Annex	**II**	Acute toxicity - Oral
Point addressed	**5.8.1**	

1.2	**Title**	Acute Oral Toxicity in the Rat (Limit Test)
1.3	**Report and/or project N°** **Novartis File N° (Desire)**	963100 62826 / 08
1.4	**Lab. Report N°**	963100
1.5	**Cross reference to original study / report**	5.8.1/05
1.6	**Authors**	Report: 5.1.2.e Woo Summary:
1.7	**Date of report**	October 1, 1996
1.8	**Published / owner**	Unpublished / Novartis Crop Protection AG
2.1	**Testing facility**	Ciba-Geigy Limited, Short-/Longterm Toxicology, 4332 Stein, Switzerland
2.2	**Dates of experimental work**	September 3 to September 17, 1996
3	**Objectives**	Determination of the acute oral toxicity in the rat
4.1	**Test substance**	CGA 62826 technical (metabolite of CGA 48988 and CGA 329351)
4.2	**Specification**	Batch RV-1592/4, purity 100%
4.3	**Storage stability**	Stable; reanalysis date: August 1999
4.4	**Stability in vehicle**	Stable under the conditions of the test
4.5	**Homogeneity in vehicle**	Not applicable
4.6	**Validity**	Not applicable
5	**Vehicle / solvent**	Distilled water
6	**Physical form**	Solid
7.1	**Test method**	OECD 401; EEC 92/69, B.1
7.2	**Justification**	Not applicable
7.3	**Copy of method**	Not applicable; standard guideline study, procedural details are given in the report
8	**Choice of method**	Not applicable
9	**Deviations**	No deviations from EC Directive 92/69 B.1 were noted
10.1	**Certified laboratory**	Yes
10.2	**Certifying authority**	Eidgenössisches Departement des Inneren (Federal Department of Home Affairs), Bern, Switzerland
10.3	**GLP**	Yes
10.4	**Justification**	Not applicable
11.1	**GEP**	Not applicable
11.2	**Type of facility (official or officially recognized)**	Not applicable
11.3	**Justification**	Not applicable

12 Test system

Animal species:	Rat, TIF: RAI f (SPF)
Source:	Ciba-Geigy Limited, Laboratory Animal Breeding, Pharma Division, 4332 Stein, Switzerland
Dose level:	2000 mg/kg
Group size:	5 animals of each sex
Age/weight:	Approximately 8 weeks / 182-228 g
Administration:	Single dose (10 ml/kg) by gastric intubation
Study duration:	14 days
General study design:	Standard according to OECD and EEC guidelines
Mortality:	Checked twice daily, morning and afternoon
Clinical signs:	Checked and recorded at 1, 3, and 5 hours after dosing, then daily for the duration of the observation period
Body weight:	Measured and recorded immediately before dose administration, then on Days 7 and 14
Necropsy:	All animals sacrificed at test termination were subjected to a necropsy examination.

13 Findings

Mortality: There were no mortalities in the study.

Clinical signs: There were no remarkable clinical signs.

Body weight: Body weights were not affected by treatment.

Necropsy: Necropsy examinations revealed no observable abnormalities.

LD_{50}:

Males:	> 2000 mg/kg
Females:	> 2000 mg/kg
Both sexes:	> 2000 mg/kg

14 Statistics

No statistical methods were used in this study

15 References (published)

No references to literature were made in this summary

16 Unpublished data

No references to unpublished data were made in this summary

CP 2.321/JG, August 5, 1997

8

Acute Oral Toxicity in the Rat (Limit test)

Test No. 963100

CGA 62826 tech. (Metabolite of CGA 48988)

Report

Study director:	Dr.
Testing facility:	Short-/Long-term Toxicology CIBA-GEIGY Limited 4332 Stein / Switzerland
Test guideline:	OECD 401, 92/69/EEC, B.1.
Study completed:	October 1, 1996
Sponsor:	CIBA-GEIGY Limited Crop Protection Division 4002 Basel / Switzerland

This report contains: 20 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: 5.1.2.e Woc

Signature: ..... Date: October 04, 1996

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 89/87 concerning the 'Compliance with Principles of Good Laboratory Practice', adopted on October 2, 1989).
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 160 (FIFRA); Federal Register, August 17, 1989.
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 792 (TSCA); Federal Register, August 17, 1989.
- Japan Ministry of Agriculture, Forestry and Fisheries, NohSan, Notification No. 3850, Agricultural Production Bureau, August 10, 1984.

Study director: PD Dr. med. vet. 5.1.2.e Woo FVH

Signature: .. 5.1.2.e Woo ... Date: October 1, 1996

Reserved page for flagging statements

Quality Assurance Statement

Ciba-Geigy Ltd., GLP Quality Assurance Product Safety, 4002 Basel

Project	963100
Test Substance	CGA 62826 tech.
Study Title	Acute Oral Toxicity in the Rat
Study Director	Dr. 5.1.2.e Woo
QA-Inspector	5.1.2.e Woo

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

Activity	Performed	Reported
Facility Inspection	March 13, 1996	March 19, 1996
Process Based Inspection	August 30, 1996	August 30, 1996
Protocol Audit	September 02, 1996	September 02, 1996
Final Report Audit	October 01, 1996	October 01, 1996

October 3, 1996
Date
Form. QSSTAT12

5.1.2.e Woo
Inspector Quality Assurance

01 Summary

Upon single dose, oral administration of 2000 mg/kg to male and female rats (Limit test) and a 14 day post-treatment observation period, the following LD50 was determined for CGA 62826 tech. (Metabolite of CGA 48988):

LD50 in male rats: greater than 2000 mg/kg body weight

LD50 in female rats: greater than 2000 mg/kg body weight

LD50 in rats of both sexes: greater than 2000 mg/kg body weight

Observations

All animals survived to the scheduled sacrifice.

There were no in-life observations indicating treatment related effects.

Body weights were not affected by the treatment.

At necropsy, no deviations from normal morphology were found in all animals.

02 Introduction

02.01 Purpose

On request of the Crop Protection Division of CIBA-GEIGY Limited, this study was conducted to determine the acute oral toxicity of CGA 62826 tech. (Metabolite of CGA 48988) in albino rats.

02.02 Basis

The study design followed the test guidelines OECD 401, 'Acute Oral Toxicity' adopted February 24, 1987, and Council Directive 67/548/EEC, Commission Directive 92/69/EEC of July 31, 1992.

On request of the sponsor, the whole study was subjected to quality assurance.

02.03 Testing Facility

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

Technical assistant: Ms.

Reporting assistant: Mr.

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.

02.04 Dates

Test order received: August 20, 1996

Date of protocol: August 30, 1996

Date of administration: September 3, 1996 (males and females)

Experimental completion date: September 17, 1996

02.05 Distribution

- Sponsor (Dr. 5.1.2.e Woo)
- Archives

03 Materials and Methods

03.01 Test Article

Test article:	CGA 62826 tech. (Metabolite of CGA 48988)
Purity:	100%
Batch No.:	RV-1592/4
Physical properties:	solid
Storage conditions:	< +10°C
Date of reanalysis:	August 1999
Test material received:	August 20, 1996

03.02 Animals

03.02.01 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
Laboratory Animal Breeding
Pharma Division
4332 Stein / Switzerland

Initial body weight range: 182 to 228 g

03.02.02 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, NAFAG, Gossau/SG, Switzerland - and water were provided ad libitum. Prior to dosing, the animals were fasted overnight.

03.02.03 Group Size and Identification

The animals, separated by sex, were group-housed (5 animals per cage). Within groups animals were identified by a color code on the tail (a dash-dot code), painted with a felt-tipped waterproof marker. 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.

03.03 Design and Procedure

Administration of the test article:	one single oral dose, by gastric intubation (gavage)
Dose levels, sex group:	2000 mg/kg, males and females
Total number of animals:	10 (5 males / 5 females)
Vehicle:	distilled water
Volume applied:	10 ml/kg body weight
Observation period:	14 days

03.04 Observations and Records

Signs and symptoms:	daily for 14 days
Body weight:	immediately before administration and on days 7 and 14
Mortality:	twice daily; a.m. and p.m.
Necropsies:	Spontaneously dying animals were submitted to a gross necropsy as soon as possible; survivors at the end of the observation period.

03.05 Rationale for Dose Selection

The dose level was selected according to OECD 401 (limit test; single application of 2000 mg/kg body weight).

04 Results

04.01 In-life Observations

There were no in-life observations indicating treatment related effects (Tables 2 and 3).

04.02 Body Weight and Body Weight Change

Individual body weights and body weight change, group means and standard deviations are listed in Tables 4 and 5.

Body weights were not affected by the treatment.

04.03 Mortality

All animals survived to the scheduled sacrifice.

See Tables 1, 2 and 3.

04.04 Necropsies

At necropsy, no deviations from normal morphology were found in all animals (Table 6).

Table 1: Mortality

Males	No. of Deaths	% of Deaths
Group 1 (2000 mg/kg)	0 / 5	0

Females	No. of Deaths	% of Deaths
Group 1 (2000 mg/kg)	0 / 5	0

Table 2: Summary of In-life Observations and Mortality (# of affected animals)

MALES

	HOURS			DAYS														TOTAL
	1	3	5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	DEATHS
Group 1 (2000 mg/kg)																		
NO REMARKABLE CLINICAL OBSERVATIONS	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
MORTALITY CHECK AFTERNOON	0	0	0	5	5	5	5	5	5	5	5	5	5	5	5	5	0	
DEATHS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	5

FEMALES

	HOURS			DAYS														TOTAL
	1	3	5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	DEATHS
Group 1 (2000 mg/kg)																		
NO REMARKABLE CLINICAL OBSERVATIONS	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
MORTALITY CHECK AFTERNOON	0	0	0	5	5	5	5	5	5	5	5	5	5	5	5	5	0	
DEATHS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	5

Table 3: Individual In-life Observations and Mortality

Group 1 (2000 mg/kg)

		HOURS								DAYS														
MALE#	OBSERVATIONS	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
2	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
3	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
4	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
5	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P

GRADE CODE: 1=slight 2=moderate 3=severe P=present

Table 3: Individual In-life Observations and Mortality (cont'd)

Group 1 (2000 mg/kg)

		HOURS								DAYS														
FEMALE#	OBSERVATIONS	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	9	10	11	12	13	14
101	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
102	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
103	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
104	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P
105	NO REMARKABLE CLINICAL OBSERVATIONS	P		P	P					P	P	P	P	P	P	P	P	P	P	P	P	P	P
	MORTALITY CHECK AFTERNOON								P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice																						P

GRADE CODE: 1=slight 2=moderate 3=severe P=present

Table 4: Body Weight

MALES

	DAY AFTER TREATMENT		
ANIMAL#	0	7	14
Group 1 (2000 mg/kg)			
1	221.0	290.4	334.0
2	227.7	308.5	364.0
3	221.8	304.8	350.8
4	218.4	280.1	316.7
5	212.7	285.4	322.2
MEAN	220.3	293.9	337.5
S.D.	5.5	12.3	19.7
N	5	5	5

FEMALES

	DAY AFTER TREATMENT		
ANIMAL#	0	7	14
Group 1 (2000 mg/kg)			
101	187.1	211.1	225.8
102	193.6	221.5	232.9
103	182.4	213.4	221.8
104	197.1	232.9	254.7
105	192.4	216.9	230.1
MEAN	190.5	219.2	233.0
S.D.	5.8	8.6	12.8
N	5	5	5

Table 5: Body Weight Change

MALES

ANIMAL#	DAY 0	AFTER TREATMENT 7	0 14
Group 1 (2000 mg/kg)			
1	69.4	43.6	113.0
2	80.8	55.5	136.2
3	83.0	46.0	129.0
4	61.7	36.6	98.3
5	72.8	36.8	109.6
MEAN	73.5	43.7	117.2
S.D.	8.7	7.8	15.3
N	5	5	5

FEMALES

ANIMAL#	DAY 0	AFTER TREATMENT 7	0 14
Group 1 (2000 mg/kg)			
101	24.0	14.8	38.8
102	27.8	11.4	39.2
103	31.0	8.3	39.3
104	35.9	21.7	57.6
105	24.5	13.1	37.6
MEAN	28.6	13.9	42.5
S.D.	4.9	5.0	8.5
N	5	5	5

Table 6: Necropsy Findings

Group 1 (2000 mg/kg) MALES

ANIMAL#	ORGAN	OBSERVATION
1		NO REMARKABLE OBSERVATIONS
2		NO REMARKABLE OBSERVATIONS
3		NO REMARKABLE OBSERVATIONS
4		NO REMARKABLE OBSERVATIONS
5		NO REMARKABLE OBSERVATIONS

Group 1 (2000 mg/kg) FEMALES

ANIMAL#	ORGAN	OBSERVATION
101		NO REMARKABLE OBSERVATIONS
102		NO REMARKABLE OBSERVATIONS
103		NO REMARKABLE OBSERVATIONS
104		NO REMARKABLE OBSERVATIONS
105		NO REMARKABLE OBSERVATIONS

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