



Primary Skin Irritation of a preparation of
1 % Octopirox, 0.33 % citric acid,
75 % PEG 400 and 23.67 % water (pH 7.0)
in New Zealand rabbits (patch test).
Report No 764/79

Summary:

A patch test for skin tolerance carried out under the experimental conditions laid down in the FDA guide lines showed that this Octopirox preparation was slightly irritant to the skin.

The PEG 400 - water mixture used as a control proved to be non-irritant according to the FDA guide lines.

Material and methods

Albino New Zealand rabbits (supplier: Erkrath) weighing 2.36 - 2.98 kg (\bar{x} = 2.68 kg) were used as experimental animals. They were caged singly and received standard feeds ERKA 8300 (Feed stuff manufacturer Robert Koch OHG, Hamm/Westf.). Feed and Water were supplied in unlimited quantities.

"Octopirox^R" - H 72 6146 A was supplied in a 1 % solution in 0.33 % citric acid, 75 % PEG 400 and 23.67 % water. The pH of the colourless solution was adjusted to 7.0. The vehicle PEG 400 - water (3 : 1) was used as a control on the same animals.

The experiments were carried out during the period 26.11. until 29.11.79.

Experimental procedure:

An area of at least 6 x 3 cm on both flanks of six rabbits was shaved with an electric razor. One half of each shaved area was, in addition, abraded with a scarifier.

The substance under test and the vehicle on its own were applied in 0.5 ml quantities on pieces of gauze sized 2.5 x 2.5 cm. They were attached to the prepared skin with strips of adhesive plaster and covered with inert, impervious PVC film, 6 - 8 cm wide, and an elastic bandage was then wound round the animals' trunks. The period of application was 24 hours, at the end of which time the bandages were removed and the first inspection carried out, followed by further assessment at 24 and 72 hours.

The findings were used to determine the primary irritation score according to para 1500.41 of Federal Register 38, No 187, 27.09.1973, p 27019 (Appendix 1).

Results:

The Octopirox preparation produced a primary irritation score of 1.3. After 24 hours' application, mild reddening and swelling was noted in four animals, and distinct erythema in two. According to the FDA guidelines, this Octopirox preparation must, therefore, be considered slightly irritant to the skin. The application of the vehicle on its own produced mild swelling of the skin in one animal. The vehicle PEG 400 - water (3 : 1) is thus non-irritant.

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Appendix
Classification

Evaluation of Primary Skin Irritation
(Patch Test after FDA)

The table is reproduced from U.S. Code of Federal Regulations § 1500.41 "Method of testing primary irritant substances" as published in Federal Register 38, 27019 (1973).

	<u>Value</u>
1. 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 (injuries in depth)	4
2. Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

"The 'value' recorded for each reading is the average value of the six or more animals subject to the test.

Add the values for erythema and eschar formation at 24 and 72 hours for intact skin to the values on abraded skin at 24 and 72 hours (four values). Similarly, add the values for edema formation at 24 and 72 hours for intact and abraded skin (four values). The total of the eight values is divided by four to give the primary irritation score."

Evaluation

0.0 - 0.5	Non-irritant	(nicht reizend)
0.6 - 3.0	Slightly irritant	(leicht reizend)
3.1 - 5.0	Moderately irritant	(mäßig reizend)
5.1 - 8.0	Severely irritant	(stark reizend)

Annex
Report No. 764/79
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DERMAL TOLERANCE - PATCH TEST													Study No.:						
Substance: Octopirox - H 72 6146 A							Dose: 2 x 0,5 ml/g on 3 x 3 cm skin surface						Investigator: Vatter						
Concentration: 1 %ig in PEG 400/+ water				Application 1 x intact h flank r scarif. f flank				Species: Albino New Zealand rabbit				Study start: 26.11.1979							
Time after appl.		24 h					48 h					72 h							
Animal No.		535	536	537	538	539	541	535	536	537	538	539	541	535	536	537	538	539	541
scarified	Erythema	1	1	1	1	2	3	1	0	0	0	2	2	0	0	0	0	1	0
	Edema	1	1	0	1	1	1	1	0	0	0	0	1	0	0	0	0	0	0
intact	Erythema	1	1	1	1	2	2	0	0	0	0	2	2	0	0	0	0	1	0
	Edema	1	0	2	1	2	1	1	0	0	0	0	1	0	0	0	0	0	0
Sum		30					13					2							
Skin dry, rough																			
Skin with fine scales																			
Skin with coarse scales																			
Skin hardened																			
Skin raised																			
Skin parchment-like																			
Skin chapped (superf.)																			
Skin chapped (deep)																			
Eschar formation																			
Necrosis																			
Desquamation, small-sized																			
Desquamation, large-sized																			
Open wound																			
Exudation (clear)																			
Exudation (reddish)																			
Scratch marks																			
Discolorations																			
isolated																			
extensive																			
primary irritation index: Sum of all rabbits, 24 + 72 h-value= 32 : 24= 1,3																			
Remarks:																			
h = hindflank						535 - 2 732						538 - 2 976							
f = foreflank						536 - 2 356						539 - 2 494							
r = right						537 - 2 702						541 - 2 800							

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DERMAL TOLERANCE - PATCH TEST													Study No.:								
Substance: PEG 400 / water						Dose: 2 x 0,5 ml/g on 3 x 3 cm skin surface						Investigator: Vatter									
Concentration: 3 : 1			Application 1 x intact h flank 1 scarif. f flank			Species: Albino New Zealand rabbit						Study start: 26.11.1979									
Time after appl.			24 h						48 h						72 h						
Animal No.			535	536	537	538	539	541	535	536	537	538	539	541	535	536	537	538	539	541	
scarified	Erythema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Edema	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	
intact	Erythema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Edema	0	0	0	0	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	
Sum			3						2						0						
Skin dry, rough																					
Skin with fine scales																					
Skin with coarse scales																					
Skin hardened																					
Skin raised																					
Skin parchment-like																					
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Open wound																					
Exudation (clear)																					
Exudation (reddish)																					
Scratch marks			X																		
Discolorations																					
isolated																					
extensive																					
primary irritation index: Sum of all rabbits, 24 + 72 h-value=													3 : 24= 0,1								
Remarks: h = hindflank 1 = left f = foreflank																					