





Hoechst Aktiengesellschaft  
Pharma Research  
Toxicology  
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Skin tolerance of a preparation of  
1.0 % Octopirox (Op. E 001), 0.3 % citric acid  
and 98.7 % 1,2-propylene glycol (pH 7.0)  
in rabbits  
Report No. 737/79

## Summary

Testing the skin tolerance under the described test conditions according to FDA standards for patch testing has shown that the present preparation must be judged as slightly irritant to the skin.

1,2-propylene glycol used as control was shown not to be irritant to the skin according to FDA standards.

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Material and method

Albino Himalayan rabbits (strain: Hoe: HIMK (SPFWiga): our own breed) weighing 1.5 to 2.0 kg were used for the experiment. The animals were kept in single cages and received standard feed ERKA 8300 (Futtermittelwerk Robert Koch OHG, Hamm/Westf.). Feed and water were supplied ad libitum.

The preparation of 1 % Octopirox<sup>R</sup> = (H 72 6146 A), 0.3 % citric acid and 98.7 % of 1,2-propylene glycol was a clear solution. The pH was adjusted to 7. The vehicle (1,2-propylene glycol) was tested in the same animals as control.

The experiment was carried out from 06.11. to 09.11.1979.

Procedure:

Areas of at least 6 x 3 cm on both flanks were depilated with electric hair clippers. One half of the shorn area was also scarified.

0.5 ml of the solution or the vehicle were applied on pieces of gauze each 2.5 x 2.5 cm in size. The gauze was fixed to the prepared skin with a strip of adhesive plaster and covered with a sheet of inert, impervious PVC 6 - 8 cm wide. Finally a permanent elastic bandage (Dauerbine<sup>R</sup> K) was wrapped round the body of the animal. Exposure time was 24 hours. The first assessment of the irritant effect was made immediately after taking off the dressing; further assessments were made at 48 and 72 hours after application.

The irritability index was calculated from the results in accordance with the classification described under § 1500.41 in the Federal Register 38, No. 187, 27.09.1973, p 27019 (Appendix 1).

Result:

After application of the solution of the test substance an irritability index of 2.6 was found. In addition, the skin of one animal was dry and chapped with coarse scales. According to FDA standards Octopirox<sup>R</sup> 1 % in 1,2-propylene glycol is slightly irritant to the skin. The 1,2-propylene glycol applied as control caused transient slight to distinct oedema in 4 animals. The irritation index of 0.5 determined at the end of the experiment shows that 1,2-propylene glycol is not irritant to the skin according to FDA standards.

Dr. L/Bo  
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Pharma Research Toxicology  
HOECHST AKTIENGESELLSCHAFT

Dr. Leist  
Head of Laboratory

Dr. Weigand  
Coordination Industrial  
Toxicology

Appendices  
Evaluations

Evaluation of Primary Skin Irritation  
(Patch Test after FDA)

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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>
<b>1. Erythema and Eschar Formation</b>	
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
 <b>2. Edema Formation</b>	
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  
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DERMAL TOLERANCE - PATCH TEST														Study No.:					
Substances: Octopirox <sup>R</sup> (in 1,2-propylene glycol)							Dose: 2 x 0,5 ml/g on 3 x 3 cm skin surface							Investigator: Böcher / Vatter					
Concentrations: Original				Application intact h flank r scarif. f flank r				Species: Albino Himalayan rabbit				Study start: 06.11.1979							
Time after appl.		24 h						48 h						72 h					
Animal No.		157	158	159	160	161	162	157	158	159	160	161	162	157	158	159	160	161	162
scarified	Erythema	2	2	1	1	2	3	2	3	1	1	3	3	2	2	1	1	2	2
	Ecema	1	3	1	1	2	3	0	0	1	0	0	1	0	0	0	0	0	0
intact	Erythema	0	3	2	2	2	3	2	3	1	2	3	3	1	2	0	1	2	2
	Ecema	1	1	2	3	2	2	0	0	1	0	0	1	0	0	0	0	0	0
Sum		45						31						18					
Skin dry, rough																			X
Skin with fine scales																			
Skin with coarse scales																			X
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= 63 : 24= 2,6

Remarks: h = hindflank      r = right  
f = foreflank

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DERMAL TOLERANCE - PATCH TEST													Study No.:							
Substance: 1,2-propylene glycol						Dose: 2 x 0,5 ml/g on 3 x 3 cm skin surface						Investigator: Böcher / Vatter								
Concentration: Original			Application intact h flank 1 scarif. f flank			Species: Albino Himalayan rabbit						Study start: 06.11.1979								
Time after appl.			24 h						48 h						72 h					
Animal No.			157	158	159	160	161	162	157	158	159	160	161	162	157	158	159	160	161	162
scarified	Erythema	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
	Ecema	2	0	0	1	2	1	1	0	0	0	1	0	0	1	0	0	0	0	0
intact	Erythema	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
	Ecema	2	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Sum			11						6						1					
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= 12 : 24= 0,5

Remarks: h = hindflank      1 = left  
f = foreflank