DIETARY EXPOSURE OF MINK TO FISH FROM THE HOUSATONIC RIVER: EFFECTS ON REPRODUCTION AND SURVIVAL

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INTRODUCTION

During the last two decades, there has been considerable concern regarding the presence of environmental contaminants, especially planar halogenated hydrocarbons (PHHs) that include primarily polychlorinated biphenyls (PCBs) and, to a lesser extent, polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), in the biota and sediments of the Housatonic River. The Housatonic River flows from western Massachusetts and Connecticut into Long Island Sound. Because consumption of fish containing elevated concentrations of PCBs might pose a serious health risk to humans, parts of the Housatonic River were closed to all but catch and release fishing. A similar concern has been raised for pisciverous wildlife that inhabit the margins of the river. The Housatonic River flows through habitat that has historically sustained viable populations of piscivorous species, such as mink. Recent field studies have demonstrated a paucity of this wildlife along the more highly contaminated sections of the river. Viable populations inhabit nearby reference areas, suggesting that PCBs potentially have an adverse effect on these species. Thus, the present study was designed to evaluate whether farm-raised mink fed diets containing PCB-contaminated fish from the Housatonic River would exhibit impaired reproductive performance and/or offspring (kit) growth and survival.

METHODS

Fish Preparation

Fish were collected from the Woods Pond and Deep Reach area of the Housatonic River and shipped frozen to the Michigan State University Experimental Fur Farm. The fish was ground, blended, sampled and frozen for subsequent incorporation into mink feed. "Control" fish was Atlantic Ocean herring that was processed in an identical manner as the Housatonic River fish.

The herring contained 0.051 $\pm$ 0.001 ug total PCBs/g and the Housatonic River fish blend contained 113.3 $\pm$ 5.4 ug total PCBs/g.

Dietary Treatments

The treatment diets were based on the Michigan State University Experimental Fur Farm ranch diet formulated to meet the nutritional requirements of mink. Each diet contained 30% fish, which is the approximate quantity of fish consumed by mink in the wild. The control diet contained 30% ocean herring and the remaining five treatment diets contained a mixture of ocean fish and Housatonic River fish such that dietary concentrations of total PCBs were 0.03, 0.34, 0.61, 0.96, 1.6, and 3.7 ug total PCBs/g feed.

Animals

Seventy-two first-year (virgin), natural dark, female mink from the Michigan State University Experimental Fur Farm herd were randomly assigned to the six treatment groups (12 mink/group).

Housing

Mink were housed individually in wire cages in an open-sided shed. Feed and water were available *ad libitum*.

Acclimation Period

Mink were fed the standard ranch diet from 22 December 99 until 27 December 99 and then switched to the control diet (30 % ocean herring; 0.03 ug total PCBs/g feed) on 27 December 99 for a seven-day acclimation period.

Definitive Trial

Mink were started on their respective treatment diets on 4 January 00. Feed consumption was determined for the same two-day period each week and body weights were recorded every

two weeks until initiation of breeding. Females were mated to untreated males between 1 March and 22 March 00. Whelping began on 17 April 00 and ended 5 May 00. Kits were counted and their gender determined. Body weights of kits were recorded at birth and at three and six weeks of age. Body weights of females were recorded at the same time their litters were weighed. All surviving adults and six kits from each treatment were necropsied when kits were six weeks old. Tissues were removed, weighed and processed for histological examination. Samples of liver were taken for determination of microsomal enzyme activities and contaminant analysis. Twelve kits from each treatment group were maintained on their respective treatment diets. Body weights were determined every four weeks beginning at six weeks of age. On 28 November 00, six kits from each treatment were necropsied with tissues being handled as described above.

RESULTS AND DISCUSSION

Concentrations of Selected Organochlorine Pesticides in Fish Samples

The concentrations of 26 organochlorine pesticides were determined in blended samples of ocean herring and Housatonic River fish. p,p'-DDE and p,p'-DDD were the predominant pesticides in the Housatonic River fish. They occurred at concentrations considerably lower than those reported to cause reproductive effects in mink.

Concentration of PHHs and TEQs in Diets

Concentration of toxic equivalents (TEQs) ranged from 1.1 pg/g feed in the control diet to 68.5 pg/g feed in the diet containing 3.7-ug total PCBs/g feed. Over 90% of the TEQs were contributed by non-ortho and mono-ortho PCB congeners. 3,3'4,4',5-pentachlorobiphenyl (IUPAC #126) was the predominant PCB congener in terms of TEQ contribution.

Adult Feed Consumption

Feed intake was not significantly affected by consumption of diets containing up to 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed. Other PCB feeding studies with mink have reported variable effects on feed consumption.

Reproductive Performance and Kit Survivability

Reproductive performance was not adversely affected in the present study, but kit survivability at six weeks of age was lower in animals exposed to 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed. In a study utilizing Saginaw Bay, Lake Huron, MI fish as the source of PCBs that was conducted in a similar manner as the present one, kit survivability was adversely affected at a dietary concentration of 0.72 (22.2 pg TEQs/g) ug total PCBs/g feed.

Body Weights

Body weights of adult mink were not affected, but three-week kit body weights were lower in animals fed 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed compared to controls. Because adult feed consumption was not depressed by consumption of PCB-contaminated feed, the lack of an effect on adult body weights is not unexpected. The decrease in kit body weights at three weeks of age may have reflected the importance of lactation as a source of PCBs for the nursing kits.

Absolute and Relative Organ Weights

Organ weights were not consistently affected in the present study. In mink studies where organ weights were affected, an increase in liver weight was most often reported. A numerical increase in adult female liver weights was noted at the two highest dietary concentrations of PCBs in the present study.

Histopathology of Tissues

The most consistent lesions observed in adult and kit tissues were extramedullary hematopoiesis in the liver and/or spleen. Because these lesions were observed in all but one

animal, it was assumed that extramedullary hematopoiesis is a normal process for this species. Histological evidence of mandibular and maxillary squamous cell proliferation was apparent in kits exposed to 0.96 ug total PCBs/g feed and higher that were necropsied at the end of the trial. This is the first time that the jaw lesion has been reported in animals exposed to environmentally derived PCBs and at a TEQ concentration (9.2 pg/g feed) so low.

Mortality of Adults and Kits Beyond Six Weeks of Age

Five adult females and two kits beyond six weeks of age died. The cause of death of four of the five adult females as well as the two weaned kits was thought to be due to hemorrhagic cystitis and urolithiasis rather than exposure to PCBs. The cause of death of the fifth female could not be determined due to lack of gross lesions and minimal histological lesions.

Hepatic Enzyme Activities

Induction of CYPIA1-related hepatic enzyme activities (ethoxycoumarin-O-deethylase or ECOD and ethoxyresorufin-O-deethylase or EROD) occurred in a dose-dependent fashion in all ages of mink examined. Significant increases in EROD activity occurred at dietary concentrations as low as 0.61 (5.7 pg TEQs/g) ug total PCBs in the adult females and in kits necropsied at the end of the trial while ECOD activity was significantly increased at the same dietary concentrations in kits necropsied at the end of the trial. In contrast, induction of CYP2B-related activity (benzyloxyresorufin-O-deethylase or BROD and pentoxyresorufin-O-deethylase or PROD) was not dramatic at any of the dietary PCB concentrations and none of the increases occurred in a dose-dependent fashion.

Concentrations of PHHs and TEQs in Mink Livers

The dietary concentration of PCBs in the present study that caused a decrease in kit survival (3.7 [68.5 pg TEQs/g] ug total PCBs/g feed) resulted in a maternal hepatic total PCB

concentration of 3.1 ug/g wet weight. The contribution of PCDDs, PCDFs, and non-ortho and mono-ortho PCB congeners to the total TEQs in the liver was similar to their contribution to dietary TEQs. The dietary concentration that caused reduced kit survival resulted in a maternal hepatic TEQ concentration of 218 pg/g wet weight. Mandibular and maxillary squamous cell proliferation was detected in kits necropsied at the end of the trial that were fed dietary concentrations as low as 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed. These animals had a hepatic total PCB concentration of 1.7 ug/g wet weight or 40.2 pg TEQs/g wet weight. Significant increases in EROD and ECOD activities occurred at dietary concentrations as low as 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed in adult females and/or kits necropsied at the end of the trial. Hepatic total PCB concentrations were 0.58 (22.4 pg TEQs/g wet weight) and 0.73 (19.1 pg TEQs/g wet weight) ug total PCBs/g wet weight in these adults and kits, respectively.

NOAEL, LOAEL and Estimated Threshold Dose

The no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL) and estimated threshold doses based on decreased kit survival were calculated. The estimated threshold dose expressed as dietary total PCBs is 2.4 ug total PCBs/g feed. If expressed as dietary TEQ concentrations, the estimated threshold dose is 33.2 pg TEQs/g feed or 3.6 pg TEQs/g body weight/day. When expressed as hepatic TEQ concentration, the estimated threshold dose is 111 pg TEQs/g.

The point is made that while there were differences between this study and other mink studies in terms of the amount of PCBs consumed that caused reduced kit survivability, if hepatic concentrations of total PCBs and/or TEQs at LOAELs for kit survival are examined, this study compares favorably with the other studies.

CONCLUSION

Results of the study indicate that survivability of mink kits between three and six weeks of age and three-week body weights of mink kits were significantly lower compared to controls when their dams were fed 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed derived from fish collected from the Housatonic River from two months prior to breeding through lactation. This dose resulted in hepatic concentrations of 3.1 ug total PCBs/g and 218 pg TEQs/g in adult females. Because inclusion of PCB-contaminated fish that comprised less than 4% of the diet impacted mink kit survival, it is likely that consumption of up to 8-fold that quantity of HR fish, as could be expected for wild mink, would have an adverse effect on wild mink populations. Results also indicated that induction of mandibular and maxillary squamous cell proliferation occurred in kits exposed to 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed and above in utero and throughout the growth period, which corresponded to 0.89% HR fish in the diet and that hepatic CYPIA1 activities were induced by dietary concentrations as low as 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed, or 0.44% dietary HR fish, in all three age groups. While inducement of hepatic enzyme activity and squamous cell proliferation may not result in population-level effects, these changes are an indication that physiological alterations are occurring at very low concentrations of fish in the diet.

1. INTRODUCTION

During the last two decades, there has been considerable concern regarding the presence of environmental contaminants, especially planar halogenated hydrocarbons (PHHs) that include primarily polychlorinated biphenyls (PCBs) and, to a lesser extent, polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), in the biota and sediments of the Housatonic River. The Housatonic River flows through western Massachusetts and Connecticut into Long Island Sound. PCB concentrations greater than 200 ug/g have been reported in sediments and fish taken downstream from a General Electric facility located on the East Branch of the Housatonic River at Pittsfield, Massachusetts (WESTON, 2000).

Because consumption of fish containing elevated concentrations of PCBs might pose a serious health risk to humans, parts of the Housatonic River were closed to all but catch and release fishing in 1982 (EPA, 1999). A similar concern has been raised for piscivorous wildlife that inhabit the margins of the river. The Housatonic River flows through habitat that historically has sustained viable populations of piscivorous species, such as mink (Langois, 2000). Recent field studies have demonstrated a paucity of this wildlife along the more highly contaminated sections of the river (TechLaw, 1999). Viable populations inhabit nearby reference areas, suggesting that PCBs potentially have an adverse effect on these species. Thus, the present study was designed to evaluate whether farm-raised mink fed diets containing PCB-contaminated fish from the Housatonic River would exhibit impaired reproductive performance and/or offspring (kit) growth and survival.

Mink (*Mustela vison*) was the species of choice for testing this hypothesis because: (1) they are a semiaquatic piscivorous species native to the area; (2) they are among the most sensitive mammalian species to PCBs (Ringer *et al.*, 1972; Aulerich and Ringer, 1977; Ringer *et*

al., 1981; Hornshaw *et al.*, 1983; Aulerich *et al.*, 1985; Heaton *et al.*, 1995a; Restum *et al.*, 1998) and PCDDs (Hochstein *et al.*, 1988; Hochstein *et al.*, 1998; Hochstein *et al.*, 2001); (3) their nutritional requirements are well documented (National Research Council, 1982); (4) stock of known genetic origin is readily available; (5) all stages of their life cycle can be successfully perpetuated in the laboratory; and (6) mink have a large biological database (Shump *et al.*, 1976; Sundqvist, 1989; Aulerich *et al.*, 1999).

2. METHODS

2.1 Fish Preparation

Fish were collected from the Woods Pond and Deep Reach area of the Housatonic River (HR) and shipped frozen to the Michigan State University Experimental Fur Farm (East Lansing, MI). Eighty-eight gold fish (*Carassius auratus*) (70.3 kg) were received on 28 October 99 and 16 carp (*Cyprinus carpio*) (77.3 kg) were received on 29 October 99. The fish were placed in a walk-in freezer (-7º C) upon arrival until further processing. On 10 November 99, the batch of gold fish and the batch of carp were each ground (1.1 cm face plate) and blended in a paddle mixer (15 minutes). The grinder and mixer were cleaned between each batch of fish. The two batches of HR fish were then blended together by placing them in the mixer for 15 minutes. Five grab samples consisting of six sub-samples per grab sample were collected in I-Chem® jars (I-Chem, New Castle, DE) for subsequent residue analysis. Samples were stored in an ultra-cold freezer (-84º C) located in the Department of Animal Science's toxicology laboratory in Anthony Hall until shipment. The blended fish was stored in plastic-lined 18.9-liter containers that were placed in the walk-in freezer until diet preparation. "Control" fish consisted of Atlantic Ocean herring (*Clupea harengus*) purchased from Boston Feed Company (Natick, MA). Ocean herring was chosen because it, like goldfish and carp, is among those species of fish that contain the

enzyme thiaminase. If mink are fed raw fish containing thiaminase, thiamine is destroyed resulting in thiamine deficiency or Chastek paralysis. This problem can be corrected by cooking fish at 83º C for 5 minutes or by providing a thiamine supplement (National Research Council, 1982). In the present study, supplemental thiamine was provided to the mink. The frozen herring (1818 kg) was received on 12 October 99 and placed in a walk-in freezer until further processing. On 10 November 99, 37.3 kg of herring were ground, blended and sampled as described above. On 11 November 99, three grab samples each of HR fish and herring were shipped frozen to Severn Trent Laboratories (Burlington, VT) for total PCB analysis. Results indicated that the herring contained an average of 0.051 $\pm$ 0.001 ug total PCBs/g (mean $\pm$ standard error) and the HR fish contained an average of 113.3 ± 5.4 ug total PCBs/g (mean $\pm$ standard error).

2.2 Dietary Treatments

The treatment diets (Tables 1 and 2) were based on the MSU Experimental Fur Farm ranch diet formulated to meet the nutritional requirements of mink (National Research Council, 1982). Each diet contained 30% fish, which is the approximate quantity of fish consumed by mink in the wild (Heaton *et al.*, 1995a). The control diet contained 30% ocean herring and the remaining five treatment diets contained a mixture of ocean fish and HR fish such that targeted concentrations of total PCBs were 0.00, 0.25, 0.50, 1.0, 2.0, or 4.0 ug/g feed. Analysis of diets for total PCBs indicated that the measured concentrations were 0.03, 0.34, 0.61, 0.96, 1.6, and 3.7 ug total PCBs/g feed. The control, 0.34 and 0.61 ug total PCBs/g feed diets were initially mixed on 14 December 99 and the 0.96, 1.6 and 3.7 ug total PCBs/g feed diets on 16 December 99. A second batch of the control diet was mixed on 29 June 00 and second batches of the 0.34, 0.61, 0.96, 1.6 and 3.7 ug total PCBs/g feed diets were mixed on 19 July 00. In all cases, water

was added to the mixer first, followed by biotin and ocean herring/HR fish with a 5-minute mixing interval. Cereal was added next with another 5-minute mixing interval. The remaining ingredients were then added with a 15-minute mixing interval. Near the end of the 15-minute mixing interval, six grab samples consisting of six sub-samples per grab sample were collected. Three grab samples to be used for contaminant analysis were placed in I-Chem® jars and three grab samples to be used for nutrient analysis were placed in Whirl-Pak® bags (Nasco, Fort Atkinson, WI). All diet samples were stored in the ultra-cold freezer located in Anthony Hall until shipment. One sample of each treatment diet was shipped on dry ice to the Columbia Environmental Research Center (Columbia, MO) for contaminant analysis (organochlorine pesticides, total PCBs, and non-ortho and mono-ortho PCB, PCDD and PCDF congeners) on 10 January 00 (first mixing) and on 27 September 00 (second mixing). One sample of each treatment diet was shipped on dry ice to Litchfield Analytical Services (Litchfield, MI) for nutrient analysis on 10 January 00 (first mixing) and 31 October 00 (second mixing). The treatment diets were packed in labeled, plastic-lined, 18.9-liter containers that were stored in the walk-in freezer. Twenty-fours hours prior to use, containers were transferred from the walk-in freezer to a walk-in cooler (4º C) to allow the feed to thaw. One container was sufficient to feed a group of 12 mink for approximately three days.

2.3 Animals

Seventy-two first-year (virgin), natural dark, female mink from the MSU Experimental Fur Farm herd were randomly assigned on 22 December 99 to the six treatment groups (12 mink/group) except that litter mates were not placed in the same treatment group to minimize genetic predisposition to PCB toxicity. Untreated, natural dark, male mink were used for breeding purposes only.

2.4 Housing

Mink were housed individually in wire cages (76 cm L x 61 cm W x 46 cm H) on the two outside aisles of an open-sided mink shed. Four animals per treatment group were assigned to a bank of four cages separated from the next bank of four cages by an empty cage. Assignment of treatments to banks of cages was done randomly. A wooden nest box (38 cm L x 28 cm W x 27 cm H) bedded with aspen shavings and excelsior ("wood wool") was attached to the outside of each cage. Cages were suspended above the ground in an open-sided shed. Feed and water were available *ad libitum*. Housing of animals exceeded guidelines specified in the Standard Guidelines for the Operation of Mink Farms in the United States (Fur Commission USA, 1995)

2.5 Acclimation Period

Mink were fed the standard ranch diet from 22 December 99 until 27 December 99. The mink were switched to the control diet (30% ocean herring; 0.03 ug total PCBs/g feed) on 27 December 99 for a seven-day acclimation period. The animals were provided with a thiamine supplement on a daily basis. Twenty-five mg thiamine hydrochloride (USB, Cleveland, OH) were dissolved in 50 ml water and then mixed into 950 g of ranch feed. Each mink was fed approximately 10 g of the thiamine-containing feed, which provided 0.25 mg thiamine hydrochloride/day, at least two hours before feeding of the treatment diets. Mink body weights were recorded on the first (27 December 99) and last (3 January 00) days of the acclimation period. Feed consumption was measured for two consecutive days (28 December 99 – 30 December 99) during the acclimation period.

2.6 Definitive Trial

Mink were started on their respective treatment diets on 4 January 00. Thiamine-containing feed was provided to the mink each day at least two hours prior to feeding of the

treatment diets, as described above. Mink were observed daily to assess health status. Animals that died during the course of the trial were submitted to MSU's Animal Health Diagnostic Laboratory (AHDL) for necropsy by a veterinary pathologist. Feed consumption was determined for the same two-day period each week and body weights were recorded every two weeks. Measurement of feed consumption and determination of body weights were discontinued at the initiation of breeding.

The females were mated to untreated males between 1 March and 22 March 00. Each female was given an opportunity to mate every fourth day until a successful mating was obtained. All matings were verified by the presence of "normal" appearing, motile spermatozoa in vaginal aspirations collected immediately after mating. Mated females were given an opportunity for additional matings (with different males) the day following the initial mating and on the eighth and ninth days after the first successful mating (a common commercial mink breeding practice).

The whelping period began on 17 April 00 and ended on 5 May 00. Nest boxes were checked on a daily basis for the presence of mink kits. The gender of the kits was determined at birth, and the live and stillborn young were counted. Body weights of kits were recorded at birth and at three and six weeks of age. Body weights of adult females were recorded at the time their litters were weighed.

All surviving adults and six kits (three males and three females that were randomly chosen) from each treatment group were euthanized with CO_2 and necropsied when kits were six weeks old (30 May to 16 June 00; approximately 160 days on trial). The liver was removed quickly, rinsed in 0.9% sodium chloride, blotted, and weighed. A one-gram sample of the liver was placed in a cryogenic vial (Corning Costar Corporation, Cambridge, MA) and frozen in

liquid nitrogen for subsequent determination of microsomal enzyme activities (ethoxycoumarin-O-deethylase [ECOD], ethoxyresorufin-O-deethylase [EROD], benzyloxyresorufin-O-deethylase [BROD] and pentoxyresorufin-O-deethylase [PROD]) as described in Tillitt *et al.* (2003). A second sample of the liver was placed in an I-Chem® jar and frozen on dry ice for subsequent contaminant analysis. The remainder of the liver was placed in a 10% formalin-saline solution (10% formalin in 0.9% sodium chloride) for subsequent histological examination. The brain, kidneys, spleen, heart and adrenal glands were also removed, weighed and placed in the formalin-saline solution for subsequent histological examination. After removal of the brain, the head was placed in a container of formalin-saline solution for histological examination. Both sets of frozen liver samples were transferred to the ultra-cold freezer in Anthony Hall. Tissues preserved in the formalin-saline solution were submitted to the AHDL on 22 June 00. On 26 June 00, the frozen liver samples were shipped in a liquid nitrogen dry shipper (cryovials) or on dry ice (I-Chem® jars) to the Columbia Environmental Research Center.

Twelve kits (six males and six females that were randomly chosen) from each treatment group were maintained on their respective treatment diets. Housing was such that the original cage assignment to treatment was maintained. Body weights were determined every four weeks beginning at six weeks of age. On 28 November 00, six kits (three males and three females that were randomly chosen) from each treatment group were necropsied with tissues being handled as described above. Liver samples for contaminant analysis were shipped on dry ice to the Columbia Environmental Research Center on 7 December 00 and liver samples for microsomal enzyme activity were shipped in a liquid nitrogen dry shipper on 11 December 00 to the Columbia Environmental Research Center. Tissue samples for histological assessment were submitted to the AHDL on 14 December 00. On 4 September 02, heads of the 36 kits that were

necropsied at the end of the trial were submitted to the AHDL for evaluation of mandibular and maxillary squamous cell proliferation.

2.7 Statistical Analyses

All statistical analyses were performed using SAS® software (SAS; Statistical Analysis Systems, Release 8.0, Cary, NC). Feed consumption, adult body weights during the pre-breeding period, adult body weights during whelping, kit body weights from 10 weeks of age to the end of the trial and kit survivability were analyzed by analysis of variance (ANOVA) involving the factors treatment and sex (when applicable), with repeated measurements on mink, over another factor, date. SAS PROC MIXED was used to model a first-order autoregressive correlation structure for repeated measurements over dates within mink, as residuals involving measurements taken at adjacent time periods are more likely to be highly correlated than measurements taken further apart in time (Gill, 1990). Where applicable, all two-way interactions between treatment, sex, and dates were modeled. After performing the PROC MIXED analysis on kit survivability at birth, three weeks of age and six weeks of age, the decision was made to analyze each time period separately because the data numerically showed possible treatment differences at each time priod. It was determined that pooling the least square means for kit survivability across the three time periods was confounding the pair-wise treatment comparisons. Thus, the SAS PROC MIXED command for kit survivability assumed a treatment by date interaction to allow for pair-wise treatment comparisons at each individual time period. SAS PROC GLM was used to model a one-way ANOVA involving the factor treatment on adult body weights at the beginning of the trial, adult body weights at necropsy, adult absolute and relative organ weights and gestation length. Kit body weights as well as absolute and relative organ weights were analyzed by a two-way ANOVA model involving the factors treatment and

sex. Adult and kit relative organ weights and kit survivability were percentage (p) data subjected to arcsine, square root transformation [$x = \sin^{-1}(\sqrt{p})$] prior to statistical analysis. As standard errors are not readily back-transformed, the reported means and 95% confidence intervals for treatment means of adult and kit relative organ weights and kit survivability were back-transformed [$p=(\sin(x))^2$] to the scale of observation. Residual plots were used to check for homogeneity of variance and for aberrant values. Residual plots for feed consumption of adults and kit body weights at 10 weeks of age to the end of the trial indicated increasing variability with higher responses; therefore those data were log transformed to stabilize variance. The reported means and 95% confidence intervals for treatment means of feed consumption and kit body weights from 10 weeks of age to the end of the trial were back (anti-log) transformed to the scale of observation. Hepatic enzyme data were analyzed using the GLM (genearal linear models) procedures to evaluate main treatment effects and interactions of all the response variables. Values less than the detection limit were set to one half of the detection limit, while values less than the limit of quantitation were set to one half the quantitation limit for these analyses and the comparison of means among treatment groups. Treatment group means were reported as the least squares mean plus or minus the standard deviation. Treatment means were reported separately for each sex and/or date, if treatment by sex and/or treatment by date interactions, respectively, were statistically significant. Otherwise, reported treatment means and mean differences were based on pooling information over the sexes and/or dates. To control for experimental Type 1 error rates, a Tukey's honestly significant difference procedure was used to test comparisons between means based on the total number of pairwise comparisons. In the following sections, reference to significant differences (higher or lower) across compared values indicate statistical differences at $p< 0.05$.

3. RESULTS

3.1 Concentrations of Selected Organochlorine Pesticides in Fish Samples

The concentrations of 26 organochlorine pesticides in blended samples of Atlantic Ocean herring and fish collected from the Housatonic River are presented in Table 3. *p,p'*-DDE was the predominant pesticide in both blends with its concentration being 22 times greater in the HR fish compared to the herring.

3.2 Concentrations of PHHs and TEQs in Diets

Concentrations of the individual PHH contaminants in the diets and the toxic equivalents (TEQs) contributed by them are presented in Table 4. The concentration of TEQs ranged from 1.1 pg/g in the control diet to 68.5 pg/g in the diet containing 3.7 ug total PCBs/g feed. The percent contribution of PCDDs, PCDFs, non-ortho-PCBs, and mono-ortho PCBs to the total TEQs in the treatment diets averaged 2.8 $\pm$ 0.8%, 6.8 $\pm$ 1.9%, 59.1 $\pm$ 1.4 %, and 32.1 $\pm$ 0.3 %, respectively.

3.3 Adult Feed Consumption

The presence of PCBs in the diet had no significant effect on feed consumption of adult female mink, which was measured during the acclimation (27 December 99 to 3 January 00) and pre-breeding periods (4 January to 1 March 00) only. Because there was no treatment by date interaction, average feed consumption values for the six treatment groups during the acclimation and pre-breeding periods are presented in Table 5. Using the average feed consumption values presented in Table 5, and the average body weights for the period that feed consumption was measured, the quantity of total PCBs and TEQs ingested by the adult female mink in the control, 0.34, 0.61, 0.96, 1.6 and 3.7 ug total PCBs/g feed groups over approximately 160 days were derived and are presented in Table 6.

3.4 Reproductive Performance and Kit Survivability

Consumption of diets containing PCBs derived from Housatonic River fish had no obvious effect on breeding success (number of females bred/total number of females) or whelping success (number of females whelping/number of females bred) of female mink (Table 7). Gestation length was not significantly altered by exposure to PCBs (Table 8).

The average litter size was similar across the six treatment groups (4.6, 5.6, 4.6, 6.5, 5.6 and 5.5 kits for females in the control, and 0.34, 0.61, 0.96, 1.6 and 3.7 ug total PCBs/g feed groups, respectively). There was a treatment by date interaction in kit survivability at three weeks to six weeks of age. Therefore, kit survivability from birth to six weeks of age was reported separately. There were no significant differences in kit survivability at birth and at three weeks of age. Percent survivability of kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group at six weeks of age was significantly lower compared to kits in the control and 1.6 (16.1 pg TEQs/g) ug total PCBs/g feed groups (Table 9).

3.5 Body Weights

There were no significant differences in adult female body weights at the beginning of the trial (data not presented) and during the pre-breeding period (Table 10). There was a significant treatment by date interaction for female body weights at whelping, and at three and six weeks post-whelping, but there were no significant differences between treatment groups (Table 11). There were no significant differences in adult female body weights at necropsy (approximately six weeks post-whelping) (Table 11).

There was a significant treatment by date interaction for kit body weights from birth to six weeks of age. There were no significant differences in birth weights between groups. At three weeks of age, kits in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group had significantly

greater body weights when compared to kits in the other five groups and kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group had significantly lower body weights when compared to kits in the other groups. At six weeks of age, kits in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group had significantly greater body weights than kits in the control, and 0.96, 1.6 and 3.7 (9.2, 16.1 and 68.5 pg TEQs/g) ug total PCBs/g feed groups, respectively (Table 11). Body weights of the six kits per treatment group that were necropsied at approximately six weeks of age are presented in Table 11. There were no significant differences in six-week necropsy body weights. From 10 to 30 weeks of age, there was a significant treatment by date interaction. At 10 weeks of age, kits in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group had significantly greater body weights than control, 1.6 (16.1 pg TEQs/g) and 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed kits, whereas kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group had significantly lower body weights than kits in the 0.61 (5.7 pg TEQs/g) and 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed groups. At 22 weeks of age, kits in the 0.34 (3.5 pg TEQs/g) and 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed groups had significantly greater body weights than control kits. There were no significant differences in body weights at 14, 18, 26 and 30 weeks of age (Table 12). Body weights of the six kits per treatment that were necropsied at the end of the trial (approximately 31 weeks of age) are presented in Table 12. There were no significant differences in the end-of-trial necropsy body weights.

3.6 Absolute and Relative Organ Weights

Absolute and relative (expressed as a percentage of body weight) brain, heart, spleen, liver, kidney and adrenal gland weights of adult females were not significantly different between treatment groups at necropsy (Tables 13 and 14).

Absolute brain, spleen, kidney and adrenal gland weights of kits necropsied at six weeks of age were not significantly different between treatment groups (Table 15). The absolute heart weights of kits in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group were significantly greater than absolute heart weights of kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group (Table 15). There was a significant treatment by sex interaction for absolute liver weights. There were no differences in absolute liver weights of male kits. Female kits in the 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed group had significantly greater absolute liver weights compared to female kits in the other five treatment groups, while kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group had lower absolute liver weights when compared to kits in the 0.61 (5.7 pg TEQs/g) and 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed groups (Table 17). Relative spleen and adrenal gland weights were not significantly different between treatment groups (Table 17). There was a significant treatment by sex interaction for relative brain, liver, kidney and heart weights. There were no significant differences in the relative weights of the brain, liver, kidneys and heart in males and of the heart in females. The females in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group had significantly greater relative brain and kidney weights compared to females in the other five treatment groups. Relative liver weights of females in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group were significantly greater compared to females in the control, and 0.34 (3.5 pg TEQs/g) and 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed groups (Table 18).

Absolute brain, heart and adrenal gland weights in kits necropsied at the end of the trial were not significantly different between treatment groups (Table 19). Absolute spleen weights in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group were significantly greater compared to kits in the control and 0.34 (3.5 pg TEQs/g) ug total PCBs/g feed group and absolute liver weights in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group were significantly greater compared to the

0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group. There was a significant treatment by sex interaction for absolute kidney weights. There were no significant differences in absolute kidney weights between treatment groups for either sex (Table 20). Relative brain, heart and adrenal gland weights were not significantly different between treatment groups (Table 21). The relative spleen weights of kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group were significantly greater compared to the control and 0.34 (3.5 pg TEQs/g) ug total PCBs/g feed groups and the relative liver weights of kits in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group were significantly lower compared to kits in the control, and 1.6 (16.1 pg TEQs/g) and 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed groups (Table 21). There was a significant treatment by sex interaction for relative kidney weights. There were no significant differences between treatment groups for males, however, the relative kidney weights of females in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group were significantly lower compared to control females (Table 22).

3.7 Histopathology of Tissues

The most consistent lesions observed in adult tissues were extramedullary hematopoiesis in the liver and/or spleen, which occurred in every animal with the exception of one female in the 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed group that had no lesions in any tissue. There were animals in every group that had lesions in addition to the splenic/hepatic extramedullary hematopoiesis. Two control animals had renal inflammatory cell infiltration and one had hepatic inflammatory cell infiltration. Three females in the 0.34 (3.5 pg TEQs/g) ug total PCBs/g feed group had hepatic inflammatory cell infiltration, one female had renal inflammatory cell infiltration and one female had nephritis. In the group fed 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed, one female had inflammatory cell infiltration in the kidney while a second female had inflammatory cell infiltration in the liver, brain and adrenal glands. Two females in the 0.96 (9.2

pg TEQs/g) ug total PCBs/g feed group had hepatic inflammatory cell infiltration. One female of three in the 1.6 (16.1 pg TEQs/g) ug total PCBs/g feed group had only hepatic inflammatory cell infiltration and the other two females also had renal or splenic inflammatory cell infiltration. In addition, one female had hepatic sinusoidal amyloidosis. In the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group, three females had hepatic inflammatory cell infiltration and one female had renal inflammatory cell infiltration. A summary of the histopathology results is presented in Table 23.

The predominant histological lesions reported for kits necropsied at six weeks of age were extramedullary hematopoiesis in the liver and spleen (Table 24). In addition, a male in the 0.34 (3.5 pg TEQs/g) ug total PCBs/g feed group had hepatic lymphoplasmacytic inflammatory cell infiltration and bacterial colonies in the hepatic sinusoids and renal tubules. A male in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group had bacterial colonies in the hepatic sinusoids and renal tubules. A male in the 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed group had hepatic lymphoplasmacytic inflammatory cell infiltration. A female in the 1.6 (16.1 pg TEQs/g) ug total PCBs/g feed group had hepatic lymphoplasmacytic inflammatory cell infiltration with bacterial colonies in hepatic sinusoids and two males in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group had hepatic lymphoplasmacytic inflammatory cell infiltration.

Similar histological results were obtained for kits necropsied at the end of the trial in that the predominant lesions were splenic and hepatic extramedullary hematopoiesis (Table 25). One male and two female control kits, two female kits in the 0.34 (3.5 pg TEQs/g) ug total PCBs/g feed group and one male kit in the 1.6 (16.1 pg TEQs/g) ug total PCBs/g feed group had hepatic lymphoplasmacytic inflammatory cell infiltration. In addition, a male kit in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group had glomerulo-interstitial nephritis. Histological evidence

of mandibular and maxillary squamous cell proliferation was apparent in one of six kits, two of six kits and six of six kits in the 0.96 (9.2 pg TEQs/g), 1.6 (16.1 pg TEQs/g) and 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed groups, respectively (Table 26). In all cases, the lesion appeared to start from the caudal molar region of the jaw and advance to the pre-molar, canine and incisor regions. The initial lesions in the molar region usually consisted of large cysts lined with thick layers of stratified squamous epithelium and filled with floating, sloughed squamous cells. The subsequent lesions in the pre-molar, canine and incisor regions of the jaw were characterized as multiple nodules of compact stratified squamous epithelium.

3.8 Mortality of Adults and Kits Beyond Six Weeks of Age

Five adult females died during the course of the trial. A control female was euthanized on 16 March 00 because of a suspected bladder infection. The gross necropsy results (Table 27) substantiated the initial diagnosis. One female in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group was euthanized on 19 April 00 because of inappetance and progressive weight loss. A second female in the same group was found dead on 23 April 00. Both females were pregnant. The gross necropsy reports for each of the two females were similar in that the uterus was congested and hemorrhagic and the urinary bladder was also hemorrhagic (Table 27). A female in the 1.6 (16.1 pg TEQs/g) ug total PCBs/g feed group was found dead on 24 April 00. As with the other animals, this female had a congested and hemorrhagic uterus and urinary bladder (Table 27). The fifth adult female (3.7 [68.5 pg TEQs/g] ug total PCBs/g feed) was found dead on 6 June 00 and had no apparent gross lesions.

After 10 weeks of age, two kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed treatment group died on 12 July 00 and 22 September 00, respectively. The pathology reports for these two animals are summarized in Table 28.

3.9 Liver Enzyme Activities

The isozymes of cytochrome P450 that catalyze the dealkylation of benzyloxyresorufin and pentoxyresorufin are in the CYP2B family. These isozymes are inducible by a variety of chemicals that are generally known as 'phenobarbital-like' in mammals. Mean basal rates of BROD were 12, 14, and 5 pmol/min/mg in the adult females, six-week-old kits and kits necropsied at the end of the trial (Tables 29, 30 and 31, respectively). There was no significant induction of BROD by any of the dietary treatments in the adult females (Table 29). Hepatic BROD activity in the six-week-old kits was not significantly different from activity in the control mink in any of the treatments except at the dietary concentration of 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed where activity was significantly reduced compared to control activity (Table 30). Thus, no dose-response relationship was apparent in either the adult females or six-week-old kits. However, hepatic BROD activity was significantly elevated at all of the dietary concentrations in the kits necropsied at the end of the trial (Table 31). The dose-response in these kits was not monotonic in relation to the treatments, and the significance of the increased hepatic BROD activity in these kits may be due to the reduced activity in the control mink in this age group. The induction of PROD in adult female mink and their offspring was minimal and significant only in the six-week-old kits exposed to 0.34 (3.5 pg TEQs/g) ug total PCBs/g feed (Tables 29-31). The mean basal rates of PROD were 13, 3, and 4 pmol/min/mg in the adult females, six-week-old kits and kits necropsied at the end of the trial, respectively.

The isozymes that catalyze the dealkylation reactions toward ethoxycoumarin and ethoxyresorufin are part of the cytochrome P450IA1 subfamily, also known as CYPIA1 isozymes. CYPIA1 isozymes are under transcriptional regulation of the aryl hydrocarbon receptor (AhR) and are inducible by compounds resembling 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

(TCDD), including other PCDDs, PCDFs and planar PCBs. ECOD activity was elevated in every treatment group and in every age group evaluated relative to the control groups (Tables 29-31). In the adult females, ECOD activity was significantly greater than control activity in animals fed 1.6 (16.1 pg TEQs/g) and 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed (Table 29). Hepatic ECOD rates were elevated in the all of the six-week-old kits on diets containing HR fish, but the increases were not statistically significant relative to the control kits (Table 30). The hepatic ECOD rates in the kits necropsied at the end of the trial increased at each dietary treatment in a monotonic fashion relative to the control kits at this age (Table 31). The increases in hepatic ECOD activities were significant at dietary concentrations of 0.61 (5.7 pg TEQs/g), 0.96 (9.2 pg TEQs/g), 1.6 (16.1 pg TEQs/g) and 3.7 (68.5 pg/g) ug total PCBs/g feed. Hepatic EROD, also an indicator of exposure to dioxin-like compounds and transcriptional activation of AhR-related toxicities, was elevated in every treatment group. Adult female mink had dose-related increases in hepatic EROD activity that were significantly greater than control activity at all but the lowest dietary concentration (Table 29). A similar dose-related increase in hepatic EROD activity was observed in six-week-old mink kits, with significantly greater hepatic EROD activities compared to control activity at dietary concentrations as low as 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed. The greatest induction of hepatic EROD in mink was observed in the kits necropsied at the end of the trial and this induction was dose-related. Significant induction of hepatic EROD activity relative to that of controls was observed at all dietary concentrations with the exception of the lowest concentration (0.34 [3.5 pg TEQs/g] ug total PCBs/g feed) (Table 31).

3.10 Concentrations of PHHs and TEQs in Mink Livers

PCDDs, PCDFs, and PCBs were detected in livers of adult and kit mink from all of the treatment groups (Tables 32-34). Hepatic total PCB concentrations increased with increasing dietary PCB concentrations. The hepatic concentrations of total PCBS were similar in adult females, six-week-old kits, and kits necropsied at the end of the trial, with one exception. The livers of kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group that were necropsied at the end of the trial had total PCB concentrations that were approximately two-fold greater compared to adults and six-week-old kits in the same treatment group. The contribution of each PHH class to the total TEQs in the liver was similar to the contribution of each class to dietary TEQs. In adult females, PCDDs, PCDFs, non-ortho PCBs and mono-ortho PCBs contributed an average of 4.7 $\pm$ 1.7%, 11.7 $\pm$ 1.5%, 67.9 $\pm$ 4.1% and 15.8 $\pm$ 1.3% of the total TEQs in the liver respectively, while the contribution was 3.6 $\pm$ 1.3%, 8.0 $\pm$ 0.6%, 68.1 $\pm$ 2.8% and 20.2 $\pm$ 1.6%, respectively, for six-week-old kits and 3.1 $\pm$ 1.1%, 11.2 $\pm$ 0.9%, 64.3 $\pm$ 1.3% and 21.2 $\pm$ 1.5%, respectively, for kits necropsied at the end of the trial.

4. DISCUSSION

4.1 Toxic Equivalency Factors and Toxic Equivalents

The sensitivity of mink to PCBs, particularly environmentally-derived PCBs, has been amply demonstrated (Ringer *et al.*, 1972; Aulerich and Ringer, 1977; Ringer *et al.*, 1981; Hornshaw *et al.*, 1983; Aulerich *et al.*, 1985; Heaton *et al.*, 1995a; Restum *et al.*, 1998) as has their sensitivity to PCDDs (Hochstein *et al.*, 1988; Hochstein *et al.*, 1998; Hochstein *et al.*, 2001). Because the mixture of PCBs, PCDDs and PCDFs present in the ecosytem differs from the technical mixtures released into the environment, the evaluation of their effects on the health of wildlife can be difficult. However, several of the PCDDs, PCDFs and coplanar PCB congeners cause a set of toxic responses very similar to those caused by TCDD, the most toxic of these chemicals (Safe,

1990). The toxic responses result from the initial binding of the TCDD-like congeners to the AhR, translocation of the ligand-AhR complex into the nucleus and activation of specific genes such as CYPIA1, which encodes the protein cytochrome P450IAI. Enhanced expression of the CYPIA1 gene and other genes by this ligand-activated transcription factor leads to the pleiotropic responses of TCDD (Safe, 1990). The fact that these different PCB, PCDD and PCDF congeners act via a common mechanism (binding to the AhR) has led to the development of the toxic equivalency factor (TEF) concept. In using the TEF approach, the potency of an individual congener is expressed relative to the potency of TCDD based on the dose required to produce a specific response. The toxicity of a complex mixture of congeners acting by the same mechanism can be assessed by determining the product of the prey tissue concentration of each congener and its TEF value to give the concentration of TCDD toxic equivalents or TEQs contributed by each congener. The TEQs contributed by each congener can then be summed to give the total concentration of TEQs present in fish or other prey. Determination of the concentration of TEQs present in a food source provides a more accurate assessment of the quantity of toxic material ingested by the predator rather than considering only total PCB concentration. Furthermore, in situations where results of different studies assessing the effects of consumption of environmentally-derived PCBs are being compared, the comparison of TEQ consumption could be more valid than comparison of total PCB consumption.

4.2 Concentrations of Selected Organochlorine Pesticides in Fish Samples

p,p'-DDE was the predominant pesticide detected in both the Atlantic Ocean herring and fish collected from the Housatonic River. *p,p'*-DDD was the second most abundant pesticide detected in the HR fish (Table 3). Heaton *et al*. (1995a) reported similar results for fish collected Saginaw Bay, Lake Huron, MI in that *p,p'*-DDD and *p,p'*-DDE were the predominant pesticides

and they occurred at concentrations similar to those reported here. Aulerich and Ringer (1977) reported that pesticides such as DDT and dieldrin did not affect reproduction in mink at concentrations much higher than those found in the fish collected from the Housatonic River.

4.3 Concentrations of PHHs and TEQs in Diets

Analysis of the treatment diets for total PCBs indicated that targeted dietary concentrations of PCBs were relatively close to measured concentrations. Assessment of PCDD, PCDF and PCB congener concentrations in the treatment diets and associated TEQs indicated that relatively few TEQs were contributed by PCDDs and PCDFs (Table 4). Approximately 60% of TEQs were contributed by the non-ortho PCB congeners, primarily 3,3',4,4',5-pentachlorobiphenyl (IUPAC #126), while 30% were contributed by the mono-ortho PCB congeners. This profile resembles that described by Tillitt *et al.* (1996) for feed containing carp collected from Saginaw Bay if the TEF values presented in Van den Berg *et al.* (1998) are applied rather than the H4IIE TEF values used by Tillitt and associates. In the report by Tillitt *et al.* (1996), non-ortho PCB congeners contributed 46% of the TEQs and the mono-ortho PCB congeners contributed 28%. PCDDs and PCDFs contributed 16 and 11% of the TEQs, respectively. As in the present study, the greatest contributor to total TEQs in the diets containing Saginaw Bay fish was PCB 126, which contributed essentially all of the TEQs associated with the non-ortho PCB congeners.

The concentration of TEQs in the 3.7 ug total PCBs/g feed diet (68.5 pg TEQs/g) was over four times the concentration of TEQs in the 1.6 ug total PCBs/g feed diet (16.1 pg TEQs/g) rather than the expected two-fold increase (Table 4).

4.4 Adult Feed Consumption

Mink exhibit a wasting syndrome that is characterized by reduced feed consumption and body weight loss when threshold quantities of chlorinated chemicals have been ingested

(Aulerich *et al.*, 1987; Hochstein *et al.*, 1988). In a trial that was conducted in a similar manner as the present study, Heaton *et al.* (1995a) reported that feed consumption of mink fed diets containing from 0.72 to 2.56 ug total PCBs/g feed derived from Saginaw Bay carp (or 22.2 to 85.0 pg TEQs/g [using congener concentrations presented in Tillitt *et al.* {1996} and TEF values presented in Van den Berg *et al.* {1998}]) was depressed in a dose-related manner over the 12-week measurement period. Conversely, in the present study, feed consumption was not influenced by inclusion of environmentally-derived PCBs at concentrations up to 3.7 ug total PCBs/g feed or 68.5 pg TEQs/g (Table 5).

If expressed on a TEQ basis, the range of effective doses in the Heaton *et al*. study (1995a) using TEQs based on congener concentrations presented in Tillitt *et al.* (1996) and TEF values presented in Van den Berg *et al.* (1998). was 3.9 to 10.2 pg TEQ/g body weight/day or cumulative doses of 407 to 1073 ng TEQs/mink. In the present study, animals in the highest dose group consumed 7.7 pg TEQs/g body weight/day, which corresponds to a cumulative dose of 754 ng TEQ over the first 84 days of the trial.

Average daily feed consumption of control animals in the present trial (128 g) was 48% of the average daily feed consumption (265 g) of controls in the study by Heaton *et al.* (1995a). However, the control feed consumption value reported by Heaton *et al.* (1995a) is over two-fold greater than the value reported for female mink (115 g/d) by Bleavins and Aulerich (1981). The value reported by Heaton *et al*. (1995a) for animals in the 2.56 ug total PCBs/g feed group (134 g/d) was closer to the value reported by Bleavins and Aulerich (1981) as well as to the values reported here.

4.5 Reproductive Performance and Kit Survivability

Consumption of diets containing PCBs derived from fish collected from the Housatonic River did not have an adverse effect on adult mink reproduction as assessed by breeding success, whelping success and gestation length (Tables 7 and 8). Kit survivability at six weeks of age was decreased in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group (Table 9).

In a study by Hornshaw *et al.* (1983), female mink fed a diet containing 1.5 ug total PCBs/g feed derived from Saginaw Bay fish for seven months prior to breeding failed to whelp any kits. Restum *et al.* (1998) reported that female mink fed 1.0 ug total PCBs/g feed derived from Saginaw Bay fish beginning two months prior to breeding had similar reproductive success as the control mink, but kit survivability at birth and at three and six weeks of age was significantly lower compared to controls. Halbrook *et al*. (1999) fed mink diets containing up to 1.86 ug total PCBs/g feed derived from fish collected from Poplar Creek (located on the Oak Ridge Reservation, Oak Ridge, TN) from three months prior to breeding through weaning. They reported that mink consuming the 1.86 ug total PCBs/g feed diet had the smallest average litter size (4.3 kits vs. 6.5 kits for the controls; not significant), but kit survivability in this group through six weeks of age was the highest (91% vs. 51% for the controls, not significant). The estimated total PCB intake was 55 mg/mink, compared to 78 mg/mink in the present study. Heaton *et al.* (1995a) reported no differences in breeding and whelping success in mink fed diets containing from 0.72 to 2.56 ug total PCBs/g feed derived from Saginaw Bay fish. However, the number of live kits whelped by females fed 2.56 ug total PCBs/g feed (85.0 pg TEQs/g; Tillitt *et al*. [1996] using TEF values presented in Van den Berg *et al.* [1998]) was significantly lower compared to the control group and groups fed 0.72 (22.2 pg TEQs/g; Tillitt *et al*. [1996]; Van den Berg *et al*. [1998]) and 1.53 (43.0 pg TEQs/g; Tillitt *et al*. [1996]; Van den Berg *et al*. [1998]) ug total PCBs/g feed (0.7, 5.0, 3.8 and 4.8 kits, respectively). Additionally, all of the kits

whelped by females fed 2.56 ug total PCBs/g feed were either stillborn or died within 24 hours. Percent kit survival to six weeks of age was 85% for the controls and 28% and 12 % for the kits in the 0.72 and 1.53 ug total PCBs/g feed groups, respectively.

While there appears to be a disparity between the dietary lowest observable adverse effect level (LOAEL) in the present study (3.7 ug total PCBs/g feed) based on kit survivability and dietary LOAELs for the same parameter reported in other studies conducted in a similar manner (0.72 ug total PCBs/ g feed in the Heaton *et al*. [1995a]/Tillitt *et al*. [1996] study and 1.0 ug total PCBs/g feed in the Restum *et al*. [1998] study), comparison of TEQ consumption suggests that results of these studies are similar. Daily TEQ consumption by the females in the study by Heaton *et al.* (1995a) was estimated to be 4.8, 8.5 and 12.8 ng TEQs/mink/day in the 0.72, 1.53 and 2.56 ug total PCBs/g feed groups, respectively or cumulative doses of 407, 710, and 1073 ng TEQs/mink (Tillitt *et al*. [1996]; Van den Berg *et al*. [1998]). This compares to a maximum consumption of 8.97 ng TEQs/mink/day (3.7 ug total PCBs/g feed group) or a cumulative dose of 1436 ng TEQs/mink in the present study.

A number of mink reproductive studies have been conducted utilizing commercial PCB products. Aulerich and Ringer (1977) reported that female mink fed a diet containing 5 ug Aroclor 1254/g feed beginning two months prior to breeding had a litter average of 0.8 kits/female compared to 5 kits/female for controls. They estimated a total PCB intake of 75 mg/mink compared to the maximum intake of 78 mg/mink in the present study, which did not affect litter size but did affect kit survivability. Jensen *et al.* (1977) fed mink a diet containing 3.3 ug total PCBs/g feed (commercial product was not identified) from 30 days prior to breeding for 66 days. Consumption of this diet resulted in a reported cumulative dose of 65 mg/mink, which caused a significant decrease in litter size compared to controls. Aulerich *et al*. (1985) fed

mink a diet containing 2.5 ug Aroclor 1254/g feed beginning 30 days prior to breeding through seven days post-parturition. The cumulative dose of 26 mg Aroclor 1254/mink resulted in no viable kits being whelped.

4.6 Body Weights

The lack of an effect of PCBs on adult body weights (Table 10) during the trial is not unexpected because feed consumption was not depressed. Heaton *et al.* (1995a) reported that, despite a dose-related PCB-induced decrease in feed consumption, body weights of adult females were not significantly affected. Similarly, adult mink body weights were not affected in the contaminated fish-feeding study conducted by Halbrook *et al.* (1999). In addition, mink fed diets containing up to 5 ug of commercial PCB products/g feed were not significantly affected in terms of body weight (Aulerich and Ringer, 1977; Jensen *et al*., 1977; Aulerich *et al*., 1985).

Body weights of kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group at three weeks of age were significantly lower compared to body weights of kits in the other five groups, but this was the only time point at which body weights of treated kits were significantly lower compared to controls (Table 11). Both Heaton *et al.* (1995a) and Restum *et al.* (1998) reported decreased body weights of kits exposed to as low as 0.72 (22.2 pg TEQ/g, Tillitt *et al*. [1996]; Van den Berg *et al*. [1998]) and 0.25 ug total PCBs/g feed, derived from Saginaw Bay carp, respectively, at three and six weeks of age. Birth weights of kits were significantly decreased in the 1.53 (43.0 pg TEQs/g, Tillitt *et al*. [1996]; Van den Berg *et al*. [1998]) ug total PCBs/g feed group in the Heaton *et al.* (1995a) study and in the 0.50 ug total PCBs/g feed group in the Restum *et al.* (1998) study. Halbrook *et al.* (1999) reported that body weights of six-week-old male kits exposed to 1.86 ug total PCBs/g feed were significantly less compared to controls.

Jensen *et al*. (1977) reported lower birth weights of kits whelped by females fed a diet containing 3.3 ug total PCBs/g feed compared to controls.

There is passage of PCBs from the female mink to the fetus through the placenta, but a greater proportion of PCBs is transferred to the kits via lactation (Bleavins *et al.*, 1982). This could explain why three-week body weights were depressed in kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group, while birth weights were similar to control kit birth weights. From birth to three weeks of age, the sole source of nourishment of a mink kit is from its mother's milk. Between three and six weeks of age, mink kits gradually make the transition from consumption of milk to consumption of solid feed. In the present study, it is possible that the quantity of PCBs ingested from birth to three weeks of age was sufficient to retard growth but that after three weeks of age, the quantity of PCBs ingested was below the threshold required to cause a continued effect on growth. An alternative explanation is that unthrifty kits in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group died by six weeks of age, leaving only those kits that were relatively healthy. However, because kits were not individually identified until six weeks of age, it was not possible to track individual animals from birth to weaning.

4.7 Absolute and Relative Organ Weights

There were no changes in absolute and relative organ weights of the adult female mink after consumption of PCB-containing diets for approximately 160 days (Tables 13 and 14). Heaton *et al.* (1995a) reported a general dose-dependent increase in relative organ weights (expressed as a percent of brain weight) with liver and spleen weights increased at all PCB concentrations (0.72 to 2.56 ug total PCBs/g feed), adrenal gland weights increased at 1.53 and 2.56 ug total PCBs/g feed and kidney weights increased at 2.56 ug total PCBs/g feed. Restum *et al.* (1998) reported increased absolute and relative (percent of brain weight) liver weights of male mink fed 1.0 ug

total PCBs/g feed for 18 months and an increase in absolute liver weights of males fed 0.5 ug total PCBs/g feed for the same length of time. The increase in liver weight was thought to be due to adaptive hypertrophy associated with lipidosis. Restum *et al*. (1998) also reported that absolute and relative spleen weights of females fed 1.0 ug total PCBs/g feed were significantly greater compared to controls after 18 months of exposure. Adult female mink fed 2.5 ug Aroclor 1254/g feed had significantly greater relative liver weights (expressed as a percent of brain weight) compared to controls after 90 days of exposure (Aulerich *et al.,* 1985).

In kits necropsied at six weeks of age, absolute liver weights of kits in the 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed group were greater compared to the other treatment groups, while relative brain, kidney and liver weights of females in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group were significantly greater compared to controls. These results are in contrast to those reported by Heaton *et al.* (1995a) in that there was a general decrease in six-week-old kit relative organ weights at doses of 0.72 and 1.53 ug total PCBs/g feed (no kits exposed to 2.56 ug total PCBs/g feed survived beyond 24 hours post-whelping).

In kits necropsied at the end of the trial (approximately 31 weeks of age), those fed 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed had significantly higher absolute and relative spleen weights. In the Restum *et al.* (1998) study, mink kits exposed to PCBs for 60 weeks also had increased absolute (0.25 and 1.0 ug total PCBs/g feed) and relative (0.25, 0.50 and 1.0 ug total PCBs/g feed) spleen weights while absolute brain (1.0 ug total PCBs/g feed), kidney (0.50 and 1.0 ug total PCBs/g feed) and heart (1.0 ug total PCBs/g feed) weights were decreased.

The most consistent effect of PCBs on mink organ weights has been on the liver. While absolute/relative liver weights were not consistently affected in the present study, liver weights

of adult females in the 1.6 (16.1 pg TEQs/g) and 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed groups were numerically greater compared to controls.

4.8 Histopathology of Tissues

Histologic examination of the major internal organs of the adult female mink and their kits did not show any remarkable changes attributable to the diets containing PCB-contaminated fish (Tables 23-25) except for the maxillary and mandibular squamous cell proliferation in the kits necropsied at the end of the trial (Table 26). With one exception, all animals in the control and treated groups had mild to severe extramedullary hematopoiesis of the liver and/or spleen. This appears to be a normal process for this species. Four control (one adult and three kits) and 19 treated (11 adults and eight kits) mink had mild multifocal areas of lymphoplasmacytic inflammatory cell infiltration in the liver. Mild inflammatory reaction in the liver of these animals was most likely a non-specific reaction to antigens carried to the liver through the portal vein. There was no gross or histologic evidence of a systemic microbial infection. Two control adults and six treated animals (five adults and one kit) had mild to severe lymphoplasmacytic inflammatory cell infiltration in the pelvic regions and interstitium of the kidney. Some of these animals had problems with hemorrhagic cystitis and urinary tract infections, secondary to urinary calculi. Histologic changes in the kidney of these animals were most likely due to a chronic reaction to the uroliths. One adult mink in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group had mild multifocal infiltration of lymphoplasmacytic inflammatory cells in the brain, adrenal glands and liver. The cause of this was not determined based on histological examination. One control kit and three treated mink (two adults and one kit) had a mild diffuse vacuolation of hepatocytes and two treated kits had bacterial colonies in the renal tubules.

Heaton *et al.* (1995b) reported that adult female mink exposed to PCBs through inclusion of Saginaw Bay carp into the diet had enlarged and diffusely yellow livers. Histologically, the livers had various degrees of congestion, hepatocellular fatty changes and scattered aggregrates of lymphocytes. Other studies have reported gross and cellular hepatic changes, including hepatic lipidosis, in mink exposed to PCBs (Aulerich *et al.*, 1971; Aulerich *et al.*, 1973; Platonow and Karstad, 1973; Aulerich and Ringer, 1977; Gillette *et al.*, 1987; Bergman *et al.*, 1992).

Previous studies have shown that feeding PCB 126 and TCDD induces periodontal squamous proliferation in the jaws of mink. In the initial study (Render *et al*., 2000), 12-week-old mink were fed a diet containing 24 ng PCB 126/g feed. After 31 days on trial, one of the animals had swelling of the upper and lower jaws with nodular proliferations of the mandibular and maxillary gingiva and loose teeth. The cleaned skull of this animal had marked porosity of maxillary and mandibular bone. Histological examination of tissues from other exposed animals showed that the mucosal epithelium was thickened and mucosal epithelium adjacent to teeth extended into the underlying bone as thin cords. The principal lesion was the presence of nests and cords of squamous epithelial cells within the periodontal ligament of multiple teeth. The nests and cords of epithelial cells extended into the adjacent alveolar bone, which was markedly irregular because of osteolysis. Large gaps occurred within the bone that corresponded with the loss of bone observed grossly. The nests of squamous epithelial cells were variable in size and some had cystic centers filled with exfoliated squamous cells. Over the subsequent 38 days of exposure, the remaining 19 mink being fed PCB 126 were affected in a similar manner.

In a subsequent study (Render *et al*., 2001), six- and 12-week-old mink were fed 2.4 ng TCDD/g feed. Many of these animals had loose and displaced incisor teeth by day 15 (12-week-

old animals) and day 28 (six-week-old animals) of exposure. Canine teeth were grossly more prominent. Radiographs showed maxillary and mandibular osteolysis of the lamina dura in exposed mink. Histologically, there was loss of alveolar bone and solid cystic nests and cords of infiltrative squamous epithelium in the periodontal ligament. The centers of the cysts contained exfoliated squamous cells and keratin.

Unpublished results from our laboratory indicated that 15 of 18 seven-month-old mink kits exposed to 0.24 ng PCB 126/g feed in utero, during lactation and throughout the growth period had histological evidence of this lesion. While none of the mink kits had gross abnormalities of the maxilla and mandible, histologically, there was proliferation of periodontal squamous epithelial cells. Nests of squamous epithelium were present adjacent to the teeth and some had cystic centers. The proliferation resulted in focal loss of alveolar bone.

The lowest dietary concentration of PCB 126 that resulted in the lesion in the above studies (0.24 ng PCB 126/g feed) is between the two highest dietary concentrations of PCB 126 in the present study. The 3.7 ug total PCBs/g feed diet contained 0.41 ng PCB 126/g feed and the 1.6 ug total PCBs/g feed diet contained 0.098 ng PCB 126/g feed.

These results of the present study indicate that dietary concentrations of environmentally derived PCB 126 as low as 0.054 ng/g feed (0.96 ug total PCBs/g feed) can induce maxillary and mandibular squamous cell proliferation. Exposure of mink to higher concentrations of PCB 126 for longer periods of time, as would be expected in the Housatonic River ecosystem, would undoubtedly cause increased severity of the lesion leading to erosion of the mandible and maxilla with concomitant loss of teeth. Such an effect would ultimately cause the animal to die of starvation.

4.9 Mortality of Adults and Kits Beyond Six Weeks of Age

The cause of death of four of the five adult females during the first 160 days of the trial as well as the two weaned kits was thought to be due to reasons other than exposure to PCBs (Table 26). The control female died of severe bacterial hemorrhagic cystitis. The two pregnant females in the 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed group and the pregnant female in the 1.6 (16.1 pg TEQs/g) ug total PCBs/g feed group died of severe bacterial cystitis, metritis and necro-suppurative placentitis. The fifth adult female that died was in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group and the cause of death of this animal could not be determined based on lack of gross lesions and minimal histological lesions. The two weaned kits that died were both in the 3.7 (68.5 pg TEQs/g) ug total PCBs/g feed group, but the cause of death was attributed to hemorrhagic cystitis and urolithiasis rather than exposure to PCBs.

Cystitis is inflammation of the bladder, usually occurring secondary to ascending urinary tract infections. A diagnosis of urinary tract infections is rarely made before animals succumb to toxemia due to obstruction of the urethra by fibrinopurulent exudates, which may contain calcerous material (Lauerman and Berman, 1961). Urolithiasis, or formation of urinary calculi, is frequently encountered on mink ranches and is largely confined to two distinct periods of the year. In the spring, calculi are found primarily in female mink during pregnancy or soon after whelping. The development of calculi before whelping is generally associated with the presence of a large number of unborn kits. In the summer months, calculi occur mainly in male kits (Leoschke *et al.,* 1952). The main component of urinary calculi in mink is magnesium ammonium phosphate hexahydrate (Leoschke and Elvehjam, 1954). The formation of this type of calculi occurs in alkaline urine and is often considered to be a result of urea-splitting bacterial infections. Organisms such as *Staphylococcus*, *Pseudomonas*, and *Proteus* are able to split urea, thereby inducing alkalinity and oversaturation of urine with respect to magnesium ammonium

phosphate. The presence of bacteria may also cause renal damage, which may affect mineral reabsorption and calculi formation. Renal injury also may result in polymerization of normal urinary mycoproteins or release of cellular debris, thus initiating calculi growth (Nguyen *et al*., 1979). While it is possible that exposure to PCBs depressed the immune system of the mink, thus making them more susceptible to bacterial infections, the causes of mortality reported here are not uncommon on a commercial mink ranch.

4.10 Liver Enzyme Activities

Induction of hepatic CYP2B-related activity in mink was not dramatic at any of the dietary concentrations of fish collected from the Housatonic River. Only a few dose-age treatment combinations had significant inductions of BROD or PROD activities. Further, none of the increases in BROD or PROD activities occurred in a dose-dependent fashion (Tables 29-31). Thus, the concentrations of di-, tri- and tetra-ortho-chloro-substituted PCBs, the PCB congeners thought to be responsible for CYP2B-related enzyme inductions, were either below a threshold of activation of these enzymes in the dietary treatments or the enzyme induction pathways were saturated. Further analysis (protein content or message) would be required to discern which of these occurred in these studies. PCB induction of phenobarbitol-like activity in hepatic P450 enzymes of mink has been observed previously (Brunström, 1992). Amino pyrene N-demethylase activity in adult mink was induced (less than two fold) by 2 mg Aroclor 1254/mink, which was administered daily.

Induction of CYPIA1-related hepatic enzyme activities (ECOD and EROD) was observed to occur in a dose-dependent fashion in all ages of mink examined. Significant increases in these AhR regulated enzymes were observed even at low dietary PCB concentrations (0.61 [5.7 pg TEQs/g] ug total PCBs) (Tables 29-31). Shipp *et al*. (1998)

reported induction of hepatic EROD in mink fed diets containing fish collected from Saginaw Bay. Total PCB concentrations in this study ranged from 0.25 to 1.0 µg/g feed. The induction of EROD and ECOD confirm that mink are sensitive to PCBs, PCDDs, PCDFs and related dioxin-like compounds and indicate that only a small amount of fish (less than 0.5%) from the Housatonic River would be required in the diets of mink to activate AhR pathways and processes in mink.

4.11 Concentrations of PHHs and TEQs in Mink Livers

Hepatic concentrations of total PCBs were generally similar in adult females and six-week-old mink while hepatic concentrations in kits necropsied at the end of the trial were generally greater compared to the other age groups (Tables 32-34). This could be because the adult females were transferring a portion of their body burden to their kits during lactation, while kits necropsied at the end of the trial had been accumulating PCBs from conception through the early growth period. The dose in the present study that caused a decreased kit survival (3.7 [68.5 pg TEQs/g] ug total PCBs/g feed) resulted in a hepatic total PCB concentration of 3.1 ug/g wet weight. This compares to a total PCB concentration of 2.19 ug/g wet weight at the 0.72 ug total PCBs/g feed dose that resulted in reduced kit survival in the Heaton *et al*. (1995a) study. Halbrook *et al.* (1999) reported a hepatic concentration of 7.25 ug total PCBs/g in adult female mink that had 34% fewer kits than controls. Mandibular and maxillary squamous cell proliferation was detected in kits necropsied at the end of the trial that were fed at a dietary concentration as low as 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed. These animals had a hepatic total PCB concentration of 1.7 ug/g wet weight. Significant increases in EROD and ECOD activities occurred at dietary concentrations as low as 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed

in adult females and/or kits necropsied at the end of the trial. Hepatic total PCB concentrations were 0.58 and 0.73 ug total PCBs/g wet weight in these adults and kits, respectively.

The contribution of PCDDs, PCDFs, and non-ortho and mono-ortho PCB congeners to the total TEQs in the liver was similar to their contribution to dietary TEQs (Tables 32-34). There was a tendency for PCDDs, PCDFs and non-ortho PCB congeners to contribute a greater percentage of TEQs in the liver compared to the diet while the contribution of mono-ortho PCB congeners to total TEQs in the liver was somewhat less compared to the diet. Total hepatic TEQs were also similar in adult females and kits that were six weeks and approximately 31 weeks old. In the present study, the dietary concentrations that caused reduced kit survival (3.7 [68.5 pg TEQs/g] ug total PCBs/g feed), resulted in a hepatic TEQ concentration of 218 pg/g. This compares to a concentration of 210 pg/g reported by Tillitt *et al*. (1996) using TEF values presented in Van den Berg *et al*. (1998) in mink fed a diet containing 0.72 ug total PCBs/g feed that resulted in reduced kit survivability (Heaton *et al.*, 1995a). Hepatic TEQ concentrations in mink kits necropsied at the end of the trial that had evidence of mandibular and maxillary squamous cell proliferation ranged from 40.2 to 197.3 pg/g wet weight. EROD and ECOD activities were induced in adult females with a hepatic concentration of 22.4 pg TEQs/g wet weight and in kits necropsied at the end of the trial that had a hepatic concentration of 19.1 pg TEQs/g wet weight.

4.12 NOAEL, LOAEL and Estimated Threshold Dose

In the present study, mink kit survivability at six weeks of age was considered to be the most important parameter adversely affected by exposure to dietary PCBs. Table 35 presents no observed adverse effect level (NOAEL) and LOAEL values and estimated tolerated doses expressed in a variety of ways based on decreased kit survival. Tillitt *et al.* (1996) reported that

the estimated tolerated dose to protect against reproductive toxicity expressed as dietary TEQ concentration was 4.7 pg/g using TEF values presented in Van den Berg *et al*. (1998) compared to 33.2 pg/g reported here. Expressed as quantity of TEQs consumed on a daily basis, Tillitt *et al*. (1996) reported an estimated threshold dose of 1.03 pg TEQs/g body weight/day using TEF values presented in Van den Berg *et al*. (1998) compared to 3.6 pg TEQs/g body weight/day. When expressed as hepatic TEQ concentration, the estimated threshold dose in the Tillitt *et al*. (1996) study was 61 pg TEQs/g using TEF values presented in Van den Berg *et al*. (1998) compared to 111 pg TEQs/g in the present study.

However, it is more appropriate to compare LOAELs between the two studies because Heaton *et al*. (1995a) did not report a NOAEL. There is some difference between dietary LOAELS (0.72 vs 3.7 ug total PCBs/g feed and 22.2 vs 68.5 pg TEQs/g) in the Heaton *et al*. (1995)/Tillitt *et al.* (1996) study using TEF values presented in Van den Berg *et al*. (1998) and the present study, respectively. LOAELs based on hepatic concentrations of total PCBs (2.19 vs 3.1 ug/g) and TEQs (210 vs 218 pg/g) in the Heaton *et al.* (1995a)/Tillitt *et al*. (1996) study using TEF values presented in Van den Berg *et al*. (1998) and the present study, respectively, are very close to one another. Leonards *et al*. (1995) summarized available PCB toxicity data for mink and estimated median effect levels (EC50) for reproduction. They report EC50 values of 2.36 ug total PCBs/g whole-body and 200 pg TEQs/g whole-body for kit survivability. These values compare favorably with the hepatic concentrations reported in the present study (3.1 ug total PCBs/g liver and 218 pg TEQs/g liver).

5. CONCLUSION

Results of the study indicate that survivability of mink kits between three and six weeks of age and three-week body weights of mink kits were significantly lower compared to controls

when their dams were fed 3.7 ug total PCBs/g feed or 68.5 pg TEQs/g derived from fish collected from the Housatonic River from two months prior to breeding through lactation. This dose resulted in hepatic concentrations of 3.1 ug total PCBs/g and 218 pg TEQs/g in adult females. While the dietary concentration that resulted in reduced kit survivability in the present study was greater compared to other studies (Aulerich and Ringer, 1977; Jensen *et al*., 1977; Aulerich *et al*., 1985; Heaton *et al*., 1995a; Restum *et al*., 1998; Halbrook *et al*., 1999), the hepatic concentrations of total PCBs and TEQs reported here are comparable to values reported by Heaton *et al*. (1995a)/Tillitt *et al.* (1996) using TEF values presented in Van den Berg *et al*. (1998) and Leonards *et al*. (1995). Because inclusion of PCB-contaminated fish that comprised less than 4% of the diet impacted mink kit survival, it is likely that consumption of up to 8-fold that quantity of HR fish, as could be expected for wild mink, would have an adverse effect on wild mink populations. Results also indicated that induction of mandibular and maxillary squamous cell proliferation occurred in kits exposed to 0.96 (9.2 pg TEQs/g) ug total PCBs/g feed and above in utero and throughout the growth period, which corresponded to 0.89% HR fish in the diet and that hepatic CYPIA1 activities were induced by dietary concentrations as low as 0.61 (5.7 pg TEQs/g) ug total PCBs/g feed, or 0.44% dietary HR fish, in all three age groups. While inducement of hepatic enzyme activity and squamous cell proliferation may not result in population-level effects, these changes are an indication that physiological alterations are occurring at very low concentrations of fish in the diet.

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Table 1. Composition and Nutrient Analysis of Experimental Diets Mixed in December, 1999.

Composition (%)	Dietary Treatment (ug total PCBs/g feed)					
	Control	0.34	0.61	0.96	1.6	3.7
Housatonic River Fish	0.00	0.22	0.44	0.89	1.77	3.54
Ocean Herring[a]	30.00	29.78	29.56	29.11	28.23	26.46
Commercial Mink Cereal[b]	25	25	25	25	25	25
Duck Offal[c]	20	20	20	20	20	20
Water	12.5	12.5	12.5	12.5	12.5	12.5
Spray-dried Chicken Liver[d]	2.5	2.5	2.5	2.5	2.5	2.5
Raw Eggs	10	10	10	10	10	10
d-Biotin[e] (mg/kg eggs)	0.6	0.6	0.6	0.6	0.6	0.6
Nutrient Analysis (%)[f]						
Moisture	55.02	54.48	54.91	53.74	55.46	54.69
Protein	14.73	14.67	14.64	15.15	14.63	14.33
Fat	9.76	9.86	9.85	10.20	9.62	9.79
Ash	3.78	3.82	3.61	3.75	3.74	3.81
Crude Fiber	1.10	1.14	1.22	1.04	1.22	0.95
Total Digestible Nutrients	43.36	43.87	43.64	44.89	42.84	43.75

[a]Boston Feed Supply, Natick, MA
[b]XK-40 mink food, XK Mink Foods, Inc., Plymouth, WI
[c]United Feeds Inc, Plymouth, WI
[d]Van Elderen Inc., Martin, MI
[e]Archer Daniel Midland, Des Moines, IA
[f]Litchfield Analytical Services, Litchfield, MI

Table 2. Composition and Nutrient Analysis of Experimental Diets Mixed in June and July, 2000.

Composition (%)	Dietary Treatment (ug total PCBs/g feed)					
	Control	0.34	0.61	0.96	1.6	3.7
Housatonic River Fish	0.00	0.22	0.44	0.88	1.75	3.51
Ocean Herring[a]	29.76	29.54	29.32	28.88	28.01	26.25
Commercial Mink Cereal[b]	24.8	24.8	24.8	24.8	24.8	24.8
Duck Offal[c]	19.8	19.8	19.8	19.8	19.8	19.8
Water	12.4	12.4	12.4	12.4	12.4	12.4
Spray-dried Chicken Liver[d]	2.5	2.5	2.5	2.5	2.5	2.5
Raw Eggs	9.9	9.9	9.9	9.9	9.9	9.9
75% Phosphoric Acid[e]	0.8	0.8	0.8	0.8	0.8	0.8
d-Biotin[f] (mg/kg eggs)	0.6	0.6	0.6	0.6	0.6	0.6
Larvadex 2SL[g] (ml/kg diet)	0.15	0.15	0.15	0.15	0.15	0.15
Nutrient Analysis (%)[h]						
Moisture	57.52	57.01	56.49	56.03	56.47	56.53
Protein	14.26	14.20	14.85	14.18	14.24	14.35
Fat	8.90	9.87	9.29	9.94	9.88	10.19
Ash	3.85	3.85	4.02	3.79	3.88	3.76
Crude Fiber	1.70	1.83	1.61	1.65	1.44	1.37
Total Digestible Nutrients	40.11	41.35	41.19	42.43	41.98	42.31

[a]Boston Feed Supply, Natick, MA
[b]XK-40 mink food, XK Mink Foods, Inc., Plymouth, WI
[c]United Feeds Inc., Plymouth, WI
[d]Van Elderen Inc., Martin, MI
[e]Alexander Chemical Corporation, Kingsbury, IN
[f]Archer Daniel Midland, Des Moines, IA
[g]Novartis Animal Health, Greensboro, NC
[h]Litchfield Analytical Services, Litchfield, MI

Table 3. Concentrations of Selected Organochlorines Pesticides in Atlantic Ocean Herring and Housatonic River Fish Blends.

Pesticide	Concentration (ng/g wet weight)[a]	
	Atlantic Ocean Herring	Housatonic River Fish
Hexachlorobenzene	1.5 ± 0.2	7.5 ± 1.2
PCA	4.1 ± 1.2	5.4 ± 2.6
α-BHC	1.7 ± 0.0	4.8 ± 3.5
β-BHC	0.3 ± 0.1	0.7 ± 0.4
Lindane	0.4 ± 0.0	1.8 ± 0.9
delta-BHC	0.2 ± 0.0	<0.4
Heptachlor	<0.4	<0.4
Heptachlor expoxide	0.7 ± 0.2	1.4 ± 1.3
Docthal	0.8 ± 0.2	1.8 ± 0.5
Dieldrin	2.5 ± 0.2	5.6 ± 0.7
Endrin	1.7	4.2 ± 0.5
Oxychlordane	1.0 ± 0.3	3.4 ± 1.5
cis-Chlordane	1.6 ± 0.3	11.0 ± 0.8
trans-Chlordane	1.5 ± 1.2	14.0 ± 16.0
cis-Nonachlor	0.9 ± 0.0	4.9 ± 0.7
trans-Nonachlor	2.5 ± 0.1	12.0 ± 2.6
o,p'-DDE	1.5 ± 0.2	4.0 ± 0.5
o,p'-DDD	0.7	12.0 ± 2.6
o,p'-DDT	1.6 ± 0.7	0.5 ± 0.3
p,p'-DDE	8.5 ± 2.2	190.0 ± 36.0
p,p'-DDD	2.6 ± 0.1	53.0 ± 5.9
p,p'-DDT	1.1 ± 0.5	0.8 ± 0.2
Endosulfan I	0.5	1.0 ± 0.4
Endosulfan II	1.9	3.0 ± 1.7
Endosulfate	<0.01	<0.01
Methoxychlor	2.8 ± 0.2	11.0 ± 2.0
Mirex	0.2	<0.01

[a]Data expressed as mean ± standard deviation. Sample size was 3.

Table 4. Dietary Concentrations (pg/g) of PCDDs, PCDFs, PCBs, and TEQs.

		Dietary Treatment (ug total PCBs/g feed)[a]					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
PCDDs							
2,3,7,8-TCDD	1.00000	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.5 (0.5)
1,2,3,7,8-PeCDD	1.00000	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.3 (0.3)
1,2,3,4,7,8-HxCDD	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
1,2,3,6,7,8-HxCDD	0.10000	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.3 (0.0)	0.2 (0.0)	0.5 (0.1)
1,2,3,7,8,9-HxCDD	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
1,2,3,4,6,7,8-HpCDD	0.01000	1.1 (0.0)	2.2 (0.0)	2.0 (0.0)	2.8 (0.0)	2.0 (0.0)	2.6 (0.0)
OCDD	0.00010	6.6 (0.0)	10.4 (0.0)	9.6 (0.0)	11.6 (0.0)	9.1 (0.0)	11.2 (0.0)
Total PCDDs		8.2 (0.2)	13.2 (0.2)	12.2 (0.2)	15.1 (0.2)	11.7 (0.2)	15.3 (0.9)
% total TEQs		18.2	5.7	3.5	2.2	1.2	1.3
PCDFs							
2,3,7,8-TCDF	0.10000	0.6 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)	1.2 (0.1)	3.0 (0.3)
1,2,3,7,8-PeCDF	0.05000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)	0.3 (0.0)	1.2 (0.1)
2,3,4,7,8-PeCDF	0.50000	0.1 (0.1)	0.4 (0.2)	0.5 (0.3)	0.7 (0.4)	1.2 (0.6)	4.6 (2.3)
1,2,3,4,7,8-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.5 (0.1)
1,2,3,6,7,8-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0 (0.0)	0 (0.0)	0.5 (0.1)
1,2,3,7,8,9-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.3 (0.0)
2,3,4,6,7,8-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.5 (0.1)
1,2,3,4,6,7,8-HpCDF	0.01000	0.3 (0.0)	0.4 (0.0)	0.5 (0.0)	0.4 (0.0)	0.4 (0.0)	0.7 (0.0)
1,2,3,4,7,8,9-HpCDF	0.01000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)
OCDF	0.00010	2.1 (0.0)	2.4 (0.0)	2.3 (0.0)	2.4 (0.0)	2.3 (0.0)	2.9 (0.0)
Total PCDFs		3.7 (0.2)	4.5 (0.3)	4.6 (0.4)	4.9 (0.5)	5.8 (0.7)	14.4 (3.0)
% total TEQs		18.2	8.6	7.0	5.4	4.3	4.4

Table 4 continued. Dietary Concentrations (pg/g) of PCDDs, PCDFs, PCBs, and TEQs in the Diets Fed to Mink

		Dietary Treatment (ug total PCBs/g feed)[a]					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Non-Ortho PCBs							
77	0.00010	20 (0.0)	24.1 (0.0)	30 (0.0)	41 (0.0)	65 (0.0)	190 (0.0)
81	0.00010	0.6 (0.0)	1.1 (0.0)	1.3 (0.0)	1.8 (0.0)	3.5 (0.0)	13 (0.0)
126	0.10000	4.9 (0.5)	19.4 (1.9)	32 (3.2)	54 (5.4)	98 (9.8)	410 (41.0)
169	0.01000	1 (0.0)	4.5 (0.0)	8.1 (0.1)	12 (0.1)	24 (0.2)	105 (1.1)
Total non-ortho PCBs		26.5 (0.5)	49.1 (1.9)	71.4 (3.3)	108.8 (5.5)	190.5 (10.0)	718 (42.1)
% total TEQs		45.5	54.3	57.9	59.8	62.1	61.5
Mono-Ortho PCBs							
105	0.00010	490 (0.0)	1200 (0.1)	2000 (0.2)	3000 (0.3)	5200 (0.5)	22000 (2.2)
114	0.00050	10 (0.0)	100 (0.1)	210 (0.1)	390 (0.2)	470 (0.2)	2900 (1.5)
118	0.00010	1500 (0.2)	450 (0.0)	810 (0.1)	1300 (0.1)	2500 (0.3)	11000 (1.1)
123	0.00010	10 (0.0)	1800 (0.2)	3000 (0.3)	4900 (0.5)	8800 (0.9)	38000 (3.8)
156	0.00050	70 (0.0)	1100 (0.6)	1900 (1.0)	3100 (1.6)	5500 (2.8)	23000 (11.5)
157	0.00050	30 (0.0)	160 (0.1)	260 (0.1)	430 (0.2)	760 (0.4)	3400 (1.7)
167	0.00001	50 (0.0)	380 (0.0)	680 (0.0)	1200 (0.0)	2100 (0.0)	8200 (0.1)
189	0.00010	60 (0.0)	300 (0.0)	490 (0.0)	800 (0.1)	1400 (0.1)	5800 (0.6)
Total mono-ortho PCBs		2220 (0.2)	5490 (1.1)	9350 (1.8)	15120 (3.0)	26730 (5.2)	114300 (22.5)
% total TEQs		18.2	31.4	31.6	32.6	32.3	32.8
Grand Total TEQs (pg/g)		**1.1**	**3.5**	**5.7**	**9.2**	**16.1**	**68.5**

[a]Data presented as dietary concentrations (pg/g) with the toxic equivalents (TEQs) in parentheses.
[b]Van den Berg *et al*., 1998.

Table 5. The Effect of PCBs Derived From Housatonic River Fish on Feed Consumption of Adult Female Mink During the Acclimation and Pre-breeding Periods[a].	
Dietary Treatment (ug total PCBs/g feed)	Feed Consumption (g/d)
Control	128.4 (97.7 - 168.8)
0.34	122.4 (93.0 - 161.0)
0.61	124.1 (94.3 - 163.2)
0.96	131.7 (100.2 - 173.2)
1.6	124.5 (94.6 - 163.8)
3.7	131.4 (99.9 - 172.8)
[a]Data are presented as mean (95% confidence intervals). The acclimation period was from 12/27/99 to 1/3/00 and the pre-breeding period was from 1/4/00 to 3/1/00.	

Table 6. Consumption of Total PCBs and TEQs Derived From Housatonic River Fish by Adult Female Mink.

	Dietary Treatment (ug total PCBs/g feed)					
Component	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Average daily feed consumption (g)[a]	128	122	124	132	125	131
Average body weight (g)[b]	1198	1162	1202	1233	1184	1170
Dietary PCB concentration (ug/g)	0.03	0.34	0.61	0.96	1.6	3.7
mg PCBs/mink/d	0.004	0.041	0.076	0.127	0.200	0.485
mg PCBs/kg body weight/d	0.003	0.036	0.063	0.103	0.169	0.414
Cumulative PCB dose (mg/mink)[c]	0.6	6.6	12.1	20.4	32.0	77.6
Dietary TEQ concentrations (pg/g)	1.1	3.5	5.7	9.2	16.1	68.5
ng TEQs/mink/d	0.141	0.427	0.707	1.205	1.996	8.974
ng TEQs/kg body weight/d	0.118	0.367	0.588	0.978	1.686	7.671
Cumulative TEQ dose (ng/mink)[c]	22.6	68.3	113.1	192.8	319.4	1435.8

[a]Determined during pre-breeding period only.
[b]Pre-breeding body weights.
[c]Based on 160 days exposure.

Table 7. The Effect of PCBs Derived From Housatonic River Fish on the Number of Females Bred and the Number of Females that Whelped.

Dietary Treatment (ug total PCBs/g feed)	Number of Females Bred/ Total Number of Females	Number of Females Whelping/ Number of Females Bred
Control	11/11	10/11
0.34	12/12	9/12
0.61	11/12	9/11
0.96	12/12	11/12
1.6	11/12	11/11
3.7	11/12	8/11

Table 8. The Effect of PCBs Derived From Housatonic River Fish on the Gestation Length of Adult Female Mink (days)[a].

Dietary Treatment (ug total PCBs/g feed)	Gestation Length
Control	44.8 ± 1.0
0.34	46.2 ± 1.1
0.61	47.8 ± 1.1
0.96	44.7 ± 1.0
1.6	45.9 ± 1.1
3.7	46.1 ± 1.1

[a]Data are presented as mean ± standard error of the mean.

Table 9. The Effect of PCBs Derived From Housatonic River Fish on the Kit Survivability (%) From Birth to Six Weeks of Age[a].

Dietary Treatment (ug total PCBs/g feed)	Birth	Three Weeks of Age	Six Weeks of Age
Control	96 (80.1 – 99.4)	85 (61.2 – 98.3)	85^{A} (61.2 – 98.3)
0.34	95 (76.0 – 99.7)	81 (55.0 – 97.3)	78^{AB} (50.9 – 95.8)
0.61	95 (76.8 – 99.5)	66 (37.9 – 89.0)	66^{AB} (37.9 – 89.0)
0.96	91 (71.1 – 99.7)	68 (42.4 – 88.5)	68^{AB} (42.4 – 88.5)
1.6	97 (82.4 – 99.3)	93 (74.2 – 100.0)	93^{A} (74.2 – 100.0)
3.7	99 (53.6 – 96.7)	77 (47.9 – 96.0)	46^{B} (18.1 – 74.7)

[a]Data are presented as mean (95% confidence intervals). Means with different superscripts are significantly different within the column ($p < 0.05$).

Table 10. The Effect of PCBs Derived From Housatonic River Fish on Body Weights (g) of Adult Female Mink[a].

Dietary Treatment (ug total PCBs/g feed)	Pre-Breeding[b]	Whelping[b]	Three Weeks Post-whelping[b]	Six Weeks Post-whelping[b]	Necropsy[b]
Control	1198.0 ± 34.2	1230.4 ± 36.8	1041.6 ± 40.2	925.9 ± 44.8	958.9 ± 44.1
0.34	1162.4 ± 34.2	1233.8 ± 38.7	1105.9 ± 42.3	1064.7 ± 47.2	1011.5 ± 42.2
0.61	1202.1 ± 34.2	1199.3 ± 38.7	1023.0 ± 42.3	936.0 ± 47.2	961.9 ± 46.2
0.96	1232.5 ± 34.2	1216.7 ± 35.0	1063.9 ± 36.7	1013.2 ± 44.8	1000.6 ± 42.2
1.6	1184.1 ± 34.2	1214.4 ± 35.0	1072.5 ± 38.3	953.4 ± 42.7	953.4 ± 44.1
3.7	1169.9 ± 34.2	1162.0 ± 41.1	1115.8 ± 44.9	917.9 ± 50.0	979.3 ± 44.1

[a]Data are presented as mean ± standard error of the mean.
[b]The pre-breeding period was from 1/4/00 to 3/1/00, the whelping period was from 4/17/00 to 5/5/00 and the adult mink were necropsied from 5/30/00 to 6/15/00.

Table 11. The Effect of PCBs Derived From Housatonic River Fish on Body Weight (g) of Kits from Birth to Six Weeks of Age[a].

Dietary Treatment (ug total PCBs/g feed)	Birth	Three Weeks of Age	Six Weeks of Age	Necropsy at Six Weeks of Age
Control	10.1 ± 0.29	107.8 ± 3.6^{A}	293.4 ± 11.3S^{A}	314.0 ± 26.3
0.34	9.4 ± 0.28	105.6 ± 3.5^{A}	300.9 ± 12.0^{AB}	310.8 ± 26.3
0.61	11.2 ± 0.31	127.4 ± 4.1^{B}	345.6 ± 13.8^{B}	346.0 ± 26.3
0.96	10.2 ± 0.25	99.6 ± 3.3^{A}	273.2 ± 11.1^{A}	307.8 ± 26.3
1.6	9.9 ± 0.25	99.7 ± 2.9^{A}	274.0 ± 9.9^{A}	272.3 ± 26.3
3.7	9.0 ± 0.29	82.0 ± 3.9^{C}	251.0 ± 16.2^{A}	232.5 ± 26.3

[a]Data are presented as mean ± standard error of the mean. Means with different superscripts are significantly different within the column ($p < 0.05$).

Table 12. The Effect of PCBs Derived From Housatonic River Fish on Body Weights (g) of Kits at 10 Weeks of Age to the End of the Trial[a].

Dietary Treatment (ug total PCBs/g feed)	10 Weeks of Age	14 Weeks of Age	18 Weeks of Age	22 Weeks of Age	26 Weeks of Age	30 Weeks of Age	Necropsy at End of Trial
Control	808.8^{AC} (754.2 - 867.6)	1157.8 (1079.6 - 1241.8)	1432.8 (1336.0 - 1536.9)	1537.0^{A} (1433.0 - 1648.5)	1615.0 (1505.8 - 1732.3)	1611.1 (1502.2 - 1728.0)	1548.5 $\pm$ 70.1
0.34	823.9^{ABC} (768.1 - 883.6)	1220.8 (1138.2 - 1309.4)	1544.4 (1439.9 - 1656.4)	1708.2^{B} (1592.7 - 1832.3)	1774.9 (1654.7 - 1903.6)	1733.9 (1616.5 - 1859.6)	1579.7 $\pm$ 70.1
0.61	907.4^{B} (846.1 - 973.3)	1264.3 (1178.7 - 1356.0)	1534.7 (1431.0 - 1646.2)	1637.5^{AB} (1526.8 - 1756.4)	1752.2 (1633.7 - 1879.4)	1671.4 (1558.4 - 1792.7)	1652.2 $\pm$ 70.1
0.96	836.7^{AB} (780.1 - 897.4)	1205.7 (1124.1 - 1293.1)	1544.4 (1439.9 - 1656.4)	1727.8^{B} (1611.0 - 1853.3)	1775.1 (1654.9 - 1903.8)	1679.9 (1566.3 - 1801.9)	1597.5 $\pm$ 70.1
1.6	800.3^{AC} (746.2 - 858.4)	1171.3 (1092.1 - 1256.4)	1449.8 (1351.7 - 1555.0)	1633.5^{AB} (1522.9 - 1752.0)	1656.6 (1544.4 - 1776.7)	1632.2 (1521.9 - 1750.8)	1594.0 $\pm$ 70.1
3.7	754.9^{C} (701.4 - 812.4)	1157.7 (1075.8 - 1246.0)	1398.7 (1299.7 - 1505.4)	1583.5^{AB} (1470.1 - 1705.5)	1624.9 (1507.6 - 1751.3)	1575.3 (1460.7 - 1698.7)	1524.7 $\pm$ 70.1

[a]Data are presented as means (95% confidence intervals) or means $\pm$ the standard error of the mean . Means with different superscripts are significantly different within the column ($p < 0.05$). The end of the trial was 11/0/00 resulting in approximately 31 weeks of exposure to PCBs.

Table 13. The Effect of PCBs Derived From Housatonic River Fish on Absolute Organ Weights (g) of Adult Female Mink[a].

Dietary Treatment (ug total PCBs/g feed)	Brain	Liver	Spleen	Kidneys	Heart	Adrenal Glands
Control	8.3 ± 0.16	38.5 ± 2.2	2.6 ± 0.29	6.6 ± 0.29	6.1 ± 0.21	0.08 ± 0.03
0.34	8.2 ± 0.15	40.8 ± 2.2	2.7 ± 0.29	7.0 ± 0.28	6.1 ± 0.20	0.15 ± 0.03
0.61	8.5 ± 0.16	35.6 ± 2.4	2.7 ± 0.30	6.8 ± 0.30	6.2 ± 0.22	0.08 ± 0.04
0.96	8.4 ± 0.15	39.1 ± 2.2	2.6 ± 0.28	6.7 ± 0.28	6.3 ± 0.20	0.08 ± 0.03
1.6	8.3 ± 0.16	43.8 ± 2.2	2.6 ± 0.29	6.5 ± 0.29	6.0 ± 0.21	0.09 ± 0.03
3.7	8.4 ± 0.16	43.9 ± 2.2	3.1 ± 0.29	6.7 ± 0.29	6.3 ± 0.21	0.08 ± 0.03

[a]Data are presented as mean ± standard error of the mean.

Table 14. The Effect of PCBs Derived From Housatonic River Fish on Relative Organ Weights (%) of Adult Female Mink[a].

Dietary Treatment (ug total PCBs/g feed)	Brain	Liver	Spleen	Kidneys	Heart	Adrenal Glands
Control	0.88 (0.81 - 0.96)	4.1 (3.7 - 4.5)	0.27 (0.22 - 0.33)	0.70 (0.64 - 0.77)	0.64 (0.58 - 0.70)	0.008 (0.004 - 0.012)
0.34	0.83 (0.86 - 0.90)	4.0 (3.6 - 4.4)	0.27 (0.22 - 0.32)	0.69 (0.63 - 0.76)	0.61 (0.63 - 0.76)	0.011 (0.007 - 0.016)
0.61	0.89 (0.82 - 0.98)	3.7 (3.3 - 4.1)	0.27 (0.21 - 0.33)	0.71 (0.65 - 0.79)	0.66 (0.60 - 0.72)	0.013 (0.008 - 0.018)
0.96	0.84 (0.77 - 0.91)	3.9 (3.5 - 4.3)	0.26 (0.21 - 0.31)	0.67 (0.61 - 0.73)	0.63 (0.58 - 0.69)	0.008 (0.005 - 0.013)
1.6	0.86 (0.80 - 0.95)	4.6 (4.1 - 5.0)	0.26 (0.21 - 0.32)	0.69 (0.62 - 0.75)	0.64 (0.58 - 0.69)	0.009 (0.005 - 0.014)
3.7	0.86 (0.79 - 0.93)	4.5 (4.1 - 5.0)	0.31 (0.26 - 0.37)	0.69 (0.62 - 0.76)	0.65 (0.59 - 0.71)	0.008 (0.004 - 0.012)

[a]Data are presented as mean (95% confidence intervals). Relative organ weights are expressed as a percentage of body weight.

Table 15. The Effect of PCBs Derived From Housatonic River Fish on Absolute Organ Weights (g) of Kits Necropsied at Six Weeks of Age[a].

Dietary Treatment (ug total PCBs/g feed)	Brain	Spleen	Kidneys	Heart	Adrenal Glands
Control	9.8 ± 0.35	2.0 ± 0.24	3.2 ± 0.26	2.4 ± 0.20^{AB}	0.04 ± 0.003
0.34	9.8 ± 0.35	1.9 ± 0.24	3.2 ± 0.26	2.1 ± 0.20^{AB}	0.03 ± 0.003
0.61	10.0 ± 0.35	1.8 ± 0.24	3.7 ± 0.26	2.5 ± 0.20^{B}	0.04 ± 0.003
0.96	9.5 ± 0.35	2.0 ± 0.24	3.2 ± 0.26	2.2 ± 0.20^{AB}	0.04 ± 0.003
1.6	9.5 ± 0.35	1.7 ± 0.24	2.9 ± 0.26	2.1 ± 0.20^{AB}	0.04 ± 0.003
3.7	9.5 ± 0.35	1.3 ± 0.24	2.7 ± 0.26	1.6 ± 0.20^{A}	0.03 ± 0.003

[a]Data are presented as mean ± standard error of the mean. Means with different superscripts are significantly different within the column ($p < 0.05$).

Table 16. The Effect of PCBs Derived From Housatonic River Fish on Absolute Liver Weight (g) of Male and Female Kits Necropsied at Six Weeks of Age[a].

	Liver	
Dietary Treatment (ug total PCBs/g feed)	Male	Female
Control	20.6 ± 2.1	13.6 ± 1.1^{AC}
0.34	16.3 ± 2.1	14.5 ± 1.1^{AC}
0.61	18.2 ± 2.1	16.4 ± 1.1^{A}
0.96	14.8 ± 2.1	19.6 ± 1.1^{B}
1.6	15.7 ± 2.1	14.5 ± 1.1^{AC}
3.7	16.7 ± 2.1	10.5 ± 1.1^{C}

[a]Data are presented as mean $\pm$ standard error of the mean. Means with different superscripts are significantly different within the column ($p < 0.05$).

Table 17. The Effect of PCBs Derived From Housatonic River Fish on Relative Spleen and Adrenal Gland Weights (%) of Kits Necropsied at Six Weeks of Age[a].

Dietary Treatment (ug total PCBs/g feed)	Spleen	Adrenal Glands
Control	0.64 (0.53 - 0.75)	0.011 (0.010 - 0.013)
0.34	0.59 (0.49 - 0.71)	0.011 (0.010 - 0.013)
0.61	0.54 (0.44 - 0.64)	0.013 (0.011 - 0.015)
0.96	0.61 (0.51 - 0.73)	0.012 (0.010 - 0.014)
1.6	0.62 (0.51 - 0.73)	0.014 (0.012 - 0.016)
3.7	0.56 (0.46 - 0.67)	0.014 (0.012 - 0.016)

[a]Data are presented as mean (95% confidence intervals). Relative organ weights are expressed as a percentage of body weight.

Table 18. The Effect of PCBs Derived From Housatonic River Fish on Relative Brain, Liver, Kidney, and Heart Weights (%) of Male and Female Kits Necropsied at Six Weeks of Age[a].

	Males			
Dietary Treatment (ug total PCBs/g feed)	Brain	Liver	Kidneys	Heart
Control	3.1 (2.3 - 4.1)	6.1 (5.4 - 6.8)	1.0 (0.9 - 1.2)	0.86 (0.70 - 1.03)
0.34	3.3 (2.4 - 4.2)	5.1 (4.5 - 5.7)	1.1 (1.0 - 1.2)	0.64 (0.50 - 0.79)
0.61	3.3 (2.4 - 4.2)	5.5 (4.8 - 6.2)	1.2 (1.0 - 1.3)	0.81 (0.65 - 0.98)
0.96	3.8 (2.9 - 4.8)	5.5 (4.9 - 6.2)	1.1 (1.0 - 1.3)	0.71 (0.57 - 0.87)
1.6	3.5 (2.7 - 4.5)	5.4 (4.8 - 6.1)	1.1 (1.0 - 1.2)	0.73 (0.58 - 0.89)
3.7	3.6 (2.8 - 4.6)	5.6 (4.9 - 6.2)	1.1 (1.0 - 1.2)	0.62 (0.49 - 0.77)
	Females			
Dietary Treatment (ug total PCBs/g feed)	Brain	Liver	Kidneys	Heart
Control	3.1^{A} (2.6 - 3.7)	4.7^{A} (4.2 - 5.3)	0.98^{A} (0.87 - 1.1)	0.66 (0.57 - 0.75)
0.34	3.1^{A} (2.6 - 3.7)	4.8^{A} (4.3 - 5.4)	0.94^{A} (0.82 - 1.1)	0.72 (0.62 - 0.81)
0.61	2.7^{A} (2.2 - 3.3)	4.7^{A} (4.2 - 5.3)	1.0^{A} (0.88 - 1.1)	0.67 (0.58 - 0.76)
0.96	2.7^{A} (2.2 - 3.2)	5.7^{AB} (5.1 - 6.3)	1.0^{A} (0.88 - 1.1)	0.70 (0.61 - 0.80)
1.6	3.7^{A} (3.1 - 4.3)	5.7^{AB} (5.1 - 6.3)	1.1^{A} (0.96 - 1.2)	0.83 (0.73 - 0.93)
3.7	5.3^{B} (4.6 - 6.0)	6.8^{B} (6.1 - 7.5)	1.4^{B} (1.2 - 1.5)	0.78 (0.68 - 0.88)

[a]Data are presented as mean (95% confidence intervals). Means with different superscripts are significantly different within the column ($p < 0.05$). Relative organ weights are expressed as a percentage of body weight.

Table 19. The Effect of PCBs Derived From Housatonic River Fish on Absolute Organ Weights (g) of Kits Necropsied at the End of the Trial[a].

Dietary Treatment (ug total PCBs/g feed)	Brain	Spleen	Liver	Heart	Adrenal Glands
Control	10.4 ± 0.33	3.3 ± 0.43^{A}	66.1 ± 3.8^{AB}	8.8 ± 0.60	0.10 ± 0.008
0.34	10.11 ± 0.33	3.2 ± 0.43^{A}	62.7 ± 3.8^{AB}	7.8 ± 0.60	0.10 ± 0.008
0.61	10.6 ± 0.33	3.6 ± 0.43^{AB}	53.7 ± 3.8^{B}	8.7 ± 0.60	0.10 ± 0.008
0.96	9.7 ± 0.33	3.7 ± 0.43^{AB}	61.0 ± 3.8^{AB}	8.5 ± 0.60	0.11 ± 0.008
1.6	9.8 ± 0.33	4.4 ± 0.43^{AB}	63.0 ± 3.8^{AB}	8.4 ± 0.60	0.10 ± 0.008
3.7	9.8 ± 0.33	5.2 ± 0.43^{B}	70.7 ± 3.8^{A}	8.7 ± 0.60	0.10 ± 0.008

[a]Data are presented as mean ± standard error of the mean. Means with different superscripts are significantly different within the column ($p < 0.05$). The end of the trial was 11/28/00 resulting in approximately 31 weeks of exposure to PCBs.

Table 20. The Effect of PCBs Derived From Housatonic River Fish on Absolute Kidney Weights (g) of Male and Female Kits Necropsied at the End of the Trial[a].		
	Kidneys	
Dietary Treatment (ug total PCBs/g feed)	Male	Female
Control	11.2 ± 1.1	9.9 ± 0.80
0.34	11.2 ± 1.1	8.2 ± 0.80
0.61	13.2 ± 1.1	7.1 ± 0.80
0.96	13.3 ± 1.1	7.1 ± 0.80
1.6	11.6 ± 1.1	7.4 ± 0.80
3.7	14.9 ± 1.1	7.8 ± 0.80
[a]Data are presented as mean ± standard error of the mean. The end of the trial was 11/28/00 resulting in approximately 31 weeks of exposure to PCBs.		

Table 21. The Effect of PCBs Derived From Housatonic River Fish on Relative Organ Weights (%) of Kits Necropsied at the End of the Trial[a].

Dietary Treatment (ug total PCBs/g feed)	Brain	Spleen	Liver	Heart	Adrenals
Control	0.70 (0.63 - 0.77)	0.22^{A} (0.17 - 0.27)	4.3^{A} (4.0 - 4.7)	0.57 (0.51 - 0.65)	0.007 (0.006 - 0.008)
0.34	0.67 (0.60 - 0.75)	0.20^{A} (0.15 - 0.26)	4.0^{AB} (3.6 - 4.4)	0.51 (0.44 - 0.57 0	0.007 (0.006 - 0.008)
0.61	0.68 (0.61 - 0.76)	0.22^{AB} (0.17 - 0.26)	3.3^{B} (3.0 - 3.6)	0.53 (0.46 - 0.59)	0.006 (0.005 - 0.007)
0.96	0.65 (0.58 - 0.72)	0.23^{AB} (0.18 - 0.29)	3.9^{AB} (3.5 - 4.2)	0.54 (0.48 - 0.61)	0.007 (0.006 - 0.008)
1.6	0.66 (0.59 - 0.74)	0.29^{AB} (0.23 - 0.35)	4.1^{A} (3.7 - 4.5)	0.54 (0.48 - 0.61)	0.007 (0.006 - 0.008)
3.7	0.68 (0.60 - 0.75)	0.35^{B} (0.28 - 0.42)	4.6^{A} (4.3 - 5.0)	0.57 (0.50 - 0.64)	0.007 (0.006 - 0.008)

[a]Data are presented as mean (95% confidence intervals). Means with different superscripts are significantly different within the column ($p < 0.05$). Relative organ weights are expressed as a percentage of body weight. The end of the trial was 11/28/00 resulting in approximately 31 weeks of exposure to PCBs.

Table 22. The Effect of PCBs Derived From Housatonic River Fish on Relative Kidney Weights (%) of Male and Female Kits Necropsied at the End of the Trial[a].

	Kidneys	
Dietary Treatment (ug total PCBs/g feed)	Male	Female
Control	0.59 (0.49 - 0.69)	0.81^{A} (0.73 - 0.90)
0.34	0.56 (0.47 - 0.66)	0.70^{AB} (0.62 - 0.79)
0.61	0.61 (0.51 - 0.72)	0.62^{B} (0.55 - 0.70)
0.96	0.64 (0.54 - 0.75)	0.63^{AB} (0.56 - 0.71)
1.6	0.56 (0.46 - 0.66)	0.68^{AB} (0.60 - 0.76)
3.7	0.76 (0.65 - 0.88)	0.71^{AB} (0.63 - 0.80)

[a]Data are presented as mean (95% confidence intervals). Means with different superscripts are significantly different within the column ($p < 0.05$). Relative organ weights are expressed as a percentage of body weight. The end of the trial was 11/28/00 resulting in approximately 31 weeks of exposure to PCBs.

Table 23. The Histopathological Assessment of Tissues from Adult Female Mink Fed Diets Containing PCB-Contaminated Fish.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P980	Control	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P774	Control	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P1294	Control	Liver: Mild extramedullary hematopoiesis
P1310	Control	Spleen: Mild extramedullary hematopoiesis
P930	Control	Liver: Mild extramedullary hematopoiesis
P740	Control	Spleen: Mild extramedullary hematopoiesis
P942	Control	Liver: Mild extramedullary hematopoiesis
P1004	Control	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis Kidney: Mild inflammatory cell infiltration in pelvic region
P1094	Control	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis
P1080	Control	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P950	Control	Spleen: Mild extramedullary hematopoiesis Kidney: Mild multifocal lymphoplasmacytic inflammatory cell infiltration

Table 23 continued. The Histopathological Assessment of Tissues from Adult Female Mink Fed Diets Containing PCB-Contaminated Fish.		
Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P1070	0.34	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P922	0.34	Spleen: Moderate extramedullary hematopoiesis
P974	0.34	Spleen: Mild extramedullary hematopoiesis
P1202	0.34	Spleen: Mild extramedullary hematopoiesis
P814	0.34	Spleen: Mild extramedullary hematopoiesis
P952	0.34	Spleen: Mild extramedullary hematopoiesis
P852	0.34	Spleen: Mild extramedullary hematopoiesis
P1180	0.34	Spleen: Mild extramedullary hematopoiesis
P1002	0.34	Liver: Moderate periportal extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Severe extramedullary hematopoiesis
P830	0.34	Liver: Moderate extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Severe extramedullary hematopoiesis
P1760	0.34	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis Kidney: Mild multifocal interstitial nephritis
P1190	0.34	Spleen: Mild extramedullary hematopoiesis Kidney: Mild focal periglomerular inflammatory cell infiltration

Table 23 continued. The Histopathological Assessment of Tissues from Adult Female Mink Fed Diets Containing PCB-Contaminated Fish.		
Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P770	0.61	Spleen: Moderate extramedullary hematopoiesis
P1312	0.61	Liver: Moderate periportal extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P910	0.61	Spleen: Moderate extramedullary hematopoiesis
P782	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P1370	0.61	Spleen: Mild extramedullary hematopoiesis
P714	0.61	Spleen: Mild extramedullary hematopoiesis
P1212	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P810	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P1290	0.61	Spleen: Mild extramedullary hematopoiesis Kidney: Mild focal interstitial inflammatory cell infiltration
P1220	0.61	Liver: Mild multifocal lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis Brain: Mild multifocal lymphoplasmacytic inflammatory cell infiltration Adrenal glands: Mild multifocal lymphoplasmacytic inflammatory cell infiltration

Table 23 continued. The Histopathological Assessment of Tissues from Adult Female Mink Fed Diets Containing PCB-Contaminated Fish.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P764	0.96	Spleen: Moderate extramedullary hematopoiesis
P822	0.96	Spleen: Mild extramedullary hematopoiesis
P752	0.96	Spleen: Mild extramedullary hematopoiesis
P790	0.96	Spleen: Mild extramedullary hematopoiesis
P860	0.96	No changes noted
P1320	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1216	0.96	Liver: Mild vacuolation Spleen: Severe extramedullary hematopoiesis
P1300	0.96	Spleen: Mild extramedullary hematopoiesis
P1292	0.96	Spleen: Mild extramedullary hematopoiesis
P1222	0.96	Spleen: Moderate extramedullary hematopoiesis
P870	0.96	Liver: Moderate extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Moderate extremedullary hematopoiesis
P882	0.96	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration

Table 23 continued. The Histopathological Assessment of Tissues from Adult Female Mink Fed Diets Containing PCB-Contaminated Fish.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P794	1.6	Spleen: Mild extramedullary hematopoiesis
P890	1.6	Spleen: Mild extramedullary hematopoiesis
P834	1.6	Spleen: Mild extramedullary hematopoiesis
P872	1.6	Liver: Mild vacuolation Spleen: Mild extramedullary hematopoiesis
P1214	1.6	Spleen: Mild extramedullary hematopoiesis
P780	1.6	Spleen: Mild extramedullary hematopoiesis
P1182	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P1374	1.6	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration
P744	1.6	Liver: Mild diffuse sinusoidal amyloidosis Spleen: Moderate extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration
P1316	1.6	Liver: Moderate extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis
P880	1.6	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis Kidney: Severe focal lymphoplasmacytic inflammatory cell infiltration in pelvic region

Table 23 continued. The Histopathological Assessment of Tissues from Adult Female Mink Fed Diets Containing PCB-Contaminated Fish.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P832	3.7	Spleen: Moderate extramedullary hematopoiesis
P792	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P776	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1006	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P892	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1210	3.7	Spleen: Mild extramedullary hematopoiesis
P920	3.7	Spleen: Mild extramedullary hematopoiesis
P730	3.7	Liver: Mild extramedullary hematopoiesis; lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis
P1296	3.7	Spleen: Moderate extramedullary hematopoiesis Kidney: Severe focal lymphoplasmacytic inflammatory cell infiltration
P742	3.7	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis
P1314	3.7	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis

Table 24. The Histopathological Assessment of Tissues from Mink Kits Exposed to PCBs Through Six Weeks of Age.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P1294 (M1-6W)	Control	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1004 (M1-6W)	Control	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1094 (M1-6W)	Control	Spleen: Mild extramedullary hematopoiesis
P1310 (F1-6W)	Control	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P930 (F1-6W)	Control	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P974 (M1-6W)	0.34	Spleen: Severe extramedullary hematopoiesis
P830 (M1-6W)	0.34	Liver: Mild to moderate extramedullary hematopoiesis Spleen: Mild to moderate extramedullary hematopoiesis
P814 (M1-6W)	0.34	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration; bacterial colonies in hepatic sinusoids Kidney: Bacterial colonies in renal tubules
P952 (F1-6W)	0.34	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1202 (F1-6W)	0.34	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P852 (F1-6W)	0.34	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis

Table 24 continued. The Histopathological Assessment of Tissues from Mink Kits Exposed to PCBs Through Six Weeks of Age.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P770 (M1-6W)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1370 (M1-6W)	0.61	Liver: Mild extramedullary hematopoiesis; mild multifocal hepatocellular vacuolation Spleen: Severe extramedullary hematopoiesis
P714 (M1-6W)	0.61	Liver: Mild extramedullary hematopoiesis; bacterial colonies in hepatic sinusoids Spleen: Mild extramedullary hematopoiesis Kidney: Bacterial colonies in renal tubules
P782 (F1-6W)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P1212 (F1-6W)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P810 (F1-6W)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P752 (M1-6W)	0.96	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Severe extramedullary hematopoiesis
P860 (M1-6W)	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1216 (M1-6W)	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P870 (F1-6W)	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1320 (F1-6W)	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1292 (F1-6W)	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis

Table 24 continued. The Histopathological Assessment of Tissues from Mink Kits Exposed to PCBs Through Six Weeks of Age.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P1374 (M1-6W)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P794 (M1-6W)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P834 (M1-6W)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P872 (F1-6W)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P890 (F1-6W)	1.6	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration; bacterial colonies in hepatic sinusoids Spleen: Mild extramedullary hematopoiesis
P744 (F1-6W)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P892 (M1-6W)	3.7	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Severe extramedullary hematopoiesis
P1314 (M2-6W)	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1314 (M1-6W)	3.7	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Moderate extramedullary hematopoiesis
P1296 (F1-6W)	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P1200 (F2-6W)	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P1200 (F1-6W)	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis

Table 25. The Histopathological Assessment of Tissues from Mink Kits Exposed to PCBs Through 31 Weeks of Age.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P740 (M11-6M)	Control	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P930 (M11-6M)	Control	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1094 (M11-6M)	Control	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration; multiple small blood-filled spaces Spleen: Mild extramedullary hematopoiesis
P1310 (F11-6M)	Control	Spleen: Mild to moderate extramedullary hematopoiesis
P1030 (F11-6M)	Control	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Moderate extramedullary hematopoiesis
P774 (F11-6M)	Control	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Moderate extramedullary hematopoiesis
P852 (M11-6M)	0.34	Spleen: Moderate extramedullary hematopoiesis
P1180 (M11-6M)	0.34	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P952 (M11-6M)	0.34	Spleen: Mild to moderate extramedullary hematopoiesis
P974 (F11-6M)	0.34	Spleen: Mild extramedullary hematopoiesis
P1180 (F11-6M)	0.34	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis
P952 (F11-6M)	0.34	Liver: Mild extramedullary hematopoiesis; mild lymphoplasmacytic inflammatory cell infiltration Spleen: Mild extramedullary hematopoiesis

Table 25 continued. The Histopathological Assessment of Tissues from Mink Kits Exposed to PCBs Through 31 Weeks of Age.		
Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P782 (M11-6M)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Mild extramedullary hematopoiesis
P810 (M11-6M)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1290 (M1106M)	0.61	Spleen: Mild extramedullary hematopoiesis
P770 (F12-6M)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P770 (F11-6M)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1290 (F11-6M)	0.61	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P882 (M11-6M)	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1300 (M11-6M)	0.96	Spleen: Mild extramedullary hematopoiesis
P790 (M11-6M)	0.96	Liver: Moderate extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1222 (F11-6M)	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1292 (F11-6M0	0.96	Liver: Mild extramedullary hematopoiesis Spleen: Severe extramedullary hematopoiesis
P870 (F11-6M)	0.96	Spleen: Moderate extramedullary hematopoiesis

Table 25 continued. The Histopathological Assessment of Tissues from Mink Kits Exposed to PCBs Through 31 Weeks of Age.		
Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation
P794 (M11-6M)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1182 (M11-6M)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P1316 (M11-6M)	1.6	Liver: Mild extramedullary hematopoiesis; lymphoplasmacytic inflammatory cell infiltration Spleen: Moderate extramedullary hematopoiesis
P1214 (F11-6M)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P880 (F11-6M)	1.6	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P834 (F11-6M)	1.6	Spleen: Moderate extramedullary hematopoiesis
P1314 (M11-6M)	3.7	Spleen: Mild extramedullary hematopoiesis
P1314 (M12-6M)	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P892 (M12-6M)	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis Kidney: Mild multifocal glomerulo-interstitial nephritis
P1314 (F11-6M)	3.7	Liver: Mild extramedullary hematopoiesis Spleen: Moderate extramedullary hematopoiesis
P892 (F11-6M)	3.7	Spleen: Moderate extramedullary hematopoiesis
P892 (F13-6M)	3.7	Spleen: Mild to moderate extramedullary hematopoiesis

Table 26. The Histopathological Assessment of Squamous Cell Proliferation in the Maxillae and Mandibles from Mink Kits Exposed to PCBs through 31 Weeks of Age.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation on Occurrence and Numbers of Foci of Squamous Cell Proliferation
P740 (M11-6M)	Control	No lesions
P930 (M11-6M)	Control	No lesions
P1094 (M11-6M)	Control	No lesions
P1310 (F11-6M)	Control	No lesions
P1030 (F111-6M)	Control	No lesions
P774 (F11-6M)	Control	No lesions
P852 (M11-6M)	0.34	No lesions
P1180 (M11-6M)	0.34	No lesions
P952 (M11-6M)	0.34	No lesions
P974 (F11-6M)	0.34	No lesions
P1180 (F11-6M)	0.34	No lesions
P952 (F11-6M)	0.34	No lesions
P782 (M11-6M)	0.61	No lesions
P810 (M11-6M)	0.61	No lesions
P1290 (M11-6M)	0.61	No lesions
P770 (F12-6M)	0.61	No lesions
P770 (F11-6M)	0.61	No lesions
P1290 (F11-6M)	0.61	No lesions

Table 26 continued. The Histopathological Assessment of Squamous Cell Proliferation in the Maxillae and Mandibles from Mink Kits Exposed to PCBs through 31 Weeks of Age.		
Animal ID	Dietary Treatment (ug total PCBs/g feed)	Observation on Occurrence and Numbers of Foci of Squamous Cell Proliferation
P882 (M11-6M)	0.96	No lesions
P1300 (M11-6M)	0.96	No lesions
P790 (M11-6M)	0.96	Left mandible, 1 focus, mild
P1222 (F11-6M)	0.96	No lesions
P1292 (F11-6M)	0.96	No lesions
P870 (F11-6M)	0.96	No lesions
P794 (M11-6M)	1.6	Right maxilla, 1 focus, mild
P1182 (M11-6M)	1.6	No lesions
P1316 (M11-6M)	1.6	Right maxilla, 2 foci, moderate
P834 (F11-6M)	1.6	No lesions
P1214 (F11-6M)	1.6	No lesions
P880 (F11-6M)	1.6	No lesions
P1314 (M11-6M)	3.7	Right maxilla, 1 focus, mild; Left maxilla, 3 foci, moderate
P1314 (M12-6M)	3.7	Right maxilla, 2 foci, moderate
P892 (M12-6M)	3.7	Right maxilla, 1 focus, mild; Left maxilla, 1 focus, mild; Left mandible, 1 focus, mild
P1314 (F11-6M)	3.7	Right maxilla, 1 focus, mild
P892 (F11-6M)	3.7	Right maxilla, 3 foci, moderate; Left maxilla, 6 foci, severe
P892 (F13-6M)	3.7	Right maxilla, 1 focus, mild; Left maxilla, 1 focus, mild

Table 27. Final Report of Laboratory Examination of Adult Female Mink That Died on Trial.			
Animal ID	Dietary Treatment (ug total PCBs/g feed)	Date of Death	Summary
P1204	Control	3/16/00	Body judged to be in good nutritional state, weighing 910 gm. Internally, the urinary bladder was distended with blood clots and blood. There were no other gross lesions of diagnostic significance.
P1192	0.61	4/19/00	Body judged to be in good nutritional state, weighing 860 gm. Externally, the perineal region was wet and matted with a brownish substance. Internally, the animal was pregnant. Approximately 50% of the caudal areas of the uterus and uterine horns adjacent to the cervix was extensively congested and hemorrhagic. Three fetuses in the caudal part of the uterus were macerated, necrotic and hemorrhagic. The placentas in this region were necrotic and hemorrhagic. Two fetuses in the cranial part of the uterus were normal. The urinary bladder was hemorrhagic. There were no other remarkable gross lesions of diagnostic significance.
P1206	0.61	4/23/00	Body judged to be in good nutritional state, weighing 660 gm. Externally, the perineal region was red. Internally, 50% of the total uterus and uterine horns adjacent to the cervix was extensively congested and hemorrhagic. The centers of these fetuses were necrotic and hemorrhagic. The cervix was closed and the vagina contained hemorrhagic exudates. Three fetuses in the cranial part of the uterus were normal, weighing approximately 2.8 gm each. The urinary bladder was diffusely hemorrhagic. There were no other remarkable gross lesions of diagnostic significance.
P1200	3.7	6/6/00	The animal was found dead, weighing 663 grams. No gross lesions were apparent. Histology indicated mild to moderate extramedullary hematopoiesis in the liver and spleen.

Table 27 continued. Final Report of Laboratory Examination of Adult Mink That Died on Trial.			
Animal ID	Dietary Treatment (ug total PCBs/g feed)	Date of Death	Summary
P824	1.6	4/24/00	Body judged to be in good nutritional state, weighing 1,135 gm. Externally, the perineal region was wet and matted with a brownish substance. Internally, the abdominal cavity contained approximately 10 ml of dark red, thick fluid. Approximately 70% of the total uterus and uterine horns adjacent to the cervix was diffusely congested and hemorrhagic. Four fetuses in this region were macerated, necrotic and hemorrhagic. The placentas of these fetuses were necrotic and hemorrhagic. Two fetuses in the cranial part of the uterine horns were normal. The average weight of the normal fetuses was about 7 gm. The mucosal surface of the urinary bladder was covered with a thick layer of yellowish-green fibrino-suppurative membrane. Major histologic lesions occurred in the urinary bladder, uterus and placenta. Sections of the urinary bladder had mutlifocal areas of ulceration and hyperplasia of the mucosa. The mucosa was diffusely covered by thick layers of inflammatory cells, predominantly neutrophils, mixed with necrotic debris, fibrin and bacterial colonies. The submucosa propria contained mixed populations of inflammatory cells, with macrophages and a few giant cells. The lumen of the bladder contained suppurative exudates and bacterial colonies. Sections of the placenta had diffuse necrosis and hemorrhage. Extensive rod-shaped bacterial colonization was present throughout sections. There were also multifocal areas of inflammatory cell infiltration, predominantly neutrophils. Sections of the liver had multifocal areas of a mild infiltration of a mixed population of inflammatory cells. Sections of other organs had no remarkable lesions.

Table 28. Final Report of Laboratory Examination of Mink Kits That Died on Trial After Six Weeks of Age.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Date of Death	Summary
P892 (M11-6M)	3.7	9/22/00	Postmortem examination revealed stomach ulceration. The stomach and entire intestine were filled with blood. Thick greenish purulent exudate was present throughout the right perirenal region and peritoneum. The urinary bladder was diffusely thickened, with hemorrhagic mucosa. A urolith approximately 5 x 10 mm in diameter was present in the urinary bladder. Multiple sections of major internal organs were examined. Sections of lung had a diffuse thickening and hypercellularity of alveolar walls by infiltration of a mixed population of inflammatory cells. Sections of kidney had a diffuse thickening of the capsule by proliferation of fibrous connective tissue and neovascularization. The capsule was covered with thick layers of fibrin, cellular necrotic debris and extensive infiltration of inflammatory cells that were predominantly neutrophils. Intralesional coccoid bacterial colonies were also present. The inflammatory reaction extended to the perirenal fat and peritoneum. There was also multifocal, moderate infiltration of a mixed population of inflammatory cells throughout the interstitium of the kidney that extended to the pelvic region. There was intrastitial fibrosis and neutrophils. The epithelial lining of the pelvic region appeared hyperplastic associated with moderate infiltration of a mixed population of inflammatory cells. The urinary bladder had hyperplastic to eroded and ulcerated epithelium. There was diffuse submucosal mineralization. There were also areas of hemorrhage and locally extensive areas of inflammatory cell infiltration and fibrosis. The serosal surface had diffuse mesothelial cell

Table 28 continued. Final Report of Laboratory Examination of Mink Kits That Died on Trial After Six Weeks of Age.

Animal ID	Dietary Treatment (ug total PCBs/g feed)	Date of Death	Summary
			hyperplasia with multifocal areas of hemorrhage, granulation tissue and inflammatory cell infiltration that were predominantly neutrophils. The inflammation was extended to the peritoneal fat. Sections of other organs had no remarkable lesions.
P892 (F12-6M)	3.7	7/12/00	The animal was discovered dead, weighing 712 grams. There was red-colored fluid in the fur around the perineal area. Two uroliths (each 5 x 5 mm) were found in the bladder. There was evidence of hemorrhaging in the urinary bladder. Histological examination indicated hemorrhages in the urinary bladder and mild extramedullary hematopoiesis in the spleen and liver. Cause of death was urolithiasis and hemorrhagic cystitis.

Table 29. The Effect of PCBs Derived From Housatonic River Fish on Hepatic Microsomal Activities (pmol/min/mg) of Adult Female Mink.

		Hepatic Microsomal Activities[a]			
Dietary Treatment (ug total PCBs/g feed)	N	BROD	PROD	ECOD	EROD
Control	11	12 ± 6.7^{A}	13 ± 11^{A}	65 ± 100^{A}	67 ± 32^{A}
0.34	12	14 ± 5.3^{A}	9 ± 7.4^{A}	130 ± 100^{A}	130 ± 55^{AB}
0.61	10	13 ± 5.4^{A}	8 ± 5.5^{A}	130 ± 98^{A}	190 ± 80^{BC}
0.96	12	13 ± 6.2^{A}	10 ± 9.7^{A}	150 ± 180^{A}	250 ± 73^{C}
1.6	11	12 ± 6.0^{A}	6 ± 4.4^{A}	390 ± 240^{B}	340 ± 110^{A}
3.7	11	10 ± 7.7^{A}	7 ± 7.4^{A}	480 ± 290^{B}	490 ± 160^{E}

[a]BROD refers to benzyloxyresorufin-O-deethylase, PROD refers to pentoxyresorufin-O-deethylase, ECOD refers to ethoxycoumarin-O-deethylase, and EROD refers to ethoxyresorufin-O-deethylase. N represents the number of livers sampled for each dietary treatment. Data presented as mean ± standard deviation of the mean. Means with different superscripts are significantly different within the column ($p<0.05$).

Table 30. The Effect of PCBs Derived From Housatonic River Fish on Hepatic Microsomal Activities (pmol/min/mg) of Kits Necropsied at Six-Weeks of Age.

		Hepatic Microsomal Activities[a]			
Dietary Treatment (ug total PCBs/g feed)	N	BROD	PROD	ECOD	EROD
Control	6	14 ± 12^{A}	3 ± 4.0^{A}	2 ± 0^{A}	81 ± 45^{A}
0.34	6	14 ± 5.1^{A}	16 ± 16^{B}	5 ± 7.4^{A}	99 ± 20^{A}
0.61	6	11 ± 6.6^{AB}	4 ± 2.6^{A}	65 ± 97^{A}	150 ± 82^{AB}
0.96	6	8.1 ± 2.7^{AB}	7 ± 6.0^{A}	42 ± 50^{A}	200 ± 52^{B}
1.6	6	9.6 ± 3.6^{AB}	8 ± 6.7^{A}	90 ± 110^{A}	280 ± 48^{C}
3.7	6	6.1 ± 3.0^{B}	4 ± 4.7^{A}	79 ± 130^{A}	350 ± 89^{C}

[a] BROD refers to benzyloxyresorufin-O-deethylase, PROD refers to pentoxyresorufin-O-deethylase, ECOD refers to ethoxycoumarin-O-deethylase, and EROD refers to ethoxyresorufin-O-deethylase. N represents the number of livers sampled for each dietary treatment. Data presented as mean ± standard deviation of the mean. Means with different superscripts are significantly different within the column ($p<0.05$).

Table 31. The Effect of PCBs Derived From Housatonic River Fish on Hepatic Microsomal Activities (pmol/min/mg) of Kits Necropsied at the End of the Trial.

		Hepatic Microsomal Activities[a]			
Dietary Treatment (ug total PCBs/g feed)	N	BROD	PROD	ECOD	EROD
Control	6	5 ± 2.7^{A}	4 ± 1.0^{AC}	18 ± 21^{A}	80 ± 30^{A}
0.34	6	17 ± 10^{B}	11 ± 4.6^{BC}	83 ± 54^{AB}	150 ± 44^{AB}
0.61	6	16 ± 6.9^{B}	8.3 ± 4.4^{ABC}	140 ± 50^{BC}	300 ± 130^{BC}
0.96	6	15 ± 12^{B}	8.9 ± 4.6^{BC}	150 ± 110^{BC}	410 ± 170^{CD}
1.6	6	14 ± 5.3^{AB}	6.2 ± 2.0^{AC}	220 ± 82^{C}	540 ± 63^{D}
3.7	6	14 ± 11^{AB}	7.1 ± 1.7^{ABC}	190 ± 110^{C}	700 ± 200^{E}

[a]BROD refers to benzyloxyresorufin-O-deethylase, PROD refers to pentoxyresorufin-O-deethylase, ECOD refers to ethoxycoumarin-O-deethylase, and EROD refers to ethoxyresorufin-O-deethylase. N represents the number of livers sampled for each dietary treatment. Data presented as mean ± standard deviation of the mean. Means with different superscripts are significantly different within the column ($p<0.05$).

Table 32. Concentrations of Total PCBs, PCDDs, PCDFs, Non-ortho PCBs, Mono-ortho PCBs and TEQs in Livers of Adult Female Mink.

		Dietary Treatment (ug total PCBs/g feed)[a]					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Total PCBS		104	385	582	1147	3083	3133
PCDDs							
2,3,7,8-TCDD	1.00000	0.1 (0.1)	0.4 (0.4)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.8 (0.8)
1,2,3,7,8-PeCDD	1.00000	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)
1,2,3,4,7,8-HxCDD	0.10000	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.3 (0.0)	0.3 (0.0)
1,2,3,6,7,8-HxCDD	0.10000	4.3 (0.4)	4.5 (0.5)	6.7 (0.7)	7.0 (0.7)	0.3 (0.0)	9.2 (0.9)
1,2,3,7,8,9-HxCDD	0.10000	0.4 (0.0)	0.4 (0.0)	0.4 (0.0)	0.5 (0.1)	0.3 (0.0)	0.6 (0.1)
1,2,3,4,6,7,8-HpCDD	0.01000	19.2 (0.2)	18.8 (0.2)	34.4 (0.3)	37.9 (0.4)	32.0 (0.3)	41.6 (0.4)
OCDD	0.00010	29.3 (0.0)	37.8 (0.0)	68.7 (0.0)	89.0 (0.0)	109.0 (0.0)	195.0 (0.0)
Total PCDDs		53.6 (0.9)	62.1 (1.2)	110.7 (1.4)	135.0 (1.6)	142.4 (0.9)	247.8 (2.5)
% total TEQs		19.3	10.4	6.2	4.2	1.6	1.2
PCDFs							
2,3,7,8-TCDF	0.10000	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.1 (0.0)	0.1 (0.0)	0.3 (0.0)
1,2,3,7,8-PeCDF	0.05000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)
2,3,4,7,8-PeCDF	0.50000	1.7 (0.9)	3.1 (1.6)	5.5 (2.8)	8.7 (4.4)	7 (3.5)	43 (21.5)
1,2,3,4,7,8-HxCDF	0.10000	0.1 (0.0)	0.3 (0.0)	0.5 (0.1)	0.8 (0.1)	0.3 (0.0)	3.4 (0.3)
1,2,3,6,7,8-HxCDF	0.10000	0.2 (0.0)	0.3 (0.0)	0.6 (0.1)	0.8 (0.1)	0.3 (0.0)	3.1 (0.3)
1,2,3,7,8,9-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.3 (0.0)	0.1 (0.0)
2,3,4,6,7,8-HxCDF	0.10000	0.4 (0.0)	0.6 (0.1)	1.2 (0.1)	1.7 (0.2)	0.3 (0.0)	6 (0.6)
1,2,3,4,6,7,8-HpCDF	0.01000	0.4 (0.0)	0.5 (0.0)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	2.1 (0.0)
1,2,3,4,7,8,9-HpCDF	0.01000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	5.3 (0.1)	0.2 (0.0)
OCDF	0.00010	3.9 (0.0)	4.1 (0.0)	4.6 (0.0)	5.1 (0.0)	0.3 (0.0)	7.3 (0.0)
Total PCDFs		7.1 (1.0)	9.4 (1.7)	13.9 (3.0)	18.5 (4.7)	15.1 (3.7)	65.7 (22.8)
% total TEQs		20.8	14.9	13.5	12.9	6.6	10.5

Table 32 continued. Concentrations of Total PCBS, PCDDs, PCDFs, Non-ortho PCBs, Mono-ortho PCBs and TEQs in Livers of Adult Female Mink.

		Dietary Treatment (ug total PCBs/g feed)[a]					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Non-Ortho PCBs							
77	0.00010	5.3 (0.0)	5.5 (0.0)	7.0 (0.0)	8.6 (0.0)	150.0 (0.0)	23.0 (0.0)
81	0.00010	0.5 (0.0)	0.6 (0.0)	0.8 (0.0)	1.0 (0.0)	6.3 (0.0)	2.7 (0.0)
126	0.10000	20.0 (2.0)	65.9 (6.6)	136.0 (13.6)	238.0 (23.8)	440.0 (44.0)	1610.0 (161.0)
169	0.01000	1.6 (0.0)	5.4 (0.1)	15.0 (0.2)	25.0 (0.3)	55.0 (0.6)	220.0 (2.2)
Total non-ortho PCBs		27.4 (2.0)	77.4 (6.6)	158.8 (13.8)	272.6 (24.1)	651.3 (44.6)	1855.7 (163.2)
% total TEQs		44.0	58.0	61.3	65.6	79.8	74.7
Mono-Ortho PCBs							
105	0.00010	920 (0.1)	1600 (0.2)	3200 (0.3)	4600 (0.5)	4500 (0.5)	18000 (1.8)
114	0.00050	90 (0.0)	110 (0.1)	190 (0.1)	240 (0.1)	560 (0.3)	1500 (0.8)
118	0.00010	3100 (0.3)	7000 (0.7)	15000 (1.5)	23000 (2.3)	27000 (2.7)	89000 (8.9)
123	0.00010	40 (0.0)	70 (0.0)	160 (0.0)	250 (0.0)	650 (0.1)	1000 (0.1)
156	0.00050	470 (0.2)	1600 (0.8)	3900 (2.0)	5600 (2.8)	5100 (2.6)	30000 (15.0)
157	0.00050	60 (0.0)	300 (0.2)	600 (0.3)	1000 (0.5)	1100 (0.6)	5000 (2.5)
167	0.00001	130 (0.0)	470 (0.0)	1200 (0.0)	1800 (0.0)	2000 (0.0)	7700 (0.1)
189	0.00010	90 (0.0)	360 (0.0)	950 (0.1)	1300 (0.1)	640 (0.1)	6900 (0.7)
Total mono-ortho PCBs		4900 (0.7)	11510 (1.9)	25200 (4.3)	37790 (6.4)	41550 (6.7)	159100 (29.8)
% total TEQs		15.9	16.7	19.1	17.3	12.0	13.7
Grand total TEQs (pg/g)		**4.6**	**11.5**	**22.4**	**36.7**	**55.9**	**218.4**

[a]Total PCB concentrations are expressed as ng/g wet weight and concentrations of PCDFs, PCDDs, non-ortho PCBs, mono-ortho PCBs and TEQs (in parentheses) are expressed as pg/g wet weight.
[b]Van den Berg et al., 1998.

Table 33. Concentrations of Total PCBs, PCDDs, PCDFs, Non-ortho PCBs, Mono-ortho PCBs and TEQs in Livers of Kits Necropsied at Six-Weeks of Age[a].

		Dietary Treatment (ug total PCBs/g feed)					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Total PCBs		117	357	457	850	1922	3700
PCDDs							
2,3,7,8-TCDD	1.00000	0.4 (0.4)	0.6 (0.6)	0.3 (0.3)	0.3 (0.3)	0.6 (0.6)	0.8 (0.8)
1,2,3,7,8-PeCDD	1.00000	0.3 (0.3)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)
1,2,3,4,7,8-HxCDD	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)
1,2,3,6,7,8-HxCDD	0.10000	2.8 (0.3)	2.5 (0.3)	3 (0.3)	3.5 (0.4)	4.5 (0.5)	4.7 (0.5)
1,2,3,7,8,9-HxCDD	0.10000	0.3 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	0.3 (0.0)	0.4 (0.0)
1,2,3,4,6,7,8-HpCDD	0.01000	5.2 (0.1)	5.9 (0.1)	8.5 (0.1)	15 (0.2)	10.9 (0.1)	15.1 (0.2)
OCDD	0.00010	15 (0.0)	21 (0.0)	28.2 (0.0)	49 (0.0)	45 (0.0)	63 (0.0)
Total PCDDs		24.1 (1.1)	30.4 (1.0)	40.5 (0.9)	68.4 (1.0)	61.6 (1.4)	84.5 (1.8)
% total TEQs		20.0	7.9	5.1	2.9	1.5	0.9
PCDFs							
2,3,7,8-TCDF	0.10000	0.3 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	0.4 (0.0)	0.4 (0.0)
1,2,3,7,8-PeCDF	0.05000	0.1 (0.0)	0 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)
2,3,4,7,8-PeCDF	0.50000	0.8 (0.4)	2 (1.0)	2.4 (1.2)	7 (3.5)	14 (7.0)	27 (13.5)
1,2,3,4,7,8-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.4 (0.0)	0.9 (0.1)	2 (0.2)
1,2,3,6,7,8-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)	0.4 (0.0)	0.8 (0.1)	1.7 (0.2)
1,2,3,7,8,9-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
2,3,4,6,7,8-HxCDF	0.10000	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.5 (0.1)	0.9 (0.1)	2 (0.2)
1,2,3,4,6,7,8-HpCDF	0.01000	0.3 (0.0)	0.4 (0.0)	0.4 (0.0)	0.8 (0.0)	0.8 (0.0)	1.4 (0.0)
1,2,3,4,7,8,9-HpCDF	0.01000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
OCDF	0.00010	2.5 (0.0)	2.4 (0.0)	3.5 (0.0)	3.8 (0.0)	3.1 (0.0)	3.3 (0.0)
Total PCDFs		4.5 (0.5)	5.6 (1.1)	7.3 (1.3)	13.4 (3.7)	21.2 (7.3)	38.2 (14.1)
% total TEQs		8.9	8.1	7.1	10.1	7.9	6.9

Table 33 continued. Concentrations of Total PCBs, PCDDs, PCDFs, Non-ortho PCBs, Mono-ortho PCBs and TEQs in Livers of Kits Necropsied at Six-Weeks of Age[a].

		Dietary Treatment (ug total PCBs/g feed)					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Non-Ortho PCBs							
77	0.00010	7.2 (0.0)	9.1 (0.0)	10.2 (0.0)	18 (0.0)	21 (0.0)	27 (0.0)
81	0.00010	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)	1.3 (0.0)	1.5 (0.0)	2.3 (0.0)
126	0.10000	26 (2.6)	79 (7.9)	113 (11.3)	249 (24.9)	657 (65.7)	1520 (152.0)
169	0.01000	3.4 (0.0)	9.2 (0.1)	14.2 (0.1)	27 (0.3)	82 (0.8)	240 (2.4)
Total non-ortho PCBs		37.5 (2.6)	98.2 (8.0)	138.3 (11.4)	295.3 (25.2)	761.5 (66.5)	1789.3 (154.4)
% total TEQs		49.1	60.6	63.3	69.2	71.9	75.7
Mono-Ortho PCBs							
105	0.00010	2200 (0.2)	3800 (0.4)	5300 (0.5)	7000 (0.7)	15000 (1.5)	22000 (2.2)
114	0.00050	130 (0.1)	260 (0.1)	330 (0.2)	450 (0.2)	980 (0.5)	1700 (0.9)
118	0.00010	5500 (0.6)	13000 (1.3)	18000 (1.8)	24000 (2.4)	56000 (5.6)	87000 (8.7)
123	0.00010	60 (0.0)	130 (0.0)	180 (0.0)	220 (0.0)	460 (0.0)	540 (0.1)
156	0.00050	480 (0.2)	1900 (1.0)	2900 (1.5)	4900 (2.5)	16000 (8.0)	37000 (18.5)
157	0.00050	160 (0.1)	480 (0.2)	690 (0.3)	1100 (0.6)	2500 (1.3)	5200 (2.6)
167	0.00001	360 (0.0)	970 (0.0)	1500 (0.0)	2100 (0.0)	5100 (0.1)	8600 (0.1)
189	0.00010	170 (0.0)	670 (0.1)	1000 (0.1)	1400 (0.1)	3400 (0.3)	6000 (0.6)
Total mono-ortho PCBs		9060 (1.2)	21210 (3.1)	29900 (4.4)	41170 (6.5)	99440 (17.3)	168040 (33.6)
% total TEQs		22.0	23.4	24.5	17.9	18.7	16.5
Grand total TEQs (pg/g)		**5.4**	**13.2**	**18.1**	**36.4**	**92.5**	**203.9**

[a]Total PCB concentrations are expressed as ng/g wet weight and concentrations of PCDFs, PCDDs, non-ortho PCBs, mono-ortho PCBs and TEQs (in parentheses) are expressed as pg/g wet weight.
[b]Van den Berg et al., 1998.

Table 34. Concentrations of Total PCBs, PCDDs, PCDFs, Non-ortho PCBs, Mono-ortho PCBs, and TEQs in Livers of Kits Necropsied at the End of the Trial [a].

		Dietary Treatment (ug total PCBs/g feed)					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Total PCBs		41	457	727	1698	3450	8561
PCDDs							
2,3,7,8-TCDD	1.00000	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)	0.4 (0.4)	0.5 (0.5)
1,2,3,7,8-PeCDD	1.00000	0.2 (0.2)	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)
1,2,3,4,7,8-HxCDD	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)
1,2,3,6,7,8-HxCDD	0.10000	0.7 (0.1)	1.6 (0.2)	1.3 (0.1)	2.2 (0.2)	2.6 (0.3)	2.8 (0.3)
1,2,3,7,8,9-HxCDD	0.10000	0.1 (0.0)	0.2 (0.0)	0.3 (0.0)	0.3 (0.0)	0.3 (0.0)	0.4 (0.0)
1,2,3,4,6,7,8-HpCDD	0.01000	8.7 (0.1)	27.8 (0.3)	24.2 (0.2)	34.6 (0.3)	39.9 (0.4)	36.8 (0.4)
OCDD	0.00010	32.8 (0.0)	70 (0.0)	83 (0.0)	108 (0.0)	154 (0.0)	180 (0.0)
Total PCDDs		42.8 (0.6)	100 (0.8)	109.2 (0.7)	145.7 (1.1)	197.5 (1.3)	221 (1.5)
% total TEQs		23.1	7.1	3.8	2.8	1.3	0.8
PCDFs							
2,3,7,8-TCDF	0.10000	0.3 (0.0)	0.2 (0.0)	0.3 (0.0)	0.2 (0.0)	0.3 (0.0)	0.2 (0.0)
1,2,3,7,8-PeCDF	0.05000	0.1 (0.0)	0.0 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
2,3,4,7,8-PeCDF	0.50000	1.0 (0.5)	2.5 (1.3)	4.7 (2.4)	8.6 (4.3)	18.1 (9.1)	32 (16.0)
1,2,3,4,7,8-HxCDF	0.10000	0.1 (0.0)	0.3 (0.0)	0.4 (0.0)	0.7 (0.1)	1.5 (0.2)	2.5 (0.3)
1,2,3,6,7,8-HxCDF	0.10000	0.1 (0.0)	0.3 (0.0)	0.4 (0.0)	0.6 (0.1)	1.3 (0.1)	2.3 (0.2)
1,2,3,7,8,9-HxCDF	0.10000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
2,3,4,6,7,8-HxCDF	0.10000	0.3 (0.0)	0.5 (0.1)	0.8 (0.1)	1.3 (0.1)	3.0 (0.3)	4.7 (0.5)
1,2,3,4,6,7,8-HpCDF	0.01000	0.5 (0.0)	1.0 (0.0)	0.8 (0.0)	1.6 (0.0)	1.9 (0.0)	2.2 (0.0)
1,2,3,4,7,8,9-HpCDF	0.01000	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)	0.3 (0.0)
OCDF	0.00010	1.8 (0.0)	1.8 (0.0)	2.1 (0.0)	3.2 (0.0)	2.6 (0.0)	3.0 (0.0)
Total PCDFs		4.4 (0.6)	6.8 (1.4)	9.8 (2.6)	16.5 (4.6)	29.1 (9.7)	47.4 (17.0)
% total TEQs		23.9	12.8	13.4	11.5	9.9	8.6

Table 34 continued. Concentrations of Total PCBs, PCDDs, PCDFs, Non-ortho PCBs, Mono-ortho PCBs, and TEQs in Livers of Kits Necropsied at the End of the Trial[a].

		Dietary Treatment (ug total PCBs/g feed)[a]					
Compound	**TEF[b]**	**Control**	**0.34**	**0.61**	**0.96**	**1.6**	**3.7**
Non-Ortho PCBs							
77	0.00010	4.6 (0.0)	4.8 (0.0)	5.2 (0.0)	10.5 (0.0)	14 (0.0)	28 (0.0)
81	0.00010	0.6 (0.0)	1.0 (0.0)	0.9 (0.0)	1.6 (0.0)	1.7 (0.0)	2.7 (0.0)
126	0.10000	9.8 (1.0)	64 (6.4)	126 (12.6)	257 (25.7)	636 (63.6)	1270 (127.0)
169	0.01000	0.9 (0.0)	7.6 (0.1)	12.1 (0.1)	30.2 (0.3)	80 (0.8)	182 (1.8)
Total non-ortho PCBs		15.9 (1.0)	77.4 (6.5)	144.2 (12.7)	299.3 (26.0)	731.7 (64.4)	1482.7 (128.8)
% total TEQs		39.3	59.2	66.7	64.6	66.0	65.3
Mono-Ortho PCBs							
105	0.00010	730 (0.1)	2600 (0.3)	3400 (0.3)	7700 (0.8)	15000 (1.5)	29000 (2.9)
114	0.00050	40 (0.0)	210 (0.1)	370 (0.2)	680 (0.3)	1200 (0.6)	2500 (1.3)
118	0.00010	1700 (0.2)	11000 (1.1)	14000 (1.4)	32000 (3.2)	64000 (6.4)	140000 (14.0)
123	0.00010	10 (0.0)	90 (0.0)	170 (0.0)	360 (0.0)	750 (0.1)	1800 (0.2)
156	0.00050	80 (0.0)	1100 (0.6)	1600 (0.8)	6400 (3.2)	23000 (11.5)	54000 (27.0)
157	0.00050	80 (0.0)	370 (0.2)	430 (0.2)	1400 (0.7)	3200 (1.6)	6700 (3.4)
167	0.00001	110 (0.0)	780 (0.0)	1100 (0.0)	2800 (0.0)	5900 (0.1)	13000 (0.1)
189	0.00010	10 (0.0)	680 (0.1)	910 (0.1)	2200 (0.2)	4600 (0.5)	12000 (1.2)
Total mono-ortho PCBs		2760 (0.3)	16830 (2.3)	21980 (3.1)	53540 (8.5)	117650 (22.2)	259000 (50.0)
% total TEQs		13.8	20.9	16.0	21.1	22.7	25.3
Grand total TEQs (pg/g)		**2.5**	**11.0**	**19.1**	**40.2**	**97.6**	**197.3**

[a]Total PCB concentrations are expressed as ng/g wet weight and concentrations of PCDFs, PCDDs, non-ortho PCBs, mono-ortho PCBs and TEQs (in parentheses) are expressed as pg/g wet weight.
[b]Van den Berg et al., 1998.

Table 35. Mink Reproductive NOAEL, Estimated Threshold Dose, and LOAEL for TEQs[a].

Component	NOAEL	Estimated Threshold Dose	LOAEL
Dietary TEQ (pg/g)	16.1	33.2	68.5
Cumulative TEQ dose (ng/mink)	319	677	1436
ng TEQs/mink/day	1.996	4.232	8.974
ng TEQs/kg body weight/day	1.686	3.596	7.670
Liver TEQs (pg/g)[b]	55.9	110.5	218.4

[a]LOAEL based on 3.7 ug total PCBs/g feed dietary concentration; NOAEL based on 1.6 ug total PCBs/g feed dietary concentration; estimated threshold dose based on geometric mean of NOAEL and LOAEL.
[b]Liver TEQs are from adult females.