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# Dietary Exposure of Mink to Carp from Saginaw Bay, Michigan: 2. Hematology and Liver Pathology

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**Abstract.** The effects of consumption of environmental contaminants contained in carp *(Cyprinus carpio)* from Saginaw Bay, Michigan on various hematological parameters and liver integrity of adult female mink *(Mustela vison)* were determined. Mink were fed diets that contained 0 (control), 10, 20, or 40% carp prior to and throughout the reproductive period (182 days). The diets contained 0.015, 0.72, 1.53, and 2.56 mg polychlorinated biphenyls (PCBs)/kg diet and 1.0, 19, 40, and 81 pg 2,3,7,8-tetrachlorodibenzo-*p*-dioxin equivalents (TEQs)/g diet, respectively. Mink fed the diets containing carp showed a general dose-dependent occurrence of clinical signs commonly associated with chlorinated hydrocarbon toxicity, including listlessness, nervousness when approached, anorexia, and melena. Erythrocyte counts were less in mink exposed to Saginaw Bay carp than in controls, while the number of white blood cells was greater than in controls. Significant differences ($p < 0.05$) in the concentrations of neutrophils, lymphocytes, monocytes, and eosinophils were also found between the control and carp-fed groups, but are considered to be of limited clinical or biological importance. Hematocrit values for the mink fed the 20 and 40% carp diets were significantly less than those of mink in the control and 10% carp groups. There were no significant differences in hemoglobin concentrations among the groups. Necropsies revealed enlarged yellowish livers in many of the carp-fed mink, especially those fed the 40% carp diet. Liver, spleen, and lung weights of carp-fed mink were significantly greater than those of control mink. Histopathologic examination of the livers revealed various degrees of congestion, hepatocellular fatty changes, and scattered portal lymphocytic infiltration which were most prevalent in mink fed the carp diets. These clinical signs, hematological effects, and histologic alterations are similar to those previously described for chlorinated hydrocarbon toxicoses in mink.

Environmental contaminants, particularly polychlorinated biphenyls (PCBs) and organochlorine pesticides, have been implicated as causative agents in the decline of wild mustelid populations throughout the world (Chanin and Jeffries 1978; Henny *et al.* 1981; Olsson *et al.* 1981; MacDonald 1983; Mason *et al.* 1986; Jefferies 1989; Mason 1989). Results of toxicity studies with ranch mink fed fish from the Great Lakes (Aulerich *et al.* 1971, 1973; Aulerich and Ringer 1977; Hornshaw *et al.* 1983) in conjunction with tissue residue data from trapped wild mink (Henny *et al.* 1981; O'Shea *et al.* 1981; Proulx *et al.* 1987; Foley *et al.* 1988) strongly suggest that polychlorinated hydrocarbon contaminants in the fish, particularly PCBs, are at least partly responsible for the declines in some mink and otter populations in the Great Lakes region.

Exposure of animals to PCBs causes delayed reproduction, reproductive failure, birth defects, skin lesions, tumors, thymic atrophy, liver disorders, teratogenic effects, behavioral changes, histopathological alterations, body weight loss, decreased food consumption, and, in more sensitive species, death (Aulerich *et al.* 1970; Barsotti *et al.* 1976; Eisler 1986; Gillette *et al.* 1987a). Mink feeding studies involving commercial PCB mixtures (Ringer *et al.* 1972; Platonow and Karstad 1973; Bleavins *et al.* 1980; Ringer *et al.* 1981; Aulerich *et al.* 1985), purified PCB congeners (Aulerich *et al.* 1985, 1987; Gillette *et al.* 1987a,b), as well as other organochlorine com-

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pounds (Aulerich and Ringer 1970; Rush *et al.* 1983; Bleavins *et al.* 1984; Hochstein *et al.* 1988; Aulerich *et al.* 1990; Crum *et al.* 1993) have demonstrated the high sensitivity of mink to these compounds.

This study was conducted to: 1) characterize the effects of dietary exposure to environmental contaminants (particularly PCBs) contained in carp from Saginaw Bay, Michigan on the reproductive performance of mink, and 2) determine the PCB and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxic equivalent (TEQ) threshold concentrations at which adverse reproductive effects in mink could be expected to occur. In this paper, we report on the effects of consumption of diets containing carp from Saginaw Bay on hematological parameters and liver pathology in adult female mink.

## Materials and Methods

The mink feeding study was conducted at the Michigan State University Experimental Fur Farm from December 29, 1988 through June 28, 1989. The procedures employed in the study have been presented previously (Heaton 1992; Heaton *et al.* 1995) and are briefly described herein.

Sixty standard dark ranch mink *(Mustela vison)* were randomly assigned to four treatment groups, except that littermates were not placed in the same group. Each group consisted of three males and 12 females. The mink were fed *ad libitum* diets that contained 0 (control), 10, 20, or 40% carp *(Cyprinus carpio)* obtained from Saginaw Bay, Michigan. The carp was substituted for ocean fish in a basal mink diet. The diets contained 0.015, 0.72, 1.53, and 2.56 mg PCBs/kg diet, or 1.0, 19, 40, and 81 pg TEQs/g diet, as determined by the H4IIE rat hepatoma bioassay (Tillitt *et al.* 1991), respectively. This procedure accounts for all of the 2,3,7,8-TCDD-like activity from PCBs, polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, as well as a number of other compounds which are known to cause toxicity through the same mechanism (Giesy *et al.* 1994a). The mink were fed the experimental diets for 182 days from two months prior to breeding through gestation, lactation, and early kit growth (see Heaton *et al.* 1995 for the composition and nutrient analysis of the diets and mink feed consumption data). Any mink that died during the trial were necropsied, their organs (brain, liver, kidney, spleen, lungs, heart, and adrenal and thyroid glands) weighed, and samples of liver collected for histologic examination and residue analyses.

At the termination of the feeding trial, the mink kits were weaned and the 45 surviving adult female mink were anesthetized (0.2 ml ketamine HCl[1]) and weighed. A 5 ml blood sample was collected via cardiac puncture from each mink. A portion of each blood sample was used to fill two heparinized micro-capillary tubes for determination of hematocrit values and to make blood smears for differential cell counts. Three ml of blood from each sample were pooled to provide three composite samples per dietary group for thyroxine profile determinations. The remainder of each sample was used to determine red and white blood cell counts and hemoglobin concentrations.

Hematocrit values were measured in duplicate using a micro-capillary centrifuge[2] and micro-capillary reader.[3] The differential cell counts were made in duplicate on blood smears stained with Wright's stain and read with a light microscope[4] at 1000×. Duplicate red and white blood cell counts were obtained with a Coulter Counter[5] calibrated for mink blood analysis (Pruden and Winstead 1964) using a 1:50,000 dilution of whole blood in Isoton.[6] Hemoglobin concentration was determined using a hemoglobinometer.[7]

The pooled blood samples for thyroxine profile analyses were centrifuged and the serum was collected and submitted to the Michigan State University Animal Health Diagnostic Laboratory for radioimmunoassay determination of total thyroxine ($T_4$), free (unbound) $T_4$, total triiodothyronine ($T_3$), and free (unbound) $T_3$ concentrations.

Following collection of the blood samples, the adult female mink were euthanized ($CO_2$). During necropsy, organ weights (brain, liver, kidneys, spleen, lungs, heart, and adrenal and thyroid glands) and any gross abnormalities were recorded. Samples of liver were collected for residue analyses and for histological examination. Samples of the liver were fixed in 10% neutral-buffered formalin, trimmed, embedded in paraffin, sectioned (5 μm), mounted on microscope slides, and stained with hematoxylin and eosin according to routine histological procedures.

Comparisons among treatment groups were made by one-way analysis of variance (SAS Institute Inc. 1987). Where the F value statistic was significant at $p < 0.05$, differences among treatment means were examined by Tukey's honestly significant difference test statistic.

## Results

Two female mink fed the 40% carp diet and one fed the 10% carp diet died before the termination of the trial. The mink that died and several others in the 40% carp group were listless, became nervous when approached, and had melena. One of the females in the 40% carp group became anorexic and displayed hindlimb paralysis and sporadic seizures prior to death after eight weeks on trial. During a necropsy of this mink, the liver was found to be diffusely yellow with a prominent lobular pattern. Histologically, there was moderate hepatocellular fatty change. No lesions were found in the other mink.

Consumption of the carp diets had significant effects on several hematologic parameters of the mink. As shown in Table 1, mink fed carp in the diet had a lesser concentration of red blood cells relative to the controls. The concentration of red blood cells was inversely proportional to the content of carp in the diet. The numbers of white blood cells in the blood of mink fed 10 or 20% carp were significantly greater than in mink fed no carp. The numbers of neutrophils in the blood of the mink fed the carp diets were significantly greater than those of mink fed the control diet. The number of lymphocytes was significantly greater in the mink fed 20% carp than those of mink fed the control diet. There was a statistically significant inverse relationship between the number of monocytes and the proportion of carp in the diet. Eosinophil counts in the 10 and 20% carp groups were significantly greater than those in the control group. Hematocrit values were significantly less in the mink fed the 20 or 40% carp diets compared to those in the control or 10% carp groups. However, no significant differences in hemoglobin concentrations were noted between the dietary groups (Table 1).

Mean concentrations of total and free (unbound) triiodothyronine ($T_3$) and thyroxine ($T_4$) in blood of adult female mink in

[1] 100 mg/ml; Veterinary Products, Bristol Laboratory, Syracuse, NY
[2] Model MB; International Equipment Co, Boston, MA
[3] International Equipment Co, Boston, MA
[4] Zeiss Photomicroscope III, Carl Zeiss Inc., New York
[5] Coulter Electronics, Inc, Hialeah, FL
[6] Isotonic saline; Coulter Diagnostics, Inc, Hialeah, FL
[7] Coulter Electronics, Inc, Hialeah, FL

**Table 1.** Hematologic values for adult female mink fed various percentages of carp from Saginaw Bay, Michigan

| Parameter | Diet | | | |
|---|---|---|---|---|
| | 0% carp (control) | 10% carp | 20% carp | 40% carp |
| Number of mink | 12 | 11 | 12 | 10 |
| Red blood cells ($10^6$/mm$^3$) | 7.23 ± 0.29$^{aA}$ | 6.64 ± 0.26$^{B}$ | 6.24 ± 0.15$^{C}$ | 5.81 ± 0.18$^{D}$ |
| White blood cells ($10^3$/mm$^3$) | 6.42 ± 0.56$^{A}$ | 7.13 ± 0.58$^{B}$ | 7.31 ± 0.61$^{B}$ | 7.07 ± 0.79$^{AB}$ |
| *Differential cell counts* | | | | |
| Neutrophils ($10^3$/mm$^3$) | 3.72 ± 0.36$^{A}$ | 4.25 ± 0.44$^{B}$ | 4.21 ± 0.92$^{B}$ | 4.31 ± 2.06$^{B}$ |
| Percent | 58.4 | 60.1 | 60.0 | 60.0 |
| Lymphocytes ($10^3$/mm$^3$) | 2.28 ± 0.24$^{A}$ | 2.19 ± 0.31$^{A}$ | 2.63 ± 0.33$^{B}$ | 2.54 ± 0.37$^{AB}$ |
| Percent | 36.0 | 34.6 | 36.0 | 36.4 |
| Monocytes ($10^3$/mm$^3$) | 0.22 ± 0.04$^{A}$ | 0.21 ± 0.01$^{B}$ | 0.20 ± 0.05$^{B}$ | 0.13 ± 0.03$^{B}$ |
| Percent | 3.6 | 2.6 | 2.0 | 1.9 |
| Eosinophils ($10^3$/mm$^3$) | 0.13 ± 0.03$^{A}$ | 0.18 ± 0.04$^{B}$ | 0.20 ± 0.06$^{B}$ | 0.14 ± 0.03$^{AB}$ |
| Percent | 1.7 | 2.5 | 1.8 | 1.7 |
| Hematocrit (%) | 57.2 ± 1.5$^{A}$ | 57.1 ± 0.7$^{A}$ | 54.6 ± 1.0$^{B}$ | 55.0 ± 0.8$^{B}$ |
| Hemogloblin (gm/dl) | 19.2 ± 0.9$^{A}$ | 18.9 ± 0.3$^{A}$ | 19.2 ± 1.0$^{A}$ | 18.6 ± 0.5$^{A}$ |

[a]Mean ± S.E. Means in the same row with the same superscript are not significantly different ($p > 0.05$)

**Table 2.** Mean thyroxine ($T_4$) and triiodothyronine ($T_3$) concentrations in blood serum of female mink fed diets containing various percentages of Saginaw Bay carp[a]

| Serum parameter | Diet | | | |
|---|---|---|---|---|
| | 0% carp (control) | 10% carp | 20% carp | 40% carp |
| Total $T_4$ (nmol/L) | 61.4 ± 2.65[b] | 69.5 ± 5.72 | 67.4 ± 3.08 | 66.1 ± 6.67 |
| Free (unbound) $T_4$ (pmol/L) | 24.6 ± 1.92 | 32.4 ± 3.21 | 29.6 ± 1.53 | 30.4 ± 2.24 |
| Total $T_3$ (nmol/L) | 1.17 ± 0.13 | 1.03 ± 0.12 | 1.07 ± 0.03 | 0.93 ± 0.03 |
| Free (unbound) $T_3$ (pmol/L) | 3.00 ± 0.45 | 2.83 ± 0.20 | 2.87 ± 0.20 | 2.73 ± 0.23 |

[a]Three pooled samples per treatment group
[b]Mean ± S.E

the various groups are presented in Table 2. The composite samples from mink fed the diets that contained carp had greater concentrations of both total and free $T_4$ and lesser concentrations of both total (except for the 10% carp group) and free $T_3$ than the control mink. However, no statistically significant differences were noted between the control and treatment groups.

During necropsy of the females that survived to the end of the trial, many of the mink had enlarged, diffusely yellow livers, especially mink fed the 40% carp diet. Histologically, the livers of the female mink that survived to the end of the trial had various degrees of congestion, hepatocellular fatty changes (Figure 1), and scattered aggregates of lymphocytes, as shown in Table 3. These hepatic alterations were most prevalent in mink fed the carp diets, although two mink in the control group had periportal hepatocellular lipidosis. One mink in the 10% carp group had hemorrhages in the brain, cervical subcutaneous edema, and pulmonary edema with pulmonary congestion. The spleens of 3 of the 12 mink in the 20% carp group were irregular in shape.

Organ weights of the mink were summarized and presented previously (Heaton *et al.* 1995). When expressed as a percent of brain weight, the mink livers, spleens, kidneys, lungs, hearts, and thyroid and adrenal glands were greater than in the control mink in a dose-dependent manner. Absolute liver, spleen, and lung weights of the mink in the three carp-fed groups were all significantly greater than control values. The results of the liver residue analyses will be reported in Part 3 of this series.

## Discussion

The clinical signs associated with PCB toxicity in mink have been well documented (Platonow and Karstad 1973; Bleavins *et al.* 1980; Aulerich and Ringer 1977; Aulerich *et al.* 1986; Gillette *et al.* 1987a) and are similar to those observed in the mink fed the diets that contained carp from Saginaw Bay in this study. Anorexia, melena, fatty livers, and hemorrhagic gastric ulcers were common clinical signs and lesions observed in mink fed 30% Lake Michigan coho salmon that had PCB and total DDT residue concentrations of 10-15 and 18-23 ppm, respectively (Aulerich *et al.* 1971, 1973). Paralysis and seizures, as observed in a mink that died during this trial, have not been commonly reported as clinical signs of PCB exposure for mink, although mink treated with 3,3′,4,4′-tetrachlorobiphenyl (TCB) were noted to show tremors and contorted postures (Gillette *et al.* 1987a).

The mean values for most of the hematological parameters were generally within the ranges reported for adult female ranch mink (Kennedy 1935; Kubin and Mason 1948; Rotenberg and Jorgensen 1971). The relative (%) and absolute numbers of

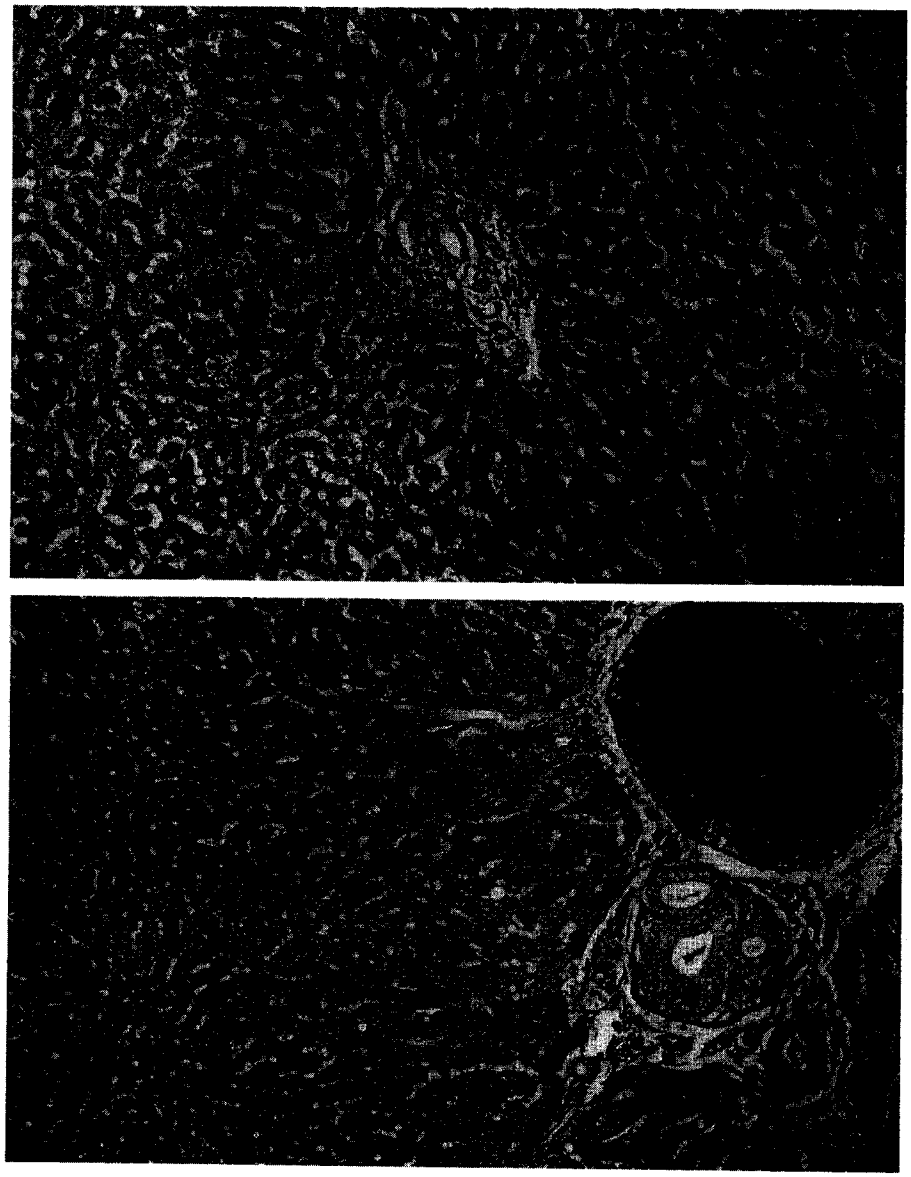

**Fig. 1. Above.** Section of liver from a control mink showing no histological lesions. Hepatocytes are normal with very little lipid accumulation. Sinusoids appear free of congestion (140×). **Below.** Section of liver with diffuse hepatocellular lipidosis from a mink fed 40% carp (560×; sections stained with hematoxylin and eosin)

monocytes for both the control and carp-fed groups were slightly less than those reported for mink by Fletch and Karstad (1972) and Asher *et al.* (1976), but were within the normal ranges given by Kennedy (1935) and Kubin and Mason (1948). Thus, the statistical differences in the white blood cell parameters noted among the groups in our study are probably not of great clinical or biological importance. The dose-dependent inverse relationship between the number of red blood cells and positive relationship of white blood cells of mink fed carp in the diets compared to the control group were, however, similar to the results reported for mink treated with 50 ppm 3,3′,4,4′-TCB (Gillette *et al.* 1987b).

The greater concentrations of $T_4$ in blood of female mink fed the diets containing carp were unexpected and opposite the effects elicited by PCB exposure in most species (Anon 1991; Lans *et al.* 1994). $T_4$ concentrations in blood of mink fed 0.05 ppm 3,3′,4,4′,5,5′-hexachlorobiphenyl (Aulerich *et al.* 1987) and rat pups fed 500 ppm Aroclor 1254 (Collins and Caspen 1980) were significantly less relative to that of the controls.

Polychlorinated biphenyls and TCDD may displace thyroxine from the retinol-thyroxine carrier protein complex and irreversibly bind to the thyroxine receptors of tissues resulting in low circulating $T_4$ concentrations and thyroid gland hyperplasia (McKinney *et al.* 1985; Anon 1991). The significant increase in weights of the thyroid glands of the mink fed 20 or 40% carp in the diet that was observed in this study would not be expected for mink with elevated $T_4$ concentrations. Sonstegard and Leatherland (1979) reported reduced $T_4$ concentrations and enlarged thyroid glands in rats fed coho salmon from Lakes Ontario and Michigan. Perhaps substances in the carp from Saginaw Bay, other than PCBs and TCDD, had an influence on

**Table 3.** Incidence of histological changes in livers of female mink fed various percentages of carp from Saginaw Bay

| Histological change | Diet | | | |
|---|---|---|---|---|
| | 0% carp (control) | 10% carp | 20% carp | 40% carp |
| Periportal hepatocellular lipidosis | 2/12[a] | 2/11 | 0/12 | 2/11 |
| Scattered portal lymphocytic infiltration | 0/12 | 2/11 | 3/12 | 0/11 |
| Diffuse hepatocellular vascular lipidosis | 0/12 | 1/11 | 1/12 | 0/11 |
| Diffuse pallor and swelling | 0/12 | 0/11 | 1/12 | 0/11 |

[a] Number of animals showing alteration per number examined

thyroid function of the mink. DDT, dieldrin, polybrominated biphenyls, TCDD, mirex, octachlorostyrene, and chlorinated benzenes have been shown to alter thyroid function in lab animals (Anon 1991).

The liver is a primary site for accumulation of orally administered PCBs in mammals (Allen and Barsotti 1976; Gillette *et al.* 1987b; Hansen *et al.* 1975). Both gross and cellular hepatic changes, including hepatic lipidosis, have been reported in mink (Aulerich *et al.* 1971, 1973, 1977; Platonow and Karstad 1973; Gillette *et al.* 1987b; Bergman *et al.* 1992) and other animals (Vos and Koeman 1970; Koller and Zinkl 1973; Burse *et al.* 1974) exposed to PCBs. Binding of lipid-soluble contaminants, such as PCBs, with fatty acids and their entry into the hepatocytes may result in metabolic disturbances and retention of triglycerides within the hepatocytes (Plaa 1986). The portal accumulation of lymphocytes observed in some of the mink is not an uncommon lesion in mink treated with PCBs (Gillette *et al.* 1987b; Bergman *et al.* 1992) but is a nonspecific alteration and may not be related to the toxicosis.

The greater liver weights of mink fed the 20 or 40% carp diets in this study were comparable to those observed in mink fed 30% carp from Saginaw Bay by Hornshaw (1981) and are probably due to hypertrophy of the liver (Allen and Abrahamson 1979). In the Hornshaw study, feeding 30% carp to female mink for nine months resulted in a 29.5% greater mean liver weight (28.9% if expressed as a percent of brain weight) compared to the control, while in our study, mink fed the 20 or 40% carp diets had mean liver weights that were 18.1% (18.0% on a brain weight basis) and 39.1% (38.4% on a brain weight basis) greater, respectively, than control mink liver weights.

Bergman *et al.* (1992) observed greater incidences of changes in the livers of mink exposed to commercial PCBs, combinations of three and four different fractions from commercial PCBs, and to a combination of one *ortho* and two to four *ortho* chlorobiphenyls than in animals treated with single chlorobiphenyl fractions administered in doses equivalent to those given for commercial PCBs. The least pronounced hepatic effects in mink treated with combinations of chlorobiphenyl fractions were found in mink given two to four *ortho* and no *ortho* chlorobiphenyls. The degree of liver alterations in the mink was attributed to the combined effects on the different chlorobiphenyl congeners in commercial PCBs rather than to specific effects of individual congeners.

The results of this study revealed significant effects on hematologic parameters and liver integrity of adult female mink from consumption of environmentally-weathered contaminants in carp from Saginaw Bay. These findings support the previously established LOAEL (lowest observed adverse effect level) of 10% Saginaw Bay carp in the diet of mink or 0.72 mg PCB/kg diet and 19.41 pg TEQs/g diet (Heaton *et al.* 1995). Consumption of comparable quantities of similarly contaminated prey species could have serious potential health effects in wild mink populations (Giesy *et al.* 1994b).

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