmol/l) week:	5	5.540	6.910	5.620	5.400	6.170	
Creat (umol/l) week:	5	25.80	19.70	19.80	17.50	19.40	
Bili-tot (umol/l) week:	5	1.360	1.210	1.220	1.180	1.090	
Prot (g/l) week:	5	68.54	67.48	67.62	66.53	65.58	
Alb (g/l) week:	5	34.73	34.03	34.86	34.96	33.78	
Glob (g/l) week:	5	33.81	33.45	32.76	31.57	31.80	

Blood chemistry (individuals): males

group 4
 200 mg/kg

		21	22	23	24	25
		Animal no				
A/G (1) week:	5	1.030	1.020	1.060	1.110	1.060
Chol (mmol/l) week:	5	2.430	1.480	1.430	1.580	1.540
Na+ (mmol/l) week:	5	145.3	147.6	143.4	143.8	144.4
K+ (mmol/l) week:	5	4.010	4.705	3.820	4.120	3.820
Ca++ (mmol/l) week:	5	2.640	2.720	2.670	2.600	2.660
Cl- (mmol/l) week:	5	93.90	99.70	95.60	97.20	94.90
PO4-in (mmol/l) week:	5	2.110	2.250	1.970	1.750	2.040
ASAT (GOT) (U/l) week:	5	69.20	78.80	71.80	61.90	74.50
ALAT (GPT) (U/l) week:	5	28.90	31.40	38.70	28.00	37.20
ALP (U/l) week:	5	199.5	128.3	162.0	158.8	231.4

28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)
 Test No.: 963103
 Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

326

Blood chemistry (individuals): males group 5
1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
Gluc (mmol/l) week:	5	7.650	7.400	6.290	5.900	6.530	7.640	7.650	6.570	6.990	7.180
	9						7.260	8.180	8.630	8.270	8.040
Urea (mmol/l) week:	5	6.960	5.770	6.630	5.990	4.670	9.250	5.040	5.670	5.010	5.540
	9						8.080	5.410	6.270	6.800	5.780
Creat (umol/l) week:	5	22.60	18.00	21.10	18.30	17.50	24.70	18.40	20.40	19.50	20.30
	9						25.30	20.80	20.60	18.60	24.50
Bili-tot (umol/l) week:	5	1.230	1.140	0.960	1.130	1.090	1.030	0.880	0.990	1.280	0.900
	9						1.460	1.810	1.790	1.770	1.910
Prot (g/l) week:	5	66.22	69.66	66.20	62.79	63.64	64.58	65.94	66.41	65.89	66.06
	9						68.01	69.45	68.57	68.11	65.95
Alb (g/l) week:	5	33.76	35.12	33.46	32.72	33.43	32.89	34.10	33.65	34.29	33.53
	9						34.13	34.96	33.01	34.98	32.89
Glob (g/l) week:	5	32.46	34.54	32.74	30.07	30.21	31.69	31.84	32.76	31.60	32.53
	9						33.88	34.49	35.56	33.13	33.06
A/G (1) week:	5	1.040	1.020	1.020	1.090	1.110	1.040	1.070	1.030	1.090	1.030
	9						1.010	1.010	0.930	1.060	0.990

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

327

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): males

group 5
1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
Chol (mmol/l)	week: 5	1.950	2.310	1.810	1.890	1.610	1.830	1.720	1.540	2.200	1.760
	9					1.760	1.590	1.420	1.850	1.640	
Na+ (mmol/l)	week: 5	141.7	143.8	142.9	144.0	149.9	142.9	147.8	144.3	144.2	143.8
	9					145.4	144.4	144.3	145.1	143.8	
K+ (mmol/l)	week: 5	3.940	4.905	3.940	3.910	4.195	3.670	4.230	3.790	4.330	3.660
	9					3.490	3.450	3.210	3.670	3.470	
Ca++ (mmol/l)	week: 5	2.700	2.790	2.710	2.630	2.590	2.640	2.670	2.690	2.700	2.630
	9					2.730	2.650	2.690	2.680	2.630	
Cl- (mmol/l)	week: 5	92.35	95.60	93.10	90.75	97.30	92.50	97.40	91.20	94.90	93.00
	9					98.50	100.7	97.90	99.70	100.0	
PO4-in (mmol/l)	week: 5	2.090	2.120	2.150	1.710	1.800	2.020	1.960	2.180	1.930	1.920
	9					2.040	1.880	2.120	1.990	1.970	
ASAT (GOT) (U/l)	week: 5	63.90	66.70	70.50	71.80	78.05	56.30	69.70	68.10	73.10	64.20
	9					66.10	93.00	82.40	82.80	92.10	
ALAT (GPT) (U/l)	week: 5	26.50	28.20	26.30	23.20	26.20	28.10	33.70	28.50	33.00	26.30
	9					36.00	42.10	44.80	38.40	32.60	

28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)
 Test No.: 963103
 Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

328

Blood chemistry (individuals): males group 5
1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
ALP (U/l) week:	5	125.4	118.4	133.4	150.0	138.6	112.0	160.1	160.7	154.4	171.0
	9					84.50	121.6	106.9	112.1	116.8	

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Blood chemistry (individuals): females

group 1
 0 mg/kg

		Animal no									
		36	37	38	39	40	41	42	43	44	45
Gluc (mmol/l)	week: 5	6.040	5.880	6.170	7.820	7.220	6.440	6.420	6.100	7.160	6.900
	9						7.270	6.880	6.580	8.910	6.590
Urea (mmol/l)	week: 5	6.500	5.860	8.750	7.190	6.310	7.800	6.810	6.800	5.360	7.170
	9						8.040	8.280	9.120	8.770	9.420
Creat (umol/l)	week: 5	22.30	22.60	29.70	22.20	22.60	23.10	21.10	21.50	18.40	23.30
	9						22.30	23.00	23.30	24.20	25.50
Bili-tot (umol/l)	week: 5	1.830	1.530	1.910	1.840	1.830	1.190	1.380	1.740	1.460	1.320
	9						1.780	1.770	1.780	1.540	1.295
Prot (g/l)	week: 5	66.83	67.86	64.28	69.81	70.37	69.41	68.31	69.57	65.57	68.85
	9						66.11	67.37	70.73	64.48	70.09
Alb (g/l)	week: 5	35.65	35.06	35.05	37.84	36.95	35.39	35.73	37.34	35.20	38.38
	9						33.10	35.25	37.34	33.28	37.86
Glob (g/l)	week: 5	31.18	32.80	29.23	31.97	33.42	34.02	32.58	32.23	30.37	30.47
	9						33.01	32.12	33.39	31.20	32.23
A/G (1)	week: 5	1.140	1.070	1.200	1.180	1.110	1.040	1.100	1.160	1.160	1.260
	9						1.000	1.100	1.120	1.070	1.170

Blood chemistry (individuals): females

group 1
 0 mg/kg

		Animal no									
		36	37	38	39	40	41	42	43	44	45
Chol (mmol/l)	week: 5	1.950	2.430	2.010	1.980	1.480	1.750	1.990	2.210	1.700	1.770
	9						1.770	1.680	1.990	1.340	1.800
Na+ (mmol/l)	week: 5	143.2	142.8	140.0	144.0	144.3	143.0	143.3	144.2	143.1	144.6
	9						144.0	143.7	143.2	141.1	142.1
K+ (mmol/l)	week: 5	4.090	3.610	3.670	3.760	3.510	3.720	3.740	3.370	3.640	3.420
	9						3.000	3.110	3.130	3.780	2.770
Ca++ (mmol/l)	week: 5	2.600	2.630	2.530	2.620	2.520	2.660	2.630	2.640	2.680	2.540
	9						2.600	2.630	2.640	2.580	2.570
Cl- (mmol/l)	week: 5	96.00	99.40	97.40	99.40	99.50	95.40	97.30	98.70	97.10	98.40
	9						102.3	101.5	104.2	100.2	99.70
PO4-in (mmol/l)	week: 5	1.810	1.690	1.510	1.520	1.550	2.170	1.980	1.430	1.810	1.680
	9						1.720	1.630	1.140	1.610	1.330
ASAT (GOT) (U/l)	week: 5	72.20	60.90	70.60	55.90	70.00	82.20	71.00	61.00	71.30	66.20
	9						75.70	88.00	62.00	90.60	67.10
ALAT (GPT) (U/l)	week: 5	28.00	29.90	27.60	24.10	27.90	29.20	34.60	20.10	22.90	23.90
	9						24.10	41.50	23.40	25.50	30.90

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

331

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): females

group 1
0 mg/kg

		Animal no									
		36	37	38	39	40	41	42	43	44	45
ALP (U/l) week:	5	104.2	130.0	121.0	113.7	79.00	111.4	134.5	75.70	120.0	95.20
	9						78.10	75.80	54.40	93.00	66.70

Blood chemistry (individuals): females

group 2
10 mg/kg

		Animal no			
		46	48	49	50
Gluc (mmol/l) week:	5	7.260	7.060	5.800	6.780
Urea (mmol/l) week:	5	6.830	6.060	6.620	7.370
Creat (umol/l) week:	5	22.20	22.50	24.20	25.90
Bili-tot (umol/l) week:	5	1.990	1.210	1.690	1.230
Prot (g/l) week:	5	69.21	67.02	66.92	71.02
Alb (g/l) week:	5	36.67	36.71	36.06	36.23

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

332

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): females

group 2
10 mg/kg

		Animal no			
		46	48	49	50
Glob (g/l)					
week:	5	32.54	30.31	30.86	34.79
A/G (1)					
week:	5	1.130	1.210	1.170	1.040
Chol (mmol/l)					
week:	5	2.080	1.710	1.820	1.760
Na+ (mmol/l)					
week:	5	145.3	143.0	142.8	145.0
K+ (mmol/l)					
week:	5	3.090	3.310	3.480	3.300
Ca++ (mmol/l)					
week:	5	2.390	2.390	2.610	2.630
Cl- (mmol/l)					
week:	5	99.50	98.70	99.20	103.0
PO4-in (mmol/l)					
week:	5	1.780	1.390	1.660	1.540
ASAT (GOT) (U/l)					
week:	5	84.10	61.60	67.40	84.50
ALAT (GPT) (U/l)					
week:	5	25.90	20.30	27.60	29.50

Blood chemistry (individuals): females

group 2
10 mg/kg

		46	48	49	50	Animal no
ALP (U/l) week:	5	100.0	98.50	90.10	70.75	

Blood chemistry (individuals): females

group 3
50 mg/kg

		51	52	53	54	55	Animal no
Gluc (mmol/l) week:	5	6.710	5.860	7.220	6.420	7.510	
Urea (mmol/l) week:	5	5.650	7.270	5.930	6.110	5.600	
Creat (umol/l) week:	5	21.20	25.60	23.30	20.00	21.90	
Bili-tot (umol/l) week:	5	1.420	1.670	1.320	0.960	1.360	
Prot (g/l) week:	5	69.43	64.41	65.61	67.00	68.42	
Alb (g/l) week:	5	35.40	34.87	35.91	33.53	36.23	
Glob (g/l) week:	5	34.03	29.54	29.70	33.47	32.19	

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

334

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): females

group 3
50 mg/kg

		Animal no				
		51	52	53	54	55
A/G (1)						
week:	5	1.040	1.180	1.210	1.000	1.130
Chol (mmol/l)						
week:	5	1.880	1.970	2.010	1.890	2.250
Na+ (mmol/l)						
week:	5	144.8	146.4	145.0	142.9	145.5
K+ (mmol/l)						
week:	5	3.460	3.960	3.740	3.410	3.300
Ca++ (mmol/l)						
week:	5	2.470	2.370	2.530	2.560	2.430
Cl- (mmol/l)						
week:	5	98.90	100.3	99.40	97.40	99.80
PO4-in (mmol/l)						
week:	5	1.850	1.850	1.630	2.040	1.225
ASAT (GOT) (U/l)						
week:	5	66.10	84.40	69.40	63.10	64.00
ALAT (GPT) (U/l)						
week:	5	22.80	24.70	22.40	30.60	22.70
AlP (U/l)						
week:	5	124.7	117.5	112.5	95.60	149.8

Blood chemistry (individuals): females

group 4
 200 mg/kg

		56	57	58	59	60
		Animal no				
Gluc (mmol/l) week: 5		7.350	8.650	6.000	6.310	5.940
Urea (mmol/l) week: 5		7.550	6.750	6.170	9.910	7.210
Creat (umol/l) week: 5		25.90	25.10	22.80	24.20	29.30
Bili-tot (umol/l) week: 5		1.350	1.110	1.700	1.210	1.760
Prot (g/l) week: 5		69.53	68.74	61.79	67.92	65.86
Alb (g/l) week: 5		37.07	36.55	33.79	37.00	33.22
Glob (g/l) week: 5		32.46	32.19	28.00	30.92	32.64
A/G (l) week: 5		1.140	1.140	1.210	1.200	1.020
Chol (mmol/l) week: 5		1.950	2.130	2.210	1.560	1.720
Na+ (mmol/l) week: 5		148.3	144.9	144.6	142.0	142.5

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

336

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): females

group 4
200 mg/kg

		Animal no				
		56	57	58	59	60
K+	(mmol/l)					
week:	5	3.220	4.365	3.530	3.350	3.370
Ca++	(mmol/l)					
week:	5	2.575	2.370	2.400	2.570	2.590
Cl-	(mmol/l)					
week:	5	101.4	98.00	100.5	96.60	99.50
PO4-in	(mmol/l)					
week:	5	1.500	1.600	1.630	1.760	1.670
ASAT (GOT)	(U/l)					
week:	5	55.90	84.10	70.50	59.10	76.50
ALAT (GPT)	(U/l)					
week:	5	26.20	28.60	22.70	20.20	25.10
ALP	(U/l)					
week:	5	144.6	168.2	71.60	82.00	110.6

Blood chemistry (individuals): females

group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
Gluc	(mmol/l)										
week:	5	7.200	6.570	6.510	5.910	6.040	6.660	6.920	7.620	6.130	7.050
	9						6.710	10.76	7.650	6.400	7.520

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

337

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): females

group 5
1000 mg/kg

	Animal no										
	61	62	63	64	65	66	67	68	69	70	
Urea (mmol/l)											
week:	5	6.700	10.33	7.960	9.430	8.680	7.760	6.900	10.46	8.830	6.960
	9						8.100	6.620	7.320	8.710	8.720
Creat (umol/l)											
week:	5	23.60	25.40	22.50	25.60	24.50	23.70	25.80	28.87	24.00	22.30
	9						24.20	24.20	25.00	23.00	20.90
Bili-tot (umol/l)											
week:	5	1.200	1.790	1.740	1.290	1.560	1.100	1.520	1.680	1.090	0.960
	9						1.900	2.120	1.680	1.980	2.110
Prot (g/l)											
week:	5	68.97	69.15	69.13	64.84	65.49	65.89	69.69	67.79	66.37	61.80
	9						67.48	69.89	69.55	71.15	65.14
Alb (g/l)											
week:	5	33.54	37.97	37.87	35.65	35.23	34.35	37.27	36.99	35.92	34.49
	9						34.46	36.81	38.03	36.48	35.00
Glob (g/l)											
week:	5	35.43	31.18	31.26	29.19	30.26	31.54	32.42	30.80	30.45	27.31
	9						33.02	33.08	31.52	34.67	30.14
A/G (1)											
week:	5	0.950	1.220	1.210	1.220	1.160	1.090	1.150	1.200	1.180	1.260
	9						1.040	1.110	1.210	1.050	1.160
Chol (mmol/l)											
week:	5	2.090	1.920	1.610	1.850	1.950	2.700	2.640	1.840	1.820	1.560
	9						2.250	2.510	1.760	2.080	1.520

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

338

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Blood chemistry (individuals): females

group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
Na+	(mmol/l)										
	week:	5	144.6	141.9	144.5	143.9	143.2	143.0	145.2	144.7	141.6
		9					141.3	143.2	144.0	144.0	144.7
K+	(mmol/l)										
	week:	5	3.450	3.710	3.520	4.310	3.640	3.600	3.340	4.240	3.840
		9					3.430	3.210	3.290	3.380	3.110
Ca++	(mmol/l)										
	week:	5	2.630	2.660	2.630	2.550	2.530	2.530	2.610	2.580	2.600
		9					2.510	2.570	2.620	2.690	2.560
Cl-	(mmol/l)										
	week:	5	98.30	95.50	97.90	98.00	100.1	97.50	100.5	94.80	96.60
		9					103.4	103.0	102.6	99.80	103.5
PO4-in	(mmol/l)										
	week:	5	1.710	1.550	1.400	1.750	1.610	1.660	1.630	1.840	1.720
		9					1.130	1.080	1.100	1.360	1.430
ASAT (GOT)	(U/l)										
	week:	5	77.30	74.10	61.10	81.60	68.20	64.70	54.70	75.80	77.40
		9					64.80	61.30	57.20	73.20	74.50
ALAT (GPT)	(U/l)										
	week:	5	28.20	23.30	24.70	28.50	25.00	23.30	18.25	20.80	26.90
		9					27.20	24.50	18.10	31.90	28.40
ALP	(U/l)										
	week:	5	89.00	144.5	104.6	151.7	165.3	126.9	134.0	83.60	156.6
		9					88.90	96.70	49.30	104.8	92.00

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

9.10. Urine analysis (individuals)

Urine analysis (individuals): males

group 1
0 mg/kg

		Animal no								
		1	3	4	5	6	7	8	9	
Volume (ml)	week: 5	4.800	7.000	2.300	4.900	7.500	6.300	4.400	4.300	
	9					4.600	6.700	4.500	3.800	
Rel dens (1)	week: 5	1.042	1.030	1.040	1.035	1.032	1.031	1.029	1.047	
	9					1.039	1.030	1.044	1.048	
pH (1)	week: 5	6.000	7.000	5.000	6.000	6.500	6.500	6.500	6.000	
	9					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	0.250	0.750	
	9					0.250	0.250	0.250	0.750	
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	1.500	0.500	0.500	0.500	0.000	0.500	0.500	0.500	
	9					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	
	9					0.000	0.000	0.000	0.000	

Urine analysis (individuals): males group 1
0 mg/kg

		Animal no							
		1	3	4	5	6	7	8	9
BIL (umol/l)									
week:	5	0.000	0.000	0.000	17.00	0.000	0.000	0.000	0.000
	9					0.000	0.000	0.000	0.000
ERY (per ul)									
week:	5	10.00	10.00	10.00	10.00	25.00	10.00	10.00	10.00
	9					10.00	0.000	10.00	10.00

Urine analysis (individuals): males group 2
10 mg/kg

		Animal no				
		11	12	13	14	15
Volume (ml)						
week:	5	6.900	6.400	4.900	3.700	5.500
Rel dens (1)						
week:	5	1.033	1.028	1.030	1.036	1.037
pH (1)						
week:	5	6.500	7.000	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

Urine analysis (individuals): males

group 2
 10 mg/kg

		Animal no				
		11	12	13	14	15
KET (mmol/l)						
week:	5	0.500	0.500	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	17.00	0.000	0.000	17.00	17.00
ERY (per ul)						
week:	5	50.00	10.00	10.00	10.00	10.00

Urine analysis (individuals): males

group 3
 50 mg/kg

		Animal no				
		16	17	18	19	20
Volume (ml)						
week:	5	4.900	8.700	6.300	3.400	4.300
Rel dens (1)						
week:	5	1.037	1.032	1.032	1.062	1.044
pH (1)						
week:	5	6.500	6.500	6.500	6.500	6.500
PRO (g/l)						
week:	5	0.750	0.250	0.750	0.750	0.750

Urine analysis (individuals): males

group 3
 50 mg/kg

		Animal no				
		16	17	18	19	20
GLU (mmol/l)						
week:	5	0.000	0.000	0.000	0.000	0.000
KET (mmol/l)						
week:	5	0.500	0.500	0.000	1.500	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	17.00	0.000	17.00
ERY (per ul)						
week:	5	10.00	10.00	10.00	10.00	25.00

Urine analysis (individuals): males

group 4
 200 mg/kg

		Animal no				
		21	22	23	24	25
Volume (ml)						
week:	5	7.700	5.100	5.900	4.000	2.600
Rel dens (1)						
week:	5	1.027	1.039	1.039	1.050	1.039
pH (1)						
week:	5	7.000	6.500	6.500	6.500	6.000

Urine analysis (individuals): males

group 4
200 mg/kg

		21	22	23	24	25
		Animal no				
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	1.500
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	0.000
ERY (per ul)						
week:	5	10.00	10.00	10.00	10.00	25.00

Urine analysis (individuals): males

group 5
1000 mg/kg

		26	27	28	29	30	31	32	33	34	35
		Animal no									
Volume (ml)											
week:	5	5.200	2.600	3.000	4.100	5.300	6.000	4.400	3.800	4.400	3.800
	9						5.600	5.000	3.800	5.300	3.100

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

344

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Urine analysis (individuals): males

group 5
1000 mg/kg

		Animal no									
		26	27	28	29	30	31	32	33	34	35
Rel dens											
(1)											
week:	5	1.044	1.064	1.028	1.048	1.041	1.040	1.032	1.060	1.046	1.027
	9						1.029	1.026	1.045	1.039	1.067
pH											
(1)											
week:	5	5.000	6.500	6.000	6.500	6.500	6.500	5.000	5.000	6.500	5.000
	9						6.500	6.500	6.000	7.000	6.500
PRO											
(g/l)											
week:	5	0.750	0.750	0.250	0.750	0.750	0.750	0.750	0.750	0.750	0.750
	9						0.250	0.250	0.750	0.250	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	0.000
	9						0.000	0.000	0.000	0.000	0.000
KET											
(mmol/l)											
week:	5	0.500	0.500	1.500	0.500	0.500	0.000	1.500	0.500	0.500	0.500
	9						0.000	0.500	1.500	0.000	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
BIL											
(umol/l)											
week:	5	17.00	0.000	0.000	0.000	0.000	17.00	0.000	0.000	0.000	0.000
	9						0.000	0.000	0.000	0.000	0.000
ERY											
(per ul)											
week:	5	0.000	10.00	10.00	0.000	0.000	10.00	10.00	0.000	10.00	10.00
	9						0.000	10.00	10.00	0.000	10.00

Urine analysis (individuals): females

group 1
 0 mg/kg

		Animal no									
		36	37	38	39	40	41	42	43	44	45
Volume (ml)	week: 5	3.300	2.500	2.700	4.200	3.200	4.300	4.300	2.500	3.300	2.500
	9					1.500	1.800	1.300	1.300	1.600	
Rel dens (1)	week: 5	1.040	1.045	1.048	1.036	1.046	1.038	1.035	1.042	1.036	1.015
	9					1.064	1.051	1.077	1.068	1.060	
pH (1)	week: 5	6.000	5.000	5.000	6.000	6.500	6.000	6.500	6.000	6.500	5.000
	9						7.000	6.000	5.000	6.000	6.000
PRO (g/l)	week: 5	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.750	0.750
	9						0.750	0.750	0.750	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	0.500	0.500	0.500	0.500	1.500	0.500	0.500	0.500	0.500	0.500
	9						0.500	0.500	1.500	1.500	0.500
UBG (umol/l)	week: 5	0.000	0.000	0.000	0.000	17.00	17.00	0.000	17.00	0.000	17.00
	9						17.00	0.000	17.00	17.00	0.000
BIL (umol/l)	week: 5	0.000	0.000	17.00	0.000	0.000	17.00	17.00	0.000	0.000	0.000
	9						17.00	0.000	0.000	0.000	0.000

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

346

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Urine analysis (individuals): females

group 1
0 mg/kg

		Animal no									
		36	37	38	39	40	41	42	43	44	45
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	0.000	10.00	0.000	0.000	

Urine analysis (individuals): females

group 2
10 mg/kg

		Animal no			
		46	48	49	50
Volume (ml)	week: 5	2.800	2.900	3.200	4.800
Rel dens (1)	week: 5	1.049	1.043	1.048	1.034
pH (1)	week: 5	6.500	6.500	6.000	6.500
PRO (g/l)	week: 5	0.750	0.750	0.750	0.250
GLU (mmol/l)	week: 5	0.000	0.000	0.000	0.000
KET (mmol/l)	week: 5	1.500	0.500	0.500	0.500

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

347

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Urine analysis (individuals): females

group 2
10 mg/kg

		46	48	49	50	Animal no
UBG (umol/l) week: 5		17.00	0.000	17.00	0.000	
BIL (umol/l) week: 5		17.00	0.000	17.00	0.000	
ERY (per ul) week: 5		10.00	25.00	10.00	10.00	

Urine analysis (individuals): females

group 3
50 mg/kg

		51	52	53	54	55	Animal no
Volume (ml) week: 5		4.500	4.000	4.000	2.400	3.000	
Rel dens (1) week: 5		1.040	1.038	1.034	1.045	1.039	
pH (1) week: 5		6.500	6.500	6.500	5.000	6.500	
PRO (g/l) week: 5		0.750	0.250	0.250	0.750	0.250	
GLU (mmol/l) week: 5		0.000	0.000	0.000	0.000	0.000	

Urine analysis (individuals): females

group 3
50 mg/kg

		51	52	53	54	55	Animal no
KET (mmol/l)							
week:	5	0.500	0.500	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	17.00	17.00	0.000	0.000	0.000	
ERY (per ul)							
week:	5	10.00	10.00	10.00	50.00	10.00	

Urine analysis (individuals): females

group 4
200 mg/kg

		56	57	58	59	60	Animal no
Volume (ml)							
week:	5	4.000	3.100	2.900	2.200	1.200	
Rel dens (l)							
week:	5	1.029	1.045	1.044	1.047	1.077	
pH (l)							
week:	5	7.000	5.000	6.000	6.000	5.000	
PRO (g/l)							
week:	5	0.250	0.750	0.750	0.750	0.750	

Urine analysis (individuals): females

group 4
200 mg/kg

		Animal no				
		56	57	58	59	60
GLU (mmol/l)						
week:	5	0.000	0.000	0.000	0.000	0.000
KET (mmol/l)						
week:	5	0.000	0.500	0.500	0.500	0.500
UBG (umol/l)						
week:	5	0.000	17.00	17.00	0.000	17.00
BIL (umol/l)						
week:	5	0.000	0.000	17.00	0.000	0.000
ERY (per ul)						
week:	5	0.000	10.00	10.00	10.00	10.00

Urine analysis (individuals): females

group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
Volume (ml)											
week:	5	6.000	2.600	3.100	2.300	5.800	2.400	3.300	6.400	2.100	3.500
	9						2.000	5.800	3.500	1.200	2.300
Rel dens (l)											
week:	5	1.029	1.063	1.048	1.063	1.037	1.045	1.039	1.022	1.035	1.042
	9						1.084	1.027	1.038	1.038	1.062

Urine analysis (individuals): females group 5
1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
pH (1)	week: 5	6.500	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000
	9					6.000	7.000	6.000	5.000	6.000	
PRO (g/l)	week: 5	0.250	0.750	0.750	0.750	0.250	0.750	0.250	0.250	0.750	0.750
	9					0.750	0.250	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	0.000
	9					0.000	0.000	0.000	0.000	0.000	0.000
KET (mmol/l)	week: 5	0.500	0.500	0.000	0.500	0.000	0.500	0.000	0.000	0.500	0.500
	9					1.500	0.000	0.000	0.500	0.500	
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					17.00	0.000	0.000	17.00	0.000	
BIL (umol/l)	week: 5	0.000	0.000	0.000	0.000	17.00	17.00	0.000	0.000	17.00	0.000
	9					0.000	0.000	0.000	0.000	0.000	
ERY (per ul)	week: 5	10.00	25.00	10.00	10.00	10.00	10.00	10.00	0.000	150.0	10.00
	9					150.0	0.000	10.00	10.00	0.000	

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Urine analysis (individuals): males group 1
0 mg/kg

		1	3	4	5	6	7	8	9	
		Animal no								
Color (choice)										
week: 5		N	N	N	N	N	N	N	N	
9										

Urine analysis (individuals): males group 2
10 mg/kg

		11	12	13	14	15
		Animal no				
Color (choice)						
week: 5		N	N	N	N	N

Urine analysis (individuals): males group 3
50 mg/kg

		16	17	18	19	20
		Animal no				
Color (choice)						
week: 5		N	N	N	N	N

Urine analysis (individuals): males group 4
200 mg/kg

		21	22	23	24	25	Animal no
Color (choice) week: 5	N	N	N	N	N	N	

Urine analysis (individuals): males group 5
1000 mg/kg

		26	27	28	29	30	31	32	33	34	35	Animal no
Color (choice) week: 5	N	N	N	N	N	N	N	N	N	N	N	
Color (choice) week: 9	N	N	N	N	N	N	N	N	N	N	N	

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Urine analysis (individuals): females

group 1
0 mg/kg

		36	37	38	39	40	41	42	43	44	45
		Animal no									
Color (choice) week:	5	N	N	N	N	N	N	N	N	N	N
	9										

Urine analysis (individuals): females

group 2
10 mg/kg

		46	48	49	50
		Animal no			
Color (choice) week:	5	N	N	N	N

Urine analysis (individuals): females

group 3
50 mg/kg

		51	52	53	54	55
		Animal no				
Color (choice) week:	5	N	N	N	N	N

Urine analysis (individuals): females group 4
 200 mg/kg

		Animal no				
		56	57	58	59	60
Color (choice) week:	5	N	N	N	N	N

Urine analysis (individuals): females group 5
 1000 mg/kg

		Animal no									
		61	62	63	64	65	66	67	68	69	70
Color (choice) week:	5	N	N	N	N	N	N	N	N	N	N
	9										

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9.11. Organ weights and ratios (individuals)

9.11.1. Organ weights (individuals)

Organ weights (individuals) : males

group 1 : 0 mg/kg week 5

	Animal no			
	1	3	4	5
Body (g)	331.7	386.8	335.6	330.7
Brain (g)	2.060	2.308	2.253	2.231
Heart (g)	1.121	1.379	1.321	1.076
Liver (g)	14.95	17.65	14.38	14.23
Kidney (both) (g)	2.413	2.343	2.484	2.360
Adrenal (both) (mg)	74.30	94.30	85.40	74.00
Thymus (mg)	677.1	795.1	672.6	1213
Testis (both) (g)	3.347	3.838	3.234	3.221
Spleen (g)	0.485	0.635	0.639	0.545
Epididymis (g)	1.115	1.217	1.402	1.205

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ weights (individuals) : males

group 2 : 10 mg/kg

week 5

	Animal no				
	11	12	13	14	15
Body (g)	321.6	329.1	322.3	270.9	280.2
Brain (g)	2.325	1.982	2.145	2.038	2.096
Heart (g)	1.201	1.135	1.063	0.945	1.189
Liver (g)	15.23	14.43	13.78	12.14	11.58
Kidney (both) (g)	2.486	2.518	2.262	2.056	2.121
Adrenal (both) (mg)	71.80	81.30	73.30	69.90	66.00
Thymus (mg)	629.8	755.6	711.8	651.2	481.0
Testis (both) (g)	3.227	3.333	3.380	3.147	3.258
Spleen (g)	0.600	0.528	0.628	0.587	0.583
Epididymis (g)	1.009	1.010	1.211	1.251	1.088

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Organ weights (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Body (g)	306.8	364.0	323.3	310.9	255.8
Brain (g)	2.238	2.047	2.116	2.223	2.051
Heart (g)	1.067	1.289	1.085	1.065	0.991
Liver (g)	13.45	15.93	14.80	12.72	12.13
Kidney (both) (g)	2.208	2.782	2.528	2.439	1.846
Adrenal (both) (mg)	67.40	95.30	82.00	77.20	70.00
Thymus (mg)	509.6	722.2	529.2	595.4	483.4
Testis (both) (g)	3.538	3.570	3.494	3.601	2.918
Spleen (g)	0.686	0.659	0.560	0.507	0.508
Epididymis (g)	1.152	1.268	1.184	1.206	1.077

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

358

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ weights (individuals) : males

group 4 : 200 mg/kg

week 5

	Animal no				
	21	22	23	24	25
Body (g)	346.9	321.4	356.5	314.4	310.2
Brain (g)	2.135	2.357	2.162	2.306	2.128
Heart (g)	1.174	1.162	1.342	1.177	1.273
Liver (g)	15.39	15.78	16.63	13.70	14.27
Kidney (both) (g)	2.185	2.541	2.363	2.297	2.184
Adrenal (both) (mg)	70.30	72.40	79.80	65.80	64.40
Thymus (mg)	883.2	824.1	582.1	820.1	828.9
Testis (both) (g)	3.493	3.566	3.226	3.754	3.042
Spleen (g)	0.640	0.781	0.599	0.563	0.708
Epididymis (g)	1.060	1.327	1.104	1.145	0.912

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ weights (individuals) : males

group 5 : 1000 mg/kg

week 5

	Animal no				
	26	27	28	29	30
Body (g)	346.0	351.7	298.9	312.3	299.8
Brain (g)	2.138	2.050	2.127	2.246	2.357
Heart (g)	1.145	1.208	0.968	1.017	0.946
Liver (g)	15.63	17.07	13.69	14.82	14.59
Kidney (both) (g)	2.473	2.537	2.032	2.238	2.392
Adrenal (both) (mg)	89.90	86.00	73.30	85.90	64.90
Thymus (mg)	828.9	808.7	511.3	884.7	698.4
Testis (both) (g)	3.584	3.407	3.180	3.549	3.649
Spleen (g)	0.692	0.552	0.628	0.477	0.611
Epididymis (g)	1.141	1.102	1.227	1.350	1.222

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

360

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ weights (individuals) : females

group 1 : 0 mg/kg week 5

	Animal no				
	36	37	38	39	40
Body (g)	191.3	222.8	201.6	225.2	198.6
Brain (g)	1.913	2.069	1.969	2.181	2.146
Heart (g)	0.726	0.802	0.797	0.915	0.838
Liver (g)	8.392	9.879	7.773	10.75	7.876
Kidney (both) (g)	1.725	1.879	1.473	1.866	1.844
Adrenal (both) (mg)	104.5	96.60	77.00	92.10	122.5
Thymus (mg)	542.5	454.6	529.7	550.1	642.8
Ovary (both) (mg)	145.6	151.8	132.1	180.7	159.5
Spleen (g)	0.477	0.630	0.508	0.479	0.369

Organ weights (individuals) : females

group 2 : 10 mg/kg week 5

	Animal no			
	46	48	49	50
Body (g)	206.2	183.2	205.1	222.8
Brain (g)	1.917	2.001	1.993	2.068

Organ weights (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no			
	46	48	49	50
Heart (g)	0.874	0.681	0.932	0.906
Liver (g)	8.930	7.703	8.067	9.378
Kidney (both) (g)	1.742	1.683	1.495	1.815
Adrenal (both) (mg)	94.80	93.00	87.10	100.7
Thymus (mg)	471.5	373.0	428.7	625.4
Ovary (both) (mg)	175.2	167.4	130.4	201.1
Spleen (g)	0.630	0.498	0.423	0.520

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	51	52	53	54	55
Body (g)	220.2	227.7	225.5	212.2	224.2
Brain (g)	2.152	2.306	1.986	2.181	2.214
Heart (g)	0.883	0.795	0.839	0.888	0.888
Liver (g)	10.10	10.17	9.050	10.86	10.54

Organ weights (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	51	52	53	54	55
Kidney (both) (g)	2.056	1.835	1.797	2.062	2.092
Adrenal (both) (mg)	118.1	89.50	81.80	106.8	101.5
Thymus (mg)	412.2	714.2	611.3	485.4	482.5
Ovary (both) (mg)	210.2	206.6	143.9	167.8	185.9
Spleen (g)	0.554	0.554	0.592	0.655	0.495

Organ weights (individuals) : females

group 4 : 200 mg/kg

week 5

	Animal no				
	56	57	58	59	60
Body (g)	205.2	250.8	168.5	216.7	217.7
Brain (g)	2.050	2.095	1.890	2.075	1.984
Heart (g)	0.930	0.894	0.745	0.848	0.885
Liver (g)	8.563	10.42	6.624	9.903	8.439
Kidney (both) (g)	1.596	2.010	1.458	2.003	1.759
Adrenal (both) (mg)	87.90	96.20	86.70	78.50	77.20

Organ weights (individuals) : females

group 4 : 200 mg/kg week 5

	Animal no				
	56	57	58	59	60
Thymus (mg)	547.6	548.1	484.4	562.3	383.0
Ovary (both) (mg)	135.8	145.8	137.5	168.4	136.8
Spleen (g)	0.496	0.495	0.497	0.577	0.454

Organ weights (individuals) : females

group 5 : 1000 mg/kg week 5

	Animal no				
	61	62	63	64	65
Body (g)	217.6	199.7	203.7	190.9	213.6
Brain (g)	2.242	2.070	2.007	1.959	1.953
Heart (g)	0.833	0.718	0.801	0.782	0.804
Liver (g)	12.05	8.016	9.375	8.208	9.042
Kidney (both) (g)	2.018	1.951	1.823	1.638	1.698
Adrenal (both) (mg)	100.3	109.5	81.20	81.00	88.40
Thymus (mg)	478.1	441.3	556.3	704.3	576.5
Ovary (both) (mg)	191.9	182.5	165.1	119.2	155.3

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

364

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ weights (individuals) : females

group 5 : 1000 mg/kg

week 5

	Animal no				
	61	62	63	64	65
Spleen (g)	0.549	0.573	0.552	0.539	0.634

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

Test No.: 963103

365

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

9.11.2. Organ to body weight ratios (individuals)

Organ to body weight ratios (individuals) : males

group 1 : 0 mg/kg week 5

	1	3	4	5	Animal no
Brain (o/oo)	6.209	5.967	6.713	6.745	
Heart (o/oo)	3.378	3.566	3.936	3.252	
Liver (o/oo)	45.06	45.64	42.84	43.04	
Kidney (both) (o/oo)	7.275	6.058	7.404	7.135	
Adrenal (both) (o/oo)	0.224	0.244	0.255	0.224	
Thymus (o/oo)	2.041	2.055	2.004	3.667	
Testis (both) (o/oo)	10.09	9.923	9.638	9.739	
Spleen (o/oo)	1.461	1.641	1.904	1.649	
Epididymis (o/oo)	3.361	3.145	4.177	3.644	

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

366

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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)	7.229	6.022	6.656	7.523	7.481
Heart (o/oo)	3.734	3.450	3.299	3.487	4.242
Liver (o/oo)	47.35	43.86	42.76	44.81	41.32
Kidney (both) (o/oo)	7.730	7.651	7.017	7.587	7.568
Adrenal (both) (o/oo)	0.223	0.247	0.227	0.258	0.236
Thymus (o/oo)	1.958	2.296	2.208	2.403	1.717
Testis (both) (o/oo)	10.03	10.13	10.49	11.62	11.63
Spleen (o/oo)	1.866	1.604	1.948	2.165	2.081
Epididymis (o/oo)	3.138	3.069	3.756	4.618	3.883

Organ to body weight ratios (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Brain (o/oo)	7.294	5.622	6.544	7.151	8.020
Heart (o/oo)	3.477	3.540	3.355	3.424	3.873

Organ to body weight ratios (individuals) : males

group 3 : 50 mg/kg

week 5

	Animal no				
	16	17	18	19	20
Liver (o/oo)	43.82	43.76	45.76	40.92	47.43
Kidney (both) (o/oo)	7.197	7.642	7.819	7.844	7.217
Adrenal (both) (o/oo)	0.220	0.262	0.254	0.248	0.274
Thymus (o/oo)	1.661	1.984	1.637	1.915	1.890
Testis (both) (o/oo)	11.53	9.808	10.81	11.58	11.41
Spleen (o/oo)	2.234	1.809	1.731	1.630	1.985
Epididymis (o/oo)	3.755	3.483	3.663	3.880	4.211

Organ to body weight ratios (individuals) : males

group 4 : 200 mg/kg

week 5

	Animal no				
	21	22	23	24	25
Brain (o/oo)	6.156	7.333	6.064	7.334	6.860
Heart (o/oo)	3.385	3.614	3.764	3.743	4.105
Liver (o/oo)	44.38	49.08	46.64	43.58	46.01
Kidney (both) (o/oo)	6.298	7.904	6.629	7.306	7.041

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

368

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ to body weight ratios (individuals) : males

group 4 : 200 mg/kg

week 5

	Animal no				
	21	22	23	24	25
Adrenal (both) (o/oo)	0.203	0.225	0.224	0.209	0.208
Thymus (o/oo)	2.546	2.564	1.633	2.608	2.672
Testis (both) (o/oo)	10.07	11.09	9.048	11.94	9.806
Spleen (o/oo)	1.845	2.428	1.679	1.790	2.281
Epididymis (o/oo)	3.056	4.127	3.096	3.641	2.941

Organ to body weight ratios (individuals) : males

group 5 : 1000 mg/kg

week 5

	Animal no				
	26	27	28	29	30
Brain (o/oo)	6.178	5.828	7.117	7.191	7.863
Heart (o/oo)	3.309	3.435	3.237	3.256	3.155
Liver (o/oo)	45.19	48.52	45.80	47.44	48.67
Kidney (both) (o/oo)	7.148	7.212	6.797	7.166	7.979
Adrenal (both) (o/oo)	0.260	0.245	0.245	0.275	0.217
Thymus (o/oo)	2.396	2.299	1.711	2.833	2.330

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ to body weight ratios (individuals) : males

group 5 : 1000 mg/kg week 5

	Animal no				
	26	27	28	29	30
Testis (both) (o/oo)	10.36	9.688	10.64	11.36	12.17
Spleen (o/oo)	2.000	1.570	2.102	1.528	2.037
Epididymis (o/oo)	3.299	3.133	4.104	4.324	4.075

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Organ to body weight ratios (individuals) : females

group 1 : 0 mg/kg week 5

	Animal no				
	36	37	38	39	40
Brain (o/oo)	10.00	9.286	9.764	9.684	10.80
Heart (o/oo)	3.797	3.601	3.952	4.062	4.218
Liver (o/oo)	43.87	44.35	38.55	47.74	39.65
Kidney (both) (o/oo)	9.015	8.436	7.307	8.286	9.285
Adrenal (both) (o/oo)	0.546	0.434	0.382	0.409	0.617
Thymus (o/oo)	2.836	2.041	2.627	2.443	3.236
Ovary (both) (o/oo)	0.761	0.681	0.655	0.803	0.803
Spleen (o/oo)	2.492	2.827	2.521	2.125	1.860

Organ to body weight ratios (individuals) : females

group 2 : 10 mg/kg week 5

	Animal no			
	46	48	49	50
Brain (o/oo)	9.299	10.92	9.715	9.280
Heart (o/oo)	4.237	3.716	4.541	4.065
Liver (o/oo)	43.31	42.04	39.33	42.09

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ to body weight ratios (individuals) : females

group 2 : 10 mg/kg

week 5

	Animal no			
	46	48	49	50
Kidney (both) (o/oo)	8.451	9.189	7.289	8.143
Adrenal (both) (o/oo)	0.460	0.508	0.425	0.452
Thymus (o/oo)	2.287	2.036	2.090	2.807
Ovary (both) (o/oo)	0.850	0.914	0.636	0.902
Spleen (o/oo)	3.057	2.716	2.063	2.334

Organ to body weight ratios (individuals) : females

group 3 : 50 mg/kg

week 5

	Animal no				
	51	52	53	54	55
Brain (o/oo)	9.772	10.13	8.805	10.28	9.873
Heart (o/oo)	4.008	3.491	3.722	4.184	3.958
Liver (o/oo)	45.85	44.68	40.12	51.20	47.00
Kidney (both) (o/oo)	9.335	8.058	7.968	9.717	9.328
Adrenal (both) (o/oo)	0.536	0.393	0.363	0.503	0.453
Thymus (o/oo)	1.872	3.137	2.710	2.288	2.152

Organ to body weight ratios (individuals) : females

group 3 : 50 mg/kg week 5

	Animal no				
	51	52	53	54	55
Ovary (both) (o/oo)	0.954	0.907	0.638	0.791	0.829
Spleen (o/oo)	2.517	2.433	2.626	3.086	2.208

Organ to body weight ratios (individuals) : females

group 4 : 200 mg/kg week 5

	Animal no				
	56	57	58	59	60
Brain (o/oo)	9.991	8.355	11.22	9.575	9.114
Heart (o/oo)	4.531	3.566	4.422	3.913	4.064
Liver (o/oo)	41.73	41.54	39.32	45.71	38.76
Kidney (both) (o/oo)	7.777	8.016	8.652	9.245	8.082
Adrenal (both) (o/oo)	0.428	0.384	0.515	0.362	0.355
Thymus (o/oo)	2.669	2.185	2.875	2.595	1.759
Ovary (both) (o/oo)	0.662	0.581	0.816	0.777	0.628
Spleen (o/oo)	2.417	1.973	2.948	2.662	2.083

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

373

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ to body weight ratios (individuals) : females

group 5 : 1000 mg/kg week 5

	Animal no				
	61	62	63	64	65
Brain (o/oo)	10.30	10.37	9.853	10.26	9.143
Heart (o/oo)	3.826	3.595	3.931	4.093	3.765
Liver (o/oo)	55.38	40.14	46.02	42.99	42.33
Kidney (both) (o/oo)	9.273	9.771	8.950	8.581	7.948
Adrenal (both) (o/oo)	0.461	0.548	0.399	0.424	0.414
Thymus (o/oo)	2.197	2.210	2.731	3.689	2.699
Ovary (both) (o/oo)	0.882	0.914	0.810	0.624	0.727
Spleen (o/oo)	2.523	2.868	2.712	2.824	2.966

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9.11.3. Organ weights (individuals): 2. sacrifice

Organ weights (individuals) : males

group 1 : 0 mg/kg

week 9

Animal no

	6	7	8	9
Body (g)	374.6	369.6	378.2	402.9
Brain (g)	2.146	2.156	2.238	2.268
Heart (g)	1.184	1.230	1.310	1.369
Liver (g)	13.59	16.23	15.35	16.24
Kidney (both) (g)	2.380	2.547	2.477	2.573
Adrenal (both) (mg)	77.00	69.10	83.50	79.20
Thymus (mg)	583.1	657.0	622.6	554.6
Testis (both) (g)	3.337	3.829	3.818	3.907
Spleen (g)	0.532	0.789	0.630	0.613
Epididymis (g)	1.501	1.388	1.624	1.603

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ weights (individuals) : males

group 5 : 1000 mg/kg

week 9

	Animal no				
	31	32	33	34	35
Body (g)	339.0	461.5	416.3	349.2	452.9
Brain (g)	2.206	2.356	2.184	2.139	2.197
Heart (g)	1.123	1.335	1.345	1.072	1.635
Liver (g)	13.50	16.28	17.92	14.55	19.11
Kidney (both) (g)	2.076	2.748	2.781	2.403	2.754
Adrenal (both) (mg)	69.70	60.10	70.00	87.40	74.20
Thymus (mg)	518.4	769.3	427.6	736.7	869.9
Testis (both) (g)	3.241	4.286	3.900	3.610	3.455
Spleen (g)	0.558	0.636	0.689	0.688	0.945
Epididymis (g)	1.406	1.756	1.549	1.327	1.487

Organ weights (individuals) : females

group 1 : 0 mg/kg

week 9

	Animal no				
	41	42	43	44	45
Body (g)	233.4	235.9	221.7	233.5	237.6
Brain (g)	2.201	2.108	2.090	2.068	2.142
Heart (g)	0.909	0.892	0.749	0.991	0.943
Liver (g)	9.392	9.661	9.003	10.18	9.396
Kidney (both) (g)	2.052	2.033	1.670	1.940	1.647
Adrenal (both) (mg)	89.10	92.70	82.10	117.2	81.60
Thymus (mg)	307.8	361.9	439.1	404.0	426.9
Ovary (both) (mg)	153.3	171.7	157.5	255.9	184.5
Spleen (g)	0.593	0.521	0.391	0.576	0.461

Organ weights (individuals) : females

group 5 : 1000 mg/kg

week 9

	Animal no				
	66	67	68	69	70
Body (g)	241.6	249.0	254.3	220.2	219.3
Brain (g)	2.081	2.117	2.208	1.954	2.155

Organ weights (individuals) : females

group 5 : 1000 mg/kg week 9

	Animal no				
	66	67	68	69	70
Heart (g)	0.876	0.930	0.946	0.827	0.859
Liver (g)	10.03	10.60	10.13	7.985	10.66
Kidney (both) (g)	2.152	1.965	1.766	1.760	2.030
Adrenal (both) (mg)	89.70	98.30	110.7	75.50	114.0
Thymus (mg)	407.7	361.4	719.4	441.2	500.0
Ovary (both) (mg)	187.0	135.2	191.4	149.6	166.5
Spleen (g)	0.445	0.491	0.524	0.444	0.542

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9.11.4. Organ to body weight ratios (individuals):
 2. sacrifice

Organ to body weight ratios (individuals) : males

group 1 : 0 mg/kg week 9

	Animal no.			
	6	7	8	9
Brain (o/oo)	5.729	5.833	5.917	5.629
Heart (o/oo)	3.161	3.329	3.465	3.398
Liver (o/oo)	36.28	43.92	40.58	40.30
Kidney (both) (o/oo)	6.353	6.892	6.549	6.387
Adrenal (both) (o/oo)	0.206	0.187	0.221	0.197
Thymus (o/oo)	1.557	1.778	1.646	1.377
Testis (both) (o/oo)	8.907	10.36	10.09	9.696
Spleen (o/oo)	1.421	2.134	1.666	1.520
Epididymis (o/oo)	4.007	3.756	4.293	3.979

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ to body weight ratios (individuals) : males

group 5 : 1000 mg/kg week 9

	Animal no				
	31	32	33	34	35
Brain (o/oo)	6.506	5.106	5.246	6.127	4.851
Heart (o/oo)	3.314	2.893	3.231	3.069	3.610
Liver (o/oo)	39.81	35.28	43.05	41.66	42.19
Kidney (both) (o/oo)	6.122	5.954	6.680	6.882	6.082
Adrenal (both) (o/oo)	0.206	0.130	0.168	0.250	0.164
Thymus (o/oo)	1.529	1.667	1.027	2.110	1.921
Testis (both) (o/oo)	9.561	9.287	9.369	10.34	7.630
Spleen (o/oo)	1.646	1.379	1.654	1.971	2.086
Epididymis (o/oo)	4.149	3.805	3.721	3.801	3.284

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Organ to body weight ratios (individuals) : females

group 1 : 0 mg/kg

week 9

	Animal no				
	41	42	43	44	45
Brain (o/oo)	9.428	8.935	9.425	8.858	9.016
Heart (o/oo)	3.892	3.780	3.377	4.243	3.968
Liver (o/oo)	40.23	40.95	40.61	43.59	39.54
Kidney (both) (o/oo)	8.792	8.617	7.531	8.309	6.931
Adrenal (both) (o/oo)	0.382	0.393	0.370	0.502	0.343
Thymus (o/oo)	1.319	1.534	1.981	1.730	1.797
Ovary (both) (o/oo)	0.657	0.728	0.710	1.096	0.776
Spleen (o/oo)	2.542	2.209	1.765	2.468	1.940

Organ to body weight ratios (individuals) : females

group 5 : 1000 mg/kg

week 9

	Animal no				
	66	67	68	69	70
Brain (o/oo)	8.613	8.503	8.684	8.873	9.825
Heart (o/oo)	3.624	3.733	3.721	3.757	3.916
Liver (o/oo)	41.52	42.55	39.82	36.27	48.62

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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

Organ to body weight ratios (individuals) : females

group 5 : 1000 mg/kg week 9

	Animal no				
	66	67	68	69	70
Kidney (both) (o/oo)	8.906	7.891	6.946	7.993	9.258
Adrenal (both) (o/oo)	0.371	0.395	0.435	0.343	0.520
Thymus (o/oo)	1.687	1.451	2.829	2.004	2.280
Ovary (both) (o/oo)	0.774	0.543	0.753	0.680	0.759
Spleen (o/oo)	1.840	1.970	2.059	2.018	2.471

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

Test No. 963103

CGA 62826 tech. (Metabolite of CGA 48988)

FINAL REPORT

Author: Dr. phil.- nat. 532eW30

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 (adopted July 95)
EEC 92/69 B.7

Final Report issued: May 21, 1997

Sponsor: Novartis Crop Protection AG
4002 Basel / Switzerland

This report contains: 532 pages

Table of contents

Page

VOLUME 1 OF 2

0.1	Reserved Page for Proprietary Information or Statement of No Data Confidentiality Claims.....	2
0.2	Certification of Good Laboratory Practices.....	3
0.3	Reserved Page for Flagging Statements.....	4
0.4	Signatures.....	5
0.5	Quality Assurance Statement.....	6
0.6	Table of contents.....	7
1	Summary and conclusion.....	11
2	Introduction.....	14
	Purpose.....	14
	Good laboratory practice.....	14
	Basis of the study.....	14
	Sponsor.....	14
	Testing facility.....	15
	Study dates.....	15
	Personnel and responsible scientists.....	16
	Archiving and distribution.....	17
2.1	Deviations.....	18
3	Materials and methods.....	19
3.1	Test article.....	19
	Pretest analytics.....	19
3.2	Test system.....	20
	3.2.1 Experimental animals.....	20
	3.2.2 Husbandry.....	20
	3.2.3 Identification.....	21
3.3	Procedures.....	21
	3.3.1 Study schedule.....	21
	3.3.2 Animal number and distribution.....	22
	3.3.3 Acclimatization.....	22
	3.3.4 Treatment.....	23
	3.3.5 Dose levels.....	23
	3.3.6 Rationale for dose selection.....	23
3.4	Test article administration and diet.....	24
	Route of administration.....	24
	Frequency of administration.....	24
	Preparation of suspension.....	24
	Vehicle.....	24
	Volume of suspension applied.....	24
	Control analyses.....	24
	Control animals.....	25
	3.4.1 Diet.....	25
	3.4.2 Water.....	25
3.5	Observations and records.....	26
	3.5.1 Standard animal observations.....	26
3.6	Neurotoxicologic examinations.....	27
	3.6.1 Detailed clinical observations.....	27

	Page
3.6.2 Functional observational battery (FOB).....	27
3.6.3 Motor activity.....	29
3.7 Laboratory investigations.....	30
3.7.1 Parameters and methods used in hematology....	31
3.7.2 Parameters and methods used in blood chemistry.....	32
3.7.3 Parameters and methods used in urinalysis....	34
3.8 Pathology.....	35
3.8.1 Macroscopical examination.....	35
3.8.2 Microscopical examination.....	36
3.8.3 Acquisition and presentation of pathology data.....	37
3.9 Statistical analysis.....	39
4 Results.....	41
4.1 Analytical results.....	41
Pretest analytics.....	41
Test analytics.....	42
4.2 In-life observations.....	42
4.2.1 Clinical signs.....	42
4.2.2 Functional observational battery (FOB).....	42
4.2.3 Motor activity.....	42
4.2.4 Mortality.....	43
4.2.5 Body weight.....	43
4.2.6 Food consumption.....	43
4.2.7 Food consumption ratios.....	43
4.2.8 Water consumption.....	44
4.2.9 Hematology.....	44
4.2.10 Blood chemistry.....	45
4.2.11 Urine analysis.....	45
4.3 Organ weights and ratios.....	46
4.4 Pathology.....	47
4.4.1 Macroscopical findings.....	47
4.4.2 Microscopical findings.....	47
5 Discussion.....	48
6 References.....	50
7 Figures.....	51
7.1 Functional observational battery (Measurements)...	52
7.2 Motor activity.....	54
7.2.1 Mean session totals males.....	54
7.2.2 Mean session totals females.....	55
7.2.3 Motor activity (within-session time course) males.....	56
7.2.4 Motor activity (within-session time course) females.....	58
7.3 Body weight.....	60
7.4 Food consumption.....	62
7.5 Food consumption ratios.....	64
7.6 Water consumption.....	66

	Page
8 Tables (means, statistics).....	68
8.1 Analytical results.....	69
Pretest analytics.....	69
Test analytics.....	69
8.2 Clinical signs.....	70
8.3 Functional observational battery (means).....	71
8.4 Functional observational battery (statistics).....	76
8.5 Motor activity (means).....	83
8.6 Motor activity (statistics).....	88
8.7 Summary of animal fate.....	97
8.8 Body weight (means).....	98
8.9 Body weight (statistics).....	99
8.10 Food consumption (means).....	105
8.11 Food consumption (statistics).....	106
8.12 Food consumption ratios (means).....	112
8.13 Water consumption (means).....	113
8.14 Water consumption (statistics).....	114
8.15 Hematology (means).....	120
8.16 Hematology (statistics).....	126
8.17 Blood chemistry (means).....	150
8.18 Blood chemistry (statistics).....	156
8.19 Urine analysis (means).....	174
8.20 Urine analysis (statistics).....	180
8.21 Organ weights and ratios (means).....	190
8.21.1 Organ weights (means).....	190
8.21.2 Organ to body weight ratios (means).....	192
8.21.3 Organ weights (means): 2. sacrifice.....	194
8.21.4 Organ to body weight ratios (means): 2. sacrifice.....	196
8.22 Organ weights and ratios (statistics).....	198
8.22.1 Organ weights (statistics).....	198
8.22.2 Organ to body weight ratios (statistics).....	204
8.22.3 Organ weights (statistics): 2. sacrifice.....	209
8.22.4 Organ to body weight ratios (statistics): 2. sacrifice.....	214
9 Appendix A: Individual data.....	218
9.1 Clinical signs (individuals).....	219
9.2 Functional observational battery (individuals).....	223
9.3 Motor activity (individuals).....	240
9.4 Mortality (individuals).....	268
9.5 Body weight (individuals).....	272
9.6 Food consumption (individuals).....	278
9.7 Water consumption (individuals).....	284
9.8 Hematology (individuals).....	290
9.9 Blood chemistry (individuals).....	318
9.10 Urine analysis (individuals).....	339
9.11 Organ weights and ratios (individuals).....	355
9.11.1 Organ weights (individuals).....	355
9.11.2 Organ to body weight ratios (individuals).....	365
9.11.3 Organ weights (individuals): 2. sacrifice.....	374
9.11.4 Organ to body weight ratios (individuals): 2. sacrifice.....	378

Page

VOLUME 2 OF 2 OF SUBMISSION

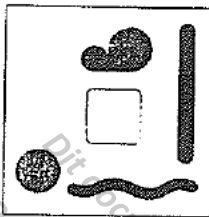
10 Appendix B: Analytical report.....	386
11 Appendix C: Reference values.....	406
11.1 Scoring criteria used in FOB.....	406
11.2 Assignment of signs and functions to functional domains.....	414
11.3 Units used in hematology.....	415
11.4 Reference values: Hematology.....	416
11.5 Reference values: Blood chemistry.....	420
11.6 Reference values: Urine analysis.....	424
11.7 Reference values: Organ weights.....	426
12 Appendix D: Pathology report.....	434
13 Appendix E: Study protocol and amendment.....	499

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10. APPENDIX B: ANALYTICAL REPORT

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DETERMINATION OF CONCENTRATION, HOMOGENEITY,
AND STABILITY OF CGA 62826 TECH. (METABOLITE OF CGA 48988)
IN DISTILLED WATER WITH 0.5% CMC AND 0.1% TWEEN 80

ANALYTICAL REPORT TO NOVARTIS CROP PROTECTION STUDY NO. 963103:
28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Authors:

Mr.

5.1.2.2 Wood

Mrs.

Completion Date:

April 15, 1997

Performing Laboratory:

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

Study Project No.:

NOVARTIS CROP PROTECTION STUDY NO. 963103
RCC PROJECT 636827

Sponsor:

Novartis Crop Protection AG
CH-4002 Basle

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE

NOVARTIS CROP PROTECTION STUDY NO.: 963103

RCC PROJECT NO.: 636827

TEST ARTICLE: CGA 62826 Tech. (Metabolite of CGA 48988)

PRINCIPAL INVESTIGATOR ANALYTICS: Mr. 5.1.2.e Woo

TITLE: Determination of Concentration, Homogeneity, and Stability of CGA 62826 Tech. (Metabolite 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 15, 1997

QUALITY ASSURANCE UNIT

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

STATEMENT

NOVARTIS CROP PROTECTION STUDY NO.: 963103

RCC PROJECT NO.: 636827

TEST ARTICLE: CGA 62826 Tech. (Metabolite of CGA 48988)

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TITLE: Determination of Concentration, Homogeneity, and Stability of CGA 62826 Tech. (Metabolite 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
November 12, 1996	Process based	November 14, 1996
April 15, 1997	Final analytical report	April 15, 1997

Manager, Quality Assurance Unit:

Mrs. 5.1.2.e Woo

5.1.2.e Woo

Date: April 16, 1997

CONTENTS

	Page
TITLE PAGE	1
STATEMENT OF COMPLIANCE	2
QUALITY ASSURANCE UNIT	3
CONTENTS	4
GENERAL INFORMATION	5
SIGNATURE PAGE	6
ABSTRACT	7
1 INTRODUCTION	8
2 MATERIALS AND METHODS	9
2.1 TEST ARTICLE	9
2.2 SAMPLES	9
2.3 SAMPLE PREPARATION AND STORAGE	10
2.4 ANALYTICAL PROCEDURE	10
2.4.1 Standard Solutions	10
2.4.2 Analysis of Samples	10
2.4.3 High Performance Liquid Chromatographic Determination	11
2.4.4 Evaluation of Results	12
3 RESULTS	13
TABLES	
Table 1: Example of Calibration Curve	14
Table 2: Concentration, Homogeneity, and Stability of Test Article in Vehicle	15
Table 3: Concentration of Test Article in Vehicle	16
Table 4: Overall Mean Concentrations	17
FIGURES	
Figure 1: Typical Chromatograms of Standard Solutions	18
Figure 2: Typical Chromatograms of Test Samples	19

GENERAL INFORMATION

GENERAL

Title: Determination of Concentration, Homogeneity, and Stability of CGA 62826 Tech. (Metabolite 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.: 636827

Novartis Crop Protection Study No.: 963103

Sponsor: Novartis Crop Protection AG
4002 Basle / Switzerland

Study Director: Dr. 5.1.2.e Wood
Novartis Crop Protection AG
Toxicology / Experimental Toxicology
4332 Stein / Switzerland

Test Article: CGA 62826 Tech. (Metabolite of CGA 48988)

Testing Facility: RCC UMWELTCHEMIE AG
CH-4452 Itingen / Switzerland

PROJECT STAFF

Principal Investigator Analytics: Mr. 5.1.2.a Wood

SCHEDULE

Dates of Analyses: See Section 2.2

Completion Date: April 15, 1997 /ula

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.

5.12.e Woo

Date:

April 15, 1997

MANAGING DIRECTOR:

Mr.

5.12.e Woo

Date:

April 16, 1997

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ABSTRACT

This chemical analysis determined the concentration, homogeneity, and stability of CGA 62826 Tech. (Metabolite 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 103.5%, 101.8%, 99.5% and 99.9% of the nominal concentrations for dose group 2 (1 mg/ml), for dose group 3 (5 mg/ml), for dose group 4 (30 mg/ml) and for dose group 5 (100 mg/ml) respectively. The individual concentrations varied in the range from -3% to +4% of the mean concentrations. Therefore, the test article was found to be homogenous.

Test:

The overall mean concentrations of the content samples taken during administration were found to be 108.5%, 107.5%, 111.3%, and 111.3% 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 62826 Tech. (Metabolite of CGA 48988) was found to be stable in the vehicle at room temperature over a period of four hours.

1 INTRODUCTION

This report describes the analytical method applied for determination of concentration, homogeneity, and stability of CGA 62826 Tech. (metabolite of CGA 48988) in distilled water with 0.5% CMC and 0.1% Tween 80.

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

Evaluation of stability was performed by analyzing samples of each dose group being taken right after preparation and after having stored for four hours at room temperature, respectively.

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2 MATERIALS AND METHODS

2.1 TEST ARTICLE

Company code no.: CGA 62826 Tech.
Batch number: RV-1592/4
Purity: 100%
Description: Solid
Date of receipt: August 20, 1996
Storage conditions: below 10 °C
Stability: August 1999

2.2 SAMPLES

Pretest:

- Shipment no.: 01
- Prepared by sponsor on: 27-AUG-96
- Sampled by sponsor on: 27-AUG-96
- Received at RCC on: 28-AUG-96
- Date of analysis: 11-SEP-96

Test:

- Shipment no.:	01	02
- Prepared by sponsor on:	23-OCT-96	30-OCT-96
- Sampled by sponsor on:	23-OCT-96	30-OCT-96
- Received at RCC on:	24-OCT-96	30-OCT-96
- Date of analysis:	31-OCT-96	31-OCT-96
- Shipment no.:	03	04
- Prepared by sponsor on:	06-NOV-96	13-NOV-96
- Sampled by sponsor on:	06-NOV-96	13-NOV-96
- Received at RCC on:	07-NOV-96	14-NOV-96
- Date of analysis:	15-NOV-96	15-NOV-96

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/bi-distilled water (90+10 v/v) with concentrations of 200 µg/ml, 203 µg/ml, and 208 µg/ml were prepared as follows: A 20.0-mg, 20.3-mg, and 20.8-mg portion of test article was each weighed into a 100-ml volumetric flask and dissolved in 10 ml of bi-distilled water and about 60 ml of acetonitrile by means of an ultrasonic bath. Afterwards, the volumetric flasks were filled to volume with acetonitrile. Next, various standard solutions were prepared by respective dilution of these stock solutions with solvent A¹⁾ to yield concentrations in the range from 5 µg/ml to 52 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 10 ml of bi-distilled water by means of an ultrasonic bath. Afterwards, the sample solutions were quantitatively transferred to 100-ml volumetric flasks with acetonitrile which were then filled to the mark with acetonitrile. Depending on the dose group, the latter sample solutions were further diluted with solvent A¹⁾ to yield concentrations within the calibration range. Finally, a 10-µl aliquot was quantified by HPLC.

1) Solvent A: 700 ml bi-distilled water + 300 ml acetonitrile + 0.7 ml conc. phosphoric acid

2) In the case of group 1 (untreated samples), a 2.0-g portion was taken from the sample (ca. 30 g) delivered by the sponsor

2.4.3 High Performance Liquid Chromatographic Determination

Typical Operating Conditions

Apparatus:	Merck L-6200 pump Merck L-4200 UV-VIS-detector Merck D-2500 integrator Merck AS 2000A sampling unit
Column:	Lichrospher RP-8; 5 μ m; 125 x 4 mm (i.d.)
Temperature:	Room temperature
Eluent:	700 ml bi-distilled water + 300 ml + 0.7 ml conc. phosphoric acid
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 peak areas of the test article in counts with reference to the calibration curve. The latter was obtained by correlation of the 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 = peak areas of injected sample in counts in injected sample

a = y-axis intercept

b = slope

X = $\mu\text{g/ml}$ CGA 62826 Tech. (Metabolite of CGA 48988)

The concentration of CGA 62826 Tech. (Metabolite 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 62826 Tech. (Metabolite 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 62826 Tech. (Metabolite 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 103.5%, 101.8%, 99.5% and 99.9% of the nominal concentrations for dose group 2 (1 mg/ml), for dose group 3 (5 mg/ml), for dose group 4 (30 mg/ml) and for dose group 5 (100 mg/ml) respectively. The individual concentrations varied in the range from -3% to +4% of the mean concentrations. Therefore, the test article was found to be homogenous.

Test:

The overall mean concentrations of the content samples taken during administration were found to be 108.5%, 107.5%, 111.3%, and 111.3% 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 62826 Tech. (Metabolite 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 62826 Tech. (Metabolite of CGA 48988) is listed in Table 1. Detailed results of the concentrations 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: Example of Calibration Curve

Date of Analysis: 15-NOV-1996

Standard Concentration (µg/ml) (X)	Peak Area (Counts) (Y)	
	before samples	after samples
5	29712	
10	67962	
20	131621	
50	332893	
5.075		33855
10.15		*
20.3		134447
50.75		335424

* outlier; not considered in the calculation

$$Y = -813 + 6651 \cdot X \quad (R^2 = 1.000)$$

where

Y = Peak areas of injected sample (in counts)

X = µg/ml CGA 62826 Tech. (Intermediate of 48988) in injected sample

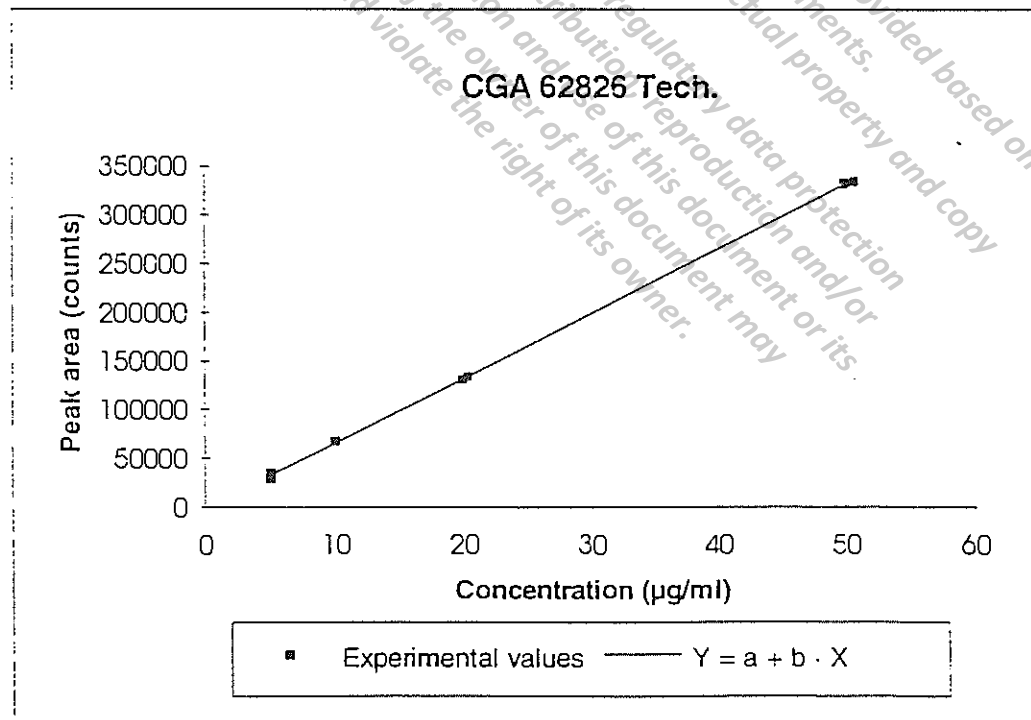


Table 2: Concentration, Homogeneity, and Stability of Test Article in Vehicle

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: August 27, 1996)									
1	0	I	--	0	11-SEP-96	0.000	---	---	---
2	1	2A	T	0	11-SEP-96	1.024	102.4	103.5	-3 / +4
		2B	M	0	11-SEP-96	1.009	100.9		
		2C	B	0	11-SEP-96	1.072	107.2		
		2S		4	11-SEP-96	1.039	103.9		
3	5	3A	T	0	11-SEP-96	5.093	101.9	101.8	±0
		3B	M	0	11-SEP-96	5.084	101.7		
		3C	B	0	11-SEP-96	5.092	101.8		
		3S		4	11-SEP-96	5.071	101.4		
4	30	4A	T	0	11-SEP-96	29.64	98.8	99.5	-1 / +1
		4B	M	0	11-SEP-96	30.01	100.0		
		4C	B	0	11-SEP-96	29.90	99.7		
		4S		4	11-SEP-96	30.87	102.9		
5	100	5A	T	0	11-SEP-96	99.08	99.1	99.9	-1 / +1
		5B	M	0	11-SEP-96	100.8	100.8		
		5C	B	0	11-SEP-96	99.73	99.7		
		5S		4	11-SEP-96	100.2	100.2		

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 Nom.
(Date of Preparation: October 23, 1996)					
1	0	1S	31-OCT-96	0.000	---
2	1	2S	31-OCT-96	1.090	109.0
3	5	3S	31-OCT-96	5.238	104.8
4	20	4S	31-OCT-96	22.11	110.6
5	100	5S	31-OCT-96	110.8	110.8
(Date of Preparation: October 30, 1996)					
1	0	1S	31-OCT-96	0.000	---
2	1	2S	31-OCT-96	1.141	114.1
3	5	3S	31-OCT-96	5.298	106.0
4	20	4S	31-OCT-96	23.09	115.5
5	100	5S	31-OCT-96	117.5	117.5
(Date of Preparation: November 06, 1996)					
1	0	1S	15-NOV-96	0.000	---
2	1	2S	15-NOV-96	0.986	98.6
3	5	3S	15-NOV-96	5.509	110.2
4	20	4S	15-NOV-96	22.40	112.0
5	100	5S	15-NOV-96	108.0	108.0
(Date of Preparation: November 13, 1996)					
1	0	1S	15-NOV-96	0.000	---
2	1	2S	15-NOV-96	1.124	112.4
3	5	3S	15-NOV-96	5.455	109.1
4	20	4S	15-NOV-96	21.42	107.1
5	100	5S	15-NOV-96	108.7	108.7

Table 4: Overall Mean Concentrations*

Dose Group	Nominal Concentration (mg/ml)	n	Mean % of Nominal	Standard Deviation (%)
2	1	4	108.5	6.9
3	5	4	107.5	2.5
4	20	4	111.3	3.5
5	100	4	111.3	4.3

* Pretest excluded

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Figure 1: Typical Chromatograms of Standard Solutions

- (A) Standard solution 5 µg/ml, before samples
- (B) Standard solution 50 µg/ml, before samples

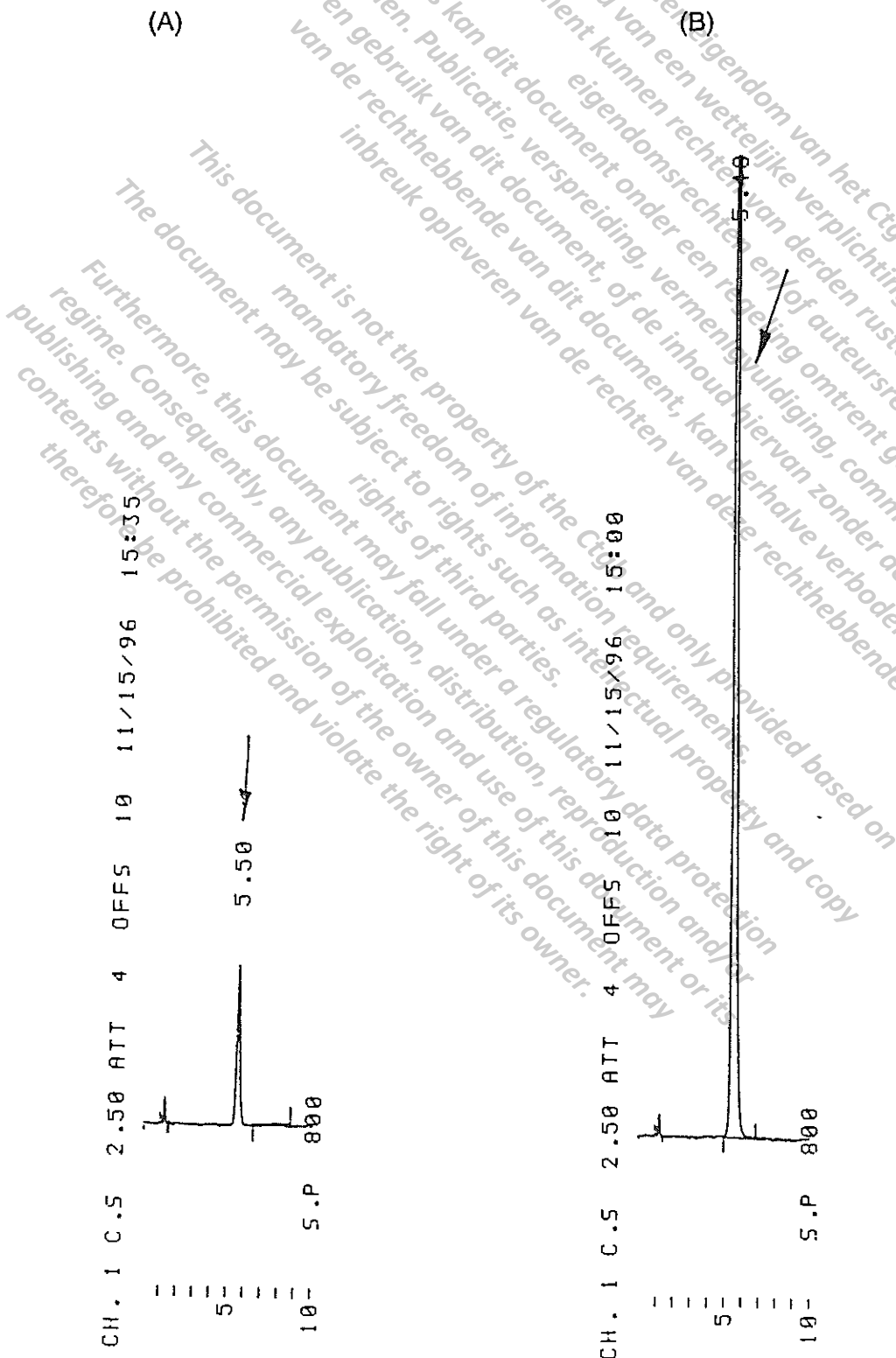
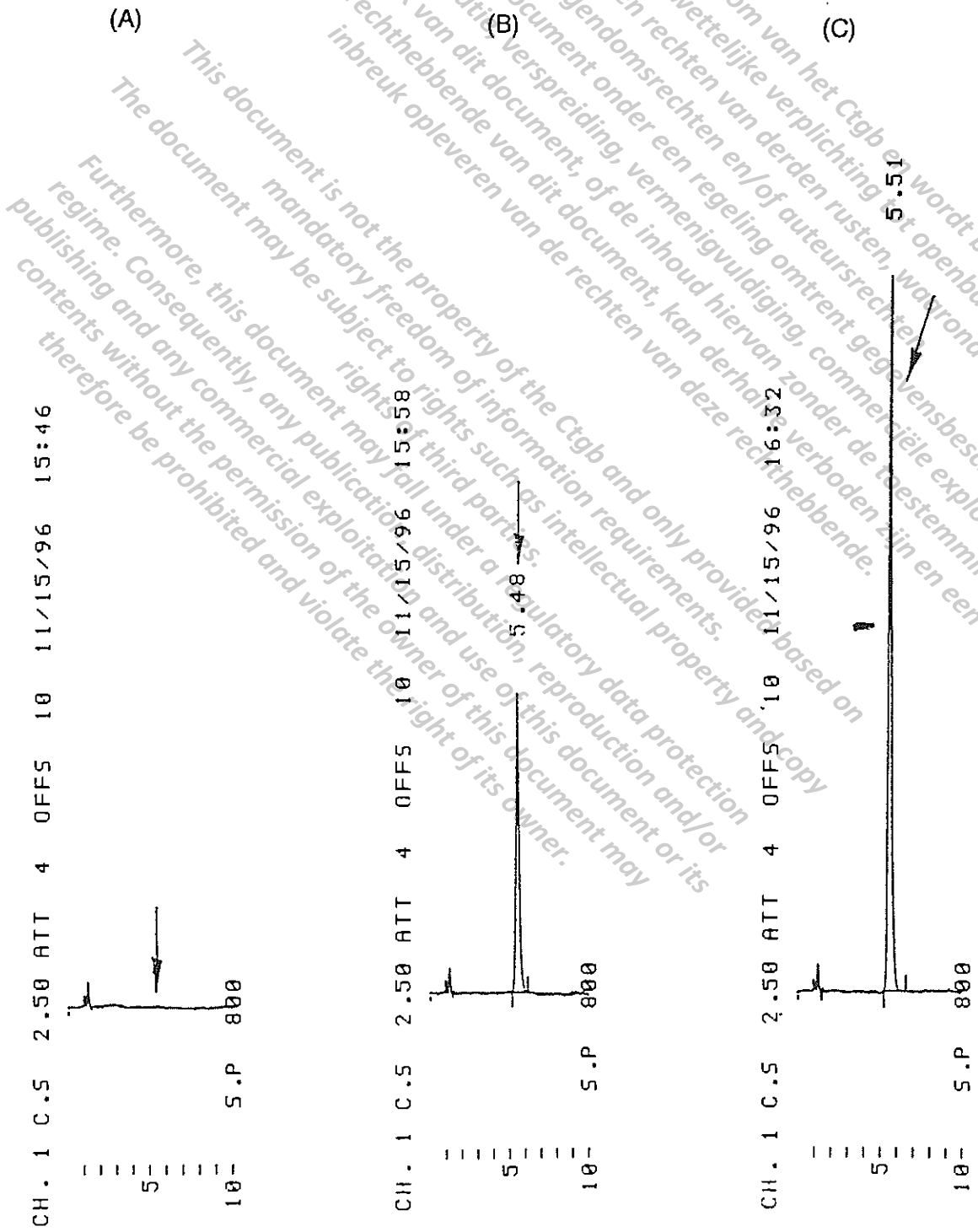


Figure 2: Typical Chromatograms of Test Samples

- (A) Dose group 2, control sample, diluted 2x
- (B) Dose group 2, nominal concentration: 1 mg/ml, diluted 2x
- (C) Dose group 5, nominal concentration: 100 mg/ml, diluted 100x

Date of Sampling: November 06, 1996



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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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite 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

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

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.: 963103

Test Article: CGA 62826 tech. (Metabolite 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

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: 0 normal skin temperature
1 animal feels cold to touch

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

hairloss

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.: 963103

Test Article: CGA 62826 tech. (Metabolite 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**orienting 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.: 963103

Test Article: CGA 62826 tech. (Metabolite 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 mHz, 80 db, 10 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.: 963103

Test Article: CGA 62826 tech. (Metabolite 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	
	padding 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	
	orienting 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	
	orienting 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	
	piloerection	+2	
	fur unkempt	+1	
	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

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	1	%	100
Mean Corpuscular Volume	fl	μm^3	1
Red Cell Volume Distribution Width	1	%	100
Mean Corpuscular Hemoglobin	fmol	pg	16.11
Mean Corpuscular Hemoglobin Concentration	mmol/l	g/100 ml (%)	1.511
Hemoglobin Concentration Distribution Width	mmol/l	g/100 ml	1.511
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
Easophils	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

11.4. Reference values: Hematology

HEMATOLOGY REFERENCE VALUES
 UNTREATED MALE RATS Tif: RAIF (SPF)

Age : 9 - 12 weeks Period : 08.04.91 - 27.02.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	591	7.300	7.810	8.400
Hb	M0002	mmol/l	591	9.000	9.500	10.10
Hct	M0002	l	591	0.425	0.452	0.479
MCV	M0002	fl	591	54.10	57.80	61.90
RDW	M0002	l	591	0.106	0.119	0.144
MCH	M0002	fmol	591	1.140	1.220	1.290
MCHC	M0002	mmol/l	591	20.09	21.01	22.02
HDW	M0002	mmol/l	591	1.280	1.540	2.145
Reti	M0002	l	89	0.016	0.029	0.044
	M0003	l	35	0.042	0.056	0.081
WBC	M0002	G/l	591	8.590	13.06	20.07
Neut	M0002	l	591	0.049	0.081	0.147
Eos	M0002	l	591	0.003	0.006	0.015
Baso	M0002	l	591	0.002	0.005	0.007
Lympho	M0002	l	591	0.764	0.847	0.897
Mono	M0002	l	591	0.019	0.034	0.059
Luc	M0002	l	591	0.010	0.022	0.042
Neut	M0002	G/l	233	0.680	1.160	2.220
Eos	M0002	G/l	233	0.040	0.090	0.210
Baso	M0002	G/l	233	0.030	0.070	0.140
Lympho	M0002	G/l	233	7.550	11.71	17.37
Mono	M0002	G/l	233	0.260	0.510	1.050
Luc	M0002	G/l	233	0.170	0.350	0.790
Plt	M0002	G/l	591	815.0	1004	1164
PT(CS)	M0001	sec	453	29.89	37.62	51.95
MetHb	M0001	l	297	0.004	0.007	0.010
Heinz B	M0001	l	10	0.000	0.000	0.000

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

417

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

HEMATOLOGY REFERENCE VALUES
UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 06.05.91 - 27.03.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	129	7.760	8.290	8.900
Hb	M0002	mmol/l	129	9.000	9.600	10.10
Hct	M0002	l	129	0.422	0.449	0.474
MCV	M0002	fl	129	51.10	54.30	57.60
RDW	M0002	l	129	0.118	0.132	0.154
MCH	M0002	fmol	129	1.090	1.150	1.230
MCHC	M0002	mmol/l	129	20.16	21.24	22.19
HDW	M0002	mmol/l	129	1.440	1.650	2.060
Reti	M0002	l	10	0.014	0.021	0.038
	M0003	l	10	0.011	0.029	0.043
WBC	M0002	G/l	129	7.780	11.57	17.92
Neut	M0002	l	129	0.069	0.103	0.170
Eos	M0002	l	129	0.005	0.010	0.018
Baso	M0002	l	129	0.002	0.004	0.007
Lympho	M0002	l	129	0.735	0.824	0.872
Mono	M0002	l	129	0.021	0.036	0.067
Luc	M0002	l	129	0.013	0.024	0.041
Neut	M0002	G/l	54	0.700	1.220	1.790
Eos	M0002	G/l	54	0.060	0.100	0.230
Baso	M0002	G/l	54	0.030	0.055	0.100
Lympho	M0002	G/l	54	6.390	10.11	15.40
Mono	M0002	G/l	54	0.240	0.455	0.860
Luc	M0002	G/l	54	0.180	0.330	0.580
Plt	M0002	G/l	129	788.0	941.0	1097
PT(CS)	M0001	sec	129	28.31	36.00	49.39
MetHb	M0001	l	114	0.006	0.007	0.012

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

418

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

HEMATOLOGY REFERENCE VALUES
 UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks

Period : 08.04.91 - 27.02.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	476	7.140	7.680	8.280
Hb	M0002	mmol/l	476	8.800	9.400	10.00
Hct	M0002	l	476	0.409	0.438	0.468
MCV	M0002	fl	476	53.80	57.20	60.40
RDW	M0002	l	476	0.103	0.118	0.149
MCH	M0002	fmol	476	1.160	1.220	1.290
MCHC	M0002	mmol/l	476	20.49	21.35	22.39
HDW	M0002	mmol/l	476	1.220	1.420	1.940
Reti	M0001	l	10	0.011	0.030	0.035
	M0002	l	85	0.014	0.026	0.054
	M0003	l	54	0.031	0.047	0.074
WBC	M0002	G/l	476	5.010	8.545	13.07
Neut	M0002	l	476	0.044	0.081	0.166
Eos	M0002	l	476	0.005	0.010	0.020
Baso	M0002	l	476	0.001	0.003	0.005
Lympho	M0002	l	476	0.762	0.847	0.904
Mono	M0002	l	476	0.017	0.032	0.057
Luc	M0002	l	476	0.009	0.020	0.040
Neut	M0002	G/l	224	0.390	0.690	1.355
Eos	M0002	G/l	224	0.050	0.090	0.180
Baso	M0002	G/l	224	0.010	0.030	0.070
Lympho	M0002	G/l	224	4.050	7.410	11.46
Mono	M0002	G/l	224	0.130	0.310	0.620
Luc	M0002	G/l	224	0.080	0.200	0.410
Plt	M0002	G/l	476	849.0	1046	1228
PT(CS)	M0001	sec	460	23.85	30.21	37.18
MetHb	M0001	l	293	0.004	0.007	0.010
Heinz B	M0001	l	10	0.000	0.000	0.000

HEMATOLOGY REFERENCE VALUES
 UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 06.05.91 - 27.03.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
RBC	M0002	T/l	127	7.400	7.880	8.370
Hb	M0002	mmol/l	127	8.800	9.400	10.00
Hct	M0002	l	127	0.413	0.438	0.469
MCV	M0002	fl	127	53.15	55.90	59.20
RDW	M0002	l	127	0.112	0.123	0.147
MCH	M0002	fmol	127	1.140	1.190	1.260
MCHC	M0002	mmol/l	127	20.46	21.32	22.23
HDW	M0002	mmol/l	127	1.190	1.330	1.710
Reti	M0003	l	10	0.011	0.021	0.037
WBC	M0002	G/l	127	3.780	6.840	10.84
Neut	M0002	l	127	0.054	0.091	0.171
Eos	M0002	l	127	0.006	0.012	0.021
Baso	M0002	l	127	0.001	0.003	0.004
Lympho	M0002	l	127	0.737	0.832	0.881
Mono	M0002	l	127	0.021	0.035	0.056
Luc	M0002	l	127	0.009	0.021	0.049
Neut	M0002	G/l	55	0.330	0.640	1.010
Eos	M0002	G/l	55	0.050	0.100	0.160
Baso	M0002	G/l	55	0.010	0.020	0.070
Lympho	M0002	G/l	55	3.300	5.970	10.18
Mono	M0002	G/l	55	0.110	0.290	0.460
Luc	M0002	G/l	55	0.090	0.170	0.320
Plt	M0002	G/l	127	776.0	965.0	1154
PT(CS)	M0001	sec	128	24.52	29.44	36.43
MetHb	M0001	l	113	0.005	0.007	0.012

11.5. Reference values: Blood chemistry

BLOOD CHEMISTRY REFERENCE VALUES
 UNTREATED MALE RATS Tif: RAIF (SPF)

Age : 9 - 12 weeks Period : 08.04.91 - 27.02.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	592	5.350	7.105	8.970
Urea	M0001	mmol/l	592	4.460	6.110	8.270
Creat-e	M0001	umol/l	472	41.00	60.60	79.00
Bili-tot	M0001	umol/l	467	1.740	2.390	3.160
Prot	M0001	g/l	592	60.42	64.47	69.32
Alb	M0001	g/l	462	34.65	36.73	38.65
Glob	M0001	g/l	462	24.54	27.45	31.47
A/G	M0001	l	462	1.170	1.340	1.500
Chol	M0001	mmol/l	592	1.400	1.800	2.290
Trigly	M0001	mmol/l	287	0.440	0.780	1.490
Phos-Lip	M0001	mmol/l	5	1.270	1.510	1.790
Na+	M0001	mmol/l	592	141.0	143.4	146.6
K+	M0001	mmol/l	592	3.020	3.530	3.990
Ca++	M0001	mmol/l	462	2.560	2.690	2.840
Cl-	M0001	mmol/l	462	94.80	98.20	101.4
PO4-in	M0001	mmol/l	462	1.830	2.120	2.540
ASAT (GOT)	M0001	U/l	592	45.40	56.40	71.50
ALAT (GPT)	M0001	U/l	592	22.40	33.90	52.40
ALP	M0001	U/l	592	109.3	174.2	322.3
GGT	M0001	U/l	412	0.000	0.000	2.100
ChE-Pl	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

BLOOD CHEMISTRY REFERENCE VALUES
 UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 06.05.91 - 27.03.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	129	6.010	7.540	9.700
Urea	M0001	mmol/l	129	4.920	6.390	8.180
Creat-e	M0001	umol/l	129	45.70	62.80	79.10
Bili-tot	M0001	umol/l	129	1.850	2.410	3.050
Prot	M0001	g/l	129	62.01	65.96	71.19
Alb	M0001	g/l	129	34.70	37.19	38.69
Glob	M0001	g/l	129	25.65	29.07	33.69
A/G	M0001	1	129	1.110	1.270	1.440
Chol	M0001	mmol/l	129	1.360	1.760	2.290
Trigly	M0001	mmol/l	114	0.540	0.880	1.670
Na+	M0001	mmol/l	129	141.2	143.5	148.3
K+	M0001	mmol/l	129	3.060	3.490	3.890
Ca++	M0001	mmol/l	129	2.550	2.660	2.800
Cl-	M0001	mmol/l	129	96.10	98.70	102.6
PO4-in	M0001	mmol/l	129	1.400	1.760	2.020
ASAT (GOT)	M0001	U/l	129	45.40	56.50	86.40
ALAT (GPT)	M0001	U/l	129	21.80	34.40	50.80
ALP	M0001	U/l	129	83.20	121.5	185.7
GGT	M0001	U/l	124	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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

BLOOD CHEMISTRY REFERENCE VALUES
 UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks

Period : 08.04.91 - 27.02.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	476	4.860	6.090	7.780
Urea	M0001	mmol/l	476	4.780	6.860	8.760
Creat-e	M0001	umol/l	471	39.90	58.20	80.30
Bili-tot	M0001	umol/l	461	1.830	2.610	3.700
Prot	M0001	g/l	476	59.53	64.02	69.88
Alb	M0001	g/l	461	34.79	37.47	39.86
Glob	M0001	g/l	461	23.30	26.59	30.77
A/G	M0001	l	461	1.220	1.400	1.590
Chol	M0001	mmol/l	476	1.480	2.030	2.600
Trigly	M0001	mmol/l	282	0.380	0.565	1.080
Na+	M0001	mmol/l	476	138.9	142.5	146.0
K+	M0001	mmol/l	476	2.720	3.215	3.720
Ca++	M0001	mmol/l	461	2.480	2.620	2.770
Cl-	M0001	mmol/l	461	95.90	99.70	103.9
PO4-in	M0001	mmol/l	461	1.390	1.790	2.220
ASAT (GOT)	M0001	U/l	496	45.70	57.00	71.80
ALAT (GPT)	M0001	U/l	496	18.50	29.00	46.30
ALP	M0001	U/l	496	74.70	118.1	199.8
GGT	M0001	U/l	322	0.000	0.000	0.000
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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

BLOOD CHEMISTRY REFERENCE VALUES
UNTREATED FEMALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 06.05.91 - 27.03.95

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Gluc	M0001	mmol/l	128	5.400	7.085	8.730
Urea	M0001	mmol/l	128	5.190	7.105	9.700
Creat-e	M0001	umol/l	128	45.60	59.25	86.20
Bili-tot	M0001	umol/l	128	1.740	2.650	3.650
Prot	M0001	g/l	128	61.42	66.58	71.22
Alb	M0001	g/l	128	35.53	38.27	41.59
Glob	M0001	g/l	128	23.69	28.07	31.95
A/G	M0001	l	128	1.200	1.370	1.590
Chol	M0001	mmol/l	128	1.390	1.950	2.660
Trigly	M0001	mmol/l	113	0.450	0.640	1.220
Na+	M0001	mmol/l	128	139.9	142.5	147.8
K+	M0001	mmol/l	128	2.690	3.020	3.430
Ca++	M0001	mmol/l	128	2.460	2.575	2.690
Cl-	M0001	mmol/l	128	97.20	100.8	104.9
PO4-in	M0001	mmol/l	128	1.030	1.320	1.680
ASAT (GOT)	M0001	U/l	138	44.80	55.80	78.30
ALAT (GPT)	M0001	U/l	138	20.20	29.60	47.60
ALP	M0001	U/l	138	52.40	80.25	123.3
GGT	M0001	U/l	123	0.000	0.000	2.500
ChE-Pl	M0001	U/l	10	1198	1439	2156
ChE-RBC	M0002	U/l	5	878.0	1288	1361
ChE-Br	M0002	U/g	5	3.704	3.810	4.095

11.6. Reference values: Urine analysis

URINE ANALYSIS REFERENCE VALUES
 UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 9 - 12 weeks Period : 17.12.91 - 02.11.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	223	3.400	6.100	10.80
Rel dens	M0001	1	223	1.031	1.043	1.061
pH	M0001	1	203	6.000	6.500	7.000

URINE ANALYSIS REFERENCE VALUES
 UNTREATED MALE RATS Tif: RAIf (SPF)

Age : 13 - 16 weeks Period : 14.01.92 - 12.09.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	69	3.500	5.800	10.50
Rel dens	M0001	1	69	1.025	1.042	1.065
pH	M0001	1	59	6.000	6.500	7.000

URINE ANALYSIS REFERENCE VALUES
 UNTREATED FEMALE RATS Tif: RAIF (SPF)

Age : 9 - 12 weeks Period : 17.12.91 - 02.11.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	224	1.600	3.900	7.900
Rel dens	M0001	1	224	1.030	1.043	1.064
pH	M0001	1	204	6.000	6.500	6.500

URINE ANALYSIS REFERENCE VALUES
 UNTREATED FEMALE RATS Tif: RAIF (SPF)

Age : 13 - 16 weeks Period : 14.01.92 - 12.09.94

PARAMETER	METHOD	UNIT	N	5%	MEDIAN	95%
Volume	M0001	ml	70	1.500	4.500	7.700
Rel dens	M0001	1	70	1.028	1.039	1.072
pH	M0001	1	60	6.000	6.500	7.000

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

11.7. Reference values: Organ weights

The following historical values of organ weights were summarized from control animals of the same strain during the following previously conducted studies:

OBS	SPEC	SEX	TEST NO.	ADMIN	WEEKS	YEAR	ANIMALS
1	RAT	M	891322	GAV	5	90	10
2	RAT	M	894127	GAV	5	90	5
3	RAT	M	894186	GAV	5	89	5
4	RAT	M	894340	GAV	5	90	5
5	RAT	M	894346	GAV	5	90	5
6	RAT	M	894433	GAV	5	91	5
7	RAT	M	894470	GAV	5	90	5
8	RAT	M	894503	GAV	5	90	5
9	RAT	M	900001	GAV	5	94	5
10	RAT	M	904196	GAV	5	91	5
11	RAT	M	904257	GAV	5	91	5
12	RAT	M	911317	GAV	5	92	5
13	RAT	M	911401	GAV	5	92	5
14	RAT	M	914054	GAV	5	91	5
15	RAT	M	914082	GAV	5	91	5
16	RAT	M	914136	GAV	5	91	5
17	RAT	M	921043	GAV	5	92	10
18	RAT	M	921091	GAV	5	92	10
19	RAT	M	921192	GAV	5	92	10
20	RAT	M	922002	GAV	5	92	10
21	RAT	M	923137	GAV	5	93	10
22	RAT	M	924020	GAV	5	92	5
23	RAT	M	924032	GAV	5	92	5
24	RAT	M	924164	GAV	5	92	10
25	RAT	M	925015	GAV	5	92	5
26	RAT	M	925022	GAV	5	92	5
27	RAT	M	925066	GAV	5	92	4
28	RAT	M	925082	GAV	5	92	5
29	RAT	M	925092	GAV	5	92	5
30	RAT	M	925103	GAV	5	92	5
31	RAT	M	945028	GAV	5	94	5
32	RAT	M	945093	GAV	5	94	5
33	RAT	M	945101	GAV	5	94	5
1	RAT	F	891322	GAV	5	90	10
2	RAT	F	894127	GAV	5	90	5
3	RAT	F	894340	GAV	5	90	5
4	RAT	F	894346	GAV	5	90	5
5	RAT	F	894433	GAV	5	91	5
6	RAT	F	894470	GAV	5	90	5
7	RAT	F	894503	GAV	5	90	5
8	RAT	F	900001	GAV	5	94	5
9	RAT	F	904196	GAV	5	91	5
10	RAT	F	904257	GAV	5	91	5
11	RAT	F	911317	GAV	5	92	5
12	RAT	F	911401	GAV	5	92	5
13	RAT	F	914054	GAV	5	91	5
14	RAT	F	914082	GAV	5	91	5
15	RAT	F	914136	GAV	5	91	5
16	RAT	F	921043	GAV	5	92	10
17	RAT	F	921091	GAV	5	92	10
18	RAT	F	921148	GAV	5	92	10
19	RAT	F	921192	GAV	5	92	10
20	RAT	F	922002	GAV	5	92	10
21	RAT	F	923137	GAV	5	93	10
22	RAT	F	924020	GAV	5	92	5
23	RAT	F	924032	GAV	5	92	5
24	RAT	F	924164	GAV	5	92	10
25	RAT	F	925015	GAV	5	92	5
26	RAT	F	925022	GAV	5	92	5
27	RAT	F	925066	GAV	5	92	5
28	RAT	F	925082	GAV	5	92	5
29	RAT	F	925092	GAV	5	92	5
30	RAT	F	925103	GAV	5	92	5
31	RAT	F	945028	GAV	5	94	5
32	RAT	F	945093	GAV	5	94	5
33	RAT	F	945101	GAV	5	94	5

OBS OBSERVATION NO. (SOFTWARE SPECIFIC)
 SPEC ANIMAL SPECIES
 ADMIN TYPE OF ADMINISTRATION (GAVAGE, IN FOOD OR WATER)
 WEEKS NO. OF WEEKS IN STUDY
 YEAR YEAR OF SACRIFICE
 ANIMALS NO. CONTROL-ANIMALS PER SEX

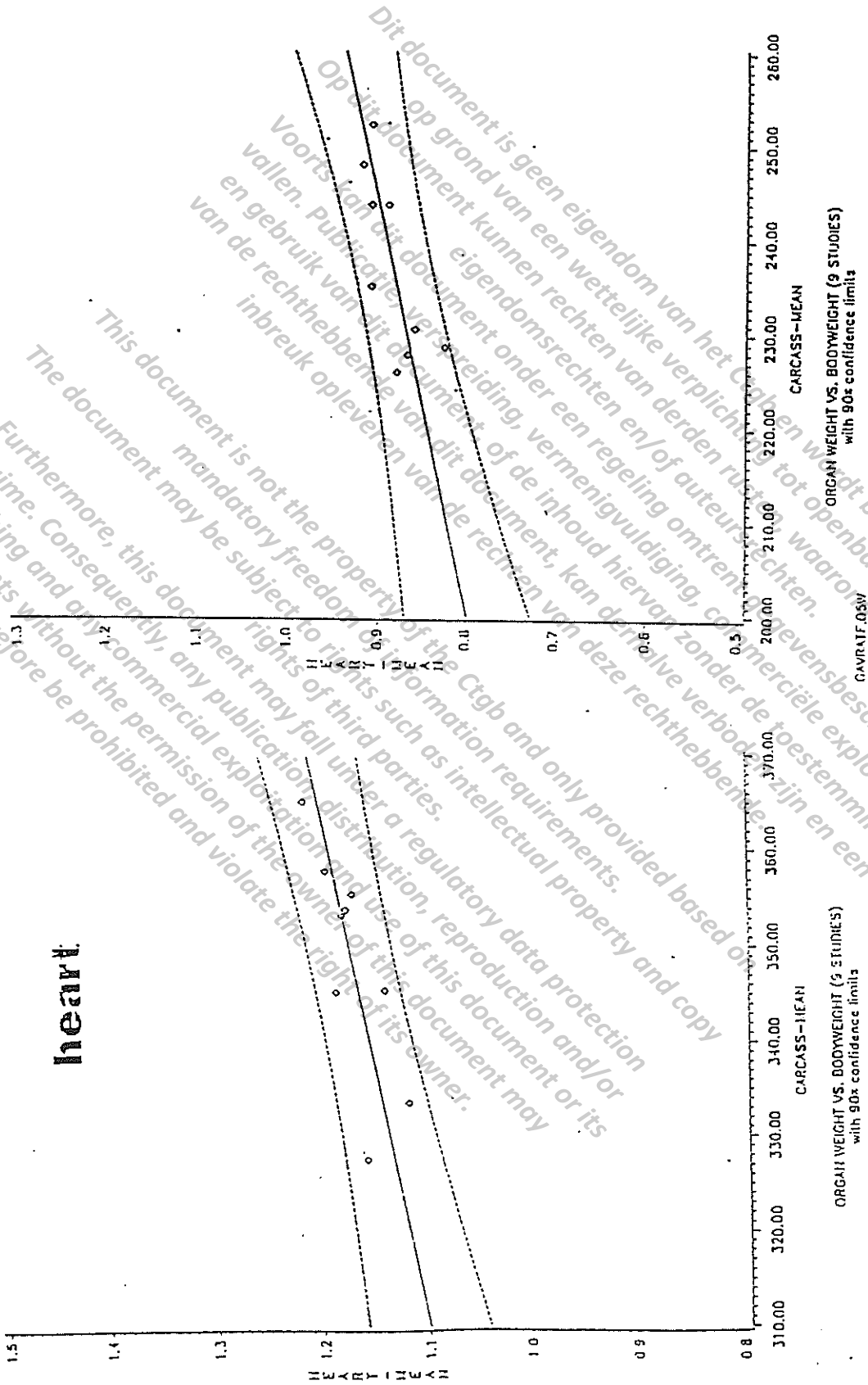
Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

UNTREATED FEMALE RATS, GAVAGE, WEEK 5

UNTREATED MALE RATS, GAVAGE, WEEK 5

heart



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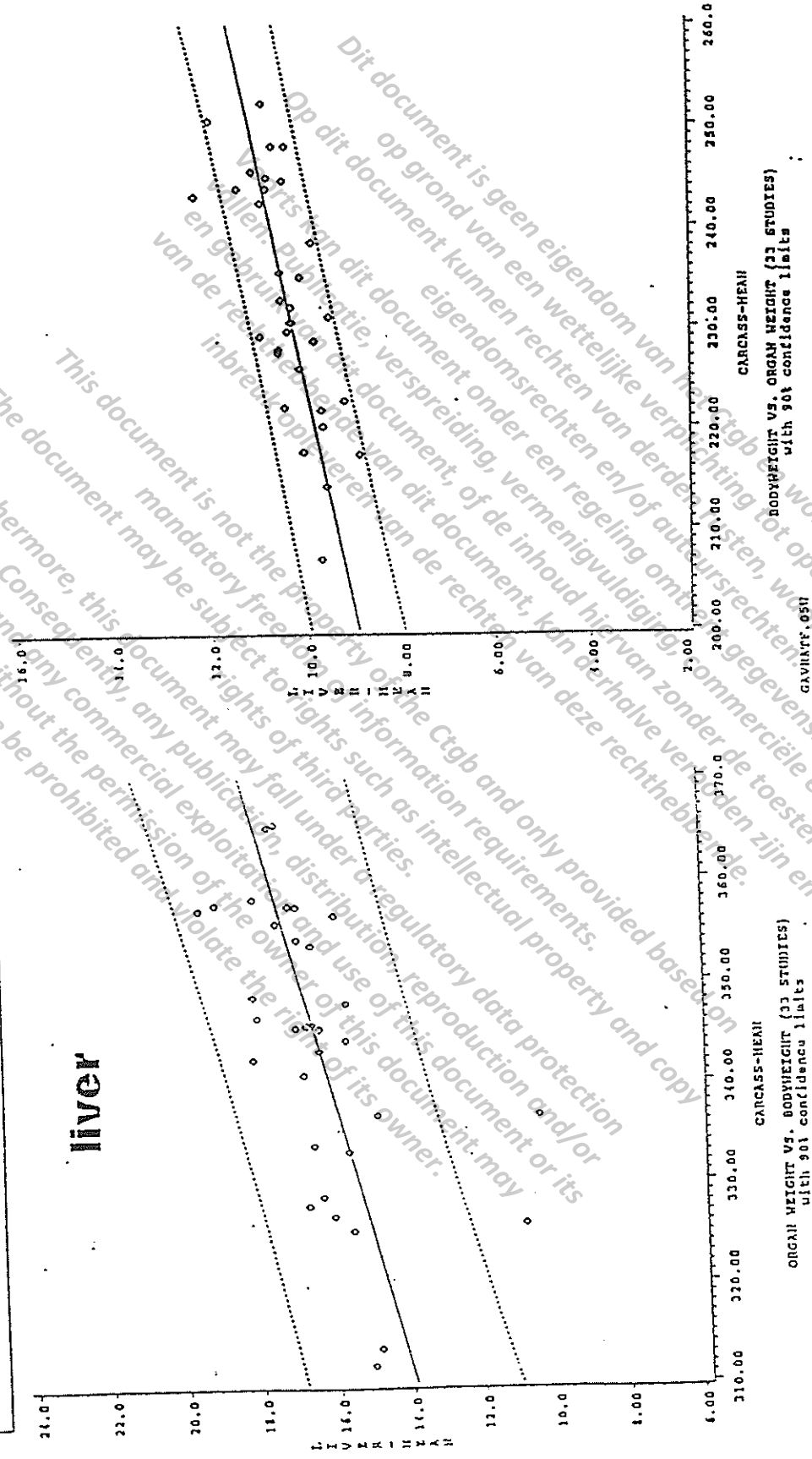
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UNTREATED FEMALE RATS, GAVAGE, WEEK 5

UNTREATED MALE RATS, GAVAGE, WEEK 5

liver



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

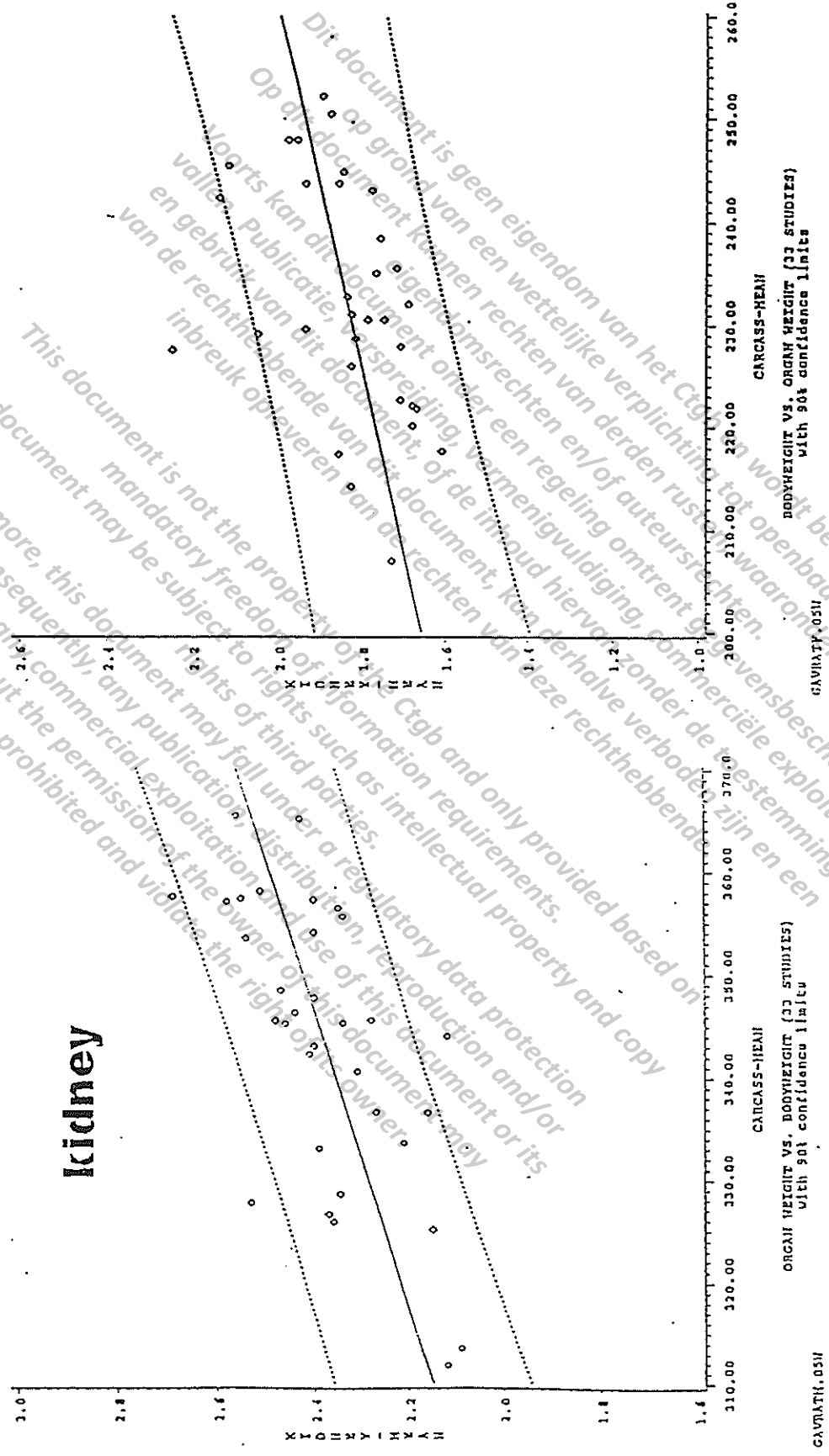
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UNTREATED FEMALE RATS, GAVAGE, WEEK 5

UNTREATED MALE RATS, GAVAGE, WEEK 5

kidney



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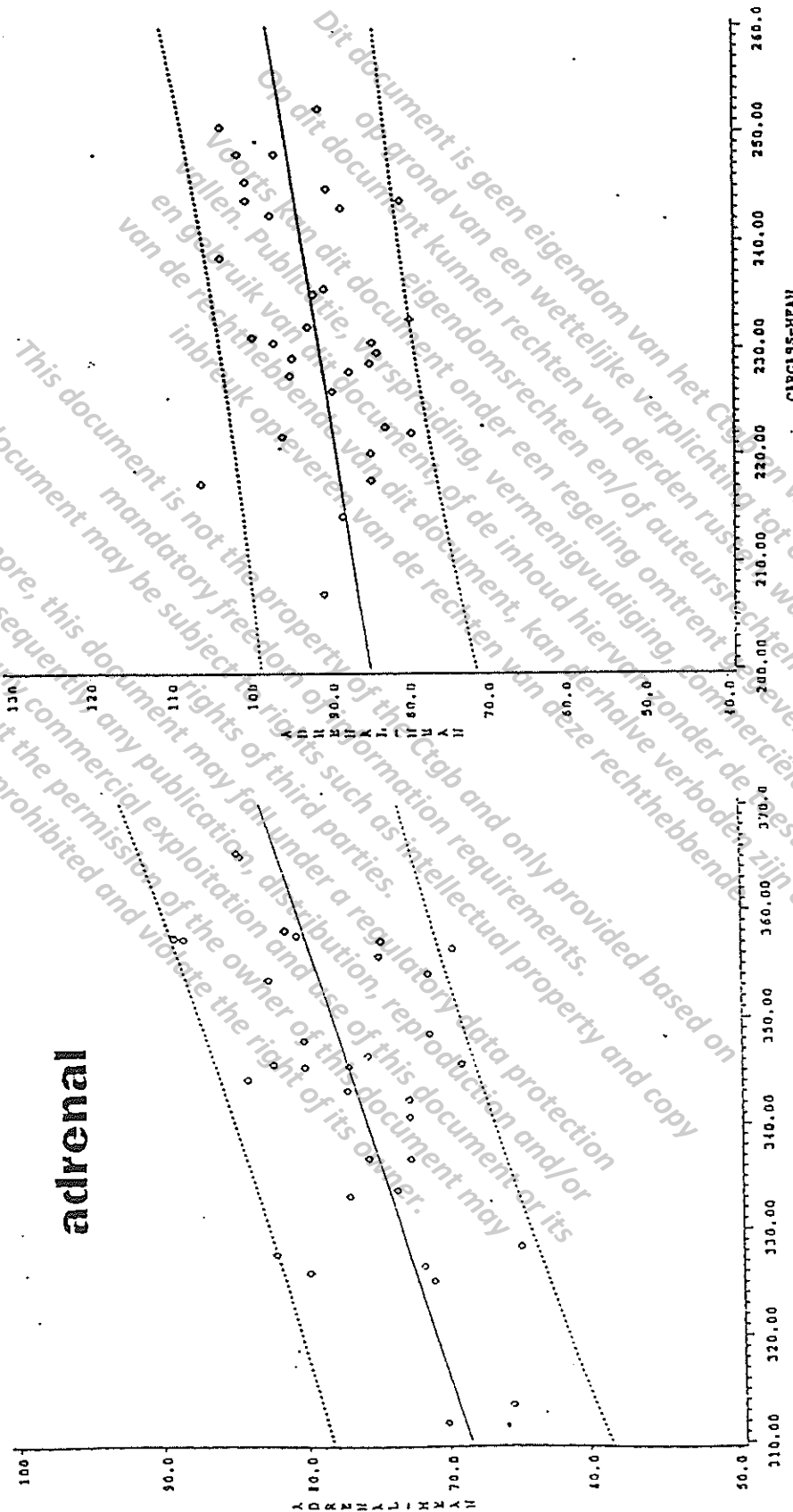
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Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

UNTREATED FEMALE RATS, GAVAGE, WEEK 5

UNTREATED MALE RATS, GAVAGE, WEEK 5

adrenal



ORGAN WEIGHT VS. BODYWEIGHT (33 STUDIES)
with 90% confidence limits
GAVRATTI, OSIF

CARCASS-WEIGHT
ORGAN WEIGHT VS. BODYWEIGHT (33 STUDIES)
with 90% confidence limits
GAVRATTI, OSIF

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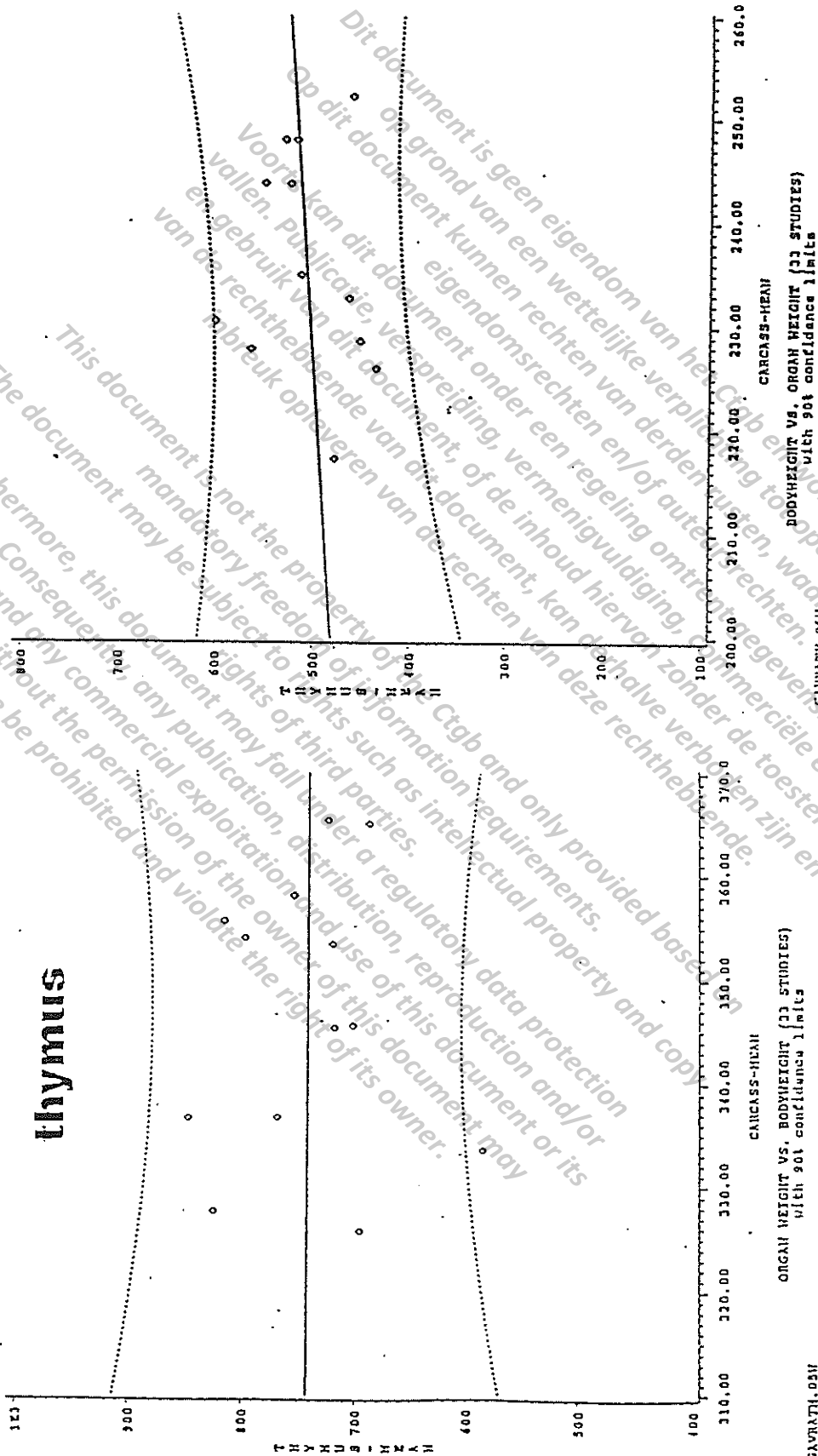
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UNTREATED FEMALE RATS, GAVAGE, WEEK 5

UNTREATED MALE RATS, GAVAGE, WEEK 5

Thymus



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ORGAN WEIGHT VS. BODYWEIGHT (23 STUDIES)
 WITH 95% CONFIDENCE LIMITS
 GAVIATY.05H

CARCASS-WEIGHT

ORGAN WEIGHT VS. BODYWEIGHT (23 STUDIES)
 WITH 95% CONFIDENCE LIMITS
 GAVIATY.05H

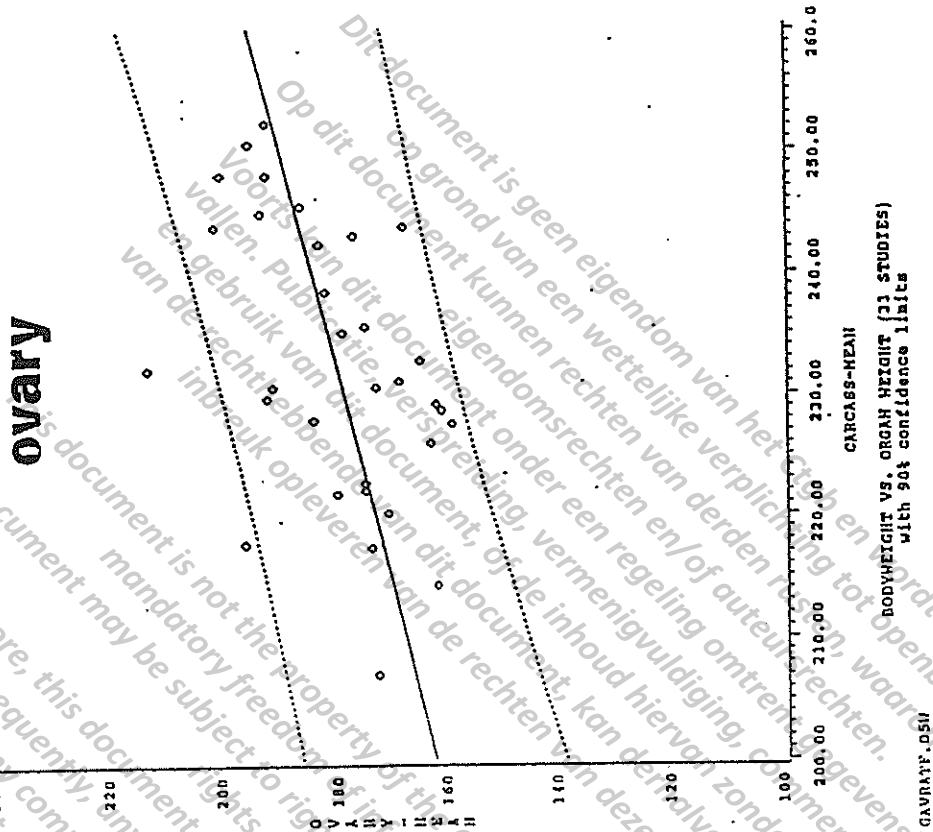
CARCASS-WEIGHT

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

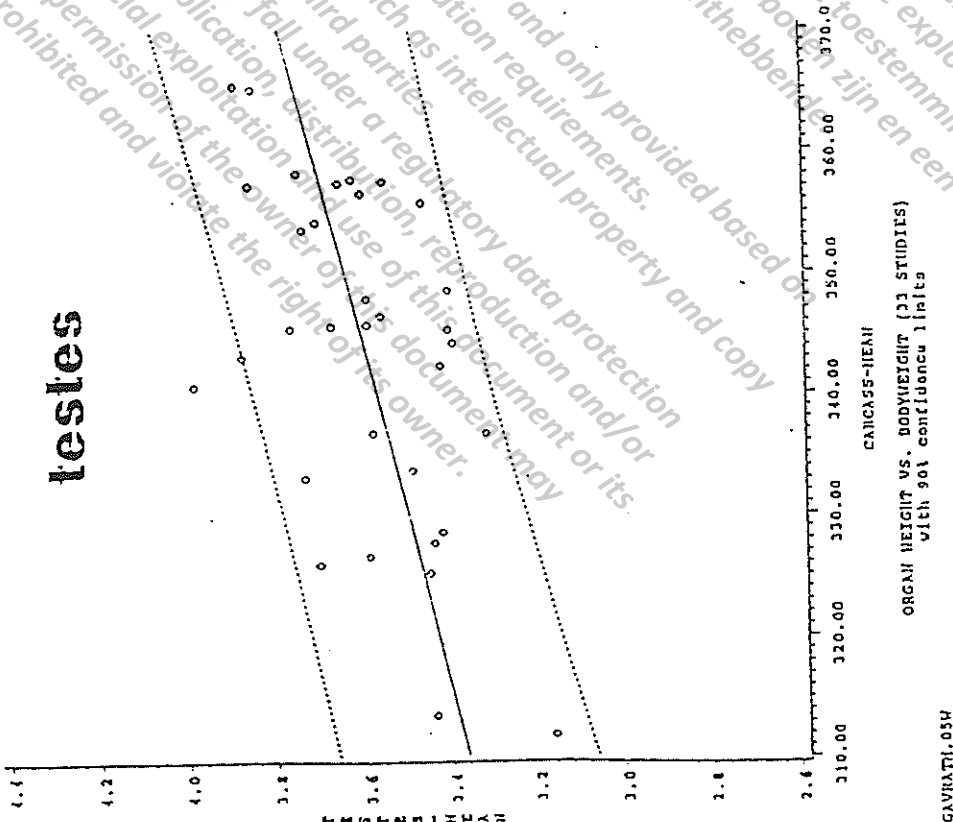
Test No.: 963103

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UNTREATED FEMALE RATS, GAVAGE, WEEK 5



UNTREATED MALE RATS, GAVAGE, WEEK 5



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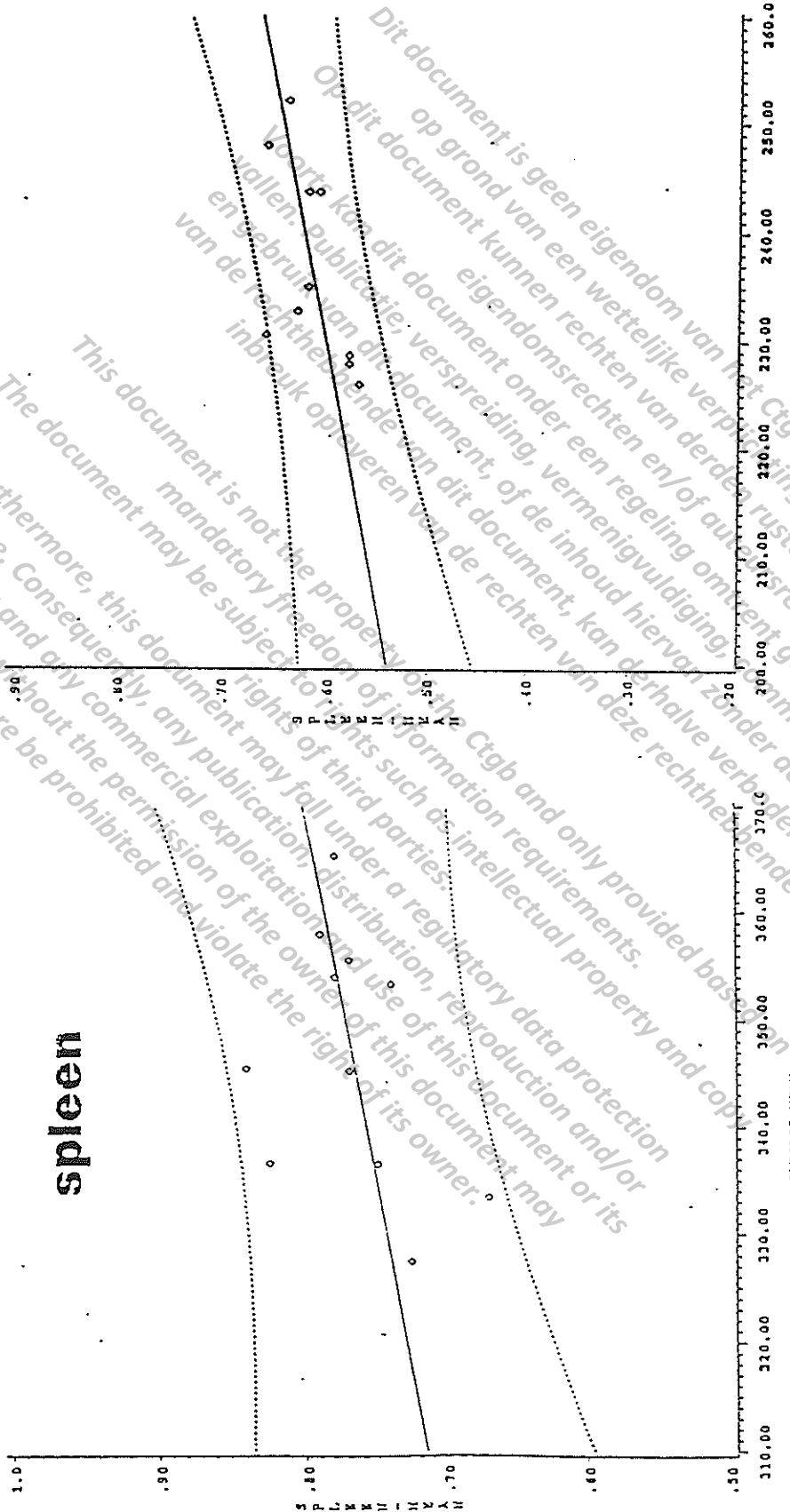
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UNTREATED FEMALE RATS, GAVAGE, WEEK 5

UNTREATED MALE RATS, GAVAGE, WEEK 5

spleen



ORGAN HEIGHT VS. BODY HEIGHT (33 STUDIES)
With 90% confidence limits
GAVRATH.03IV

ORGAN HEIGHT VS. BODY HEIGHT (33 STUDIES)
With 90% confidence limits
GAVRATH.03IV

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28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)
Test No.: 963103
Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

434

12. APPENDIX D: PATHOLOGY REPORT

PATHOLOGY REPORT	P963103
TEST ARTICLE : CGA 62826 tech.	PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL	DATE : 11-APR-97
SPONSOR : Crop Protection Sector	PATHDATA SYSTEM V3.6B

PREPARED BY: Dr. 5.12.e Woo
Senior Pathologist

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PATHOLOGY REPORT PAGE : I
 P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
 TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
 SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TABLE OF CONTENTS

	PAGE :
AUTHENTICATION	437
EXPLANATION OF CODES AND SYMBOLS	438
SUMMARY TABLES	
INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0,, MALE	439
INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: R1, MALE	440
INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0,, FEMALE	441
INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: R1, FEMALE	442
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0, INCL. +	443 - 444
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: R1	445
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0, INCL. +	446 - 447
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: R1	448

PATHOLOGY REPORT PAGE : II
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TABLE OF CONTENTS

PAGE :

INDIVIDUAL ANIMAL DATA		
ANIMAL HEADING DATA DOSE GROUP 1		449
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 1	450 -	462
ANIMAL HEADING DATA DOSE GROUP 2		463
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 2	464 -	470
ANIMAL HEADING DATA DOSE GROUP 3		471
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 3	472 -	479
ANIMAL HEADING DATA DOSE GROUP 4		480
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 4	481 -	486
ANIMAL HEADING DATA DOSE GROUP 5		487
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 5	488 -	498

PATHOLOGY REPORT

PAGE : 437
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

AUTHENTICATION

The undersigned hereby declares that the histopathology data in this report were compiled by him, and that they reflect accurately the primary data records.

5.1.2.e Woo

for Dr. 5.1.2.e Woo (absent)
Senior Pathologist

Novartis Crop Protection AG
Toxicology
CH-4002 Basle
Switzerland

TEST ARTICLE	: CGA 62826 tech.	PATHOL. NO.:	10031 AMA
TEST SYSTEM	: RAT, 28 DAYS, ORAL	DATE	: 11-APR-97
SPONSOR	: Crop Protection Sector	PATHDATA SYSTEM	V3.6B

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
- + = INTERCURRENT DEATH/SACRIFICED MORIBUND
- +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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TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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

ORGAN/FINDING	DOSE GROUP:				
	1	2	3	4	5
	6	5	5	5	5

ADRENAL GLANDS :
- ONE ORGAN, DAMAGED DURING AUTOPSY : 1

BODY SURFACES :
- SCAB FORMATION : 1

BRAIN :
- DAMAGED DURING AUTOPSY : 1

SKIN/SUBCUTIS :
- SCAB FORMATION : 1

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MACROSCOPIC PATHOLOGY
SUMMARY TABLES

PAGE : 440
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1 MALE

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

LUNG
- MOTTLED

1

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MACROSCOPIC PATHOLOGY
SUMMARY TABLES

PAGE : 441
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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

ORGAN/FINDING	DOSE GROUP:				
	1	2	3	4	5
	ANIM. EXAM.:				
	5	5	5	5	5
LIVER					
- FIBRINOUS ADHESION					1
RENAL PELVES					
- DILATATION		1			
THYMUS					
- MOTTLED			1	1	

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MACROSCOPIC PATHOLOGY
SUMMARY TABLES

PAGE : 442
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

INCIDENCE TABLE OF ANIMALS WITH NECROPSY FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1 FEMALE

ORGAN/FINDING	DOSE GROUP:	1	2	3	4	5
	ANIM. EXAM.:	5				5
BODY SURFACES						
- SCAB FORMATION		1				

END OF REPORT SECTION

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PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 443
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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:	6	5	5	5	5
AXILLARY LYMPH NODES	NO. EXAM.:	6	5	5	4	5
- ATROPHY		1	1			
- HYPERPLAS. REACT. CHR.				1		
HEART	NO. EXAM.:	6	5	5	5	5
- INFILT. INFLAM. CELL		3	1	1		
KIDNEYS	NO. EXAM.:	6	5	5	5	5
- ATROPHY TUBULAR		1		1		1
LIVER	NO. EXAM.:	6	5	5	5	5
- CONGESTION ACUTE		1				
- INFILT. INFLAM. CELL		2	1			
- CHANGE FATTY		2				
- HYPERTROPH. HEPATOCEL		1	1	1	3	4
LUNG	NO. EXAM.:	6	5	5	5	5
- CONGESTION ACUTE		2				
- HEMORRHAGE		1	1			
- FOAM CELLS		3	3	3	2	3
PITUITARY GLAND	NO. EXAM.:	6	5	5	5	5
- CYST DEVELOPMENTAL					1	
PROSTATE GLAND	NO. EXAM.:	6	5	5	5	5
- INFL. CHRONIC			1			
RENAL PELVES	NO. EXAM.:	6	5	5	5	5
- DILATATION					1	
SKIN/SUBCUTIS	NO. EXAM.:	1		1		
- INFL. CHRONIC		1				
- ULCERATION				1		
SPLEEN	NO. EXAM.:	6	5	5	5	5
- CONGESTION ACUTE		2	3	1	2	

**PATHOLOGY REPORT
SUMMARY TABLES**

**PAGE : 444
P963103**

**TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B**

**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0, INCL. +**

ORGAN/FINDING	SEX	DOSE GROUP:	1	2	3	4	5	MALE
		NO. ANIMALS:	6	5	5	5	5	
TESTES		NO. EXAM.:	6	5	5	5	5	
- IMMATURE			2					
THYMUS		NO. EXAM.:	6	5	5	5	5	
- HEMORRHAGE			2					
- CONGESTION ACUTE			1					
- ATROPHY				1			1	
THYROID GLAND		NO. EXAM.:	6	5	5	5	5	
- CYST DEVELOPMENTAL				1	2			

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PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 445
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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

ORGAN/FINDING	DOSE GROUP:	SEX : MALE				
		1	2	3	4	5
	NO. ANIMALS:	4				5
LIVER	NO. EXAM.:	4				5
- HYPERTROPH. HEPATOCEL		2				2
.....						
LUNG	NO. EXAM.:					1
- HEMORRHAGE						1
.....						

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PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 446
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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
ABDOMINAL CAVITY	NO. EXAM.:					1
- INFL. CHRONIC						1
HEART	NO. EXAM.:	5	5	5	5	5
- INFILT. INFLAM. CELL						1
KIDNEYS	NO. EXAM.:	5	5	5	5	5
- ATROPHY TUBULAR		4	1	1	1	3
- MINERALIZ. CORTICOMED		5	5	5	5	5
LIVER	NO. EXAM.:	5	5	5	5	5
- NECROSIS LOBAR						1
- CONGESTION ACUTE			1			
- INFILT. INFLAM. CELL		2			2	
- HYPERTROPH. HEPATOCYEL		1	1	3	2	3
LUNG	NO. EXAM.:	5	5	5	5	5
- CONGESTION ACUTE			1			
- FOAM CELLS		1			1	
PITUITARY GLAND	NO. EXAM.:	5	5	5	5	5
- CYST DEVELOPMENTAL				1		
RENAL PELVES	NO. EXAM.:	5	5	5	5	5
- DILATATION			1			
SPLEEN	NO. EXAM.:	5	5	5	5	5
- CONGESTION ACUTE		1	3			
THYMUS	NO. EXAM.:	5	5	5	5	5
- HEMORRHAGE				1	1	
- CONGESTION ACUTE			1			
THYROID GLAND	NO. EXAM.:	5	5	5	5	5
- CYST DEVELOPMENTAL			3	2		

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 447
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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
UTERUS	NO. EXAM.:	5	5	5	5	5
- DILATATION		2	1	1	1	1

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PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 448
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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

ORGAN/FINDING	SEX :	FEMALE				
	DOSE GROUP:	1	2	3	4	5
	NO. ANIMALS:	5				5
LIVER	NO. EXAM.:	5				5
- INFILT. INFLAM. CELL		2				
- HYPERTROPH. HEPATOCEL		1				1
SKIN/SUBCUTIS	NO. EXAM.:	1				
- ULCERATION		1				

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PATHOLOGY REPORT

PAGE : 449

INDIVIDUAL ANIMAL DATA

P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
 TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
 SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

ANIMAL HEADING DATA

DOSE GROUP : 1, Control

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
1	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
2	M	KO	+1	5	22-OCT-96	26-OCT-96	26-OCT-96
3	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
4	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
5	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
6	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
7	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
8	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
9	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
10	M	KO	+1	5	22-OCT-96	26-OCT-96	26-OCT-96
36	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
37	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
38	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
39	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
40	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
41	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
42	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
43	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
44	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
45	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 450
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

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

HEART:

-INFLAMMATORY CELL INFILTRATION, GRADE 2

LARGE INTESTINE PEYER'S PATCHES:

TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION

LUNG:

-FOAM CELLS, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO/+1
DAYS ON TEST : 5 * ANIMAL NO. : 2

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

AXILLARY LYMPH NODES:

-ATROPHY, GRADE 2

KIDNEYS:

-TUBULAR ATROPHY, UNILATERAL, GRADE 1

LIVER:

-FATTY CHANGE, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 451
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 1, Control MALE

CONT./FF. ANIMAL NO. : 2

LUNG:

-ACUTE CONGESTION, GRADE 2

TESTES:

-IMMATURE

THYMUS:

-HEMORRHAGE, GRADE 1

-ACUTE CONGESTION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 3

* NECROPSY FINDINGS

BODY SURFACES:

01: BACK SCAB FORMATION A.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

BODY SURFACES:

FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER: SKIN/SUBCUTIS.

HEART:

-INFLAMMATORY CELL INFILTRATION, GRADE 2

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

SKIN/SUBCUTIS:

-CHRONIC INFLAMMATION, GRADE 3

THIS FINDING CORRESPONDS WITH NECROPSY OBSERVATION NO: 01

IN THE BODY SURFACES.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 452
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

CONT./FF. ANIMAL NO. : 3

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 4

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-FOAM CELLS, GRADE 2

SPLEEN:

-ACUTE CONGESTION, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 5

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 453
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

CONT./FF. ANIMAL NO. : 5

* MICROSCOPIC FINDINGS

HEART:

-INFLAMMATORY CELL INFILTRATION, GRADE 2

LIVER:

-INFLAMMATORY CELL INFILTRATION, GRADE 1

LUNG:

-FOAM CELLS, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1

DAYS ON TEST : 58

* ANIMAL NO. : 6

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 454
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 7

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 8

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 455
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 1, Control MALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 9

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1

* STATE AT NECROPSY: KO/+1
DAYS ON TEST : 5 * ANIMAL NO. : 10

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-ACUTE CONGESTION, GRADE 1
-INFLAMMATORY CELL INFILTRATION, GRADE 1
-FATTY CHANGE, GRADE 1

LUNG:
-ACUTE CONGESTION, GRADE 2
-HEMORRHAGE, GRADE 1

SPLEEN:
-ACUTE CONGESTION, GRADE 1

TESTES:
-IMMATURE

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 456
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control MALE

CONT./FF ANIMAL NO. : 10

THYMUS:
-HEMORRHAGE, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 457
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 1, Control FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 36

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR ATROPHY, UNILATERAL, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, GRADE 4
UTERUS:
-DILATATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 37

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
LIVER:
-INFLAMMATORY CELL INFILTRATION, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 458
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 1, Control FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 38

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR ATROPHY, UNILATERAL, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
SPLEEN:
-ACUTE CONGESTION, GRADE 1
UTERUS:
-DILATATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 39

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR ATROPHY, UNILATERAL, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 459
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

CONT./FF. ANIMAL NO. : 39

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO * ANIMAL NO. : 40
DAYS ON TEST : 30

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
KIDNEYS:
-TUBULAR ATROPHY, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, GRADE 4
LIVER:
-INFLAMMATORY CELL INFILTRATION, GRADE 1
LUNG:
-FOAM CELLS, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 460
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 41

* NECROPSY FINDINGS

BODY SURFACES:
01: NECK SCAB FORMATION A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

BODY SURFACES:
FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER: SKIN/SUBCUTIS.
LIVER:
-INFLAMMATORY CELL INFILTRATION, GRADE 1
SKIN/SUBCUTIS:
-ULCERATION, GRADE 2
THIS FINDING CORRESPONDS WITH NECROPSY OBSERVATION NO: 01
IN THE BODY SURFACES.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO.: 42

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 461
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

CONT./FF. ANIMAL NO. : 42

* MICROSCOPIC FINDINGS

LIVER:

-INFLAMMATORY CELL INFILTRATION, GRADE 1

* STATE AT NECROPSY: R1

DAYS ON TEST : 58

* ANIMAL NO. : 43

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

* STATE AT NECROPSY: R1

DAYS ON TEST : 58

* ANIMAL NO. : 44

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT PAGE : 462
INDIVIDUAL ANIMAL DATA P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 1, Control FEMALE

CONT./FF. ANIMAL NO. : 44

* MICROSCOPIC FINDINGS

LIVER:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 45

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 463
P963103

TEST ARTICLE : CGA 62826 tech.
TEST SYSTEM : RAT, 28 DAYS, ORAL
SPONSOR : Crop Protection Sector

PATHOL. NO.: 10031 AMA
DATE : 11-APR-97
PATHDATA SYSTEM V3.6B

ANIMAL HEADING DATA

DOSE GROUP : 2, 10 mg/kg

ANIMAL NUMBER	SEX M/F	DEFINED STATE	AND FINAL NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST TEST	DATE OF NECROPSY
11	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
12	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
13	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
14	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
15	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
46	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
47	F	KO	+1	5	22-OCT-96	26-OCT-96	26-OCT-96
48	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
49	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
50	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 464
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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

AXILLARY LYMPH NODES:

-ATROPHY, GRADE 2

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

LUNG:

-FOAM CELLS, GRADE 2

SPLEEN:

-ACUTE CONGESTION, GRADE 1

THYROID GLAND:

-DEVELOPMENTAL CYST

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 12

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 465
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 12

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30 * ANIMAL NO. : 13

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-INFLAMMATORY CELL INFILTRATION, GRADE 1

LUNG:

-FOAM CELLS, GRADE 2

PROSTATE GLAND:

-CHRONIC INFLAMMATION, GRADE 3

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 466
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 14

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

HEART:
-INFLAMMATORY CELL INFILTRATION, GRADE 2
LUNG:
-FOAM CELLS, GRADE 2
SPLEEN:
-ACUTE CONGESTION, GRADE 1
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

LUNG:
-HEMORRHAGE, GRADE 2
SPLEEN:
-ACUTE CONGESTION, GRADE 1
THYMUS:
-ATROPHY, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 467
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 15

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 468
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 46

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
SPLEEN:
-ACUTE CONGESTION, GRADE 1
THYROID GLAND:
-DEVELOPMENTAL CYST
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO/+1
DAYS ON TEST : 5 * ANIMAL NO. : 47

* NECROPSY FINDINGS

RENAL PELVES:
01: DILATATION BIL A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 4
LIVER:
-ACUTE CONGESTION, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 469
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 47

LUNG:

-ACUTE CONGESTION, GRADE 3

RENAL PELVES:

-DILATATION, GRADE 3

THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.

SPLEEN:

-ACUTE CONGESTION, GRADE 1

THYMUS:

-ACUTE CONGESTION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 48

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 3

SPLEEN:

-ACUTE CONGESTION, GRADE 1

THYROID GLAND:

-DEVELOPMENTAL CYST

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT PAGE : 470
INDIVIDUAL ANIMAL DATA P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 49

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR ATROPHY, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 50

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 4
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
THYROID GLAND:
-DEVELOPMENTAL CYST
UTERUS:
-DILATATION, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 471
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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 NECROPSY	TEST DAYS	FIRST DAY	AND LAST DAY UNDER TEST	DATE OF NECROPSY
16	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
17	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
18	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
19	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
20	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
51	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
52	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
53	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
54	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
55	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 472
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:
-FOAM CELLS, GRADE 2
SPLEEN:
-ACUTE CONGESTION, GRADE 1
THYROID GLAND:
-DEVELOPMENTAL CYST
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 17

* NECROPSY FINDINGS

BRAIN:
01: DAMAGED DURING AUTOPSY
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

BRAIN:
NO MICROSCOPIC FINDING CORRESPONDING TO NECROPSY OBSERVATION NO. 01.
KIDNEYS:
-TUBULAR ATROPHY, UNILATERAL, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 473
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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

THYROID GLAND:
-DEVELOPMENTAL CYST
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO * ANIMAL NO. : 18
DAYS ON TEST : 30

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
HEART:
-INFLAMMATORY CELL INFILTRATION, GRADE 3
LUNG:
-FOAM CELLS, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 474
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 19

* NECROPSY FINDINGS

ADRENAL GLANDS:
01: ONE ORGAN, DAMAGED DURING AUTOPSY RI
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
NO MICROSCOPIC FINDING CORRESPONDING TO NECROPSY OBSERVATION NO. 01.
NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 20

* NECROPSY FINDINGS

SKIN/SUBCUTIS:
01: SCAB FORMATION A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

AXILLARY LYMPH NODES:
-CHRONIC REACTIVE HYPERPLASIA, GRADE 2
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
LUNG:
-FOAM CELLS, GRADE 2

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 475
P963103

TEST ARTICLE : CGA 62826 tech.
TEST SYSTEM : RAT, 28 DAYS, ORAL
SPONSOR : Crop Protection Sector

PATHOL. NO.: 10031 AMA
DATE : 11-APR-97
PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 3, 50 mg/kg

MALE

CONT./FF. ANIMAL NO. : 20

SKIN/SUBCUTIS:
-ULCERATION, GRADE 3

THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 476
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 3, 50 mg/kg FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 51

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
THYROID GLAND:
-DEVELOPMENTAL CYST
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

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 4
LARGE INTESTINE PEYER'S PATCHES:
TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION
PITUITARY GLAND:
-DEVELOPMENTAL CYST

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 477
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 52

THYROID GLAND:

-DEVELOPMENTAL CYST

UTERUS:

-DILATATION, GRADE 3

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 3

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 478
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
SPONSOR : Crop Protection Sector PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 3, 50 mg/kg FEMALE

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 54

* NECROPSY FINDINGS

THYMUS:
01: MOTTLED A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
THYMUS:
-HEMORRHAGE, GRADE 1
THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 55

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 479
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 55

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR ATROPHY, GRADE 1
- CORTICOMEDULLARY MINERALIZATION, GRADE 3

LIVER:

- HEPATOCELLULAR HYPERTROPHY, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 480
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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 NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY
21	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
22	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
23	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
24	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
25	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
56	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
57	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
58	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
59	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
60	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 481
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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

SPLEEN:

-ACUTE CONGESTION, GRADE 1

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

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

RENAL PELVES:

-DILATATION, UNILATERAL, GRADE 2

SPLEEN:

-ACUTE CONGESTION, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 482
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

PITUITARY GLAND:

-DEVELOPMENTAL CYST

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

LUNG:

-FOAM CELLS, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 483
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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 * ANIMAL NO. : 25
DAYS ON TEST : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

AXILLARY LYMPH NODES:
TISSUE NOT PRESENT FOR HISTOLOGIC EXAMINATION
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
LUNG:
-FOAM CELLS, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 484
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
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
DAYS ON TEST : 30 * ANIMAL NO. : 56

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 3

LIVER:

-INFLAMMATORY CELL INFILTRATION, GRADE 1

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 57

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 3

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 485
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
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
DAYS ON TEST : 30 * ANIMAL NO. : 58

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
UTERUS:
-DILATATION, GRADE 3
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 59

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 486
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-97
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

DAYS ON TEST : 30

* ANIMAL NO. : 60

* NECROPSY FINDINGS

THYMUS:

01: MOTTLED A.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR ATROPHY, UNILATERAL, GRADE 1

-CORTICOMEDULLARY MINERALIZATION, GRADE 3

LIVER:

-INFLAMMATORY CELL INFILTRATION, GRADE 1

LUNG:

-FOAM CELLS, GRADE 2

THYMUS:

-HEMORRHAGE, GRADE 1

THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 487
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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 UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY
26	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
27	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
28	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
29	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
30	M	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
31	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
32	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
33	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
34	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
35	M	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
61	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
62	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
63	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
64	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
65	F	KO	KO	30	22-OCT-96	20-NOV-96	20-NOV-96
66	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
67	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
68	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
69	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96
70	F	R1	R1	58	22-OCT-96	18-DEC-96	18-DEC-96

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 488
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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: KO
DAYS ON TEST : 30 * ANIMAL NO. : 26

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 27

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 489
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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: KO
DAYS ON TEST : 30 * ANIMAL NO. : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-FOAM CELLS, GRADE 2

THYMUS:

-ATROPHY, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO
DAYS ON TEST : 30 * ANIMAL NO. : 29

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR ATROPHY, UNILATERAL, GRADE 1

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

LUNG:

-FOAM CELLS, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 490
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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: KO
DAYS ON TEST : 30 * ANIMAL NO. : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

LUNG:

-FOAM CELLS, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 31

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT

PAGE : 491
P963103

INDIVIDUAL ANIMAL DATA

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 32

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 33

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1

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PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 492
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 34

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 35

* NECROPSY FINDINGS

LUNG:
01: MOTTLED A.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
LUNG:
-HEMORRHAGE, GRADE 1
THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 493
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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: KO
DAYS ON TEST : 30 * ANIMAL NO. : 61

* NECROPSY FINDINGS

LIVER:

01: FIBRINOUS ADHESION A.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

ABDOMINAL CAVITY:

-CHRONIC INFLAMMATION, GRADE 3

THIS FINDING CORRESPONDS WITH NECROPSY OBSERVATION NO: 01
IN THE LIVER.

KIDNEYS:

-TUBULAR ATROPHY, UNILATERAL, GRADE 1

-CORTICOMEDULLARY MINERALIZATION, GRADE 2

LIVER:

FOR DIAGNOSIS OF NECROPSY OBSERVATION NO. 01 SEE UNDER:

ABDOMINAL CAVITY.

-LOBAR NECROSIS

THIS FINDING CORRESPONDS TO NECROPSY OBSERVATION NO: 01.

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 494
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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: KO
DAYS ON TEST : 30 * ANIMAL NO. : 62

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR ATROPHY, UNILATERAL, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, GRADE 3
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

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, GRADE 2
LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT

PAGE : 495

INDIVIDUAL ANIMAL DATA

P963103

TEST ARTICLE : CGA 62826 tech.
TEST SYSTEM : RAT, 28 DAYS, ORAL
SPONSOR : Crop Protection Sector

PATHOL. NO.: 10031 AMA
DATE : 11-APR-97
PATHDATA SYSTEM V3.6B

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 5, 1000 mg/kg

FEMALE

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 64

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

HEART:

-INFLAMMATORY CELL INFILTRATION, GRADE 2

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, GRADE 4

LIVER:

-HEPATOCELLULAR HYPERTROPHY, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: KO

DAYS ON TEST : 30

* ANIMAL NO. : 65

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR ATROPHY, UNILATERAL, GRADE 1

-CORTICOMEDULLARY MINERALIZATION, GRADE 3

UTERUS:

-DILATATION, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 496
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 66

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: R1
DAYS ON TEST : 58 * ANIMAL NO. : 67

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT

PAGE : 497

INDIVIDUAL ANIMAL DATA

P963103

TEST ARTICLE : CGA 62826 tech.
TEST SYSTEM : RAT, 28 DAYS, ORAL
SPONSOR : Crop Protection Sector

PATHOL. NO.: 10031 AMA
DATE : 11-APR-97
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. : 68

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: R1

DAYS ON TEST : 58

* ANIMAL NO. : 69

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 498
P963103

TEST ARTICLE : CGA 62826 tech. PATHOL. NO.: 10031 AMA
TEST SYSTEM : RAT, 28 DAYS, ORAL DATE : 11-APR-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. : 70

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-HEPATOCELLULAR HYPERTROPHY, GRADE 1

END OF REPORT SECTION
LAST PAGE OF REPORT

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13. APPENDIX E: STUDY PROTOCOL AND AMENDMENT

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

Test No. 963103

CGA 62826 tech. (Metabolite of CGA 48988)

FINAL PROTOCOL

Study Director: Dr. phil.-nat. **1.2.e Woo**

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

Test Guidelines: OECD 407 (adopted July 95)
EEC 92/69 B.7.

Protocol proposed: September 16, 1996

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

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Protocol proposed by

Dr. phil.- nat.
Study Director

5.1.2.e Woo

5.1.2.e Woo

date: September 16, 1996

Facility Management

Ph.D.,
D.A.B.T... A.T.S.

5.1.2.e Woo

date: September 18, 1996

Responsible for
Laboratory Investigations

Dr. med. vet.

(absent)

5.1.2.e Woo

date: September 17, 1996

Responsible for Necropsy
and Pathology Services

Dr. med. vet.

(absent)

5.1.2.e Woo

date: September 17, 1996

Responsible for Pathology

Dr. med. vet.

FVH Pathology

(absent)

5.1.2.e Woo

date: September 14, 1996

Responsible for
Neurotoxicology

Dr. sc. nat.

5.1.2.e Woo

5.1.2.e Woo

date: September 16, 1996

For the Sponsor

Dr. 5.1.2.e Woo

5.1.2.e Woo

date: September 18, 1996

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:	October 15, 1996
Starting date of administration:	October 22, 1996
Date of completion, experimental group I:	November 20, 1996
Starting date of recovery period:	November 19, 1996
Recovery end date, experimental group II:	December 18, 1996
Submission of the final report for audit:	March 1997
Submission of the final report:	April 1996

Personnel and responsible scientists

Study director: Dr. phil.-nat. [REDACTED]
Longterm Toxicology

Technical assistant: [REDACTED]
Longterm Toxicology

Supervisor: [REDACTED]
Longterm Toxicology

Responsible for laboratory investigations: Dr. med. vet. [REDACTED]
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]
EVH Pathology
Toxicological Pathology

Study pathologist: Dr. med. vet. [REDACTED]
B. V. M. S., M. R. C. V. S.,
FTA Pathology
Toxicological Pathology

Responsible for analytics: [REDACTED]
RCC 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 $\pm 20\%$ of the mean value for each sex.

Identification

The animal number is identical with the cage number and is tattooed on the tail root.

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 ± 2 °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). 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 62826 tech.
Batch No.: RV-1592/4
Purity: 100 %
Description: solid
Date of receipt: August 20, 1996
Storage conditions: below 10°C
Stability: August 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 RCC Umweltchemie AG, 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 62826 tech. was stable in the vehicle over a period of 4 hours at room temperature.

Estimated quantity of test article needed

175 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

70 (total)

5 males, 5 females per dose group (experimental group I); additionally, 5 males, 5 females will be used at the control and high dose level for recovery evaluation (experimental group II).

Distribution

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

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 with the test article 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 possible 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

To detect delayed occurrence, or persistence of, or recovery from toxic effects, the recovery group (experimental group II) will be kept for a consecutive treatment-free 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. 963100
Short/Long-term Toxicology, CIBA-GEIGY Limited, Stein
Acute Oral Toxicity in the Rat (preliminary results)
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.

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)

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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 ($22 \pm 2^\circ\text{C}$, 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

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Urine analysis

urine color
volume
relative density
pH-value
protein
glucose
ketones
urobilinogen
bilirubin
erythrocytes

Proposed dates

at the end of the application period: November 19, 1996,
for the animals of the experimental groups I and II.

at the end of the recovery period: December 17, 1996,
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
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 with peripheral nerve (sciatic nerve)
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 intestine)
Peyer's patches (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
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

Test No.: 963103

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

muzzle
tongue
any tissue with gross lesions

Proposed date for necropsy and sampling

at the end of the application period: November 20, 1996,
for the animals of the experimental group I.

at the end of the recovery period: December 18, 1996,
for the animals of the experimental group II.

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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
bone marrow (femur)
trachea
lung
heart
liver
stomach
small intestine (duodenum, ileum, jejunum)
large intestine (cecum, colon, rectum)
Peyer's patches (small intestine)
Peyer's patches (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.

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> E.L. Lehmann, Nonparametrics: Statistical Methods Based on Ranks. Holden-Day (1975): pp. 5-31, 95, 232-238
- <2> Y. Lepage, Biometrika (1971) 58: pp. 213-217
- <3> A.R. Jonckheere, 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 analyzing 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.

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

Test No.: 963103

523

Test Article: CGA 62826 tech. (Metabolite of CGA 48988)

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.

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TABLE OF CONTENTS

	Page
0.1 Proprietary Information.....	2
1 PURPOSE.....	4
2 GENERAL.....	4
Sponsor.....	4
Testing facility.....	4
Proposed dates.....	4
Personnel and responsible scientists.....	5
Good laboratory practice.....	6
Basis of the study.....	6
Alteration of design.....	6
3 METHODS.....	7
3.1 Test system.....	7
3.1.1 Experimental animals.....	7
Stock.....	7
Source.....	7
Rationale for selection of species.....	7
Age.....	7
Body weight.....	7
Identification.....	7
3.1.2 Husbandry.....	8
Conditions.....	8
Diet.....	8
Water.....	8
3.2 Test article.....	9
Analytical pretests.....	9
Estimated quantity of test article needed.....	9
Safety precautions.....	9
3.3 Study conduct.....	10
3.3.1 Design.....	10
Number of animals.....	10
Distribution.....	10
Control of bias.....	10
3.3.2 Acclimatization.....	11
Duration of the acclimatization period.....	11
3.3.3 Treatment.....	11
Duration of treatment period.....	11
Route of administration.....	11
Rationale for route of administration.....	11
Frequency of administration.....	11
Vehicle.....	11
Volume applied.....	12
Preparation of suspension.....	12
Control analyses.....	12

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	Control animals.....	12
3.3.4	Recovery.....	12
	Duration of the recovery period.....	12
3.3.5	Dose levels.....	13
	Rationale for dose level selection.....	13
3.4	Study evaluation.....	14
3.4.1	Standard animal observations.....	14
3.4.2	Neurotoxicologic examinations.....	15
	Functional observational battery (FOB).....	15
	Motor activity.....	16
3.4.3	Laboratory investigations.....	17
	Hematology.....	17
	Clinical chemistry.....	17
	Urine analysis.....	18
	Proposed dates.....	18
3.4.4	Pathology.....	18
	Necropsies.....	18
	Organ weights.....	19
	Organ samples.....	20
	Proposed date for necropsy and sampling.....	21
	Histopathological evaluation.....	22
3.4.5	Statistical analysis.....	23
4	REPORTING.....	

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PROTOCOL AMENDMENT

CIBA-GEIGY Limited
SHORT/LONG-TERM TOXICOLOGY
4332 STEIN / SWITZERLAND

TYPE OF AMENDMENT:
Tissue processing
AMENDMENT NO: 1 (first)

DATE OF ISSUE OF AMENDMENT: October 23, 1996
DATE OF ISSUE OF PROTOCOL: September 16, 1996
SPONSOR DIVISION: Crop Protection Division

STUDY DIRECTOR

Dr. phil. - nat.

5.1.2.5 WOO
date: October 23, 1996

FACILITY MANAGEMENT

5.1.2.5 WOO
D.A.B.T., A.T.S.

5.1.2.5 WOO
date: October 24, 1996
Dr. med. vet.

FOR PATHOLOGY SERVICES

FOR THE SPONSOR

5.1.2.5 WOO
date: October 29, 1996
Dr.

1. AMENDMENT

As proposed by Short/Long-term Toxicology the tissue processing and slide preparation from animals of experimental group I will be contracted to the following laboratory:

ProPath (UK) LTD.
Willow Court
Netherwood Road
Hereford HR2 6JU
England

2. SCOPE

2.1 Quality assurance

At ProPath laboratories, the tissue processing and slide preparation will be conducted according to the current British GLP regulations and according to ProPath and Ciba-Geigy Limited Standard Operating Procedures.

2.2 Organs and tissues

An inventory of the delivered tissues will be kept at Short/Long-term Toxicology.

2.3 Archivation

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

COPIES

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TABLE OF CONTENTS

Page

VOLUME 1 OF 2

0.1	Reserved Page for Proprietary Information or Statement of No Data Confidentiality Claims.....	2
0.2	Certification of Good Laboratory Practices.....	3
0.3	Reserved Page for Flagging Statements.....	4
0.4	Signatures.....	5
0.5	Quality Assurance Statement.....	6
0.6	Table of contents.....	7
1	Summary and conclusion.....	11
2	Introduction.....	14
	Purpose.....	14
	Good laboratory practice.....	14
	Basis of the study.....	14
	Sponsor.....	14
	Testing facility.....	15
	Study dates.....	15
	Personnel and responsible scientists.....	16
	Archiving and distribution.....	17
2.1	Deviations.....	18
3	Materials and methods.....	19
3.1	Test article.....	19
	Pretest analytics.....	19
3.2	Test system.....	20
3.2.1	Experimental animals.....	20
3.2.2	Husbandry.....	20
3.2.3	Identification.....	21
3.3	Procedures.....	21
3.3.1	Study schedule.....	21
3.3.2	Animal number and distribution.....	22
3.3.3	Acclimatization.....	22
3.3.4	Treatment.....	23
3.3.5	Dose levels.....	23
3.3.6	Rationale for dose selection.....	23
3.4	Test article administration and diet.....	24
	Route of administration.....	24
	Frequency of administration.....	24
	Preparation of suspension.....	24
	Vehicle.....	24
	Volume of suspension applied.....	24

	Control analyses.....	24
	Control animals.....	25
3.4.1	Diet.....	25
3.4.2	Water.....	25
3.5	Observations and records.....	26
3.5.1	Standard animal observations.....	26
3.6	Neurotoxicologic examinations.....	27
3.6.1	Detailed clinical observations.....	27
3.6.2	Functional observational battery (FOB).....	27
3.6.3	Motor activity.....	29
3.7	Laboratory investigations.....	30
3.7.1	Parameters and methods used in hematology....	31
3.7.2	Parameters and methods used in blood chemistry.....	32
3.7.3	Parameters and methods used in urinalysis....	34
3.8	Pathology.....	35
3.8.1	Macroscopical examination.....	35
3.8.2	Microscopical examination.....	36
3.8.3	Acquisition and presentation of pathology data.....	37
3.9	Statistical analysis.....	39
4	Results.....	41
4.1	Analytical results.....	41
	Pretest analytics.....	41
	Test analytics.....	42
4.2	In-life observations.....	42
4.2.1	Clinical signs.....	42
4.2.2	Functional observational battery (FOB).....	42
4.2.3	Motor activity.....	42
4.2.4	Mortality.....	43
4.2.5	Body weight.....	43
4.2.6	Food consumption.....	43
4.2.7	Food consumption ratios.....	43
4.2.8	Water consumption.....	44
4.2.9	Hematology.....	44
4.2.10	Blood chemistry.....	45
4.2.11	Urine analysis.....	45
4.3	Organ weights and ratios.....	46
4.4	Pathology.....	47
4.4.1	Macroscopical findings.....	47
4.4.2	Microscopical findings.....	47
5	Discussion.....	48
6	References.....	50
7	Figures.....	51
7.1	Functional observational battery (Measurements)...	52
7.2	Motor activity.....	54
7.2.1	Mean session totals males.....	54
7.2.2	Mean session totals females.....	55
7.2.3	Motor activity (within-session time course) males.....	56

7.2.4	Motor activity (within-session time course) females.....	58
7.3	Body weight.....	60
7.4	Food consumption.....	62
7.5	Food consumption ratios.....	64
7.6	Water consumption.....	66
8	Tables (means, statistics).....	68
8.1	Analytical results.....	69
	Pretest analytics.....	69
	Test analytics.....	69
8.2	Clinical signs.....	70
8.3	Functional observational battery (means).....	71
8.4	Functional observational battery (statistics).....	76
8.5	Motor activity (means).....	83
8.6	Motor activity (statistics).....	88
8.7	Summary of animal fate.....	97
8.8	Body weight (means).....	98
8.9	Body weight (statistics).....	99
8.10	Food consumption (means).....	105
8.11	Food consumption (statistics).....	106
8.12	Food consumption ratios (means).....	112
8.13	Water consumption (means).....	113
8.14	Water consumption (statistics).....	114
8.15	Hematology (means).....	120
8.16	Hematology (statistics).....	126
8.17	Blood chemistry (means).....	150
8.18	Blood chemistry (statistics).....	156
8.19	Urine analysis (means).....	174
8.20	Urine analysis (statistics).....	180
8.21	Organ weights and ratios (means).....	190
	8.21.1 Organ weights (means).....	190
	8.21.2 Organ to body weight ratios (means).....	192
	8.21.3 Organ weights (means): 2. sacrifice.....	194
	8.21.4 Organ to body weight ratios (means): 2. sacrifice.....	196
8.22	Organ weights and ratios (statistics).....	198
	8.22.1 Organ weights (statistics).....	198
	8.22.2 Organ to body weight ratios (statistics).....	204
	8.22.3 Organ weights (statistics): 2. sacrifice.....	209
	8.22.4 Organ to body weight ratios (statistics): 2. sacrifice.....	214
9	Appendix A: Individual data.....	218
9.1	Clinical signs (individuals).....	219
9.2	Functional observational battery (individuals).....	223
9.3	Motor activity (individuals).....	240
9.4	Mortality (individuals).....	268
9.5	Body weight (individuals).....	272
9.6	Food consumption (individuals).....	278
9.7	Water consumption (individuals).....	284
9.8	Hematology (individuals).....	290
9.9	Blood chemistry (individuals).....	318

9.10	Urine analysis (individuals)	339
9.11	Organ weights and ratios (individuals)	355
9.11.1	Organ weights (individuals)	355
9.11.2	Organ to body weight ratios (individuals)	365
9.11.3	Organ weights (individuals): 2. sacrifice	374
9.11.4	Organ to body weight ratios (individuals): 2. sacrifice	378

VOLUME 2 OF 2 OF SUBMISSION

10	Appendix B: Analytical report	386
11	Appendix C: Reference values	406
11.1	Scoring criteria used in FOB	406
11.2	Assignment of signs and functions to functional domains	414
11.3	Units used in hematology	415
11.4	Reference values: Hematology	416
11.5	Reference values: Blood chemistry	420
11.6	Reference values: Urine analysis	424
11.7	Reference values: Organ weights	426
12	Appendix D: Pathology report	434
13	Appendix E: Study protocol and amendment	499

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