Annex	II	Acute toxicity - Percutaneous
Point addressed	5.8.1	

1.2	Title	Acute Dermal Toxicity in the Rat (Limit Test)
1.3	Report and/or project N° Novartis File N° (Desire)	963126 108906 / 5
1.4	Lab. Report N°	963126
1.5	Cross reference to original study / report	5.8.1/09
1.6	Authors	Report: Summary:
1.7	Date of report	December 16, 1996
1.8	Published / owner	Unpublished / Novartis Crop Protection AG
2.1	Testing facility	Ciba-Geigy Limited, Short-/LongtermToxicology, 4332 Stein, Switzerland
2.2	Dates of experimental work	November 20 to December 10, 1996
3	Objectives	Determination of the acute dermal toxicity in the rat
4.1	Test substance	CGA 108906 technical (metabolite of CGA 48988 and CGA 329351)
4.2	Specification	Batch KI-5240/3, purity 99%
4.3	Storage stability	Stable; reanalysis date: October 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 402; EEC 92/69, B.3
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.3 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 / 222-261 g
	Administration:	Single dermal application (4 ml/kg) under semiocclusive conditions for 24 hours
	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 within the first hour after dosing, then daily for the duration of the observation period
	Local tolerance:	Application site examined daily for signs of skin irritation 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.
Local tolerance:	Slight erythema at the application site was observed in one male on Days 5-11 after patch removal and two females on Days 5 and 6. There were no other remarkable observations at the application site.
Body weight:	A very slight body weight loss was noted for one female at Day 14; other 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

European Registration Dossier
Dossier File N° : 5.8.1/09
NOVARTIS File N° : 108906/5

Acute Dermal Toxicity in the Rat (Limit Test)

Test No. 963126

CGA 108906 tech. (Metabolite of CGA 48988)

Report

Study director: Dr. [redacted]

Testing facility: Short-/Long-term Toxicology
CIBA-GEIGY Limited
4332 Stein / Switzerland

Test Guideline: OECD 402; 92/69/EEC, B.3.

Study completed: December 16, 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:

Signature: 5.1.2e Woo Date: December 17, 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: December 16, 1996

Reserved page for flagging statements

Quality Assurance Statement

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

Project	963126
Test Substance	CGA 108906 tech.
Study Title	Acute Dermal 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	October 03, 1996	October 09, 1996
Protocol Audit	November 20, 1996	November 20, 1996
Process Based Inspection	November 21, 1996	November 21, 1996
Final Report Audit	December 13, 1996	December 13, 1996

December 16, 1996

Date
Form. QSSTAT12

5.1.2.e Woo

5.1.2.e Woo, supst.
Inspector Quality Assurance

01 Summary

Upon single dose, dermal 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 108906 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 related to toxicity of the test article.

Slight local erythema at the skin application site was recorded in 1 of 5 males from day 5 up to and including day 11 after treatment and in 2 of 5 females on days 5 and 6 after treatment.

A loss of body weight was recorded in 1 female rat during the second week after treatment.

At autopsy, no deviations from normal morphology were found.

02 Introduction

02.01 Purpose

On request of the Crop Protection Division of CIBA-GEIGY Limited, this study was conducted to determine the acute dermal toxicity of CGA 108906 tech. (Metabolite of CGA 48988) in albino rats.

02.02 Basis

The study design followed the test guidelines OECD 402, 'Acute Dermal 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. 5.1.2.e Woo

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 test facility.

02.04 Dates

Date of protocol:	November 19, 1996
Date of administration:	November 20, 1996 (males) November 26, 1996 (females)
Experimental completion date:	December 10, 1996

02.05 Distribution

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

03 Materials and Methods

03.01 Test Article

Test article:	CGA 108906 tech. (Metabolite of CGA 48988)
Purity:	99%
Batch No.:	KI-5240/3
Physical properties:	solid
Storage conditions:	< +10°C
Date of reanalysis:	October 1999
Test material received:	October 23, 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 dermal 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: 222 to 261 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%.

Animals were individually housed in Macrolon cages type 3, with standardized soft wood bedding (Societe Parisienne des Sciures, Pantin, France). They were acclimatized for at least 5 days before exposure.

Rat diet - NAFAG 890, NAFAG, Gossau/SG, Switzerland - and water were provided ad libitum.

03.02.03 Group Size and Identification

The dose group consisted of 10 rats (5 males and 5 females). Animals were identified by a color code on the tail (a dash-dot code), painted with a felt-tipped waterproof marker. During and after exposure, animals were placed in their cages marked with date of administration, test system and dose group.

03.03 Design and Procedure

Pretreatment:	Approximately 24 hours before treatment an area on the back of the rat of at least 10% of the body surface was shaved with an electric clipper.
Application:	The test article was evenly dispersed on the skin. It was covered with a gauze-lined semiocclusive dressing fastened around the trunk with an adhesive elastic bandage. After 24 hours the dressing was removed and the skin was cleaned with lukewarm water. Thereafter the skin reaction was appraised repeatedly.
Frequency of application:	One single dose.
Dose level:	2000 mg/kg body weight
Total number of animals:	10 (5 males / 5 females)
Vehicle:	distilled water
Volume applied:	4 ml/kg body weight
Observation period:	14 days

03.04 Observations and Records

Mortality:	twice daily; a.m. and p.m.
Signs and symptoms:	daily for 14 days
Body weight:	immediately before application and on days 7 and 14
Necropsies:	The animals were submitted to a gross necropsy at the end of the observation period.

03.05 Rationale for Dose Selection

The dose level was selected according to OECD 402 (limit test; single application of at least 2000 mg/kg body weight).

04 Results

04.01 In-life Observations

There were no in-life observations related to toxicity of the test article after single dose, dermal application (Tables 2 and 3).

Slight local erythema at the skin application site was recorded in 1 of 5 males (no. 4) from day 5 up to and including day 11 after treatment and in 2 of 5 females (no. 101 and 102) on days 5 and 6 after treatment.

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.

A loss of body weighy was recorded in 1 female rat (no. 102) during the second week after treatment.

04.03 Mortality

All animals survived to the scheduled sacrifice (Table 1, 2 and 3).

04.04 Necropsies

At necropsy, no deviations from normal morphology were found (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

	GROUP#	DAY OF STUDY 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	TOTAL
# OF ANIMALS EXAMINED	1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
NORMAL																	
NO REMARKABLE CLINICAL OBSERVATIONS	1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
MORTALITY CHECK AFTERNOON	1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	0	5
DEAD																	
scheduled sacrifice	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	5
SKIN (APPL-SITE)																	
no skin irritation	1	0	5	5	5	5	4	4	4	4	4	4	4	5	5	5	5
erythema	1	0	0	0	0	0	1	1	1	1	1	1	1	0	0	0	1

FEMALES

	GROUP#	DAY OF STUDY 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	TOTAL
# OF ANIMALS EXAMINED	1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
NORMAL																	
NO REMARKABLE CLINICAL OBSERVATIONS	1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
MORTALITY CHECK AFTERNOON	1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	0	5
DEAD																	
scheduled sacrifice	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	5
SKIN (APPL-SITE)																	
no skin irritation	1	0	5	5	5	5	3	3	5	5	5	5	5	5	5	5	5
erythema	1	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	2

Table 3: Individual In-life Observations and Mortality

MALES Group 1 (2000 mg/kg)

ANIMAL#	OBSERVATIONS	0	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
	MORTALITY CHECK AFTERNOON	P	P	P	P	P	P	P	P	P	P	P	P	P	P	
	scheduled sacrifice															P
	SKIN (APPL-SITE): no skin irritation		P	P	P	P	P	P	P	P	P	P	P	P	P	P
2	NO REMARKABLE CLINICAL OBSERVATIONS	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
	SKIN (APPL-SITE): no skin irritation		P	P	P	P	P	P	P	P	P	P	P	P	P	P
3	NO REMARKABLE CLINICAL OBSERVATIONS	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
	SKIN (APPL-SITE): no skin irritation		P	P	P	P	P	P	P	P	P	P	P	P	P	P
4	NO REMARKABLE CLINICAL OBSERVATIONS	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
	SKIN (APPL-SITE): no skin irritation		P	P	P	P								P	P	P
	SKIN (APPL-SITE): erythema						1	1	1	1	1	1	1			
5	NO REMARKABLE CLINICAL OBSERVATIONS	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
	SKIN (APPL-SITE): no skin irritation		P	P	P	P	P	P	P	P	P	P	P	P	P	P

(Columns 0–14: DAY OF STUDY)

CODE: 1-SLIGHT 2-MODERATE 3-MARKED P-PRESENT

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

FEMALES Group 1 (2000 mg/kg)

ANIMAL#	OBSERVATIONS	DAY OF STUDY 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4
101	NO REMARKABLE CLINICAL OBSERVATIONS	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
	scheduled sacrifice	P
	SKIN (APPL-SITE): no skin irritation	P P P P P P P P P
	SKIN (APPL-SITE): erythema	1 1
102	NO REMARKABLE CLINICAL OBSERVATIONS	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
	scheduled sacrifice	P
	SKIN (APPL-SITE): no skin irritation	P P P P P P P P P
	SKIN (APPL-SITE): erythema	1 1
103	NO REMARKABLE CLINICAL OBSERVATIONS	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
	scheduled sacrifice	P
	SKIN (APPL-SITE): no skin irritation	P P P P P P P P P P P P P
104	NO REMARKABLE CLINICAL OBSERVATIONS	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
	scheduled sacrifice	P
	SKIN (APPL-SITE): no skin irritation	P P P P P P P P P P P P P
105	NO REMARKABLE CLINICAL OBSERVATIONS	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
	scheduled sacrifice	P
	SKIN (APPL-SITE): no skin irritation	P P P P P P P P P P P P P

CODE: 1-SLIGHT 2-MODERATE 3-MARKED P-PRESENT

Table 4: Body Weight

MALES Group 1 (2000 mg/kg)

ANIMAL#	DAY OF AFTER TREATEMENT 0	7	14
1	242.8	280.6	319.7
2	241.4	276.4	312.1
3	232.1	255.2	279.3
4	231.6	261.4	285.3
5	253.8	285.4	327.8
MEAN	240.3	271.8	304.9
S.D.	9.1	12.9	21.4
N	5	5	5

FEMALES Group 1 (2000 mg/kg)

ANIMAL#	DAY OF AFTER TREATEMENT 0	7	14
101	222.2	226.0	239.2
102	261.1	261.5	261.2
103	234.1	249.2	260.5
104	225.6	241.9	261.7
105	249.4	251.6	269.7
MEAN	238.5	246.1	258.5
S.D.	16.5	13.2	11.4
N	5	5	5

Table 5: Body Weight Change

MALES Group 1 (2000 mg/kg)

ANIMAL#	DAY OF STUDY 0	7	0
	7	14	14
1	37.8	39.1	76.9
2	35.0	35.8	70.8
3	23.1	24.1	47.2
4	29.8	23.9	53.7
5	31.5	42.5	74.0
MEAN	31.4	33.1	64.5
S.D.	5.6	8.6	13.2
N	5	5	5

FEMALES Group 1 (2000 mg/kg)

ANIMAL#	DAY OF STUDY 0	7	0
	7	14	14
101	3.8	13.1	17.0
102	0.4	-0.3	0.1
103	15.1	11.3	26.4
104	16.4	19.8	36.1
105	2.2	18.1	20.3
MEAN	7.6	12.4	20.0
S.D.	7.6	7.9	13.3
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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