Fetal Risks of Environmental Chemicals: The Motherisk Approach to the Organic Mercury Fish Consumption Scare

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While fish is rich in essential nutrients and women are encouraged to consume fish products, fish may contain methylmercury, which is an established neurotoxin to the fetus. Not surprisingly, there are high levels of anxiety among women of reproductive age regarding fish consumption. To be able to counsel women in this complex area, we have developed a two-step program: (1) probing women of reproductive age for their perceptions regarding the safety of consuming fish, and (2) piloting an intervention program with women of reproductive age to ensure mercury levels are below the recently proposed Lowest Observable Adverse Effect Level. This method may be used as a template to improve the understanding of clinicians, legal experts, and policy makers on the fetal risk-benefit ratio of environmental chemicals.

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INTRODUCTION

Women of reproductive age are commonly advised to consume fish because it is rich in essential nutrients such as high quality protein and omega-3 polyunsaturated fatty acids. These nutrients are essential for the perinatal growth of the developing brain.[1] Health authorities recommend that women of reproductive age consume at least two Food Guide Servings (two servings of seventy-five grams each) of fish each week during pregnancy.[2]

A major drawback of fish consumption is that some species of fish contain methylmercury in sufficient amounts to cause adverse neurodevelopmental effects.[3] Organic methylmercury is formed from inorganic mercury by the action of anaerobic organisms that live in aquatic environments.[4] It is difficult for fish to eliminate the heavy metal from their bodies, and this allows methylmercury to bioaccumulate in predatory fish.[5] Dietary fish consumption is the major source of human methylmercury exposure.[6] Of greatest concern are the predatory fish that contain the highest levels of methylmercury.[7] Individuals who consume

1. Sheila M. Innis, *Dietary Omega 3 Fatty Acids and the Developing Brain*, 1237 BRAIN RES. 35, 35–43 (2008).

2. U.S. FOOD & DRUG ADMIN., WHAT YOU NEED TO KNOW ABOUT MERCURY IN FISH AND SHELLFISH (2004).

3. Ping Li et al., *Methylmercury Exposure and Health Effects from Rice and Fish Consumption: A Review*, 7 INT'L J. ENVTL. RES. PUB. HEALTH 2666, 2666–91 (2010).

4. *Id.*

5. Thomas W. Clarkson & Lazlo Magos, *The Toxicology of Mercury and Its Chemical Compounds*, 36 CRITICAL REV. TOXICOLOGY 609, 609–62 (2006).

6. Thomas Clarkson et al., *The Toxicology of Mercury—Current Exposures and Clinical Manifestations*, 349 NEW ENG. J. MED. 1731, 1731–37 (2003).

7. Gary J. Myers et al., *Nutrient and Methyl Mercury Exposure from Consuming Fish*, 137 J. NUTRITION 2805, 2805–08 (2007).

fish on a regular basis, especially large predatory fish, can achieve a hair methylmercury level of ten μg/g,[8] a threshold toxicological level defined by Thomas Clarkson and his colleagues as being associated with adverse fetal effects.[9]

The fetus is significantly more sensitive to the adverse effects of methylmercury than the mother; therefore, exposure is a source of major concern for pregnant women.[10] Methylmercury crosses the placenta and is found at higher concentrations in fetal blood than in the mother's blood.[11] Two epidemics in Japan and Iraq in which large numbers of people were affected by methylmercury demonstrated that methylmercury poisonings can cause severe neurodevelopment effects to the fetus.[12] Presently, general concern is focused on more subtle effects that occur at much lower concentrations of methylmercury consumed by heavy fish-eating populations.[13]

In 2004, the U.S. Environmental Protection Agency and Food and Drug Administration issued a joint warning for women of reproductive age, pregnant women, nursing mothers, and young children to limit their fish intake to twelve ounces per week due to potential mercury contamination in the fish.[14] Following this advisory, it was reported that women were eating less than the recommended amount of fish out of fear of harming their babies.[15] This study concluded that a broadly disseminated health advisory may substantially change dietary behavior among pregnant women.[16]

There has been broad media coverage on the topic, presenting contradictory information regarding the benefits and risks of fish consumption.[17] Contradictory information can lead to confusion in the

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8. ALTA. HEALTH & WELLNESS, GOV'T OF ALTA., HUMAN HEALTH RISK ASSESSMENT: MERCURY IN FISH IN THE PINE COULEE AND TWIN VALLEY RESERVOIRS 18–19 (2009).

9. Clarkson et al., *supra* note 6, at 1731–37.

10. MARTHA H. KEATING, U.S. ENVTL. PROT. AGENCY, MERCURY STUDY REPORT TO CONGRESS—VOL. II: AN INVENTORY OF ANTHROPOGENIC MERCURY EMISSIONS IN THE UNITED STATES (1997).

11. Joëlle Morrissette et al., *Temporal Variation of Blood and Hair Mercury Levels in Pregnancy in Relation to Fish Consumption History in a Population Living Along the St. Lawrence River*, 95 ENVTL. RES. 363, 363–74 (2004).

12. Laman Amin-Zaki et al., *Intra-Uterine Methylmercury Poisoning in Iraq*, 54 PEDIATRICS 587, 587–95 (1974); Masazumi Harada, *Minamata Disease: Methylmercury Poisoning in Japan Caused by Environmental Pollution*, 25 CRITICAL REV. TOXICOLOGY 1, 1–24 (1995).

13. Anne Spurgeon, *Prenatal Methylmercury Exposure and Developmental Outcomes: Review of the Evidence and Discussion of Future Direction*, 114 ENVTL. HEALTH PERSP. 307, 307–12 (2006).

14. Emily Oken et al., *Decline in Fish Consumption Among Pregnant Women After a National Mercury Advisory*, 102 OBSTETRICS GYNECOLOGY 346, 346–351 (2003).

15. *Id.*

16. *Id.*

17. Jennifer E. Vardeman & Linda Aldoory, *A Qualitative Study of How Women Make Meaning of Contradictory Media Messages About the Risks of Eating Fish*, 23 HEALTH COMMC'N 282, 282–91 (2008).

public that includes skepticism about the media source, anxiety, and stress.[18] In a recent systematic review of thirty longitudinal and eighteen cross-sectional studies, we defined the Lowest Observable Adverse Effect Level ("LOAEL") of maternal hair mercury at 0.3 μg/g of hair. This is the level above which adverse neurocognitive effects have been reported in some but not all studies reviewed.[19] The No Observable Adverse Effect Level ("NOAEL") was defined as 0.5 μg/g based on all the longitudinal studies conducted in the systematic review, where no adverse neurodevelopment effect had been detected at this level of maternal hair mercury concentration.[20] This means that when levels are above this mark, certain studies began to detect adverse cognitive effects in the offspring.

The objective of this Article is to describe how we utilized these scientific findings to improve the care of pregnant women by allowing mothers to consume fish while protecting fetuses from potentially adverse cognitive effects.

I. METHODS

A. MEASURING WOMEN'S RISK PERCEPTION

Upon approval by the Research Ethics Committee at the Hospital for Sick Children in Toronto, Canadian women who had been counseled by the Motherisk Program between January 2006 and 2007 about the reproductive safety of consuming fish during pregnancy were identified. The Motherisk Program provides information and counseling services that assess maternal and fetal risks following exposure to medications, recreational drugs, and various environmental chemicals during pregnancy and lactation. Potential subjects for our study were identified using a prospectively collected database. Women were excluded if they refused verbal informed consent, could not be reached by telephone, had insufficient English to answer the questions or communicate over the phone, confirmed that they did not call about mercury in fish, or had other mercury exposures (for example, occupational exposure).

Once the study was fully explained, verbal consent was obtained from the women before the start of the telephone interview. The interview consisted of a semi-structured questionnaire to assess the women's fish consumption habits and their perceptions of risk. Women were queried about their perceptions about eating fish during pregnancy using five open-ended questions that allowed participants to introduce

18. *Id*.

19. Katherine Schoeman et al., *Defining a Lowest Observable Adverse Effect Hair Concentrations of Mercury for Neurodevelopmental Effects of Prenatal Methylmercury Exposure Through Maternal Fish Consumption: A Systematic Review*, 31 THERAPEUTIC DRUG MONITOR 670, 670–82 (2009).

20. *Id*.

other issues and concerns. Women were questioned about their general knowledge of mercury toxicity and what provoked them to initially call the Motherisk Program for information on consuming fish during pregnancy. They were then asked about how they became aware of the mercury issue and the potentially negative health implications of consuming fish for their unborn child. They were also queried about their ideas regarding the health benefits of eating fish. On a scale from zero to ten, the women were asked how worried they were about consuming fish during pregnancy, with zero being the least worried and ten being the most worried. Comments and the discussion of ideas and concerns regarding fish consumption were encouraged. We subsequently collected hair samples from 22% of the women who completed the questionnaire.

B. Intervention Pilot

Hair samples were collected from twenty women of reproductive age who had called the Motherisk program between June 2009 and October 2009. Women exhibiting hair mercury levels above the NOAEL of 0.5 µg/g were invited to participate in a program aiming at decreasing their body load of methylmercury (n=6). After a detailed interview regarding their typical diet, they were offered diet modifications to reduce their mercury body burden (n=5). Hair mercury determinations were repeated after at least six months with the new diet and were then compared to baseline levels.

Each individual was given a specific dietary plan based on her mercury content and fish consumption habits. For the purpose of assessment, it was assumed that 100% of total mercury in an individual is in the form of methylmercury. Probable Daily Intake ("PDI") of methylmercury was calculated for each woman according to the following formula, where PDI is given in micrograms per kilogram of body weight ("bw") per day:

$$\text{PDI} = \frac{\text{Fish muscle intake } \left(\frac{\text{g}}{\text{day}}\right) \times \left[\text{methylmercury concentration } \left(\mu\frac{\text{g}}{\text{g}}\right)\right]}{\text{Average body weight (kg)}}.$$

The methylmercury concentration for each fish species was based on the summary data for fish that were found by the Canadian Food Inspection Agency to contain, on average, approximately 0.2 ppm or less total mercury. In 2003, the Joint World Health Organization and Food and Agriculture Organization of the United Nations Expert Committee on Food Additives recommended a provisional tolerable weekly intake for methylmercury of 1.6 µg/kg bw/week, equivalent to 0.23 µg

methylmercury/kg bw/day.[21] The women with PDI levels higher than the provisional tolerable daily intake were to reduce their intake of either fish with higher methylmercury content—or the fish that the individual consumed the most—in order to reach the recommended provisional tolerable weekly intake.

C. Hair Mercury Analysis

Mercury analysis of all collected hair samples was conducted at the London Health Sciences Centre Trace Elements Laboratory in London, Ontario. Hair samples were analyzed by the High Resolution Inductively Coupled Plasma Mass Spectrometer.

II. Results

A. Women's Risk Perception

All callers who were counseled about mercury in fish during pregnancy by the Motherisk Program between January 2006 and January 2007 were identified (n=253), and consenting mothers who were accessible by telephone were contacted (n=100). The demographics of the sample are presented in Table I.

There were multiple reasons that provoked these women to call the Motherisk program for guidance. Some aspects of mercury toxicity were well understood by respondents while others were poorly understood. Specifically, the majority of women were aware that eating fish high in mercury content during their pregnancy could be harmful to their babies (n=90). Some concerned women were also aware that fish is a healthy food choice and thus wanted to include it in their diets (n=40). These women called for a definitive answer on how much seafood was safe to eat during pregnancy as well as the safe types of seafood. One quarter of the women were prompted to call for information after hearing about the issue through media sources or reading material that led them to question their regular eating habits. Some women called for clarity on the issue, as the information given to them seemed to be controversial (n=9). These women mentioned that there were two schools of thought regarding eating fish during pregnancy. Some women had heard about the mercury issue through family or friends, making them more nervous and prompting them to call to clarify (n=17). In a minority of cases their physicians had recommended the Motherisk program if they still had questions about the safety of consuming seafood (n=5). Two women were going on a vacation to the Caribbean and wanted to know what fish

21. World Health Org., Joint FAO/WHO Expert Commission on Food Additives, Sixty-First Meeting: Summary and Conclusions 9 (2003).

was safe to eat. One woman called out of general interest as she had heard about PCBs (polychlorinated biphenyl) and pesticides.

Half of the participants stated that they initially became aware of the issue of mercury in fish through electronic and printed media (Figure 1) and almost all had called for clarity after what they had heard from these sources. Those who had searched the Internet found a vast amount of information, some of which was described by them as dramatic and overstated (n=13). After reading the controversial and varied opinions, they wanted clarity. Fifteen percent learned about the mercury issue through prenatal books, and three of these women said that it was specifically reading the book *What to Expect When You're Expecting* that informed them of the issue.[22] Another three women stated that it was just a well-known fact that harmful levels of mercury exist in fish (Figure 1).

Most respondents were unable to describe specific toxic effects of mercury (n=66), while 21% stated that mercury could cause neurological problems or affect brain development. Most of these sixty-six individuals went on to describe why they chose to avoid fish even without ever knowing the toxic consequences. Some answered that knowing mercury was potentially harmful for their babies was sufficient for them to be scared (n=16). Some said that methylmercury was a toxin that could be "detrimental to their babies' health" (n=7). Some could recall the warnings to avoid fish but not the consequences (n=3). Some stated that mercury could cause malformations, deformities, birth defects, or abnormalities (n=12). Some women believed mercury exposure produced autism (n=7). Two women cited issues of development and memory.

While most women did not know the harmful effects of mercury, most were able to quote benefits of eating fish during pregnancy (n=89). Forty-six of them enumerated omega-3 polyunsaturated fatty acids ("n-3 PUFAs") as the source of the health benefits, and some of them mentioned that these were good for brain development. Some stated that fish was a good source of protein, nutrients, and a lean form of meat (n=9). A few women mentioned that they ate salmon specifically because it had high n-3 PUFAs content (n=5), while some stated that they obtained the recommended amount from other sources such as fish oil, or supplements during and after pregnancy (n=5). Ten women stated that, due to the known health benefits, they were consuming fish despite the mercury controversy or despite its taste. Three women mentioned that although they were aware of the benefits, the potential harm outweighed the benefits.

22. HEIDI MURKOFF, WHAT TO EXPECT WHEN YOU'RE EXPECTING (2009).

When asked to rate their level of anxiety regarding eating fish on a scale from zero to ten, the majority of women ranked themselves at five (Figure 2). Sixteen percent of the women were "most worried" compared to only 1% that were not worried at all. Those who ranked themselves a ten (most worried) mentioned that they completely avoided eating fish (n=7). Forty-seven women went on to justify their ranking further. Interestingly, women who were not concerned (those who ranked themselves below five) mentioned that they minimized their risk by avoiding seafood completely during their pregnancy (n=12). Some stated that they ranked themselves below five because they had called the Motherisk program and were aware of the safe types of fish to consume and what to avoid (n=4), while one woman stopped eating fish entirely after calling the Motherisk program. Three women were worried about the consumption of tuna and other large types of fish.

B. Intervention Pilot

Five women of reproductive age who had hair mercury levels above the LOAEL of 0.5 μg/g in the initial sample (n=20) agreed to participate in a pilot program. They were counseled on how to decrease nutrition rich in methylmercury, after which hair mercury measurements were repeated. In all five cases there was a decrease upon repeated hair mercury measurements that ranged from 28.5% to 82% ($P<0.01$) (Table II).

III. Discussion

Over the last thirty-five years, research has demonstrated mixed results about the effects of prenatal methylmercury exposure on child development.[23] While some studies have shown adverse effects, others show positive developmental outcomes.[24] However, important differences in study design and sample characteristics may have contributed to these discrepancies. Regulatory bodies have performed benchmark dose analysis on a number of endpoints from three longitudinal prospective studies.[25]

Overall, the results from these studies suggest that maternal mercury exposure through the consumption of fish during pregnancy is associated with adverse effects on brain function and thus is associated with detectable neuropsychological deficits.[26] Both longitudinal and cross-sectional studies reported the LOAEL of hair mercury associated with an adverse neurodevelopmental effect as 0.5 μg/g. One must acknowledge, however, that comparisons across studies are limited by

23. Schoeman et al., *supra* note 19, at 670–82.
24. *Id.*
25. *Id.*
26. *Id.*

the heterogeneity of the studies, designs across these longitudinal and cross-sectional studies and the methods of accessing exposure, neurologic tests administered, age at testing, sources of exposure, and statistical analyses all possibly adding to variations in the results.

However, to ensure the health and development of babies all around the world, it is most reasonable to use the *precautionary principle* and set the LOAEL on the lowest level of maternal hair mercury associated with measurable adverse outcome. Importantly, this LOAEL of 0.5 μg/g is in the range shown in different populations of women of reproductive age around the globe, highlighting the importance of therapeutic drug monitoring of mercury in these populations rather than recommending that women avoid eating fish completely.[27] In the present study, the response of Canadian women who were sufficiently concerned about fish consumption to call a consultation service, demonstrates heightened perception of teratogenic risk. We have recently completed a systematic review on the effects of methylmercury on the human fetus caused by in utero exposure through fish consumption in an attempt to define a LOAEL causing these effects.[28] Both longitudinal and cross-sectional studies reported varying effects. We defined our LOAEL at 0.5 μg/g of mercury in maternal hair, but there is considerable uncertainty with this estimation.

Importantly, the results of the hair analysis of the twenty-two women in the risk perception study showed that 64% of these women were above our LOAEL of 0.5 μg/g, with the mean mercury content of this cohort being at 0.5 μg/g. Overall, these twenty-two women consumed a median number of four fish servings per month.[29] A correlation was found between their hair mercury content, the number of fish servings they consumed, and also their estimated intake dose of mercury.[30]

Our participating women were a self-selected group of concerned mothers-to-be who had shown an initial concern regarding the safety of consuming fish and other seafood products during pregnancy. Their level of fish consumption was significantly higher than a comparison group of women who did not call Motherisk.[31] Therefore the results obtained are risk perceptions of women of reproductive age that are concerned about consuming fish. Most of our participants in this study were confused over what was safe for their babies, as they had often been presented with contradictory information and called the Motherisk program for

27. *Id.*

28. *Id.*

29. Katherine Schoeman et al., *Hair Mercury Levels of Women of Reproductive Age in Ontario, Canada: Implications to Fetal Safety and Fish Consumption*, 157 J. PEDIATRICS 127, 127–31 (2010).

30. *Id.*

31. *Id.*

clarification. Many women were conflicted about trying to balance the benefits of fish consumption with the risks of exposure to methylmercury. It was evident from these results that even participants who were not concerned said that they had minimized their risk by avoiding fish all together. Our data indicated that the heightened risk perception exhibited in this group is justified based on their measured hair mercury, the most valid biological marker of long-term exposure to this toxic metal.[32]

Measuring methylmercury content by hair analysis is non-invasive and estimates mercury exposures over time. More than 80% of hair mercury is in the form of methylmercury.[33] Blood and toenail mercury are also good indictors of mercury content.[34] However, blood samples reflect mercury concentrations of a single point in time and hair grows at a much quicker rate than toenails. Hair grows approximately one centimeter per month, thus providing a better window into exposure over a long period of time.[35]

Our pilot intervention study shows that the modification of fish consumption among women exhibiting hair mercury levels above the LOAEL is an effective means for decreasing body mercury burden to levels that are safer for the unborn baby. This personalized approach is more accurate than general population guidelines and may be suitable for select groups of women consuming large amounts of seafood. We believe that this biomonitoring study was the first of its kind, and the main goal was to indicate that diet modifications in women of reproductive age that are at risk could decrease their mercury levels before fetal exposure.

CONCLUSION

Women who are of childbearing age, pregnant, or breastfeeding should avoid eating large, top-of-the-food-web predatory fish with high levels of methylmercury in order to avoid potential harmful effects on their babies. However, it is not wise to entirely remove fish from one's diets. Safety information on low levels of methylmercury needs to be addressed for management of a healthy diet in women of reproductive age. Health professionals can help women better understand the role fish plays in a healthy pregnancy. Given the large variability in the correlation between mercury intake and maternal hair levels,[36] therapeutic monitoring using personal hair analysis and the development

32. *Id.*
33. *Id.*
34. Li et al., *supra* note 3, at 2666–91.
35. Clarkson & Magos, *supra* note 5, at 609–62.
36. Schoeman et al., *supra* note 29, at 127–31.

of precise individual dietary guidelines should be considered as a novel public health measure for women of reproductive age.

Women with hair mercury levels above 0.5 ug/g are at risk of having a baby with attenuated neurodevelopment.[37] By calculating their PDI according to their fish diet (type and number of fish servings per week), the main source of methylmercury exposure from fish consumption can be identified. Depending on the preference of the individual, the amount of certain types of fish can be eliminated, reduced, or substituted to reach appropriate mercury levels to both benefit and avoid the adverse effect of consuming fish.

In this study, the amount of fish with higher mercury content was reduced in women's diets. The hair mercury content of the individual can be reanalyzed after diet adjustments to ensure that the mercury contents have decreased. This biomonitoring procedure has many advantages. First, the procedure of hair collection is non-invasive and also less costly than other techniques. Second, it is very specific for each individual, and this will allow individuals to choose to either change the type or amount of certain preferred fish to lower their mercury content. Last, modification of diet to decrease methylmercury body burdens can be effectively monitored by analyzing the mercury content of hair. However, there are some limitations. Since hair grows approximately one centimeter per month, at least three to four months are required in order to reanalyze the hair mercury concentrations.[38] Also, based on the individual's report on the amount and type of fish consumed, only an estimation of her mercury intake from certain fish can be determined.

The present paper describes a stepwise approach that can be used in the investigation of other fetal toxins. It starts with a systematic review of all available evidence needed to define the risk and the biological markers that can estimate that risk. It then defines the threshold of exposure that will likely lead to fetal damage. Typically, there is a wide range of risk thresholds among studies. We adopted the precautionary principle, which dictates selection of the lowest risk level presented. The next step is to use the biological marker in a given population and define that population's risk. The last and most meaningful step is then to mitigate the risk and prevent fetal damage by decreasing maternal exposure to the culprit toxin. Lastly, it is critical to study women's knowledge and perceptions regarding potential fetal risk and risk prevention on this and other subjects. This is crucial for the effective uptake and translation of relevant information.

37. Schoeman et al., *supra* note 19, at 670–82.

38. Li et al., *supra* note 3, at 2666–91.

TABLE 1: CHARACTERISTICS OF STUDY PARTICIPANTS

Variable	**Mean (SD)**
Age (yrs)	34.7 (4.6)
Parity (offspring)	1.4 (0.7)
Dental amalgams	55
Smoked during pregnancy	1

TABLE 2: COMPARISON OF HAIR MERCURY CONTENT BEFORE AND AFTER DIETARY PLAN

Subject Code	**Hair mercury (µg/g) before dietary plan**	**Hair mercury (µg/g) after dietary plan**	**Decrease after dietary plan**
1	1.62	0.68	58%
2	0.67	0.12	82%
3	0.50	0.21	58%
4	0.57	0.41	28.5%
5	0.56	0.24	57%
Mean± STD	0.78± 0.46	0.33± 0.22	56.7%±18.97

FIGURE 1: VARIOUS SOURCES OF INFORMATION ON MERCURY

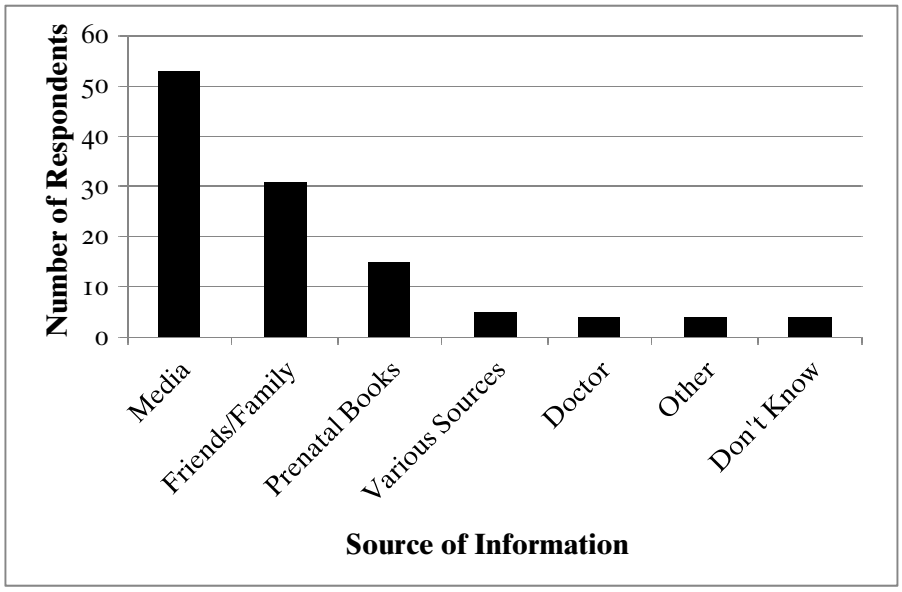

FIGURE 2: ESTIMATION OF THE LEVEL OF CONCERN IN WOMEN TOWARDS MERCURY EXPOSURE THROUGH FISH CONSUMPTION