

Report Title: Acute Oral Toxicity (LD50) Study in Albino Rats.

Test Type: Acute Oral Toxicity (LD50)

Conducting Laboratory and Location: International Research and Development Corporation

Test Substance(s): #T7120 - 2% Octopirox in shampoo at pH 4.5. Undiluted material used for dosing.

Species: Rat

of Animals: 20 male, 20 female

Test Conditions: Dosed orally with 8.26, 10.00, 12.10, and 14.70 g/kg.

Results: Combined: LD₅₀>11.92 g/kg. See related studies 191-080, 191-082

Study #: 191-081

Report Date: 11/9/77

Accession #: 19197

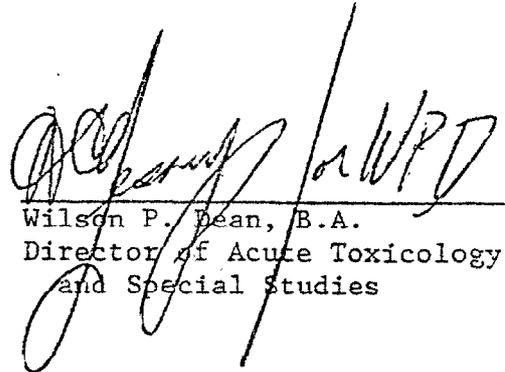
14304

#4

Final
2/9/77

International Research and Development Corporation

SPONSOR: Procter and Gamble Company
TEST MATERIAL: T-7120
STUDY NUMBER: 191-081 ¹³⁹⁶
SUBJECT: Acute Oral Toxicity (LD₅₀) Study
in Albino Rats.



Wilson P. Dean, B.A.
Director of Acute Toxicology
and Special Studies

Approved by: D. Clifford Jessup, Ph.D.
Associate Director of Research

RECEIVED BY
JAN 3 1978
H. A. DERNER

Date: November 9, 1977

International Research and Development Corporation

TABLE OF CONTENTS

	<u>Page</u>
I. Synopsis	1
II. Test Material	2
III. Method	3
IV. Results	4
A. Mortality and LD ₅₀ Value	4
B. Pharmacotoxic Signs	4
C. Body Weights	4
D. Necropsy Findings	5

I. SYNOPSIS

The median effective dose and 95% confidence limits of T-7120 was found to be 11923 (10651 - 13811) 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 gold colored viscous liquid.

III. METHOD

Twenty male and 20 female rats of the Charles River CD strain (obtained from Charles River Breeding Labs, Portage, Michigan), weighing 206 to 256 grams (pre-fasting body weight), were used for this study. The rats were housed by sex in groups of 5 rats per cage 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 rats were conditioned for 14 days prior to study initiation. Water and Purina Laboratory Chow were available ad libitum except for an overnight period of 19½ to 20 hours preceding oral administration during which food, but not water was withheld.

The test material was administered orally, as received, undiluted, at the following dosage levels to male and female rats: 8260, 10000, 12100 and 14700 mg/kg.

Five rats of each sex were used at each dosage level. Volumes administered were as follows:

8260 mg/kg level - 8.15 ml/kg.
10000 mg/kg level - 9.87 ml/kg.
12100 mg/kg level - 11.94 ml/kg.
14700 mg/kg level - 14.51 ml/kg.

Observations for pharmacotoxic signs and mortality were made at 15, 30 and 60 minutes and at 2, 4 and 24 hours and daily thereafter for a total of 14 days. Body weights were recorded prior to fasting, immediately preceding dosing and at 7 and 14 days. All rats which died on study were subjected to gross necropsy examination as were all survivors at the end of the 14-day observation period.

IV. RESULTS

A. MORTALITY AND LD₅₀ VALUE:

Dose - Mortality Data

Dosage Level mg/kg	Number of Deaths														Total Mortalities					
	Hrs.		Days												Male	Female	Total			
	0-4		1	2	3	4	5	6	7-14											
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F					
8260	1														0/5	1/5	1/10			
10000			1	1													1/5	1/5	2/10	
12100			3	1													3/5	1/5	4/10	
14700	2		4	2	1													4/5	5/5	9/10

Median Effective Dose and 95% Confidence Limits

Combined Male and Female: 11923 (10651 - 13811) mg/kg.

Statistical Reference

Computations were performed by Mr. R. Bruce, Statistician, Procter and Gamble Company, using the computer program BLISS 17, written by D. J. Finney, University of Edinburgh, Scotland.

B. PHARMACOTOXIC SIGNS:

See attached Appendix 2.

C. BODY WEIGHTS:

All surviving rats exhibited normal body weight gains during the 14-day observation period except for 1 male (#66233) at the 8260 mg/kg dosage level and 1 male (#66244) at the 10000 mg/kg dosage level which showed less than normal body weight gains and 1 male (#66254) at the 12100 mg/kg dosage level which showed a body weight loss. (See attached Appendix 1.)

D. NECROPSY FINDINGS:

The following necropsy findings were obtained during the study period:

Gross Necropsy Observations:

Gross Necropsy Observations	Dosage Level (mg/kg)							
	Number Showing Sign/Number Died							
	8260		10000		12100		14700	
	Male	Female	Male	Female	Male	Female	Male	Female
A. Rats which died during the study period.								
Congestion of lungs		1/1						
Consolidation, lungs					1/4			
Red-yellow fluid, stomach							1/4	3/5
Distended stomach		1/1						
Hemorrhage of stomach mucosa			1/1		2/4			
Focal adhesion of abdominal wall					1/4			
Stomach mucosa covered with material					1/4			
Hyperemia, stomach mucosa							1/4	2/5
Congestion, stomach mucosa		1/1						1/5
Congestion of non-glandular stomach mucosa								1/5
Hemorrhage, non-glandular stomach mucosa							1/4	
Red-yellow fluid in small intestine and or cecum			1/1				2/4	3/5
Small and colon contain loose fecal material							1/4	2/5
Urine stained abdomen			1/1		3/4	1/1	4/4	1/5

Gross Necropsy Observations:

Gross Necropsy Observations	Dosage Level (mg/kg)							
	Number Showing Sign/Number Necropsied							
	8260		10000		12100		14700	
	Male	Female	Male	Female	Male	Female	Male	Female
3. Rats which were necropsied at the end of the observation period.								
Foci, lung	1/5			3/5				
Consolidation of lung	1/5							
Thickening of forestomach mucosa	4/5	4/4	4/4	4/5	1/5	4/4	1/1	
Erosion of forestomach	1/5	3/4	2/4	1/5		4/4	1/1	
Hyperemia stomach mucosa				1/5				
Yellow-red fluid in stomach				1/5				
Focal adhesion to liver and abdominal wall						1/4		
Hydrometra, Uterus				1/5		1/4		

191-081

APPENDIX 1

IRDC # A-326

LD50 - RECORD OF INDIVIDUAL DOSE LEVEL

Dose level g/kg bw 8.260 P&G Code T-7120
Number of animals dosed Male 5 Female 5

All data are based on sample as received.

Sample Preparation: - g of sample was mixed with - (g) (ml) solvent - to make a dosing solution of - % (w/w) - (w/v).

Specific Gravity: 10 ml of sample weighed 10.13 g at 22 °C, S.G. = 1.013 g/ml.

Individual Animal Data

Table with columns for Date, Animal #, Sex, Prefasted Wt. g, Fasted Wt. g, Dose/Rat ml, Time of Death, 14 Day Wt. g, and Survival Day Wt (g). Rows include dates 8/31/77 and 9/1/77, and animal numbers 66233-66241.

Avg. prefasted weight 211.4 g
Avg. prefasted weight of survivors 211.8 g
Avg. 14 day weight of survivors 252.6 g
Total Dead: Male 0 Female 1
Animals Received: 8/12/77

8.260 g/kg = 8.15 ml/kg
1.013 g/ml

Worker's Signature Gene Harris
Corroborating Witness B. Rowing

Date 9/1/77
Date 9/1/77

191-081

APPENDIX I

IRDC # A 326

LD50 - RECORD OF INDIVIDUAL DOSE LEVEL

Dose level g/kg bw 10.000 P&G Code T-7120
Number of animals dosed Male 5 Female 5

All data are based on sample as received.

Sample Preparation: g of sample was mixed with (g) (ml) solvent to make a dosing solution of % (w/w) (w/v).

Specific Gravity: 10 ml of sample weighed 10.13 g at 22 °C, S.G. = 1.013 g/ml.

Individual Animal Data

Table with columns for Date, Animal #, Sex, Prefasted Wt. g, Fasted Wt. g, Dose/Rat ml, Time of Death, 14 Day Wt. g, and 7 Day Wt (g). Rows include data for animals 66243-66251 and 66249-66251.

Avg. prefasted weight 230.7 g
Avg. prefasted weight of survivors 277.3 g
Avg. 14 day weight of survivors 274.1 g
Total Dead: Male 1 Female 1
Animals Received: 3/15/77

10.000 g/kg = 9.87 ml/kg
1.013 g/ml

Worker's Signature Gene Harris
Corroborating Witness H. Harris

Date 9/1/77
Date 9/1/77

191-081

APPENDIX 1

IRDC = A-326

LD50 - RECORD OF INDIVIDUAL DOSE LEVEL

Dose level g/kg bw 12.100 P&G Code T-7120
Number of animals dosed Male 5 Female 5

All data are based on sample as received.

Sample Preparation: — g of sample was mixed with — (g) (ml) solvent — to make a dosing solution of — % — (w/w) — (w/v).

Specific Gravity: 10 ml of sample weighed 10.13 g at 22 °C, S.G. = 1.013 g/ml.

Individual Animal Data

STARTED 3:00		1	2	3	4	5	1	2	3	4	5
Date	Animal #	66253	66254	66255	66256	66257	66258	66259	66260	66261	66262
	Sex	♂	♂	♂	♂	♂	♀	♀	♀	♀	♀
8/31/77	Prefasted Wt. g	241	235	231	256	238	233	239	253	223	237
9/1/77	Fasted Wt. g	225	221	217	240	222	220	225	217	209	220
9/1/77	Dose/Rat ml	2.69	2.64	2.51	2.87	2.65	2.63	2.69	2.59	2.50	2.63
	Time of Death	X DAY 1		X DAY 1	X DAY 1			X DAY 1			
	14 Day Wt. g		150			339	271		262	265	265
			188			304	250		240	252	243

Avg. prefasted weight 236.6 g
Avg. prefasted weight of survivors 233.2 g
Avg. 14 day weight of survivors 258.7 g
Total Dead: Male 3 Female 1
Animals Received: 8/10/77

$\frac{12.100 \text{ g/kg}}{1.013 \text{ g/ml}} = 11.94 \text{ ml/kg}$

Worker's Signature Gene Harris
Corroborating Witness B. King

Date 9/1/77
Date 9/1/77

191-081

APPENDIX 1

IRDC # A-326

LD50 - RECORD OF INDIVIDUAL DOSE LEVEL

Dose level g/kg bw 14.700 P&G Code T-7120
Number of animals dosed Male 5 Female 5

All data are based on sample as received.

Sample Preparation: g of sample was mixed with (g) (ml) solvent to make a dosing solution of % (w/v) (w/v).

Specific Gravity: 10 ml of sample weighed 10.13 g at 22 °C, S.G. = 1.013 g/ml.

Individual Animal Data

Table with columns for Date, Animal #, Sex, Prefasted Wt. g, Fasted Wt. g, Dose/Rat ml, Time of Death, and 14 Day Wt. g. Includes handwritten entries for dates like 8/31/77 and 9/1/77, and animal numbers 66263-66271.

Avg. prefasted weight 239.1 g
Avg. prefasted weight of survivors 209 g
Avg. 14 day weight of survivors 242 g
Total Dead: Male 4 Female 5
Animals Received: 8/11/77

14.700 g/kg / 1.013 g/ml = 14.51 mg/kg

Worker's Signature Gene Harris
Corroborating Witness G Rowley

Date 9/1/77
Date 9/1/77

ACUTE ORAL TOXICITY OBSERVATION DATA

No. of Males/Females Affected - Blank Square = Normal

P&G Code T-7120

Dose Level g/kg 8.260

Dose Time 10:15 AM

Dose Date 9/1/77

SYMPTOM:	Time	Hours					Days													
		1/4	1/2	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Motor activity increase																				
Motor activity decrease		5(3)	3(2)	8(3)	9(4)	9(4)	3(1)	1(0)	1(0)	1(0)	1(0)	1(0)								
Respiratory rate increase			1																	
Respiratory rate decrease																				
Fine body tremors																				
Coarse body tremors																				
Blanching			1																	
Cyanosis																				
Gasping																				
Abdominal Gripping																				
Diarrhea		1(0)	1(0)	1(0)	1(0)	0														
Pilo Erection																				
Other:																				
ATAXIA			2(0)	6(2)	7(2)	2(1)			1(0)	1(0)	1(0)	1(0)	0							
URINATION				2(0)	4(2)	0	1(0)													
PROSTRATE																				
PTOSIS		1(0)	1(0)																	
limb tone decrease																				
SALIVATION					2(0)	0														
Worker's Initials		RL	BL	JM	JM	R	W	DP	DP	DP	JM	JP	RL	JM	RL	GH	W	JM	W	W

DEAD

1(1)

Special Notes: (Including Necropsy Observations)

ACUTE ORAL TOXICITY OBSERVATION DATA

No. of Males/Females Affected - Blank Square = Normal

P&G Code T-7120

Dose Level g/kg 10.000

Dose Time 10:25

Dose Date 9/1/77

SYMPTOMS: Time	Hours					Days														
	1/4	1/2	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Motor activity increase																				
Motor activity decrease	7(3)	5(8)	6(3)	10(5)	10(5)	4(2)	2(0)	2(0)	3(1)	3(1)	0									
Respiratory rate increase																				
Respiratory rate decrease																				
Fine body tremors																				
Coarse body tremors																				
Blanching																				
Cyanosis																				
Gasping																				
Abdominal Gripping																				
Diarrhea			1(0)	1(0)	1(0)															
Pilo Erection	2(2)					2(0)	1(0)	0												
Other:																				
URINATION	3(0)		4(2)	4(1)	4(1)	1(0)														
ATAXIA		2(0)	5(2)	6(2)	6(2)	1(0)				1(1)	0									
LIMB TONE DECREASE		2(1)																		
SALIVATION																				
Dead						2(1)														
Worker's Initials	BH	MH	JM	JM	R	Wm	DP	DP	DP	JM	JP	BG	JM	BG	GP	Wm	JM	Wm	Wm	Wm

Special Notes: (Including Necropsy Observations)

ACUTE ORAL TOXICITY OBSERVATION DATA

No. of Males/Females Affected - Blank Square = Normal

P&G Code T-7120 Dose Level g/kg 12.100 Dose Time 10:35 AM Dose Date 9/1/77

SYMPTOM: Time	Hours					Days														
	1/4	1/2	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Motor activity increase																				
Motor activity decrease	5(4)	7(3)	7(3)	9(4)	10(5)	4(2)	2(1)	2(1)	1(0)	2(0)	2(0)		1(0)			1(0)	1(0)	1(0)	1(0)	
Respiratory rate increase																				
Respiratory rate decrease																				
Fine body tremors																				
Coarse body tremors																				
Chancing																				
Opacities DYSPNEA																			1(0)	1(0)
Aspling																				
Abdominal Gripping																				
Diarrhea			2(0)	1(0)		2(1)	1(0)													
Uro Erection																				
Other:	2(1)	3(1)				2(1)	1(0)													
Salivation	3(2)	3(2)	5(2)	4(0)	4(0)															
ATAxia		3(0)	7(3)	5(0)	6(2)			1(0)	1(0)	1(0)	1(0)					1(0)	1(0)	1(0)	1(0)	
URINATION			3(2)	4(1)	5(1)	5(4)	2(2)													
LIMB TONE DECREASE																				
RESPIRATORY CONGESTION																				
DEAD						4(0)														
Worker's Initials	PK	PK	JM	JM	BL	nam	DP	DP	DP	JM	SP	AG	JM	PK	GH		JM	nam		

Special Notes: (Including Necropsy Observations)

ACUTE ORAL TOXICITY OBSERVATION DATA

No. of Males/Females Affected - Blank Square = Normal

P&G Code T-7120 Dose Level g/kg 14.700 Dose Time 10:50 AM Dose Date 9/1/77

SYMPTOMS: Time	Hours					Days														
	1/4	1/2	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Motor activity increase																				
Motor activity decrease	7(3)	7(3)	9(4)	10(5)	8(3)	2(1)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)						
Respiratory rate increase		1																		
Respiratory rate decrease																				
Fine body tremors																				
Coarse body tremors																				
Blanching		1																		
Cyanosis																				
Gasping																				
Abdominal Gripping	1(1)																			
Diarrhea		3(1)	4(2)	4(1)	5(2)	1(0)														
Pilo Erection	5(2)					1(1)														
Other: Salivation	2(0)	5(2)	7(3)	3(0)	3(0)															
ATAVIA	5(2)	6(2)	8(3)	7(3)	8(3)	2(1)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	1(0)	0						
URINATION			3(1)	6(3)	6(3)	1(1)														
limb Tense Dec.						1(1)														
PROSTRATION																				
DEAD					2(2)	6(2)	1(1)													
Worker's Initials	JK	JM	JM	JM	JK	JK	DP	DP	DP	JM	JP	JK	JM	JK	JK	JK	JM	JK	JK	JK

Special Notes: (Including Necropsy Observations)

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

191-079, 080,

Lab Project No. 081, 082 Sheet 2 Date 8/31/77 Authorized by [Signature] W. Dea

DISTRIBUTION

r. Wazeter	_____	Mr. Cain	<u>X</u>	Mrs. Finlay	_____	Dr. Cookson	_____
Dr. Goldenthal	_____	Mr. Vollmar	_____	Dr. Leong	_____	Miss Lohrberg	_____
Dr. Gail	_____	Miss Emmons	_____	Mr. Benson	_____	Mr. Urbancic	_____
Dr. Jessup	<u>X</u>	Mrs. Melville	_____	Mr. Rodwell	_____	Mr. Dean	<u>X</u>
Dr. Griffith	_____	Mr. Pangburn	_____	Mrs. Schwartz	_____	Mr. Thompson	<u>X</u>
				Miss Morseth	_____	Dr. Thorstenson	_____

<u>Compound</u>	<u>Identification Number</u>	<u>IRDC No.</u>
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

TITLE: ACUTE TOXICITY STUDIES IN RATS AND RABBITS

All test materials, for each of the 4 studies referenced above, will be dosed undiluted.

Procter & Gamble
Standard Procedure for Toxicological Evaluation

Acute Oral Toxicity - Rats

Date:

Issue #2

Purpose:

To measure the acute oral toxicity of a substance in order that it might be compared to more familiar materials.

Animals:

Rats, Charles River Caesarean-derived, 190-270 g, conditioned to the environment for a minimum of 7 days. Maintain the animals according to standards outlined in the Guide For the Care and Use of Laboratory Animals, DHEW No. (NIH-74-23), 1974.

Procedure:

Place 10 animals in each group, divided equally by sex. Determine prefasted and fasted body weights. Fast the animals for 18-20 hours before administering the test material.

Dissolve or suspend the test material in an appropriate vehicle at the required concentrations and record quantities mixed. Deliver the test material into the stomach of the animal from a syringe fitted with a size 8 catheter as a stomach tube or from a syringe fitted with a 13-gauge animal-feeding needle.

Choose 4 dosage levels, with the lowest being approximately the highest no-death dosage level observed in range-finding studies, or being estimated from prior results with similar compounds. Unless otherwise specified, choose higher dosage levels according to a geometric progression of 1.4 (i.e. the second dose equals the first dose $\times [1.4]^2$, the third dose equals the first dose $\times [1.4]^3$, etc.). Administer each dosage level to one group of 10 animals. Adjust the dose for each animal according to fasted weight to give the specified quantities of material per unit of body weight. Administer additional dose levels, as needed, so that the total number of dead is sufficient to calculate an LD₅₀ value. Immediately after dosing, return the animal to ad libitum feeding. Record all of the above information on the "LD₅₀ Record of Individual Dose Level" sheet (Appendix I).

Observations:

Observe the animals and their behavior at intervals of 15, 30, 60, 120 and 240 minutes after dosing and daily thereafter for 14 days. Use the "Toxicity Observation Data" sheet (Appendix 2) to record symptoms and number of animals involved. Unusual observations or symptoms not listed on the "Toxicity Observation Data" sheet should be noted where appropriate (under "Symptoms" or "Special Notes"). Necropsy all animals that die during the course of the study. At 14 days, weigh all surviving animals and record weights. Necropsy surviving animals and examine them grossly for abnormalities.

Acute Oral Toxicity - Rats (P&G Procedure) (cont'd)

Report:

Report all data recorded on the Record of Individual Dose Level and the Acute Oral Toxicity Observation Data sheets. Report the LD₅₀ and 95% confidence limits of the test material as calculated by the Probit Method*. File the final report within 3 weeks after completion of the experiment.

Principal Investigator: M. J. Winrow

Date 7/28/77

APPENDIX I
LD₅₀ - RECORD OF INDIVIDUAL DOSE LEVEL

Dose level g/kg bw _____ P&G Code _____
 Number of animals dosed Male _____ Female _____

All data are based on sample as received.

Sample Preparation: _____ g of sample was mixed with _____ (g) (ml)
 solvent _____ to make a dosing solution of
 _____ % _____ (w/w) _____ (w/v).

Specific Gravity: _____ ml of sample weighed _____ g at _____ °C,
 S.G. = _____ g/ml.

Individual Animal Data

Date	Animal #										
	Sex										
	Prefasted Wt. g										
	Fasted Wt. g										
	Dose/Rat ml										
	Time of Death										
	14 Day Wt. g										

Avg. prefasted weight _____ g
 Avg. prefasted weight of survivors _____ g
 Avg. 14 day weight of survivors _____ g
 Total Dead: Male _____ Female _____

Worker's Signature _____

Date _____

Corroborating Witness _____

Date _____

