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Developmental neurotoxicity: methylmercury and prenatal exposure protection in the context of the Minamata Convention

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ABSTRACT

Mercury *is a global pollutant of public environmental health concern due to its long-range atmospheric distribution, environmental distribution, and neurotoxic effects. Following biological methylation, methylmercury (MeHg) can be un-evenly bioaccumulated within aquatic food chains. Fish consumption can be a significant route of human exposure to MeHg. MeHg exposure in the prenatal stage, at relatively low levels, has recently been established as harmful during neurological development, potentially leading to intellectual disability. The Minamata Convention on Mercury is a global agreement, currently under ratification, to protect human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds. The resolution regarding the role of the World Health Organization and ministries of health in the implementation of the Convention includes protection of human health from critical exposures to MeHg. Riverside populations living in areas with artisanal small-scale gold mining, and relying heavily on fish consumption, have been identified as the most vulnerable population in terms of MeHg exposure and developmental neurotoxicity. This article focuses on the proper design and dissemination of fish advisories within the context of implementation of the Convention.*

Key words: mercury, toxicity; mercury poisoning; methylmercury compounds, toxicity; mercury poisoning, nervous system; environmental exposure; New Zealand; Seychelles; Latin America; Caribbean Region.

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MERCURY TOXICITY AS A PUBLIC ENVIRONMENTAL HEALTH CONCERN

Mercury is a global pollutant that is a public environmental health concern due to its long-range atmospheric distribution, environmental distribution, and neurotoxic effects. When distributed in the environment, mercury undergoes complex chemical and physical changes. A related process—biological methylation of inorganic mercury—occurs mostly in the aquatic environment. Methylmercury can easily bioaccumulate in food chains, and fish consumption can be a significant route of human exposure to methylmercury (MeHg) (1, 2).

MeHg exposure during the prenatal stage, at relatively low levels, has recently been established as harmful during neurological development, potentially leading to intellectual disability (3, 4). Critical prenatal exposure to MeHg through the consumption of fish and other food chain organisms by human populations relying heavily on these food chain resources has been declared a major public environmental health concern in recent reviews (5–7). On the other hand, the consumption of fish has many health benefits. Fish is major source of omega-3 fatty unsaturated acids, which are known to have a positive influence on gestation duration, with benefits for the newborn (8). According to some research, assessment of MeHg-related health risks of consuming fish must also consider the balance of omega-3 and omega-6 fatty unsaturated acids (9).

Major anthropogenic sources of atmospheric mercury emissions include coal burning, mining and smelting, cement production, and oil refining, among others. The release of mercury in these processes and from these products is mostly unintentional, as opposed to artisanal small-scale gold mining (ASGM), in which mercury is used intentionally for amalgamation with granulometric gold. Additional sources of atmospheric mercury emissions include deforestation, erosion, and volcanic eruptions. Mercury is also used in a large number of products, including batteries, electrical and electronic devices, thermometers, blood-pressure gauges, dental amalgam, fluorescent and energy-saving lamps, some antibacterial medicines, and cosmetics. Waste from these products and processes (especially incineration) often ends up in atmospheric, terrestrial, and aquatic ecosystems. Other industrial processes that involve mercury include those used 1) at chlor-alkali plants for the production of chlorine and caustic soda and 2) in the production of vinyl chloride. Recent estimates of global mercury atmospheric emissions for 2010 indicate that of the total output of almost 2 000 metric tons (t), 37% (727 t) was derived from

ASGM and 24% (474 t) was derived from coal burning (10). In Latin America and the Caribbean, the ASGM sector contributes 29% (208 t) to global atmospheric emissions (11).

The Minamata Convention on Mercury is a binding global agreement currently under ratification. The objective of the convention is "… to protect the human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds" (12). Given the significant neurotoxicity of some mercury forms and compounds, the Convention's ultimate goal is to prevent developmental neurotoxicity.

Health is directly addressed in one Convention article that calls for the identification and protection of populations at risk from exposure to mercury and mercury compounds, and the provision of health care services and professional training. For countries where ASGM has been identified as more than insignificant, the Convention requires national action plans to reduce or eliminate the use of mercury in gold amalgamation. Public health strategies are also required in the action plans. Other issues related to health are acknowledged in the Convention articles about information, education, and research. Additional recommendations related to health include the phaseout of the manufacture, import, and export of mercury-added products, such as thermometers, sphygmomanometers, and antiseptics and skin-lightening cosmetics with mercury (12). In support of the Convention's core goal of protecting human health, the 67th World Health Assembly (Geneva, 19–24 May 2014) adopted a resolution on "public health impacts of exposure to mercury and mercury compounds: the role of WHO and ministries of public health in the implementation of the Minamata Convention" (13).

PRENATAL METHYLMERCURY EXPOSURE AND INTELLECTUAL DISABILITY

The high susceptibility of the developing brain to MeHg damage compared to the mature brain can be explained by the fact that MeHg affects three processes unique to the developing brain: cell proliferation, differentiation, and migration. These effects disturb the brain cytoarchitecture. Mitotic arrest due to the prevention of the mitotic spindle apparatus formation is the most significant feature of MeHg toxicity. Other effects of MeHg toxicity include enzymatic disruptions, which can lead to metabolic disturbance that result in neuronal death and disruption of myelination, and changes in synaptic formations and neurotransmitters, which can alter the functioning of neuronal circuits. In the developing central nervous system, MeHg toxicity can cause neurological disorders, including cerebral and cerebellar atrophy with widespread neuronal degeneration, cell loss, and gliosis (14, 15).

Prenatal exposure to MeHg has been associated with impairment in central nervous system development, resulting in intellectual disability, as indicated by several studies that conducted neurobehavioral assessments after MeHg prenatal exposure (8). Hair is the best biomarker of MeHg exposure because it contains sulfhydryl groups for which MeHg cations have high affinity. MeHg can bind to hair strands during hair formation in proportion to the MeHg concentration in blood (1, 2).

Epidemiological studies on MeHg have been conducted among populations with heavy fish consumption in the Faroe Islands, New Zealand, and the Seychelles (as summarized in (8)). Different series of neurobehavioral tests were applied among children of various ages to compare the effects of maternal MeHg exposure during pregnancy. Neurobehavioral outcomes most often studied include cognitive; language; motor (finger tapping, hand–eye coordination); adaptive behavior; and socio-emotional development. Briefly, the NOAELs (no observed adverse effect levels) identified for the Seychelles study ranged from 20 to 30 parts per million (ppm) of hair mercury concentration and the NOAELs identified for the Faroe Islands ranged from 2 to 30 ppm. The NOAELs identified in the New Zealand study were presented with and without the maternal hair mercury concentration for one subject that was much higher than all the others (86 ppm), resulting in levels of 20–23 ppm and 7–10 ppm respectively.

The reasons for the discrepancies across the three studies include differences in 1) the types of neurobehavioral tests that were applied and the age of the children at the time of study; 2) the frequency of exposure to MeHg (ongoing exposure through fish consumption in the Seychelles versus less frequent exposure resulting from sporadic consumption of pilot whales in the Faroe Islands); and 3) the biomarkers that were used (MeHg in cord blood in the Seychelles, and maternal hair MeHg concentration in the Faroe Islands). Overall, the range in maternal hair mercury concentrations across the three studies (10–20 ppm) seemed reasonable for neurodevelopment NOAELs. Interconvert factors were used to translate mercury concentrations in hair and blood into mercury intake (1, 2) based on certain assumptions (including 95% of mercury absorption by the human body, and a hair:blood ratio of 250:1) and uncertainty factors. The 10–20 ppm range in hair mercury was used by the Joint Food and Agriculture Organization (FAO) / WHO Expert Committee on Food Additives (JECFA) (16) to revise neurodevelopment NOAELs and to establish a provisional tolerable weekly intake (PTWI) of 1.6 µg per kg of body weight, replacing the previous PTWI of 3.3 µg per kg of body weight (17). However, multiple discrepancies in MeHg toxicity reference levels remain. For example, in the United States, the Environmental Protection Agency (EPA) recommends a MeHg reference dose of 0.1 µg per kg of body weight, whereas the U.S. Agency of Toxic Substance and Disease Registry indicates a minimal risk level of 0.3 µg per kg of body weight (8).

Results from the epidemiological studies in the Faroe Islands, New Zealand, and the Seychelles have been used to develop quantitative dose–response functions, using intelligence quotient (IQ) deficits and maternal hair mercury concentrations during

pregnancy time. Estimates indicate that each 1-ppm increase in maternal hair mercury concentration results in a loss of 0.7 IQ points (ranging from 0 to 1.5 IQ points) during childhood development (18). Given the wide-ranging mercury concentrations of the diverse fish species that are consumed, and the changes in fish consumption patterns that can be achieved through properly designed and disseminated fish advisories, significant efforts should be made to use these public health tools, and their impact evaluations, effectively (19).

Health effects associated with high levels of MeHg prenatal exposure (about 700 ppm), such as those that occurred in Minamata Bay, Japan, caused by the release of mercury in industrial wastewater between 1932 and 1968 (20), have included cerebral palsy, severe intellectual disability, movement and coordination disorders, dysarthria, and sensory impairments (1).

METHYLMERCURY INTAKE

Methylmercury intake is a function of the amount of fish consumed and the mercury concentration in the fish consumed. The amount of fish consumed varies across different populations and often depends on access to other types of protein. The PTWI of 1.6 µg per kg of body weight established by the JECFA would translate to almost 100 µg of mercury for a female adult weighing about 60 k, or weekly consumption of 200 g of fish with a mercury concentration of 0.50 ppm.

However, MeHg is unevenly distributed within the food chain. For example, high–trophic level species, such as piscivorous fish, have higher mercury levels than lower–trophic level species, such as herbivorous or detritivorous species. Fish size, age, migration pattern, metabolic rate, and other ecological factors can also affect MeHg bioaccumulation. Knowledge about these factors is key for designing locally tailored fish advisories.

Information about MeHg concentrations in fish is available in the scientific literature and in some government databases. In the United States, the Food and Drug Administration (FDA) database (21) on mercury concentration in commercial fish (1990–2010) includes the relatively low-level mercury concentrations (e.g., < 0.020 ppm) found mostly in low–trophic level small species such as anchovies, sardines, and tilapia, and the higher mercury concentrations (e.g., > 0.50 ppm) found mostly in high–trophic level species such as swordfish, shark, and orange roughy (21). The diversity of trophic levels and wide range in mercury concentrations across different fish species, even those that are closely related, makes the design of appropriate fish advisories challenging. For example, mackerel (Atlantic, King, Pacific, and Spanish) have mercury concentrations ranging from 0.050 to 0.730, and those of different tuna species range from 0.128 to 0.689 ppm (21).

Based on a recent systematic review addressing prenatal MeHg exposure worldwide (5), riverside populations living near ASGM (including those in the Amazon) and consumers of marine mammals in Arctic regions were found to have MeHg intake levels above the WHO/FAO JECFA reference level (1.6 µg per kg of body weight). Using data from the Madeira River population in the Amazon, linear regression models were developed to account for factors associated with in utero and lactational exposure that may affect infant hair mercury levels (22). With a mean hair mercury concentration of 10.2 ppm (ranging from 1.0 to 34.2 ppm) from 89 infants, a mean hair mercury concentration of 12.6 ppm (ranging from 0.8 to 28.3 ppm) from 90 mothers, and a mean mercury concentration of 5.7×10^{-3} ppm (ranging from "undetectable" to 24.8×10^{-3} ppm) from 44 breast-milk samples, significant regression coefficients ranging from 0.31×10^{-3} ppm (for breast-milk mercury) to 0.90 ppm (for maternal hair mercury) were found to predict infant exposure.

Research has shown that in Amazonian ecosystems with ASGM, deforestation, slash-and-burn agriculture, erosion, and other sources of mercury, food chains have often been unevenly contaminated (23, 24). Amazonian biodiversity comprises large numbers of fish species with wide-ranging ecological niches that can change according to the fish life stage, ecosystem, season, and seasonal water volume flooding system. Following the pattern of mercury bioaccumulation, low–trophic level detritivorous and herbivorous species had mean mercury concentrations < 0.28 ppm and < 0.36 ppm respectively, whereas the mean mercury concentrations in high–trophic level species and piscivorous species were as high as 1.34 ppm. Omnivore species had a wide range of mercury concentration levels (0.17–1.44 ppm) (5, 23). A similar pattern was observed among fish species with commercial value in the Amazon: mercury concentration means for detritivorous, herbivorous, and omnivorous species were below 0.10 ppm, whereas piscivorous species had concentrations as high as 0.53 ppm (25).

Among human populations with heavy fish consumption, the pattern of the consumption (i.e., the fish species mostly, regularly, and least often consumed) is also important. The fish consumption pattern is assumed to vary by season, personal preferences, and cultural influence. Among the Madeira River population in Brazil, it was observed that the fish species most often consumed included smaller-size herbivorous and detritivorous species with lower mercury concentrations (23). On the other hand, among the Tapajos River population in Brazil, piscivorous species constituted around 45% of the fish diet (24). It is possible that because of their higher commercial value the larger species (including catfish) are sold rather than consumed for subsistence.

Many riverside populations, such as those in the Amazon, are likely to consume more than 200 g of fish per week. To keep these populations' MeHg intake under 1.6 µg per kg of body weight, fish advisories must advocate local consumption of fish species with low trophic levels and low mercury concentrations, especially for those who are pregnant or breastfeeding.

When designing fish advisories, the benefits of fish consumption must also be considered. As mentioned above, fish is the primary source of omega-3 fatty unsaturated acids, which are considered essential

for optimal fetal neurodevelopment and prevention of various adverse effects, given the likely increase of gestation duration and the associated benefits to the newborn, as observed in studies evaluating omega-3 fatty unsaturated acids intake (8, 9).

Locally tailored fish advisories

The Minamata Convention covers the identification and protection of populations at increased risk of MeHg exposure, as well as information exchange, education, and research, which are all key elements of properly designed and disseminated fish advisories at the local level.

Social and environmental contexts in which there is heavy fish consumption due to the lack or cost of other protein sources require the use of different strategies. One advantage of fishing communities is their wealth of knowledge on fish ecology, which facilitates communication regarding mercury bioaccumulation. However, in many such communities, the diversity of fish species consumed is high. For example, in the Amazon, one single family meal can contain more than a half-dozen different fish species, with different trophic levels, distributed among family members with different preferences and health statuses.

Training at the local level for stakeholders with potential influence on community members' knowledge and behaviors, such as health care personnel and schoolteachers, using educational materials adapted to local conditions and tested for validity, can lead to positive results (26). Stakeholders should be encouraged to consider the potential effects of methylmercury intake and other subclinical aspects of intellectual disability that, in the context of other competing ill-health demands, might not be perceived or considered relevant for health and well-being. While neurobehavioral testing is indicated, neurological issues must be addressed with sensitivity when returning test results to community participants. In this context, fish advisories are provided as partial mitigation opportunities. Creative efforts are required to take advantage of opportunities and overcome challenges. For example, a study was conducted in Boston (Massachusetts, United States) to determine whether a nuanced public health message advocating the avoidance of high-mercury fish and the consumption of more low-mercury fish could be implemented among women attending obstetrics clinics (n = 61). One intervention group was given fish consumption advice and gift cards to purchase fish. Results indicated increased consumption of fish with low levels of mercury and high levels of omega-3 unsaturated fatty acids among this group compared to the other intervention group (who received only fish consumption advice) and the control group (who received the standard pregnancy food guide provided during prenatal care) (27).

CONCLUSIONS

Decreasing human exposure to methylmercury due to fish consumption among populations with critical levels of exposure in communities where alternate food resources are likely scarce will require several decades and significant amounts of work. The Implementation of the Minamata Convention should help countries achieve these goals, and health sector participation is key to this effort, especially for health risk mitigation. Capacity building should be carried out among health professionals to enable the design and dissemination of fish advisories that convey the proper health warnings about MeHg and increase awareness about the benefits of fish consumption, especially among communities with ASGM and limited access to animal proteins.

Conflicts of interest. None.

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RESUMEN

Neurotoxicidad durante el desarrollo: metilmercurio y protección frente a la exposición prenatal a este contaminante en el contexto del Convenio de Minamata

El mercurio es un contaminante global motivo de preocupación en materia de salud pública ambiental como consecuencia de su amplia distribución atmosférica, su distribución ambiental y sus efectos neurotóxicos. Tras su metilación biológica, el metilmercurio (MeHg) se puede bioacumular de manera desigual en las cadenas alimentarias acuáticas. El consumo de pescado puede ser una ruta significativa de exposición humana al MeHg. Recientemente, se ha establecido que la exposición a niveles relativamente bajos de MeHg en la etapa prenatal es perjudicial para el neurodesarrollo, pudiendo ocasionar discapacidad intelectual. El Convenio de Minamata sobre el Mercurio es un acuerdo a escala mundial, actualmente en fase de ratificación, cuyo objeto es proteger la salud humana y el medio ambiente de las emisiones antropogénicas y los vertidos de mercurio y sus compuestos. La resolución referente a la función de la Organización Mundial de la Salud y los ministerios de salud en la aplicación del Convenio incluye la protección de la salud humana de exposiciones importantes al MeHg. Se ha establecido que las poblaciones ribereñas que residen en zonas de extracción artesanal de oro a pequeña escala, y que dependen en gran medida del consumo de pescado, son las más vulnerables en términos de exposición al MeHg y neurotoxicidad durante el desarrollo. Este artículo se centra en el diseño y la difusión adecuados de las recomendaciones relativas al consumo de pescado en el contexto de la aplicación del Convenio.

Palabras clave: mercurio, toxicidad; intoxicación por mercurio; compuestos del metilmercurio; toxicidad; intoxicación del sistema nervioso por mercurio; exposición a riesgos ambientales; Nueva Zelanda; América Latina; Región del Caribe.

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