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6 MONTHS CHRONIC PERCUTANEOUS TOXICITY OF PIROCTONE OLAMINE IN RATS

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6 Months Chronic Percutaneous Toxicity of Piroctone Olamine (PO) in Rats

Summary

1. 6 months treatment groups

a) General symptoms and body weight changes

Scratches were found at the application sites of the treatment groups including the propylene glycol (PG) treated group. However, other toxic signs such as reddening and edema were not found in any other part of the body. In the PG treated females, the scratches disappeared by the second month of application.

However, in the PG treated males and 0.5 % PO treated males and females, a few examples of scratches were still seen at the termination of the experiment.

At the 1.0 % PO level, almost all the males and females kept scratches until the end of the experiment. There were no other abnormalities in general symptoms, and no deaths occurred. Suppression in body weight gain was seen in the 1.0 % PO treated males and PG treated females.

b) Histopathology

Very slight to slight thickening of the epidermis was seen in the PG treated males and PO treated males and females. The only other toxic sign was the non-idiosyncratic changes sporadically observed in the liver and kidney of the control and all the treatment groups including the PG treated group.

c) Others

No changes considered to be related to the compound application were observed in the eyeground, urinalysis, hematology, biochemistry, wet organ weights, necropsy and in the bone marrow.

2. Recovery groups

By three weeks after the end of application, both sexes of the 1.0 % PO group recovered from the scratches which were still seen when the 6-months application ended. Furthermore, histopathological studies revealed no changes considered to be related to the compound.

Conclusion

1. Changes

Scratches were found at the application sites of all the treatment groups including the PG treated group. However, evidence of irritancy such as reddening and edema were not observed in any other site. In the PG treated females, the scratches disappeared by the second month of application.

At the termination of application, however, a few examples of scratches were seen in the PG treated males and 0.5 % PO treated males and females, and most of the 1.0 % PO treated animals (both sexes) still staged the scratches. These scratches were supposed to have resulted from itching and animals' uncomfortableness with the foreign compounds. During the recovery period, the 1.0 % PO treated animals showed a quick recovery from the scratches, and no other abnormalities were staged in any of the groups.

Though suppressed body weight gain was seen in the PG treated females and the 1.0 % PO treated males, this could have been induced by the secondary effects of the scratching; physiological phenomena such as sleeping could have been affected by the scratching, which could have had an effect on animals' body weights. Changes in body weight gain observed at the termination of application were all within physiological variances and thus not worthy of consideration.

Slight thickening of the epidermis found at the histopathological investigations could be dismissed, because there were no other changes considered to be related to the compound. The recovery experiment further confirmed the safety of the compound by disclosing no histopathological changes of the skin.

2. Safety

PG and solutions of PO (0.5 and 1.0 %) in PG were applied to the skin of rats for 6 months consecutively. The only toxic sign observed was the slight thickening of the epidermis, and there were no general toxicities. And the thickening of the epidermis was no longer seen at the end of the recovery experiment.

From the above-mentioned result, we concluded that the use of PO (up to about 1 %) in a shampoo or a rinse would be no problem when the compound was put to practical use.

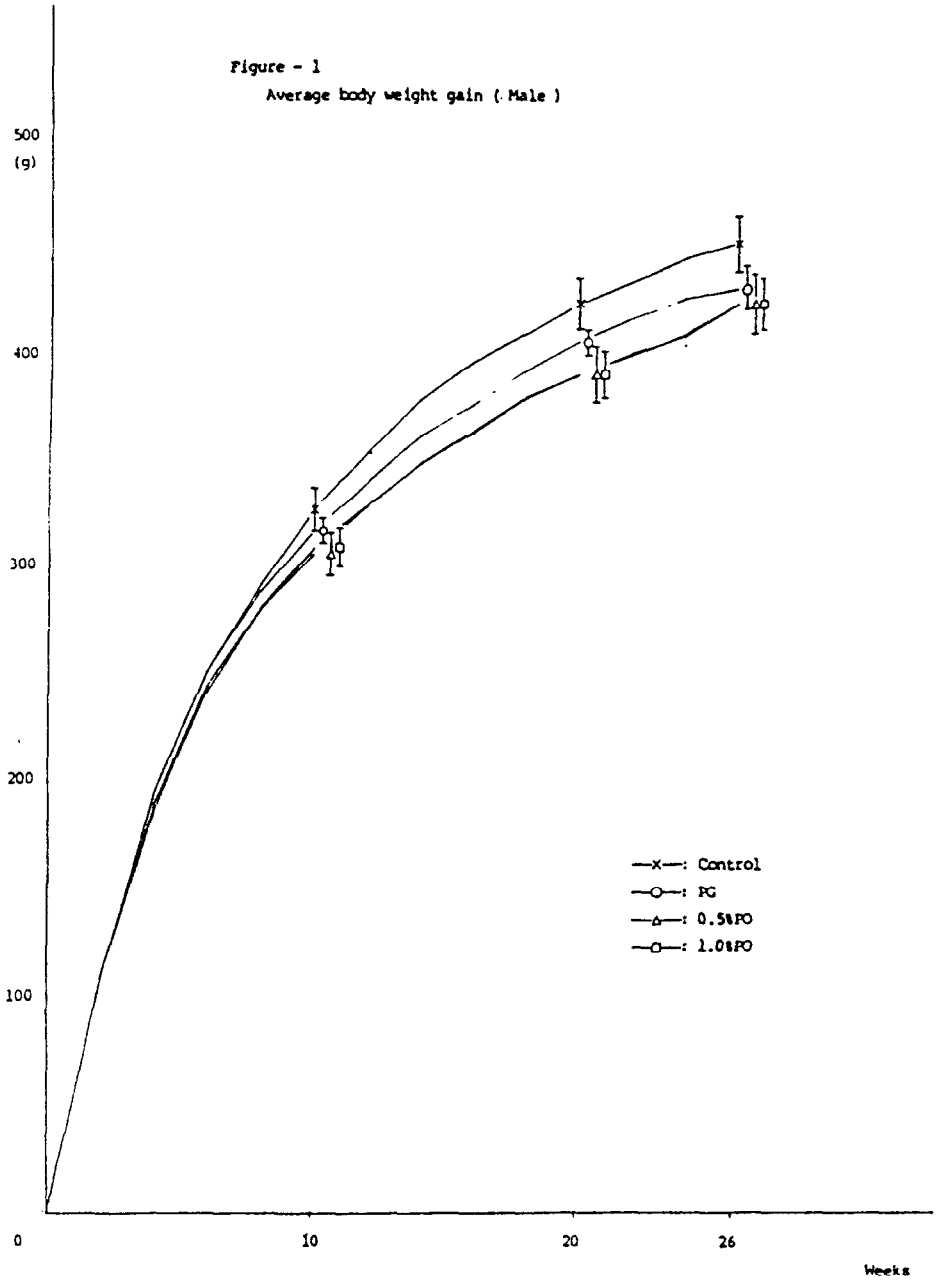


Figure - 1
Average body weight gain (Male)
500
(g)
400
300
200
100
0
10
20
26
Weeks
—x—: Control
—o—: PG
—Δ—: 0.5%PO
—□—: 1.0%PO

Figure - 2

Average body weight gain (Female)

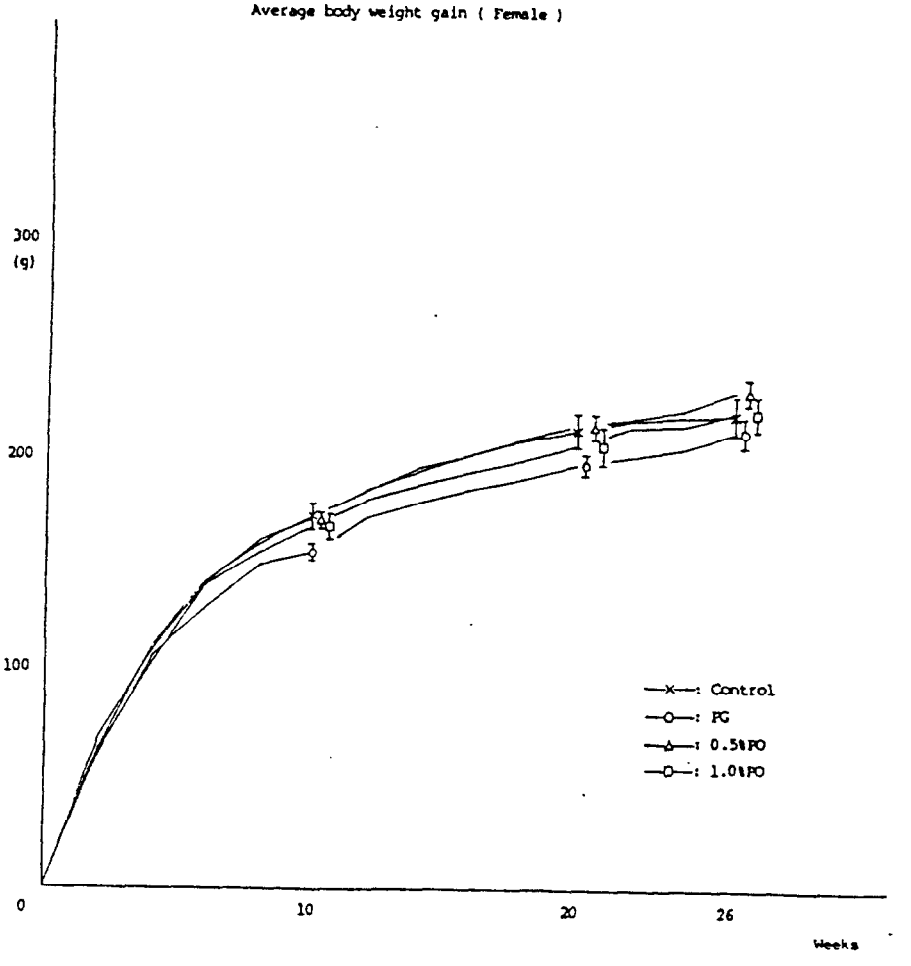


Table - 1 - 1

Average body weight of male rats

Sample	Number of animals	Weeks													
		Start	1	2	3	4	5	6	7	8	9	10	11	12	13
Control	16	147.7 ± 3.5	202.4 ± 5.7	257.9 ±12.5	303.3 ±21.1	341.5 ±27.9	373.6 ±31.3	399.0 ±36.0	419.6 ±38.2	439.1 ±37.2	459.4 ±39.8	473.8 ±41.6	488.1 ±42.6	499.8 ±43.8	514.4 ±42.8
PG	16	147.4 ± 5.8	203.1 ± 9.4	258.4 ±17.5	305.2 ±17.1	342.1 ±19.5	373.7 ±21.4	397.6 ±23.4	417.5 ±23.5	435.8 ±22.5	449.2 ±24.7	463.9 ±25.5	474.7 ±25.6	485.8 ±27.1	497.4 ±26.7
0.5%PO	16	147.3 ± 5.7	202.2 ± 9.6	255.5 ±14.9	300.1 ±22.4	333.8 ±24.4	366.9 ±26.7	388.4 ±30.6	407.6 ±33.5	426.0 ±37.1	440.9 ±38.5	452.7 ±42.7	463.1 ±43.5	474.2 ±45.9	487.0 ±48.9
1.0%PO	16	147.3 ± 6.0	202.3 ± 8.0	257.4 ± 9.8	302.6 ±10.8	336.6 ±16.0	368.4 ±22.0	391.4 ±24.4	410.1 ±26.9	427.1 ±29.2	441.9 ±32.5	455.5 ±35.0	463.8 ±37.0	475.2 ±38.4	487.9 ±40.3

Weeks												
14	15	16	17	18	19	20	21	22	23	24	25	26
525.1 ±41.0	533.1 ±41.1	541.8 ±42.6	549.1 ±43.0	554.3 ±45.5	560.1 ±46.4	569.0 ±47.4	575.5 ±48.0	580.8 ±49.4	584.4 ±50.1	590.1 ±50.6	595.2 ±50.7	596.2 ±52.3
507.3 ±27.6	512.3 ±28.7	521.7 ±29.6	530.5 ±28.7	537.5 ±29.3	542.4 ±28.7	550.4 ±28.7	556.8 ±31.6	561.7 ±32.9	563.7 ±34.4	570.1 ±34.1	573.2 ±35.8	575.4 ±37.0
495.4 ±50.4	501.3 ±50.8	509.0 ±52.8	516.6 ±53.8	525.0 ±52.0	528.7 ±54.6	534.9 ±55.0	539.8 ±54.9	545.3 ±56.8	547.0 ±57.9	552.4 ±57.8	556.7 ±56.9	558.4 ±57.8
494.4* ±40.1	500.9* ±42.0	508.3* ±42.8	515.3* ±43.6	524.5 ±45.5	529.2 ±44.9	535.4* ±44.9	540.4* ±45.6	544.1* ±45.4	546.1* ±46.0	553.0* ±45.7	557.4* ±47.4	557.9* ±47.9

(g , Mean ± S.D.)

* : Significantly different from control ($p<0.05$)

** : Significantly different from control ($p<0.01$)

Table - 1 - 2

Average body weight of female rats

Sample	Number of animals	Weeks													
		Start	1	2	3	4	5	6	7	8	9	10	11	12	13
Control	16	106.8 ± 4.3	141.3 ± 7.1	169.9 ±13.0	197.3 ±13.1	217.6 ±15.9	237.1 ±19.9	249.1 ±19.0	256.4 ±19.1	266.4 ±21.8	272.8 ±24.5	280.2 ±23.7	284.9 ±22.9	290.4 ±24.5	296.4 ±27.4
PG	16	107.3 ± 5.1	138.8 ± 6.9	167.6 ± 9.2	189.8 ±11.0	203.8* ±12.7	222.8* ±11.7	235.8* ±13.5	243.4* ±16.2	256.8 ±14.9	258.3 ±14.4	263.6* ±14.7	268.3* ±15.3	279.4 ±17.2	280.9 ±19.2
0.5%PO	16	106.6 ± 5.1	142.2 ± 7.4	174.1 ±10.9	198.2 ±13.2	215.6 ±17.8	234.6 ±17.1	247.4 ±17.6	258.8 ±21.7	268.9 ±18.4	271.9 ±19.8	277.2 ±19.6	282.6 ±20.2	291.8 ±19.2	295.4 ±20.9
1.0%PO	16	107.1 ± 4.3	141.0 ± 7.5	170.9 ±10.5	197.1 ±14.6	210.1 ±15.1	229.9 ±19.0	244.6 ±20.7	250.6 ±21.0	263.1 ±25.9	268.6 ±26.2	275.2 ±25.8	278.9 ±26.5	286.9 ±27.9	289.0 ±28.1

Sample	Weeks												
	14	15	16	17	18	19	20	21	22	23	24	25	26
Control	301.3 ±25.4	304.0 ±27.4	307.8 ±27.4	312.1 ±28.2	315.0 ±29.7	316.4 ±30.6	320.0 ±32.1	324.7 ±33.4	325.1 ±32.2	325.5 ±32.2	326.4 ±31.5	330.7 ±34.7	337.6 ±35.8
PG	286.2 ±19.0	288.4 ±20.4	292.3 ±18.9	294.6 ±20.7	297.4 ±20.7	300.3 ±20.2	303.9 ±19.7	304.9 ±20.8	307.4 ±23.1	310.2 ±24.3	312.6 ±25.7	315.7 ±25.8	320.7 ±26.6
0.5%PO	299.7 ±21.8	303.5 ±21.4	307.3 ±23.6	311.4 ±23.8	315.8 ±25.3	316.1 ±24.3	321.4 ±26.0	323.3 ±28.2	325.9 ±27.1	326.8 ±28.7	329.8 ±27.4	333.5 ±28.0	338.4 ±28.4
1.0%PO	293.9 ±27.3	297.4 ±26.1	300.0 ±27.4	302.8 ±29.7	306.1 ±31.8	308.6 ±33.1	312.6 ±35.8	316.3 ±36.2	321.6 ±36.1	320.6 ±36.5	323.1 ±35.3	324.3 ±34.9	329.3 ±35.0

(g , Mean ± S.D.)

* : Significantly different from control ($p<0.05$)

** : Significantly different from control ($p<0.01$)

Table - 2 - 1

Average body weight gain of male rats

Sample	Number of animals	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
Control	16	54.7 ± 5.9	110.3 ±12.7	155.6 ±21.6	193.8 ±28.2	225.9 ±31.7	251.3 ±36.2	271.9 ±38.4	291.4 ±37.6	311.7 ±40.0	326.1 ±41.7	340.4 ±42.7	352.1 ±43.9	366.8 ±43.2
FG	16	55.6 ± 4.5	110.9 ±13.7	157.8 ±13.2	194.6 ±15.7	226.3 ±17.3	250.2 ±19.0	270.1 ±19.7	288.4 ±18.9	301.8 ±21.3	316.4 ±22.4	327.3 ±22.8	338.3 ±24.1	350.0 ±23.8
0.5%P.O.	16	54.9 ± 6.2	108.3 ±12.1	152.9 ±19.9	186.6 ±22.3	219.7 ±24.9	241.2 ±29.2	260.4 ±31.9	278.8 ±35.7	293.7 ±36.7	305.4 ±40.9	315.8 ±41.9	326.9 ±44.2	339.8 ±47.1
1.0%P.O.	16	55.0 ± 4.1	110.2 ± 7.1	155.4 ± 9.9	189.3 ±15.2	221.2 ±21.3	244.2 ±23.9	262.9 ±26.7	279.9 ±28.9	294.7 ±31.9	308.3 ±34.7	316.6 ±36.6	327.9 ±38.2	340.6 ±39.9

Sample	Weeks 14	15	16	17	18	19	20	21	22	23	24	25	26
Control	377.4 ±41.5	385.4 ±41.5	394.1 ±42.7	401.4 ±43.0	406.6 ±45.6	412.4 ±46.3	421.3 ±47.4	427.8 ±47.9	433.1 ±49.1	436.8 ±49.8	442.4 ±50.3	447.5 ±50.3	448.5 ±52.0
FG	359.8 ±24.6	364.9 ±25.8	374.3 ±26.7	383.1 ±25.6	390.1 ±26.1	395.0 ±25.7	402.9 ±25.7	409.3 ±28.6	414.3 ±29.7	416.3 ±31.4	422.7 ±31.3	425.8 ±33.4	428.0 ±34.6
0.5%P.O.	348.2 ±48.6	354.0 ±49.1	361.8 ±51.0	369.4 ±52.1	377.8 ±50.3	381.4 ±52.8	387.7 ±53.2	392.6 ±52.9	398.0 ±54.9	399.8 ±56.1	405.1 ±56.0	409.4 ±55.3	411.2 ±56.3
1.0%P.O.	347.1* ±39.8	353.6* ±42.0	361.1* ±42.9	368.1* ±43.5	377.3 ±45.7	381.9 ±45.1	388.2 ±45.0	393.2* ±46.0	396.8* ±45.7	398.9* ±46.4	405.8* ±46.0	410.2* ±47.6	410.6* ±48.3

(g , Mean ± S.D.)

* : Significantly different from control ($p<0.05$)

** : Significantly different from control ($p<0.01$)

Table - 2 - 2

Average body weight gain of female rats

Sample	Number of animals	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
Control	16	14.5 ± 5.1	63.2 ±11.0	90.5 ±11.4	110.9 ±14.6	130.3 ±19.2	142.4 ±18.2	149.7 ±18.5	159.6 ±21.2	166.0 ±24.0	173.4 ±23.3	178.2 ±23.1	183.7 ±24.6	189.7 ±24.8
PG	16	31.4 ± 6.4	60.3 ± 8.8	82.4* ±10.1	96.4** ±12.6	115.5* ±11.8	128.5* ±13.1	136.1* ±15.8	149.5 ±14.2	150.9* ±14.6	156.3* ±14.1	160.9* ±15.0	172.1 ±16.8	173.6* ±18.5
0.5%P.O.	16	35.6 ± 4.6	67.5 ± 6.7	91.6 ±10.1	108.9 ±14.0	127.9 ±13.6	140.8 ±14.0	152.2 ±17.7	162.3 ±15.0	165.3 ±16.4	170.6 ±15.8	175.9 ±16.5	185.2 ±15.7	188.8 ±17.5
1.0%P.O.	16	33.9 ± 4.9	63.8 ± 8.3	90.0 ±12.3	101.0 ±13.3	122.9 ±16.8	137.6 ±18.4	143.6 ±19.0	156.1 ±23.9	161.6 ±24.0	168.1 ±23.5	171.8 ±24.4	179.9 ±26.1	181.9 ±26.0

Sample	Weeks 14	15	16	17	18	19	20	21	22	23	24	25	26
Control	194.5 ±25.5	197.3 ±27.1	201.1 ±27.1	205.4 ±28.0	208.3 ±29.4	209.6 ±30.5	213.3 ±31.9	217.9 ±33.4	218.4 ±32.0	218.8 ±32.1	219.7 ±31.6	223.9 ±34.5	230.8 ±35.3
PG	178.9 ±18.4	181.1 ±19.7	185.0 ±18.3	187.3* ±20.0	190.1 ±20.0	192.9 ±19.5	196.6 ±18.7	197.6* ±19.8	200.1 ±22.2	202.9 ±23.3	205.3 ±24.8	208.4 ±25.2	213.4 ±25.9
0.5%P.O.	193.1 ±18.2	196.9 ±18.0	200.6 ±21.1	204.8 ±21.4	209.2 ±22.5	209.5 ±21.3	214.8 ±22.9	216.6 ±25.2	219.3 ±24.2	220.1 ±25.8	223.1 ±24.2	226.9 ±25.1	231.8 ±25.4
1.0%P.O.	186.8 ±25.3	190.3 ±24.4	192.9 ±25.7	195.8 ±27.9	199.0 ±29.9	201.5 ±31.1	205.5 ±33.8	209.2 ±34.2	214.5 ±34.2	213.6 ±34.5	216.0 ±33.4	217.2 ±32.9	222.3 ±33.0

(g , Mean ± S.D.)

* : Significantly different from control ($p<0.05$)

** : Significantly different from control ($p<0.01$)

Table - 3
Food efficacy of rats

Sex	Sample	Number of animals	5 weeks			13 weeks			26 weeks		
			Body weight gain (g)	Total food consumption (g)	Efficacy (%)	Body weight gain (g)	Total food consumption (g)	Efficacy (%)	Body weight gain (g)	Total food consumption (g)	Efficacy (%)
Male	Control	16	225.9	963.0	23.5	366.8	2502.4	14.7	448.5	4948.4	9.1
	PG	16	226.3	961.6	23.5	350.0	2480.1	14.1	428.0	4837.8	8.8
	0.5% PO	16	219.7	941.1	23.3	339.8	2421.7	14.0	411.2	4682.1	8.8
	1.0% PO	16	221.2	954.6	23.2	340.6	2466.9	13.8	410.6	4795.6	8.6
Female	Control	16	130.3	726.1	17.9	189.7	1929.8	9.8	230.8	3828.8	6.0
	PG	16	115.5	691.3	16.7	173.6	1817.8	9.6	213.4	3650.1	5.8
	0.5%PO	16	127.9	720.7	17.8	188.8	1892.4	10.0	231.8	3749.8	6.2
	1.0%PO	16	122.9	798.4	17.3	181.9	1869.9	9.7	222.3	3745.9	5.9

Table - 4

Urinary findings of rats

Sex	Sample	Number of animals	pH					Protein					Glucose	Ketone body		Occult blood		Bilirubin	Urobilinogen	
			6.0	6.5	7.0	7.5	8.0	T	+	++	+++	++++	-	-	+	-	+	-	±	+
Male	Control	12	2	4	3	2	1	1	0	2	7	2	12	11	1	12	0	12	12	0
	PG	12	5	3	3	1	0	0	1	2	6	3	12	10	2	11	1	12	12	0
	0.5%PO	12	4	3	3	2	0	1	2	5	4	0	12	12	0	12	0	12	12	0
	1.0%PO	12	11	0	1	0	0	0	1	7	3	1	12	8	4	11	1	12	12	0
Female	Control	12	7	1	4	0	0	0	7	3	2	0	12	8	4	12	0	12	12	0
	PG	12	8	2	0	2	0	2	4	4	2	0	12	9	3	12	0	12	12	0
	0.5%PO	12	8	4	0	0	0	3	4	1	3	1	12	8	4	12	0	12	10	2
	1.0%PO	12	6	5	1	0	0	2	5	0	3	2	12	9	3	12	0	12	12	0

T : Trace

Table - 5

Urinary sediment of rats

Sex	Sample	Number of animals	RBC				WBC		Epithelial cells		Casts		Crystals				Others
			-	±	+	*	-	±	-	±	-	±	-	±	+	*	
Male	Control	5	4	1	0	0	5	0	0	5	5	0	1	3	1	0	Sp(2)
	PG	5	4	0	1	0	4	1	2	3	5		1	3	0	1	
	0.5%PO	5	5	0	0	0	5	0	1	4	5	0	4	0	1	0	
	1.0%PO	5	4	1	0	0	5	0	1	4	5	0	2	3	0	0	Sp(1)
Female	Control	5	5	0	0	0	5	0	0	5	5	0	5	0	0	0	
	PG	5	4	1	0	0	4	1	1	4	3	Hy(2)	2	3	0	0	
	0.5%PO	5	4	1	0	0	5	0	2	3	4	Hy(1)	5	0	0	0	
	1.0%PO	5	4	1	0	0	5	0	0	5	5	0	4	1	0	0	

RBC , Epithelial cells , Crystals

- : 0 / 100 fields
± : 1-99 / 100 fields
+ : 100-999 / 100 fields
* : 1000-4999 / 100 fields

WBC , Casts

- : 0 / 100 fields
± : 1-9 / 100 fields

Hy : Hyaline

Sp : Spermatozoa

Table - 6

Average hematological findings of rats

Sex	Sample	Number of animals	RBC ($10^4/mm^3$)	Hb (g/dl)	Ht (%)	MCV (μ^3)	MCHC (%)	Platelet ($10^4/mm^3$)	WBC ($10^2/mm^3$)	Differential blood count (%)					
										Baso	Eosino	N-st	N-seg	Lymph	Mono
male	Control	12	690.0 ±34.4	14.68 ±0.63	43.7 ±2.1	63.3 ±2.5	33.7 ±1.5	75.8 ±11.3	51.8 ±21.2	0.0 ±0.0	1.6 ±1.1	0.8 ±1.1	11.9 ±3.9	82.2 ±6.4	3.6 ±2.8
	PG	12	688.2 ±47.0	14.32 ±0.97	42.3 ±2.8	61.6 ±3.3	33.8 ±1.0	74.6 ±15.9	40.3 ±19.5	0.0 ±0.0	0.8 ±0.7	1.1 ±1.0	13.4 ±4.5	79.9 ±7.9	4.8 ±4.7
	0.5%PO	12	696.6 ±43.6	14.66 ±0.78	43.4 ±2.2	62.5 ±3.5	33.8 ±1.6	73.7 ±10.8	48.4 ±23.5	0.0 ±0.0	0.9 ±1.2	1.5 ±1.4	11.5 ±6.7	82.4 ±8.8	3.7 ±2.1
	1.0%PO	12	667.7 ±47.9	14.53 ±1.57	42.1 ±3.2	63.1 ±2.5	34.5 ±2.5	67.3 ±16.0	39.8 ±10.2	0.0 ±0.0	0.8 ±0.7	1.2 ±1.1	10.8 ±2.2	82.8 ±2.6	4.4 ±1.9
Female	Control	12	690.3 ±50.0	14.89 ±0.75	43.6 ±2.2	63.3 ±2.8	34.2 ±1.0	70.0 ±14.5	44.3 ±11.8	0.0 ±0.0	0.8 ±0.8	1.8 ±1.7	10.8 ±3.0	78.8 ±7.1	7.9 ±4.2
	PG	12	691.8 ±41.0	15.14 ±0.79	44.3 ±2.1	64.1 ±4.3	34.2 ±0.9	68.8 ± 8.5	46.0 ±10.4	0.0 ±0.0	1.4 ±1.1	0.9 ±0.7	10.6 ±4.1	83.3 ±4.2	3.8** ±1.7
	0.5%PO	12	684.2 ±33.9	14.84 ±0.71	43.3 ±2.1	63.3 ±2.6	34.3 ±1.3	71.3 ± 7.6	39.8 ± 7.8	0.0 ±0.0	1.4 ±1.5	1.4 ±1.0	15.1 ±8.2	78.5 ±9.4	3.6** ±1.3
	1.0%PO	12	691.6 ±44.7	14.73 ±0.67	42.5 ±2.3	61.2 ±3.7	34.6 ±1.0	73.2 ± 9.0	42.7 ± 7.8	0.0 ±0.0	1.3 ±1.2	1.8 ±1.9	13.2 ±4.4	79.8 ±6.3	3.9** ±2.5

(Mean ± S.D.)

* : Significantly different from control ($p<0.05$)

** : Significantly different from control ($p<0.01$)

Table - 7

Average biochemical findings of rats

Sex	Sample	Number of animals	s-GOT (mu/ml)	s-GPT (mu/ml)	Al-phos. (mu/ml)	Dilirubin (mg/dl)	T. cholesterol (mg/dl)	Glucose (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)	T. protein (g/dl)	Albumin (g/dl)	A/G (ratio)	Na^+ (mEq/l)	K^+ (mEq/l)	Cl^- (mEq/l)	P (mg/dl)
Male	Control	12	166.9 ±25.9	41.8 ±17.2	141.4 ±30.6	0.27 ±0.09	71.3 ±21.2	271.0 ±24.6	20.0 ±2.3	0.66 ±0.07	5.78 ±0.39	3.23 ±0.22	1.27 ±0.13	149.8 ± 5.2	4.78 ±0.24	105.0 ± 2.6	5.44 ±0.30
	FG	12	104.1** ±17.2	29.9 ±10.3	135.7 ±32.3	0.23 ±0.05	56.9 ±17.0	256.8 ±24.1	16.3** ±1.9	0.65 ±0.09	5.45 ±0.49	3.05 ±0.35	1.27 ±0.11	152.4 ± 6.8	4.59 ±0.22	101.5 ± 7.4	5.41 ±0.45
	0.5%PO	12	117.1** ±21.3	29.4* ±11.0	108.1** ±21.0	0.24 ±0.07	57.4 ±11.2	263.7 ±28.6	16.0** ±1.8	0.64 ±0.10	5.77 ±0.30	3.21 ±0.19	1.26 ±0.13	148.6 ± 6.4	4.58 ±0.26	105.3 ± 3.3	5.49 ±0.39
	1.0%PO	12	103.8** ±24.8	29.0* ±11.1	109.9** ±16.5	0.27 ±0.07	52.9* ±13.4	241.4** ±13.7	16.3** ±1.0	0.59 ±0.09	5.31** ±0.27	3.03* ±0.17	1.33 ±0.07	153.9 ± 5.5	4.50* ±0.32	101.2* ± 4.6	5.63 ±0.45
Female	Control	12	150.2 ±29.1	50.7 ±30.2	79.1 ±14.9	0.22 ±0.07	74.3 ±12.5	274.5 ±22.3	21.9 ±2.7	0.71 ±0.09	6.65 ±0.39	3.96 ±0.29	1.49 ±0.25	158.9 ± 6.9	4.57 ±0.35	106.8 ± 2.8	5.38 ±0.37
	FG	12	199.2 ±117.2	78.7 ±56.0	53.2** ±13.0	0.26 ±0.05	73.5 ±13.7	259.7 ±43.4	19.8 ±2.8	0.70 ±0.06	6.80 ±0.47	3.98 ±0.29	1.42 ±0.09	156.2 ± 6.7	4.60 ±0.33	108.4 ± 3.1	5.70 ±0.58
	0.5%PO	12	226.2 ±175.2	72.3 ±42.7	61.0* ±18.8	0.26 ±0.07	77.6 ±11.3	245.0** ±25.9	19.8* ±1.6	0.69 ±0.09	6.83 ±0.33	4.02 ±0.23	1.44 ±0.19	156.6 ± 6.7	4.68 ±0.31	107.2 ± 2.9	5.78 ±0.60
	1.0%PO	12	136.8 ±44.7	41.8 ±20.5	50.5** ±13.1	0.26 ±0.05	85.2 ±34.5	231.8** ±30.3	21.8 ±7.9	0.79 ±0.26	6.73 ±0.48	3.85 ±0.34	1.35 ±0.16	154.8 ± 5.4	4.94* ±0.48	107.3 ± 2.7	6.02** ±0.47

(Mean ± S.D.)

* : Significantly different from control($p<0.05$)

** : Significantly different from control($p<0.01$)

Table - 8

Average absolute wet organ weight of rats

Sex	Sample	Number of animals	Final B.W.	Liver	Kidney R	Kidney L	Spleen	Adrenal gland R	Adrenal gland L	Heart	Lung	Brain	Pituitary	Thymus	Testis or Ovary R	Testis or Ovary L
Male	Control	12	597.2 ±51.6	19.124 ±2.715	1.825 ±0.202	1.813 ±0.196	0.887 ±0.095	27.3 ±4.7	29.1 ±3.4	1.623 ±0.155	1.564 ±0.099	2.022 ±0.110	12.2 ±1.7	0.228 ±0.064	1.679 ±0.070	1.683 ±0.083
	PG	12	575.3 ±37.5	17.993 ±1.075	1.831 ±0.151	1.730 ±0.136	0.865 ±0.100	26.8 ±4.6	28.9 ±5.2	1.530 ±0.103	1.533 ±0.171	2.021 ±0.076	11.9 ±1.4	0.195 ±0.032	1.523 ±0.436	1.665 ±0.114
	0.5%PO	12	577.3 ±44.9	17.239 ±2.219	1.735 ±0.114	1.707 ±0.124	0.800 ±0.183	28.4 ±6.4	29.3 ±4.1	1.548 ±0.148	1.501 ±0.141	2.033 ±0.054	10.5 ±2.5	0.192 ±0.047	1.698 ±0.143	1.692 ±0.118
	1.0%PO	12	566.8 ±48.0	16.445* ±1.925	1.725 ±0.160	1.676 ±0.119	0.948 ±0.454	27.1 ±3.3	27.4 ±3.0	1.505* ±0.105	1.533 ±0.114	2.024 ±0.058	10.8 ±2.2	0.187 ±0.047	1.643 ±0.148	1.631 ±0.142
Female	Control	12	340.2 ±36.1	11.432 ±1.776	1.113 ±0.168	1.068 ±0.146	0.577 ±0.090	37.7 ±6.6	37.8 ±7.2	1.068 ±0.094	1.142 ±0.062	1.919 ±0.117	17.8 ±6.1	0.159 ±0.038	36.7 ±11.6	33.5 ±13.5
	PG	12	317.8 ±21.6	10.449 ±0.900	1.041 ±0.091	1.020 ±0.087	0.551 ±0.005	34.7 ±4.8	38.2 ±8.4	1.048 ±0.075	1.127 ±0.086	1.863 ±0.043	20.3 ±5.6	0.182 ±0.051	34.5 ±11.2	32.6 ±10.0
	0.5%PO	12	336.0 ±30.8	10.933 ±0.907	1.137 ±0.109	1.091 ±0.110	0.570 ±0.099	33.2 ±6.8	38.3 ±4.7	1.070 ±0.070	1.137 ±0.082	1.869 ±0.084	21.9 ±5.9	0.191 ±0.047	29.5 ± 7.9	28.6 ±11.4
	1.0%PO	12	336.0 ±33.9	11.007 ±1.796	1.133 ±0.185	1.088 ±0.144	0.600 ±0.076	38.8 ±9.2	42.8 ±7.0	1.034 ±0.102	1.200 ±0.116	1.871 ±0.077	22.2 ±6.6	0.170 ±0.045	33.6 ±10.7	34.5 ±12.2

(g , ‖: mg , Mean ± S.D.)

* : Significantly different from control($p<0.05$)

** : Significantly different from control($p<0.01$)

Table - 9

Average relative wet organ weight of rats

Sex	Sample	Number of animals	Final B.W.	Liver	Kidney R	Kidney L	Spleen	Adrenal gland R	Adrenal gland L	Heart	Lung	Brain	Pituitary	Thymus	Testis or Ovary R	Testis or Ovary L
Male	Control	12	597.2 ±51.6	3.192 ±0.205	0.306 ±0.030	0.304 ±0.024	0.150 ±0.012	4.58 ±0.75	4.92 ±0.86	0.273 ±0.023	0.263 ±0.015	0.339 ±0.026	2.03 ±0.29	0.038 ±0.011	0.283 ±0.019	0.283 ±0.023
	PG	12	575.3 ±37.5	3.123 ±0.226	0.319 ±0.026	0.301 ±0.024	0.150 ±0.019	4.65 ±0.66	5.03 ±0.78	0.268 ±0.017	0.265 ±0.022	0.354 ±0.029	2.07 ±0.25	0.034 ±0.007	0.267 ±0.078	0.291 ±0.025
	0.5%PO	12	577.3 ±44.9	3.027 ±0.301	0.306 ±0.024	0.302 ±0.025	0.140 ±0.025	4.98 ±1.21	5.08 ±0.79	0.272 ±0.019	0.265 ±0.018	0.359 ±0.030	1.83 ±0.45	0.033 ±0.010	0.298 ±0.025	0.298 ±0.022
	1.0%PO	12	566.8 ±48.0	2.897** ±0.152	0.304 ±0.019	0.297 ±0.014	0.165 ±0.065	4.78 ±0.57	4.85 ±0.55	0.267 ±0.020	0.273 ±0.019	0.359 ±0.024	1.90 ±0.35	0.033 ±0.010	0.291 ±0.031	0.288 ±0.027
Female	Control	12	340.2 ±36.1	3.368 ±0.422	0.328 ±0.036	0.315 ±0.033	0.169 ±0.019	11.08 ±1.45	11.15 ±1.92	0.315 ±0.025	0.339 ±0.038	0.569 ±0.064	5.27 ±1.81	0.048 ±0.011	10.78 ±3.20	9.84 ±3.54
	PG	12	317.8 ±21.6	3.293 ±0.241	0.328 ±0.025	0.323 ±0.023	0.173 ±0.023	10.98 ±1.74	12.09 ±3.07	0.329 ±0.020	0.357 ±0.030	0.589 ±0.041	6.39 ±1.78	0.059* ±0.016	10.88 ±3.46	10.30 ±3.28
	0.5%PO	12	336.0 ±30.8	3.262 ±0.184	0.340 ±0.031	0.326 ±0.028	0.170 ±0.029	10.02 ±2.52	11.53 ±2.09	0.320 ±0.026	0.341 ±0.032	0.562 ±0.053	6.56 ±1.77	0.057 ±0.013	8.73 ±1.93	8.43 ±2.96
	1.0%PO	12	336.0 ±33.9	3.262 ±0.278	0.336 ±0.035	0.324 ±0.029	0.180 ±0.023	11.63 ±3.05	12.80 ±2.08	0.309 ±0.031	0.359 ±0.025	0.563 ±0.067	6.55 ±1.58	0.051 ±0.014	10.08 ±3.58	10.40 ±4.00

(%, ‰: 10^{-3}, Mean ± S.D.)

* : Significantly different from control($p<0.05$)

** : Significantly different from control($p<0.01$)

English Translation

Table - 10 - 1

Histopathological findings of rats

臓器	所見	♂ Control 12				♂ FG 12				♂ 0.5%PO 12				♂ 1.0%PO 12				♀ Control 12				♀ FG 12				♀ 0.5%PO 12				♀ 1.0%PO 12			
		±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++
Liver	Large fatty droplets	2																															
	Focal necrosis	3																1															
	Activation of the Kupffer cells	2																3								1				4			
	Cell infiltration of the lobule													1				1															
	Cyst	1																															
	Degeneration																	1															
	Fatty degeneration						1																										
	Abscess																						1										
	Atrophy																													1	1		
	Dilation of the sinusoids																													1			
Kidney	Degeneration of the tubular epithelium	1	1																							1							
	Hyaline cast	1	1			1								1				2								1				2			
	Small round cell infiltration in the interstitium	5	1			1								1	1											1					1	2	
	Dilation of the tubular lumen	3	1			1								1				1													2		
	Cyst	3	2																							1				1			
	Calcification	1					1																							1	1		
	Dilation of the pelvis							1										1															
	Interstitial Nephritis																	1													1		

Kidney : Right/Left

± : very slight
+ : slight
++ : medium
+++ : serious

English Translation

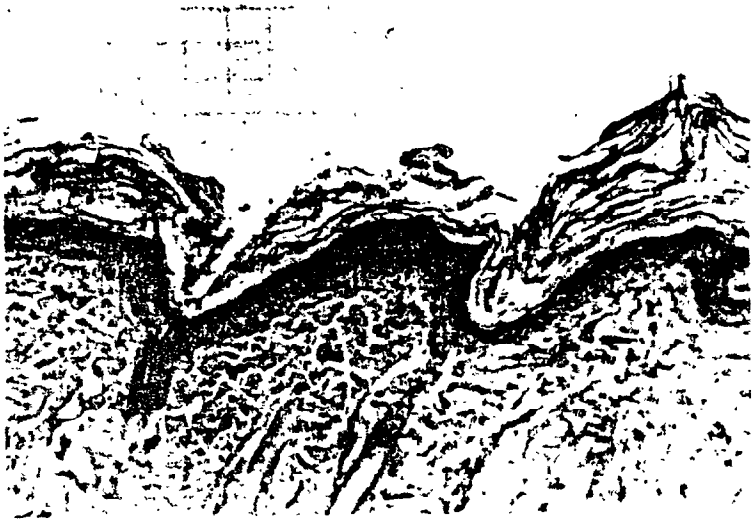
Table - 10 - 2

Histopathological findings of rats

臓器	所見	♂ Control 12				♂ PG 12				♂ 0.5%PO 12				♂ 1.0%PO 12				♀ Control 12				♀ PG 12				♀ 0.5%PO 12				♀ 1.0%PO 12			
		±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++	±	+	++	+++
Kidney	Flattened epithelium and dilation of the lumen																									1				1		2	
Adrenal	Large fatty droplets in the reticularis	1																															
	Congestion in the cortex																	1															
Heart	Myocardia							1		1																							
Lung	Foaming cells									1																							
Pituitary	Hypertrophy																													1			
Genitals	Spermary Cells in cavity	1																															
	Spermary Atrophy, dilation						1																										
Pancreas	Fibrosis of Lannelhans islets					1																											
Stomach	Cyst in the submucosa	1																															
	Cell composition in the gastric pit																	1															
Lymphonodi	Hypertrophy of the axillary lymphonodi					1												1															
Prostate	Prostatitis									1																							
Skin	Thickening of the epidermis					1				2	2			7	1											1	2			3	2		

Genitals, Adrenal : Right/Left

± : very slight
+ : slight
++ : medium
+++ : serious



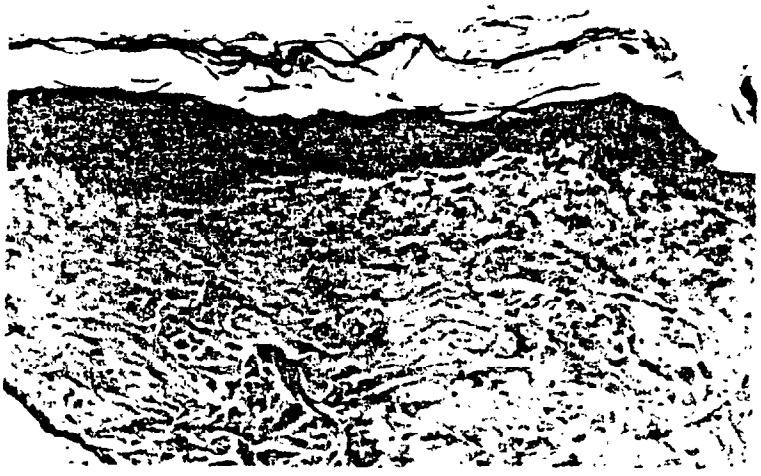
対照群　　皮膚

water

対照群　　皮膚

water

PG　　皮膚



1%PO　　皮膚

Excerpt from the supplement of the Colipa Data Sheet
of Nov. 15, 1984

LONG TERM TOXICITY

Species: Sprague-Dawley rat; 147.4 ± 5.2 g ♂; 106.9 ± 4.6 g ♀

Number of animals: 16 per sex; 32 per group including 8 for recovery study; 128 total; two control groups: 1. vehicle treatment
2. dist. water treatment

Method of administration: Painting/open patch on dorsal area (3 x 4 cm)

Concentration, vehicle and quantity:
0 %; 0.5 %; 1 %; 1,2-propylene glycol; 0.2 ml/animal

Dose level: 0; 1; 2 mg/animal

Dosing: (day/week, animal age at start dosing): 6 days/week; ca. 4 weeks

Total duration: 6 months

Survival rate: (number and age of survivors when killed)
128; 30 weeks and 33 weeks resp. (recovery group)

Main findings:

- Body weight: slightly reduced at 1 % in males
- Hematology: no changes due to Piroctone Olamine
- Biochemistry: dto.
- Urine: dto.
- Autopsy: dto.
- Organ weight: dto. (liver, kidney, spleen, adrenal gland, heart, lung, brain, pituitary, thymus, testis or ovary)
- Histology: very slight to slight thickening of the epidermis in Piroctone Olamine treated males and females; same effect in the vehicle control in females; quickly reversible in the recovery period (3 weeks). The animals recovered quickly from the skin scratches after cessation of treatment.
  No histopathological changes in liver, kidney, adrenal, heart, lung, pituitary, genitals, pancreas, stomach, lymphonodi, prostate.

Result: The study did not disclose any toxic effects which are prohibitive for the use in concentrations up to 1 %

Reference: 6 Months chronic percutaneous toxicity of Piroctone Olamine on rats; Report No. T-368-1 of R. Itoh (Toho University, School of Medicine) and S. Kajiwara (Yokosuka Institute for Applied Pharmacology), February 15, 1983.