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Toxic Effects in C57B1/6 and DBA/2 Mice Following Consumption of Halogenated Aromatic Hydrocarbon-Contaminated Great Lakes Coho Salmon (*Oncorhynchus kisutch* Walbaum)

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Diets containing coho salmon (*Oncorhynchus kisutch* Walbaum) from the Pacific Ocean or from Lakes Erie, Michigan, and Ontario [containing a gradation from low to high of halogenated aromatic hydrocarbons, (HAHs)] were fed to C57B1/6 and DBA/2 mice. Following a 4-month dietary exposure to Lake Ontario salmon, both strains of mice demonstrated hepatomegaly. The ethoxyresorufin-*O*-deethylase (ERR) enzyme levels were elevated in livers of C57B1/6 mice fed diets of salmon from all of the Great Lakes studied, with exceptionally high levels detected in C57B1/6 mice fed Lake Ontario salmon. Induction of ERR enzyme levels was detected in DBA/2 mice only following dietary exposure to Lake Ontario salmon. Serum levels of L-thyroxine (T4) and triiodo-L-thryonine (T3) were suppressed in C57B1/6 mice following consumption of Lake Ontario coho salmon, but T3 and T4 levels remained unchanged in DBA/2 mice. In general, pathobiological effects correlated with both dietary HAH exposure level and Ah receptor status.

Introduction

Recent evidence suggests that one of the most significant human chronic exposures to halogenated aromatic hydrocarbons (HAHs) involves the consumption of fish from contaminated lakes and streams by sport fishermen (*1*). Lake Michigan salmon fishermen eat 24 to 25 lb of fish per year, with upper yearly limits reaching 180 lb and one reported consumption of 260 lb in a single year (*1*).

The chronic exposure of fish, birds, and mammals, including man, to a mixture of xenobiotics derived from the consumption of contaminated fish may have serious ramifications to their health. Experimental exposures to toxic levels of HAHs have correlated with body wasting, hepatomegaly, lymphoid involution, and chloracne in a variety of species (*2*). In mice and rats, the responses to HAHs are determined by the *Ah* gene locus, which codes for a cytosolic aromatic hydrocarbon receptor (*2,3*). Poland and Knutson (*2*) suggest that HAH toxicity is mediated through this receptor and that the initial event is stereoscopic recognition and binding by this receptor. HAH toxicity also correlates with congeners which form planar configurations due to their halogen substitutions and tend to bind with high affinity to Ah receptors in *Ah* positive (Ah^+) laboratory animals (*3,4*). Subsequent receptor-related events must be required, but to date, the actual mechanism of toxic action of HAHs is unknown. Further, it has been demonstrated that the C57B1/6 (Ah^+) strain of mouse tends to be susceptible to the toxic effects of certain isomers of HAHs, whereas the DBA/2 (Ah^-) strain is more resistant (*2,5*).

The studies described herein were designed to assess the health effects associated with dietary consumption of coho salmon containing HAHs and other compounds naturally bioaccumulated from the Great Lakes. Diets of coho salmon collected from the Pacific Ocean or from the Great Lakes were fed to C57B1/6 and DBA/2 mice. A number of generalized toxicity parameters characteristic of HAH exposure, including weight loss, hepatomegaly, ethoxyresorufin-*O*-deethylase enzyme induction, and changes in serum thyroid hormone levels were examined.

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Materials and Methods

Mice

Three-week-old weanling male C57B1/6 and DBA/2 mice were obtained from the Jackson Laboratory (Bar Harbor, ME). Mice were housed five to a cage on a 12-hr daily light cycle and fed control or fish-supplemented diets and water *ad libitum* for 4 months.

Diets

Adult coho salmon (*Oncorhynchus kisutch* Walbaum) were obtained during the 1982 fall spawning runs from Lake Ontario (Credit River, Streetsville, Ontario), Lake Erie (Walnut Creek, Fairview, PA), Lake Michigan (Platte River, Honor, MI), and Pacific Ocean coho salmon were obtained from Alaskan Seafoods Inc. (Kodiak, AK). Fish were beheaded, eviscerated, and minced in a meat grinder.

Powdered rodent chow (Purina No. 5001) was supplemented with 33% pooled coho salmon mince (based on the dry weight of fish). Mouse diets were fortified with 10 mg/kg of vitamins, (Teklad No. 40060), 10 mg/kg of minerals, (Teklad No.170710), 4.5% corn oil (Mazola), and 100 mg of thiamine (Swiss) to ensure nutritional quality. All additives were based on the dry weight of fish. Diets were mixed in a commercial food mixer (Hobart), pelletized, and stored frozen at −20°C. Control mice were fed rodent pellets (Purina No. 5001).

HAH Analysis of Coho Salmon Used to Supplement Mouse Diets

Ten 15-g samples were taken at random from each pooled coho salmon mince preparation, and the samples from each coho salmon source were pooled. The specimens were extracted as described by Bligh and Dyer (*6*) and analyzed by gas chromatography to determine a profile of HAH contaminants as described by Oliver and Nicol (*7*).

Ethoxyresorufin-*O*-Deethylase Assay

Mouse body weights were recorded, and freshly dissected livers were weighed and immediately frozen in liquid nitrogen. Frozen livers were individually homogenized in 5 mL/g of calcium and magnesium-free phosphate buffered saline, pH 7.4 (PBS). The debris was removed by centrifugation (9000*g* for 20 min, and the microsomal fraction was pelleted from the supernatant fluid by ultracentrifugation (100,000*g* for 60 min) and resuspended in PBS. The monooxygenase enzyme activity of the liver microsomes was assessed spectrofluorometrically by the ethoxyresorufin-*O*-deethylase (ERR) assay as described by Burke and Mayer (*8*).

Thyroid Hormone Assays

The levels of the thyroid hormones L-thyroxine (T4) and triiodo-L-thryonine (T3) in the serum of mice which had been fed control or coho salmon-supplemented diets for 4 months were determined. Mice were weighed, sacrificed by decapitation, and blood was collected into microcentrifuge tubes. Following clot formation at 4°C overnight, the blood serum fraction was removed and stored frozen at −20°C. Serum T4 and T3 levels were measured using a highly specific radioimmunoassay (Canadian Biochemicals Inc., Scarborough, Ontario). All assays were performed in duplicate or triplicate, and all assays from a single experiment were measured in a single assay run. The intra-assay coefficient of variation was <6%.

Results

Gas Chromatographic Analysis of the HAH Content of Coho Salmon

Gas chromatographic analysis of the coho salmon used as dietary supplements for laboratory mice indicated that Pacific Ocean coho salmon contained a total polychlorinated biphenyl (PCB) content of 20 ng/g, Lake Erie coho salmon contained 500 ng/g, Lake Michigan coho salmon contained 860 ng/g, and Lake Ontario coho salmon contained 2900 ng/g (Table 1). The pesticide hexachlorobenzene (HCB) was detected in coho salmon from the Pacific Ocean and the Great Lakes; the highest levels was in salmon from Lake Ontario (9.1 ng/g) (Table 1). Coho salmon from the Pacific Ocean were the only specimens that contained detectable levels of α-hexachlorocyclohexane (α-BHC). Lindane was not detected in any of the fish examined and mirex was found only in salmon from Lake Ontario (150 ng/g). The pesticides *pp*-DDE and *pp*-DDT followed a pattern similar to the PCB distribution of low levels in Pacific Ocean coho salmon followed by increasing levels in coho salmon from Lakes Erie, Michigan, and Ontario. Lake Erie coho salmon contained higher levels of *pp*-DDD than Lake

Table 1. Gas chromatographic analysis of halogenated aromatic hydrocarbons in coho salmon used to supplement mouse diets.[a]

	Halogenated aromatic hydrocarbon content, ng/g				
	Control chow	Pacific coho	Lake Erie coho	Lake Michigan coho	Lake Ontario coho
Total PCBs	0.4	20	500	860	2900
HCB	ND	2.8	1.3	2.5	9.1
α-BHC	ND	8.0	ND	ND	ND
Mirex	ND	ND	ND	ND	150
OCS	ND	ND	3.4	ND	27
γ-CL	0.2	ND	5.9	15	12
pp-DDE	0.1	10	79	240	670
pp-DDD	ND	2.7	15	9.3	27
pp-DDT	0.1	6.6	12	37	61

Abbreviations: PCBs, polychlorinated biphenyls; HCB, hexachlorobenzene; α-BHC, α-hexachlorocylohexane; OCS, octachlorostyrene; γ-CL: γ-chlordane; *pp*-DDE, 2,2-*bis*-(*p*-chlorophenyl)-1,1-dichloroethylene; *pp*-DDD, 2,2-*bis*-(p-chlorophenyl)-1,1-dichlorethane; *pp*-DDT, 1,1-*bis*-(*p*-chlorophenyl)-2,2,2-trichloroethane; ND, not detected.

[a] Adapted from Cleland et al. (*13*).

Michigan coho salmon, but both levels were less than those detected in Lake Ontario coho salmon (27 ng/g).

Analysis of control Purina mouse chow revealed very low levels of PCBs (0.4 ng/g) and pesticide residues (Table 1).

Effect of HAH on Body and Liver Weights

Body weights were significantly increased above control values in both C57B1/6 and DBA/2 mice that were fed Pacific Ocean coho salmon, as well as in DBA/2 mice that were fed Lake Michigan coho salmon (Table 2). C57B1/6 mice that were fed Lake Ontario coho salmon had liver weights that were greater than control values and percent liver weights that were greater than those of all other C57B1/6 dietary groups. In the DBA/2 mice, all Great Lakes salmon diets correlated with increased percent liver weights compared to those of control mice; however, increases in percent liver weight compared to both control mice and mice fed coho salmon from the Pacific Ocean were found only in mice fed Lake Ontario coho salmon.

Effect of HAH on Ethoxyresorufin-*O*-Deethylase (ERR) Enzyme Induction

ERR enzyme activity was significantly induced in liver microsomes in C57B1/6 mice fed coho salmon from any of the Great Lakes (Table 3). Compared to levels in control or Pacific Ocean salmon diets, the ERR enzyme induction in C57B1/6 mice that had been fed Lake Michigan coho salmon was increased approximately twofold. In the Lake Ontario coho salmon-fed C57B1/6 mice, the increases compared to control and Pacific salmon diets were 17.6- and 20.1-fold, respectively.

Table 2. Effect of dietary exposure to halogenated aromatic hydrocarbon-contaminated coho salmon on body and liver weights of C57B1/6 and DBA/2 mice.

Diet	Body weight, g[a]	Liver weight, g[a]	% Liver weight[a]
C57B1/6 mice			
Control chow	24.7 ± 0.4	1.4 ± 0.0	5.3 ± 0.1
Pacific coho	27.9 ± 0.8*	1.5 ± 0.1	5.3 ± 0.1
Lake Erie coho	26.4 ± 1.1	1.4 ± 0.1	5.6 ± 0.3
Lake Michigan coho	27.0 ± 0.7	1.5 ± 0.1	5.6 ± 0.1
Lake Ontario coho	25.8 ± 0.5	1.6 ± 0.0*	6.9 ± 0.3*†‡§
DBA/2 mice			
Control chow	26.3 ± 0.4	1.4 ± 0.1	5.4 ± 0.1
Pacific coho	29.7 ± 0.4*	1.7 ± 0.5*	5.7 ± 0.2
Lake Erie coho	28.6 ± 0.7	1.7 ± 0.1	5.9 ± 0.1*
Lake Michigan coho	26.7 ± 0.8†	1.6 ± 0.0	6.0 ± 0.1*
Lake Ontario coho	27.0 ± 1.0	1.7 ± 0.1*	6.4 ± 0.2*†

[a] Mean ± SEM ($n = 8$).
* Significantly different from control ($p < 0.05$).
† Significantly different from Pacific coho ($p < 0.05$).
‡ Significantly different from Lake Erie coho ($p < 0.05$).
§ Significantly different from Lake Michigan coho ($p < 0.05$).

Table 3. Effect of dietary exposure to halogenated aromatic hydrocarbon-contaminated coho salmon on ethoxyresorufin-*O*-deethylase (ERR) enzyme induction in C57B1/6 and DBA/2 mouse liver.

	ERR, nmole/mL/min/g of liver[a]	
	Mouse strain	
Diet	C57B1/6	DBA/2
Control chow	0.332 ± 0.043	0.350 ± 0.039
Pacific coho	0.291 ± 0.008	0.440 ± 0.026
Lake Erie coho	0.497 ± 0.019*†	0.445 ± 0.026
Lake Michigan coho	0.688 ± 0.033*†‡	0.546 ± 0.053*
Lake Ontario coho	5.850 ± 0.096*†‡§	0.715 ± 0.063*†‡

[a] Mean ± SEM ($n = 8$).
* Significantly different from control ($p < 0.05$).
† Significantly different from Pacific coho ($p < 0.05$).
‡ Significantly different from Lake Erie coho ($p < 0.05$).
§ Significantly different from Lake Michigan coho ($p < 0.05$).

The liver microsomal ERR enzyme activity of Lake Ontario coho salmon-fed DBA/2 mice was induced approximately twofold. This was the only DBA/2 mouse dietary group in which the ERR enzyme activity was significantly greater than levels in both control and Pacific Ocean coho salmon-fed mice.

Effect of HAH on Serum L-Thyroxine and Triiodo-L-Thryonine Levels

The T4 levels in the sera of C57B1/6 mice fed coho salmon from Lake Ontario were significantly lower than levels in any of the other dietary groups (Table 4). Dietary consumption of other Great Lakes salmon did not significantly alter C57B1/6 mouse T4 levels. Similarly, the T3 levels in the C57B1/6 mice fed Lake Ontario coho were significantly lower than levels in either control or Pacific coho salmon-fed C57B1/6 mice. The T4 levels in DBA/2 mice fed Lake Erie coho salmon were less than levels in those fed salmon from the Pacific Ocean, but not significantly different than control DBA/2 values. The T3 levels in DBA/2 mice that ate Pacific Ocean coho salmon were greater than levels in any of the other dietary groups; however, T3 levels in mice fed coho salmon from Lakes Erie, Michigan, or Ontario were not different from levels found in control animals.

Discussion

Historically, the health hazards associated with chronic exposure to toxic environmental contaminants have been difficult to assess. Exposures have been poorly defined, and the relationships of the health effects in laboratory animals to man have not been well understood. Laboratory studies of pure chemicals have rarely reflected the combinations of compounds and/or metabolites to which man and animals are chronically exposed. As an approach to this situation, these studies were undertaken to assess the potential health effects associated with the consumption of Great Lakes coho salmon that contain complex mixtures of bioaccumu-

Table 4. Effect of dietary exposure to halogenated aromatic hydrocarbon-contaminated coho salmon on serum levels of L-thyroxine (T4) and triiodo-L-thryonine (T3) in C57B1/6 and DBA/2 mice.

	Mouse strain			
	C57B1/6		DBA/2	
Diet	T4, ng/mL[a]	T3, ng/mL[a]	T4, ng/mL[a]	T3, ng/mL[a]
Control chow	660 ± 40	8.8 ± 0.8	620 ± 30	8.9 ± 0.4
Pacific coho	600 ± 30	9.5 ± 1.0	730 ± 40	11.5 ± 1.0*
Lake Erie coho	560 ± 40	7.7 ± 0.6	530 ± 30†	7.8 ± 0.5†
Lake Michigan coho	570 ± 30	8.1 ± 0.4	610 ± 60	8.9 ± 0.7†
Lake Ontario coho	410 ± 30*†‡§	6.3 ± 0.8*†	630 ± 50	7.8 ± 0.7†

[a] Mean ± SEM ($n = 8$).
* Significantly different from control ($p < 0.05$).
† Significantly different from Pacific coho ($p < 0.05$).
‡ Significantly different from Lake Erie coho ($p < 0.05$).
§ Significantly different from Lake Michigan coho ($p < 0.05$).

lated environmental contaminants. As such, this approach may provide a window to human and animal health in response to dietary exposure to a mixture of environmental contaminants.

Dietary consumption of Great Lakes coho salmon by sports fishermen has been identified as a significant source of chronic exposure to HAHs in man (*1*). Lake Michigan fish consumption has been correlated with PCB levels in human maternal serum and milk (*9,10*); mothers that eat Lake Michigan coho salmon have total PCB levels of 980.9 ng/g in their milk (*10*). Recent studies have addressed neonatal defects in the offspring of women chronically exposed to low levels of PCBs through the consumption of fish from Lake Michigan. The infants exposed *in utero* were smaller and born earlier than nonexposed controls and demonstrated serious behavioral abnormalities (*11*), symptoms consistent with fetal hypothyroidism (*12*).

It has been demonstrated that a gradation of halogenated aromatic hydrocarbon levels exist in the body tissue of adult coho salmon within the Great Lakes basin. In a previous study, congener analysis of the PCB content of the coho salmon used as diet supplements revealed that the Lake Ontario coho salmon contained higher levels of all congeners seen in other fish groups (*13*).

Although body wasting is a widely reported symptom of toxicity due to HAH exposure, body weights were not significantly reduced by dietary exposure to Great Lakes coho salmon in either strain of mice compared to control values. Body weights were increased in mice fed Pacific Ocean coho salmon diets compared to the control and groups fed other fish diets. This may be a reflection of the elevated lipid levels in Pacific Ocean salmon [4.2% versus an average of 2.1% in Great Lakes salmon (*13*)], although all fish diets were fortified with 4.5% corn oil to meet nutritional requirements.

An increase in the percent liver weight (hepatomegaly) is also widely regarded as an index of toxicity in rodents (*2*). C57B1/6 mice fed Lake Ontario coho salmon had percent liver weights that were significantly greater than those in any other diet groups. DBA/2 mice fed Lake Ontario coho salmon had percent liver weights that significantly exceeded values found in both control and Pacific Ocean coho salmon-fed mice.

Liver microsomal ethoxyresorufin-*O*-deethylase enzyme activity has been reported to be complementary to aryl hydrocarbon hydroxylase (*14*) and has been suggested to be a more sensitive indicator of mixed-function oxidase enzyme induction by HAHs than either aryl hydrocarbon hydroxylase or cytochrome P-450 measurements (*15,16*). Microsomal ERR enzyme activity in livers of C57B1/6 mice that consumed Lake Erie coho salmon was induced 1.5-fold over control values, while it was induced to a greater extent in livers of Lake Michigan coho salmon eaters (2.1-fold) and in livers of Lake Ontario coho salmon-fed C57B1/6 mice (17.6-fold). The microsomal ERR enzyme activity in liver tissue of DBA/2 mice was to a greater extent compared to control and Pacific Ocean coho salmon dietary groups only in the Lake Ontario coho salmon-fed mice, although only to a level which was eightfold less than that found in C57B1/6 mice. Similar near-20-fold increases in ERR induction have been described in the literature following injection of C57B1/6 mice with Aroclor 1254 (*16*).

Thyroid hormones have been suggested to play an important role in the metabolism of HAHs (*17*), and several HAH compounds have been shown to reduce serum thyroxine (T4) levels in a dose-dependent manner (*18,19*). McKinney et al. (*20*) suggested that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) may act as a T4 analogue, and Jones et al. (*1*) concluded that TCDD may alter hormone receptor coupling. Hypothyroidism has also been reported in four men (11.4% of those examined) who were employed in a factory that produces PBBs (*22*). Therefore, we examined thyroid hormone levels in C57B1/6 and DBA/2 mice following dietary consumption of Great Lakes coho salmon.

Serum T4 and T3 levels were reduced in C57B1/6 mice following dietary consumption of Lake Ontario coho salmon. The serum T4 levels in DBA/2 mice were unaffected by dietary exposure to any Great Lakes coho salmon diet (with the possible exception of Lake Erie salmon-fed DBA/2 mice in which serum T4 levels were higher than those seen in DBA/2 mice fed Pacific Ocean salmon, but not different than control values). The interstrain differences observed in mice may also be re-

lated to the low level cytosolic Ah receptor which has been described in DBA/2 mice (*3*). The serum T3 levels in DBA/2 mice were elevated following consumption of coho salmon from the Pacific Ocean. Hypothyroidism has been reported in rats following dietary consumption of Lake Ontario coho salmon (*23,24*) and in coho salmon following dietary exposure to mirex and PCBs (*25*). The health problems associated with hypothyroidism in adult humans may be correctable with dietary supplements; however, the level of risk to the developing fetus is potentially very serious and may affect embryonic physical and mental development. For example, infants exposed *in utero* during the Yusho incident (PCB-contaminated rice oil accidentally consumed in Japan in 1968) tended to be born small and prematurely (*26*). Follow-up studies revealed growth impairment and an average IQ of 70 in these children (*27*).

The current studies focus on the evaluation of the health hazards associated with chronic dietary exposures to complex mixtures of environmental chemicals. We have demonstrated that dietary exposure to Great Lakes coho salmon correlated with toxic effects in both strains of mice. The use of genetically dissimilar strains of mice indicated that there was a correlation of the severity of the pathobiological responses with the mouse Ah receptor status and with the HAH content of the dietary Great Lakes salmon. It is possible that factors other than HAH may have contributed to the toxicity observed; however, the symptoms were similar to those attributed to HAHs in the literature (*2,4*). These studies suggest that eating HAH contaminated Great Lakes coho salmon carries with it a risk of toxic effects in man and animals. The potential health hazard will almost certainly vary with the source of the fish, levels and composition of HAHs, the amount eaten, and as well may be dependent upon the as yet unknown Ah receptor status of man.

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