European Registration Dossier
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Acute Oral Toxicity in the Rat

Test No. 933179

CGA 329351 techn. (d-enantiomer of CGA 48988)

Report

Study director:	Dr. med. vet. 5.1.2.e Woo
Testing facility:	Short-term Toxicology CIBA-GEIGY Limited 4332 Stein / Switzerland
Test guideline:	OECD 401, 92/69/EEC, B.1.
Study completed:	April 6, 1994
Sponsor:	CIBA-GEIGY Limited Plant Protection 4002 Basel / Switzerland

This report contains: 19 pages

Certification of GLP and verification of the report

(Certification of Good Laboratory Practice and verification of a complete and unaltered copy of the report by the sponsor)

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

For the Sponsor:

Signature: ..... Date: April 17, 1994

Statement of compliance with Good Laboratory Practice

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

- OECD Principles of Good Laboratory Practice (Council Decision 81/30, adopted on May 12, 1981, and the OECD Recommendation 83/95 concerning the 'Mutual Recognition of Compliance with Good Laboratory Practice', adopted on July 26, 1983).

- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 160 (FIFRA); Federal Register, August 17, 1989.

- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 792 (TSCA); Federal Register, August 17, 1989.

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

Study director: Dr. med. vet. [redacted]

Signature: [redacted] .... Date: April 6, 1994

Reserved page for flagging statements

Quality assurance statement

Test Article:	**CGA 329351 techn. (d-enantiomer of CGA 48988)**
Study Title:	**Acute Oral Toxicity in the Rat**
Test Number:	**933179**
Study Director:	**Dr. med. vet.** 5.1.2.e Woo

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

QA-Activity	Date performed	Date reported
Facility Inspection	September 16, 1993	September 17, 1993
Protocol Audit	January 7, 1994	January 7, 1994
Study Inspection	January 6, 1994	January 7, 1994
Final Report Audit	March 14, 1994	March 16, 1994

Quality Assurance Inspector: 5.1.2.e Woo

Signature: .... Date: April 7, 1994

1. SUMMARY AND CONCLUSIONS

Upon an acute oral administration and a 14 day post-treatment observation period, the following LD50 (with 95% confidence limits calculated, where possible) was determined for CGA 329351 techn. (d-enantiomer of CGA 48988)

LD50 in male rats: 953 (574 - 1451) mg/kg body weight

LD50 in female rats: 375 mg/kg body weight

LD50 in rats of both sexes: 667 (443 - 1004) mg/kg body weight

Observations

Piloerection, abnormal body positions, and dyspnea were seen, being common symptoms in acute tests.

Additionally, reduced locomotor activity was observed in all animals. Convulsions and/or tonic spasms were noticed in 2 males and 4 females dosed with 500 and all males dosed with 1000 and 2000 mg/kg. Ataxia was displayed by 2 females dosed with 200, tremor by one male dosed with 500 mg/kg. Four females dosed with 500 mg/kg showed raised irritability. In the males dosed with 2000 mg/kg vocalizations, respiratory sounds and cyanosis were recorded.

The surviving animals recovered within 3 to 6 days.

At necropsy, a spotted thymus was found in one male dosed with 2000 mg/kg. No deviations from normal morphology were found in the remaining animals.

2. INTRODUCTION

2.1. Purpose

At the request of the Plant Protection of CIBA-GEIGY Limited, Test No. 933179, was conducted to determine the acute oral toxicity of CGA 329351 techn. (d-enantiomer of CGA 48988) in albino rats.

2.2. Basis

The study design followed the test guidelines OECD 401, 92/69/EEC, B.1.

As requested by the sponsor, the whole study was subjected to quality assurance.

2.3. Testing facility

All the work was done in the testing facility:
CIBA-GEIGY Limited
Short-term Toxicology
4332 Stein / Switzerland

Technical assistant: Mr. 5.1.2.e Woo

Archives are located at:
CIBA-GEIGY Limited
Werk Stein
4332 Stein / Switzerland
Raw data, protocol and report will be stored at this location.

The job descriptions and the summaries of training and professional experience for all personnel participating in this study are archived in the testing facility.

2.4. Dates

Date of protocol:	January 5, 1994
Date of administration:	January 6, 1994 January 7, 1994 January 10, 1994 January 11, 1994
Experimental completion date:	January 25, 1994

2.5. Distribution

Sponsor (Dr.
Archives

3. MATERIALS AND METHODS

3.1. Test Article

Test article:	CGA 329351 techn. (d-enantiomer of CGA 48988)
Batch No.:	KGL4634/5
Purity/Contents:	97.9%
Storage conditions:	room temperature
Date of reanalysis:	December, 1995
Safety precautions:	gloves and face masks
Test material received:	December 21, 1993

3.2. Animals

3.2.1. Choice of species

The rat has been selected for this test as being a standard species for the determination of the acute oral toxicity.

Young adult albino rats of both sexes (Tif: RAI f (SPF), bred and raised on the premises, were used in the experiment.

Source:	CIBA-GEIGY Limited Animal Production 4332 Stein / Switzerland
Initial body weight range:	185 to 249 g

3.2.2. Husbandry and Diet

The rats were kept in an animal room under conventional laboratory conditions, on a 12 hour/day light cycle. The air conditioning system (approximately 15 air changes per hour) maintained a temperature of 22 ± 2 °C and a relative humidity of 55 ± 10 %.

The animals were housed in Macrolon cages type 4, with standardized soft wood bedding (Societe Parisienne des Sciures, Pantin, France). They were acclimatized at least for 5 days before administration. Rat diet (NAFAG 890 Tox, NAFAG, Gossau/SG, Switzerland) and water were provided ad libitum. Prior to dosing, the animals were fasted overnight.

3.2.3. Group size and identification

The animals, segregated by sex, were group-housed (5 animals per cage). Within the groups the animals were identified with numbers from 1 to 5 using picric acid stain on the fur. After dosing, the animals were placed in their cages, which were marked with a cage card containing the date of administration and the characteristics of the experiment and dose group.

3.3. Design and Procedure

Administration of the test article:	one single oral dose, by gastric intubation (gavage)
Dose levels, sex group:	200 mg/kg, females 500 mg/kg, males and females 1000 mg/kg, males 2000 mg/kg, males
Total number of animals:	25
Vehicle:	0.5 % (w/v) carboxymethylcellulose in 0.1 % (w/v) aqueous polysorbate 80
Volume applied:	10 ml/kg body weight
Observation period:	14 days

3.4. Observations and records

Mortality:	daily; a.m. and p.m. on working days, a.m. on weekend days
Signs and symptoms:	daily for 14 days
Body weight:	immediately before administration and on days 7 and 14

Necropsies: Spontaneously dying animals were submitted to a gross necropsy as soon as possible; survivors at the end of the observation period.

3.5. Statistical Analysis

From the body weights, the group means and their standard deviations were calculated.

LD50 values of males with 95% confidence limits and the females were computed by the logit model [redacted] Stat. Ass. 39 (1944), 357-365).

The LD50 value (including their 95% confidence limits) of both sexes were computed by the probit / maximum likelihood model [redacted] Journal of Toxicology and Environmental Health 3 (1977), 797-809).

4. RESULTS

4.1. In-life observations

In-life observations are depicted in table 1.

Piloerection, abnormal body positions, and dyspnea were seen, being common symptoms in acute tests.

Additionally, reduced locomotor activity was observed in all animals. Convulsions and/or tonic spasms were noticed in 2 males and 4 females dosed with 500 and all males dosed with 1000 and 2000 mg/kg. Ataxia was displayed by 2 females dosed with 200, tremor by one male dosed with 500 mg/kg. Four females dosed with 500 mg/kg showed raised irritability. In the males dosed with 2000 mg/kg vocalizations, respiratory sounds and cyanosis were recorded.

The surviving animals recovered within 3 to 6 days.

4.2. Body weight changes

Individual body weight, their group means and standard deviations are shown in table 3.

4.3. Mortalities

See table 2.

4.4. Necropsies

At necropsy, a spotted thymus was found in one male dosed with 2000 mg/kg. No deviations from normal morphology were found in the remaining animals.

See table 3.

TABLE 1

In-life observations

Animal No.	Observations	Admin.day 1h	3h	5h	Days after administration 1	2	3	4	5	6	7	8	9
200 mg/kg, females													
1 - 5	piloerection	+	+	+	+	+	+	+	+				
1 - 5	hunched post	+	+	+	+	+							
1 - 5	dyspnea	+	+	+	+								
1 - 5	red.loc.act.		+	+									
1,5	ataxia		+										
500 mg/kg, males													
1 - 5	piloerection	+	+	+	+	+							
1,3-5	hunched post	+	+	+	+	+							
2	hunched post			+	+	+							
2	laterocumb.	+	+										
1 - 5	dyspnea	+	+	+	+								
1 - 5	red.loc.act.	+	+										
2	convulsions	+++	+										
2	tremor	+											
500 mg/kg, females													
1-3,5	piloerection	+	+										
4	piloerection	+	+	+	+	+	+						
4	hunched post	+	+	+	+	+							
1	laterocumb.	+	+										
2,3,5	laterocumb.		+										
2,3,5	ventr.recumb	+											
1-3,5	dyspnea	++	++										
4	dyspnea	++	++	+	+								
1-3,5	red.loc.act.	++	+										
4	red.loc.act.	++	+	+	+								
1-3,5	irritability		+										
1-3,5	convulsions	++	++										
1-3,5	tonic spasms	+	+										

+ = slight, ++ = moderate, +++ = severe

In-life observations (continued)

Animal No.	Observations	Admin.day 1h	3h	5h	Days after administration 1	2	3	4	5	6	7	8	9
1000 mg/kg, males													
1, 3	piloerection	+	+	++	++	+	+	+					
2, 4	piloerection	+	+	++									
5	piloerection	+											
2,4	hunched post	+											
1,3	hunched post	+			+	+	+						
5	laterocumb.	+											
2	laterocumb.		+										
4	laterocumb.		+	+									
2	ventr.recumb.			+									
1, 3	dyspnea	++	++	++	+								
2, 4	dyspnea	++	++	++									
5	dyspnea	++											
1 - 4	red.loc.act.	+	++	++									
5	red.loc.act.	+											
1 - 4	convulsions	++	++	++									
5	convulsions	++											
2000 mg/kg, males													
1 - 5	piloerection	+											
2	ventr.recumb	+											
1,3-5	laterocumb.	+											
1 - 5	dyspnea	+++											
1 - 5	resp.sounds	+											
1 - 5	red.loc.act.	++											
1 - 5	convulsions	+++											
1 - 5	tonic spasms	+											
1 - 5	cyanosis	+											
1 - 5	vocalization	+											

+ = slight, ++ = moderate, +++ = severe
hunched post = hunched posture
ventr.recumb = ventral recumbency
laterocumb. = laterocumbency
resp.sounds = respiratory sounds
red.loc.act. = reduced locomotor activity

TABLE 2

Mortalities

Dose group	No.of deaths	Per cent	Hours after administration	Days after (No.of deaths)
Males				
500 mg/kg	0 / 5	0		
1000 mg/kg	3 / 5	60		1(1), 6(2)
2000 mg/kg	5 / 5	100		1(4), 3(1)
Females				
200 mg/kg	0 / 5	0		
500 mg/kg	4 / 5	80		5(4)

TABLE 3

Body weight and necropsy findings

Animal Number	Body Weights (g) d 0	d 7	d 14	*	Gross Necropsy Findings
200 mg/kg, females					
1	204	230	242	TS	NOA
2	205	222	240	TS	NOA
3	185	208	226	TS	NOA
4	192	206	210	TS	NOA
5	194	222	239	TS	NOA
mean	196	218	231		
SD	8.5	10.2	13.5		
500 mg/kg, males					
1	221	301	354	TS	NOA
2	209	282	342	TS	NOA
3	210	284	319	TS	NOA
4	236	330	388	TS	NOA
5	220	293	358	TS	NOA
mean	219	298	352		
SD	10.9	19.4	25.1		
500 mg/kg, females					
1	201			5 h	NOA
2	204			5 h	NOA
3	218			5 h	NOA
4	204	254	251	TS	NOA
5	209			5 h	NOA
mean	207				
SD	6.7				

Body weight and necropsy findings (continued)

Animal Number	Body Weights (g) d 0	d 7	d 14	*	Gross Necropsy Findings
1000 mg/kg, males					
1	241	318	362	TS	NOA
2	205			6 h	NOA
3	223	294	355	TS	NOA
4	205			6 h	NOA
5	227			1 h	NOA
mean	220	306	359		
SD	15.4	17.0	4.9		
2000 mg/kg, males					
1	248			1 h	thymus spotted
2	246			3 h	NOA
3	249			1 h	NOA
4	245			1 h	NOA
5	247			1 h	NOA
mean	247				
SD	1.6				

* TS terminal sacrifice
* <>h found dead < > hours after administration
NOA no observable abnormalities

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