

9.0 CONTINUATION SHEET

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Continuation of 2.1

As MKH 3586 Oxadiazolinon caused corneal damage which was present 21 days after instillation into the eye of two out of three rabbits, this study would place MKH 3586 Oxadiazolinon in Toxicity Category I. Thus, the results from this study are being reported..

Abstract

The primary eye irritation potential of MKH 3586 Oxadiazolinon was evaluated in three male Himalayan rabbits.

Under the present test conditions, a single application of 0.1 ml MKH 3586 Oxadiazolinon per animal into the conjunctival sac of the right eye caused the following effects:

Corneal opacity was observed in animal no. one 1 to 48 hours (grade 3), 72 hours (grade 2), and 4 to 21 days (grade 1) after instillation; in animal no. two 1 to 48 hours (grade 3), and 72 hours to 21 days (grade 1) after instillation; in animal no. three 1 hour (grade 4), 24 and 48 hours (grade 3), and 72 hours to 14 days (grade 1) after instillation.

The fluorescein tests, performed after 24 hours, revealed corneal staining in all animals (whole corneal surface). The fluorescein test performed after 7 days revealed corneal staining in all animals (3/4 of the corneal surface). The fluorescein test performed after 14 days revealed corneal staining in all animals (animal no. 1: 1/2 of the corneal surface; animal no. 2: 3/4 of the corneal surface; animal no. 3: 1/4 of the corneal surface). The fluorescein test performed after 21 days revealed corneal staining in animal no. 1 (1/2 of the surface) and in animal no. 2 (3/4 of the corneal surface) after instillation.

Irritation of the iris (grade 2) was observed in animal nos. one and two 1 hour to 21 days, and in animal no. three 1 to 48 hours after instillation. An irritation of grade 1 was observed in animal no. three 72 hours to 14 days after instillation.

The conjunctiva was not affected by instillation of the test compound.

There were no systemic reactions.

STUDY TITLE

Acute Eye Irritation Study of
MKH 3586 Oxadiazolinon by Instillation into the
Conjunctival Sac of Rabbits

DATA REQUIREMENT

US EPA OPPTS Guideline No. 870.2400

AUTHOR

Dr. P.J. Leuschner

109091

STUDY COMPLETION DATE

April 26, 1999

FILE

8942

PERFORMING LABORATORY

LPT Laboratory of Pharmacology and Toxicology
Redderweg 8
D-21147 Hamburg
Germany

SPONSOR

BAYER AG
DEPARTMENT OF TOXICOLOGY
Friedrich-Ebert-Strasse 217-233
D-42096 Wuppertal
Germany

LABORATORY PROJECT ID

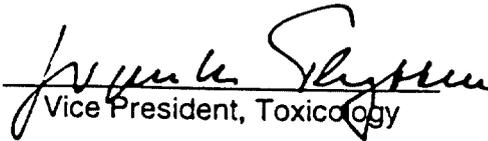
Bayer AG Report No. R 7411
Bayer AG Study No. T8067195

STATEMENT OF DATA CONFIDENTIALITY

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10(d)(1)(A), (B), or (C):

BAYER CORPORATION

Dr. J.H. Thyssen:


Vice President, Toxicology

Date:

6-24-99

GLP COMPLIANCE STATEMENT

**ACUTE EYE IRRITATION STUDY OF
MKH 3586 OXADIAZOLINON
BY INSTILLATION INTO THE CONJUNCTIVAL SAC OF RABBITS**

- according to EC guideline B.5. and OECD guideline 405 -

This study was conducted in compliance with the OECD Principles of Good Laboratory Practice (GLP)¹ and with the Principles of Good Laboratory Practice according to Annex I ChemG² and meets the FIFRA Good Laboratory Practice Standards (40 CFR Part 160), with the exception that recognized differences exist between the GLP principles/standards of OECD and FIFRA (for instance, authority granted Agency inspectors and certain record retention requirements).

STUDY DIRECTOR

LPT LABORATORY OF PHARMACOLOGY AND TOXICOLOGY

J. Leuschner
Dr. phil. J. Leuschner

26 April 1999
Date

SPONSOR

BAYER AG

B. Stahl
Name

May 06, 1999
Date

Dr. Bernhard Stahl D.A.B.T.

SUBMITTER

BAYER Corporation

Frank H. Schyom
Name

6-24-99
Date

VP - Toxicology

¹ Bundesanzeiger No. 42a (March 2nd, 1983) (German version)

² Bundesgesetzblatt, Part I (July 29th, 1994)

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QUALITY ASSURANCE STATEMENT

Based on a quality assurance review, it was concluded that this report accurately reflects the data for the study

**ACUTE EYE IRRITATION STUDY OF
MKH 3586 OXADIAZOLINON
BY INSTILLATION INTO THE CONJUNCTIVAL SAC OF RABBITS**

- according to EC guideline B.5. and OECD guideline 405 -

Protocol dated July 7th, 1995 and 2 amendments.

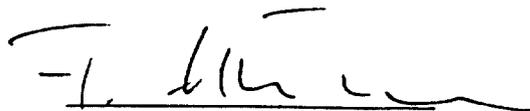
Controls on accuracy and correspondence with the protocol were performed on

March 23rd, 1999 animal housing, instillation, eye evaluation, test substance and retention sample

April 26th, 1999 final report

The results were reported to the study director and the management on the same working days.

Approved and submitted by



F. Hübscher
Director of Quality Assurance Unit (QAU)

26.4.99

Date

1. SUMMARY

Test system acute eye irritation study by instillation into the conjunctival sac of rabbits according to EC guideline B.5. and OECD guideline 405

Test substance **MKH 3586 Oxadiazolinon**

Under the present test conditions a single application of 0.1 ml MKH 3586 Oxadiazolinon per animal into the conjunctival sac of the right eye of three rabbits caused the following effects:

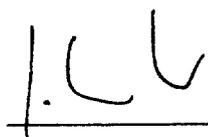
Corneal opacity was observed in animal no. one 1 to 48 hours (grade 3), 72 hours (grade 2) and 4 to 21 days (grade 1) after instillation; in animal no. two 1 to 48 hours (grade 3) and 72 hours to 21 days (grade 1) after instillation; in animal no. three 1 hour (grade 4), 24 and 48 hours (grade 3) and 72 hours to 21 days (grade 1) after instillation.

The fluorescein tests performed after 24 hours revealed **corneal staining** in all animals (whole corneal surface). The fluorescein test performed after 7 days revealed corneal staining in all animals (3/4 of the corneal surface). The fluorescein test performed after 14 days revealed corneal staining in all animals (animal no. 1: 1/2 of the corneal surface; animal no. 2: 3/4 of the corneal surface; animal no. 3: 1/4 of the corneal surface). The fluorescein test performed after 21 days revealed corneal staining in animal no. 1 (1/2 of the surface) and in animal no. 2 (3/4 of the corneal surface) after instillation.

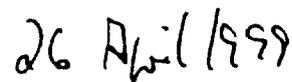
An irritation of the **iris** (grade 2) was observed in animal nos. one and two 1 hour to 21 days, in animal no. three 1 to 48 hours after instillation. An irritation of grade 1 was observed in animal no. three 72 hours to 14 days after instillation.

The conjunctivae were not affected by instillation of the test compound.

There were no systemic intolerance reactions.



Dr. phil. J. Leuschner
(Study director)



Date

2. INTRODUCTION

The aim of this experiment was to examine the influence of MKH 3586 Oxadiazolinon on rabbit eyes (irritation/corrosion test).

The study was performed in compliance with:

- the OECD Guideline for Testing of Chemicals No. 405, adopted February 24th, 1987;
- the EC guidelines: Official Journal of the European Communities L 383 A: Acute toxicity (eye irritation) B.5., dated December 29th, 1992.

3. GENERAL INFORMATION ON THE TEST SUBSTANCE

Test compound profile	designation	MKH 3586 Oxadiazolinon
	CAS no.	1711-88-2
	indication	herbicide
	batch no.	LVK 2302/3/1
	article no.	05339537
	LPT receipt no.	19137
	date of receipt	02.03.1999
	stable	17.05.1999
	characteristics	liquid
	storage conditions	at room temperature
	purity	99.8%
		see also Appendix 2 'Approval of Preparation Sample'
	Study dates	start
termination		13.04.1999
date of draft report		26.04.1999
protocol		07.07.1995
amendment no. 1		01.09.1997
amendment no. 2		12.03.1999
LPT study code number		
(Δ report number)		9301/344/95
Sponsor	Bayer AG	
	Werk Elberfeld	
	Institut für Toxikologie	
	Friedrich-Ebert-Str. 217 - 333	
	D-42096 Wuppertal	
Testing facility	LPT Laboratory of Pharmacology and Toxicology	
	Redderweg 8, D-21147 Hamburg	
	in-life phase:	
	LPT - Mienenbüttel	

**study protocol, evaluation, report:
LPT - Hamburg**

Staff employed

Study director	Dr. phil. J. Leuschner LPT, Redderweg 8, D-21147 Hamburg
Management	Dr. med. I. Leuschner
Veterinarian	Dr. med. vet. I. Beyer
Ophthalmology	Dr. med. vet. A. Wiederhold
Conduct of study/ Animal husbandry	R. Klie
Quality Assurance Unit (QAU)	F. Hübscher

Animals

Species/strain/stock/breeder	rabbit/Himalayan/ CHR. FRED LEUSCHNER & CO. D-24601 Löhndorf/Post Wankendorf
Number of animals examined	3 male rabbits
Initial age	approx. 4.5 months
Initial body weight	2.0 - 2.5 kg
Reason for selection	the rabbit is a commonly used non-rodent species for acute eye irritation tests
Identification	by tattooed number assigned by the Löhndorf breeding station and continuous number 1 - 3
Duration of study	at least 20 adaptation days, 1 test day and a follow-up period of 21 days
Administration route	single instillation into the conjunctival sac
Selection of route of administration	according to international guidelines
Dose level	0.1 ml/animal

4. METHODS

Conduct

A dose of 0.1 ml MKH 3586 Oxadiazolinon was administered into the conjunctival sac of the right eye of rabbits after gently pulling the lower lid away from the eyeball. The lid was then gently held together for about one second in order to prevent loss of test material.

The left eye, which remained untreated, served as a control.

After the administration the animals were kept separately in special restrainers which allowed free movement of the head but prevented a complete body turn, wiping of the eyes by the paws and excluded irritation of the eyes by excrements and urine.

Examination of the eyes: the eyes were examined ophthalmoscopically with a slit lamp prior to the administration and also 1, 24, 48 and 72 hours and 4 to 21 days after the administration. The eye reactions were observed and registered.

24 hours, 7, 14 and 21 days after administration the eyes were treated additionally with fluorescein³ and examined.

The effects observed were graded according to the scheme given in Appendix 1 to this report.

Based on most recent guidelines the eye reactions are monitored until the changes observed have completely subsided, however for not more than 21 days after application. Animals that do not reveal any lesions anymore for 24 hours following the first 72 hours of observation are sacrificed.

General criteria: body weight of all animals was measured at the beginning of the study.

All standard information including the grading scheme is given in the Appendix 1.

³ Fluorescein SE Thilo eye drops (Alcon Pharma GmbH, D-79108 Freiburg)

5. RESULTS

Under the present test conditions a single application of 0.1 ml MKH 3586 Oxadiazolinon per animal into the conjunctival sac of the right eye of three rabbits caused the following effects:

Corneal opacity was observed in animal no. one 1 to 48 hours (grade 3), 72 hours (grade 2) and 4 to 21 days (grade 1) after instillation; in animal no. two 1 to 48 hours (grade 3) and 72 hours to 21 days (grade 1) after instillation; in animal no. three 1 hour (grade 4), 24 and 48 hours (grade 3) and 72 hours to 21 days (grade 1) after instillation.

The fluorescein tests performed after 24 hours revealed **corneal staining** in all animals (whole corneal surface). The fluorescein test performed after 7 days revealed corneal staining in all animals (3/4 of the corneal surface). The fluorescein test performed after 14 days revealed corneal staining in all animals (animal no. 1: 1/2 of the corneal surface; animal no. 2: 3/4 of the corneal surface; animal no. 3: 1/4 of the corneal surface). The fluorescein test performed after 21 days revealed corneal staining in animal no. 1 (1/2 of the surface) and in animal no. 2 (3/4 of the corneal surface) after instillation.

An irritation of the **iris** (grade 2) was observed in animal nos. one and two 1 hour to 21 days, in animal no. three 1 to 48 hours after instillation. An irritation of grade 1 was observed in animal no. three 72 hours to 14 days after instillation.

The conjunctivæ were not affected by instillation of the test compound.

There were no systemic intolerance reactions.

See the table for detailed results.

TABLE
 Acute eye irritation study of
 MKH 3586 Oxadiazolinon
 by instillation into the conjunctival sac of rabbits

Time after administration	<u>CORNEA</u>	<u>IRIS</u>	<u>CONJUNCTIVAE</u>	
	Opacity		Redness	Chemosis
Animal no. : 1 / 2 / 3				

right eye: 0.1 ml MKH 3586 Oxadiazolinon/animal

before dosing	0/0/0	0/0/0	0/0/0	0/0/0
1 h	3/3/4	2/2/2	0/0/0	0/0/0
24 hrs	3/3/3	2/2/2	0/0/0	0/0/0
48 hrs	3/3/3	2/2/2	0/0/0	0/0/0
72 hrs	2/1/1	2/2/1	0/0/0	0/0/0
4 days	1/1/1	2/2/1	0/0/0	0/0/0
5 days	1/1/1	2/2/1	0/0/0	0/0/0
6 days	1/1/1	2/2/1	0/0/0	0/0/0
7 days	1/1/1	2/2/1	0/0/0	0/0/0
8 days	1/1/1	2/2/1	0/0/0	0/0/0
9 days	1/1/1	2/2/1	0/0/0	0/0/0
10 days	1/1/1	2/2/1	0/0/0	0/0/0
11 days	1/1/1	2/2/1	0/0/0	0/0/0
12 days	1/1/1	2/2/1	0/0/0	0/0/0
13 days	1/1/1	2/2/1	0/0/0	0/0/0
14 days	1/1/1	2/2/1	0/0/0	0/0/0
15 days	1/1/0	2/2/0	0/0/0	0/0/0
16 days	1/1/-	2/2/-	0/0/-	0/0/-
17 days	1/1/-	2/2/-	0/0/-	0/0/-
18 days	1/1/-	2/2/-	0/0/-	0/0/-
19 days	1/1/-	2/2/-	0/0/-	0/0/-
20 days	1/1/-	2/2/-	0/0/-	0/0/-
21 days	1/1/-	2/2/-	0/0/-	0/0/-

24 hrs fluorescein test: all animals: corneal staining (whole surface)
 7 days fluorescein test: all animals: corneal staining (3/4 of the surface)
 14 days fluorescein test: animal no. 1: corneal staining (1/2 of the surface)
 animal no. 2: corneal staining (3/4 of the surface)
 animal no. 3: corneal staining (1/4 of the surface)
 21 days fluorescein test: animal no. 1: corneal staining (1/2 of the surface)
 animal no. 2: corneal staining (3/4 of the surface)

TABLE Acute eye irritation study of
 MKH 3586 Oxadiazolinon
 by instillation into the conjunctival sac of rabbits

Time after administration	CORNEA		IRIS		CONJUNCTIVAE	
	Opacity				Redness	Chemosis
	Animal no. : 1 / 2 / 3					

left eye: untreated

before dosing	0/0/0	0/0/0	0/0/0	0/0/0
1 h	0/0/0	0/0/0	0/0/0	0/0/0
24 hrs	0/0/0	0/0/0	0/0/0	0/0/0
48 hrs	0/0/0	0/0/0	0/0/0	0/0/0
72 hrs	0/0/0	0/0/0	0/0/0	0/0/0
4 days	0/0/0	0/0/0	0/0/0	0/0/0
5 days	0/0/0	0/0/0	0/0/0	0/0/0
6 days	0/0/0	0/0/0	0/0/0	0/0/0
7 days	0/0/0	0/0/0	0/0/0	0/0/0
8 days	0/0/0	0/0/0	0/0/0	0/0/0
9 days	0/0/0	0/0/0	0/0/0	0/0/0
10 days	0/0/0	0/0/0	0/0/0	0/0/0
12 days	0/0/0	0/0/0	0/0/0	0/0/0
13 days	0/0/0	0/0/0	0/0/0	0/0/0
14 days	0/0/0	0/0/0	0/0/0	0/0/0
15 days	0/0/0	0/0/0	0/0/0	0/0/0
16 days	0/0/-	0/0/-	0/0/-	0/0/-
17 days	0/0/-	0/0/-	0/0/-	0/0/-
18 days	0/0/-	0/0/-	0/0/-	0/0/-
19 days	0/0/-	0/0/-	0/0/-	0/0/-
20 days	0/0/-	0/0/-	0/0/-	0/0/-
21 days	0/0/-	0/0/-	0/0/-	0/0/-

24 hrs fluorescein test: no pathological findings
 7 days fluorescein test: no pathological findings
 14 days fluorescein test: no pathological findings
 21 days fluorescein test: no pathological findings

6. APPENDIX 1

6.1 Standard information

Archives of data (including analysis results), raw material, samples of test compound

during the study: in the depot, LPT Laboratory of Pharmacology and Toxicology, Redderweg 8, D-21147 Hamburg

after reporting: written raw data, and a copy of the final report in the archive 11, LPT, Redderweg 8, D-21147 Hamburg

sample of the test compound: at LPT, Redderweg 8, D-21147 Hamburg

duration of storage: according to the periods laid down in the German 'Chemikaliengesetz'; afterwards the sponsor will decide on further use

Technical conduct all works were carried out according to standard operating procedures (SOPs) which were followed for all stages of this study; SOPs may be inspected in those divisions which were engaged in the study and in the Quality Assurance Unit (QAU)

Identification of the test compound after receipt at LPT the test compound was inspected; batch number(s), amount and characteristics (i.e. colour, form and size of particles and simple physico-chemical parameters such as density or melting point) were determined, if possible, and compared with information given by the sponsor; an identification sheet is filed with the raw data:

Parameter	LPT Identification	Sponsor Identification
colour consistency	reddish, clear liquid	none liquid

No further identification was carried out by LPT.

6.2 Diet and housing

Diet

Altromin 2023 (ALTROMIN GmbH, D-32791 Lage/Lippe, see 6.2.1: Composition of the diet) served as food. The food was available ad libitum before and after the exposure period.

Samples of the food are analysed for contaminants based on EPA/USA⁴ by LUFA-ITL⁵ twice a year (see 6.2.2: Limitation for contaminants in the diet). Certificates of analysis of the content and for contaminants were provided by the manufacturer and are included in the raw data.

Drinking water

Tap water was offered ad libitum before and after the exposure period.

Samples of the drinking water are taken twice a year by the Wasserbeschaffungsverband Harburg, D-21220 Seevetal, and are analysed according to the 'Deutsche Trinkwasserverordnung, Bundesgesetzblatt, Jahrgang 1990' (see 6.2.3: Limitation for contaminants in the drinking water).

Housing

For 8 hours following test substance application, the animals were kept singly in special restrainers which allowed free movement of the head but prevented a complete body turn and wiping of the eyes.

During the acclimatisation period and after the 8-hour period in restrainers, the rabbits were kept separately in cages with dimensions of 425 mm x 600 mm x 380 mm (manufacturer: Dipl. Ing. W. EHRET GmbH, D-16352 Schönwalde) at a room temperature of 20°C ± 3°C (maximum range). Relative humidity was 50% ± 20% (maximum range). Deviations from the maximum range caused for example during cleaning procedures are dealt within SOPs. The rooms were alternately lit (150 lux at approx. 1.5 m room height) and darkened for periods of 12 hours each.

The cages excluded the possibility of irritation of the eye by excrements and urine.

⁴ EPA/USA, Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules, Federal Register 44, 27334 - 27375, May 1979

⁵ Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Institut für Tiergesundheit und Lebensmittelqualität · Kiel der Landwirtschaftskammer Schleswig-Holstein, D-24116 Kiel

6.2.1 Composition of the diet

Standard diet for rabbits
ALTROMIN 2023
 (ALTROMIN GmbH, D-32791 Lage/Lippe)

Ingredients		Amino Acids	
(average % content in the diet)		(average % content in the diet)	
crude protein	17.5	lysine	0.80
crude fat	4.0	methionine	0.35
crude fibres	14.5	cystine	0.25
ash	9.0	phenylalanine	0.80
moisture	12.0	tyrosine	0.50
nitrogen-free extract	43.0	arginine	0.90
		histidine	0.40
		tryptophane	0.20
		threonine	0.60
		isoleucine	0.90
		leucine	1.30
		valine	0.90
Metabolizable Energy			
kcal/kg	2400.0		
MJ/kg	10.1		
Minerals		Trace Elements	
(average % content in the diet)		(average content in mg per 1000 g of diet)	
calcium	0.95	manganese	60.0
phosphorus	0.70	iron	160.0
magnesium	0.20	copper	17.0
sodium	0.20	zinc	50.0
potassium	1.60	iodine	0.9
		fluorine	10.0
Vitamins			
(additive per 1000 g of diet)			
vitamin A	15000.0	IU	
vitamin D ₃	600.0	IU	
vitamin E	75.0	mg	
vitamin K ₃	3.0	mg	
vitamin B ₁	18.0	mg	
vitamin B ₂	12.0	mg	
vitamin B ₆	9.0	mg	
vitamin B ₁₂	24.0	µg	
nicotinic acid	36.0	mg	
pantothenic acid	21.0	mg	
folic acid	2.0	mg	
biotin	60.0	µg	
choline	600.0	mg	
vitamin C	36.0	mg	

6.2.2 Limitation for contaminants in the diet

	min.	max.
Aflatoxin (B ₁ , B ₂ , G ₁ , G ₂), ppb total		5.0
Lindane, ppb		20.0
Heptachlor, ppb		20.0
Malathion, ppm		2.5
DDT (Total), ppb		100.0
Dieldrine, ppb		20.0
Cadmium, ppb		160.0
Arsenic, ppm		1.0
Lead, ppm		1.5
Mercury, ppb		100.0
Selenium, ppm	0.1	0.6
PCB, ppb		50.0

6.2.3 Limitation for contaminants in the drinking water (in mg/l)

		max.
Iron (Fe)		0.2
Manganese (Mn)		0.05
Ammonium (NH ₄ ⁺)		0.5
Chloride (Cl ⁻)		250.0
Arsenic (As)		0.01
Lead (Pb)		0.04
Cadmium (Cd)		0.005
Chromium (Cr)		0.05
Cyanide (CN ⁻)		0.05
Fluoride (F ⁻)		1.5
Nickel (Ni)		0.05
Nitrite (NO ₂ ⁻)		0.1
Nitrate (NO ₃ ⁻)		50.0
Mercury (Hg)		0.001
Polycyclic aromatic hydrocarbons		
- Fluoroanthene		
- Benzo-(b)-fluoroanthene		
- Benzo-(k)-fluoroanthene		
- Benzo-(a)-pyrene		
- Benzo-(ghi)-perylene		
- Indeno-(1,2,3-cd)-pyrene	total	0.0002
Chlorinated organic compounds		
- 1,1,1-Trichloroethane		
- Trichloroethene		
- Tetrachloroethene		
- Dichloromethane	total	0.01
- Tetrachloromethane		0.003
Organic chemical compounds used as pesticides and herbicides including their toxic metabolites		maximum of 0.0001/substance maximum total of 0.0005
pH		between 6.5 and 9.5

6.3 Grading scheme

Reactions were scored according to the following scheme:

CORNEA

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

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

IRIS

- 0 normal
- 1 markedly deepened 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)
- 2 no reaction to light, haemorrhage, gross destruction (any or all of these)

CONJUNCTIVAE

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

- 0 blood vessels normal
- 1 some blood vessels definitely hyperaemic (injected)
- 2 diffuse, crimson colour, individual vessels not easily discernible
- 3 diffuse beefy red

Chemosis: lids and/or nictitating membrane

- 0 no swelling
- 1 any swelling above normal (including nictitating membranes)
- 2 obvious swelling with partial eversion of lids
- 3 swelling with lids about half-closed
- 4 swelling with lids more than half-closed

Any further lesions are listed.

6.4 Evaluation

Based on the EC-directive 67/548/EEC and its subsequent amendments (Annex VI (L 110 A, May 4th, 1993) to Commission Directive 93/21/EEC) the test substance is classified as irritant and the risk phrase is assigned in accordance with the following criteria:

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,
- oedema of the conjunctivae (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 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 the scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

- Substances or preparations which cause significant ocular lesions, based on practical experience in humans.
- Organic peroxides except where evidence to the contrary is available.

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 of the scores of the eye irritation test in Annex V have any values:

- cornea opacity equal 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.

- Substances and preparations which cause severe ocular lesions, based on practical experience in humans.

Note: When a substance or preparation is classified as corrosive and assigned R34 or R35, the risk of severe damage to eyes is considered implicit and R41 is not included in the label. However, in the case of preparations, when calculating the sum of quotients by the formulae in 3.5 (f)(ii) and 3.5 (h)(ii) of Directive 88/379/EEC substances classified as corrosive shall be considered as if R41 had been assigned.

APPENDIX 2

Approval of Preparation Sample

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23.02.99

Bayer AG
PF-PM/PPA

Approval of Preparation Sample

Preparation Sample TOX 4910

Sample: MKH 3586 Oxadiazolinon

Article-No.: 05339537

Indication:

Batch No.: LVK 2302/311

Origin of sample: PF-PIVE, DR. V. LAAK

Responsible Analyst: Dr. Gau

Laboratory: PB-A

Analytical Methods: HPLC, Fl.-%

Approvals:

<u>TOX</u>	<u>Purity</u>		<u>Approved until</u>	<u>Date of Analysis</u>	<u>Comment</u>
4910-00	99.8 %		17.05.99	19.02.99	



(H. Baum, PF-PM/PPA)

A reserve sample will be retained.

Test system acute eye irritation study by instillation into the conjunctival sac of rabbits according to EC guideline B.5. and OECD guideline 405

Test substance MKH 3586 Oxadiazolinon

According to the EC-Commission directive 67/548/EEC and its subsequent amendments on the approximation of the laws, regulations and administrative provision relating to the classification, packaging and labelling of dangerous substances and the results obtained under the present test conditions

MKH 3586 Oxadiazolinon
was
risk of serious damage
to eyes
(labelling requirement: R41)

J.L.L.