Birth defects risk associated with maternal sport fish consumption: potential effect modification by sex of offspring

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Abstract

Contaminated sport fish consumption may result in exposure to various reproductive and developmental toxicants, including pesticides and other suspected endocrine disruptors. We investigated the relation between maternal sport fish meals and risk of major birth defects among infants born to members of the New York State (NYS) Angler Cohort between 1986 and 1991 (n = 2237 births). Birth defects (n = 125 cases) were ascertained from both newborn medical records and the NYS Congenital Malformations Registry. For sport fish meals eaten during pregnancy, the odds ratio (OR) for all major malformations combined was slightly elevated for \( \leq 1 \) meal/month (OR = 1.26, 95% confidence interval (CI): 0.84, 1.89) and \( \geq 2 \) meals/month (OR = 1.51, CI = 0.74, 3.09), with no meals during pregnancy as the reference category. Higher ORs were consistently observed among male offspring compared with females. For \( \geq 2 \) meals/month, the risk for males was significantly elevated (males: OR = 3.01, CI: 1.2, 7.5; females: OR = 0.73, CI: 0.2, 2.4). Exposure during pregnancy and effect modification by infants sex could be important considerations for future studies of birth outcomes associated with endocrine disruptors.

1. Introduction

Consumption of contaminated sport fish from the Great Lakes has been associated with exposure to many persistent lipophilic chemicals including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), and pesticides such as dichlorodiphenyl dichloroethene (DDE), hexachlorobenzene, and mirex (Fitzgerald et al., 2001; Falk et al., 1999; Humphrey, 1988; Fiore et al., 1989; Hovinga et al., 1993; Kostyniak et al., 1999). PCBs, PCDDs, DDE, and other pesticides are known to cross the placenta and thereby serve as a prenatal source of exposure for the developing fetus (Kodama and Ota, 1977; Jacobson et al., 1984). These compounds may interfere with endocrine function (Daston et al., 1997; Peterson et al., 1993). The potential teratogenic effects of these exposures have been
observed in wildlife and laboratory animals, raising concern about human health effects (National Research Council, 1999). From a public health perspective, this body of evidence has resulted in fish consumption advisories that are issued by state and local governments. A national listing of fish and wildlife advisories indicates that most involve five primary contaminants: mercury, PCBs, chlordane, dioxins, and metabolites of dichlorodiphenyl trichloroethane, such as DDE (United States Environmental Protection Agency, 2003). These advisories typically recommend that women of reproductive age eat no fish from the most contaminated water bodies and eat limited amounts of other, less contaminated, sport fish.

PCBs, DDE, and certain other pesticides are persistent lipophilic compounds and will bioaccumulate with continued exposure (Humphrey, 1987). Exposure from contaminated fish consumption prior to pregnancy will result in a body burden of these persistent contaminants. In addition, contaminated sport fish meals cause a substantial acute increase in circulating blood levels of many potentially endocrine-disrupting compounds, levels far above the accumulated background body burden associated with chronic exposure (Humphrey, 1987, 1988). If this acute exposure occurs during a critical window of organogenesis, it may increase birth defect risk. Male fetuses may be more susceptible than female fetuses to potential perturbations in the hormonal milieu during pregnancy, since fetal androgens are critical for the normal development of the male urogenital organs.

The New York State Angler Cohort Study was implemented in 1991 to address the potential reproductive and developmental effects of contaminated sport fish consumption. The purpose of this analysis was to assess the relation between maternal consumption of sport fish meals and risk of major birth defects and to evaluate potential effect modification of this relationship by infant sex. This is the first North American epidemiologic study of sport fish consumption and birth defect risk.

2. Materials and methods

2.1. Study population

Details regarding the methods of the New York State Angler Cohort have been published elsewhere (Vena et al., 1996). Briefly, this was a population-based study of licensed anglers aged 18 to 40 years in 1991. All cohort members purchased fishing licenses in one of 16 New York State (NYS) counties surrounding Lakes Erie and Ontario and answered detailed mailed questionnaires including fish consumption and reproductive histories. Of 4229 children born to cohort members between June 1986 and June 1991, 3758 (89%) had complete exposure and outcome data and 3366 (80%) also had complete data on potential confounders. Since neither exposures or outcomes would be independent among children born to the same mother, we restricted the analysis to the first child listed on each mother’s questionnaire, resulting in 2237 (66%) of the children remaining in the analysis.

2.2. Exposure assessment

Sport fish consumption was ascertained at cohort enrollment in 1991 using a food frequency approach. Specifically, mothers were asked to “Please indicate the frequency with which you ate sport-caught fish from New York waters when you were pregnant (bold on questionnaire) anytime since June 1, 1986.” This heading was followed by a request to indicate “Your average number of sport-caught fish meals eaten during pregnancy...” for each child listed. Three exposure categories were developed based on the distribution of values observed: no meals (reference), less than or equal to one meal per month, and two or more meals per month during pregnancy. This measure of fish consumption from New York waters represents a large range of potential exposure scenarios, since some fish are highly contaminated and others are not. No information was available on the specific species eaten or bodies of water fished for sport fish meals during pregnancy.

In addition to pregnancy meals, exposure was also characterized by the number of years the mother reported eating sport fish from Lake Ontario and its tributaries. Women were asked to check each year from 1955 to 1991 during which they ate Lake Ontario sport fish and the total number of years prior to the birth year of the index infant were summed for this variable. Duration was categorized into three groups based on the distribution of values: none (reference), 5 years or less, and 6 years or more. While current levels are declining, Lake Ontario sport fish were some of the most highly contaminated of all Great Lakes fish during this time, particularly with respect to dioxin (O’Keefe et al., 1983). This measure of duration reflects each mother’s chronic body burden accumulated throughout her lifetime as well as her likelihood of compliance with fishing advisories. The NYS Department of Health Fishing Advisory recommends that children under 15 and women of reproductive age eat no sport fish of any species from Lake Ontario (New York State Department of Health, 2003), and this recommendation has been in place since 1976.

2.3. Outcome assessment

Newborn medical records were abstracted for 93% of all cohort children (n = 3910). Over 1200 records with
suspected congenital anomalies were systematically reviewed by a dysmorphologist (LKR) who was blind to maternal sport fish consumption status. A similar number of children (94%) had sufficient information to attempt a match with the New York State Congenital Malformations Registry \((n = 3964)\). Since 1982, all hospitals and physicians in New York State are required by law to report cases of major malformations diagnosed up to age 2 years.

We observed some variation in both the number and nature of the specific diagnoses from both data sources (medical record and registry). While careful review suggested that all children classified as cases were likely to have one or more major anomalies, all of the specific defects could not be confidently ascertained. For example, some cases had additional diagnostic codes in one data source that did not appear in the other and some cases were reported only in one source. For the purpose of these analyses, cases are defined as any registry match or confirmed newborn medical record notation of a congenital anomaly (ICD 9 740.0–759.9) after application of the Metropolitan Atlanta Congenital Defect program exclusion criteria for minor anomalies (United States Department of Health and Human Services, 1993).

In general, the lack of confidence about complete ascertainment of all associated diagnostic codes and small numbers precludes analyses by organ system or specific defect. Since contaminated sport fish consumption may be related to endocrine disruptor exposures, we report the prevalence of hypospadias to illustrate an anomaly that might plausibly be related to hormone disturbances. A diagnosis of hypospadias was noted for 12 infants. Of these, 3 were ascertained from medical records only and 9 from both data sources. Of the 12 cases, 9 had isolated defects and 3, all with information from the registry, had additional diagnoses.

2.4. Measurement of confounders and effect modifiers

We evaluated a series of potential confounders including smoking, alcohol consumption, hypertension, and gestational diabetes, but none were significantly associated with the outcome. Maternal age at delivery (measured in years), maternal diabetes (excluding gestational diabetes), and infant sex were included in the models a priori and all data were abstracted from the hospital delivery records.

2.5. Analytic methods

Descriptive statistics and assessment of confounding and potential collinearity were conducted. Stratified analyses assessed potential effect modification by infant sex. Logistic regression was performed with exposure categories entered into the models as dummy variables.

 Mothers who reported no sport-caught fish meals during pregnancy formed the reference group for analyses on pregnancy meals. Mothers who never consumed Lake Ontario sport fish were the reference group for analyses on duration. The unadjusted prevalence of hypospadias among male infants is also reported for all exposure categories.

3. Results

On average, mothers were 28 years old at delivery and less than 1% were diabetic (see Table 1). Slightly more than half of the infants were male (52.5%) and more than 30% of mothers ate some sport-caught fish meals during pregnancy. Lake Ontario sport fish was consumed prior to the year of birth by 36% of study mothers and 337 (15%) reported six or more years of consumption.

Over 5% of the children had a major birth defect \((n = 125)\). Major birth defects were reported in both the newborn medical record and the registry for 46 of those children (37%). For those children, 39 had diagnoses that matched exactly, 3 matched to the first decimal place of the ICD code, 6 matched to organ system, and only 3 children, all of whom had multiple anomalies did

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the study population, New York State Angler Cohort mothers and children for births 1986–1991, (n = 2237^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28.1 (4.0)</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>9</td>
</tr>
<tr>
<td>Male infant</td>
<td>1174</td>
</tr>
<tr>
<td>Number of sport-caught meals from any New York State waters per month during pregnancy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1551</td>
</tr>
<tr>
<td>1 or less</td>
<td>567</td>
</tr>
<tr>
<td>2 or more</td>
<td>119</td>
</tr>
<tr>
<td>Number of years eating Lake Ontario sport fish prior to pregnancy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1429</td>
</tr>
<tr>
<td>5 or less</td>
<td>471</td>
</tr>
<tr>
<td>6 or more</td>
<td>337</td>
</tr>
<tr>
<td>Number of major birth defects and source of ascertainment</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2112</td>
</tr>
<tr>
<td>Total cases</td>
<td>125</td>
</tr>
<tr>
<td>Medical record only</td>
<td>54</td>
</tr>
<tr>
<td>Registry only</td>
<td>25</td>
</tr>
<tr>
<td>Both</td>
<td>46</td>
</tr>
</tbody>
</table>

\(^a\) Subset of one child per mother with complete data on study variables.

\(^b\) Number of years from 1955 up to and including the year prior to the birth of the index child during which Lake Ontario fish was eaten.
not match by diagnostic category. Twenty-five cases (20%) were only reported to the registry, but most of these could be anticipated given that many anomalies are not routinely diagnosed during the newborn admission (e.g., certain heart defects). The remaining 54 cases (43%) were only reported in the medical record. The majority of these (n = 26) were musculoskeletal defects such as congenital hip dislocations.

Some suggestion of increased risk for major birth defects was observed in offspring of mothers who consumed sport fish meals during pregnancy compared to mothers who did not, although the confidence intervals all include one (see Table 2). In logistic models that included sex (data not shown), no main effect for sex was observed in relation to birth defects risk (p = 0.30) and the interaction of sex and sport fish meals during pregnancy was not significant (p = 0.17). However, stratifying the data by infant sex resulted in substantially higher risk estimates in male offspring and significantly higher risk for males whose mothers ate two or more meals per month (odds ratio (OR) = 3.01, 95% confidence interval (95% CI) = 1.20, 7.52), while no risk was observed for females.

No increased risk was observed by duration of Lake Ontario sport fish consumption. An attenuated but similar pattern of effect modification was observed with

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adjusted² odds of any major birth defect associated with maternal sport fish consumption by infant sex, New York State Angler Cohort for children born 1986–1991, n = 2237ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All children</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Number of sport-caught fish meals from all New York State waters during pregnancy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1553</td>
</tr>
<tr>
<td>≤1 meal per month</td>
<td>567</td>
</tr>
<tr>
<td>≥2 meals per month</td>
<td>119</td>
</tr>
<tr>
<td>Duration of lifetime Lake Ontario sport fish consumption⁴</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1429</td>
</tr>
<tr>
<td>1–5 years</td>
<td>471</td>
</tr>
<tr>
<td>≥6 years</td>
<td>337</td>
</tr>
</tbody>
</table>

²All analyses are adjusted for maternal age and diabetes.
ᵇSubset of one child per mother with complete data on study variables.
³CI = confidence interval
⁴Number of years from 1955 up to and including the year prior to the birth of the index child during which Lake Ontario fish was eaten.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Case summaries of birth defects reported for infants of mothers consuming two or more sport fish meals per month during pregnancy, New York State Angler Cohort children born 1986–1991, n = 119ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case number</td>
<td>Diagnoses (source)</td>
</tr>
<tr>
<td>Males (total n = 52; 6 children with defects)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>751.1</td>
</tr>
<tr>
<td>2</td>
<td>752.6</td>
</tr>
<tr>
<td>3</td>
<td>759.7</td>
</tr>
<tr>
<td>4</td>
<td>743.65</td>
</tr>
<tr>
<td>4</td>
<td>746.89</td>
</tr>
<tr>
<td>5</td>
<td>752.6</td>
</tr>
<tr>
<td>6</td>
<td>758.2</td>
</tr>
<tr>
<td>746.02</td>
<td>Pulmonary valve stenosis (registry)</td>
</tr>
<tr>
<td>746.83</td>
<td>Infundibular pulmonic stenosis (registry)</td>
</tr>
<tr>
<td>747.3</td>
<td>Pulmonary artery anomalies (registry)</td>
</tr>
<tr>
<td>759.89</td>
<td>Other specified congenital syndrome (registry)</td>
</tr>
<tr>
<td>Females (total n = 67; 3 children with defects)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>754.51</td>
</tr>
<tr>
<td>8</td>
<td>749.0</td>
</tr>
<tr>
<td>9</td>
<td>754.3</td>
</tr>
</tbody>
</table>

ᵃSubset of one child per mother.
The prevalence of hypospadias associated with maternal sport fish consumption among New York State Angler Cohort children born 1986–1991, \( n = 1174^a \)

<table>
<thead>
<tr>
<th>Hypospadias present</th>
<th>( n ) (%)</th>
<th>( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sport-caught fish meals from all New York State waters during pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8 (0.9)</td>
<td>840 (99.1)</td>
</tr>
<tr>
<td>≤ 1 meal per month</td>
<td>2 (0.7)</td>
<td>272 (99.3)</td>
</tr>
<tr>
<td>2+ meals per month</td>
<td>2 (3.8)</td>
<td>50 (96.2)</td>
</tr>
<tr>
<td>Duration of lifetime Lake Ontario sport fish consumption(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6 (0.8)</td>
<td>774 (99.2)</td>
</tr>
<tr>
<td>1–5 years</td>
<td>3 (1.2)</td>
<td>245 (98.8)</td>
</tr>
<tr>
<td>≥ 6 years</td>
<td>3 (1.7)</td>
<td>173 (98.3)</td>
</tr>
</tbody>
</table>

\(^a\) Subset of one child per mother with complete data on study variables, males only.

\(^b\) Number of years from 1955 up to and including the year prior to the birth of the index child during which Lake Ontario fish was eaten.

higher point estimates among boys whose mothers ate Lake Ontario sport fish for 6 or more years (OR = 1.54) compared to mothers of girls with similar exposure (OR = 0.54).

For children in the highest exposure category, with mothers eating two or more meals per month, no discernable pattern of defects was observed (see Table 3). While the expected rate for major defects would be about 3–4%, nearly 12% of exposed males had defects compared to approximately 5% of females in this exposure category.

The unadjusted prevalence of hypospadias is presented in Table 4 to illustrate one potential defect of interest in male offspring. The prevalence appears to be somewhat higher in boys whose mothers are more highly exposed, particularly for sport fish meals during pregnancy, but the number of cases is small.

4. Discussion

In these data, stratified analyses suggest effect modification by infant sex in the relation between major birth defect risk and maternal sport fish consumption, particularly during pregnancy. Risk estimates were always higher for male compared to female offspring at the same level of exposure. Of additional importance is the apparent significance of sport fish meals eaten during pregnancy. The risk estimates associated with meals eaten during pregnancy were all higher than the risk estimates associated with lifetime exposure to contaminated fish meals from Lake Ontario, even though the potential contaminant exposure from Lake Ontario fish is assumed to be greater.

To place these results in context, no other study has specifically examined birth defect risk associated with contaminated fish meals eaten during pregnancy. Two prior Swedish studies did not find any increase in risk associated with Baltic Sea fish consumption. Rylander and Hagmar (1999) observed no increased risk for birth defects comparing the offspring of fishermen’s wives from the east coast of Sweden who ate contaminated Baltic Sea fish to west coast fishermen’s wives (OR = 0.87; 95% CI: 0.69, 1.11). A second study of sisters of fisherman and other women on the east and west coast of Sweden (Rylander et al., 2000) found a significant reduction in risk for major malformations among east coast women (OR = 0.6; 95% CI: 0.4, 0.09) and the authors report the results were only marginally changed with consideration of infant sex. The amount and timing of fish consumption did not appear to be included in the models for either of these Swedish cohorts, with location serving as a proxy exposure variable.

Longnecker et al. (2002) did not observe a significant association between third trimester serum levels of DDE and risk of selected malformations in male infants. Their results for cryptorchidism (OR = 1.3, 95% CI: 0.7, 2.4), hypospadias (OR = 1.2, 95% CI: 0.6, 2.4), and polythelia (OR = 1.9, 95% CI: 0.9, 4.0) were in the same range as the risk of major anomalies for males that we observed with Lake Ontario fish consumption (OR = 1.54, 95% CI: 0.7, 3.7). Their data from the Collaborative Perinatal Project, a prospective pregnancy study conducted between 1959 and 1966 in 12 study centers across the United States, had serum DDE levels that were substantially higher (4–6 μg/g lipid-based, recovery-adjusted) than would be seen in 1986–1991, even among anglers. Our measure of fish consumption is an imprecise mixture of contaminant exposures. If DDE is the responsible agent in sport fish, then the timing and nature of exposure may be important. A contaminated fish meal can raise the serum level up to 500 times over baseline during the first 10 h and remain elevated over background for days (Humphrey, 1987, 1988). This acute rise in circulating blood levels may be important for birth defect risk if it occurs during critical windows of organogenesis. Alternatively, DDE might not be the toxic agent, or the effect may only be apparent when DDE is in combination with other sport fish contaminants.

Our high-risk group was restricted to women who ate two or more sport-caught fish meals per month during pregnancy to increase the likelihood that an acute exposure occurred during a relevant time window. While this is generally plausible, we cannot determine if the sport-caught meals actually eaten during pregnancy in our study were contaminated, or whether the timing of
consumption was consistent with sensitive periods for
the development of specific organ systems. The NYS
Department of Health recommends that women of
childbearing age eat no fish from 79 waterbodies that
have at least one species of fish with contaminant levels
greater than federal standards, but the number of
species affected and level of contamination vary greatly
across waters (New York State Department of Health,
2003). Pregnancy sport fish meals could have come from
any NYS waters, many of which are not associated with
health advisories for contaminated fish. While fresh-
water fish do not have the quantity of long-chain omega
fatty acids found in ocean fish, they do provide a healthy
and important source of low-fat protein in the diet. If
the association we observed was causal, misclassification
and important source of low-fat protein in the diet. If
the association we observed was causal, misclassification
of healthy sport fish meals during pregnancy into our
high-exposure group would likely bias our results
toward the null.

As noted earlier, Great Lakes sport fish may also be
contaminated with PCBs, PCDDs, and pesticides,
including mirex. No studies of birth defects and PCB
exposures in humans have been reported. Exposure to
PCDDs after an industrial accident in Seveso, Italy, was
not associated with an increased risk for birth defects
(Mastolacovo et al., 1988). In contrast, several studies
have attempted to characterize maternal occupational
and/or residential pesticide exposures in the periconcep-
tional period and early pregnancy to examine risk for
congenital anomalies. Shaw et al. (1999) observed
associations between professional pesticide applications
to a woman’s residence and neural-tube defects (NTDs)
and limb defects. Women who reported living close to
agricultural crop areas also had an increased risk of
having an infant with an NTD. A large study of
Norwegian farm children (Kristensen et al., 1997)
observed associations between farming exposures and
NTDs, orofacial clefts, male genital defects including
hypospadias, and limb reduction defects. In Spain,
increased risk of selected anomalies was also observed
with maternal agricultural work during the first
trimester (Garcia et al., 1999). The Baltimore–Wash-
ington Infant Study found an increased risk for selected
heart defects associated with maternal herbicide and
rotenticide exposure, but not insecticides (Loffredo et al.,
2001). Fetal deaths caused by congenital malformations
were also more common among women who lived near
agricultural pesticide applications early in pregnancy,
although the findings for suspected endocrine-disruptor
exposure was not as strong as the results for exposure to
halogenated hydrocarbons (Bell et al., 2001).

Since the specific contaminant levels of pregnancy fish
meals were unknown, we investigated consumption of
other, better characterized, contaminated fish. We
suspected that women who eat sport fish meals during
pregnancy, when many food aversions are operating,
would be more likely to eat sport fish in general and
might have a higher baseline body burden of associated
reproductive toxicants than non-eaters. Of the 119
women who ate two or more sport fish meals per month
during pregnancy, more than half (n = 64) also ate Lake
Ontario fish during their lifetimes. Examining other
exposure scenarios, we continued to observe apparent
effect modification by infant sex although overall risk of
birth defects was attenuated. This was true for lifetime
duration of Lake Ontario sport fish consumption
(shown in Table 2), an estimate of lifetime PCB
exposure based on species-specific PCB levels (data not
shown) and frequency of Lake Ontario sport fish meals
in the year prior to and year of delivery (data not
shown). No significant associations were observed, but
risk estimates were always higher for male offspring
compared to females.

The effect modification observed in these data could
be a chance finding. The numbers are small and
accordingly, the risk estimates lack precision. It is not
likely to be the result of systematic reporting bias. The
diagnosis and reporting of birth defects in medical
records and to the NYS Congenital Malformations
Registry is not expected to be different based on
maternal sport-fish-eating habits. If mothers of children
with birth defects differentially reported sport fish
consumption, it would be unlikely for that tendency to
vary by infant sex.

Effect modification is biologically plausible to the extent
that male fetuses may be differentially affected by
perturbations of the hormonal milieu. While maternal
hormone levels mediate fetal growth and development
for both male and female offspring, fetal androgens are
critical for some aspects of normal male development,
particularly for the urogenital system. Since this
hormone effect would not be expected to impact all
fetal development uniformly (i.e., grouping major
malformations is likely to be a crude indicator of risk),
we built on the assumption that contaminated sport fish
meals have potentially endocrine-disrupting compounds
and inspected the prevalence of infants with hypospa-
dias in relation to sport fish consumption. The etiology
of hypospadias is multifactorial and environmental
exposures to substances that block androgens have been
suggested as potential risks (Baskin et al., 2001). There
was some suggestion in our data that the prevalence was
higher among boys whose mothers consumed sport fish
meals, but the number of cases was too small to make
any definitive statements.

Our data have many limitations. Most importantly,
the original study was not designed to examine birth
defect risk and there is insufficient power to analyze
either specific birth defects or organ system defects. The
Metropolitan Atlanta Congenital Defects Program
exclusion list for minor anomalies was applied to
increase the likelihood that only more uniformly
identifiable conditions were included in the analysis.

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The underlying assumption was that major defects are more likely to be associated with first-trimester exposure and that they would be more consistently reported. On the other hand, common urogenital anomalies such as cryptorchidism, which might be associated with endocrine disruptor exposure, are excluded from the analysis using this strategy. We also have no information on spontaneous losses or elective terminations during the study time period. This limits the analysis to infants with major defects who survived to birth and they may not represent the population of affected infants in utero.

Another limitation is the proxy measure of exposure (sport fish meals), which represents a complex mixture of contaminants. While the New York State Angler Cohort study has a rich dataset including species of fish, specific body of water, and portion size for general exposure assessment, the question on meals eaten during pregnancy is relatively nonspecific. Some New York State waters have very low levels of contamination and toxicant levels found in sport-caught fish meals vary greatly. We found the strongest risk for meals eaten during pregnancy even though the source of the fish was not specific. Specific fish meal information from Lake Ontario, the most contaminated of the Great Lakes, revealed similar effect modification by infant sex but the risk estimates were lower. From these data, it appears that the acute dose associated with pregnancy meals is important, but a chronic body burden effect cannot be ruled out.

On the other hand, these data are derived from a population-based cohort with relevant levels of exposure to observe potential adverse health effects. We have two detailed sources of case ascertainment, an extensive newborn medical record review and state-mandated registry reports. With regard to acute exposure, mothers in the highest risk group ate an average of two or more sport fish meals per month, making it very likely that some meals were eaten during critical windows of organogenesis in the first eight weeks of pregnancy. Most notably, the primary finding of effect modification by infant sex is unlikely to be influenced by the study limitations.

Birth defect risk associated with sport fish consumption was consistently higher for male offspring and no increased risk was observed for females in these data. Future studies of birth outcomes associated with endocrine-disrupting compounds should consider potential effect modification by infant sex.

Acknowledgments

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References


