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See Supplement to  
8EHQ-92-4272  
8EHQ-92-5787  
Contains No CBI

ciba

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Ardsley, New York 10502-2699  
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TDC N: 88920005787

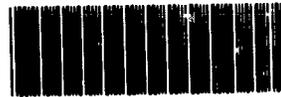
8EHQ-1193-7141  
Express Mail  
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November 16, 1993

Document Processing Center (7407)  
(Attention: Section 8(e) Coordinator)  
Office of Pollution Prevention and Toxics  
Environmental Protection Agency  
401 M St., SW  
Washington, DC 20460



8EHQ-92-7141  
SP001 11/18/93



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REC'D  
OFFICE OF POLLUTION  
PREVENTION AND TOXICS  
NOV 18 AM 11:05

Dear Section 8(e) Coordinator:

**Subject: TSCA 8(e) Notice - Supplement to 8EHQ-0592-4272 (Tinuvin 770)  
Supplement to 8EHQ-0792-5787 (Tinuvin 770)**

Ciba-Geigy Corporation (Ciba) claims no information in this letter or the attached toxicity study as Confidential Business Information.

In accordance with EPA's March 16, 1978 policy statement on Section 8(e) reporting under the Toxic Substances Control Act, and EPA's June, 1991 TSCA Section 8(e) Reporting Guide, Ciba wishes to bring to the attention of the Environmental Protection Agency neurological effects seen in a toxicity study conducted with Tinuvin 770. Tinuvin 770, identified as TK 10665 in the report, is bis(2,2,6,6-tetramethyl-4-piperidinyl) decanedioate, having CASRN 52829-07-9.

A copy of the study, entitled "Report on the 28-Day Toxicity Study Oral Administration - Rat", is enclosed. In this study, rats were dosed daily by oral gavage with 0, 600, 1000, and 2000 mg/kg for 28 days. All high dose animals died. Muscular weakness and leucocyte infiltration of spleen and parts of lung were seen in all treated animals. Those treated with the mid-dose were considered to have a lowered catecholamine (norepinephrine) content of the superior cervical ganglia when compared to controls. Based upon current EPA guidelines it is felt these results warrant reporting under TSCA 8(e). Although this study is dated several years ago, Ciba only recently obtained a copy of the study from its parent company, Ciba-Geigy Limited of Basel, Switzerland.

Three previous 8(e) notices were submitted to EPA. The first two notices were submitted under the 8(e) CAP; one on May 20, 1992 for acute inhalation toxicity (8EHQ-0592-4272), and the second one on July 15, 1992 for human repeated insult patch tests with three batches of CGL-100 (8EHQ-0792-5787). The third notice was submitted April 13, 1993 for a neuropharmacological profile of Tinuvin 770 (we have



Section 8(e) Coordinator  
page 2 of 2

not received an 8(e) Log Number for that submission, nor did we link that submission to the two previous notices submitted under the 8(e) CAP).

As a result of this new information, Ciba will revise its Material Safety Data Sheet (MSDS) and label, as necessary, to reflect this potential effect.

Please call the undersigned if you have any questions about this submittal.

Very truly yours,



Anthony DiBattista

Enclosure

0 0 0 4

CIBA-GEIGY Ltd  
Pharmaceuticals Division  
Toxicology/Pathology

Laboratory report

PREPARATION TK 10665

Report on the 28 - Day Toxicity Study  
Oral Administration - Rat

TIN. 770  
(GI 10-100)

PH 2.634/LK/do  
December 10, 1976

REC'D  
OFFICE OF POLLUTION  
PREVENTION AND TOXICS  
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TK 10665  
Wxp.-No.: 7608020

### S U M M A R Y

Preparation TK 10665 was subjected to a 28 day toxicity study in rats. The test preparation TK 10665 was administered orally by gavage once daily, seven days a week at daily doses of 600, 1000 and 2000 mg/kg. Each dose group as well as the control group, which received only the suspension medium consisted of 5 male and 5 female albino rats. Mortalities and symptoms were recorded daily, body-weight gain 3 times and food consumption once weekly. Laboratory investigations were performed at the end of the experiment. All animals of the 2000 mg/kg/day-group died between day 2 and 17. Two male rats of the 1000 mg/kg/day-group died on day 5 or 28. No mortalities occurred after 600 mg/kg/day. The main symptoms observed in all dosed groups were ptosis of eye lids, muscular hypotonia and rough coat. Sedation, brownish eye discharge and kyphotic carriage were seen in the 1000 and 2000 mg/kg/day-group. The latter showed also soiled snout and dyspnoea. Some individual rats of all dosed groups showed salivation, stiff movements, slow or irregular respiration, ventri-or laterocumbency, slight cyanosis, tremor, meteorism, dyspnoea, sedation, diarrhea and soiled snout.

Loss of bodyweight was observed in the male rats of the 2000 mg/kg/day-group. The females of this group showed stagnation of growth during the first days of the study followed by reduced weight gain up to day 12 and practically normal weight until day 16 after which all animals of this group had died.

Male and female rats of the 1000 and 600 mg/kg/day-group showed a physiological pattern of growth. Food consumption was low in the males of the 1000 mg/kg/day-group during the first two weeks of the experiment. In all other dosed groups this parameter was found to be within physiological limits. Laboratory investigations revealed an increase of neutrophilic granulocytes and a relative decrease of lymphocytes in the differential blood count. All other parameters investigated were found to be within physiological limits valid for the strain of rats used.

At termination of the study the animals were referred to pathology and autopsied. Special attention was paid to the sympathetic nervous system and ganglia. In the latter, transmitter function was checked in some rats by histochemical techniques.

Histologically increased amount of eosinophilic and neutrophilic leucocytes in the spleen and in the blood vessels and perivascular tissue in the lungs was observed in all treated animals.

The quantitative neurohistochemical examination showed that the average noradrenaline content of the principal perikarya of the superior cervical ganglion of treated rats was distinctly lower than in the controls. The measured values recorded in the striatum and the vas deferens did not deviate from the control values.

METHODS

Species : rat strain: Tif: RAI f

Husbandry : air-conditioned rooms (temperature: 22±2°C; relative humidity: 50±5%, 14 hours light/day); groups of 5 animals in Macrolon cages (size 3)

Food : pelleted standard diet (Nafag no. 390)

No. of animals/group : 5 m and 5 f

Initial bodyweight : 105 - 127 g

Initial age : 5-6 weeks

Doses : 0, 600; 1000; 2000 mg/kg/day

Preparation : TK 10665  
daily fresh suspension with tap water

Route of administration : oral by gavage

Volume administered : 10 ml/kg

Frequency of administration : daily for 7 days per week

Duration of administration : 28 days

Follow-up period : -

Concentration of active ingredient : 6; 10; 20 %

Control group received : equal volume of tap water

**Blood sampling** : retrobulbar venous plexus (animals under light ether anaesthesia)

**Urine sampling** : single oral administration of 25 ml water/kg bodyweight, urine samples of each rat are collected over a 2 hours period in metabolism cages

**Euthanasia** : exsanguination in ether anaesthesia

Observations and Records

**Mortality** : daily

**Symptoms** : daily

**Bodyweight** : 3 times weekly

**Food consumption** : weekly

**Blood chemistry** : }  
**Haematology** : } on day 28

**Urinalysis** : on day 25

**Body temperature** : -

**Eye examination** : -

**Auditory perception** : -

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The animals were referred to pathology on completion of the study (for results see pathology report).

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TK 10665

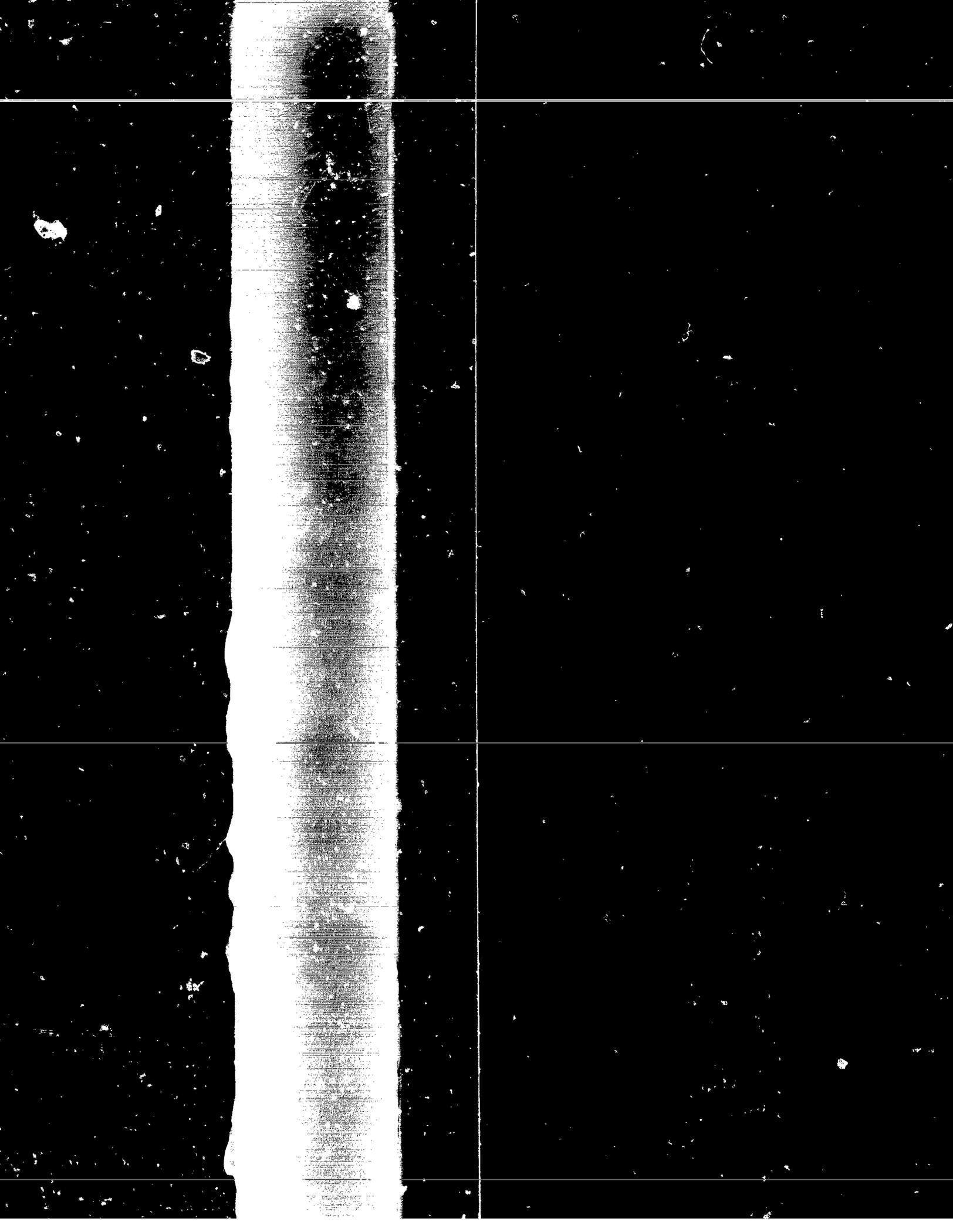
Exp. No.: 7608020

RESULTS

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MORTALITY

dose mg/kg/day p.o.	total %	animal		
		sex	no.	day of trial
0	0			
600	0			
1000	20	m	21	5.
		m	25	28.
2000	100	m	33, 34, 35	2.
		f	37	
		m	31, 32,	3.
		f	40	
		f	38, 39	
f	36	17.		



SYMPTOMS

dose mg /kg/day p.o.	day of test	animal		SYMPTOMS		
		sex	No		time after admini- stration	dura- tion approx
0		m+w	all	none		
600	1.-2.	m+w	all	eye lids half closed	3 h	>20
	7.	m	13	soiled snout	before	<20
		f	19	dyspnoea	before	<20
	9.-18	m+w	all	rough coat	1'	2h
	9.-28.	m+w	all	muscular hypotonia	6h	>20
	9.-28.	m	15	salivation	before	>20
		f	20			
	16.	m	12	diarrhea	before	<20
16.-28	m+w	all	muscular hypotonia	before	>20	
21.-28.	m	12	dyspnoea	1h	>20	
1000	1.-28	m+w	all*	muscular hypotonia, eye lids half-closed, sedation	3h	>20
	2.-28	m+w	all*	brownish eye discharge	before	>20
	3.	m	23	dyspnoea	1h	<20
	5.-7.	m	25	dyspnoea		>20
	4.-28	m+w	all*	kyphotic carriage, rough coat	1h 6h	>20
	9.-28.	f	29	dyspnoea	1h	>20
	13.-15	f	27	salivation	before	>20
	13.-28.	f	29	meteorism, slight cyanosis soiled snout, exophthalmus	before	>20
	15.	f	26,27	salivation	before	<20
		f	30	ventricumbency	30'	> 6h
2000	1.-16	m+f	all*	muscular hypotonia, eye lids half-closed irregular respiration.	3h	>20

\* = during administration; ' = minute; h = hour

0012

SYMPTOMS

(continued)

dose mg/kg/day	day of test	animal		SYMPTOMS	time after admini- stration	dura- tion approx
		sex	No			
2000	2.	f	39	ventricumbency, slight trem- bling, dyspnoe, slight cyano- sis, sedation	30'	15'
	2.-16	m+f	all*	brownish eye discharge	before	>20
	3.	f	38	ventricumbency	30'	20'
	3.-16	m+f	all*	kyphotic carriage, soiled snout	before	>20
		f	all*	sedation, dyspnoe	30'	>20
	4	f	39	laterocumbency, slow respi- ration	45'	15'
	7.-16	f	36	stiff movements, eye lids closed	before	>20
	13.-16	f	36	salivation	before	>20

+ = during administration; ' = minute; h = hour

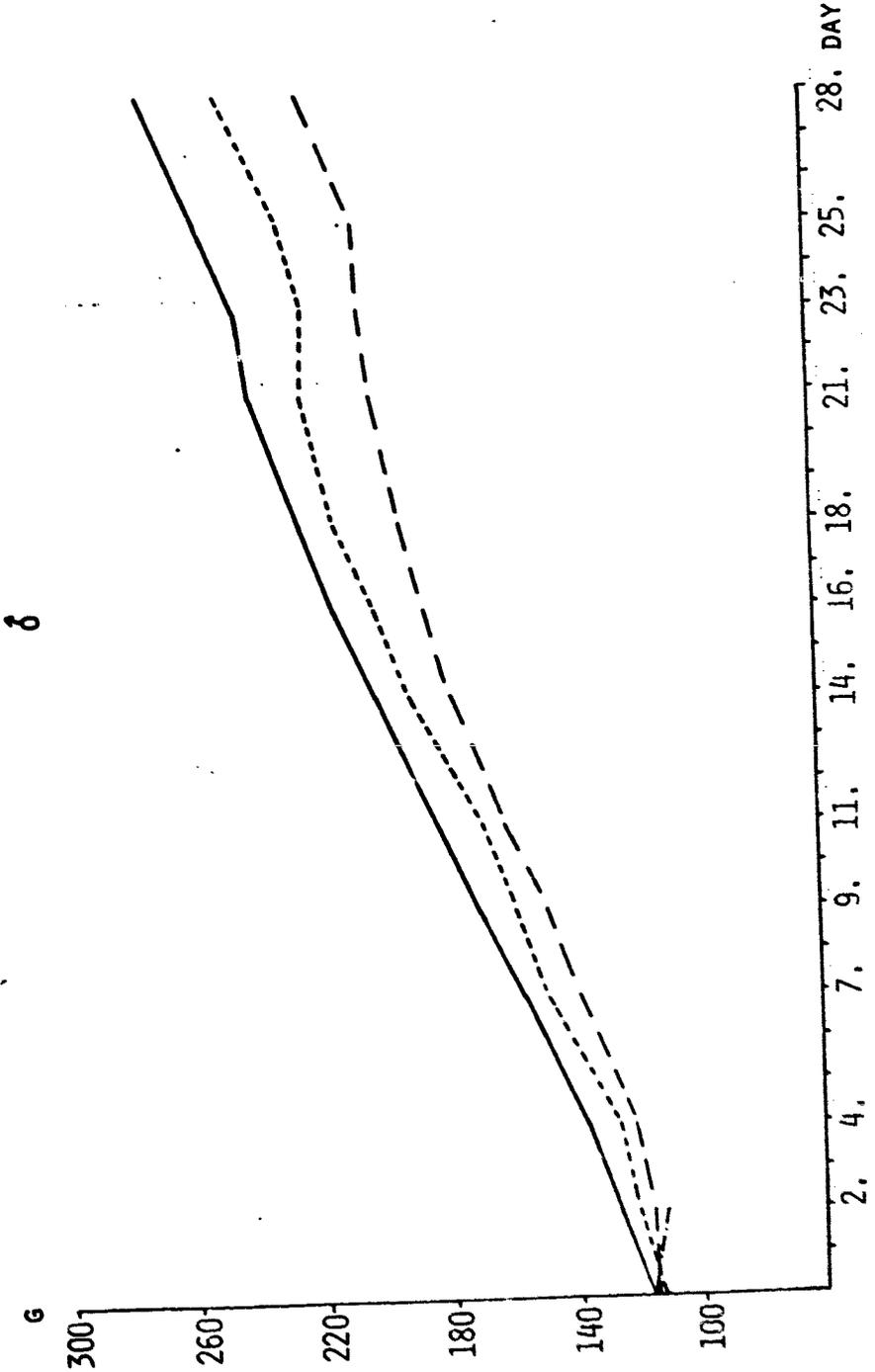
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TK 10665  
EXP. No.: 7608020  
MG/KG/DAY P.O.

0: ———  
600: - - - -  
1000: - - - -  
2000: - - - -

BODYWEIGHTING

(GROUP MEANS)



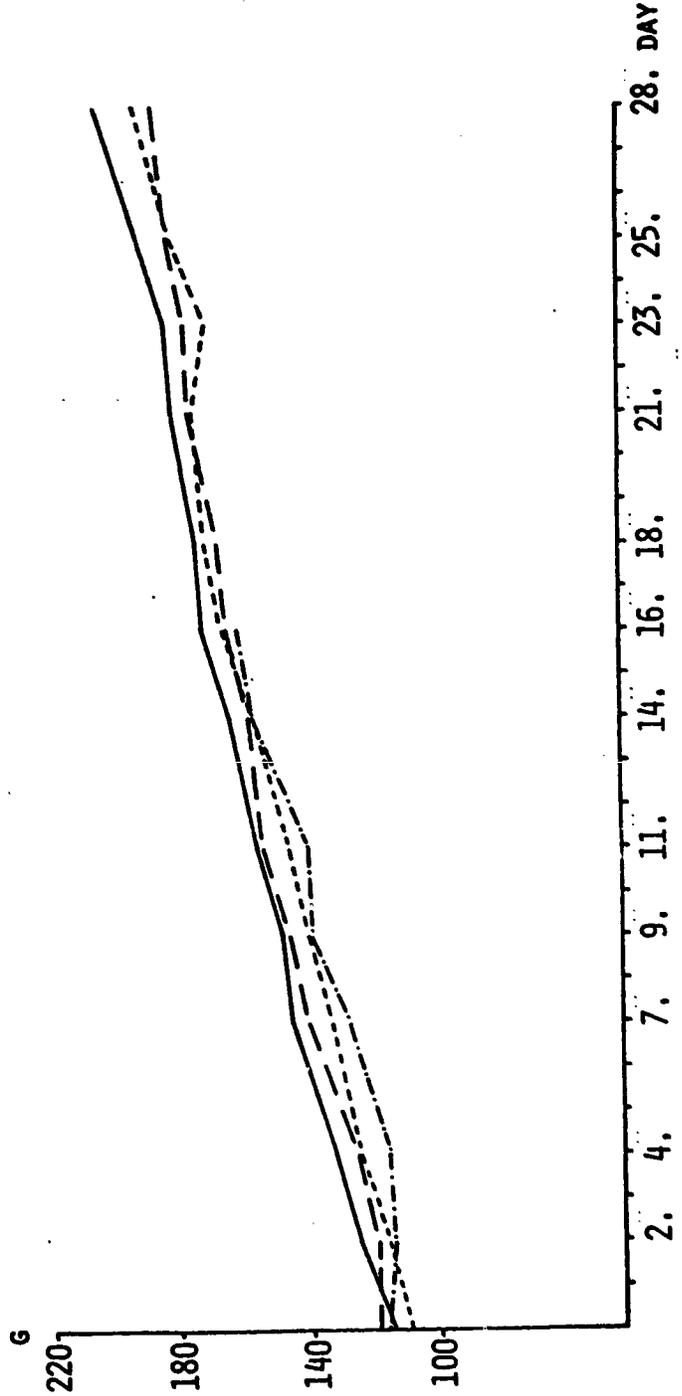
TK 10665  
EXP. No.: 7608020  
MG/KG/DAY P.O.

0: ———  
600: - - - -  
1000: - - - -  
2000: - · - · -

BODYWEIGHTING

(GROUP MEANS)

♀



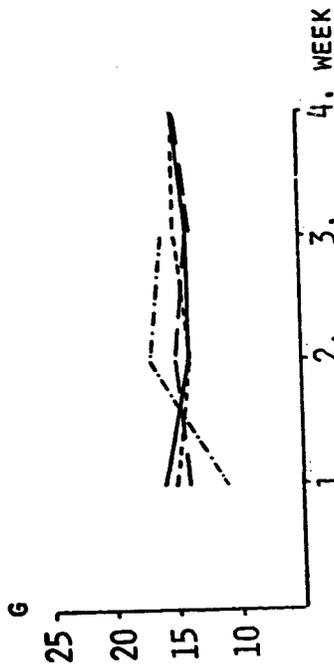
TK 10665  
Exp. No.: 7608020  
MG/KG/DAY P.O.

0: ———  
600: - - - -  
1000: - - - -  
2000: - - - -

FOOD CONSUMPTION IN G/DAY

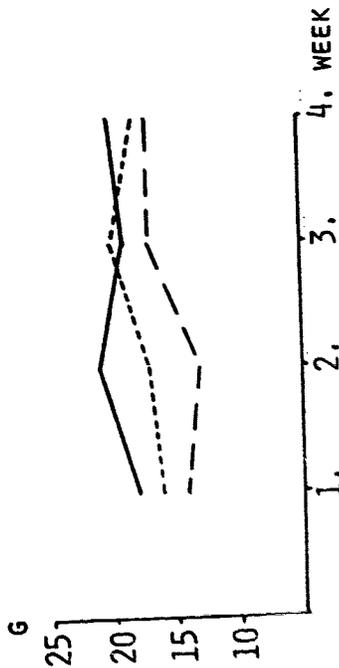
GROUP MEANS

♀



GROUP MEANS

♂



TK 40665

Exp. No.: 7608020

NORMAL VALUES

SPECIES: RAT (MAM)

WEEK 5 OF STUDY

TEST	MALE				FEMALE				MALE + FEMALE			
	NUMBER OF ANIMALS	MEAN	SD	VC %	NUMBER OF ANIMALS	MEAN	SD	VC %	NUMBER OF ANIMALS	MEAN	SD	VC %
COULM	40.0	139.9	1.4	1.0	37.0	140.9	2.9	2.1	77.0	140.4	2.3	1.6
GLASSIUM	40.0	4.1	0.4	8.8	37.0	3.9	0.3	8.7	77.0	4.0	0.4	9.1
GLUCOSIDES	14.0	106.1	5.4	5.1	11.0	105.2	3.6	3.4	25.0	105.7	4.6	4.4
GLUCOSE	37.0	144.4	25.7	17.3	38.0	156.7	19.5	12.4	75.0	152.6	23.0	15.1
U <sub>1</sub>	39.0	44.8	3.3	20.4	38.0	21.5	2.6	11.9	77.0	20.2	3.2	15.9
U <sub>2</sub>	40.0	62.1	9.1	14.8	38.0	59.8	7.9	24.4	78.0	38.7	10.5	27.2
U <sub>3</sub>	40.0	436.3	57.5	13.2	38.0	292.9	13.6	23.1	78.0	360.4	93.7	19.1
ALKALINE PHOSPHATASE	40.0	6.7	0.3	4.2	38.0	7.1	0.4	6.2	78.0	6.9	0.4	6.1
ALBUMIN	40.0	47.2	3.1	6.5	38.0	52.2	3.0	5.8	78.0	49.6	3.9	7.9
ALB A1	40.0	20.1	1.9	9.6	38.0	16.5	1.8	10.7	78.0	18.3	2.6	14.0
ALB A2	40.0	8.5	1.2	14.8	38.0	6.0	1.1	16.9	78.0	7.5	1.5	20.4
ALB A3	40.0	7.5	0.0	0.0	38.0	6.0	1.1	18.5	78.0	6.7	1.4	20.2
ALB B1	40.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ALB B2	40.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ALB S <sub>1</sub>	40.0	13.1	2.1	15.8	38.0	13.9	1.7	12.2	78.0	13.5	1.9	14.2
ALB G	40.0	3.7	1.2	32.9	38.0	5.2	1.8	35.7	78.0	4.4	1.7	38.9
HAEMOGLOBINE	39.0	15.3	0.7	4.7	38.0	14.5	0.9	6.1	77.0	14.9	0.9	5.9
HAEMATOPOIESIS	40.0	7.7	0.6	8.2	38.0	7.0	0.5	7.7	78.0	7.4	0.7	9.3
CV	40.0	47.1	1.4	3.0	38.0	45.4	1.6	3.4	78.0	46.3	1.7	3.6
LEUCOCYTES	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
THROMBOCYTES	39.0	665.4	49.8	7.5	36.0	681.4	41.8	6.1	75.0	673.1	46.5	6.9
PLATELETS	40.0	8.2	2.0	24.5	38.0	5.9	2.0	34.3	78.0	7.1	2.3	32.8
HEPATIC BLOOD FLOW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HEPATIC BLOOD FLOW	40.0	10.8	7.0	65.0	38.0	10.8	4.3	40.0	78.0	10.8	5.8	53.9
HEPATIC BLOOD FLOW	40.0	0.8	1.1	147.5	38.0	1.2	1.2	105.3	78.0	1.0	1.2	123.7
HEPATIC BLOOD FLOW	40.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HEPATIC BLOOD FLOW	40.0	1.0	0.9	91.4	38.0	1.2	1.3	102.9	79.0	1.1	1.1	99.3
HEPATIC BLOOD FLOW	40.0	87.7	7.4	8.4	38.0	86.7	4.3	5.0	78.0	87.2	6.1	7.0
HEPATIC BLOOD FLOW	40.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HEPATIC BLOOD FLOW	40.0	15.0	1.4	9.1	37.0	13.5	1.2	8.7	77.0	14.3	1.5	10.3
HEPATIC BLOOD FLOW	40.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HEPATIC BLOOD FLOW	40.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HEPATIC BLOOD FLOW	40.0	7.0	1.8	25.5	39.0	5.4	1.6	30.0	79.0	6.2	1.9	30.1
HEPATIC BLOOD FLOW	40.0	1006.7	4.8	0.5	39.0	1005.1	2.3	0.2	79.0	1005.9	3.8	0.4

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COMPOUND : TK 10665  
28-DAY OF EXP.

S T A T I S T I C S

EXPERIMENT NO.: 7608020

SPECIES : RAT (RAI-OUTBRED)

GROUP MEAN / PROBABILITY LEVEL

TEST	UNITS	DAILY DOSAGE IN MG/KG		
		0.0001	1000.000	1000.000
SCCIUM	MEQ/L	143.0	145.6 / V	142.6 /
PCTASSIUM	"	3.7	4.0 /	3.8 /
CHLORIDES	MGZ	149.9	156.7 /	155.0 /
GLUCOSE	MGZ	21.2	20.4 / V	20.9 /
ALN	RF UNITS	43.3	35.1 /	44.8 /
GPT	RF UNITS			
GOT	RF UNITS	10.3	8.2 /	8.9 /
ALKALINE PHOSPHATASE	MPH/L			
BPCMSULFCAPHTHALEIN	MGZ			
BILIRUBINE	MGZ	6.6	6.3 /	6.4 /
PROTEINS	G	54.1	48.9 /	55.0 /
ELECTROPHORESIS	GLO	17.0	16.6 /	16.1 /
	A1 %	6.9	8.2 /	7.7 /
	A2 %	5.0	6.8 /	5.1 /
	A3 %			
	F1 %			
	B2 %	13.9	14.4 /	12.3 /
	S0 %	3.2	5.1 /	3.9 /
	G %			
HAEMOGLOBINE	G Z	15.8	16.1 / V	15.4 /
ERYTHROCYTES	MILL/CPH	7.0	6.8 / V	6.7 /
PCV	%	44.9	48.9 / V	45.5 /
RETICULOCYTES	0/00			
TROMBOCYTES	1000 /CPH	560.0	515.0 /	523.3 /
LEUCOCYTES	1000 /CPH	5.2	10.5 /	6.4 /
DIFF-BLOOD COUNT				
	PAND	0.2	0.1 /	0.1 /
	SEG	14.3	23.4 /	22.0 /
	EO	0.7	1.9 / V	1.0 / V
	BA	0.0	0.0 /	0.0 /
	MO	0.8	0.9 /	1.5 /
	LY	84.0	73.8 /	75.4 /
	PL	0.0	0.0 /	0.0 /
RECALCIFICATION TIME	SEC	12.8	13.5 /	11.9 /
PROTHROMBINE TIME	SEC			
URINE VOLUME	ML	4.1	4.2 /	4.4 /
SPECIFIC GRAVITY	/1000	1005.6	1008.1 /	1006.3 /
PFENOLSULFCAPHTHALEIN	%			

\* = NOT SIGNIFICANT  
V = DIFFERENCE IN VARIANCES, P<0.01  
.05 = DIFFERENCE IN MEANS, P<0.05  
.01 = DIFFERENCE IN MEANS, P<0.01

**FOOD CONSUMPTION in g/day**

Tx 40665

Exp.No.: 7608020

weekly means

Dose: 0 mg / kg / day

Week	Animal number	
	♂ 1-5	♀ 6-10
1	17.9	16.4
2	20.6	14.3
3	19.4	14.4
4	20.1	15.4





**FOOD CONSUMPTION in g/day**

TK 10665

Exp.No.: 7608020

weekly means

Dose: 2000 mg /kg / Tag

Week	Animal number	
	♂ 34 - 35	♀ 36 - 40
1	6.4	12.2
2	-	17.1
3	-	16.5
4	-	-

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TK 10665

Exp. No.: 7608020

PATHOLOGY REPORT

0023

Compound	TK 10665
Exp.Nr.	7608020
Hist.Nr.	Ex. 360

### Summary

All treated rats from the 2000 mg/kg and 2 out of 10 rats from the 1000 mg/kg dosage groups died during the toxicity study. Acute congestion of all organs was seen in those animals which were sent for autopsy.

The terminal body weight in the treated rats of the 1000 mg/kg dosage group was slightly but significantly depressed and the relative weight of the spleen was raised. Histologically increased amount of eosinophilic and neutrophilic leucocytes in the spleen and in the blood vessels and perivascular tissue in the lungs was observed in all treated animals. No other compound related gross or histopathological changes were seen.

Compound	TK 10665
Exp.Nr.	7608020
Hist.Nr.	Ex. 36r

#### Pathology / Methods

The rats of all treated and one control groups which survived were anaesthetized with ether and bled after 28 days of treatment. The total weight of each animal was then determined. After macroscopical examination the individual weights of heart, spleen, liver, adrenals, kidneys, thymus, brain and testicles were recorded. Mean organ weights and mean organ to bodyweight ratios were calculated for each of these organs for all treated and control groups.

Tissue portions of oesophagus, trachea, thyroid, thymus, heart, aorta, lungs, liver, pancreas, stomach (fundic and pyloric) small and large intestine, spleen, lymph nodes, adrenals, kidneys, urinary bladder, testes, epididymis, seminal vesicles and prostate or ovaries and uterus, striated muscle, skin were fixed in Bouin fixative. The fixed tissue samples from all rats were embedded in paraffin wax and sectioned at 3-5  $\mu$ . The routine stain was haematoxylin and eosin. Additional frozen sections of liver and adrenals from all control and treated rats were specifically stained for fat with Sudan III.

Autopsy and histopathological examination were performed also in those animals which died during the test period unless the advanced autolysis prevented it.

Compound      TK 10665  
Exp.Nr.        7608020  
Hist.Nr.        Ex. 360

### Assessment

#### Macroscopical Findings

All details regarding the gross changes are listed within the macroscopical findings in individual rats. All rats ( 5 m+ 5 f) from the highest dosage group and 2 males from the intermediate (1000 mg/kg) dosage group died during the test period. Only 3 of them were autopsied. Acute congestion of the organs and more or less advanced autolysis were seen at gross anatomical examination in them.

In all treated rats from both 600 mg/kg and 1000 mg/kg dosage groups which survived till the end of the toxicity study no compound related changes were found.

#### Organ Weights

The terminal body weight in the treated rats of the 1000 mg/kg dosage group was slightly but significantly depressed. The spleen to body weight ratio in these animals was slightly increased.

#### Microscopical Findings

All details regarding the microscopical changes are listed in the microscopical findings in individual rats. Nearly in all treated rats increased amount of neutrophilic and eosinophilic leucocytes in the spleen, within the blood vessels and in the perivascular tissue in the lungs were observed. All other histopathological changes seen in some control and treated animals were only incidental in nature and not related to the oral administration of TK 10665.

Compound	T. 10665
Exp.Nr.	7608020
Hist.Nr.	Ex. 360

### Macroscopical Findings in Individual Rats

#### Group 1 0 mg/kg Controls

1 m	No changes seen
2 m	No changes seen
3 m	No changes seen
4 m	Lungs with red patches. Kidneys mottled
5 m	Lungs with red patches
6 f	No changes seen
7 f	No changes seen
8 f	No changes seen
9 f	No changes seen
10 f	No changes seen

#### Group 2 600 mg/kg

11 m	No changes seen
12 m	Lungs with red patches. Small haemorrhages in the thymus
13 m	No changes seen
14 m	Lungs with red patches
15 m	No changes seen
16 f	No changes seen
17 f	No changes seen
18 f	Liver with yellowish tinge
19 f	Liver with yellowish tinge
20 f	No changes seen

#### Group 3 1000 mg/kg

21 m	died on the 5 th experimental day Partially eaten by the cage mates. Advanced autolysis
22 m	Lungs with red patches
23 m	No changes seen
24 m	Lungs with red patches.
25 m	died on the 28 th experimental day. Partially eaten by the cage mates. Acute congestion of all organs. Moderately advanced autolysis.
26 f	No changes seen
27 f	No changes seen
28 f	No changes seen
29 f	Liver with yellowish tinge
30 f	No changes seen.

Compound	TK 10665
Exp.Nr.	7608020
Hist.Nr.	Ex. 360

Group 4 2000 mg/kg

All animals of this group died during the test period.

Only one rat (36f) was sent for autopsy.

36 f died on the 17 th experimental day

Acute congestion of the organs and initial autolysis.

0002 B

Compound	TK 10665
Exp.Nr.	7608020
Hist.Nr.	Ex. 360

### Microscopical Findings in Individual Rats

In order to avoid needless repetition only the pathological changes are reported.

In the liver in nearly all animals there were small lymphohistiocytic infiltrates in the interstitium and slight fatty changes of some hepatocytes. The spleen showed slight extramedullary haematopoiesis.

Apart from these findings the following changes were seen:

#### Group 1 0 mg/kg control

- |      |   |
|------|---|
| 1 m  | No other changes seen   |
| 2 m  | Spleen: congestion, small haemorrhages  |
| 3 m  | Lungs: small haemorrhages and blood within some bronchi.  |
| 4 m  | Lungs: increased amount of polymorphs and eosinophils within blood vessels and in the perivascular tissue. Focal accumulation of foamy cells within the lumen of some alveoli. Aspiration of the blood.<br>Kidney: no changes seen. |
| 5 m  | Lungs: Aspiration of the blood. Focal accumulation of foamy cells within the lumen of some alveoli.   |
| 6 f  | Lungs: increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.<br>Kidney: marked nephrocalcinosis   |
| 7 f  | Stomach: small histiocytic granuloma in the mesentery<br>Kidney: moderate nephrocalcinosis  |
| 8 f  | Kidney: moderate nephrocalcinosis   |
| 9 f  | Lungs: increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue<br>Kidney: marked nephrocalcinosis  |
| 10 f | Stomach: small histiocytic granuloma in the mesentery<br>Kidney: slight nephrocalcinosis  |

#### Group 2 600 mg/kg

- |      |  |
|------|--|
| 11 m | Lungs: small haemorrhages and blood within some bronchi.<br>Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.  |
| 12 m | Lungs: small haemorrhages and blood within some bronchi.<br>Focal accumulation of foamy cells within the lumen of some alveoli.<br>Thymus: haemorrhages not seen in sections examined.<br>Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.<br>Kidney: slight nephrocalcinosis |

Compound TK 10665  
 Exp.Nr. 7608020  
 Hist.Nr. Ex. 360

- 13 m Lungs: small haemorrhages and blood within some bronchi.  
 Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa  
 Kidney: focal basophilic proliferation of the tubular epithelium.
- 14 m Lungs: increased amount of polymorphs and eosinophils within in the blood vessels and in the perivascular tissue.  
 Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.
- 15 m No other changes seen
- 16 f Spleen: congestion, small haemorrhages  
 Large intestine: some glands cystically dilated with cellular debris within the lumen.  
 Kidney: small scars and focal basophilic proliferation of the tubular epithelium in the cortex.
- 17 f Lungs: small lymphohistiocytic infiltrates in the interstitium. Increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.  
 Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.
- 18 f No other changes seen
- 19 f Lungs: increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.  
 Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.
- 20 f Trachea: acute tracheitis with polymorphonuclear infiltrates in the mucous membrane and pus within the lumen.  
 Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.  
 Small intestine: dilated, with slight polymorphonuclear infiltration in the mucous membrane.

Group 3 1000 mg/kg

- 21 m died on the 5 th experimental day  
 Not sent for histopathology
- 22 m Lungs: massive aspiration of the blood. Increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.  
 Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.
- 23 m Trachea: slight chronic tracheitis  
 Stomach: slight polymorphonuclear infiltration in the mucous membrane  
 Large intestine: Nematode parasite within the lumen.  
 Kidney: Congestion, small haemorrhages.

Compound TK 10665  
 Exp.Nr. 7608020  
 Hist.Nr. Ex. 360

- 24 m Lungs: massive aspiration of the blood. Acute vesicular emphysema.
- 25 m died on the 28 th experimental day.  
 Trachea: purulent tracheitis  
 Lungs: acute congestion, large haemorrhages. Focal accumulation of foamy cells within the lumen of some alveoli. Numerous histiocytes, occasional polymorphs and multinucleated giant cells in the interstitium and within the lumen of some alveoli.  
 Liver: acute congestion, confluent haemorrhages, autolysis  
 Kidney: acute congestion, small haemorrhages, autolysis.
- 26 f Lungs: Increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.  
 Spleen: Congestion, confluent haemorrhages. Slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.
- 27 f Lungs: increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.  
 Spleen: Congestion, small haemorrhages. Slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.  
 Ovary: marked congestion.
- 28 f Lungs: increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.  
 Spleen: Congestion, small haemorrhages. Slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.
- 29 f Lungs: small haemorrhages and blood within some bronchi.  
 Thymus: slight atrophy of the thymic tissue  
 Spleen: very marked extramedullary haematopoiesis
- 30 f Lungs: increased amount of polymorphs and eosinophils within the blood vessels and in the perivascular tissue.  
 Spleen: slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.

Group 4 2000 mg/kg

- Only one animal (36 f) of this group was sent for histopathology.
- 36 f died on the 17 th experimental day.  
 Lungs: congestion, small haemorrhages.  
 Spleen: Congestion, small haemorrhages. Slightly increased amount of neutrophilic and eosinophilic leucocytes in the red pulpa.  
 Small intestine: slight polymorphonuclear infiltration in the mucous membrane. Initial autolysis  
 Liver: congestion, small haemorrhages  
 Kidney: congestion, small haemorrhages, autolysis.







Single and Mean Organ Weights and Ratios (g)

Compound : Tk-10665  
 Dose : 600 mg/kg

Exp. No. : 76 08020  
 Histopathol. No. : Ex 360  
 Species : Rat

28 Days

Animal No.	Sex	Body-weight	Heart	Lung	Spleen	Liver	Kidneys	Adrenals	Thyroid	Thymus	Prostate	Gonads	Brain	Pituitary
16	♀	200	0,806		0,539	9,40	1,61	0,0600		0,463			1,86	
17		170	0,623		0,357	8,20	1,45	0,0577		0,443			1,89	
18		171	0,743		0,511	8,30	1,67	0,0791		0,413			1,75	
19		180	0,719		0,405	8,65	1,34	0,0491		0,405			1,84	
20		175	0,704		0,367	8,30	1,43	0,0604		0,278			1,81	
S		904	3,595		2,159	42,85	7,50	0,3063		2,107			9,45	
M		180,8	0,799		0,4318	8,57	1,50	0,0615		0,421			1,83	
R%		-	0,398		0,229	4,74	0,830	0,0339		0,233			1,01	
249	♂	2037	7,845		4,940	100,15	16,09	0,5229		4,487			18,48	
M		208,7	0,785		0,494	10,02	1,609	0,0523		0,4437			1,848	
R%		-	0,376		0,237	4,80	0,771	0,0257		0,215			0,885	

R % = Ratio (Organ-Bodyweight - g/100 g)

S = Sum  
 M = Mean weight



Single and Mean Organ Weights and Ratios (g)

Exp. No. : 7602020  
 Histopathol. No. : 61360  
 Species : Rat  
 28 Days  
 Compound : IK 10665  
 Dose : 1000 mg/kg

Animal No. Sex	Body-weight	Heart	Lung	Spleen	Liver	Kidneys	Adrenals	Thyroid	Thymus	Prostate	Gonads	Brain	Pituitary
26 ♀	170	0.692		0.410	8.37	1.53	0.0610		0.442			1.75	
27	183	0.704		0.536	9.87	1.93	0.0754		0.470			1.91	
28	191	0.709		0.503	9.60	1.87	0.0622		0.342			1.75	
29	143	1.097		0.551	6.50	1.60	0.0712		0.109			1.73	
30	165	0.633		0.509	8.45	1.72	0.0667		0.456			1.71	
♂	877	3.841		2.514	43.29	8.65	0.3371		1.819			8.85	
M	175.4	0.768		0.503	2.66	1.73	0.0674		0.364			1.77	
R%	-	0.438		0.237	4.94	0.986	0.0384		0.207			1.01	
♂	1499	6.205		4.044	69.34	13.25	0.5095		3.310			14.27	
M	187.38	0.776		0.5055	8.62	1.66	0.0637		0.414			1.784	
R%	-	0.444		0.270	4.63	0.884	0.0340		0.221			0.952	

R % = Ratio (Organ-Bodyweight - g/100 g)

S = Sum  
 M = Mean weight





Ciba-Geigy Ltd.  
Toxicology-Pathology  
PH 2.631  
Dr G. Krinke  
K. Schnider

Laboratory Report

Effect of the Compound TK 10665 on the Catecholamine

Fluorescence in Rat Nerve Tissue

(7608020 / Ex 360)

11<sup>th</sup> May 1977

Summary

In two male rats treated orally for 28 days with 1000 mg/kg /day of TK 10 665 and in two control rats the noradrenaline content of neurons in the iris, the superior cervical ganglion and the vas deferens and the dopamine content of neurons in the striatum was estimated by means of the formaldehyde - fluorescence method. The qualitative examination of these tissues did not reveal any difference between the controls and the treated rats. The quantitative examination showed that the average noradrenaline content of the principal perikarya of the superior cervical ganglion of treated rats was distinctly lower than in the controls. The measuring values recorded in the striatum and the vas deferens did not deviate from the control values.

Material and Methods

Following male rats were used:

Rat No	Body - weight ( at autopsy )	Dose of TK 10 665 ( mg/kg/day )
22	200 g	1000
24	210 g	1000
2*	250 g	control
3*	252 g	control
4	254 g	control
5	260 g	control

\* used as uncondensed controls for background values

The rats were sacrificed under chloroform anaesthesia and the left and right superior cervical ganglion, the corpus striatum ( rostromedial part ) and the vas deferens ( distal, para - testicular part ) were processed according to formaldehyde - fluorescence method. The fluorescence in the iris, in the cytoplasm of principal neurons of the superior cervical ganglion and the one in the muscle layer of the vas deferens were considered to be due to noradrenaline fluorophore, whereas the fluorescence of the striatal neuropil was taken for dopamine. The iris was submitted to qualitative examination and in the remaining tissues the intensity of the fluorescence ( as a measure of the catecholamine concentration ) was measured by means of Zeiss - microfluorometer, the diameter of the measuring field being 3,15  $\mu$ m. For the excitation a HBO 100 W /2 mercury lamp was used with a BG 12 filter and the emission was limited by the barrier filter to 470 to 650 nm. Following numbers of measuring values were collected of particular samples:

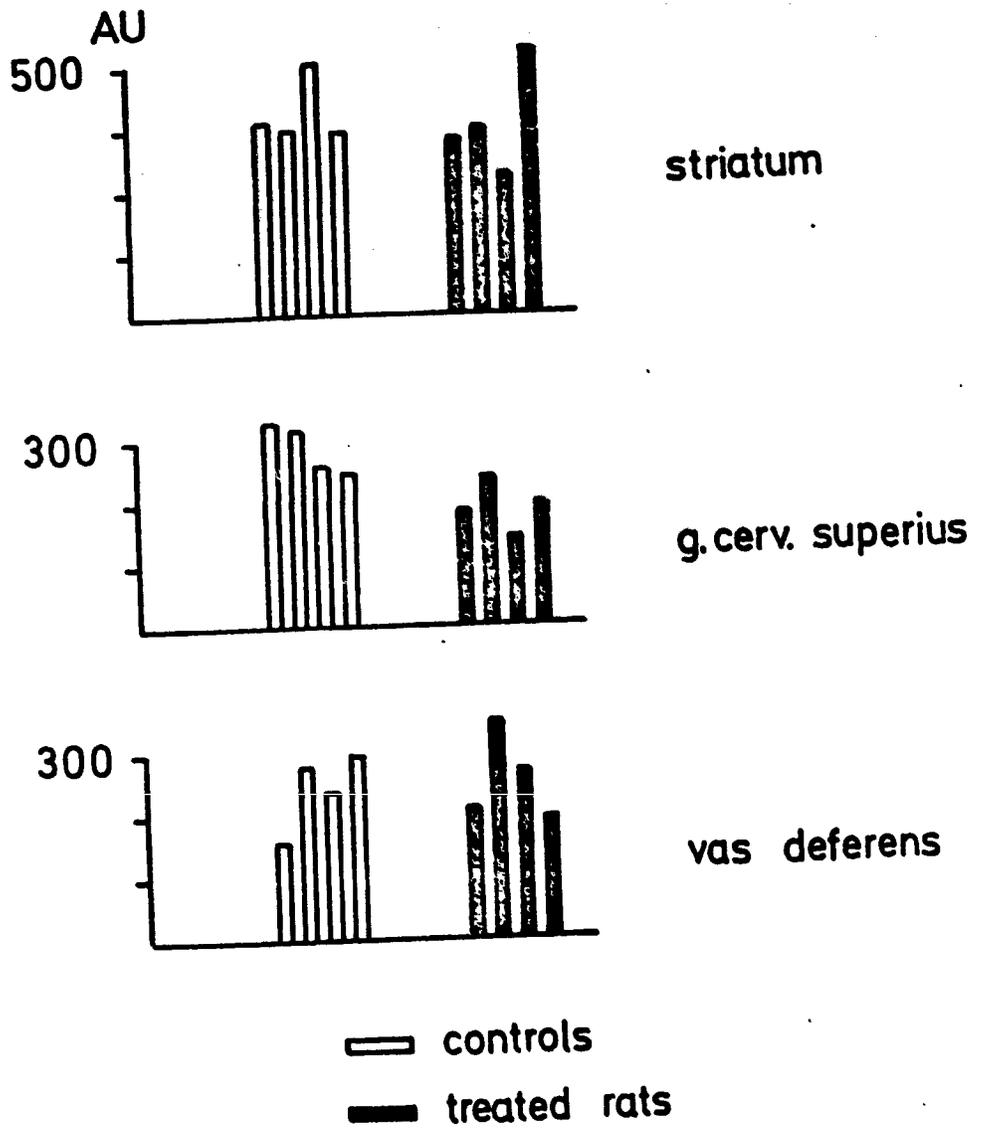
0 0 4 2

Tissue	Number of sections ( 5 $\mu$ m, paraffin )	Number of measuring values / section
superior cervical ganglion	2	20
vas deferens	3	20
striatum	3	10

The fluorescence intensity was expressed directly in arbitrary units and the results were corrected for background fluorescence by subtraction of average values of uncondensed samples.

Results

The qualitative examination did not reveal any difference between the treated rats and the controls with regard to both the distribution and the intensity of the fluorescence. The results of the quantitative evaluation are depicted in the enclosed figure. In the superior cervical ganglion of treated rats the fluorescence intensity of the principal perikarya was distinctly lower than in the controls. The fluorescence intensity of the striatum and the vas deferens was in the treated rats about the same as in the controls.



Verteiler: HH. L. Krüger (Original)

Dr. R. Leimgruber —

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Dr. F. Zak

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