

Report Title: Acute Percutaneous Toxicity Study in Rabbits

Test Type: Acute Dermal Toxicity

Conducting Laboratory and Location: International Research and Development Corporation

Test Substance(s): #T-7120 -2% Octopirox in shampoo at pH 4.5

Species: Rabbit

of Animals: 3 male, 3 female

Test Conditions: 3 male and 3 female New Zealand White Rabbits exposed to 2000 mg/kg on abraded skin for 24 hours. Rabbits were observed for 14 days.

Results: Minimum lethal dermal dose in both male and female rabbits was >2.0 g/kg.

Study #: 191-081; see related studies 191-080 and 191-082

Report Date: 12/05/77

Accession #: 19196

International Research and Development Corporation

SPONSOR: Procter and Gamble Company
TEST MATERIAL: T-7120
STUDY NUMBER: 191-081
SUBJECT: Acute Percutaneous Toxicity
Study in Rabbits.



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Approved by: D. Clifford Jessup, Ph.D.
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Date: December 5, 1977

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I. SYNOPSIS

The minimum lethal dose by dermal route of administration was found to be greater than 2000 mg/kg.

II. TEST MATERIAL

The test material was received from The Procter and Gamble Company, Cincinnati, Ohio on August 4, 1977. It was identified as "T-7120" and was received as a slightly yellow viscous liquid.

III. METHOD

Three male and 3 female New Zealand White rabbits (obtained from Kuiper's Rabbit Ranch, Gary, Indiana) were used for this study. The rabbits weighed from 2250 to 2715 grams at the beginning of the study. They were individually housed in metal metabolism cages in temperature and humidity controlled quarters. They were maintained in accordance with the recommendations contained in H.E.W. Publication No. 74-23 (N.I.H.) entitled "Guide for the Care and Use of Laboratory Animals". The rabbits were conditioned for 6 days prior to study initiation. Water and Purina Rabbit Chow were available ad libitum.

The hair was clipped from the back of each rabbit (20-30% of the body surface) with an electric clipper. The skin was abraded for one male and two females with a clipper head. The abrading was not sufficiently deep to cause bleeding. The test material was applied to the back, as received, at a dosage level of 2000 mg/kg. The application site was then covered with 8-ply gauze bandaging, rubber dam and several wrappings of 75 mm Elastoplast tape. A collar was also applied. Following the 24 hour application period, the collars and wrappings were removed and any remaining test material was wiped from the rabbits' backs with a wet disposable paper towel.

At 24 hours and daily thereafter for a total of 14 days, the rabbits were observed for pharmactoxic signs, dermal irritation (according to the scale found in the attached protocol) and mortality. Body weights were recorded initially and at 7 and 14 days of the observation period. All rabbits which died on study were subjected to gross necropsy examinations as were all survivors at the end of the 14-day observation period.

IV. RESULTS

A. MORTALITY:

One of the six rabbits died during the observation period. This death was attributed to pneumonia and was not considered to be compound related.

The minimum lethal dose by the dermal route of administration was found to be greater than 2000 mg/kg.

B. PHARMACOTOXIC SIGNS:

The following pharmacotoxic signs were observed during the 14-day observation period: See the following page.

T-7120:

2000 mg/kg

Males

	Normal	Nasal Discharge	Diarrhea	Anorexia	Cyanosis	Ataxia	Death
Days 1-2	3/3						
Day 3	2/3	1/3					
Day 4	2/3	1/3	1/3	1/3			
Day 5	2/3		1/3		1/3		
Day 6	2/3	1/3	1/3				
Days 7-9	2/3	1/3					
Day 10	1/3					2/3	
Day 11	2/3						1/3
Days 12-14	2/2						

Females

	Normal	Nasal Discharge
Days 1-2	3/3	
Days 3-4	2/3	1/3
Days 5-6	3/3	
Days 7-14	2/3	1/3

191-081

C. DERMAL IRRITATION SIGNS:

The following signs of dermal irritation were observed during the 14-day observation period: See the following pages.

T-20:

Dermal Irritation

2000 mg/kg

	Erythema				Edema				Atonia					Desquamation				
	None	Very Slight	Slight	Moderate	None	Very Slight	Slight	Moderate	None	Very Slight	Slight	Moderate	Marked	None	Very Slight	Slight	Moderate	Marked
Day 1	4/6	2/6			2/6	2/6	2/6		2/6	4/6				6/6				
Day 2		2/6	4/6			4/6	2/6			1/6	2/6	3/6		6/6				
Day 3			5/6	1/6		4/6	2/6				5/6	1/6		6/6				
Day 4			6/6			3/6	3/6			2/6	3/6	1/6		6/6				
Day 5			6/6			1/6	5/6				1/6	4/6	1/6	3/6	3/6			
Day 6			6/6			1/6	5/6					6/6		2/6	2/6	2/6		
Day 7			5/6	1/6			6/6				3/6	3/6			2/6	4/6		
Day 8		1/6	4/6	1/6			6/6			1/6	1/6	4/6			1/6	4/6	1/6	
Day 9		2/6	3/6	1/6		1/6	5/6				3/6	3/6			1/6	4/6	1/6	
Day 10		4/6	2/6			1/6	5/6			1/6	2/6	2/6	1/6			5/6	1/6	
Day 11*		4/5	1/5			1/5	4/5				3/5	2/5			3/5	2/5		
Day 12		3/5	2/5			2/5	2/5	1/5		1/5	3/5	1/5				2/5	3/5	
Day 13		4/5	1/5			3/5	1/5	1/5		2/5	2/5	1/5				2/5	3/5	
Day 14		4/5	1/5			3/5	2/5			2/5	2/5	1/5				4/5	1/5	

*1 of 6 rabbits dead.

10:

Dermal Irritation

2000 mg/kg (Cont.)

	Coriaceousness					Fissuring				Ex-foliation		Eschar	
	None	Very Slight	Slight	Moderate	Marked	None	Very Slight	Slight	Moderate	Yes	No	Yes	No
Day 1	2/6	4/6				6/6					6/6		6/6
Day 2			6/6			6/6					6/6		6/6
Day 3			6/6			5/6		1/6			6/6		6/6
Day 4			5/6	1/6		2/6	2/6	2/6			6/6		6/6
Day 5			1/6	5/6			3/6	3/6			6/6		6/6
Day 6			1/6	5/6			3/6	3/6			6/6		6/6
Day 7			2/6	4/6				6/6			6/6		6/6
Day 8			3/6	3/6				6/6			6/6		6/6
Day 9			4/6	2/6				6/6			6/6		6/6
Day 10			3/6	2/6	1/6			6/6			6/6		6/6
Day 11*			3/5	2/5				5/5			5/5		5/5
Day 12			4/5	1/5		4/5			1/5		5/5		5/5
Day 13			5/5			4/5		1/5			5/5		5/5
Day 14			5/5			3/5	1/5	1/5			5/5		5/5

*1 of 6 rabbits dead.

D. BODY WEIGHTS:

The following body weights were obtained during the 14-day study period:

<u>Dosage Level mg/kg</u>	<u>Individual Rabbit No.</u>	<u>Sex</u>	<u>Control Weight (grams)</u>	<u>7-Day Weight (grams)</u>	<u>14-Day Weight (grams)</u>
2000	29553	Male	2455	2165	Died
	29569	Male	2250	1873	1965
	29581	Male	2615	2477	2605
	29576	Female	2420	2456	2600
	29578	Female	2560	2545	2780
	29580	Female	2715	2614	2765

E. NECROPSY FINDINGS:

Necropsy findings in the rabbit which died during the observation period were as follows:

2000 mg/kg

ulceration of skin and underlying fascia; consolidation of both lungs and fibrous peritonitis of abdominal cavity.

Necropsy findings in rabbits which were sacrificed at the end of the observation period were as follows:

2000 mg/kg

no gross lesions	1/2 males	3/3 females
focal skin ulcers covered with scabs	1/2 males	
subcutaneous abscess	1/2 males	

Lab Project No. 191-081 Sheet 1 Date 8/5/77 Authorized by Dr. Jessup

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				Miss Morseth	<input type="checkbox"/>	Dr. Thorstenson	<input type="checkbox"/>

<u>Compound</u>	<u>Identification Number</u>	<u>IRDC No.</u>
T-7120		A-326

TITLE: ACUTE TOXICITY STUDIES IN RATS AND RABBITS

Conduct in accordance with the attached protocol.

Acute Percutaneous Toxicity - Rabbit

Date:

Issue #2

Purpose: To determine whether a substance is toxic when absorbed through the skin; to permit estimation of the degree of irritancy of a substance.

Animals: Rabbits, New Zealand albinos, three male and three female per test group, 2200-3000 grams.

Dosage Levels: Use 2 grams of test material per kilogram body weight.

Procedure: An area on the back of each animal approximately 25% of the total body surface is clipped with an Oster small animal clipper. The skin of three animals (two males and one female) is left intact, and the skin of the other three is abraded with a clipper head so as to penetrate the horny layer of the epidermis without causing bleeding.

Spread the test material evenly within the clipped area. Cover with a layer of 8-ply gauze, rubber dam and several wrappings of 75 mm Elastoplast tape. Dry or powdered materials are placed directly onto the gauze, which is spread over a layer of rubber dam and Elastoplast tape. Place the animal on his back over the test material and secure the Elastoplast tape around the trunk. Moistening of dry or powdered materials is optional. If this is done, record the amount and type of moisture added. Put the animals in Newmann (1) harnesses to prevent their removing the wrappings. After 24 hours, uncover the test sites, remove the test material with a wet disposable paper towel and evaluate the skin irritation following the attached scale. Record daily observations for the next two weeks. Necropsy and examine grossly all animals that succumb. On the 14th day, count, weigh, and necropsy the surviving animals.

(1) Newmann, E. A. (1963) Lab. Animal Care, 13, 207-210.

Report:

Individual animal observations including deaths, if any, degree of skin irritation as a function of time, body weights, signs of gross systemic effects and necropsy observations are reported.

Principal Investigator: M. J. Winrow

Date: 7/28/77

EVALUATION OF SKIN REACTIONS (CODE)

Erythema

- 0 - None
- 1 - Slight (barely perceptible)
- 2 - Moderate (well defined)
- 3 - Severe (beet red)

Edema

- 0 - None
- 1 - Slight (barely perceptible to well defined by definite raising)
- 2 - Moderate (raised approximately 1 mm)
- 3 - Severe (raised more than 1 mm)

Atonia (not including eschar area)

- 0 - Normal
- 1 - Slight (slight impairment of elasticity)
- 2 - Moderate (slow return to normal)
- 3 - Marked (no elasticity)

Desquamation (not including eschar area)

- 0 - None
- 1 - Slight (slight scaling)
- 2 - Moderate (scabs and flakes)
- 3 - Marked (pronounced flaking with denuded areas)

Fissuring

- 0 - None
- 1 - Slight (definite cracks in epidermis)
- 2 - Moderate (cracks in dermis)
- 3 - Marked (cracks with bleeding)

Eschar

- N - No
- Y - Yes

Exfoliation (sloughing of the eschar tissue)

- N - No
- Y - Yes

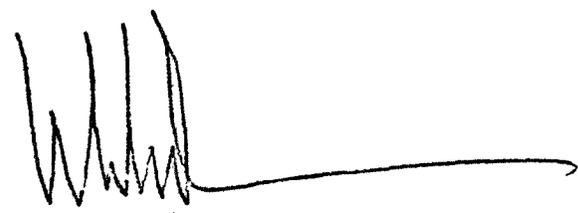
14304 Octaprox
placebo
pH 4.

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SPONSOR: The Procter and Gamble Company
TEST MATERIAL: T-7121
STUDY NUMBER: 191-082
SUBJECT: Acute Percutaneous Toxicity Study
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Final



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