TOXICOLOGICAL MANIFESTATIONS OF 2,4,5,-2′,4′,5′-, 2,3,6,2′,3′,6′-, AND 3,4,5,3′,4′,5′-HEXACHLOROBIPHENYL AND AROCLOR 1254 IN MINK

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Adult female mink were fed diets that contained 2.5 ppm Aroclor 1254, 0.1 or 0.5 ppm 3,4,5,3′,4′,5′-hexachlorobiphenyl (345 HCB), 2.5 or 5.0 ppm 2,4,5,2′,4′,5′ hexachlorobiphenyl (245 HCB) or 2,3,6,2′,3′,6′-hexachlorobiphenyl (236 HCB), or a control diet from 1 mo prior to breeding through parturition. All mink fed 0.5 ppm 345 HCB died within 60 d, while those fed 0.1 ppm showed 50% mortality after 3 mo exposure. Only one stillborn kit was whelped in the Aroclor 1254 group. No adverse reproductive effects were observed in the animals fed 236 HCB or 245 HCB. Plasma progesterone concentrations were significantly depressed by Aroclor 1254 and significantly elevated by 0.1 ppm 345 HCB. 17β-Estradiol concentrations were not significantly altered by any of the dietary treatments. Hepatic microsomal cytochrome P-450 concentrations were significantly elevated by all treatments except 236 HCB, with the largest increases occurring in mink exposed to Aroclor 1254 and 345 HCB. Aminopyrine N-demethylase activity was elevated by 5.0 ppm 236 HCB. Aroclor 1254 caused significant elevations in both benzo[a]pyrene hydroxylase and ethoxyresorufin O-deethylase activities. Benzo[a]pyrene hydroxylase activities were also significantly elevated in mink fed 245 HCB and 345 HCB. Aroclor 1254 caused a significant elevation in cerebellar and hypothalamic norepinephrine concentrations and a significant elevation in hypothalamic dopamine concentrations. Cerebral dopamine was elevated by 0.1 ppm 345 HCB, while midbrain dopamine levels were depressed. Norepinephrine concentrations were significantly elevated by 5.0 ppm 236 HCB in the midbrain and by 5.0 ppm 245 HCB in the medulla.

INTRODUCTION

Numerous studies (Ringer et al., 1972; Platonow and Karstad, 1973; Jensen et al., 1977; Aulerich and Ringer, 1977, 1980; Bleavins et al., 1980) have demonstrated that mink (*Mustela vison*) are among the most sensitive species to polychlorinated biphenyls (PCBs). LC50 values for mink fed Aroclors 1242 and 1254 (PCB trade names; formerly manufactured

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by Monsanto Co., St. Louis, Mo.) have been estimated to be 8.6 and 6.7 ppm, respectively (Ringer et al., 1981). Fetotoxicity at dietary concentrations below 5 ppm and reproductive failure at 2 ppm have been reported for mink fed these Aroclors (Aulerich and Ringer, 1977). According to Platonow and Karstad (1973) and Hornshaw et al. (1983), reproductive impairment occurs in mink at even lower concentrations when the PCBs have been first metabolized by another species, and then fed to mink.

Mink show a wide range of sensitivity to commercial preparations of PCBs, and PCB toxicity to mink has been directly related to the chlorine content of the PCB mixture, and more specifically to the percentage of molecules with highly substituted biphenyl isomers (Bleavins et al., 1980). Studies with other species have shown that, in addition to the number and location of the chlorine atoms, the rate of excretion and enzyme inducing ability of the compounds have an important bearing on their toxic potency (Matthews et al., 1978). Attempts have been made to correlate toxicity with the enzyme induction modes of PCB congeners with the 3-methylchloanthrene- (3MC-) type inducers possessing greater toxicity than the phenobarbital- (PB-) type inducers (Poland and Glover, 1977; Yoshimura et al., 1979).

Since commercial PCBs, such as the Aroclors, consist of a complex mixture of various chlorobiphenyl congeners, as well as highly toxic contaminants such as dibenzofurans (Bowes et al., 1975), which complicate hazard assessment, it was of interest to investigate the toxicodynamics of three symmetrical pure PCB congeners, 3,4,5,3′,4′,5′-hexachlorobiphenyl (345 HCB), 2,4,5,2′,4′,5′-hexachlorobiphenyl (245 HCB), and 2,3,6,2′,3′,6′-hexachlorobiphenyl (236 HCB) possessing different enzyme-inducing ability in the extremely sensitive mink.

MATERIALS AND METHODS

Ninety standard dark female mink (proven breeders) were randomly allocated into eight groups and placed on dietary treatments on January 31, 1983, as listed in Table 1.

The treated diets were prepared by dissolving Aroclor 1254 or the PCB congeners in corn oil and mixing the solution with finely ground mink cereal to form a premix, which was then added in appropriate amounts to the other ingredients of the diet to yield the desired concentrations of PCB.

The mink were housed individually in cages (72.2 cm L X 61 cm W X 45.7 cm H) with attached nest boxes (38.1 cm L X 29.2 cm W X 26.7 cm H) suspended above the ground in an open-sided pole-type building. Routine commercial mink farm procedures were followed in caring for the animals. Feed and water were provided *ad libitum*.

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TABLE 1. Mink Dietary Treatments

Group	n	Treatment
1	20	Basal diet.[a] No supplemental PCB (control).
2	10	Basal diet plus 2.5 ppm PCB Aroclor 1254.
3	10	Basal diet plus 2.5 ppm 245 HCB.[b]
4	10	Basal diet plus 5.0 ppm 245 HCB.
5	10	Basal diet plus 2.5 ppm 236 HCB.[b]
6	10	Basal diet plus 5.0 ppm 236 HCB.
7	10	Basal diet plus 0.1 ppm 345 HCB.[c]
8	10	Basal diet plus 0.5 ppm 345 HCB.

[a]Basal diet, as fed, consisted of 20% commerical mink cereal, 24% whole chicken, 15% ocean fish scrap, 8% beef tripe, 4% beef trimmings, 4% beef lungs, 4% beef liver, and 21% added water.
[b]Ultra Scientific, Hope, R.I.
[c]Pathfinder Laboratories, St. Louis, Mo.

basal (control) diet. Each female was given an opportunity for a second mating, either the day after the first mating or 8 d later (common commercial mink farm practice). All matings were verified by the presence of motile spermatozoa in vaginal aspirations taken immediately after copulation. Kits (newborn mink) were counted and weighed to the nearest g the day of birth.

Mink body weights were recorded at the start of the study and at 4 and 8 wk on treatment and at necropsy. Necropsies were performed on the females that whelped, within 1–7 d after parturition, and on all surviving barren females between April 28 (88 d) and May 12, 1983 (102 d). Prior to necropsy, blood samples were collected, via cardiac puncture, for determination of plasma 17β-estradiol and progesterone concentrations. Commercial radioimmunoassay procedures (estradiol, Serno Labs Inc., Braintree, Mass.: progesterone, Micromedic Systems Inc., Horsham, Pa.) were used in these analyses. Organ weights (brain, liver, kidneys, spleen, lungs, heart, and adrenals) were recorded, and samples of liver and brain were collected and frozen for determination of hepatic microsomal mixed-function oxidase activity and brain biogenic amine concentrations. The induction response of the PCBs was determined by assessing cytochrome P450 concentrations (Omura and Sato, 1964) and the activities of aminopyrine (AP) *N*-demethylase (Anders and Mannering, 1966), benzo[a]pyrene (BaP) hydroxylase (Van Cantfort et al., 1977), and ethoxyresorufin (ER) *O*-deethylase (Burke and Mayer, 1975). The brains were dissected into five regions (cerebellum, medulla, hypothalamus, midbrain, and cerebral hemispheres) and assayed for norepinephrine (NE) and dopamine (DA) and serotonin (5-HT) by the method of Jacobowitz and Richardson (1978).

TABLE 2. Initial Body Weights and Weight Gains (or Loss) of Female Mink Fed a Control Diet or Diets that Contained Aroclor 1254 or Various PCB Congeners

Dietary treatment	Initial weight (g), 1-31-83	Body weight gain (or loss) (g)		
		4 wk	8 wk	Necropsy (12.5–14.5 wk)
Control	927 ± 19.7[a] (20)	66 ± 11.5[b] (20)	2 ± 14.5[b] (20)	59 ± 20.7[b] (19)[f]
2.5 ppm Aroclor 1254	928 ± 31.9 (10)	21 ± 10.9[b,c] (10)	2 ± 17.9[b] (9)	4 ± 2.3[b] (9)
2.5 ppm 245 HCB	959 ± 38.3 (10)	43 ± 17.6[b] (10)	−31 ± 24.2[b,c] (10)	42 ± 30.5[b] (9)
5 ppm 245 HCB	936 ± 41.4 (10)	47 ± 12.2[b] (10)	−32 ± 19.7[b,c] (10)	32 ± 22.6[b] (10)
2.5 ppm 236 HCB	919 ± 27.9 (10)	44 ± 11.3[b] (10)	44 ± 17.3[b,c] (9)[f]	37 ± 21.8[b] (9)
5 ppm 236 HCB	938 ± 59.4 (10)	−9 ± 21.3[c] (10)	−72 ± 24.5[c] (10)	12 ± 21.4[b] (10)
0.1 ppm 345 HCB	982 ± 36.2 (10)	−61 ± 14.5[d] (10)	−233 ± 25.2[d] (8)	250 ± 15.3[c] (5)
0.5 ppm 345 HCB	972 ± 38.5 (10)	−238 ± 34.2[e] (10)	−457 ± 12.5[e] (2)	

[a]Mean ± SE, n given in parentheses.
[b–e]Means within the same column with the same superscript are not significantly different ($p < 0.05$).
[f]No mortalities. One control female and one 236 HCB-treated female were not necropsied due to injuries unrelated to treatment.

Where appropriate the data were subjected to analysis of variance (Snedecor, 1956). Comparisons between means were made by Tukey's (Snedecor, 1956) or Dunnett's two-tailed *t*-test (Gill, 1978).

RESULTS

As shown by the data presented in Table 1, the body weight gains of the mink that received the diets treated with Aroclor 1254, 2.5 or 5.0 ppm of 245 HCB, or 2.5 ppm of 236 HCB did not differ significantly from the control. Consumption of 5 ppm 236 HCB had a generally depressing effect on mink body weight gains but not nearly as great as that of the 345 HCB congener. Only 50% of the mink fed 0.1 ppm 345 HCB survived 12.5 wk of exposure, and all of the animals that received 0.5 ppm of this congener died prior to the termination of the study (Table 3).

Common clinical signs observed in the mink fed 345 HCB that died during the study included anorexia, gastric ulcers, bloody stools, ascites, degenerative changes in the kidneys, pancreatomegaly, and alopecia. The effects of the dietary treatments on relative organ weights of the mink that died during the study and of mink that were necropsied at the termination of the study are shown in Table 4. Compared to the controls, the mink fed Aroclor 1254 had increased liver weights, while those that received the 0.1 ppm 345 HCB diet showed a significant decrease in heart weight and increase in adrenal weight. The mink fed the 0.5 ppm 345 HCB diet had significantly lower spleen and heart weights and higher kidney weights than the control.

TABLE 3. Mortality and Survival Time of Female Mink That Died while Receiving PCB-Supplemented Diets.

Dietary treatment	Mortality (%)	Survival time (d)[a]	% Initial body weight at death[a]
Control	0		
5 ppm Aroclor 1254	10[b]	56	[illegible]
2.5 ppm 245 HCB	10[c]	74	[illegible]
5 ppm 245 HCB	6		
2.5 ppm 236 HCB	0		
5 ppm 236 HCB	0		
0.1 ppm 345 HCB	50	61 (51–72)	54 (50–59)
0.5 ppm 345 HCB	100	46 (29–72)	54 (45–67)

[a]Mean (range).
[b]Necropsy revealed severe urinary-tract infection.
[c]Necropsy revealed metritis.

TABLE 4. Mean Body Weight and Relative Organ Weights of Female Mink Fed a Control Diet or Diets that Contained Aroclor 1254 or Various PCB Congeners

Dietary treatment	Number[a]	Body weight (g)[b]	Brain weight (g)[b]	Organ weight (expressed as a percentage of brain weight)[b]					
				Liver	Spleen	Kidneys	Lungs	Heart	Adrenals[c]
Control	19	980 ± 19.3	7.5 ± 0.09	388 ± 21.2	69 ± 5.1	60 ± 1.5	88 ± 3.9	67 ± 1.6	0.86 ± 0.05
2.5 ppm Aroclor 1254	10 (1)	904 ± 31.7	7.4 ± 0.16	474 ± 21.8[d]	58 ± 11.4	64 ± 3.0	92 ± 6.5	65 ± 2.0	0.99 ± 0.06
2.5 ppm 245 HCB	10 (1)	976 ± 48.6	7.4 ± 0.15	467 ± 31.0	79 ± 15.1	62 ± 2.4	90 ± 3.3	66 ± 2.4	1.09 ± 0.06
5 ppm 245 HCB	10	968 ± 45.0	7.6 ± 0.17	384 ± 18.7	69 ± 5.9	57 ± 2.2	83 ± 2.3	65 ± 1.5	0.81 ± 0.05
2.5 ppm 236 HCB	9	946 ± 34.1	7.4 ± 0.18	396 ± 22.0	68 ± 6.7	56 ± 1.3	85 ± 2.6	67 ± 1.4	0.88 ± 0.04
5 ppm 236 HCB	10	925 ± 41.8	7.4 ± 0.19	367 ± 27.0	55 ± 4.6	59 ± 3.6	83 ± 3.3	66 ± 2.2	0.83 ± 0.07
0.1 ppm 345 HCB	10 (5)	666 ± 62.15[e]	7.8 ± 0.17	392 ± 27.5	46 ± 4.0	66 ± 2.1	92 ± 4.7	54 ± 2.5[e]	1.92 ± 0.26[e]
0.5 ppm 345 HCB	10 (10)	528 ± 24.7[e]	7.7 ± 0.15	351 ± 18.0	30 ± 2.5[e]	76 ± 5.8[e]	107 ± 10.4	53 ± 3.0[e]	

[a]Number in parenthesis = number of mink that died during the experiment. Survivors were necropsied after 88–102 d on treatment.
[b]Mean ± SE.
[c]No adrenal weights were recorded for mink that died during the experiment.
[d]Significantly different ($p < 0.05$) from control by Dunnett's t-test.
[e]Significantly different ($p < 0.01$) from control by Dunnett's t-test.

The reproductive performance of the mink on the various dietary treatments is presented in Table 5. No differences were noted in the reproductive parameters measured between the controls and mink fed 245 HCB or 236 HCB. Gestation in mink averages 51.3 ± 5.42 (SD) d but is normally variable because of an irregular delay in implantation of fertilized ova (Hansson, 1947).

Only one of the ten mated females that received Aroclor 1254 whelped. This female gave birth to a single stillborn kit. Six of the other females fed Aroclor 1254 showed evidence of uterine implantation sites at necropsy. The females fed 345 HCB either died prior to the mating season (March) or failed to whelp if they mated. Implantation sites were observed in 2 of the 5 females fed 0.1 ppm of 345 HCB that survived to the termination of the study. The mean plasma 17β-estradiol and progesterone concentrations of the females that survived to the termination of the study are shown in Table 6.

In this study, cytochrome P-450 concentrations were significantly increased in all groups of treated mink except those fed the 236 HCB congener (Table 7). The greatest induction occurred in the mink fed Aroclor 1254 and 345 HCB. Significant increases in AP *N*-demethylase were observed only in the animals fed the highest level of 245 HCB. Feeding Aroclor 1254 resulted in significant induction of both BaP hydroxylase and ER *O*-deethylase. BaP hydroxylase concentrations wre also significantly elevated in the mink fed the 245 HCB- and 345 HCB-treated diets. Although all the treated groups showed elevated ER *O*-deethylase activity, only the mink fed Aroclor 1254 had values significantly greater than the control (Table 7). No significant induction of any of these enzymes occurred in the mink exposed to 236 HCB.

Analyses of brain biogenic amine concentrations, as shown in Table 8, revealed several instances where PCB-treated mink has significantly elevated NE or DA concentrations in various parts of the brain when compared to the control. However, no significant ($p < 0.05$) differences from control values were noted in 5-HT concentrations of the treated mink.

DISCUSSION

The results of this study indicate that mink are considerably more sensitive to the PCB congener 345 HCB than to 245 HCB or 236 HCB or to the commerical PCB mixture, Aroclor 1254. These findings are consistent with those of Biocca et al. (1976) in which they found the 345 HCB congener to be the most toxic of several symmetrical HCB isomers (including 245 HCB and 236 HCB) when fed to chicks or mice. The relative difference in sensitivity of mink and mice to 345 HCB is, however, readily apparent when one compares the 0, 20, and 60% mortality observed in mice fed 10, 30, and 100 ppm 345 HCB, respectively, for 28 d with the

[a] No adrenal weights were recorded for mink [illegible]
[b] Significantly different ($p < 0.05$) from control by Dunnett's *t* test.
[c] Significantly different ($p < 0.01$) from control by Dunnett's *t*-test.

TABLE 5. Reproductive Performance of Female Mink Fed a Control Diet or Diets That Contained Aroclor 1254 or Various PCB Congeners

Dietary treatment	Number of females whelped per number mated	Gestation[a,b] (d)	Number of kits whelped			Litter size per female whelped[b,c]		Kit body weight at birth[b,c]
			Total	Alive	Dead	At birth	At necropsy	
Control	19/20	48.6 ± 0.88	111	105	6	5.5 ± 0.22	5.0 ± 0.27	10.1 ± 0.16
2.5 ppm Aroclor 1254	1/10	50.0	1	0	1	–	–	
2.5 ppm 245 HCB	8/10	48.5 ± 2.06	34	31	3	3.9 ± 0.72	2.5 ± 0.71	9.3 ± 0.44
5 ppm 245 HCB	10/10	48.4 ± 1.57	60	52	8	5.2 ± 0.59	5.0 ± 0.63	10.3 ± 0.19
2.5 ppm 236 HCB	9/10	49.1 ± 1.55	51	49	2	5.4 ± 0.48	5.0 ± 0.41	10.0 ± 0.24
5 ppm 236 HCB	8/10	51.6 ± 2.29	46	43	3	5.4 ± 0.84	4.9 ± 1.01	9.6 ± 0.21
0.1 ppm 345 HCB	0/8		–	–	–	–	–	
0.5 ppm 345 HCB	–/0	–	–	–	–	–	–	

[a]Based on date of last mating.
[b]Mean ± SE.
[c]Based on live kits.

[a]Based on date of last mating.
[b]Mean ± SE.
[c]Based on five kits.

TABLE 6. Plasma 17β-Estradiol and Progesterone Concentrations of Female Mink Fed a Control Diet, Aroclor 1254, or Various PCB Congeners

Dietary treatment	n	17β-Estradiol (pg/ml plasma)[a]	n	Progesterone (ng/ml plasma)[a]	Reproductive status of females
Control	17	2.2 ± 0.69	18	3.4 ± 0.20	Whelped[b]
2.5 ppm Aroclor 1254	5	7.2 ± 3.41	8	1.3 ± 0.34[e]	Mated but failed to whelp[c]
2.5 ppm 245 HCB	6	3.0 ± 1.05	8	2.5 ± 0.44	Whelped[b]
5.0 ppm 245 HCB	10	1.0 ± 0.30	10	2.4 ± 0.30	Whelped[b]
2.5 ppm 236 HCB	8	1.8 ± 0.50	9	3.5 ± 0.44	Whelped[b]
5.0 ppm 236 HCB	8	3.7 ± 1.08	8	3.4 ± 0.63	Whelped[b]
0.1 ppm 345 HCB	5	3.3 ± 0.72	5	9.1 ± 1.39[e]	Mated but failed to whelp[d]
0.5 ppm 345 HCB	–	–	–	–	Died prior to mating

[a]Mean ± SE.
[b]All females whelped and were sampled within 7 d of parturition.
[c]Blood samples collected for assay 5-3-83 or 5-12-83.
[d]Blood samples collected for assay 4-28-83.
[e]Significantly different ($p < 0.01$) from control by Dunnett's t-test.

TABLE 7. Concentration of Microsomal Cytochrome P-450 and Activity of Hepatic Mixed-Function Oxidases in Female Mink Fed a Control Diet or Diets That Contained Aroclor 1254 or Various PCB Congeners

Dietary treatment	n	Cytochrome P-450[a] (nmol/mg protein)	n	Mixed-function oxidases (nmol/mg protein/min)[a]		
				Aminopyrine N-demethylase	Benzo[a]pyrene hydroxylase	Ethoxyresorufin O-deethylase
Control	15	0.71 ± 0.109	19	2.72 ± 0.341	0.22 ± 0.017	0.08 ± 0.007
2.5 ppm Aroclor 1254	9	2.26 ± 0.326[c]	9	2.66 ± 0.277	0.71 ± 0.045[c]	0.19 ± 0.015[c]
2.5 ppm 245 HCB	8	1.50 ± 0.216[b]	9	3.50 ± 0.302	0.43 ± 0.055[c]	0.11 ± 0.015
5.0 ppm 245 HCB	8	1.51 ± 0.324[b]	10	4.76 ± 0.562[c]	0.35 ± 0.023[b]	0.12 ± 0.015
2.5 ppm 236 HCB	9	0.48 ± 0.090	10	2.26 ± 0.227	0.22 ± 0.020	0.12 ± 0.031
5.0 ppm 236 HCB	10	1.14 ± 0.220	10	2.99 ± 0.611	0.32 ± 0.039	0.11 ± 0.030
0.1 ppm 345 HCB	3	2.62 ± 0.306[c]	8	1.48 ± 0.218	0.60 ± 0.048[c]	0.15 ± 0.009
0.5 ppm 345 HCB						

[a]Mean ± SE.
[b]Significantly different ($p < 0.05$) from control by Dunnett's t-test.
[c]Significantly different ($p < 0.01$) from control by Dunnett's t-test.

[a]Mean ± SE.
[b]Significantly different ($p < 0.05$) from control by Dunnett's t-test.
[c]Significantly different ($p < 0.01$) from control by Dunnett's t-test.

TABLE 8. Biogen[illegible] Milk Fed a Control Diet or Diets That Contained Aroclor 1254 or Various PCB Congeners

Dietary treatment	n	Midbrain	Cerebral hemispheres	Medulla	Hypothalamus	Cerebellum
			Norepinephrine (ng/g)			
Control	19	195 ± 11.9[a]	46 ± 3.8	194 ± 5.0	467 ± 26.4	56 ± 3.6
2.5 ppm Aroclor 1254	9	242 ± 17.4	62 ± 6.3	222 ± 16.6	625 ± 44.5[b]	81 ± 4.7[c]
2.5 ppm 245 HCB	9	231 ± 18.7	58 ± 4.1	218 ± 11.6	470 ± 38.1	63 ± 9.8
5.0 ppm 245 HCB	10	236 ± 13.6	47 ± 3.9	232 ± 10.4[b]	487 ± 60.1	65 ± 4.3
2.5 ppm 236 HCB	10	220 ± 18.7	52 ± 6.0	220 ± 14.5	492 ± 40.4	71 ± 4.5
5.0 ppm 236 HCB	10	260 ± 14.9[c]	51 ± 5.6	226 ± 9.9	535 ± 44.7	62 ± 6.7
0.1 ppm 345 HCB	5	185 ± 19.9	66 ± 12.0	186 ± 6.1	336 ± 37.5	54 ± 6.4
0.5 ppm 345 HCB		—		—	—	—
			Dopamine (ng/g)			
Control	19	499 ± 61.5	195 ± 21.1	122 ± 5.6	522 ± 49.2	54 ± 3.0
2.5 ppm Aroclor 1254	9	546 ± 39.4	260 ± 31.7	124 ± 7.4	925 ± 64.5[c]	55 ± 7.3
2.5 ppm 245 HCB	9	464 ± 121.1	219 ± 15.6	137 ± 9.0	501 ± 86.2	55 ± 2.5
5.0 ppm 245 HCB	10	494 ± 108.4	198 ± 15.8	131 ± 8.5	557 ± 60.8	53 ± 2.7
2.5 ppm 236 HCB	10	604 ± 103.5	221 ± 23.8	133 ± 8.2	556 ± 82.6	59 ± 6.0
5.0 ppm 236 HCB	10	587 ± 77.1	197 ± 18.3	119 ± 7.5	622 ± 89.7	60 ± 6.2
0.1 ppm 345 HCB	5	130 ± 20.6[c]	324 ± 69.2[b]	108 ± 11.4	330 ± 58.2	61 ± 13.6
0.5 ppm 345 HCB		—			—	
			Serotonin (ng/g)			
Control	19	999 ± 81.7	189 ± 14.3	932 ± 36.2	577 ± 51.1	175 ± 12.5
2.5 ppm Aroclor 1254	9	1011 ± 84.1	189 ± 10.9	795 ± 57.1	516 ± 51.5	172 ± 17.0
2.5 ppm 245 HCB	9	1029 ± 126.8	193 ± 7.8	879 ± 60.8	649 ± 50.3	209 ± 28.7
5.0 ppm 245 HCB	10	943 ± 92.3	164 ± 13.9	870 ± 71.1	639 ± 55.6	191 ± 28.3
2.5 ppm 236 HCB	10	912 ± 117.8	212 ± 25.9	895 ± 56.0	587 ± 74.3	200 ± 23.5
5.0 ppm 236 HCB	10	1135 ± 111.4	209 ± 24.8	847 ± 98.6	603 ± 87.6	227 ± 18.1
0.1 ppm 345 HCB	5	902 ± 91.8	155 ± 14.6	625 ± 44.5	615 ± 71.4	90 ± 6.3
0.5 ppm 345 HCB		—		—	—	

[a]Mean ± SE.
[b]Significantly different ($p < 0.05$) from control by Dunnett's t-test.
[c]Significantly different ($p < 0.01$) from control by Dunnett's t-test.

100% mortality noted in the mink that received the 0.5 ppm 345 HCB supplemented diet in this study (see Table 3).

Assuming female mink consume 115 g feed/d (Bleavins and Aulerich, 1981), the total intake of 345 HCB by the mink fed 0.5 ppm of this congener for 46 d (mean survival time; see Table 3) would have been 3.1 mg. The mean total PCB consumption of the 5 females that died while receiving the 0.1 ppm 345 HCB diet would have been only 0.9 mg. These estimates of PCB consumption are probably high because of the anorectic condition of the females for several days prior to death. Comparison of these values with data for mink fed 5-10 ppm Aroclor 1254 and 1242 (total intake of 6.7 and 8.6 mg, respectively; Ringer, 1983) shows the extreme toxicity of the 345 HCB congener to this species.

The clinical signs and lesions observed in the mink that died following consumption of 345 HCB were generally similar to those described previously for mink fed various Aroclors (Aulerich et al., 1973; Bleavins et al., 1980). However, the mink fed 345 HCB did show a greater frequency or degree of ascites, pancreatomegaly, and alopecia than observed with commercial PCBs in our previous studies.

Although none of the congeners fed to mink in this study produced a significant effect on liver weights (Table 4), Biocca et al. (1976) reported a dose-related increase in liver weights in mice and chicks fed these congeners. Their studies, however, involved the feeding of considerably greater concentrations of the congeners. The enlarged livers observed in the mink fed the Aroclor 1254 diet were consistent with the results of other studies in which commercial PCB mixtures were fed to mink (Aulerich and Ringer, 1977), rats (Grant et al., 1971; Allen and Abrahamson, 1973; Cecil et al., 1973; Grant and Phillips, 1974; Goldstein et al., 1975), mice (Orberg and Lundberg, 1974), swine (Hansen et al., 1975), monkeys (Allen et al., 1974), and rabbits (Koller and Zinkl, 1973). The increased kidney and heart weights noted in the mink fed 345 HCB (Table 4) were also observed in previous studies (Aulerich and Ringer, 1977) in which mink were fed Aroclor 1254, but in greater concentrations and for longer periods than in this study.

Although no studies are known to have been conducted on the effects of individual PCB congeners on reproduction in the mink, the adverse effects of several commercial PCB mixtures (Ringer et al., 1972; Aulerich and Ringer, 1977, 1980; Bleavins et al., 1980), as well as metabolized forms of PCBs (Ringer et al., 1972; Platonow and Karstad, 1973; Aulerich et al., 1973; Aulerich and Ringer, 1977; Hornshaw et al., 1983) on the reproductive performance of this sensitive species have been documented. The procreativity of the females fed 2.5 ppm of Aroclor 1254 in this study was comparable to that observed in a previous experiment in which mink were fed 2 ppm of Aroclor 1254 (Aulerich and Ringer, 1977). None of the 345 HCB-treated mink that were mated and survived to the whelping period produced offspring. However, the fact that uterine resorption sites were observed at necropsy in two of the five females indicates that ovu-

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Neither concentration of 245 HCB or 236 HCB had a significant effect on the reproductive parameters measured in this study. In studies with mice exposed pre- and postnatally through daily oral administration of 2.05 mg 245 HCB to their dams between d 5 of pregnancy and d 22 postpartum, Orberg (1977) failed to observe any adverse effects on reproduction. Likewise, ip administration of 100 mg 245 HCB/kg to female mice 2 wk prior to mating also failed to alter the reproductive capacity, litter size, or growth rates of the offspring (Vodicnik et al., 1980). No differences in fetal deaths were reported in guinea pigs from feeding pregnant dams a total dose of 20 or 100 mg 245 HCB (Brunström et al., 1982).

Both pure HCB congeners and PCB mixtures have been reported in a variety of species to induce hepatic microsomal enzymes that enhance steroid metabolism (Risebrough et al., 1968; Litterst et al., 1972; Nowicki and Norman, 1972; Alvares et al., 1973; Vodicnik and Lech, 1980), altering steroid balance and impairing reproduction (Kihlstrom et al., 1973; Singer, 1983). As shown by the data presented in Table 6, both Aroclor 1254 and 345 HCB had significant, but opposite, effects on the plasma progesterone concentrations of the females but no significant ($p < 0.05$) effects on 17β-estradiol concentrations. The higher plasma progesterone concentrations in the females that received 345 HCB might suggest that this congener stimulates progesterone biosynthesis, whereas Aroclor 1254 inhibits hydroxylation of this steroid hormone. The elevated plasma progesterone concentrations may be of adrenal origin, as suggested by the increased adrenal weights in the 345 HCB-treated mink. Jonsson et al. (1976) reported decreased concentrations of plasma progesterone in the rat following prolonged (36 wk) dietary exposure to 75 and 150 ppm of Aroclor 1242. Our data are, however, difficult to interpret in light of the varied reproductive and physiological states of the females and the fact that the plasma progesterone concentration of mated female mink decreases markedly from late gestation through early lactation (Pilbeam et al., 1979). The five females fed 345 HCB that survived to the termination of the study were in a very debilitated condition (see Table 2) when blood samples were collected for hormone analysis. The possible influence of this stress on steroid synthesis may also have contributed to the elevated progesterone concentration.

The mean progesterone concentrations, shown in Table 6, for the control females and those fed the 245 HCB- and 236 HCB-treated diets are within the normal range reported for mink (Pilbeam et al., 1979) during this stage of the reproductive cycle and supported "normal" reproduction in these animals. Although the females fed Aroclor 1254 were not in a debilitated condition at necropsy, as were those survivors fed the 345 HCB diet, the lower plasma progesterone concentrations in the Aroclor 1254-fed females may have not been sufficient to maintain pregnancy

in these animals, as verified by the presence of resorption sites in the uterus at necropsy.

Based on the parameters measured in this study, the toxic responses of the mink on the various treatments are generally in agreement with the theory presented by Poland and Glover (1977) and Yoshimura et al. (1979) that 3MC-type enzyme inducers are more toxic than phenobarbital (PB-) type inducers. Based on cytochrome P-450 concentrations (as shown in Table 7), 345 HCB and Aroclor 1254 produced the greatest [illegible] and were the most toxic of the PCBs fed. Both Aroclor 1254 and 245 HCB significantly enhanced induction of BaP hydroxylase (a monooxygenase responsive to 3MC-type inducers). The induction of BaP hydroxylase by both Aroclor 1254 and 345 HCB-treated mink (218 and 269%, respectively) was similar in magnitude to the 223 and 173% increase, respectively, in cytochrome P-450 concentrations for these animals. ER *O*-deethylase (another monooxygenase responsive to 3MC-type inducers) concentrations were enhanced by 345 HCB but significantly increased by Aroclor 1254. 245 HCB was the only compound tested that showed a significant induction of AP *N*-demethylase (a PB-type induction). However, neither this congener nor 236 HCB (which failed to induce any of the monooxygenases measured) produced significant detrimental effects in the mink at the levels fed in this study. In a study in which mink were fed Aroclors 1016 and 1242, Shull et al. (1982) noted significant signs of toxicoses in mink fed Aroclor 1242, although no significant induction of 3MC-type monooxygenases (BaP hydroxylase and ethoxycoumarin *O*-deethylase) were observed. Neither of these Aroclors increased the induction of AP *N*-demethylase.

Previous studies have suggested that exposure to PCBs results in behavioral abnormalities, which in turn could be due to alterations in brain neurochemical parameters. Peakall and Peakall (1973) reported less attentive incubation behavior in doves fed 10 ppm Aroclor 1254. Based on these results, Heinz et al. (1980) examined the effect of exposure to 1, 10, and 100 ppm Aroclor 1254 on brain concentrations of DA and NE in the ring dove. They reported that 10 and 100 ppm caused a significant depression in the whole-brain concentrations of these two neurotransmitters and suggested that these changes could affect behavior. In the rat, Tilson and Cabe (1979) reported behavioral changes resulting from exposure to FireMaster FF-1, which is a commercial preparation of the closely related polybrominated biphenyls (PBBs). Johnston et al. (1980) reported that the hypothalamic NE concentration in female rats was elevated as a result of exposure to 100 ppm PBBs, but synthesis of this neurotransmitter was not altered.

Of interest in the present study is the effect of PCBs on hypothalamic neurotransmitter levels and its possible relationship to reproductive dysfunction. Of the compounds fed, only Aroclor 1254 resulted in reproductive problems (animals fed 345 HCB that mated were in an extremely

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