

R4

Study Title

Octopirox^R

Test for primary dermal irritation
in the rabbit

Authors

Dr. Hofmann, Dr. Weigand

Study completed on

04 November 1986

Performing Laboratory

Pharma Research Toxicology and Pathology
Hoechst-Aktiengesellschaft
Postfach 80 03 20
6230 Frankfurt am Main 80

Laboratory Project ID

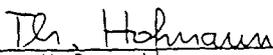
Study No. 86.1471

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STATEMENT OF COMPLIANCE

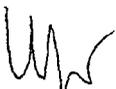
To the best of my knowledge and belief, this study was conducted in compliance with Good Laboratory Practice regulations. No unforeseen circumstances were observed which might have affected the quality or integrity of the study.

Study Director



(Dr. Hofmann)

Head of Testing Facility



(Dr. Mayer)

Quality Assurance Statement

Hoechst Aktiengesellschaft
Pharma Research
Quality Assurance (GLP)

14.11.1986

Title : Octopirox®
Testing for primary dermal irritation in the
rabbit

Date : 07.11.1986

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This study was periodically inspected and properly signed
records of these inspections were submitted to testing facility
management and the study director as shown below :

<u>Inspection</u>	<u>Report</u>
27.10.1986	27.10.1986
28.10.1986	28.10.1986
13.11.1986	14.11.1986

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1. SUMMARY

Testing of Octopirox^R for primary dermal irritation in the rabbit showed, that, based on the criteria laid down in the Directive 83/467/EEC, the substance has to be labelled as irritant (Xi) with the designation R38 - irritates the skin.

2. OBJECTIVE / GUIDELINE

Testing for primary dermal irritation provides information on the irritant effect of the test substance on the skin following a single dermal application and serves as a basis for classification and labelling.

The present study was conducted in compliance with

EEC Directive B.4. 'Acute toxicity Skin Irritation' of
the Directive 84/449/EEC:
Commission Directive of 25 April 1984
adapting to technical progress for the sixth time
Council Directive 67/548/EEC on the approximation of the laws,
regulations and administrative provisions relating to the
classification, packaging and labelling of dangerous substances

Also:

OECD Guidelines for Testing of Chemicals, 404
"Acute Dermal Irritation/Corrosion", OECD 1981
Adopted: 12 May 1981

and in compliance with the Principles of Good Laboratory Practice:

Annex 2
OECD Principles of Good Laboratory Practice
OECD - Guidelines for Testing of Chemicals 1981

No unforeseen circumstances were observed which might have affected the quality or integrity of the study.

Classification of the test substance is based on the criteria laid down in

Council Directive 83/467/EEC:
Commission Directive of 25 July 1983
adapting to technical progress for the fifth time
Council Directive 67/548/EEC on the approximation of the laws,
regulations and administrative provisions relating to the
classification, packaging and labelling of dangerous substances

3. SYNOPSIS / RESPONSIBILITIES

Study No. : 86.1471
Test substance : Octopirox^R
Test species : New Zealand albino rabbit
Test ordered by : Division L, Pharma Prod. Management
Volume applied per patch : 500 mg
Start of study : 28 October 1986
End of study : 4 November 1986

R e s p o n s i b i l i t i e s

Industrial Toxicology : Dr. W. WEIGAND
Study Director : Dr. T. HOFMANN
Quality Assurance (GLP) : S. J. HARSTON

Testing Facility and Archive: Pharma Research Toxicology and Pathology
HOECHST AKTIENGESELLSCHAFT
Postfach 80 03 20
6230 Frankfurt am Main 80

4. MATERIALS AND METHODS

4.1. Test substance

Name : Octopirox^R

Product number / Code : PKOD

Synonyms : Pirocton-olamine (INN)

CAS number : 68890-66-4

Chemical name : 1-Hydroxy-4-methyl-6-(2,2,4-bis-methylpentyl)-
1-H-pyridine-2-one, in combination with 2-
aminoethanol (1:1)

Empirical formula : C₁₄H₂₃NO₂ · C₂H₇NO

Use : Antiseborrheic

Appearance: : White to slightly yellowish white powder

Molar mass : 298.42 g/mol

Melting point : 130 - 135 °C (with onset of decomposition)

Bulk density : Approx. 0.4 kg/l

pH in water : 8.5 - 10 (suspension of 10 g/l in water at
20 °C)

Solubility : About 0.5 g soluble in water
Readily soluble in ethanol

Purity : 100.5 %

Batch and production date : Batch E 141 / Nov. 85

Certificate of Analysis : without number, dated 12.12.85 / Ph. Qual.
Control

Sample received on : 15.10.86

Storage conditions : darkness at approx. 22 °C in a fume cupboard

4.2. Test species and animal husbandry

Test species : New Zealand albino rabbit

Origin : HOECHST AG, Kastengrund, conventional breed

Number of animals : 3

Animal identification : numbered ear tags

Animal weights : 2.7 - 3.1 kg

Age of animals : about 3 - 5 months

Animal housing : in fully air-conditioned rooms, separate cages
(arranged in a battery)

Ambient temperature : 20 ± 3 °C

Relative humidity : 50 ± 20 %

Lighting time : 12 hours per day

Diet : Altromin 2123 maintenance diet - rabbits
(Altromin GmbH, Lage/Lippe), ad libitum
and hay (approx. 15 g daily)

Drinking water : deionised, chlorinated water from automatic
water dispensers, ad libitum

4.3. Test procedure

About 24 hours before the start of the study the hair in the dorsal region of the body of 3 rabbits was removed with an electric clipper over an area of about 25 cm². Only animals with intact skin were used.

Each animal was treated with 500 mg Octopirox^R [moistened with 0.4 ml isotonic saline]. The moistened substance was applied over the whole surface of a 2.5 x 2.5 cm cellulose patch on a piece of surgical plaster (specially produced by Beiersdorf AG, Hamburg). The plaster was fixed to the prepared skin area and then covered with a semi-occlusive bandage.

The exposure period was 4 hours. After the exposure period all remnants of the test substance were carefully removed from the skin with warm tap water.

Examinations of the skin took place after 30 - 60 minutes, and 24, 48 and 72 hours after removal of the patches. Because of persistent irritation 72 hours after removal of the patches, additional readings were performed after 7 days.

Erythema, eschar formation and oedema were evaluated numerically according to the technique of DRAIZE (see APPENDIX 6.1., Scale for scoring dermal reactions). All other changes of the skin were recorded.

5. RESULTS

The skin exhibited very slight to moderately severe erythema one hour to 72 hours after removal of the patches. A very slight oedema was observed in one animal 24 hours after the removal of the patches.

Seven days after application all signs of irritation were reversible. Dry and brittle skin surface occurred in two animals, and separation of scales was observed in the third animal.

The table of the individual findings is given in the Appendix (Section 6.2).

Based on the individual scores for erythema and oedema after 24, 48 and 72 hours, the following mean values were calculated:

Erythema and eschar formation:

all animals:	2.7
animal 1 :	2.3
animal 2 :	2.7
animal 3 :	3.0

Oedema formation:

all animals:	0.1
animal 1 :	0.0
animal 2 :	0.0
animal 3 :	0.3

Based on the results of this study, Octopirox^R should be classified, in accordance with the criteria layed down in Directive 83/467/EEC and taking into account all other changes, as irritant (Xi) with the designation R38 - irritates the skin.

Dr. TH/Ko

Quality Assurance (GLP)

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Pharma Research Toxicology

Th. Hofmann, 21.01.88

Dr. Th. Hofmann
Study Director

6. APPENDIX

6.1. Scale for scoring dermal reactions

According to the technique of DRAIZE

Erythema and eschar formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (lesion in depth)	4

Oedema

No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond area of exposure)	4

6.2 Individual findings

Time after removal of the patch	:	30 - 60 '	24 h	48 h	72 h	7 d
Animal no.	:	<u>1 2 3</u>				
Erythema and eschar formation	:	1 2 2	2 2 3	3 3 3	2 3 3	0 0 0
Oedema formation	:	0 0 0	0 0 1	0 0 0	0 0 0	0 0 0

Surface of the skin
- dry, brittle

x x

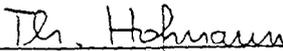
Separation of fine
scales

x

STATEMENT OF COMPLIANCE

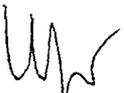
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