

CIBA-GEIGY

Agricultural Division

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8EHQ-0812-8777

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

July 31, 1992



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Office of Toxic Substances
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attention: Section 8(e) Coordinator
(CAP Agreement)

SUBJECT: 8E CAP - 0024

Dear Section 8(e) Coordinator:

Enclosed are the original and two copies of a study CIBA-GEIGY Corporation is submitting pursuant to the TSCA Section 8(e) Compliance Audit Program and CAP Agreement number 8E CAP-0024. The information being submitted is not considered Confidential Business Information. We are submitting the following information, as required by the CAP Agreement:

Company Name,	CIBA-GEIGY Corporation
Address and	Attn.: Mr. Anthony Di Battista
Telephone No.:	Toxicology, Regulatory Auditing and Compliance Department
	444 Saw Mill River Road
	Ardsley, New York 10502-2699
	Tel. No. 914-479-2776

Tested Chemical: CGA-173506 Technical;
4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1H-
pyrrole-3-carbonitrile
(Currently a research and development
pesticide)

CAS Registry No.: 13141-86-1

Report Title: Toxicity by Oral Administration to Rats
(Admixture with the Diet) for 20 Days
(Study Number 3548, June 30, 1988)



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Section 8(e) Coordinator
July 31, 1992
Page 2

Summary: Rats were fed 0, 1000, 5000, 10,000 or 20,000 ppm CGA-173506 in the diet for 20 days. Histologic examination of tissues revealed an increased incidence of tubular nephrosis, mainly at 10,000 and 20,000 ppm.

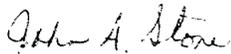
A TSCA Section 8(e) Notice has been previously submitted for this chemical, Document Control Number 8EHQ-1189-0843 S.

Category: Unit II.B.2.b

Prior Reporting: Not Applicable

Please call the undersigned at telephone number 919-632-2179 if you have any questions about this submittal.

Very truly yours,



John A. Stone
Manager, Environmental Issues

LS22CCG0715JAS/RD17

Enclosures (Two additional copies of this letter and three copies of the submitted study)

cc: Mr. A. Di Battista

0004

STUDY No. 3548 TSR/CGA 173506 tech./Test No. 87 1518

"contains NO CBI"

CGA 173506 tech.
TOXICITY BY ORAL ADMINISTRATION TO RATS
(ADMIXTURE WITH THE DIET)
FOR 20 DAYS

Addressee

Dr. B. Buttler
CIBA-GEIGY Limited
Toxicology AG 2.51
P.O. Box
CH-4002 Basel
Switzerland

Date: 30.06.88

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CERTIFICATION OF THE STUDY DIRECTOR

This study was conducted in accordance with the protocol following the O.E.C.D guideline (No. 407 - 12th May 1981) and agreed upon by CIBA-GEIGY Limited.

All the results collected during the study have been mentioned in this report, with the exception of possible minor details which cannot be considered to have any impact on the validity of the raw data or on the interpretation of the results.

This study in accordance with the Principles of Good Laboratory Practice (O.E.C.D., 12th May 1981) was performed at the Centre International de Toxicologie (C.I.T.), Miserey, 27005 Evreux, France.



J. COURCY di ROSA Date: 30.06.88
Study Director

QUALITY ASSURANCE UNIT
STATEMENT

The protocol, study and report were inspected by the C.I.T. Quality Assurance Unit on the following dates:

<u>INSPECTION</u>	<u>DATE OF INSPECTION</u>	<u>DATE OF INSPECTION REPORT</u>
Protocol	26.10.87	26.10.87
Study	24.11.87	24.11.87
Study	30.11.87	30.11.87
Study	11.12.87	11.12.87
Study	14.12.87	14.12.87
Report (first typing)	08.03.88	28.03.88
Report (final)	30.06.88	30.06.88

This study was performed in accordance with C.I.T. procedures and the principles of Good Laboratory Practice (O.E.C.D. - 12nd May 1981).

HEAD OF QUALITY ASSURANCE UNIT
AND SCIENTIFIC ARCHIVES

H. Rault

H. RAULT

Date: 30.06.88

SCIENTISTS INVOLVED IN THE STUDY

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M.H. READ Date: 30.06.88
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Toxicology



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Analytical chemistry



C. DELHOMME Date: 30.06.88
Docteur en Chimie

Macroscopic examinations



G. RADA Date: 30.06.88
Diplômé d'Etudes Zootechniques

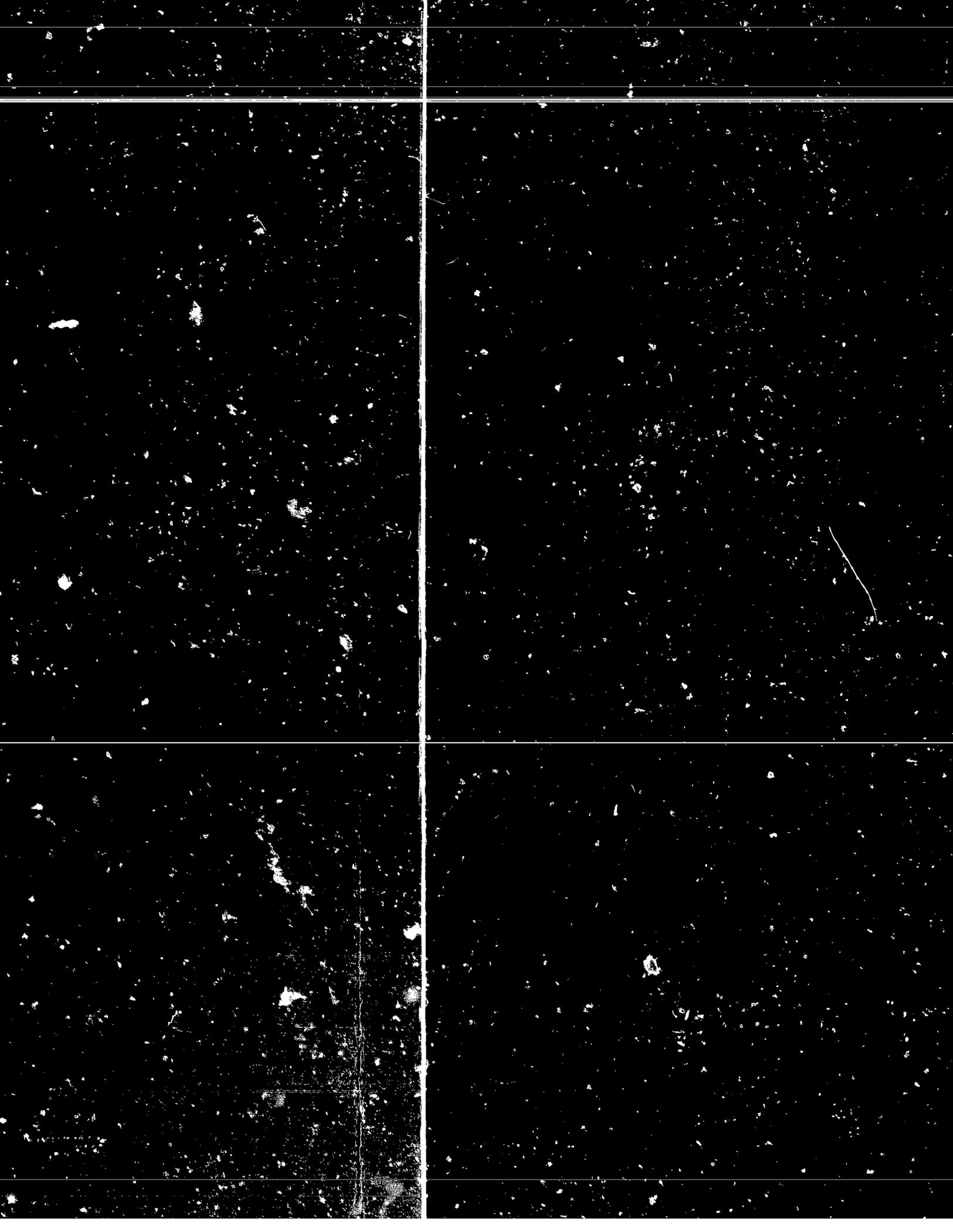
Microscopic examinations



J. IBANES-OLIVRY Date: 30.06.88
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M. ATTIA Date: 30.06.88
B.V. Msc., D.V.P., Ph.D
Head of Pathology Department



SUMMARY AND CONCLUSION

At the request of CIBA-GEIGY Limited, we evaluated the possible toxic effects of the test substance CGA 173506 tech. administered to Sprague Dawley rats by admixture with the diet over a period of 20 days for the males and 21 days for the females. The test substance is known to have fungicide properties.

Methods

Four groups of 6 male and 6 female rats in each were given the test substance in the diet at the concentrations of 1000, 5000, 10000 and 20000 ppm. A control group with the same number of animals received an untreated diet.

Animals were housed two per cage in a controlled animal room.

A clinical examination was performed at least once a day.

Mortality was checked twice a day, except at weekends and Public Holidays when it was checked once only (in the morning).

Bodyweight, food and water consumptions were recorded once a week.

Haematology, blood biochemistry examinations and urinalysis were performed after two weeks in all the animals from all the groups.

Post-mortem examinations were performed at the end of treatment.

Results

Clinical signs

At all the concentrations, no clinical signs were observed except the presence of abnormal coloured (black) faeces in males and females from the 5000, 10000 and 20000 ppm groups.

Mortality

No mortality was noted during the treatment period.

Bodyweight and food consumption

The bodyweight and food consumption values of all the treated groups were similar to those of the control group except a lower bodyweight (not statistically significant) for the males from the 20000 ppm group after 2 weeks of treatment.

Water consumption

A slight water consumption increase was noted in males and females from the 10000 and 20000 ppm groups but it was not statistically significant. This result showed no correlation with the achieved urine volume values.

Laboratory investigations

After 2 weeks of treatment, no treatment-related changes were observed among the haematological parameters. The evaluation of the blood biochemical parameters revealed changes in some parameters namely: slight decreases in the values of plasma, sodium and chloride (2 to 5%) among the animals of either sex from the 5000, 10000 and 20000 ppm groups; due to individual changes a slight increase in specific gravity (approximately 1%) and a slight decrease in urinary volume (25 to 38%) in males from the 10000 and 20000 ppm groups.

The correlation of these slight variations with the presence of tubular nephrosis could not be totally excluded.

In the absence of any other evidence, the relationship of the increase in cholesterol and decrease in glucose values in the animals from the high concentration groups to the treatment was unlikely.

Pathology

Some changes in organ weights (net and/or relative) were noted in treated males and females and with regard to the control group:

- an increase in the absolute and relative weights of kidneys for males from the 20000 ppm group (33 and 65% respectively) and for females from the 10000 ppm group (15 and 14% respectively).

The above-mentioned changes in the weights of kidneys and the macroscopic changes (paleness of the kidneys and blackish and punctiform foci in kidneys) observed in some males from the 20000 ppm group were associated with the tubular nephrosis.

Other changes in organ weights, considered irrelevant to the treatment with CGA 173506 tech. were:

- a decrease in the net weights of the heart for males from the 20000 ppm group and for females from the 5000 and 20000 ppm groups.
- a decrease in the net weights of the spleen for males from the 1000, 5000 and 20000 ppm groups and a decrease in the net and relative weights in females from the 1000 and 5000 ppm groups.
- an increase in the net weights of liver for females from the 10000 ppm group and in the relative weights for males and females from the 10000 and 20000 ppm groups.
- an increase in the relative weights of brain for males from the 20000 ppm group.

The microscopic examinations showed tubular nephrosis in:

- 1/6 males from the 5000 ppm group
- 4/6 males and 1/6 females from the 10000 ppm group
- 6/6 males and 3/6 females from the 20000 ppm group.

The incidence and severity of this lesion were dose-related. These renal changes and the increase in the weights of the kidneys were considered to be related to the treatment with the test substance.

Conclusion

The test substance CGA 173506 tech. when given to the rat over a period of 20 to 21 days was well-tolerated at the concentration of 1000 ppm; but the higher concentration levels induced a dose-related nephrotoxicity in male rats at the concentration of 5000 ppm and in both sexes at the concentrations of 10000 and 20000 ppm.

1. MATERIALS AND METHODS

1.1. TEST SUBSTANCE

1.1.1. Identification

The test substance **CGA 173506 tech.** was supplied by CIBA-GEIGY Limited.

Three plastic bottles containing a grey powder and identified as follows: "Subst -Nr.: CGA 173506 tech., Batch Nr.: PA-2882/9-16" were received at C.I.T. on the following dates:

- one bottle of 200 g on 2nd October 1987
- two bottles of 100 g and 200 g in each on 2nd November 1987.

According to the information given by the labels, the test substance was stored at room temperature from the 2nd October 1987 to the 16th October 1987. Since this date, the test substance was stored at +4°C according to the information given by the test substance data sheet.

1.1.2. Vehicle

The vehicle used was the diet U.A.R. This diet was a beige powder stored in bags of 25 kg and labelled as follows "Aliment Composé - complet, Entretien Rat et Souris A 04 C (Villemoisson-sur-Orge, 91360 Epinay), Batch Nos. 70708, 70917 and 71021.

1.1.3. Preparation

The test substance was blended in a mortar with a small quantity of diet for each concentration.

The required concentrations were then prepared by direct dilution of this premix with further quantities of untreated diet and homogeneity was obtained by mixing in a Lödige M20 mixer for 10 minutes.

1.1.4. Chemical analyses of the preparations

Homogeneity of the dietary mixtures at the lowest and highest dose levels (1000 and 20000 parts per million) checked before the beginning of the study was good.

Stability of the same mixtures kept either after 0, 4 and 7 days in closed bags or after 0, 3, 4, 7 and 10 days in open feeders maintained in the atmosphere of the animal room was satisfactory.

Concentrations of all the dietary mixtures were checked in Weeks 1 and 2. The results showed a good correlation between observed and theoretical concentrations for each dietary mixture (the highest difference was 5%).

1.2. TEST SYSTEM

1.2.1. Animals

The rat was used for this study as the recommended rodent species required by the different national and international guidelines for the study of subchronic toxicity.

Sixty-seven Sprague Dawley CrI: CD (SD) Br rats (34 males and 33 females) supplied by the "Centre d'Elevage Charles River" (76410 Saint-Aubin-les-Elbeuf, France) were received at C.I.T. on the 18.11.87. Sixty animal (30 males and 30 females) were selected for the study and the remaining animals were sacrificed on the first day of treatment.

At the beginning of treatment, the animals had an average body-weight of 150 grams for the males and 105 grams for the females. They were approximately 6 weeks old.

1.2.2 Animal management

The animals were housed in an air-conditioned animal room for the 6-day acclimatization period and then for the duration of the treatment. The ambient conditions were as follows:

- . temperature : $21 \pm 2^{\circ}\text{C}$
- . relative humidity : $60 \pm 20\%$
- . light/dark cycle : 12 h/12 h
- . air : approx. 13 cycles/hour of filtered, not recycled air

The animals were placed in suspended wire-mesh cages (43.0 x 21.5 x 18 cm) with 2 rats of the same sex and group in each. A metallic tray was placed under each cage and contained sawdust (Société Parisienne des Sciures, 03500 Pantin, France).

The absence of contaminants in the sawdust was periodically checked by the Laboratoire Municipal de Rouen (76000 Rouen, France).

Bottles and sawdust were changed once a week. Cages were not randomized in the room but placed in order, vertically on racks.

1.2.3. Diet and water

The animals were fed ad libitum with a fine ground diet ref. A 04 C. Each used batch of food was analysed by the supplier (composition and contaminants) (see appendix for analytical certificates).

The animals had free access to tap water filtered by F.G. Millipore filters (0.22 micron) and delivered in bottles with stainless steel pipettes and rubber stoppers.

Routine microbiological and chemical analyses of water were made regularly by the Laboratoire Municipal de Rouen (76000 Rouen, France) in order to detect major contaminants (see appendix).

There was no information available to the Study Director indicating that any non-nutrient substances, at a level likely to influence the effect of the test substance, were present in the diet or in the water.

1.3. TREATMENT

1.3.1. Dose levels and experimental groups

Animals were randomly assigned to the different experimental groups: T (0 ppm), A (1000 ppm), B (5000 ppm), C (10000 ppm) and D (20000 ppm) with 6 males and 6 females per group.

The concentrations of the test substance CGA 173506 tech. were agreed with CIBA-GEIGY Ltd. according to the results of a previous 28-day gavage study (861499/RCC 079222).

Individual animal numbers were tattooed on the ears.

Concentrations, groups and animal numbers were as follows:

Groups and concentrations (ppm)	Test substance	Animal No.	
		Males	Females
T 0	Food UAR	C23501	C23551
		C23502	C23552
		C23503	C23553
		C23504	C23554
		C23505	C23555
		C23506	C23556

Groups and concentrations (ppm)	Test substance	Animal No.	
		Males	Females
A 1000	CGA 173506 tech.	C23507	C23557
		C23508	C23558
		C23509	C23559
		C23510	C23560
		C23511	C23561
		C23512	C23562
B 5000	CGA 173506 tech.	C23513	C23563
		C23514	C23564
		C23515	C23565
		C23516	C23566
		C23517	C23567
		C23518	C23568
C 10000	CGA 173506 tech.	C23519	C23569
		C23520	C23570
		C23521	C23571
		C23522	C23572
		C23523	C23573
		C23524	C23574
D 20000	CGA 173506 tech.	C23525	C23575
		C23526	C23576
		C23527	C23577
		C23528	C23578
		C23529	C23579
		C23530	C23580

1.3.2. Administration of the test substance

The oral route was chosen because it is a possible route for human exposure.

The test substance was administered by admixture to the diet, 7 days a week, for 20 days for the males and 21 days for the females.

The control animals were given the untreated diet.

The concentration of the test substance in the diet remained unchanged.

1.3.3. Duration of treatment

The number of days of treatment was:

20 days: - for all the males, treated and control, that were sacrificed on the 21st day of the study.

21 days: - for all the females, treated and control, that were sacrificed on the 22nd day of the study.

1.4. CLINICAL EXAMINATIONS

1.4.1. Clinical signs

All of the rats were observed once a day, at approximately the same time, during the control of mortality.

1.4.2. Mortality

Mortality was checked every day, in the morning and the afternoon, for each animal except on Saturdays, Sundays and Public Holidays, when it was checked once in the morning. Any animal showing signs of severe debility, especially if death appeared imminent, was sacrificed and subjected to a macroscopic examination.

1.4.3. Bodyweight

Animals were weighed at the time of their allocation to the experimental groups, the first day of treatment, then at weekly intervals until the end of the study.

1.4.4. Food consumption

Food consumption was measured once a week during treatment. The food consumption was calculated over seven days and the quantity of food consumed in grams per animal/per day was determined. It was calculated from the difference between the given quantity and the remaining one in the food container of the same cage and then divided by the number of animals of the same cage.

1.4.5. Food conversion ratios

Food conversion ratio was calculated during the treatment of 20 days for males and 21 days for females.

These values were obtained by dividing the weekly mean food consumption (in grams) by the weekly mean bodyweight gain for each sex and group.

The mean food conversion ratio (FCR) achieved was the food consumed per unit of bodyweight gain.

1.4.6. Achieved dosages

The weekly group mean achieved intake of CGA 173506 tech. (mg/kg/d) was calculated from the mean median weekly bodyweight, daily food consumption data and the theoretical concentrations (ppm).

1.4.7. Water consumption

The quantity of water consumed by the animals of each cage was measured weekly during the treatment period. The water consumption was calculated in the same way as that used for the food consumption.

1.5. LABORATORY INVESTIGATIONS**1.5.1. Haematology**

Blood samples were taken from the orbital sinus of animals under light ether anaesthesia after overnight fasting and collected into tubes containing the appropriate anticoagulant. The following parameters were determined in all animals in Week 3.

Parameters	Apparatus / Methods	Unit
<u>Blood collected on complexon</u>		
Red Cell Count (RBC)	ORTHO ELT-8/ds Haematology Analyzer/Laser	$10^{12}/l = T/l$
Haemoglobin (HB)	ORTHO ELT-8/ds Haematology Analyzer/Drabkin	g/dl
Mean Cell Volume (MCV)	ORTHO ELT-8/ds Haematology Analyzer/Computed	fl
Packed Cell Volume (PCV)	ORTHO ELT-8/ds Haematology Analyzer/Computed	l
Mean Cell Haemoglobin Concentration (MCHC)	ORTHO ELT-8/ds Haematology Analyzer/Computed	g/dl
Mean Cell Haemoglobin (MCH)	ORTHO ELT-8/ds Haematology Analyzer/Computed	pg
White Cell Count (WBC)	ORTHO ELT-8/ds Haematology Analyzer/Laser	$10^9/l = G/l$
Platelet Count (PLAT)	ORTHO ELT-8/ds Haematology Analyzer/Laser	$10^9/l = G/l$
Differential White Cell Count: (1)	Microscopic with May-Grünwald staining	% and $10^9/l = G/l$
Neutrophils (N)		
Eosinophils (E)		
Basophils (B)		
Lymphocytes (L)		
Monocytes (M)		
Reticulocyte Count (2)	Microscopic; bright cresyl blue staining	p.1000
<u>Sampling of citrate</u>		
Quick time (QT)	KC 10 Dade Thromboplastin C (Dade)	s

(1) The blood smears were performed in all animals. The differential white cell count was evaluated in the control and high dose level groups.

(2) In the absence of anaemia, the smears were prepared but the count was not performed.

1.5.2. Blood biochemistry

Blood samples were taken from the orbital sinus of animals under light ether anaesthesia after overnight fasting and collected into tubes containing the appropriate anticoagulant. The following parameters were determined in all the animals in Week 3.

Parameter	Apparatus	Method	Unit
<u>Sampling on lithium heparinate</u>			
Sodium (NA ⁺)	Electrolyte 4 Analyzer	Selective electrode (Beckman)	mmol/l
Potassium (K ⁺)	Electrolyte 4 Analyzer	Selective electrode (Beckman)	mmol/l
Chloride (CL ⁻)	Electrolyte 4 Analyzer	Selective electrode (Beckman)	mmol/l
Calcium (CA ⁺⁺)	Hitachi 705	Methylthymol blue (Biomérieux)	mmol/l
Inorganic phosphorus (I.PHOS)	Hitachi 705	Molybdenum blue without deproteinisation (Biomérieux)	mmol/l
Glucose (GLUC)	Hitachi 705	GOD PAP (Boehringer)	mmol/l
Urea (UREA)	Hitachi 705	Modified Bertnelot (Boehringer)	mmol/l
Total protein (PROT)	Hitachi 705	Biuret (Boehringer)	g/l
Cholesterol (CHOL)	Hitachi 705	CHOD PAP (Boehringer)	mmol/l
Triglycerides (TRIG)	Hitachi 705	GPO PAP (Boehringer)	mmol/l
Alkaline phosphatase (ALP)	Hitachi 705	DGKC Standard (30°C) (Boehringer)	IU/l
Aspartate amino transferase (ASAT)	Hitachi 705	DGKC Standard (30°C) (Boehringer)	IU/l
Alanine amino transferase (ALAT)	Hitachi 705	DGKC Standard (30°C) (Boehringer)	IU/l
Gamma glutamyl transferase (GGT)	Hitachi 705	Szasz (Boehringer)	IU/l

Parameter	Apparatus	Method	Unit
<u>Sampling without anticoagulant</u>			
Protein electrophoresis	Cellosystem 2	Cellogel (Sébia)	
. Albumin (Alb)			% and g/l
. Alpha-1 globulins (A1-GLOB)			% and g/l
. Alpha-2 globulins (A2-GLOB)			% and g/l
. Beta-globulins (B-GLOB)			% and g/l
. Gamma-globulins (G-GLOB)			% and g/l
. Albumin/globulins ratio (A/G)			1

1.5.3. Urinalysis

Fasted animals were placed in metabolism cages and urine was collected for an overnight period. The following parameters were determined in all the animals in Week 3:

- . Volume (VOLUME, ml)
- . pH (PH), specific gravity (SP.GRAV), urobilinogen (UROB, U% = Ehrlich unit/100 ml), proteins (PROT), glucose (GLUC), ketones (CETO), bilirubin (BILI), blood (BLOOD), nitrites (NITR) using N-Multistix SG (Ames) test strips

0 0 2 2

1.6. PATHOLOGY

1.6.1. Sacrifice

On completion of the treatment period, after about 16 hours of fasting, all surviving animals were asphyxiated by carbon dioxide and killed by exsanguination. Animals were weighed before necropsy.

1.6.2. Organ weights

For all animals sacrificed at the end of treatment, the following organs were weighed wet as soon as possible after dissection: brain, liver, kidneys, testes, ovaries, spleen, thymus, heart and adrenals.

Paired organs were weighed separately except for adrenals which were weighed together.

1.6.3. Macroscopic examination

A complete gross examination was performed on all animals. Any gross observations were recorded individually.

For all animals, all gross lesions and tissues listed as well as any organs and/or tissues showing gross lesions or change in size were preserved in 10% buffered formalin (except for eyes and pituitary fixed in formol-sublimate): adrenals, aorta, brain (medulla/pons, cerebellar and cerebral cortex), caecum, colon, duodenum, epididymides, eyes with optic nerves, femoral bone with articulation, Harderian gland, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (axillary, mesenteric and popliteal), mammary glands (with skin), Muzzee with tongue, nasal cavity, oesophagus, ovaries, pancreas, pituitary, prostate, rectum, sciatic nerve, seminal vesicle, skeletal muscle, skin, spleen, spinal cord (cervical, thoracic and lumbar), sternum with bone marrow, stomach, submandibular salivary glands, testes, thymus, thyroids with parathyroids, trachea, urinary bladder, uterus (horns and cervix), vagina, Zymbal gland.

1.6.4. Microscopic examination

All tissues required for microscopical examination: spleen, thymus, kidneys, liver, adrenals and heart were embedded in paraplast, sectioned at approximately 4 microns in thickness and stained with hemalum-eosin. A microscopic examination was performed on:

1. All gross abnormalities and tissues listed in all animals of the control and high dose level groups.
2. All tissues that showed macroscopical abnormalities and kidneys from the intermediate and low dose level groups.

1.7. STATISTICAL ANALYSIS

The following sequence was used for the statistical tests of the clinical parameters (bodyweight and food consumption), haematological and blood biochemical and organ weights:

a. A normal distribution of values in the samples was checked by KOLMOGOROV-SMIRNOV's test (1). In the case of an abnormal distribution, this test is performed after the logarithmic transformation of the values.

If a significant heterogeneity persists after the logarithmic transformation of the values, the analysis of variances is not performed. A comparison between the treated groups and the control group in order to prove a treatment-related difference was made by MANN-WHITNEY's test (2).

b. In the case of the normal distribution of values according to the normal law an analysis of variances was made by BARTLETT's test (3) (more than two samples) or FISHER's test (4) (two samples).

c. A comparison between the treated and the control groups in order to prove a treatment-related difference was made by:

. DUNNETT's test (5), if no significant heterogeneity of the variances was established.

. MANN-WHITNEY's test (2), in the case of significant heterogeneity of the variance.

The level of significance achieved by the inter-group comparisons is explained in the tables of the results by the means of the international codification used for statistical analysis ($p < 0.05 = *$; $p < 0.01 = **$).

A slight difference may appear from time to time with the rounded mean and standard deviation between the individual values and the summary section of the statistical tests. These differences are due to the use of different calculators in data processing, which are not processed the same way in the central memory. These differences, when they occur, are always seen in the last decimal and do not affect the scientific value of the results.

References

- (1) SMIRNOV, N.V.: Tables for estimating the goodness of fit of empirical distributions. Ann. Math. Statist. 19 : 279-281 (1948).
- (2) MANN, H.B.; WHITNEY, D.R.: On a test of whether one of two random variables is stochastically larger than the other. Ann. Math. Statist. 18: 50-60 (1947).
- (3) BARTLETT, M.S.: Proc. Roy. Soc. Amer. 160: 268-282 (1937).
- (4) FISHER, R.A.: Statistical methods for research workers (5th ed). Edinburgh: Oliver and Boyd.
- (5) DUNNETT, C.W.: A multiple comparison procedure for comparing several treatments with a control American Statistical Association Journal. pp. 1096-1121 (1955).

1.8. ARCHIVES

The study documents and samples:

- . protocol and any amendments,
- . all raw data,
- . correspondence,
- . study report (final) with any amendments,
- . tissues in their preservative, blocks and histological sections and blood smears,
- . sample of the test substance

are stored in the archives of C.I.T., Miserey, France, for five years after the end of the in vivo study. At the end of this period, the study archives will, with the Sponsor's agreement, be either transferred to the Sponsor's premises or destroyed.

0025

1.9. CHRONOLOGY OF THE STUDY

	Dates	Days
Arrival of the animals	18.11.87	-
Beginning of treatment	24.11.87	D 1
Week 3		
. Haematology	Males 9.12.87	D 16
	Females 10.12.87	D 17
. Blood biochemistry	Males 9.12.87	D 16
	Females 10.12.87	D 17
. Urinalysis	Males 9.12.87	D 16
	Females 10.12.87	D 17
End of treatment period		
. Necropsy	Males 14.12.87	D 21
	Females 15.12.87	D 22

2. RESULTS

2.1. CLINICAL EXAMINATIONS

2.1.1. Clinical signs

There were no significant differences between treated and control groups regarding respiratory functions, behaviour and appearance.

The only treatment-related clinical sign noted after 14 days of treatment until the end of the study for the males and females (21 days for the males, 22 days for the females) at the high concentrations (5000, 10000 and 20000 ppm) was the presence of black faeces in the litter.

2.1.2. Mortality

No death was noted during the treatment period.

2.1.3. Bodyweight

Figures 1 and 2

Tables I and II

See appendix for individual values

In comparison with the control group and after 2 weeks of treatment a lower bodyweight was noted in males from the 20000 ppm group; this difference was approximately 12% but was not statistically significant.

The mean bodyweight of the males from the other treated groups and females from all the treated groups was similar to that of the males and females from the control group.

FIGURE 1
BODYWEIGHT - MALE

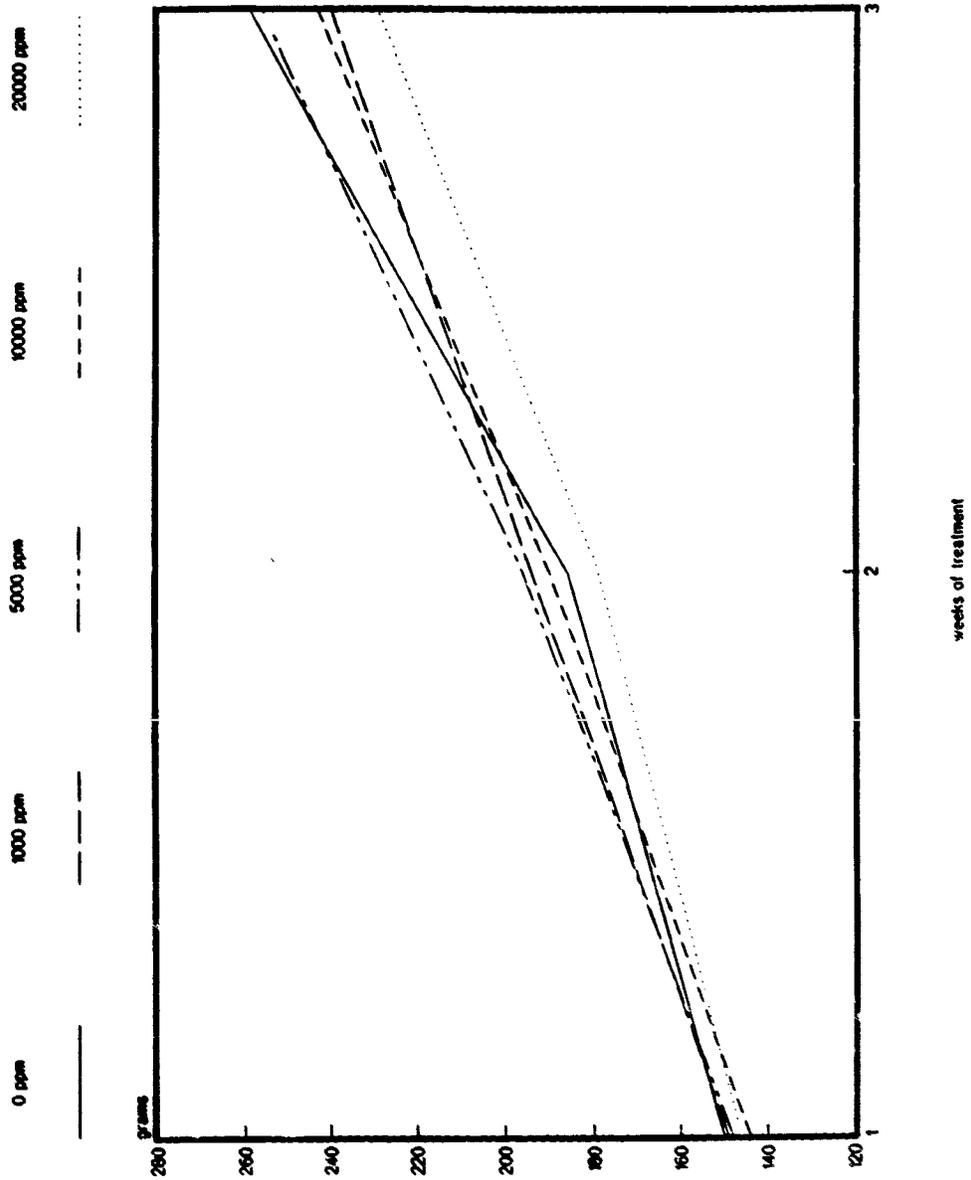


FIGURE 2
BODYWEIGHT - FEMALE

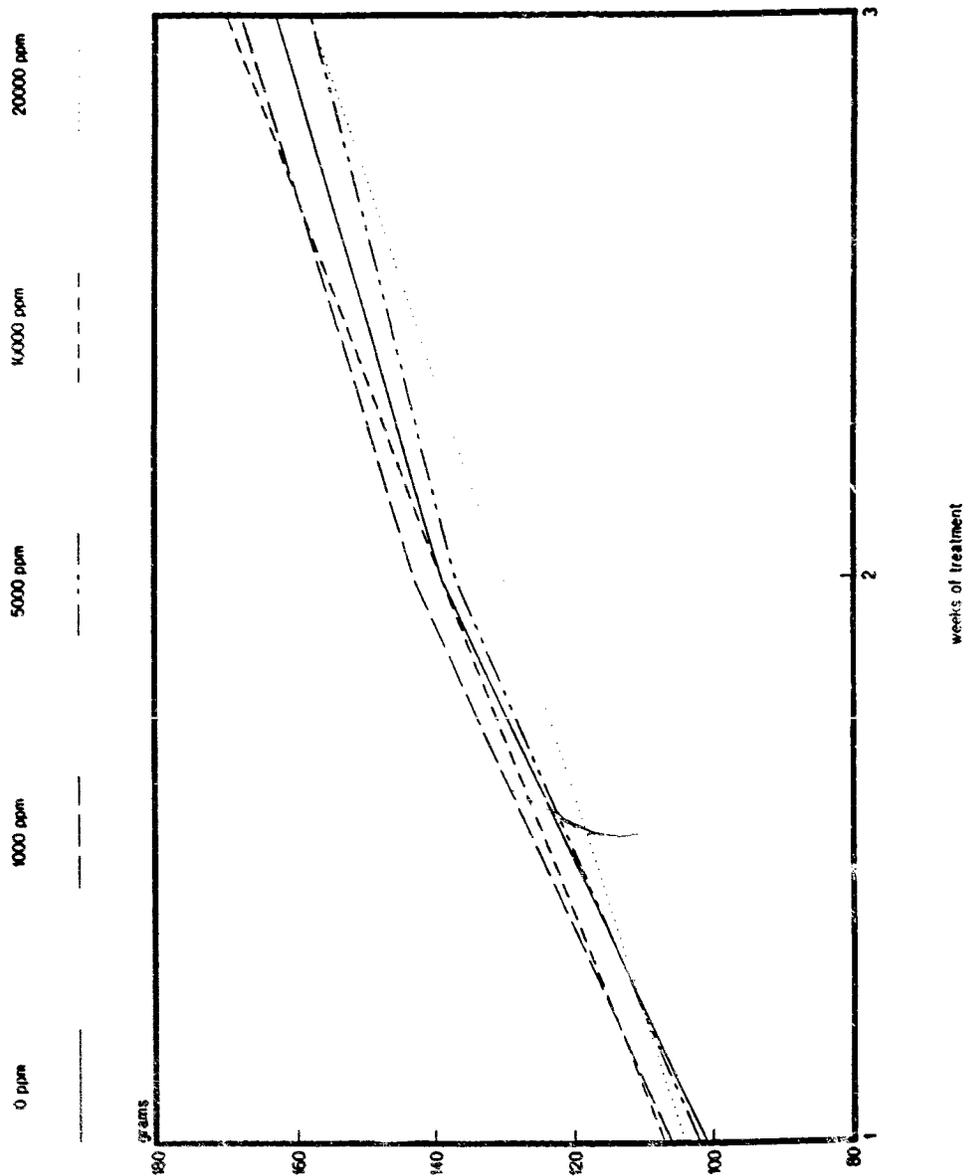


Table : I

NOBWEIGHT
(g)

16

Study : 3548 TSE/CGA 1735... tech/Test No 87 1518
Sex : Male

Concent. ppm		0	1000	5000	10000	20000
-1	n (1)	119	118	119	118	118
	SD	4.6	5.4	4.6	6.6	3.8
	n	6	6	6	6	6
1	n (1)	150	149	148	144	146
	SD	6.0	4.6	7.6	7.5	4.8
	n	6	6	6	6	6
2	n (1)	186	184	196	190	179
	SD	19.1	9.3	9.6	13.4	7.7
	n	6	6	6	6	6
3	n (1)	239	240	256	243	229
	SD	16.8	34.4	13.7	19.4	11.0
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : BUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0 0 3 0

Table : II

BODYWEIGHT
(g)

17

Study : 3948 TSR/CGA 173506 tech/Test No 87 1518
Sex : Female

Concent	ppm	0	1000	5000	10000	20000
-1	R (1)	80	80	80	80	81
	SD	3.3	3.7	3.4	2.9	4.4
	n	6	6	6	6	6
1	R (1)	101	106	102	107	104
	SD	5.9	3.8	5.8	5.3	7.3
	n	6	6	6	6	6
2	R (1)	139	143	137	139	130
	SD	17.8	7.3	8.9	7.3	14.1
	n	6	6	6	6	6
3	R (1)	163	168	158	170	158
	SD	19.2	10.1	16.3	7.8	19.3
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) - DUNNETT TEST

(2) - MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SHIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

2.1.4. Food consumption

Tables III & IV

See appendix for individual values

During the 2 weeks of treatment the food intake of the treated male and female rats was similar to that of the controls and the statistical analysis of the group mean food intake (g/rat/d) did not show any significance.

2.1.5. Food conversion ratios

Table V

The mean amount of food eaten per unit of bodyweight gain was similar between the control and treated groups during the treatment period.

2.1.6. Achieved dosages

Table VI

The achieved intakes decreased gradually, whilst the bodyweight increased. The mean experimental levels between groups moved in the same ratio as the theoretical concentrations.

2.1.7. Water consumption

Tables VII & VIII

See appendix for individual values

During the 2 weeks of treatment, an increase in water consumption was noted in males and females from the 10000 and 20000 ppm groups. This increase, although not statistically significant when compared to the control group, was in mean 20% in males and 28 % in females.

For the rats from the other groups (1000 and 5000 ppm) the water consumption was normal and comparable to those of the control group.

Table

III

FOOD CONSUMPTION
(g/animal/day)

19

Study : 3548 TSR/CGA 173506 tech/Test No 871518
Sex : Male

Concent.	ppm	0	1000	5000	10000	20000
<hr/>						
1	n	21.5	22.7	22.3	21.3	20.9
	SD	1.55	0.72	1.27	1.71	2.71
	n	3	3	3	3	3
2	n	29.3	25.2	27.1	27.0	24.7
	SD	0.36	6.35	1.83	1.50	3.22
	n	3	3	3	3	3

Table : IV

FOOD CONSUMPTION
(g/animal/day)

20

Study : 3348 TSR/CGA 173506 tech/Test No 071518

Sex : Female

Concent.	ppm	0	1000	5000	10000	20000
<hr/>						
1	n	16.1	18.4	18.0	18.1	16.7
	SD	2.78	1.18	0.56	1.63	2.34
	n	3	3	3	3	3
2	n	18.7	18.6	19.1	20.8	20.1
	SD	3.37	1.90	2.05	1.62	2.79
	n	3	3	3	3	3

0 0 3 4

TABLE No. : V
 STUDY No. : 3548 TSR / CGA 173506 tech / test n° 87 1518
 SEX : MALE - FEMALE

FOOD CONVERSION RATIOS
 (grams of food/unit of bodyweight gain)

WEEK OF TREATMENT	SEX AND CONCENTRATION (ppm)									
	MALE					FEMALE				
	0	1000	5000	10000	20000	0	1000	5000	10000	20000
1	4.2	3.5	3.3	3.2	4.4	3.0	3.5	3.6	4.0	4.5
2	2.8	3.8	3.2	3.6	3.5	5.5	5.2	6.4	4.7	5.0
MEAN	3.5	3.7	3.3	3.4	4.0	4.3	4.4	5.0	4.4	4.8

$$FCR = \frac{\text{Food consumed (g/week)}}{\text{Bodyweight gain (g/week)}}$$

TABLE No. : VI
 STUDY No. : 3548 TSR / CGA 173506 tech / test n° 87 1518
 SEX : MALE - FEMALE

ACHIEVED DOSAGES (AD)
 (mg/kg/d)

WEEK OF TREATMENT	SEX AND CONCENTRATION (ppm)							
	MALE				FEMALE			
	1000	5000	10000	20000	1000	5000	10000	20000
1	132.0	648.3	1275.4	2564.4	147	750.0	1471.5	2854.7
2	116.1	599.6	1244.2	2421.6	119	645.3	1341.9	2791.6
n	2	2	2	2	2	2	2	2
MEAN	124.1	624.0	1259.8	2493.0	133.2	697.7	1406.7	2823.2

$$AD = \frac{\text{Concentration (ppm)} \times \text{Food consumption (g/animal/d)}}{\text{Mean median weekly bodyweight (Mmw bw)}}$$

$$Mmw \text{ bw} = \frac{\text{bw week } x + \text{bw week } x + 1}{2}$$

0 0 3 4

Table : VII

WATER CONSUMPTION
(ml/animal/day)

23

Study : 3548 TSR/CGH 173506 tech/Test No 871518
Sex : Male

Concent.	ppm	0	1000	5000	10000	20000
Week						
<hr/>						
1	M	29.0	29.1	28.8	35.0	34.8
	SD	2.89	2.06	2.36	2.99	3.66
	n	3	3	3	3	3
2	M	31.5	28.4	33.2	38.8	36.0
	SD	0.90	4.31	2.93	0.95	3.75
	n	3	3	3	3	3

Table : VIII

WATER CONSUMPTION
(ml/animal/day)

24

Study : 3548 TSR/CGA 173306 tech/Test No 871518
Sex : Female

Concent	ppm	0	1000	5000	10000	20000
1	n	25.6	25.1	28.0	32.1	33.3
	SD	2.29	2.88	1.85	0.70	2.67
	n	3	3	3	3	3
2	n	25.6	23.2	25.9	31.5	34.4
	SD	2.75	1.29	3.40	2.69	7.29
	n	3	3	3	3	3

0038

2.2. LABORATORY INVESTIGATIONS

2.2.1. Haematology

Tables IX - XII

See appendix for individual values

Slight variations in the mean values of the treated groups were considered to be of no toxicological significance, since the individual values were comparable to the control values and within historical values.

Study : 3548 TSR/CER 173506 tech/Test No 87 1518
 Sex : Male
 Time : Week 3

Concent.	ppm	0	1000	5000	10000	20000
WBC G/l	R (2)	10.0	9.3	11.3	11.7	10.0
	SD	2.63	2.30	2.00	3.96	2.73
	n	5	6	5	4	4
RBC T/l	R (2)	7.62	7.61	7.87	7.46	7.30
	SD	0.371	0.610	0.206	0.482	0.376
	n	5	6	5	4	4
HB g/dl	R (2)	14.2	14.7	14.6	14.2	13.6
	SD	0.83	1.08	0.43	0.45	0.53
	n	5	6	5	4	4
PCV l	R (2)	0.56	0.57	0.57	0.55	0.53
	SD	0.023	0.034	0.004	0.022	0.025
	n	5	6	5	4	4
MCV fl	R (2)	74	75	72	73	73
	SD	1.5	1.3	1.7	2.1	1.3
	n	5	6	5	4	4
MCH pg	R (2)	18.7	19.3	18.5	19.1	18.6
	SD	0.34	0.54	0.84	1.01	0.63
	n	5	6	5	4	4
MCHC g/dl	R (2)	25.5	26.0	25.6	26.1	25.5
	SD	0.50	0.70	0.78	0.77	0.44
	n	5	6	5	4	4
PLAT G/l	R (2)	1130	1104	1159	1151	1035
	SD	122.7	116.8	120.0	99.7	192.2
	n	5	6	5	4	4
QT s	R (1)	12.4	12.7	12.8	12.8	13.0
	SD	0.39	0.57	0.15	0.53	0.75
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : DUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0040

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518
 Sex : Female
 Time : Week 3

Concent.	ppm	0	1000	5000	10000	20000
HBC	n (2)	7.4	5.7	7.7	5.3	8.2
G/1	SD	2.74	2.38	2.81	0.73	3.53
	n	6	4	5	6	5
RBC	n (2)	7.16	7.00	7.57	7.12	7.41
T/1	SD	0.953	0.408	0.554	0.213	0.203
	n	6	4	5	6	6
HB	n (2)	13.6	13.5	14.7	14.1	14.2
g/dl	SD	1.87	0.90	1.01	0.74	0.90
	n	6	4	5	6	6
PC1	n (2)	0.53	0.52	0.56	0.53	0.54
1	SD	0.062	0.029	0.038	0.018	0.011
	n	6	4	5	6	6
MCV	n (2)	74	74	73	74	73
f1	SD	2.1	1.0	0.8	0.8	0.6
	n	6	4	5	6	6
HCH	n (2)	19.0	19.2	19.4	19.7	19.2
pg	SD	0.62	0.45	0.36	0.67	0.46
	n	6	4	5	6	6
HCHC	n (2)	25.6	26.0	26.5 *	26.7 *	26.4
g/dl	SD	0.79	0.46	0.30	0.71	0.41
	n	6	4	5	6	6
PLAT	n (2)	1023	959	833	1067	966
G/1	SD	137.4	158.9	223.6	294.0	95.4
	n	6	4	5	6	6
QT	n (1)	13.5	14.3	13.8	13.6	13.4
s	SD	0.54	1.48	0.76	0.50	0.57
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) BURNETT TEST

(2) MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0041

Study : 3548 TSR/CGA 173506 tech/Test No 87 1918
 Sex : Male
 Time : Week 3

Concent. ppm 0 20000

N	N (2)	10	16
%	SD	4.3	3.7
	n	5	4
E	N (2)	0	1
%	SD	0.4	0.5
	n	5	4
B	N (2)	0	0
%	SD	0.0	0.0
	n	5	4
L	N (2)	89	83
%	SD	3.6	4.4
	n	5	4
H	N (2)	1	1
%	SD	2.1	1.0
	n	5	4
N	N (2)	0.9	1.6
G/1	SD	0.23	0.86
	n	5	4
E	N (2)	0.0	0.1
G/1	SD	0.04	0.05
	n	5	4
B	N (2)	0.0	0.0
G/1	SD	0.00	0.00
	n	5	4
L	N (2)	8.9	8.3
G/1	SD	2.57	2.02
	n	5	4
H	N (2)	0.2	0.1
G/1	SD	0.30	0.10
	n	5	4

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : BURNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0 0 4 2

Study : 3548 TSR/CSA 173306 tech/Test No 87 1518
 Sex : Female
 Time : Week 3

Concent. ppm 0 20000

N	N (1)	23	13
%	SD	12.2	6.2
	n	6	6
E	N (1)	1	1
%	SD	0.5	0.8
	n	6	6
B	N (2)	0	0
%	SD (K)	0.0	0.0
	n	6	6
L	N (1)	76	86
%	SD	12.3	6.7
	n	6	6
H	N (1)	1	0
%	SD	1.2	0.3
	n	6	6
M	N (1)	1.5	1.0
G/I	SD	0.73	0.70
	n	6	6
E	N (1)	0.1	0.1
G/I	SD	0.05	0.11
	n	6	6
B	N (2)	0.0	0.0
G/I	SD (K)	0.00	0.00
	n	6	6
L	N (1)	5.9	7.0
G/I	SD	2.74	2.95
	n	6	6
H	N (1)	0.1	0.0
G/I	SD	0.12	0.05
	n	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) DUNNETT TEST

(2) MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0043

2.2.2. Blood biochemistry

Tables XIII - XVIII

See appendix for individual values

After two weeks of treatment, slight decreases in sodium and chloride levels (approximately 2 to 5%) were noted in the males and females from the 5000, 10000 and 20000 ppm groups. Although the values of sodium and chloride showed decreases approaching the normal lower limit, their relationship to the treatment was uncertain.

The increases in the cholesterol values among the animals of either sex of the high dose level group were slight (approximately 40%) and the values were within the normal upper limit. In the absence of other evidence, their relationship to the treatment is not clear.

This also applies to the slight decrease (25 to 40%) in glucose values in the females from the 10000 and 20000 ppm groups.

The variations in the alpha-1 globulins were observed only in the males and were not dose-related (more prominent at the low and intermediate dose levels) therefore they were considered to be of no toxicological significance.

No biological significance could be attributed to the slight decreases in alkaline phosphatase and alanine amino-transferase.

Study : 3548 TSR/CCA 173506 tech/Test No 87 1518
 Sex : Male
 Time : Week 3

Concent.		ppm	0	1000	5000	10000	20000
Na+	n (1)		142.3	142.9	138.8 **	137.9 **	138.0 **
	SD		1.42	1.07	1.08	2.07	0.63
	n		6	6	6	6	6
K+	n (1)		3.87	3.70	3.66	3.72	3.57
	SD		0.553	0.483	0.310	0.330	0.273
	n		6	6	6	6	6
Cl-	n (1)		107.8	109.4	103.6 **	104.5 *	103.0 **
	SD		1.06	1.26	1.30	3.20	1.94
	n		6	6	6	6	6
Ca++	n (2)		2.55	2.60	2.53	2.60	2.73
	SD		0.185	0.165	0.047	0.151	0.427
	n (B)		6	6	6	6	6
I PHOS	n (1)		3.50	3.32	3.54	3.29	3.40
	SD		0.250	0.492	0.153	0.117	0.315
	n		6	6	6	6	6
GLUC	n (2)		5.34	6.54	4.89	6.33	5.10
	SD		0.377	1.779	0.639	2.697	0.550
	n (B)		6	6	6	6	6
UREA	n (1)		4.8	4.7	4.8	5.2	5.9
	SD		0.62	1.01	0.52	0.59	1.27
	n		6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) DUNNETT TEST

(2) MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SHIRKOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0045

Study : 3548 TSR/CCA 173506 tech/Test No 87 1918
 Sex : Female
 Time : Week 3

Concent.	ppm	0	1000	5000	10000	20000
NH ₄ ⁺ mmol/l	R (1)	136.9	138.2	133.2 **	133.4 **	133.5 **
	SD	1.17	1.30	1.13	0.70	1.77
	n	6	6	6	6	6
K ⁺ mmol/l	R (1)	3.83	3.84	3.55	3.39	3.34
	SD	0.335	0.619	0.337	0.359	0.383
	n	6	6	6	6	6
Cl ⁻ mmol/l	R (1)	103.7	104.3	100.4 **	98.3 **	101.0 **
	SD	1.64	1.62	0.50	1.00	1.41
	n	6	6	6	6	6
Ca ⁺⁺ mmol/l	R (1)	2.80	2.89	2.70	2.68	2.80
	SD	0.099	0.221	0.154	0.159	0.155
	n	6	6	6	6	6
I. PHOS mmol/l	R (1)	2.95	3.29	2.91	2.82	2.88
	SD	0.260	0.364	0.356	0.356	0.188
	n	6	6	6	6	6
GLUC mmol/l	R (1)	5.87	5.69	5.36	4.78 *	4.59 **
	SD	0.679	0.378	0.775	0.486	0.607
	n	6	6	6	6	6
UREA mmol/l	R (1)	5.8	6.7	6.0	5.2	5.3
	SD	1.04	0.50	1.24	0.73	0.25
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN TREATED AND CONTROL GROUPS

* P<0.05
 ** P<0.01
 (1) : BUNNETT TEST
 (2) : MANN-WHITNEY TEST

SAMPLE DISTRIBUTION-RELATIVE TESTS

(B) BARTLETT TEST P<0.01
 (F) FISHER TEST P<0.05
 (K) KOLMOGOROV-SHIRNOV TEST P<0.01
 (L) LOGARITHMIC TRANSFORMATION

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518
 Sex : Male
 Time : Week 3

Concent.	ppm	0	1000	5000	10000	20000
CHOL	n (1)	1.9	2.2	2.3	2.5	2.7 *
mmol/l	SD	0.64	0.44	0.24	0.46	0.49
	n	6	6	6	6	6
TRIG	n (1)	0.83	0.61	0.92	0.77	0.81
mmol/l	SD	0.534	0.223	0.283	0.278	0.191
	n	6	6	6	6	6
PROT	n (1)	71	73	74	70	70
g/l	SD	2.6	2.4	2.6	2.1	1.8
	n	6	6	6	6	6
A/G	n (1)	1.88	2.15	2.13	1.91	1.85
1	SD	0.384	0.144	0.310	0.227	0.165
	n	6	6	6	6	6
ALP	n (1)	363	472	421	417	424
UI/l	SD	195.9	87.5	104.5	121.1	79.7
	n	6	6	6	6	6
ASAT	n (1)	76	62	76	77	62
UI/l	SD	7.9	13.3	13.3	25.2	8.6
	n	6	6	6	6	6
ALAT	n (2)	27	21 *	20 *	21	18 **
UI/l	SD	3.1	2.5	3.1	7.3	0.6
	n (B)	6	6	6	6	6
GGT	n (2)	0	0	0	1	0
UI/l	SD (K)	0.0	0.4	0.0	1.2	0.0
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) - DUNNETT TEST

(2) - MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SHIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

11 00 3 4

Table : XVI

BLOOD BIOCHEMISTRY

34

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518

Sex : Female

Time : Week 3

Concent.		ppn	0	1000	5000	10000	20000
CKOL mmol/l	H (1)		2.3	2.2	2.4	2.5	3 **
	SD		0.58	0.39	0.26	0.41	0.26
	n		6	6	6	6	6
TRIG mmol/l	H (1)		0.62	0.46	0.46	0.49	0.82
	SD		0.243	0.168	0.118	0.230	0.383
	n		6	6	6	6	6
PROT g/l	H (1)		77	81	77	72	75
	SD		3.1	3.5	4.6	2.3	2.7
	n		6	6	6	6	6
B/C 1	H (2)		1.97	1.91	2.02	2.16	2.1
	SD		0.449	0.499	0.097	0.224	0.367
	n (B)		6	6	6	6	6
ALP UI/l	H (1)		382	397	313	265 **	333
	SD		86.1	28.0	49.5	37.7	52.8
	n		6	6	6	6	6
ASAT UI/l	H (1)		82	86	76	74	74
	SD		14.7	16.9	11.7	11.2	16.0
	n		6	6	6	6	6
ALAT UI/l	H (1)		25	24	21	20	18 *
	SD		7.0	2.0	3.8	3.5	3.3
	n		6	6	6	6	6
GGT UI/l	H (2)		1	0	0	0	0
	SD (K)		2.9	0.0	0.0	0.0	0.0
	n		6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : BUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SHIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0 0 4 8

Study : 3548 TSR/CGA 1/3506 tech/Test No 87 1318
 Sex : Male
 Time : Week 3

Concent.	ppm	0	1000	5000	10000	20000
ALB	n (1)	64.8	68.2	67.8	65.5	64.8
%	SD	4.23	1.47	2.95	2.73	2.03
	n	6	6	6	6	6
A1-GLOB	n (1)	6.2	3.4 **	3.4 **	3.8 **	4.4 *
%	SD	1.70	0.70	0.70	0.42	0.82
	n	6	6	6	6	6
A2-GLOB	n (1)	3.9	3.8	3.3	3.7	3.6
%	SD	0.53	0.51	0.50	0.20	0.21
	n	6	6	6	6	6
B-GLOB	n (1)	15.1	15.3	14.9	16.0	16.5
%	SD	1.95	0.74	0.72	1.37	0.70
	n	6	6	6	6	6
G-GLOB	n (1)	10.1	9.3	10.6	11.0	10.7
%	SD	2.16	1.48	2.08	2.63	2.11
	n	6	6	6	6	6
ALB	n (1)	45.7	49.9 *	49.9 *	45.7	45.3
g/l	SD	3.37	1.53	1.04	2.26	2.29
	n	6	6	6	6	6
A1-GLOB	n (1)	4.3	2.5 **	2.6 **	2.7 **	3.1 *
g/l	SD	1.22	0.53	0.58	0.36	0.50
	n	6	6	6	6	6
A2-GLOB	n (1)	2.8	2.8	2.4	2.6	2.5
g/l	SD	0.43	0.33	0.42	0.17	0.15
	n	6	6	6	6	6
B-GLOB	n (1)	10.6	11.2	11.0	11.2	11.5
g/l	SD	1.31	0.48	0.75	1.19	0.27
	n	6	6	6	6	6
G-GLOB	n (1)	7.1	6.9	7.8	7.7	7.4
g/l	SD	1.64	1.26	1.74	1.78	1.50
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
 TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) DUNNETT TEST

(2) MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

Study : 3548 ISR/CGH 173506 tech/Test No 87 1518
 Sex : Female
 Time : Week 3

Concent.	ppn	0	1000	5000	10000	20000
ALB	H (2)	65.6	64.5	66.9	68.2	70.3
%	SD	5.04	7.31	1.08	2.32	5.07
	n (B)	6	6	6	6	6
A1-GLOB	H (1)	2.3	3.0	2.7	3.4	2.2
%	SD	0.33	1.52	0.70	0.91	0.59
	n	6	6	6	6	6
A2-GLOB	H (1)	4.3	2.8	3.1	2.7	2.6
%	SD	2.24	1.15	0.95	0.58	0.86
	n	6	6	6	6	6
B-GLOB	H (1)	17.5	16.2	15.8	15.4	14.6
%	SD	4.01	2.98	1.44	1.06	2.52
	n	6	6	6	6	6
G-GLOB	H (1)	10.3	13.6	11.6	10.3	10.3
%	SD	1.82	3.34	1.15	2.72	3.49
	n	6	6	6	6	6
ALB	H (2)	50.1	52.0	41.8	49.3	53.0
g/l	SD	3.87	5.31	20.57	2.94	4.38
	n (B)	6	6	6	6	6
A1-GLOB	H (2)	1.8	2.5	1.9	2.4	1.7
g/l	SD	0.21	1.32	0.92	0.64	0.41
	n (B)	6	6	6	6	6
A2-GLOB	H (1)	3.3	2.3	2.1	2.0	2.0
g/l	SD	1.76	1.00	1.19	0.40	0.69
	n	6	6	6	6	6
B-GLOB	H (2)	13.4	13.1	9.7	11.1	11.0
g/l	SD	3.30	2.69	4.92	0.57	1.70
	n (B)	6	6	6	6	6
G-GLOB	H (1)	7.9	11.0	7.1	7.4	7.8
g/l	SD	1.64	2.76	3.60	1.97	2.75
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05
 ** P<0.01

(1) : BUNNETT TEST
 (2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01
 (F) FISHER TEST P<0.05
 (K) KOLMOGOROV-SMIRNOV TEST P<0.01
 (L) LOGARITHMIC TRANSFORMATION

2.2.3. Urinalysis

Tables XIX & XX

See appendix for individual values

After two weeks of treatment, a slight statistically significant increase (about 1%) in mean specific gravity was noted in males from the 10000 and 20000 ppm groups, with a slight decrease in mean volume (25 to 38%), not statistically significant. These were the contribution of a few individuals from these groups. Therefore, they are unlikely to be related to the administration of the test substance.

Table : XIX

URIZIMLYSIS

Study : 3348 TSR/CGA 173506 tech/Test No 87 1518
Sex : Male
Time : Week 3

Concent. ppm		0	1000	5000	10000	20000
VOLUME	n (1)	24	20	24	18	15
	SD	14.9	12.8	9.2	13.9	11.2
	n	6	6	6	6	6
SP. GRAU	n (1)	1006	1008	1013	1015 *	1021 **
-	SD	5.8	4.1	6.9	6.3	4.9
	n	6	6	6	6	6
PH	n (1)	7.3	7.6	6.9	6.6	6.6
-	SD	0.61	0.74	0.49	0.38	0.20
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05
** P<0.01
(1) : BUNNETT TEST
(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01
(F) FISHER TEST P<0.05
(K) KOLMOGOROV-SHIRNOV TEST P<0.01
(L) LOGARITHMIC TRANSFORMATION

0052

Table : XX

URINALYSIS

39

Study : 3348 TSR/GCA 173306 tech/Test No 87 1518
Sex : Female
Time : Week 3

Concent. ppm		0	1000	5000	10000	20000
<hr/>						
VOLUME	n (1)	13	10	10	10	11
nL	SD	4.9	5.8	7.2	6.6	9.5
	n	6	6	6	6	6
SP. GRAV	n (1)	1013	1019	1022	1021	1023
-	SD	2.7	10.2	9.3	10.2	9.9
	n	6	6	6	6	6
PH	n (1)	6.4	6.2	6.2	6.0	5.8
-	SD	0.49	0.41	0.41	0.55	0.61
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : DUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0 0 5 3

2.3. PATHOLOGY

2.3.1. Organ weights

Tables XXI - XXVIII

See appendix for individual values

The following changes were found:

- a decrease in the net weights of the heart in males from the 20000 ppm group and in females from the 5000 ppm and 20000 ppm groups.
- a decrease in the net weights of the spleen in males from the 1000 ppm, 5000 ppm and 20000 ppm groups and a decrease in the net and relative weights in females from the 1000 ppm and 5000 ppm groups.
- an increase in the net weights of liver in females from the 10000 ppm group and in the relative weights of liver in males and females from the 10000 ppm and 20000 ppm groups; probably due to low bodyweights.
- an increase in the relative weights of brain in males from the 20000 ppm group.

The above-mentioned changes in organ weights were not associated with any relevant histopathological finding and they were not dose-related. Therefore, they were considered to be of no toxicological significance.

- an increase in the net and relative weights of kidneys in males from the 20000 ppm group (33 and 65% respectively) and females from the 10000 ppm group (15 and 14% respectively).

The above-mentioned changes in the weights of kidneys were associated with tubular nephrosis in males from the 20000 ppm group (marked to severe) and in one female from the 10000 ppm group considered to be treatment-related.

2.3.2. Macroscopic observations

See summary tables on the following pages

See appendix for individual findings

The following changes were found in some treated animals:

- greyish or blackish colour of the stomach in 1/6 females from the 10000 ppm group and 4/6 males and 4/6 females from the 20000 ppm group.

The above-mentioned stomach changes were not associated with any relevant histopathological finding, therefore they were considered to be of no toxicological significance.

0 0, 5 4

- paleness of the kidneys in 1/6 males from the 10000 ppm group and 2/6 males from the 20000 ppm group, many blackish and punctiform foci in 1/6 males from the 20000 ppm group.

The above-mentioned kidney changes were associated with tubular nephrosis (marked to severe).

2.3.3. Microscopic observations

See summary tables on the following pages

See appendix for individual observations

The following changes were observed:

- tubular nephrosis of the kidneys in 1/6 males from the 5000 ppm group (slight), 4/6 males and 1/6 females from the 10000 ppm group (minimal to marked), 5/6 males and 3/6 females from the 20000 ppm group (minimal to severe).

The above-mentioned lesions were considered to be related to the administration of the test substance; the incidence and severity of the lesions were dose-related.

Incidence, severity and morphological characters of the microscopical changes seen in the other organs examined did not suggest a treatment-relationship.

In conclusion, the administration of CGA 173506 tech. in the diet for 20 to 21 days induced tubular nephrosis (minimal to severe) in the males at the concentration of 5000 ppm and in both sexes at 10000 and 20000 ppm.

0 0 5 5

Table : XXI

NET ORGAN WEIGHTS
(g)

42

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518
Sex : Male
Time : End of treatment

Concent. ppm		0	1000	5000	10000	20000	
BODY W. (g)	N (1)	249	238	242	231	202	***
	SD	16.3	19.9	12.1	18.7	17.6	
	n	6	6	6	6	6	
HEART	N (1)	1.130	1.087	0.962	1.055	0.857	*
	SD	0.189	0.131	0.068	0.146	0.161	
	n	6	6	6	6	6	
THYRUS	N (1)	0.589	0.564	0.540	0.453	0.425	
	SD	0.100	0.148	0.133	0.088	0.092	
	n	6	6	6	6	6	
BRAIN	N (1)	1.855	1.855	1.835	1.793	1.822	
	SD	0.066	0.115	0.065	0.115	0.057	
	n	6	6	6	6	6	

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

*** P<0.01

(1) : DUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0056

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518
 Sex : Female
 Time : End of treatment

Concent. ppm		0	1000	5000	10000	20000
BODY W. (g)	N (1)	159	156	149	161	149
	SD	17.1	9.5	10.0	3.7	13.6
	n	6	6	6	6	6
HEART	N (1)	0.863	0.740	0.666 **	0.795	0.714 *
	SD	0.125	0.100	0.035	0.084	0.085
	n	6	6	6	6	6
THYMUS	N (1)	0.444	0.420	0.367	0.406	0.397
	SD	0.044	0.126	0.044	0.084	0.063
	n	6	6	6	6	6
BRAIN	N (1)	1.768	1.743	1.648	1.699	1.740
	SD	0.073	0.098	0.043	0.085	0.103
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05
 ** P<0.01
 (1) : DUNNETT TEST
 (2) : MANN-WHITNEY TEST

(B) : BARTLETT TEST P<0.01
 (F) : FISHER TEST P<0.05
 (K) : KOLMOGOROV-SMIRNOV TEST P<0.01
 (L) : LOGARITHMIC TRANSFORMATION

0 0 5 7

Table : XXIII

NET ORGAN HEIGHTS
(g)

44

Study : J548 TSR/CGA 173506 tech/Test No 87 1518
Sex : Male
Time : End of treatment

Concent. ppm		0	1000	5000	10000	20000	
BODY W. (g)	N (1)	249	238	242	231	202	**
	SD	16.3	19.9	12.1	18.7	17.6	
	n	6	6	6	6	6	
SPLEEN	N (1)	0.677	0.527 *	0.507 *	0.624	0.467 **	
	SD	0.136	0.060	0.105	0.101	0.076	
	n	6	6	6	6	6	
ADREN	N (1)	0.047	0.043	0.050	0.045	0.045	
	SD	0.005	0.005	0.011	0.011	0.004	
	n	6	6	6	6	6	
KIDNEYS	N (1)	2.274	2.227	2.364	2.384	3.017 **	
	SD	0.293	0.341	0.295	0.370	0.342	
	n	6	6	6	6	6	
LIVER	N (1)	8.235	7.981	8.559	9.050	8.113	
	SD	0.801	0.922	0.517	0.773	0.942	
	n	6	6	6	6	6	
TESTES	N (1)	2.663	2.753	2.578	2.770	2.522	
	SD	0.116	0.141	0.459	0.417	0.416	
	n	6	6	6	6	6	

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : BUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

0.058

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518
 Sex : Female
 Time : End of treatment

Concent.	ppm	0	1000	5000	10000	20000
BOBY W. (g)	n (1)	159	156	149	161	145
	SD	17.1	9.5	10.0	3.9	13.6
	n	6	6	6	6	6
SPLEEN	n (2)	0.669	0.49* *	0.430 **	0.518	0.526
	SD	0.198	0.045	0.064	0.070	0.097
	n (B)	6	6	6	6	6
ADREN	n (1)	0.055	0.053	0.052	0.057	0.048
	SD	0.006	0.006	0.002	0.006	0.007
	n	6	6	6	6	6
KIDNEYS	n (1)	1.571	1.642	1.505	1.811 *	1.528
	SD	0.167	0.130	0.114	0.173	0.136
	n	6	6	6	6	6
LIVER	n (1)	5.879	5.915	5.901	7.323 **	6.853
	SD	0.538	0.804	0.344	0.989	0.526
	n	6	6	6	6	6
OVARIES	n (1)	0.099	0.092	0.082	0.104	0.086
	SD	0.016	0.018	0.012	0.006	0.018
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : DUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SHIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

Table : XXV

RELATIVE ORGAN HEIGHTS
(g/100g animal)

46

Study : 3548 TSR/CGR 17350c tech/Test No 87 1518
Sex : Male
Time : End of treatment

Concent. ppm		0	1000	5000	10000	20000	
BODY W. (g)	n (1)	249	238	242	231	202	**
	SD	16.3	19.9	12.1	18.7	17.6	
	n	6	6	6	6	6	
HEART	n (1)	0.455	0.457	0.398	0.456	0.423	
	SD	0.068	0.035	0.015	0.051	0.053	
	n	6	6	6	6	6	
THYRUS	n (1)	0.238	0.236	0.223	0.197	0.209	
	SD	0.040	0.054	0.051	0.039	0.031	
	n	6	6	6	6	6	
BRAIN	n (1)	0.748	0.785	0.759	0.779	0.907	**
	SD	0.043	0.067	0.027	0.069	0.072	
	n	6	6	6	6	6	

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : DUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

Table : XXVI

RELATIVE ORGAN HEIGHTS
(g/100g animal)

47

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518
Sex : Female
Time : End of treatment

Concent. ppm		0	1000	5000	10000	20000
BODY W. (g)	n (1)	159	156	149	161	149
	SD	17.1	9.5	10.0	3.9	15.6
	n	6	6	6	6	6
HEART	n (1)	0.546	0.475	0.449 *	0.493	0.479
	SD	0.075	0.054	0.034	0.052	0.029
	n	6	6	6	6	6
THYRUS	n (1)	0.281	0.267	0.248	0.252	0.268
	SD	0.021	0.068	0.034	0.053	0.048
	n	6	6	6	6	6
BRAIN	n (1)	1.122	1.120	1.112	1.054	1.174
	SD	0.113	0.059	0.081	0.043	0.099
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : DUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

Table : XXVII

RELATIVE ORGAN WEIGHTS
(g/100g animal)

48

Study : 3548 TSR/CCA 173506 tech/Test No 87 1518
Sex : Male
Time : End of treatment

Concent. ppm		0	1000	5000	10000	20000	
BODY W. (g)	N (1)	249	238	242	231	202	**
	SD	16.3	19.9	12.1	18.7	17.6	
	n	6	6	6	6	6	
SPLEEN	N (1)	0.275	0.223	0.210	0.271	0.232	
	SD	0.064	0.029	0.044	0.043	0.035	
	n	6	6	6	6	6	
ADREN	N (1)	0.019	0.018	0.021	0.019	0.022	
	SD	0.002	0.001	0.005	0.005	0.004	
	n	6	6	6	6	6	
KIDNEYS	N (2)	0.914	0.934	0.975	1.027	1.510	**
	SD	0.090	0.079	0.084	0.104	0.276	
	n (B)	6	6	6	6	6	
LIVER	N (1)	3.313	3.359	3.539	3.916	4.010	**
	SD	0.216	0.215	0.119	0.151	0.175	
	n	6	6	6	6	6	
TESTES	N (1)	1.076	1.168	1.072	1.194	1.261	
	SD	0.092	0.134	0.213	0.107	0.260	
	n	6	6	6	6	6	

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05

** P<0.01

(1) : DUNNETT TEST

(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01

(F) FISHER TEST P<0.05

(K) KOLMOGOROV-SMIRNOV TEST P<0.01

(L) LOGARITHMIC TRANSFORMATION

Table : XXVIII

RELATIVE ORGAN WEIGHTS
(g/100g animal)

Study : 3548 TSR/CGA 173506 tech/Test No 87 1518
Sex : Female
Time : End of treatment

Concent.	ppm	0	1000	5000	10000	20000
BODY W. (g)	n (1)	159	156	149	161	149
	SD	17.1	9.5	10.0	3.9	15.6
	n	6	6	6	6	6
SPLEEN	n (2)	0.435	0.315 *	0.291 *	0.321	0.354
	SD	0.186	0.011	0.052	0.041	0.068
	n (B)	6	6	6	6	6
ADREN	n (1)	0.035	0.034	0.035	0.036	0.033
	SD	0.002	0.003	0.003	0.005	0.005
	n	6	6	6	6	6
KIDNEYS	n (1)	0.991	1.055	1.012	1.125 *	1.027
	SD	0.069	0.084	0.036	0.112	0.066
	n	6	6	6	6	6
LIVER	n (1)	3.720	3.792	3.979	4.544 *	4.623 **
	SD	0.343	0.427	0.278	0.622	0.465
	n	6	6	6	6	6
OVARIES	n (1)	0.062	0.059	0.055	0.065	0.058
	SD	0.009	0.009	0.008	0.003	0.010
	n	6	6	6	6	6

SIGNIFICANCE OF THE DIFFERENCE BETWEEN
TREATED AND CONTROL GROUPS

SAMPLE DISTRIBUTION-RELATIVE TESTS

* P<0.05
** P<0.01
(1) : DUNNETT TEST
(2) : MANN-WHITNEY TEST

(B) BARTLETT TEST P<0.01
(F) FISHER TEST P<0.05
(K) KOLMOGOROV-SHIRNOV TEST P<0.01
(L) LOGARITHMIC TRANSFORMATION

MACROSCOPIC PATHOLOGY .
SUMMARY TABLES

PAGE . : 50
CIT PROJECT : 3548 TBR

TEST ARTICLE : CGA 173506 tech/Test 67 1518
TEST SYSTEM : RAT, 20 days, Oral
SPONSOR : CIBA-GEIGY

PATHDATA NO: 03548 J10
DATE : 10-MAY-68
PDS PATHDATA SYSTEM TM

INCIDENCE OF NECROPSY FINDINGS BY ORGAN/GROUP/SEX

ORGAN/FINDING	DOSE GROUP:		T		A		B		C	
	SEX:	NO. ANIMALS:	M	F	M	F	M	F	M	F
			6	6	6	6	6	6	6	6
SPLEEN										
- ENLARGED				1						
THYMUS										
KIDNEYS										
- PELVIC DILATATION				1	1	2		1		1
- DILATATION				1	1	2		1		1
- PALENESS										1
- FOCI										
ADRENAL GLANDS										
UTERUS										
- DILATATION						1				1
COLON										
- ENLARGED						1				
- REDDISH COLOR										
STOMACH										
- GREYISH COLOR										1
- BLACKISH COLOR										
URETERS										
- DILATATION										1
TESTES										
- REDUCED IN SIZE								1		
- IRREGULAR COLOR								1		
CECUM										
- DILATATION										

0.064

MACROSCOPIC PATHOLOGY .
SUMMARY TABLES

PAGE . : 51
CIT PROJECT : 3548 T5R

TEST ARTICLE : CGA 172506 Tech/Test 87 151B
TEST SYSTEM : RAT, 20 days, Oral
SPONSOR : CIBA-GEIGY

PATHDATA NO. 00948 77C
DATE : 10-MAY-68
PDS PATHDATA SYSTEM TM

INCIDENCE OF NECROPSY FINDINGS BY ORGAN/GROUP/SEX

ORGAN/FINDING	DOSE GROUP: SEX: NO. ANIMALS:	T		D	
		M	F	M	F
SPLEEN	:				
- ENLARGED			1		
THYMUS	:				
KIDNEYS	:				
- PELVIC DILATATION			1		1
- DILATATION			1		1
- PALENESS				2	
- FOCI				1	
ADRENAL GLANDS	:				
UTERUS	:				
- DILATATION					
COLON	:				
- ENLARGED					1
- REDDISH COLOR					1
STOMACH	:				
- GREYISH COLOR				2	1
- BLACKISH COLOR				2	1
URETERS	:				
- DILATATION					
TESTES	:				
- REDUCED IN SIZE				1	
- IRREGULAR COLOR				1	
CECUM	:				
- DILATATION					

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PATHOLOGY REPORT .
SUMMARY TABLES

PAGE : 52
CIT PROJECT : 3548 T6F

TEST ARTICLE : CGA 172506 Tech/Teel S2 1517
TEST SYSTEM : RAT, 90 days, Oral
SPONSOR : CIBA-GEIGY

PATHDATA NO. : 02511 01
DATE : 10-MAY-68
PDS PATHDATA SYSTEM TM

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP SEX
STATUS AT NECROPSY: K0

ORGAN/FINDING	DOSE GROUP: SEX: NO. ANIMALS:	T		A		B		C	
		M	F	M	F	M	F	M	F
LIVER	NO. EXAM.: 6	6	6						
- MONO. CELL AGGREGAT.		6	6						
- CONGESTION.		1	5						
- HEPATOCYTE VACUOLAT.		1	6						
- EXTRAMEDUL. HAEMATOP.			1						
- FOCAL NECROSIS.			1						
- SINUSOIDAL ECTASIA.			1						
- PERIDUCTAL FIBROSIS.									
.....									
SPLEEN	NO. EXAM.: 6	6	6						
- EXTRAMED. HAEMATOP.		6	6						
.....									
KIDNEYS	NO. EXAM.: 6	6	6	6	6	6	6	6	6
- PELVIC DILATATION.			1	1	2				
- TUBULAR NEPHROSIS.									
- MONO. CELL AGGREGAT.			6		6				
- TUBULAR BASOPHILIA.			6						
- CASTS.									
- TUBULAR DILATATION.									
- TUB. EPITH. CELL VAC.									
.....									
UTERUS	NO. EXAM.: 6								
- DILATATION, LUMEN.									
.....									
COLON	NO. EXAM.: 6								
- PEYER'S PATCHES HYP.									
.....									
TESTES	NO. EXAM.: 6								
- TUBULAR ATROPHY.									
.....									
CECUM	NO. EXAM.: 6								
- DILATATION- LUMEN.									
.....									

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PATHOLOGY REPORT
SUMMARY TABLES

PAGE 53
GIT PROJECT : 2548 TSP

TEST ARTICLE : CGA 173508 (incl. T-1) E7 1548
TEST SYSTEM : RAT, 60 days, Oral
SPONSOR : CIBA-GEIGY

PATHDATA NO. 02513 100
DATE : 10-MAY-88
PO5 PATHDATA SYSTEM NY

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN-GROUP, SEX
STATUS AT NECROPSY: KO

ORGAN/FINDING	NO. ANIMALS:	M		F	
		SEX:	NO. ANIMALS:	SEX:	NO. ANIMALS:
LIVER	NO. EXAM.:	5	5	5	5
- MONO. CELL AGGREGAT.		5	5	5	5
- CONGESTION.		1	1	1	1
- HEPATOCYTE VACUOLAT.		1	1	1	1
- EXTRAMEDUL.HAEMATOP.		1	1	1	1
- FOCAL NECROSIS.		1	1	1	1
- SINUSOIDAL ECTASIA.		1	1	1	1
- PERIDUCTAL FIBROSIS.					1
SPLEEN	NO. EXAM.:	5	5	5	5
- EXTRAMED.HAEMATOP.		5	5	5	5
KIDNEYS	NO. EXAM.:	5	5	5	5
- PELVIC DILATATION					1
- TUBULAR NEPHROSIS.					3
- MONO. CELL AGGREGAT.					1
- TUBULAR BASOPHILIA					1
- CASTS.					1
- TUBULAR DILATATION					1
- TUB. EPITH. CELL VAC.					1
UTERUS	NO. EXAM.:				5
- DILATATION - LYMPH.					5
COLON	NO. EXAM.:				5
- PEYER'S PATCHES VAC.					1
TESTES	NO. EXAM.:				5
- TUBULAR ATROPHY					1
RECTUM	NO. EXAM.:				5
- DILATATION - LYMPH.					5

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PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 54
CIT PROJECT : 2548 TRF

TEST ARTICLE : CGA 122504 (M) (T) (L) (S) (S) (S)
TEST SYSTEM : RAT, 90 days, Oral
SPONSOR : CIBA-GEIGY

PATHDATA NO. : 02548 TRF
DATE : 10-MAY-88
FDS PATHDATA SYSTEM TH

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GRUP SEX
STATUS AT NECROPSY: NO

ORGAN/FINDING	DOSE GROUP: SEX:	T		A		F		M	
		M	F	M	F	M	F	M	F
KIDNEYS	NO. EXAM.:	0		0	0	0	0	0	0
- TUBULAR NEPHROSIS -	GRADE 1:								
	GRADE 2:					1			
	GRADE 3:								
	GRADE 4:								
	TOTAL AFFECTED:					1			
	MEAN SEVERITY:					2.0			2.5

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PATHOLOGY REPORT .
SUMMARY TABLES

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OIT PROJECT 2549 TEP

TEST ARTICLE . . . CGA 17050A (acetyl) 27 1212 PATHDATA NO. 000 1 170
TEST SYSTEM . . . RAT, 20 cags, Oral DATE 10-NOV-66
SPONSOR CIBA-GEIGY PDS PATHDATA SYSTEM BY

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0

ORGAN/FINDING	DOSE GROUP:	M		F	
		NO. ANIMALS:	SEX:	NO. ANIMALS:	SEX:
		6	6	6	6
KIDNEYS	NO. EXAM.:	6	6	6	6
- TUBULAR NEPHROSIS,	GRADE 1:				2
	GRADE 2:				1
	GRADE 3:				0
	GRADE 4:				0
	TOTAL AFFECTED:			2	2
	MEAN SEVERITY:			0.3	0.3

END OF REPORT SECTION
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