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TOXICITY OF *o*-CRESOL TO MINK AND EUROPEAN FERRETS

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Abstract—The toxicity of *o*-cresol to mink (*Mustela vison*) and European ferrets (*Mustela putorius furo*) was evaluated through dietary LC50 and reproduction tests. Twenty-eight-day LC50 tests with each species resulted in no overt signs of toxicity or mortalities, with the highest dietary concentrations being 2,520 ppm for mink and 4,536 ppm for ferrets. Mink were more sensitive to *o*-cresol than were ferrets, based on feed consumption, body weight data and hematologic parameters. Both species routinely consumed in excess of the estimated oral LD50 in an average day's feed consumption at the highest dietary concentration. Mink in a reproduction test exhibited no significant adverse effects at dietary concentrations as high as 1,600 ppm over 6 months.

Keywords—Mink Ferrets *o*-Cresol LC50 Reproduction

INTRODUCTION

o-Cresol is widely used as a disinfectant and as an intermediate in several industrial chemical reactions. It is also a component of the phenolic wastes of several manufacturing processes and as such poses a threat to aquatic species both directly as a toxicant and indirectly as a behavior modifier [1].

This study was conducted to investigate the toxicity of *o*-cresol to mink (*Mustela vison*) and European ferrets (*Mustela putorius furo*). Previous research has shown these species to be extremely sensitive to many environmental contaminants and good animal models for toxicity testing [2–4]. This evaluation of the toxicity of *o*-cresol was conducted in conjunction with the validation of protocols developed for toxicity testing with carnivores for the Office of Toxic Substances, U.S. Environmental Protection Agency.

MATERIALS AND METHODS

Twenty-eight-day LC50 tests were conducted with mink and ferrets, and a reproduction test was conducted only with mink. Standard dark mink and agouti-colored ferrets from stock raised at the Michigan State University Experimental Fur Farm were used in the trials. Specific procedures, as developed for mammalian carnivore toxicity testing, were followed in these studies, unless specifically stated otherwise. These procedures have been detailed previously [5,6] and are briefly described here.

The mink and ferrets employed in the LC50 tests were approximately 6 months old, whereas the mink used in the reproduction test were first-year breeders, approximately 9 months of age at the initiation of the study. The animals were randomly allocated to treatment groups (with the exception that littermates were not assigned to the same group) and were acclimated to the facilities for a minimum of 13 d. For the LC50 tests, 5 males and 5 females were used per treatment group; in the reproduction test 16 animals (4 males and 12 females) were used.

A literature search yielded rat oral LD50 values ranging from 121 mg/kg [7] to 1,470 mg/kg [8] body weight for *o*-cresol; thus, range-finding tests were performed with mink and ferrets. From the

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results (Table 1), LD50s were estimated to be between 100 and 500 mg/kg for mink and between 300 and 500 mg/kg for ferrets. Based on these results, dietary concentrations of 0, 240, 432, 778, 1,400 and 2,520 ppm were chosen for mink and 0, 432, 778, 1,400, 2,520 and 4,536 ppm for ferrets in the LC50 tests.

The experimental diets were prepared by dissolving appropriate amounts of *o*-cresol (analytical reagent; Pfaltz and Bower, Stamford, CT) in corn oil and thoroughly mixing the solutions with the basal diet (24.2% mink cereal, 28.9% whole chicken, 18.1% ocean fish scrap, 9.7% beef tripe, 4.8% beef liver, 4.8% beef lungs, 4.8% beef trimmings, and 4.8% cooked eggs; "as fed," the diet contained 68.4% moisture, 14.3% protein, 7.9% fat, and 2.5% ash). Actual dietary concentrations of *o*-cresol, analyzed by a modification of an analytical technique published by Supelco [9], were as follows: 0 ppm diet, 0 ppm; 240 ppm diet, 213.5 ppm; 432 ppm diet, 473.1 ppm; 778 ppm diet, 862.3 ppm; 1,400 ppm diet, 1,533.7 ppm; 2,520 ppm diet, 3,680.3 ppm; and 4,536 ppm diet, 5,188.7 ppm.

Feed and water were provided ad libitum during all tests. In the LC50 tests, body weights and feed consumption, based on 2 consecutive days' intake, were measured weekly; these parameters were measured biweekly in the reproduction test. In all tests, the animals were observed daily for signs of intoxication, abnormal behavior or mortality. Necropsies were performed on all animals and body and organ weights were recorded.

The mink and ferret LC50 tests were begun on 9 November 1981 and ended on 7 December 1981. Upon termination of the LC50 tests, the survivors were weighed and blood samples were taken (by toe clip) for analysis of hematologic parameters. The animals were then euthanized with CO_2 gas for necropsy. Brain, liver, spleen, kidneys, lungs, heart and testes were removed and weighed. Organ weights were transformed to percentages of brain weight and body weight and these values were then analyzed by two-factor (dose and sex) analysis of variance. Significant differences were determined by Dunnett's test for comparison with a control [10]. The $p \leq 0.05$ level was used as the criterion for significance.

For the reproduction study, dietary concentrations of 0, 100, 400 and 1,600 ppm were used. The highest dietary concentration was based on the maximum tolerated dose determined in the mink LC50 trial. The test diets were begun on 7 January 1982 to allow approximately 2 months' exposure to *o*-cresol prior to mating and were continued through the weaning of the offspring (kits) at 6 weeks post partum. The measurement of body weights was limited to the prebreeding period to eliminate any possible adverse effect of handling on pregnancy. Feed consumption was measured during weeks 5 through 8 of the prebreeding period.

Table 1. Results of range-finding studies with mink and ferrets exposed to *o*-cresol by gavage

Dose (mg/kg)	Died/Total	Comments
Mink		
1,000	1/1	
500	1/1	
300	0/2	Both unconscious after dosing
200	1/2	4 d to death
100	0/2	Both lost coordination after dosing
50	0/1	No effects observed
0	0/2	No effects observed
Ferrets		
500	1/1	
400	1/1	1 d to death
300	0/2	1 unconscious, 1 lost coordination after dosing
200	0/1	Lost coordination after dosing
0	0/2	No effects observed

The mink were mated within their respectiv dietary groups during the first 3 weeks in March in accordance with standard commercial minl breeding practices. Mated females were checke daily for kits during the whelping period (20 Apr to 15 May). Kits were counted and weighed on th day of birth and at 3 and 6 weeks of age.

Upon termination of the reproduction test, th four males and four randomly chosen females pe group were weighed and samples of blood wer collected (by toe clip) for analysis of hematolog parameters. The mink were then euthanized an necropsies performed, and the organ weights wer analyzed statistically as described for the LC5 trial. The effects of *o*-cresol on the reproducti parameters measured were analyzed by singl factor analysis of variance and significant diffe ences were determined by Dunnett's method f comparison with a control. The data pertaining kit survival were analyzed by contingency tab and significant differences were tested by Bonfe roni's chi-square test [10].

RESULTS

LC50 tests

Overt signs of toxicity were not observed in either the mink or the ferret LC50 test, and no mortalities were recorded. Body weight changes and feed and *o*-cresol consumption by mink and ferrets are summarized in Tables 2 and 3, respectively. In the mink LC50 test, feed consumption was initially decreased at 2,520 ppm but returned to normal levels by the second week. Male body weight gain was also significantly decreased at this concentration. In the ferret LC50 test, a slight reduction in feed consumption was noted at 4,536 ppm, but no effects on body weight were seen. Since no mortalities occurred in either LC50 test, it must be assumed that the 28-d dietary LC50 for mink is greater than 2,520 ppm and for ferrets is greater than 4,536 ppm.

No gross lesions were noted at necropsy for

Table 2. Mean body weights, body weight changes and feed and *o*-cresol consumption by mink fed various concentrations of *o*-cresol for 28 d

Parameter measured	*o*-Cresol concentration (ppm)					
	0	240	432	778	1,400	2,520
Male body weights (g)						
Initial	1,537	1,515	1,544	1,528	1,592	1,583
Final[a]	1,836	1,763	1,967	1,767	1,807	1,593
Change	+299	+248	+423	+239	+215	+10[b]
n	5	5	5	5	5	5
Female body weights (g)						
Initial	970	981	942	1,030	1,013	938
Final[a]	1,080	1,007	1,006	1,053	1,012	887
Change	+110	+26	+64	+23	−1	−51
n	5	5	5	5	5	5
Body weight change by period[c,d] (g)						
Acclimation	+104	+41	+118	+91	+61	+112
Week 1	—	—	—	—	—	—
Week 2	+10	+4	−12	−11	−4	+28
Week 3	+21	+32	+51	+40	−13	−8
Week 4	+53	+8	+51	+48	0	+25
4 weeks cumulative	+205	+137	+243	+131	+107	−20
Feed consumption by period[c,e] (g/d)						
Acclimation	261	279	308	284	293	271
Week 1	219	256	290	222	217	121
Week 2	220	214	243	211	212	217
Week 3	245	226	291	260	195	209
Week 4	235	208	255	268	229	212
4 weeks cumulative	6,433	6,328	7,553	6,727	5,971	5,313
o-Cresol consumption by period[c,f] (mg/d)						
Acclimation	0	0	0	0	0	0
Week 1	0	61	125	173	304	304
Week 2	0	51	105	164	296	548
Week 3	0	54	126	202	272	528
Week 4	0	50	110	209	320	534
4 weeks cumulative	0	1,519	3,266	5,233	8,347	13,392

[a] Based on body weights at the necropsy kill.
[b] Significantly different from control ($p \leq 0.05$).
[c] Based on 10 mink (5 male and 5 female) per group.
[d] Week 1 body weights not recorded; therefore, cumulative body weight change was measured from the acclimation period.
[e] Feed consumption based on the average of 2 consecutive days' consumption.
[f] Daily *o*-cresol consumption calculated from average feed consumption multiplied by dietary concentration; cumulative *o*-cresol consumption calculated from the sum of daily consumption multiplied by 7.

either species. Since analysis of the hematologic data revealed no significant differences between sexes, the values for males and females were pooled prior to analysis. The hematologic parameters, summarized in Table 4, showed significant decreases in red blood cell counts at 1,400 and 2,520 ppm and in hemoglobin at 2,520 ppm for the mink, and a reduced red blood cell count at 4,536 ppm for the ferrets. No significant differences were observed in the mink organ weights when expressed as a percentage of brain weight. However, when expressed as a percentage of body weight, the liver weights were found to be increased at all concentrations except 240 ppm, and the heart weights were increased at 2,520 ppm. For the ferrets, significant increases were seen in liver weights (as a percentage of brain weight) at concentrations of 1,400 ppm or greater and also in kidney weight for females at 4,536 ppm (Table 5).

Reproduction test

As in the LC50 tests, no overt signs of toxicity were observed during the 6 months of the mink reproduction test. One female fed the 1,600 ppm

Table 3. Mean body weights, body weight changes and feed and *o*-cresol consumption by ferrets fed various concentrations of *o*-cresol for 28 d

Parameter measured	*o*-Cresol concentration (ppm)					
	0	432	778	1,400	2,520	4,536
Male body weights (g)						
Initial	1,781	1,637	1,708	1,710	1,799	1,690
Final[a]	1,913	1,781	1,817	1,795	1,998	1,803
Change	+132	+144	+109	+85	+199	+113
n	5	5	5	5	5	5
Female body weights (g)						
Initial	951	952	972	960	1,000	905
Final[a]	962	945	1,004	933	1,026	915
Change	+11	−7	+32	−27	+26	+10
n	5	5	5	5	5	5
Body weight change by period[b] (g)						
Acclimation	+70	+60	+65	+63	+64	+52
Week 1	+30	+33	+32	+12	+23	+9
Week 2	+24	+26	+17	+14	+47	+15
Week 3	+18	+5	+19	+11	+30	+29
Week 4	−1	+4	+2	+12	+12	+8
4 weeks cumulative	+71	+68	+70	+49	+112	+61
Feed consumption by period[b,c] (g/d)						
Acclimation	205	174	193	173	207	208
Week 1	199	193	204	177	217	166
Week 2	169	171	169	161	178	140
Week 3	168	169	180	158	212	145
Week 4	169	159	190	163	186	154
4 weeks cumulative	4,935	4,844	5,201	4,613	5,551	4,235
o-Cresol consumption by period[b,d] (mg/d)						
Acclimation	0	0	0	0	0	0
Week 1	0	84	159	248	546	754
Week 2	0	74	131	226	450	635
Week 3	0	73	140	221	543	660
Week 4	0	69	148	228	470	698
4 weeks cumulative	0	2,094	4,050	6,463	14,003	19,230

[a]Based on body weights at the necropsy kill.
[b]Based on 10 ferrets (5 male and 5 female) per group.
[c]Feed consumption based on the average of 2 consecutive days' consumption.
[d]Daily *o*-cresol consumption calculated from the average feed consumption multiplied by dietary concentration; cumulative *o*-cresol consumption calculated from the sum of daily consumption multiplied by 7.

diet died from enteritis, presumably unrelated to the effects of the *o*-cresol exposure. Body weight changes and feed and *o*-cresol consumption are summarized in Table 6. No effect on feed consumption was observed, although the males fed the 1,600 ppm diet gained significantly ($p < 0.01$) less weight than did the controls.

The reproductive indices, summarized in Tables 7 and 8, showed the average birth weight of kits whelped by females fed the 100 ppm diet to be

Table 4. Blood parameters in mink and ferrets fed various concentrations of *o*-cresol for 28 d

o-Cresol concentration (ppm)	*n*	Red blood cells/mm³ (×10⁶)	White blood cells/mm³ (×10³)	Hemoglobin (g/dl)	Hematocrit (%)
Mink					
0	10	11.51	—[a]	24.4	53.4
240	10	11.21	—	24.5	54.8
432	10	11.14	—	25.9	55.7
778	10	10.92	—	25.4	53.7
1,400	10	9.53[b]	—	23.1	54.9
2,520	10	9.62[b]	—	22.5[c]	53.4
SEM[d]		0.204	—	0.46	0.78
Ferrets					
0	10	10.46	27.5	20.9	50.4
432	10	10.64	25.2	22.2	51.8
778	10	10.66	24.9	21.2	50.8
1,400	10	10.52	30.2	21.5	49.9
2,520	10	10.59	36.2	21.4	52.4
4,536	10	9.52[c]	28.3	19.7	49.1
SEM[d]		0.225	1.05	0.50	0.89

[a]Not analyzed because of problems with lysing agent.
[b]Significantly different from control ($p \leq 0.01$).
[c]Significantly different from control ($p \leq 0.05$).
[d]SEM = $\sqrt{MS_E/10}$ for all groups.

Table 5. Organ weights (expressed as a percentage of brain weight) in ferrets fed various concentrations of *o*-cresol for 28 d

o-Cresol concentration (ppm)	Sex	*n*	Liver	Spleen	Kidney	Lung	Heart	Testes
0	M	5	904	156.5	119.9	130.8	81.2	38.8
	F	5	760	91.3	84.8	110.2	66.2	—
432	M	5	987	165.0	141.5	129.5	89.6	33.5
	F	5	814	92.7	91.8	102.5	73.8	—
778	M	5	992	141.7	135.6	129.6	89.3	33.8
	F	5	895	102.8	98.7	99.6	72.4	—
1,400	M	5	1,157[a]	163.8	137.0	126.1	90.8	35.8
	F	5	936	104.8	100.7	92.9	68.2	—
2,520	M	5	1,136	142.2	140.5	111.8	89.1	47.8
	F	5	1,090[b]	128.3	103.6	96.9	74.8	—
4,536	M	5	1,169[a]	168.4	131.7	110.3	85.4	43.1
	F	5	1,078[b]	98.3	112.4[a]	98.9	72.4	—
SEM[c]			61.30	16.80	6.60	6.79	3.33	5.78

[a]Significantly different from control ($p \leq 0.05$).
[b]Significantly different from control ($p \leq 0.01$).
[c]SEM = $\sqrt{MS_E/5}$ for all groups.

Table 6. Mean body weights, body weight changes and feed and *o*-cresol consumption by mink fed various concentrations of *o*-cresol during an 8-week prebreeding period prior to a reproduction test

Parameter measured	*n*	*o*-Cresol concentration (ppm)			
		0	100	400	1,600
Male body weights (g)	4				
Initial		1,748	1,714	1,698	1,753
Final		1,822	1,796	1,648	1,607
Change		+74	+82	−50	−146[a]
Female body weights (g)	12				
Initial		958	997	956	946
Final		1,010	987	971	983
Change		+52	−10	+15	+37[b]
Body weight change by period (g)	16[c]				
Acclimation		+6	+42	+35	+5
Weeks 1–2		−24	−12	−14	−79
Weeks 3–4		+17	−14	−20	0
Weeks 5–6		+83	+61	+58	+80
Weeks 7–8		−19	−22	−24	−1
8 weeks cumulative		+57	+13	0	0[b]
Feed consumption by period[d,e] (g/d)	16[c]				
Weeks 5–6		222	184	194	228[b]
Weeks 7–8		193	197	189	225[b]
o-Cresol consumption by period[f] (mg/d)	16[c]				
Weeks 5–6		0	18	78	365[b]
Weeks 7–8		0	20	76	359[b]

[a]Significantly different from control ($p \leq 0.01$).
[b]One female died from causes not related to effects of *o*-cresol and an animal designated as female was discovered to be male in the 1,600 ppm group: data from both were excluded from the values reported.
[c]Sexes combined.
[d]Feed consumption based on the average of 2 consecutive days' consumption.
[e]Feed consumption measured only for weeks 5–6 and 7–8.
[f]Daily *o*-cresol consumptions calculated from average feed consumption multiplied by dietary concentration.

increased over control kits' birth weights. No obvious birth defects were noted in this study and no gross lesions were noted in the adult animals at necropsy (29 June 1982). The hematologic parameters, summarized in Table 9, revealed a significant increase in red blood cell count in the 1,600 ppm group. No significant differences were found in the organ weights when expressed as a percentage of brain weight. However, as in the LC50 test, the liver weights were increased over those in controls when expressed as a percentage of body weight.

DISCUSSION

Examination of the body weight and feed consumption data reveals that, with the exception of body weight change in male mink fed 2,520 ppm, no significant results were observed in the mink and ferret LC50 tests. Since the cresols are known to be easily excreted as conjugated glucuronides and sulfates [11], it is assumed that the animals were able to excrete enough *o*-cresol ingested in any one feeding during the day to prevent a toxic dose from being reached, even though the mink consumed in excess of the estimated LD50 in an average day's feed consumption on the 2,520 ppm diet, and possibly on the 778 and 1,400 ppm diets as well. Similarly, the ferrets consumed in excess of the estimated LD50 on the 2,520 and 4,536 ppm diets. Similar results have been reported for rats exposed to 0.3 g/L *o*-cresol in their drinking water [12]. In the rat study, there was no effect on body weight at this concentration, even though the animals had consumed a cumulative dose in excess of the acute oral LD50 by the fourth week of the study.

In comparing results from diets with *o*-cresol concentrations that overlapped in the two tests, it appears that mink are more sensitive than ferrets

Table 7. Reproductive performance of female mink fed various concentrations of o-cresol

o-Cresol concentration (ppm)	Females bred/ Total	Females whelped/ Females bred	Gestation (d)[a,b]	Kits/Female whelped	
				Alive at birth[b]	Total[b]
0	9/12	8/9	46.8 ± 1.70[b]	4.50 ± 0.81	5.12 ± 0.78
100	11/12	9/11	47.9 ± 1.60	4.77 ± 0.76	5.33 ± 0.74
400	12/12	9/12	47.6 ± 1.60	4.89 ± 0.76	5.22 ± 0.74
1,600	9/11[c]	8/9	47.9 ± 1.70	4.25 ± 0.81	5.12 ± 0.78

[a]Gestation calculated from date of last mating.
[b]Mean ± SEM.
[c]One female died from results not related to effects of o-cresol.

Table 8. Body and litter weights and survival of mink kits raised by dams fed various concentrations of o-cresol

o-Cresol concentration (ppm)	Mean kit body weight[a] (g)			Mean litter weight[a] (g)			Kit survival (%)	
	Birth	3 weeks	6 weeks	Birth	3 weeks	6 weeks	3 weeks	6 weeks
0	8.3 ±0.32	91.0 ±4.10	250.8 ±11.25	42.9 ±7.55	491.6 ±113.16	1,630 ±276.8	75.0	72.2
100	9.4[b] ±0.30	99.0 ±3.29	240.8 ±9.31	46.7 ±7.06	461.9 ±84.34	1,144 ±195.8	97.7	88.4
400	8.7 ±0.29	97.2 ±3.50	274.9 ±10.47	42.4 ±6.65	399.7 ±84.34	1,031 ±195.8	84.1	68.2
1,600	8.0 ±0.33	96.6 ±4.54	242.6 ±13.52	33.8 ±7.06	425.0 ±113.16	1,455 ±319.7	64.7	52.9

[a]Mean ± SEM.
[b]Significantly different from control ($p \leq 0.05$).

Table 9. Blood parameters in mink fed various concentrations of o-cresol for 6 months

o-Cresol concentration (ppm)	n	Red blood cells/mm³ (×10⁶)	Hemoglobin (g/dl)	Hematocrit (%)
0	8	9.37	23.0	54.1
100	8	9.13	22.8	53.0
400	8	9.52	24.5	55.8
1,600	8	10.42[a]	23.6	55.0
SEM[b]		0.205	0.52	0.96

[a]Significantly different from control ($p \leq 0.01$).
[b]SEM = $\sqrt{MS_E/8}$ for all groups.

to o-cresol. At a dietary concentration of 2,520 ppm, body weight changes in both male and female ferrets were in excess of control values, while the body weight change in male mink was significantly less than in controls. Feed consumption was negatively affected in the first week in mink fed 2,520 ppm; it was slightly above control levels in ferrets in the first week at this dietary concentration.

This difference in sensitivity is also reflected in the hematologic parameters. Significant decreases in red blood cell count were found in the mink fed 1,400 and 2,520 ppm and in the hemoglobin concentration in mink fed 2,520 ppm, but no significant changes were noted in ferrets fed the same concentrations. It must be noted, however, that the red blood cell counts in the mink fed 1,400 and 2,520 ppm were well within the normal range for mink at this time of year. In fact, red blood cell counts in the control and 240 ppm groups were actually quite high for this time of year [13]. A puzzling result from the blood data was the decrease in red blood cell count associated with increasing dietary concentrations of o-cresol in the mink LC50 test, whereas the red blood cell count increased with concentration in the reproduction test.

In the reproduction test, no biologically signifi-

cant results were obtained. No significant negative results were observed in the body weight data or in the reproductive indices. The average birth weight of kits whelped by females fed the 100 ppm diet was significantly greater than in the controls, although the average of 9.4 g is within the range of normal birth weights. In fact, the 8.0 g average birth weight for kits whelped by females fed the 1,600 ppm diet is near the low end of the normal range for kit birth weights but was not significantly different from the 8.3 g average for the control group.

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