

Piroctone Olamine (Octopirox: Docket No. 2004N-0050)

Piroctone Olamine (Octopirox) Non-Clinical Safety Studies	Notebook Number	Tab Number
Summary Table of Non-Clinical Safety Studies for Octopirox	Notebook #1	
Octopirox Non-Clinical Safety Studies (Summary Sheet + Full Report)		
1. Acute Oral Toxicity in Rats		1
2. Acute Oral Toxicity in Rats		2
3. Acute Oral Toxicity in Rats		3
4. Acute Oral Toxicity in Rats		4
5. Acute Oral Toxicity in Rats		5
6. Acute Dermal Toxicity in Mice		6
7. Acute Percutaneous Toxicity in Rabbits		7
8. Acute Percutaneous Toxicity in Rabbits		8
9. Acute Percutaneous Toxicity in Rabbits		9
10. Acute Inhalation Toxicity in Rats		10
11. 12 Day Subchronic Percutaneous Toxicity in Rabbits		11
12. Rabbit Eye Irritation		12
13. Rabbit Eye Irritation		13
14. Rabbit Eye Irritation		14
15. Rabbit Eye Irritation		15
16. Rabbit Eye Irritation		16
17. Rabbit Eye Irritation (Low Volume)		17
18. Primary Skin Irritation in Rabbits		18
19. Primary Skin Irritation in Rabbits	19	
20. Primary Skin Irritation in Rabbits	20	
	Notebook #2	
21. Rabbit Skin Irritation Patch Test		1
22. Rabbit Skin Irritation Patch Test		2

2004N-0050

RPT2

Piroctone Olamine (Octopirox: Docket No. 2004N-0050)

23. Skin Irritation in the Muta Mouse		3
24. Guinea Pig Delayed Contact Hypersensitivity		4
25. Drosophila Mutagenicity Assay		5
26. CHO/HGPRT Mutation Assay		6
27. SHE Transformation Assay		7
28. SHE Transformation Assay		8
29. Mouse Lymphoma Assay		9
30. Mouse Lymphoma Assay (with and without transferrin)		10
31. DNA Synthesis in CD-1 Mouse Epidermis		11
32. Unscheduled DNA Synthesis		12
33. DNA, RNA, Protein Synthesis in Mouse Lymphoma and SHE Cells		13
34. DNA Synthesis		14
35. Mechanism of Cell Growth Inhibition in Mouse Epidermis		15
	Notebook #3	
36. DNA Synthesis in Muta Mouse		1
37. Mutagenicity in Muta Mouse Skin		2
38. Percutaneous Teratology in Rabbits		3
39. Range Finding Study for Reproduction/Fertility Study in Rats		4
40. Reproduction/Fertility Study in Rats		5
	Notebook #4	
41. 14 Day Range Finding Study for Reproduction/Teratology Study in Rats		1
42. A One-Generation Reproduction and Teratology Study in Rats		2
43. The Effects of Dietary Iron Supplementation on Octopirox Toxicity in the Young Growing Rat		3
44. Emetic Study in Beagle Dogs		4

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**Summary of Non-Clinical Toxicity Studies on Piroctone Olamine (Octopirox)
Full Study Reports Can Be Found in Notebooks #1-4**

No	Test Type	Test Substance	Study #	Treatment Conditions	Results
Acute Oral Toxicity					
1	Oral (LD50) -- Up and Down	#E2414.01 1.0% OP in shampoo Undiluted material used for testing	HUNT-85170D P&G 1165/AC AN 31973	Males rats dosed with a single oral dose of test materials ranging from 4.8 – 23.3 g/kg. Females rats dosed with single oral dose of test materials ranging from 4.8 – 13.8 g/kg.	Female: LD50 > 10.7 g/kg Male: LD50 > 16.9 g/kg
2	Oral (LD50)- Up and Down	#G0506.01 0.3% OP in conditioner formula Undiluted material used for dosing.	50106723 AN 30620	3 male and 3 female rats dosed orally (gavage) with initial dose of 20.0g/kg . Subsequent doses ranged from 15.4-22.3 g/kg in 4 males and 3 females.	Female: LD ₅₀ > 21.1 g/kg. Male: LD ₅₀ >20.6 g/kg
3		#T 7121 2% placebo in shampoo at pH 4.5 Undiluted material used for dosing	191-082 AN 20031	25 male and 25 female rats dosed orally (gavage) with 5.12, 8.14, 12.92 mg/kg, 20.51, and 32.55 g/kg.	Combined: LD ₅₀ > 10.31 g/kg.
4	Oral (LD50)	#T-7120 2% OP in shampoo at pH 4.5 Undiluted material used for dosing	191-081 AN 19197	20 male and 20 female rats dosed orally with 8.26, 10.00, 12.10 and 14.70 g/kg.	Combined: LD ₅₀ > 11.92 g/kg.
5		#T-7119 2% OP in shampoo at pH 7.5 Undiluted material used for dosing	191-080 AN 19195	20 male and 20 female rats dosed orally with 10.71, 15.00, 21.00, and 29.40 g/kg.	Combined: LD ₅₀ >16.16 g/kg

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Acute Dermal Toxicity					
6	Acute Dermal Toxicity in Mice	#G0539.03 5% Octopirox in propylene glycol/ethanol/water (1/2/1). The test material was diluted in neutral and alkaline pH vehicles.	B88-0215 AN 34922	Total of 40 female SKH-HR1 Hairless mice (10 per group) exposed dermally 1) neutral pH vehicle, 2) alkaline pH vehicle, 3) 5% G0539.03 (167 mg/kg BW) in a neutral pH vehicle and 4) 5% G0539.03 (167 mg/kg BW) in alkaline pH vehicle.	No biologically significant treatment related effects seen in any animals with regard to body weights, hematology and macroscopic anatomy. One animal exhibited signs of neurotoxicity (myoclonus) which occurred in acute dermal treatment of the test material in the alkaline vehicle.
7		#T-7121 2% placebo in shampoo at pH 4.5	191-082 AN 19624	3 male and 3 female New Zealand White Rabbits exposed to 2000 mg/kg on abraded skin on the back for 24 hours. Rabbits were observed for 14 days.	Minimum lethal dermal dose of T7121 in both male and female rabbits was > 2.0 g/kg.
8	Acute Percutaneous Toxicity in Rabbits	#T-7120 2% OP in shampoo at pH 4.5	191-081 AN 19196	3 male and 3 female New Zealand White Rabbits exposed to 2000 mg/kg on abraded skin on the back for 24 hours. Rabbits were observed for 14 days.	Minimum lethal dermal dose of T7120 in both male and female rabbits was > 2.0 g/kg.
9		#T-7119 2% OP in shampoo at pH 7.5 Undiluted material used for dosing	191-080 AN 19194	3 male and 3 female New Zealand White Rabbits exposed to 2000 mg/kg on abraded skin on the back for 24 hours. Rabbits were observed for 14 days.	Minimum lethal dermal dose of T7119 in both male and female rabbits was > 2.0 g/kg.

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Acute Respiratory Toxicity					
10	Acute Inhalation Toxicity in Rats	#G0539.04 Dust aerosol at 4.4, 2.0 or 4.9 mg/L. The aerodynamic diameter was 10, 4.2 and 4.4 mcm, respectively, for the three concentrations.	191-1456 AN 35755	Total of 30 male and female rats (5 in each group) exposed for 4 hours to 4.4, 4.9 , or 2.0 mg/L of a dust aerosol of G0539.04. The 4.4 mg/L dosed group received neat material. The 2.0 and 4.9 mg/L dosed groups received micronized material as the neat material has a large particle size. Animals were observed for 14 days.	The LC50 for inhalation exposure was estimated to be > 4.9 mg/L.
Subchronic Dermal Toxicity					
11	12 Day Subchronic Percutaneous Toxicity in Rabbits	G2877.01 Solid deodorant with 7.5% OP	IRDC-191-143 AN 35393	Test material was applied dermally and undiluted at 2 ml/kg to 3 male and 3 female rabbits 5 times/week for 10 applications.	No deaths or signs of toxicity during the two weeks other than skin irritation due to the exaggerated exposure condition. Necropsy and hematology revealed no notable findings.
Ocular Irritation					
12	Rabbit Eye Irritation	#T-7121 2% placebo in shampoo at pH 4.5	191-082 AN 21611	4 male and 5 female New Zealand rabbits divided into 3 groups of 3 dosed in one eye each. Group I - 0.1 ml of the undiluted test material in unwashed eyes. Group II - 0.1 ml of undiluted test material in washed eyes. Group III - 0.1 ml of a 10% (w/w) solution in water (unwashed eyes). Eyes were examined for up to 35 days.	Group I: Maximum Average Score (MAS) = 39.3; eye irritant Group II: MAS = 10.7; eye irritant Group III: MAS = 6.7; not an eye irritant No significant differences between the three formulations. Formulations are no more irritating than currently marketed products.
13		#T-7120 2% OP in shampoo at pH 4.5	191-081 AN 21612	5 male and 4 female New Zealand rabbits divided into 3 groups of 3 dosed in one eye each. Group I - 0.1 ml of the undiluted test material in unwashed eyes. Group II - 0.1 ml of undiluted test material in washed eyes. Group III - 0.1 ml of a 10% (w/w) solution in water (unwashed eyes). Eyes were examined for up to 35 days.	Group I: Maximum Average Score (MAS) = 39.3; eye irritant Group II: MAS = 10.7; eye irritant Group III: MAS = 6.7; not an eye irritant

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14		#T-7119 2% OP in shampoo at pH 7.5	191-080 AN 20032	4 male and 5 female New Zealand rabbits divided into 3 groups of 3 dosed in one eye each. Group I - 0.1 ml of the undiluted test material in unwashed eyes. Group II - 0.1 ml of undiluted test material in washed eyes. Group III - 0.1 ml of a 10% (w/w) solution in water (unwashed eyes). Eyes were examined for up to 35 days.	Group I: Maximum Average Score (MAS) = 39.3; eye irritant Group II: MAS = 10.7; eye irritant Group III: MAS = 9.0; possible eye irritant
15	Rabbit Eye Irritation	#G0506.01 0.3% OP in hair conditioner. Undiluted material was tested.	HZRT-50106724 AN 30619	6 rabbits tested with 0.01 ml of test material (unwashed).	Test material was mild to the eyes. Conjunctivitis (6 of 6 eyes) was the only sign produced (MAS=1.7). Three eyes cleared within 1 day and 3 within 2 days.
16	Rabbit Eye Irritation	#E2414.01 1% OP in shampoo Undiluted material used for testing.	ECM BTS 930 AN 31973	Group 1: 0.01 ml, undiluted, eyes unrinsed, six rabbits Group 2: 0.01 ml, undiluted, eyes rinsed after 4 seconds, three rabbits	Group 1: MAS = 11, test material is a moderate irritant Group 2: MAS < 1
17	Rabbit Eye Irritation (Low Volume)	#E2414.01 1% OP in shampoo. Undiluted material was tested.	HUNT-84981D AN 31974	Rabbits dosed with 0.01 ml; rinsed and non-rinsed	Non-rinsed: MAS = 11, C/I = 4/6, last eye clear in 14 days Rinsed: MAS = <1, C/I = 0/3, last eye clear in 2 days
Skin Irritation					
18		#T-7121 2% placebo in shampoo at pH 4.5	191-082 AN 19199	3 male New Zealand White rabbits exposed to two patches on the back with 0.4 ml applied as a 10% (w/w) solution in distilled water for 24 hr. One patch was applied to intact skin and the other to abraded skin. Test sites were graded at 24 and 72 hr.	NOT a primary skin irritant. Primary Irritation Score = 4.0
19	Primary Skin Irritation in	#T-7120 2% OP in shampoo at pH 4.5	191-081 AN 19198	1 male and 2 female New Zealand White rabbits exposed to two patches on the back with 0.4ml applied as a 10% (w/w) solution in distilled water for 24 hr. One patch was applied to intact skin and the other to abraded skin. Test sites were graded at 24 and 72 hr.	NOT a primary skin irritant. Primary Irritation Score = 4.7

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No	Test Type	Test Substance	Study #	Treatment Conditions	Results
20	Rabbits	#T-7119 2% OP in shampoo at pH 7.5 0.4 ml applied as a 10% (w/w) solution in distilled water.	191-080 AN 21613	2 male and 1 female New Zealand White rabbits exposed to two patches with 0.4ml. applied as a 10% (w/w) solution in distilled water. One patch was applied to intact skin and the other to abraded skin.	Moderately irritating to the skin.
21	Rabbit Skin Irritation Patch Test	#G0506.01 0.3% OP in conditioner. Undiluted test material was used.	B85-0065 AN30419	3 rabbits per test group. 0.4 ml of test material applied to patch. Patches were removed after 4 hrs and excess material removed. Sites were evaluated at 0.5, 24 and 72 hours post-treatment.	Primary Irritation Index = 0.44 – mild to the skin The test substance produced erythema only at 4.5 hours. This irritation cleared by 24 hrs.
22	Rabbit Skin Irritation Patch Test	#E2414.01 1% OP in shampoo	IBRE-1-3-599-84 IBRE-1-3-600-84 AN 32038	Test material tested at 1 and 5% dilution. 0.4 ml of the substance applied to pad. Applied to intact and abraded skin. The site was graded at 24 and 72 hrs after application of patch.	Primary Irritation Index at both 1 and 5 % dilution on both intact and abraded skin = 0. E2414.01 is considered to be non-irritating.
23	Skin Irritation in the Muta Mouse	#G0539.05 OP in ethanol	B91-0116 AN 36814	A single dose of Octopirox (7.5, 10 or 15 mg) was applied to the shaved dorsal skin in 0.1 ml of ethanol.	Purpose was a range finding study for a DNA synthesis inhibition study with OP. Dose response for irritation induced by Octopirox was sharp and the Maximum Tolerated Dose was determined to be 7.5 mg. Slight to moderate irritation was caused by 7.5 mg while focal ulceration and severe irritation were induced by single doses of 10 and 15 mg.
Skin Delayed Contact Hypersensitivity					
24	Guinea Pig Delayed Contact Hypersensitivity	#E2414.01 1% OP in shampoo Undiluted material used for testing.	ECMS 930 2-5-598-84 AN 31973	Modified Buchler test	No evidence of delayed contact hypersensitivity.
Genotoxicity Studies					
25	Drosophila Mutagenicity Assay	#G0539.03 OP in ethanol and sucrose	UWIS TXAS-123 AN 34137	Drosophila melanogaster males exposed by feeding for 3 days (1000 ppm in 10% ethanol and 5% sucrose) or injection (500 ppm in 5% ethanol and 0.7% NaCl).	Does not induce mutations in the post-meiotic germ cells of Drosophila melanogaster males when administered by feeding or by injection.

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26	CHO/HGPRT Mutation Assay	#G0539.02 OP in ethanol	T4920.332 AN 32637	CHO/HGPRT mutation tested in the absence and presence of an Aroclor-induced rat liver S-9 activation system. This was conducted at dose levels of 20, 15, 5 and 1 ug/ml in the non-activated study and at 150, 80, 40, 10 and 1 ug/ml in the presence of S-9.	With S-9 activation: Mutation frequencies 2X solvent control and not dose dependent. Suspect positive. Without activation: No increase in mutation frequency.
27	SHE Transformation Assay	G0539.04 OP in DMSO	B89-0174 AN 35709	SHE cells were cultured in the presence of OP for 7 days then fixed/stained. 5 doses of OP ranging from 0.1 to 0.35 ug/ml.	OP induced statistically significant increase in the morphological transformation frequency at a concentration of 0.3 ug/ml. No significant response occurred below this concentration.
28	SHE Transformation Assay	#G0539.05	B90-3001 AN 36561	Primary assay modification was the length of time of SHE cell exposure to the test material. The exposure time was reduced to 24 hours from the usual exposure of 7 days then fixed/stained. 4 doses of OP tested ranging from 0.2 to 0.35 ug/ml.	Octopirox caused a significant increase in morphological transformation frequency at four dose levels, compared to solvent controls and thus the test material is considered positive. Additionally, it can be concluded that this transformation represents a stable change in these cells, as evidenced by the persistence of this phenotype 7 days after the removal of the test material.
29	Mouse Lymphoma Assay	#G0539.01 OP in ethanol	T2982.701 AN 30869	Thymidine kinase locus of L5178Y TK+/- Mouse Lymphoma cells mutation tested in the absence and presence of Aroclor-induced rat liver S-9. Test article concentration from 1.3 to 100 ug/ml for S-9 activated cultures and 0.13 to 10 ug/ml for non-activated cultures.	With S-9 activation: No increase in mutation frequency Without S-9 activation: The increases in mutant frequency ranged from 2 to 5.8 fold.
30	Mouse Lymphoma Assay in presence and absence of transferrin	#G0539.03 OP in ethanol	0066-2400 AN 34002	Thymidine kinase locus of L5178Y TK+/- Mouse Lymphoma cells mutation tested in the absence and presence of Aroclor-induced rat liver S-9. Studies done in the presence and absence of transferrin.	Positive dose-dependent responses were produced both in the presence and absence of S-9; the test article was less toxic when treatment was performed in conjunction with S-9. No significant difference in the toxic response or mutant frequencies was evident between the cultures treated with or without transferrin in the presence of S-9.

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No.	Test Type	Test Substance	Study #	Treatment Conditions	Results
31	Inhibition of DNA Synthesis in CD-1 Mouse Epidermis <i>In Vivo</i>	#G0539.05, #BPO-5884 Shampoo containing 1% OP (with and without [6-C ¹⁴]-Octopirox Various concentrations of OP in ethanol	B90-0258B, B90-0258C, B90-0269A, B90-0269B, B90-0338B, B91-0033, B91-0044 AN36985	Female CD-1 mice were evaluated for the potential of OP to inhibit epidermal DNA synthesis in ethanol or a shampoo matrix. Epidermal DNA synthesis was determined by measuring the incorporation of [3H]-thymidine into DNA. 1) Initial studies were done to determine dose response of OP inhibition of DNA synthesis. OP was applied topically in 0.1 ml ethanol and mice sacrificed 4 hr after treatment. 2) Deposition studies were done using a single dose of 1% OP in shampoo with either 0.2-0.3 ml of shampoo applied 1, 4 or 8 consecutive days. 3) Epidermal DNA synthesis was measured after 1 or 4 daily applications of shampoo with 1% OP	1) The lowest dose producing a statistically significant inhibition of epidermal DNA synthesis was 0.3 mg or 37.8 ug/cm ² which inhibited DNA synthesis. 2) After either 1 or 4 daily applications of OP-containing shampoo, followed by rinse off, the deposition of OP was 1 ug/cm ² . 3) Consistent with this level of deposition, and the dose response of OP in ethanol, the OP-containing shampoo did not cause detectable inhibition of epidermal DNA synthesis after 1,4 or 8 daily applications.
32	Unscheduled DNA synthesis	#G0539.01 (Stock solutions made with ethanol)	T2982.380 AN 30980	Rat primary hepatocytes tested at 6 dose levels ranging from 0.2 ug/ml to 50 ug/ml.	No induction of unscheduled DNA synthesis in rat primary hepatocytes.
33	DNA, RNA, and Protein Synthesis in L5178Y Mouse Lymphoma Cells and Syrian Hamster Embryo Cells in culture.	G0539 OP in ethanol	R and DD report YE-1083, YE-1305, YE-711, YE-1159 AN 36915	DNA, RNA and protein synthesis measured.	2 hr exposure to OP or PA inhibited DNA but not RNA or protein synthesis in both cell lines. Inhibition of DNA synthesis by OP persisted for at least 24 hrs. The iron chelate of OP had no effect on the rates of DNA, RNA or protein synthesis in L5178Y mouse lymphoma cells indicating inhibition of DNA synthesis by OP is associated with its ability to chelate ferric iron.

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34	DNA Synthesis in Mouse Epidermis	G0539.04 and Compound B are both solid OP G0539.04 dissolved in Tween 80 and water Compound B was solubilized in Solution A and water	B89-5000	Part I: Two concentrations of OP (G0539.04) compared to vehicle in 6 mice/group. Mice were dosed topically with 0.05 ml. These mice were dosed with tritiated thymidine 3 hrs after treatment. Three additional mice were dosed with OP and vehicle but were not given tritiated thymidine but processed for histopathology. Part II: Partial repeat of Part I with reformulated vehicle and vigorous stirring of dose solutions.	Part I: All test preparations induced moderate erythema in all mice by 4 hours after application. The high dose of OP was discarded due to high variance. Low dose of OP decreased epidermal DNA synthesis. Part II: Test preparation had no discernible effect on skin color or thickness 4 hours after application. OP in this experiment did not decrease epidermal DNA synthesis.
35	The Mechanism of Cell Growth Inhibition by Octopirox	G0539 OP in ethanol	G0539	L1210 mouse cells: Looked at effect of OP on dATP and dTTP concentrations and ³ H-thymidine incorporation. Cells treated for 2 hr. AG1518 human fibroblasts: Looked at effects of OP on DNA synthesis and UV-induced repair	Octopirox is a potent inhibitor of mouse L1210 cell growth and DNA replicative synthesis in both mouse L1210 cells and normal human fibroblasts, as measured by [³ H] thymidine incorporation into DNA. This inhibition correlates well with decrease in dATP and dTTP concentrations. Octopirox has no direct effect on enzymes involved in DNA replication. Investigator states these data are consistent with hypothesis that the cytotoxic effects of OP result from the specific inhibition of ribonucleotide reductase.
36	Inhibition of Epidermal DNA Synthesis in Muta Mouse	G0539.05, G0539.06 OP in ethanol	B91-0153 AN 36907	Epidermal DNA synthesis in Muta Mouse was determined by measuring the incorporation of ³ H-thymidine into DNA. Single doses on shaved skin ranged from 0.075 to 7.5 mg. The dose response was determined two hours after dosing.	Octopirox transiently inhibits epidermal DNA synthesis in Muta Mouse when applied in ethanol. The stimulation of DNA synthesis by Octopirox is also consistent with the observation that it induces hyperplasia in Muta Mouse skin.
37	Mutation in the skin of Muta Mouse <i>In vivo</i>	G0539.06 OP in ethanol	B91-0227	A single application of 0.1ml of a 7.5% solution of OP in ethanol was topically applied to Muta Mouse skin. This dose was previously determined to be a maximum tolerated dose. Three mice per group were dosed.	The potential of Octopirox to induce mutations in skin was evaluated using Muta Mouse. This transgenic strain was developed to allow the detection of mutation in any tissue <i>in vivo</i> . The maximum tolerated dose was not mutagenic though in previous studies it had been shown to inhibit DNA synthesis in the Muta Mouse. See study above (B91-0153).

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Reproduction Toxicity					
38	Percutaneous Teratology of Octopirox in Rabbits	#T-0184.01	191-259 AN 31622	0, 10, and 30% OP in isopropanol/water (1/1) applied dermally (2ml/kg) for 4 hours on days 7-18 of gestation. 80 rabbits used in study.	No teratogenic or fetogenic effects. At high dose pronounced maternal toxicity believed to be due to severe skin irritation evidenced by one death, four spontaneous abortions and a severe body weight loss. At low dose, only effect was severe irritation (no maternal toxicity).
39	Range Finding Study for Reproduction/ Fertility Study in Rats	#G0539.03 OP in PEG/methylcellulose/water vehicle	IRDC-191-1394 AN 34619	0, 50, 100 and 250 mg/kg/day of test material administered by gavage as a single daily dose (2 ml/kg) for 14 consecutive days. 5 male rats per group. Blood samples taken prior to study and on Day 14.	There were no treatment related clinical signs of toxicity. The doses used in this study were selected for the fertility study.
40	Reproduction/ Fertility Study in Rats	#G0539.03 OP in PEG/methylcellulose/water vehicle	IRDC-191-1395 AN 35225	Rats were dosed via gavage with 1, 10, 100, and 250 mg/kg/day OP. 35 males and 35 females per group. Males were dosed 64 days prior to mating through sacrifice. Females were dose 14 days prior to mating through 3 wks after parturition.	NOEL for general toxicity: 10 mg/kg/day NOEL for neonatal growth: 100 mg/kg/day NOEL for reproductive parameters: 250 mg/kg/day
41	14-Day Range Finding Study in Rats for Reproduction/ Teratology Study	#G0539.01 OP in diet.	B85-0179 AN 30604	6 groups adult female Sprague-Dawley rats; OP was fed in the daily diet at doses of 0, 50, 100, 250, 500, or 1000 mg/kg/day for 14 consecutive days.	The maximum tolerated dose was determined to be 500 mg/kg.
42	A One-Generation Reproduction and Teratology Study in Rats	#G0539.02 OP in diet	B85-0460 AN 33895	Male and female Charles River CD rats (25 males and 25 females per group) were fed diets containing OP to deliver doses of 0, 50, 100, or 300 mg/kg/day for one generation.	OP was extremely toxic to rats at the 300-mg/kg/day-dose level in the diet and was believed to be due to chelation of iron as evidenced by severe anemia. At the 100-mg/kg dose a less severe anemia was produced which was not lethal in adult animals, but decrease survivability of neonates. Although OP was not frankly teratogenic, there were secondary effects on embryos and fetuses as a result of the dam's anemic state. The study was terminated after the F1B generation so no NOEL was established.

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Supplemental Toxicity					
43	The Effects of Dietary Iron Supplementation on the Toxicity of Octopirox in the Young Growing Rat	#G0539.02 OP in diet	B86-0272 AN 33376	10 female and 10 male Charles River CD rats placed in feed and dosed 300-mg/kg/ day of OP. Rats were supplemented with 0, 50, 100 or 200 ppm dietary iron for 6 weeks.	Adding supplemental iron to the diet at 3 levels completely prevented the effects of Octopirox on growth for both sexes. In either sex there were no significant differences in body weights, or in the gain in body weight, during the six-week period between the iron supplemented Octopirox treated rats and the controls. It was concluded that the mechanism of OP toxicity was the prevention of dietary iron absorption by in situ chelation.
44	Emetic Study in Beagle Dogs	#G0506.01 0.3% OP in hair conditioner	B85-6007 AN 30487	Purebred beagle dog dosed by gastric intubation with a single dose of the undiluted test material. The first dosage tested was 16.0 ml/kg.	ED50 for emesis was greater than 16.0 ml/kg. Could not go higher as volume limit would be exceeded. This test indicated that the conditioner with 0.3% OP is essentially non-emetic.

OP = Octopirox