Hoechst
Pharma Research Toxicology

Report no. 84.0229
May 4, 1984

Corresponds to study #4 in Attachment A of transmittal memo on CBI
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Perylimid

Testing the
acute irritant effects / caustic effects
on the rabbit eye

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CONTENTS

1. SUMMARY

Testing the acute irritant effect / caustic effect on the rabbit eye under the described test conditions of the OECD test guidelines has shown that according to the classification criteria of the EU guidelines, the compound Perylimid is classed as not irritating the eye.

2. PRELIMINARY REMARKS

Testing the acute irritating / caustic effects on the rabbit eye provides information about the occurrence of eye damage after single application of the test compound and serves as the basis for classification and identification.

The present examination has been carried out according to the OECD approved test guideline

OECD Guideline for Testing of Chemicals,
405 Acute Eye Irritation / Corrosion, OECD 1981

As well as the

OECD principles of best laboratory practices
(published on February 4, 1983 in the Bundesanzeiger
(German Federal Gazette).

For the purpose of classification of the test compound, the criteria of the

Council Directive dated September 18, 1979 concerning the sixth amendment of the guideline 67/548/EEC concerning the amendment of the legal and administrative regulations for the classification, packaging and identification of hazardous substances. Annex VI, Council Directive 79/831/EEC.

During the test, there were no unforeseen circumstances that may have affected the quality and integrity of the results.

3. OVERSIGHT

Test No:	84.0216
Test compound:	Perylimid
Customer:	Farben Nord, Werk Höchst
Animal species:	New Zealand albino rabbits
Test start:	April 17, 1984
Test end:	April 24, 1984
Dose:	100 mg

R E S P O N S I B L E:

Industrial toxicology:	Dr. Weigand
Test director:	Dr. Rupprich
Unit GLP :	Ap. Harston
Testing and archiving unit:	Pharma Research Toxicology HOECHST CORPORATION PO Box 80 03 20 6230 Frankfurt 80

4. MATERIAL AND METHODOLOGY

4.1 Test compound

Name:	Perylimid
Code:	EMGW 9956
Application type:	Pigment intermediate
Chemical name:	Perylen-3, 4, 9, 10-tetracarbonaciddiimide
Molecular formula:	C_{24} H_{10} N_2 04
Mol mass:	390
Appearance:	Blackish-brown powder
Melting point:	400 °C
pH value in water:	9 (due to the K0H content)
Solubility:	Water solubility: only the contaminations are soluble Liposolubility: not soluble In other solvents: not soluble
Composition:	Approx. 80% Perylimid Approx. 10% K0H Approx. 8% diverse organic contaminations Approx. 1% inorganic salts Approx. 1% water
Batch number and production Date:	Op.69/March83
Storage :	In a dark place at approx. 22 °C

4.2 Animal species and husbandry conditions

Animal species:	New Zealand albino rabbits
Strain:	Hoe: HIMK (SPFWiga)
Origin:	HOECHST AG, Kastengrund, conventional breeding
Number of animals:	3
Identification of the animals:	Numbered ear marks
Animal weight:	2.8 – 4.4 kg
Animal husbandry:	In fully climatized rooms in individual cages (battery husbandry)
Room temperature:	20 ± 2 °C
Relative humidity:	55 ± 10%
Lighting duration:	12 hours daily
Food:	Altoromin 2123 Haltungsdiät - rabbit food Altoromin GmbH, Lage/Lippe, ad libitum
Water:	Deionized water with chlorine from automatic drippers, ad libitum

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4.3 Carrying out the test

Approximately 24 hours prior to the start of the experiment, the eyes of the animals to be treated were examined under UV light for damages to cornea following application of a drip of Fluorescein-sodium solution (0.01%). The test included only animals without any eye damage.

For 3 rabbits, 100 mg of the test compound Perylimid (added to 0.05 ml 0.9% NaCl solution) were dripped once into the conjunctiva of the left eye. The untreated eye of each animal acted as a control. 24 hours after the application of the test compound, the treated eye was thoroughly washed out with physiological saline solution at a temperature of approx. 37 ^{o}C.

The eyes were evaluated 1, 24, 48 and 72 hours after application of the test compound. Damage to the cornea, iris and the conjunctiva were evaluated numerically according to Draize (see evaluation key). All further toxicologically important findings were recorded. In addition, after adding a drop of Fluorescein-sodium solution (0.01%), the eyes were examined under UV light after 24 and 72 hours after application for damage to the cornea. Because, after 72 hours, the eyes continued to show reactions, further findings were evaluated after 7 days.

4.4 Evaluation

Median values were calculated using all of the individual values of the animals tested for the eye damage sustained (including clouding of the cornea, inflammation of the iris, conjunctival redness and conjunctival edema) at observation intervals of 24, 48 and 72 hours. If all median values were below the limits mentioned above, the median values for each test animal were calculated in addition.

Any eye damage occurring within 72 hours after exposure, and lasting for 24 hours or longer, and consisting of the following conditions will lead to the classification of the test compound as being "irritant":

1. The median value for each damage type corresponds to one of the following values:

Clouding of the cornea	2 or more
Inflammation of the iris	1 or more
Conjunctival redness	2.5 or more
Conjunctival edema	2 or more

2. When carrying out the test with 3 test animals, for at least 2 test animals, one of the above values is react for clouding of the cornea or conjunctival edema. The values for inflammation of the iris must be greater or equal to 1 but below 2. Both values for conjunctival redness muss be equal to 2.

Serious damage ("Risk of serious eye damage") occurs when the median value across all test animals for clouding of the cornea is equal or greater than 3, for inflammation of the iris greater than 1.5, or when for at least 2 test animals one of the following values is reached:
Clouding of the cornea equal or greater than 3, conjunctival redness equal to 2.

A "risk of serious eye damage" occurs also when serious eye damage does not recede during the test period.

5. RESULT

The test compound Perylimid has been tested for irritating / caustic effects on the rabbit eye. 24 hours prior to the application, the rabbit eyes were washed out. 1 hour after the application, all animals showed slight swellings and redness of the conjunctiva as well as hyperemia of the iris. The symptoms of irritation were accompanied by discharge which was discolored reddish-brown by the compound.

On day 1 after the application, one animal shows a distinctive inflammation and a diffuse, carmine redness of the conjunctiva as well as a clear discharge. 48 hours after the application, the nictitating membrane of this animal was very red.

On day 7 after the application, no animal shows any symptoms of irritation.

The following median values were calculated from the numerically evaluated individual findings concerning the eye damage at the observation points after 24 hours, 48 hours and 72 hours:

Clouding of the cornea	All animals:	0	Inflammation of the iris:	All animals:	0.3
	Animal 1:	0		Animal 1:	0
	Animal 2:	0		Animal 2:	1.0
	Animal 3:	0		Animal 3:	0
Redness of the conjunctiva	All animals:	0.8	Edema of the conjunctiva	All animals:	
	Animal 1:	0.7		Animal 1:	0
	Animal 2:	1.3		Animal 2:	0.7
	Animal 3:	0.3		Animal 3:	0

According to the classification criteria of the EU guideline and taking into account all toxicologically relevant findings, the compound Perylimid is considered as non-eye irritant.

Dr. Ru/Ri

Unit GLP

Pharma Research Toxicology
of the
HOECHST AKTIENGESELLSCHAFT

Dr. Rupprich
Test director

Dr. Weigand
Coordination industrial toxicology

6. Table 1: Acute irritant effect / caustic effect in the eye

Individual findings after single application of Perylimid into the conjunctiva of the rabbit eye (first washing out of the eye after 24 hours)

Time after application:	1 h	24 h	48h	72h	7d
Animal no.	**1 2 3**	**1 2 3**	**1 2 3**	**1 2 3**	**1 2 3**
Edema of the conjunctiva	1 1 1	0 2 0	0 0 0	0 0 0	0 0 0
Redness of the conjunctiva	1 1 1	1 2 1	0 1 0	1 1 0	0 0 0
Inflammation of the iris	1 1 1	0 1 0	0 1 0	0 1 0	0 0 0
Clouding of the cornea	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
Fluorescein-Test**		1 1 0		0 1 0	

Eye discharge
- Reddish-brown due to compound discoloration: x x x
- clear: x x

Nictitating membrane very reddened: x

Legend: ** The area of lightening the cornea under UV light after adding one drop of Fluorescein-sodium (0.01%).

1 = spotty, up to ¼ of the surface of the cornea
2 = more than ¼ up to ½ of the surface of the cornea
3 = more than ½ up to ¾ of the surface of the cornea
4 = more than ¾ up to 4/4 of the surface of the cornea

7. Evaluation key

Evaluation key for eye damage according to the OECD guideline (after Draize)

CORNEA

Degree of the clouding (reading in the area of the most intense clouding)

No clouding, no ulceration	0
Clouding in individual, spread-out areas, iris details clearly visible	1*
Easily visible, transparent areas of a clouding, iris details slightly darkened	2*
Clouding appears mother-of-pearl-like, no iris details visible, size of pupil barely visible	3*
Complete clouding of the cornea, iris not visible	4*

IRIS

Normal	0
Obvious, deeply drawn lines, hyperemia, swelling, circumcorneal vascular Drawing (one or a combination of these symptoms), iris still reacts to light (slow reaction = positive)	1*
No reaction to light, bleeding, destruction of the iris (some or all symptoms)	2*

CONJUNCTIVA

Vessels normal	0
Vessels clearly injected (hyperemia)	1
Diffuse carmine reddening, single vessels not easily distinguishable	2*
Diffuse fleshy redness	3*

SWELLING

No swelling	0
Slight swelling (including nictitating membrane)	1
Distinctive swelling, partial lifting of the lid	2*
Swelling, with eye lids half closed	3*
Swelling, with eye lids more than half to fully closed	4*

*signifies positive effect

Hoechst Corporation
Pharma research
Unit GLP

May 16, 1984

Title: Perylimid
Testing the acute irritant effects / caustic effect on the rabbit eye

Date: May 4, 1984

Test no: 84.0216

This test has been inspected regularly and the written, duly signed documentation has been presented to the directors of the test institutions and the test directors as follows:

Inspection	Report
April 17, 1984	April 17, 1984
April 17, 1984	April 17, 1984
May 16, 1984	May 16, 1984

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Unit GLP