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Nutrient and Methyl Mercury Exposure from Consuming Fish[1,2]

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Abstract

There is controversy about the risks and benefits of consuming fish. Fish consumption provides nutrients, some of which are essential for brain growth and development. All fish, however, contain methyl mercury (MeHg), a known neurotoxicant. The toxic effect of MeHg seems most damaging during brain development, and thus, prenatal exposure is of greatest concern. At present the level of prenatal exposure associated with risk to a child's neurodevelopment is not known. Balancing the rewards and possible risks of fish consumption presents a dilemma to consumers and regulatory authorities. We review the nutrients in fish that are important in brain development and the current evidence of risk from MeHg at exposure levels achieved by consuming fish. We then review the findings from a large prospective cohort study of a population that consumes fish daily, the Seychelles Child Development Study. The MeHg content of the fish consumed in the Seychelles is similar to that of ocean fish available in industrialized countries, so they represent a sentinel population for any risk from fish consumption. In the Seychelles, evaluations of the children through 9 y of age show no consistent pattern of adverse associations with prenatal MeHg exposure. Recent studies in the Seychelles have focused on nutrients in fish that might influence a child's development, including long-chain polyunsaturated fatty acids, iodine, iron, and choline. Preliminary findings from this study suggest that the beneficial influence of nutrients from fish may counter any adverse effects of MeHg on the developing nervous system. J. Nutr. 137: 2805–2808, 2007.

Introduction

Fish is an important component of diets around the world. An estimated 1 billion people rely on fish as their main source of animal protein (1). Fish meal is also widely used to feed animals including poultry (2), which in turn are consumed by humans. Fish and seafood consumption varies widely by country. The United States has a relatively low consumption, averaging 22 kg per person per year (2). Other countries such as Japan and the Seychelles Islands have much higher consumption rates, at 72 and 62 kg, respectively. Many of those relying on fish for nutrition are in developing countries where fish is also a major source of energy, trace elements, and other nutrients.

Fish contain nutrients, such as long-chain polyunsaturated fatty acids (LCPUFA)[7] that are known to be essential for development of the brain and retina (3). In addition, all fish contain methyl mercury (MeHg), a known neurotoxicant in sufficient dosage (4). Consumption of MeHg-contaminated fish in Japan during the 1950s and 1960s led to severe neurological disease including mental retardation, microcephaly, and seizures (5,6). Poisoning from fish consumption has not been reported since those 2 events. However, epidemiology studies examining populations exposed to MeHg from consumption of fish and other seafood have suggested that there might be a risk to the developing fetus from MeHg. These studies are complex and open to varied interpretations. Consequently, there is controversy about whether they are valid and, if they are, at what level of MeHg exposure neurotoxicity manifests in subtle developmental deficits. This uncertainty presents a problem for authorities responsible for public health, especially in developing countries where options for nutrition are often more limited than in Western countries. Should fish consumption be encouraged for its nutritional benefits to the developing brain and adult cardiac function, or should fish be discouraged for the possible adverse effects of MeHg on the developing central nervous system (CNS)? This article reviews some of the issues and evidence regarding this controversy.

Nutrients in fish and seafood

The nutrients present in fish include LCPUFA, iodine, iron, choline, selenium, and trace elements (7,8). The LCPUFA species of special concern are those of the (n-3) and (n-6) classes.

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[7] Abbreviations used: AA, arachadonic acid; CNS, central nervous system; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; LCPUFA, long-chain polyunsaturated fatty acid; MeHg, methyl mercury; PCB, polychlorinated biphenyl.

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Eicosopentaenoic acid (EPA) and docosohexaenoic acid (DHA) are the primary (n-3) LCPUFA of concern. Both DHA and EPA can be synthesized in vivo in varying amounts from their precursor, α-linolenic acid. DHA is incorporated into neural tissue and is critical for development of the brain and retina (31). The (n-6) LCPUFA of interest is arachidonic acid (AA), which can be synthesized from its precursor, linoleic acid. Both AA and EPA are the precursors of a family of bioactive compounds called eicosanoids. Elongation and desaturation of (n-3) and (n-6) fatty acids use the same enzymes in the body, so their relative status can affect their metabolism (3). The human body is relatively inefficient at synthesizing EPA and DHA compared with AA, and often adequate amounts of these (n-3) LCPUFA need to be supplied preformed in the diet. Breast milk contains ~50% of its energy as fat and is especially rich in DHA (9). Most of the LCPUFA the fetus obtains from the mother cross the placenta during the last trimester.

Mercury in fish and seafood

All fish contain some mercury in their flesh, and nearly all of it is organic MeHg (10). The amount of MeHg present in fish varies widely and depends on the dietary habits and age of the fish. Larger predatory fish such as shark, marlin, and swordfish generally contain higher levels of MeHg, but most fish have MeHg levels lower than 0.5 μg/g. There is some evidence that the concentration of MeHg present in ocean fish has not changed over the past 90 y despite increasing anthropogenic release of Hg into the environment (11). Individuals who consume fish, especially large predatory fish, on a regular basis can easily achieve a hair Hg level of 10 μg/g (12).

Mercury toxicity

All forms of mercury are toxic, and MeHg is neurotoxic. MeHg in sufficient exposure causes damage to the CNS and can lead to death (13). Several lines of evidence indicate that the developing CNS is especially sensitive to its effects (14). In the 1950s and 1960s there were 2 outbreaks of MeHg poisoning related to fish consumption in Japan (6). Both outbreaks resulted from massive pollution of local fishing waters by industrial waste from local factories. Levels of mercury in local fish were as high as 50 μg/g. That level is some 100 times higher than is present in most oceanic fish commercially available today. The most widely known event occurred at Minamata and led to the term Minamata disease (MD) becoming synonymous with MeHg poisoning. During the Minamata outbreak, it was realized that prenatal exposure could seriously damage the developing nervous system and lead to congenital or fetal MD (5). Only a small number of congenital MD cases were described, and the exposure data from Minamata and Niigata were very limited (5,15). However, it raised concerns that small amounts of exposure might adversely affect the developing CNS.

During a subsequent epidemic of MeHg poisoning in Iraq in the winter of 1971–1972, this issue was investigated in more detail (16). Mothers who were pregnant during the epidemic were identified, and their mercury levels during pregnancy determined by analysis of their hair. Their children were then evaluated neurologically during the first few years of life. In 1989, Cox et al. reported this study (17). They found a dose-response curve based on neurological findings and the children's milestones that suggested that MeHg exposure levels as low as 10 μg/g, as measured in maternal hair growing during pregnancy, might be associated with damage to the developing CNS. It was known that MeHg levels can reach 10 μg/g or higher in individuals who consume fish regularly (12). The mean exposure in some island communities ranges from 2 to 6 μg/g (18–20).

The findings from Minamata and Iraq raised concern among public health authorities that low-level MeHg exposure from fish consumption might present a subtle risk to the fetal CNS. However, both episodes were poisonings, and the exposures were substantial. In contrast, fish consumption results in much lower exposures generally spread over a longer time period. How this exposure might influence development is not known.

Epidemiology studies of MeHg exposure from fish consumption

Several investigators have undertaken epidemiology studies to test the hypothesis that prenatal exposure to MeHg from fish consumption adversely affects children's neurodevelopment. These studies, which are still under way, have been carried out in populations exposed to MeHg from fish or seafood consumption. The investigators all hypothesized that if prenatal MeHg exposure at the levels seen from fish and seafood consumption caused adverse neurodevelopment, the findings would probably be subtle and apparent only as differences between groups of cohort subjects with higher and lower exposures. In addition, any consequences of MeHg exposure would need to be distinguished from the many other factors that are known to influence child development such as socioeconomic status, maternal IQ and age, etc. (21). Consequently, studies with small cohorts or that do not measure many of the factors that might have influenced the child's development are difficult to interpret.

However, 2 studies stand out as having careful designs, large cohorts, and adequate controls to address this issue. One is being conducted in the Republic of Seychelles (20), and the other in the Faeroe Islands (22). Both studies are examining the impact of MeHg exposure from seafood consumption in large cohorts, and each has examined its cohorts carefully over many years with sophisticated batteries of tests. Both populations consume large amounts of fish that contain amounts of MeHg similar to that of commercial fish available in the United States. Neither site has evidence of local sources of pollution. The mean MeHg exposure of mothers in the Faeroes cohort at enrollment was 4 μg/g (18), and that in the Seychelles main cohort analyzed at 66 mo was 5.9 μg/g (23).

The studies differ in several respects including the source of MeHg exposure. In the Faeroe Islands, the source of exposure is periodic consumption of pilot whale meat and blubber (18,22). The Faroese consume fish as well, but it is generally very low in Hg. In the Seychelles, marine mammals are not consumed, and the population's exposure to MeHg is only from fish consumption (24). This difference may be important because pilot whale contains up to 3 μg/g of mercury with half of it in the organic form of MeHg, whereas most fish contain $<$0.5 μg/g (25). In addition, pilot whale blubber contains polychlorinated biphenyls (PCB) and other environmental contaminants (25). Human exposure to PCB has been reported to affect children's development (26). Additionally, concomitant exposure to PCB and MeHg has been reported to increase the toxicity of each (27).

The Seychelles child development study

The Seychelles Child Development Study started in the mid-1980s and now includes several large cohorts of children whose mothers consumed fish frequently during their pregnancy. The main cohort was comprised of 779 mother-infant pairs recruited in 1989–1990 on the island of Máhe. The study objective was to determine whether prenatal MeHg exposure from fish consumption has adverse effects on the children's neurodevelopment. The Seychelles was selected because fish consumption in the islands was high, and indeed, the mothers who were enrolled

consumed a mean of 12 fish meals a week. The Seychelles also presented several advantages for an epidemiology study looking for subtle differences in developmental outcomes. These included being a Westernized developing nation; the initiation in about 1978 of a universal, readily accessible, and free system of health care and education; limited industrial development with no local sources of pollution; and low alcohol consumption among women (28).

Prenatal MeHg exposure was measured in maternal hair growing during pregnancy. The children were 6 mo of age at enrollment and were examined at that time and then had repeat evaluations at 19, 29, 66, and 107 mo of age using increasingly sophisticated batteries of psychological, motor, and developmental tests. Various covariates were measured for both the child (sex, birth weight, perinatal history, hearing level, and duration of breast-feeding) and the mother (age, IQ, medical history, and use of tobacco and alcohol), along with the family's socioeconomic status and their home environment. The association between the children's prenatal MeHg exposure and their developmental outcome was examined extensively in statistical models established a priori and confirmed in secondary statistical analyses.

Findings from the study have been extensively reported (20,23,24,29,30). The prenatal exposure of the main cohort evaluated at 9 y of age had a mean of 6.9 ± 4.5 μg/g (SEM). There were consistent associations present between developmental tests and covariates known to be associated with children's development. However, no consistent pattern of associations was present between prenatal MeHg exposure and the children's test scores. Through 107 mo of age, there were 4 statistically significant associations. Only 1 association, the grooved pegboard using the nondominant hand measured at 107 mo, was adverse. Two associations, the Preschool Language Scale total score at 66 mo and the Connor's Teacher Rating Scale at 107 mo, showed improvement in outcomes as Hg exposure increased. One association, the activity subscale on the Infant Behavior Rating Scale of the Bayley Scale of Infant Development at 29 mo, was difficult to classify. The activity of male subjects decreased as prenatal exposure increased. These results suggested that there might be unmeasured covariates that were either interacting with Hg or obscuring its effects. The most likely candidates seemed to be nutritional factors also present in fish.

A nutrition cohort was developed to explore the feasibility of a direct test of this hypothesis. In 2001, we enrolled a cohort of 300 mothers during trimester 1 of pregnancy. The objective was to determine whether nutrients were affecting the children's development and either obscuring or interfering with the influence of prenatal MeHg exposure. At enrollment and delivery we obtained hair and blood from the mothers for Hg analysis and cord blood from the infants. We measured a variety of nutritional factors in the mothers' blood that we thought might influence child development. These included (n-3) LCPUFA (specifically DHA, EPA, and α-linolenic acid), (n-6) LCPUFA (specifically AA and linoleic acid), iodine, iron, and selenium. The mothers completed a 4-d food diary during trimester 2. Following delivery, the children were evaluated at 5, 9, 22, and 30 mo of age using developmentally appropriate tests.

In this cohort, mothers consumed a mean of 1.3 fish meals daily, and there were no overt nutritional deficiencies. The prenatal MeHg exposure measured in maternal hair had a mean of 5.9 ± 3.7 μg/g (SEM). The results are still being analyzed, but initial data indicate that psychomotor developmental at 9 mo of age increased with increasing maternal serum (n-3) LCPUFA concentration and at 30 mo of age decreased with increasing maternal hair MeHg concentration. Our statistical modeling also suggested that (n-6) LCPUFA concentration may have attenuated the influence of (n-3) LCPUFA. The adverse associations with MeHg appeared only when the statistical models were adjusted for nutrient status, whereas the positive associations of developmental tests with (n-3) LCPUFA became much stronger when the models were adjusted for MeHg. In this population, the benefits of nutrients and the adverse effects of maternal exposure to MeHg from fish consumption during pregnancy may modify each other's effects on developmental outcomes in the children. These results suggest that it is critical to assess dietary nutrients as well as neurotoxic exposures in determining the risks and benefits of fish consumption.

Through 107 mo of age, the Seychelles study of prenatal exposure to MeHg from maternal fish consumption has found no consistent adverse developmental effects in the children. The mothers studied consumed fish a mean of 12 times per week and had hair Hg levels averaging 6.9 μg/g. The Seychelles study is ongoing and continues to evaluate the main and nutrition cohorts using increasingly sophisticated test methods. Preliminary data from the more recently recruited nutrition study are uncovering both benefits and risks of maternal fish consumption on subsequent neurodevelopment of the children. Given the known importance of prenatal nutrition to optimal infant development and the limited data linking prenatal MeHg exposure to adverse subtle developmental outcomes at the levels of exposure achieved by fish consumption, caution in limiting fish consumption would appear to be indicated.

Literature Cited

1. FAO (Food and Agriculture Organization of WHO). The state of the world fisheries and aquaculture. ftp://ftp.fao.org/docrep/fao/003/x8002e. Accessed 7/2/07.
2. Speedy AW. Animal source foods to improve micronutrient nutrition in developing countries: global production and consumption of animal foods. J Nutr. 2003;133:4048S–53S.
3. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. Am J Clin Nutr. 2006;83: Suppl:1467S–76S.
4. Clarkson TW, Magos L, Myers GJ. The toxicology of mercury – current exposures and clinical manifestations. N Engl J Med. 2003;349:1731–7.
5. Harada Y. Congenital (or fetal) Minamata disease. In: Study Group of Minamata Disease, eds. Minamata disease. Kumamoto: Kumamoto University; 1968. 93–118.
6. Tsubaki T, Takahashi H. Recent advances in Minamata disease studies: methylmercury poisoning in Minamata and Niigata, Japan. Tokyo: Kodansha; 1986.
7. Clarkson TW, Strain JJ. Nutritional factors may modify the toxic action of methyl mercury in fish-eating populations. J Nutr. 2003;133:1539S–43S.
8. Strain JJ, Bonham MP, Duffy EM, Wallace JMW, Robson PJ, Clarkson TW, Shamlaye C. Nutrition and neurodevelopment: the search for candidate nutrients in the Seychelles Child Development Nutrition Study. Seychelles Med Dental J. 2004;7:77–83.
9. Lawrence RA, Lawrence RM. Breastfeeding: a guide for the medical profession. Sixth Edition. Mosby: New York; 2005.
10. FDA (U. S. Food and Drug Administration). Mercury concentration in fish: FDA monitoring program (1990–2004). http://www.cfsan.fda.gov/~frf/sea-mehg.html. Accessed 7/2/07.
11. WHO (World Health Organization) International Programme on Chemical Safety. Environmental health criteria 101 methylmercury. Geneva: WHO; 1990.
12. Airey D. Mercury in human hair due to environment and diet: a review. Environ Health Perspect. 1983;52:303–16.
13. Choi BH, Lapham LW, Amin-Zaki L, Saleem T. Abnormal neuronal migration, deranged cerebral cortical organization and diffuse white

matter astrocytosis of human fetal brain: a major effect of methylmercury poisoning in utero. J Neuropathol Exp Neurol. 1978;37:719–33.
14. Burbacher TM, Rodier PM, Weiss B. Methylmercury developmental neurotoxicity: a comparison of effects in humans and animals. Neurotoxicol Teratol. 1990;12:191–202.
15. Saito H, Sekikawa T, Taguchi J, Shozawa T, Kinoshita Y, Matsumura K, Ynigihara K, Nikaido K, Urasaki S, et al. Prenatal and postnatal methyl mercury exposure in Niigata, Japan: adult outcomes. Seychelles Med Dental J. 2004;7:138–45.
16. Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, Al-Rawi NY, Tikriti S, Dhahir HI, Clarkson TW, et al. Methylmercury poisoning in Iraq. Science. 1973;181:230–41.
17. Cox C, Clarkson TW, Marsh DO, Amin-Zaki L, Tikriti S, Myers GJ. Dose-response analysis of infants prenatally exposed to methyl mercury: an application of a single compartment model to single-strand hair analysis. Environ Res. 1989;49:318–32.
18. Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R, Jorgensen PJ. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol. 1997;19:417–28.
19. Yasutake A, Matsumoto M, Yamaguchi M, Hachiya NO. Current hair mercury levels in Japanese: survey in five districts. Tohoku J Exp Med. 2003;199:161–9.
20. Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiarai E, Sloane-Reeves J, Wilding GE, Kost J, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet. 2003;361:1686–92.
21. Davidson PW, Myers GJ, Shamlaye C. Principles of studying low-level neurotoxic exposure in children: using the Seychelles Child Development Study of methyl mercury as a prototype. Seychelles Med Dental J. 2004;7:84–91.
22. Debes F, Budtz-Jorgensen E, Weihe P, White RF, Grandjean P. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. Neurotoxicol Teratol. 2006;28:363–75.
23. Davidson PW, Myers GJ, Cox C, Shamlaye C, Choisy O, Sloane-Reeves J, Cernichiari E, Marsh DO, Berlin M, et al. Longitudinal Neurodevelopmental Study of Seychellois Children following *in utero* exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months. Neurotoxicology. 1995;16:677–88.
24. Shamlaye CF, Marsh DO, Myers GJ, Cox C, Davidson PW, Choisy O, Cernichiari E, Choi A, Tanner MA, Clarkson TW. The Seychelles Child Development Study on neurodevelopmental outcomes in children following *in utero* exposure to methylmercury from a maternal fish diet: background and demographics. Neurotoxicology. 1995;16:597–612.
25. Julshamn K, Andersen A, Ringdal O, Morkore J. Trace elements intake in the Faroe Island I. Element levels in edible parts of pilot whales (Globicephalus Meleanus). Sci Total Environ. 1987;65:53–62.
26. Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med. 1996;335:783–9.
27. Risher JF, DeRosa CT, Murray HE, Jones DE. Joint PCB-methylmercury exposures and neurobehavioral outcomes. Hum Ecol Risk Assess. 2003;9:1003–10.
28. Shamlaye C, Shamlaye H, Brewer R. Health in Seychelles – an overview. Seychelles Med Dental J. 2004;7:13–20.
29. Davidson PW, Myers GJ, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, Cernichiari E, Needham L, Choi A, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. JAMA. 1998;280:701–7.
30. Myers GJ, Marsh DO, Davidson PW, Cox C, Shamlaye CF, Tanner MA, Choi A, Cernichiari E, Choisy O, Clarkson TW. Main neurodeveopmental study of Seychellois children following *in utero* exposure to methylmercury from a maternal fish diet: Outcome at six months. Neurotoxicology. 1995;16:653–64.
31. Diau GY, Hsieh AT, Sarkadi-Nagy EA, Wijendran V, Nathanielsz PW, Brenna JT. The influence of long chain polyunsaturate supplementation on docosahexaenoic acid and arachidonic acid in baboon neonate central nervous system. BMC Med. 2005;23:11.