Consumption of PCB-Contaminated Sport Fish and Risk of Spontaneous Fetal Death

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Spontaneous fetal death has been observed among various mammalian species after exposure to polychlorinated biphenyls (PCBs). Our exposure-based cohort study assessed the relationship between consumption of PCB-contaminated Lake Ontario sport fish and spontaneous fetal death using 1820 multigravid fertile women from the 1990–1991 New York State Angler Cohort Study. Fish consumption data were obtained from food frequency questionnaires and history of spontaneous fetal death from live birth certificates. Analyses were stratified by number of prior pregnancies and controlled for smoking and maternal age. No significant increases in risk for fetal death were observed across four measures of exposure: a lifetime estimate of PCB exposure based on species-specific PCB levels; the number of years of fish consumption; kilograms of sport fish consumed in 1990–1991; and a lifetime estimate of kilograms eaten. A slight risk reduction was seen for women with two prior pregnancies at the highest level of PCB exposure (odds ratio = 0.36; 95% CI, 0.14–0.92) and for women with three or more prior pregnancies with increasing years of fish consumption (odds ratio = 0.97; 95% CI, 0.94–0.99). These findings suggest that consumption of PCB-contaminated sport fish does not increase the risk of spontaneous fetal death. *Key words*: fetal death, polychlorinated biphenyls (PCBs), reproductive toxicity, spontaneous abortion. *Environ Health Perspect* 103:498–502(1995)

Polychlorinated biphenyls (PCBs) are a group of thermal-resistant compounds that were widely used from the 1930s through the mid-1970s in the manufacture of dielectric fluids used in electrical transformers and capacitors. These industrial compounds are lipophilic and resist degradation. Low concentrations of PCBs in the environment can be magnified within the aquatic food chain and reach elevated levels in predatory sport fish (*1,2*). Consumption of contaminated fish has been shown to be an important source of human exposure to organochlorine compounds including PCBs (*2–5*).

Consumers of sport fish from the Great Lakes represent a population potentially at risk for adverse reproductive and perinatal outcomes related to environmental chemical exposures. Anglers and their families who eat sport fish are exposed to a complex mixture of chemicals including persistent lipophilic compounds such as PCBs, polychlorinated dibenzo-*p*-dioxin (PCDD), polychlorinated dibenzofurans (PCDFs), pesticides such as mirex and dichlorodiphenyl dichloroethene (DDE), and mercury (*6–8*). Sport fish consumption has been estimated to deliver a dose of PCBs which is 4300 times above background exposure from inhalation or drinking water (*9*). Estimates of chemical contamination levels in 1984 and 1985 suggest that Lake Ontario sport fish contain more than twice the concentration of PCBs found in fish from the other Great Lakes (*10*).

Several mammalian species have demonstrated a relationship between various levels of PCB exposure and fetotoxicity. Exposure to PCBs has been associated with spontaneous fetal death or resorption in rats (*11–13*), minks (*14–16*), rhesus monkeys (*17–19*), and guinea pigs (*20*). In addition, significantly smaller litter sizes have been demonstrated in rabbits (*21*) and swine (*22*) exposed to commercial PCBs compared to unexposed animals.

The potential mechanisms by which PCBs may impair human health and reproduction are numerous and poorly understood. Placental transport of PCBs and other organochlorine compounds has been shown, although fetal tissue and cord blood concentrations of PCBs are consistently lower than maternal levels (*23–25*). Placental tissue from women exposed to PCBs has been found to display markedly elevated induction of microsomal benzo[*a*]pyrene despite nondetectable concentrations of placental Ah receptors (*26*). PCBs and other organochlorine contaminants have been associated with endocrine disruption, neurotoxicity, and developmental delay in humans (*27*), and may be harmful to testicular function (*28*). Because PCBs can induce cytochrome P450, it has been suggested that the effect of PCBs on the reproductive system could be related to alterations in steroid hormones (*29*). Additionally, PCBs have been found to be mutagenic, with dose-related chromosome breakage in human white blood cell lines at low levels of exposure (*30*).

The relationship between PCB exposure and spontaneous fetal death in humans has received only limited investigation. In the few reports available, fetal loss was not the primary focus of the research, and the results are limited by small sample sizes (*31*). Follow-up studies of women exposed to PCB and PCDF-contaminated cooking oil in Taiwan reported the rate of fetal death among exposed women was nearly two times greater than in a group of control women (*32*). Among 11 women who were pregnant during a similar poisoning incident in Japan, 2 had stillborn infants (*33*). Exposed women in both of these studies were acutely poisoned and experienced other adverse health effects in addition to more fetal losses.

An investigation by Dar and associates (*34*) examined reproductive outcomes associated with consumption of sport fish from Lake Michigan and Green Bay. No consistent relationship was found between fish consumption and fetal death; women with the highest fish consumption had the lowest rate of fetal loss. However, the Green Bay women had substantially lower serum levels of PCBs when compared to occupationally exposed women (*35*) and when compared to a Lake Michigan fish-eating group (*36*). The Green Bay women also had a lower-than-expected rate of fetal loss compared to the general population of Wisconsin (*34*).

Despite advisory warnings, consumption of contaminated sport fish from the Great Lakes ranges from a few meals to subsistence levels. In the New York State Angler Cohort, comprising 11,431 anglers and their families, 9% eat a sport fish meal from Lake Ontario once a week or more (*37*). The question of reproductive and perinatal risks associated with sport fish consumption deserves concentrated attention. The present study addresses this concern, using a recently constructed exposure cohort to examine the relationship between sport fish consumption and spontaneous fetal death.

Methods

Data used in this investigation were collected as part of the New York State Angler Cohort Study. Briefly, this cohort is a population-based group of New York State anglers 18–40 years old who held fishing licenses for the 1990–91 season. Self-administered questionnaires were mailed to subjects and assessed sport fish consumption patterns, knowledge of fishing advisories, attitudes toward the safety of sport fish consumption, baseline health status, and reproductive information

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focused on children born from 1986 to 1991. Responses were received from 10,518 male anglers (39% response rate) and 913 female anglers (49% response rate); 6,651 wives/partners of male anglers also completed sections of the questionnaire on their own sport fish consumption, health status, and reproductive outcomes. Telephone interviews were conducted with a random sample of 100 nonrespondents. Nonrespondents were less likely to be married and had lower levels of education and lower income than respondents. However, sport fish consumption patterns were similar for respondents and nonrespondents. The exposure levels of nonrespondents were virtually identical to respondents.

Detailed information, including hospital of birth, was available for children born between June 1986 and June 1991. Computerized live-birth certificate information was available for 2529 cohort women from the New York State Health Department (91% of women with a self-reported live birth in 1986–1991 recorded on the questionnaire). Out-of-state delivery was the most common reason for not making a birth certificate match. Primigravidas (n = 609) and women with missing reproductive history information (n = 29) or missing exposure data (n = 71) were excluded from the study. All analyses were based on the remaining 1820 multigravid, fertile women with complete data. All women in the study were multigravid, having been pregnant at least twice, and fertile, having had at least one live birth. The excluded primigravidas were, on average, younger than the study group (26.2 years compared to 28.8) and consumed Lake Ontario sport fish for an average of 1 less year (2.6 years compared to 3.5), but no differences were seen in current consumption of sport fish, maternal education, maternal smoking, or paternal age (data not shown).

Multigravid, fertile women were studied to assess the potential impact of exposure on prior history of fetal death using a computerized vital registry (live birth certificates). This rationale is supported by the animal literature previously cited (*11–22*), which generally suggests an association between exposure and increased risk of pregnancy loss rather than an inability to become pregnant. Most women who experience pregnancy losses will go on to have live births (*38*). In fact, spontaneous fetal death is a fairly common reproductive event. Approximately 11–15% of all clinically recognized pregnancies will spontaneously abort (*39*).

We used reproductive history ascertained from the most recent available New York State live-birth certificate to assess maternal history of previous spontaneous fetal death. Birth certificates for 1986 and 1987 have one field for "previous spontaneous fetal deaths" and those for 1988–1991 have two fields "previous spontaneous abortions–less than 20 weeks; –20 weeks or more." These fields are intended to collect information on all fetal deaths including stillbirths. For the purpose of the current study, prior history of spontaneous fetal death was dichotomized as any occurrence versus none. A separate reliability study of this method of identifying women with a prior spontaneous fetal death was conducted (*40*). The reliability of this method of ascertaining spontaneous fetal death proved to be excellent. As part of a telephone interview focused on reproductive events, women were asked, "Have you ever had a pregnancy end in a miscarriage, spontaneous abortion, or stillbirth?" Exact agreement on the number of prior losses between a telephone interview and the birth certificate was 90% (k = 0.83) and agreement on any prior loss versus none was 94% (k = 0.90). Parental age and education also were obtained from the live birth certificate. Smoking, alcohol and sport fish consumption were obtained from the questionnaire, as were data on paternal consumption of sport fish and other demographic variables.

We used species-specific food frequencies and sport fish consumption histories from the questionnaire to construct four measures of exposure: 1) a lifetime estimate of PCB exposure based on species-specific PCB levels; 2) the number of years of sport fish consumption; 3) kilograms of sport fish consumed in the 1990–1991 season; and 4) a lifetime estimate of kilograms of sport fish eaten. Lifetime estimates of PCB exposure were calculated using the following formula:

$$\text{Estimated exposure} = \text{years} \times \Sigma\ \text{species}\ (\text{frequency} \times \text{meal amount} \times \text{specific chemical concentration})$$

where years = total number of years fish was consumed from 1955 to 1991; species = 0, not eaten or 1, eaten for each species consumed in 1990–1991; frequency = number of species-specific fish meals in the 1990–1991 season; meal amount = usual grams of fish eaten per meal; specific chemical concentration = milligrams of PCB by species as estimated by the New York Department of Environmental Conservation/Ontario Ministry of the Environment database, 1980–1990 (*41,42*).

The value calculated for estimated lifetime exposure to milligrams of PCBs represents a static cumulative model which assumes no elimination or degradation. Current consumers of sport fish were categorized into tertiles of exposure: low (≤ 1 mg), moderate (1.01–7 mg), and high (> 7 mg). Women who did not eat sport fish during the 1990–1991 season were not asked to complete species-specific consumption questions on the questionnaire and were categorized as past consumers. Past consumers were exposed but have an unquantified level of exposure. Women who had never eaten Lake Ontario sport fish were the reference group.

The total number of years sport fish was eaten were counted from 1955 to 1991. The number of years is essentially a measure of duration of exposure and is independent of the current amount of sport fish consumed. Kilograms of fish eaten during the 1990–1991 season were calculated by multiplying the reported number of fish meals, regardless of species, by the usual cooked portion size. Lifetime estimates reflect the kilograms of fish eaten in 1990–1991 multiplied by the number of years fish was eaten from 1955 to 1991. Current consumers were categorized by tertile of lifetime consumption: low (≤ 9.48 kg), moderate (9.49–36.7 kg), and high (> 36.7 kg). Past consumers were analyzed as a separate category, similar to lifetime PCB estimates.

We used various descriptive and analytical techniques. Relative risks and 95% confidence intervals were calculated in the bivariate analysis to identify potential confounders. Unconditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals for multivariable analyses. Preliminary testing for interactions revealed a significant interaction between the number of prior pregnancies and maternal age (β = -0.0377, p = 0.02, data not shown). No other statistically significant interactions were observed during model construction. Final analyses were stratified by the number of prior pregnancies into three levels: one, two, and three or more. We chose stratification, rather than leaving an interaction term in the model, in order to better describe the relationship between maternal age and spontaneous fetal death at different levels of prior gravidity. Gravidity is also a strong predictor of fetal death because pregnancy loss is a fairly common occurrence and each prior pregnancy represents an additional opportunity for a fetal death.

Full regression models included maternal age, smoking at some time in life, and female angler status. The bivariate analysis did not reflect an association between history of prior spontaneous fetal death and marital status, race, income, husand's or partner's fish consumption, maternal consumption of alcohol, sport or store-bought fish, canned fish, restaurant fish, non-New York State sport fish, or wild duck or turtle meals during pregnancy with the youngest

child. The potential for effect modification was also evaluated using stratified analyses. Gestational age at the time of loss (available from 1988–1991 certificates), maternal smoking, and levels of paternal sport fish consumption did not modify the relationship between exposure and outcome (data not shown). Only estimates from adjusted models are presented, given their similarity to the unadjusted models for all four exposure estimates.

Results

Women in the study group were characterized with respect to outcome, exposure, demographic characteristics, and other relevant variables (Table 1). Twenty-six percent of women (n = 471) in the study had a history of spontaneous fetal death recorded on the live birth certificate. Most of these women (81%; n = 383) had only one prior spontaneous fetal death. More than half of the women (54%) had never eaten Lake Ontario sport fish, and 24% were current sport fish consumers. Among women who consumed sport fish, half did so for more than 4 years. Women who reported current consumption ate an average of 4.9 kg (SD = 8.1) in 1990-1991, and the estimate of mean lifetime sport fish consumption was 57.4 kg (SD = 133.6) for those women.

Table 1. Description of the study sample of multigravid, fertile women from the New York State Angler Cohort Study with a live birth recorded in New York state from 1986 to 1991

Characteristic	n (%)
Prevalence of spontaneous fetal death	
None	1349 (74)
Any occurrence	471 (26)
PCB exposure categories	
None ever	979 (54)
Past consumer	408 (22)
Low (≤ 1 mg)	143 (8)
Moderate (1.01–7 mg)	142 (8)
High (> 7 mg)	148 (8)
Lifetime sport fish consumption	
None ever	979 (54)
Past consumer	408 (22)
Low (≤ 9.48 kg)	140 (8)
Moderate (9.49–36.7 kg)	144 (8)
High (> 36.7 kg)	149 (8)
Number of prior pregnancies	
One	883 (49)
Two	546 (30)
Three or more	391 (21)
Smoked cigarettes at some time in life	942 (52)
	Mean (SD)
Maternal age (years)	28.8 (3.8)
Maternal education (years)	13.4 (1.8)
Consumption of sport fish	
All women (years)	3.5 (6.5)
Current consumers (years)	7.6 (7.7)
All women (kg eaten, 1990–91)	1.2 (4.6)
Current consumers (kg eaten, 1990–91)	4.9 (8.1)

Table 2 shows the adjusted regression model for each of the four exposure measures. The highest level of estimated lifetime PCB exposure was associated with a significant risk reduction for women with two prior pregnancies (OR = 0.36; 95% CI, 0.14–0.92). For the low-exposure group with one prior pregnancy and three or more prior pregnancies, the moderate-exposure group with two prior pregnancies, and for past consumers with two and three prior pregnancies, ORs > 1 were observed, but none was statistically significant. The highest level of exposure was associated with ORs < 1 at all levels of gravidity, ranging from 0.36 to 0.71, but only the group with two prior pregnancies reached significance.

The number of years of sport fish consumption was entered into logistic models as a continuous variable and analyzed in relation to history of spontaneous fetal death. All of the ORs were close to 1. A significant risk reduction was seen in the group with three or more prior pregnancies (p = 0.03). This indicates that for each year of fish consumption, among women with three or more prior pregnancies, there was a 3% reduction in the risk of spontaneous fetal death.

Current sport fish consumption in the 1990–1991 season displayed a similar relationship to spontaneous fetal death as the number of years of consumption. In both sets of analyses, the ORs were close to 1 (range, 0.95–0.98). However, the risk reduction seen in the group with three or more prior pregnancies for current sport fish consumption is of borderline significance (p = 0.06).

The results for lifetime estimate of sport fish consumption were similar to those seen for lifetime PCB level and history of spontaneous fetal death. No statistically significant relationships were seen between spontaneous fetal death and category of lifetime fish consumption at any level of gravidity. As with PCB level, ORs were > 1 for the low-exposure group with one prior pregnancy and with three or more prior pregnancies, and for the moderate-exposure group with two prior pregnancies. The past-consumer category had ORs > 1 with the exception of the group with one prior pregnancy. The highest level of lifetime fish consumption had ORs ranging from 0.51 to 0.68, suggesting a reduced risk at all levels of gravidity. All of the confidence intervals, however, included 1.

Overall, the four measures of exposure do not indicate any consistent relationship between sport fish consumption and/or PCB exposure with spontaneous fetal death. The continuous measures of exposure (number of years of consumption and kilograms of fish consumed in 1990–1991) tend to show a slight reduction in risk. The categorical exposure variables (lifetime estimates of PCB exposure and lifetime kilograms of fish consumed) show an inconsistent pattern with ORs > 1 at low or moderate levels of exposure and < 1 for high exposure.

Discussion

No consistent relationship was seen between a history of spontaneous fetal death and the four measures of PCB exposure and sport fish consumption used in

Table 2. Adjusted odds ratios (ORs) based on Lake Ontario sport fish consumption among multigravid, fertile women from the New York State Angler Cohort Study with a live birth recorded in New York State from 1986 to 1991[a]

	1 Prior pregnancy (n = 883)		2 Prior pregnancies (n = 546)		3 Prior pregnancies (n = 391)	
Exposure measures	OR	95% CI	OR	95% CI	OR	95% CI
Lifetime PCB level						
None ever	1.00	reference	1.00	reference	1.00	reference
Past consumer	0.95	0.55–1.66	1.07	0.69–1.68	1.09	0.64–1.85
Low (≤ 1mg)	1.26	0.57–2.81	0.90	0.45–1.80	1.40	0.65–2.99
Moderate (1.01–7 mg)	0.53	0.18–1.51	1.06	0.52–2.16	0.69	0.33–1.42
High (> 7 mg)	0.51	0.18–1.48	0.36	0.14–0.92	0.71	0.35–1.41
Number of years						
Each year	0.98	0.94–1.02	0.98	0.96–1.02	0.97	0.94–0.99
Number of kg eaten, 1990–91						
Each kg	0.98	0.91–1.05	0.96	0.90–1.02	0.95	0.90–1.00
Lifetime sport fish consumption						
None ever	1.00	reference	1.00	reference	1.00	reference
Past consumer	0.95	0.90–1.01	1.08	0.69–1.68	1.08	0.64–1.84
Low (≤ 9.48 kg)	1.41	0.65–3.03	0.69	0.34–1.44	1.67	0.72–3.86
Moderate (9.49–36.7 kg)	0.28	0.07–1.17	1.17	0.57–2.39	0.85	0.44–1.64
High (> 36.7 kg)	0.62	0.23–1.62	0.51	0.22–1.15	0.52	0.25–1.09

[a]ORs are stratified by maternal gravidity, calculated by logistic regression for any history of spontaneous fetal death with lifetime estimate of PCB exposure, number of years consumption, kilograms of Lake Ontario sport fish consumed in 1990–1991, and lifetime estimate of Lake Ontario sport fish consumed. ORs are adjusted for maternal age, smoking at some time in life, and female angler status.

the current study. Although the four measures are interrelated and derived from a self-administered questionnaire, the consistency of the findings across exposure estimates lends greater confidence to the results. Lake Ontario sport fish represent a complex exposure to a variety of contaminants including PCBs. No increased risk was seen with either recent or lifetime fish consumption (complex exposure), estimated PCB exposure from sport fish, or duration of exposure. The present study findings are also consistent with those reported by Dar (*34*), which failed to show an association between spontaneous fetal death and PCB exposure from sport fish consumption.

The lack of an association between spontaneous fetal death and PCB exposure and sport fish consumption could be the result of many factors. Recently, there have been reports linking consumption of marine fish (not fresh-water fish) with prolonged gestation and increased fetal weight (*43,44*). It is possible that despite high levels of chemical contamination, the benefits of fresh-water fish from the Great Lakes may offset the potential adverse effects. It is also possible that PCBs have an impact on human reproduction that does not result in recognized fetal deaths. Another explanation for the current findings may be that women at the highest level of exposure have suppressed fertility and encounter longer times to conception or more frequent unrecognized pregnancy loss. It may be that at the highest level of exposure to these contaminants, the impact on pregnancy is a very early "all-or-nothing" effect which appears in this study as a protective effect of exposure. In order to be at risk for recognized fetal death, fertilization must occur and the conceptus must survive to clinical recognition of pregnancy (*45*). By design, this study focused only on clinically recognized fetal deaths. Studies of chemically detected pregnancies and early pregnancy loss are needed to better understand the relationship between exposure and outcome.

The current study had sufficient power to find an overall significant increase in risk of 1.16 ($\alpha = 0.05$, $\beta = 0.20$). Power was limited somewhat in the stratified analyses with the ability to detect a significant increased OR of 1.41 for past consumers compared to unexposed women and 1.69 for any tertile of exposed women compared to unexposed women ($\alpha = 0.05$, $\beta = 0.20$). Nevertheless, it does not appear that the lack of association is primarily due to a lack of statistical power.

Use of the reproductive history data on birth certificates for a study of spontaneous fetal death has limitations. Although the reliability of the data was good, reproductive toxicity risk can be assessed at only one point in the spectrum of human reproduction. Still, this methodology has tremendous benefits for conducting studies to examine the relationship between environmental exposures and fetal death quickly with a modest expenditure of resources. A particular strength of this study is that it represents a novel approach for assessing reproductive toxicity related to a low-level environmental exposure. While spontaneous fetal death is considered a sensitive outcome for the assessment of environmental reproductive toxicity, fetal death registration is often quite poor. Many states, for example, require death registration only after 20 weeks of gestation, or over a certain weight limit, such as 350–500 g (*46*). In contrast, vital registration of live births is generally quite good, and research opportunities using the live birth certificate have been encouraged (*47*).

The potential for error in the exposure measures is more problematic. A validation study is currently underway for the New York State Angler Cohort study. A static model, without any direct assumption of degradation of PCBs, was used to estimate exposure. However, PCB levels in Lake Ontario sport fish were substantially higher during the 1970s (*48*). It may be that the particular years sport fish were eaten is more important than the total number of years. However, all four measures of exposure had similar findings, including years of fish consumption, which was not dependent on current consumption.

Occupational data, an important confounder in studies of environmental exposure, are also unavailable. Although current occupation for both parents is characterized on the live birth certificates, this information is not included in registry data files. In any case, current occupation at the time of the last birth cannot be expected to reflect lifetime occupational PCB exposure, and considerable error has also been described in the recording of occupation on birth certificates (*49*). Similarly, no data were available to characterize other potential dietary or environmental sources of PCB exposure.

A final and important limitation of this investigation is that both the outcome and exposure are self-reported. Although there is concern about misclassification related to the self-reported nature of the data, ascertainment of outcome and exposure was made independently. Any bias present in outcome assessment should be nondifferential and would bias results toward the null hypothesis. The reproductive history reports come from birth certificates filed before the receipt of the angler questionnaire. The level of sport fish consumption should have no relation to the reported reproductive history on the birth certificate.

The lack of any consistent increase in risk for spontaneous fetal death associated with estimated PCB exposure or sport fish consumption in the study cohort suggests the absence of any strong association in this population. Careful interpretation of these findings is called for given the limitations of the study. Lake Ontario sport fish are contaminated with a variety of organochlorines and other persistent toxic compounds and heavy metals. The human health effects of exposure to these contaminants are not well understood, and the potential long-term effects are unknown. Further investigation of the relationship between these exposures and pregnancy loss are needed, particularly given the animal literature on PCB and fetotoxicity (*50*).

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"Mechanisms and Prevention of Environmentally Caused Cancers", a symposium presented by The Lovelace Institutes, will be held October 21–25, 1995, in Santa Fe, New Mexico. The purpose of this symposium is to promote collaboration between scientists interested in the basic mechanisms of environmentally-caused cancer and investigators focusing on preventing cancer development with chemo-intervention strategies. Dr. Bruce Ames (University of California) will be the keynote speaker. Other speakers include Dr. Eric Stanbridge (UC Irvine), Dr. Stephen Friend (Harvard), and Dr. Gary Stoner (Ohio State University).

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