European Registration Dossier
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Acute Eye Irritation/Corrosion Study in the Rabbit

Test No. 943029

CGA 329351 tech.

Report

Study director:	Dr. med.vet.
Testing facility:	Short-term Toxicology CIBA-GEIGY Limited 4332 Stein / Switzerland
Test Guideline:	OECD 405; 92/69/EEC, B.5.
Study completed:	June 1, 1994
Sponsor:	CIBA-GEIGY Limited Plant Protection 4002 Basel / Switzerland

This report contains: 16 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: [redacted] 5.1.2e Woo ...... Date: June 14, 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. 5.1.2.e Woo

Signature: .... 5.1.2.e Woo . Date: June 1, 1994

Dr. med.vet. 5.1.2.e Woo D.A.B.T
Head Shortterm and Reproduction Toxicology

Signature: . 5.1.2.e Woo . Date: June 1, 1994

Reserved page for flagging statements

Quality assurance statement

Test Article: CGA 329351 tech.

Study Title: Acute Eye Irritation/Corrosion Study in the Rabbit

Test Number: 943029

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	March 23, 1994	April 08, 1994
Protocol Audit	May 03, 1994	May 03, 1994
Final Report Audit	May 31, 1994	June 01, 1994

Quality Assurance Inspector: 5.1.2.e Woo (for 5.1.2.e Woo 5.1.2.e Woo

Signature: ...../..... Date: June 8, 1994

1. SUMMARY AND CONCLUSION

Under the experimental conditions employed CGA 329351 tech. induced irritation of the cornea, iris, and conjunctiva.

The following mean scores (24 - 72 h) were calculated:

animal No.	032	996	937
conjunctiva/redness	2	2	2
conjunctiva/chemosis	1	1	1.33
cornea	1.67	1	1
iris	1	1	1

On account of the irreversible cornea reactions in animal No. 032, the risk of serious damage to eyes is expected (R41, Commision Directive 83/467/EEC).

2. GENERAL

2.1. Introduction

At the request of the Plant Protection of CIBA-GEIGY Limited, an Acute Eye Irritation/Corrosion study in albino rabbits was performed to determine the irritant or corrosive potency of CGA 329351 tech. in the albino rabbit eye and the associated mucous membranes.

This test was based on the OECD Guideline No. 405, adopted February 24, 1987, by the OECD council, and on Annex V, part B of Council Directive 79/831/EEC (Commission Directive 92/69/EEC of July 31, 1992).

The present study was started with one single animal. Because equivocal reactions were observed, two extra rabbits were added to the test later.

Date of protocol:	April 27, 1994
Start of experiment:	May 3, 1994
End of experiment:	May 24, 1994
Testing facility:	CIBA-GEIGY Limited Short-term Toxicology 4332 Stein / Switzerland
Technical assistant:	Mr. 5.1.2.e Woo

2.2. Archives

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

2.3. Distribution

Sponsor (Dr. [redacted])
Archives

3. MATERIALS AND METHODS

3.1. Test Article

Test article:	CGA 329351 tech.
Batch No.:	KGL 4634/6
Purity/Contents:	97.30%
Physical properties:	viscous
Storage conditions:	room temperature
Date of reanalysis:	February, 1998
Safety precautions:	gloves and face masks
Test material received:	March 16, 1994

3.2. Test system

The albino rabbit is the recommended species for Acute Eye Irritation/Corrosion studies.

Animal strain:	New Zealand white rabbits (Chbb:NZW)
Breeder:	Dr. [redacted] GMBH Chemisch-pharmazeutische Fabrik D-7950 Biberach/Riss
Acclimatisation period:	at least 5 days

3.3. Group size and husbandry

The test was performed on one male and two female rabbits, checked for normal eye conditions, weighing between 2270 to 2880 g. The animals were housed individually in metal cages, identified by ear tattoo, kept at a constant room temperature of 20±3 °C, at a relative humidity of 30-70 % and on a 12 hours light cycle day.

The rabbits received ad libitum standard rabbit pellet - Nafag No. 814, Gossau, Switzerland - and fresh water. All batches of the diet are assayed for nutritive ingredients and contaminant level by the manufacturer. Analytical results are available at the animal supply office.

The drinking water quality fulfilled the critical parameters in the specifications of the "Schweizerisches Lebensmittelbuch" (Edition 1972). The results of the routine chemical examination of water at source (Grundwasserfassung Stein) as conducted periodically by the water authority (Baudepartement des Kantons Aargau, Abteilung Gewaesserschutz) are available to CIBA-GEIGY Limited, as well as the results of inhouse chemical analysis by the analytical laboratories of the Pharmaceutical Division, CIBA-GEIGY Limited.

The bodyweight was recorded at start and on days 3, 7, and 14 (all animals) and on day 21 (animal No. 032) of the test.

3.4. Method

0.1 ml of CGA 329351 tech. was placed into the conjunctival sac of the left eye of each animal, after gently pulling away the lower lid from the eyeball. The lids were then held together for about one second in order to prevent loss of the test article.

The right eye remained untreated and served as a control.

The animals were checked daily for systemic symptoms and mortality (only findings reported).

The ocular reactions were evaluated 1, 24, 48, and 72 hours after the instillation of CGA 329351 tech. according to the OECD scoring system (Appendix 1). In order to determine the reversibility of the eye reactions additional evaluations of the ocular reactions were needed in this study. A slit-lamp was used to facilitate the evaluation. The irritant/corrosive potency of CGA 329351 tech. was classified according to Council Directive 67/548/EEC, adapted to technical progress by Commission Directive 93/21/EEC (Appendix 2).

4. RESULTS

The individual reaction scores of the control and treated eyes are summarised in Table 1, the individual bodyweights in Table 2.

Under the experimental conditions employed CGA 329351 tech. induced irritation of the cornea, iris, and conjunctiva.

Vascularisation was observed in animals No. 996 and No. 937 on days 7 and 10 (v in Table 1). In this two animals all symptoms were reversible until day 14. In animal No. 032 vascularisation was observed on day 14, reactions of the cornea were still present at termination of the study on day 21.

On account of the irreversible cornea reactions in animal No. 032, the risk of serious damage to eyes is expected (R41, Commision Directive 83/467/EEC).

5. TABLES

TABLE 1

Individual eye scores

animal No. 032/F	CORNEA ce/te	IRIS ce/te	CONJUNCTIVA redness ce/te	CONJUNCTIVA chemosis ce/te
after 1 hr.	0/1	0/1	0/2	0/2
after 24 hrs.	0/2	0/1	0/2	0/1
after 48 hrs.	0/2	0/1	0/2	0/1
after 72 hrs.	0/1	0/1	0/2	0/1
mean 24-72 hrs.	0/1.67	0/1	0/2	0/1
after 7 days	0/1	0/0	0/1	0/0
after 10 days	0/1	0/0	0/1	0/0
after 14 days	0/1v	0/0	0/1	0/0
after 17 days	0/1	0/0	0/0	0/0
after 21 days	0/1	0/0	0/0	0/0

animal No. 996/F	CORNEA ce/te	IRIS ce/te	CONJUNCTIVA redness ce/te	CONJUNCTIVA chemosis ce/te
after 1 hr.	0/1	0/1	0/2	0/2
after 24 hrs.	0/1	0/1	0/2	0/1
after 48 hrs.	0/1	0/1	0/2	0/1
after 72 hrs.	0/1	0/1	0/2	0/1
mean 24-72 hrs.	0/1	0/1	0/2	0/1
after 7 days	0/0v	0/0	0/1	0/0
after 10 days	0/0v	0/0	0/0	0/0
after 14 days	0/0	0/0	0/0	0/0

	CORNEA	IRIS	CONJUNCTIVA	
animal No. 937/M	ce/te	ce/te	redness ce/te	chemosis ce/te
after 1 hr.	0/1	0/1	0/2	0/2
after 24 hrs.	0/1	0/1	0/2	0/2
after 48 hrs.	0/1	0/1	0/2	0/1
after 72 hrs.	0/1	0/1	0/2	0/1
mean 24-72 hrs.	0/1	0/1	0/2	0/1.33
after 7 days	0/0v	0/0	0/1	0/0
after 10 days	0/0v	0/0	0/1	0/0
after 14 days	0/0	0/0	0/0	0/0

ce = control eye te = test eye
M = male F = female
v = vascularisation

TABLE 2

Bodyweights (g)

animal no.	032/F	996/F	937/M
at start of test	2270	2330	2880
after 3 days	2330	2490	2990
after 7 days	2530	2700	3120
after 14 days	2780	3000*	3380*
after 21 days	3060*	--	--

* = end of study

6. APPENDICES

APPENDIX 1

Scores for ocular lesions according to the OECD guideline 405

CORNEA

Opacity: degree of density (area most dense taken for reading).

No ulceration or opacity..0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre), details of iris clearly visible..1
Easily discernible translucent area, details of iris slightly obscured..2
Nacrous area, no details of iris visible, size of pupil barely discernible..3
Opaque cornea, iris not discernible through the opacity..4

IRIS

Normal..0
Markedly deepended rugae, congestion, swelling, moderate circumcorneal hyperaemia, or injection, any of these or combination of any thereof, iris still reacting to light (sluggish reaction is positive)........1
No reaction to light, haemorrhage, gross destruction (any or all of these)..2

CONJUNCTIVAE

Redness: (refers to palpebral and bulbar conjunctivae, cornea and iris)

Blood vessels normal..0
Some blood vessels definitely hyperaemic (injected).........1
Diffuse, crimson colour, individual vessels not easily discernible..2
Diffusy beefy red..3

Chemosis: lids and/or nictating membranes

No swelling..0
Any swelling above normal (includes nictating membranes)..1
Obvious swelling with partial eversion of lids..............2
Swelling with lids about half closed........................3
Swelling with lids more than, half closed...................4

APPENDIX 2

Annex IV, 3.2.6 of Council Directive 67/548/EEC (Commission Directive 93/21/EEC of April 27, 1993; Official Journal of the European Communities No. L 110 A, May 4, 1993)

R36 Irritating to eyes

- Substances and preparations which when applied to the eye of the animal, cause significant ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.
  Ocular lesions are significant if the mean scores of the eye irritation test cited in Annex V have any of the following values:

- cornea opacity equal to or greater than 2 but less than 3

- iris lesion equal to or greater than 1 but not greater than 1,5

- redness of the conjunctivae equal to or greater than 2,5

- edema of the conjuctivae (chemosis) equal to or greater than 2

or, in the case where the Annex V test has been completed using three animals if the lesions, on two or more animals, are equivalent to any of the above values except that for iris lesion the value should be equal to or greater than 1 but less than 2 and for redness of the conjunctivae the value should be equal to or greater than 2,5.

In both cases all scores at each of the reading times (24, 48, and 72 hours) for an effect should be used in calculating the respective means values.

R41 Risk of serious damage to eyes

- Substances and preparations which, when applied to the eye of the animal cause severe ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are severe if the means or the scores of the eye irritation test in Annex V have any of the values:

- Cornea opacity equal to or greater than 3

- iris lesion greater than 1,5

The same shall be the case where the test has been completed using three animals if these lesions, on two or more animals, have any of the values:

- Cornea opacity equal to or greater than 3
- iris lesion equal to 2

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

Ocular lesions are also severe when they are still present at the end of the observation time.

Ocular lesions are also severe if the substance or preparation causes irreversible colouration of the eyes.

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