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Minireview Article

Recent Advances in Evaluation of Health Effects on Mercury with Special Reference to Methylmercury – A Minireview

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Abstract

Mercury is a metal that has long been used because of its many advantages from the physical and chemical points of view. However, mercury is very toxic to many life forms, including humans, and mercury poisoning has repeatedly been reported. The main chemical forms of mercury are elemental mercury (Hg^0), divalent mercury (Hg^{2+}) and methylmercury (CH_3-Hg^+), the toxicities and metabolisms of which differ from each other. Methylmercury is converted from divalent mercury and is a well-known neurotoxicant, having been identified as the cause of Minamata disease. It bioaccumulates in the environment and is biomagnified in the food web. Human exposure to methylmercury is mainly through fish and seafood consumption. Methylmercury easily penetrates the blood-brain barrier and causes damage to the central nervous system, particularly in fetuses. In this paper, we summarize the global mercury cycle and mercury metabolism, toxicity and exposure evaluation, and the thresholds for the onset of symptoms after exposure to different chemical forms of mercury, particularly methylmercury.

Key words: mercury, methylmercury, global cycle, metabolism, toxicity

Introduction

Mercury generally exists as elemental mercury (Hg^0), divalent mercury (Hg^{2+}) and monomethylmercury (CH_3-Hg^+, commonly called methylmercury (MeHg)), all of which have different metabolisms and toxicities (1–4). MeHg bioaccumulates in biota, is biomagnified in the food web and enters the human body mainly through the consumption of fish and other seafoods. In Japan, there are two infamous epidemics caused by environmental water pollution around Minamata Bay on the Shiranui Sea coast and in the basin of the Agano River. About 3,000 people were certified to have been afflicted by the so-called "Minamata disease" in Kumamoto, Kagoshima and Niigata prefectures, although the actual number of people affected by MeHg poisoning was much larger (5) (Fig. 1). Minamata disease is defined as MeHg poisoning and the certification system only considers the clinical symptoms, which are similar to those of Hunter-Russell Syndrome, caused by direct contact with MeHg. The epidemics were the result of environmental pollution owing to the lack of environmental concern in industrial activities, particularly MeHg produced as a by-product of acetaldehyde synthesis. In addition to the outbreak of Minamata disease among children and adults, an outbreak of congenital Minamata disease occurred, characterized by an increase in the incidence of babies being born with a condition resembling cerebral palsy, caused by the MeHg poisoning of the fetus via the placenta of mothers exposed to MeHg during pregnancy. Mercury, one of the most toxic heavy metals, is released into the environment from natural sources and through human activity. Recent studies indicated that human activity contributes about 50–70% of total emission into the environment. That means the anthropogenic emission constitutes a large part of the global mercury cycle. Therefore, mercury is still important as a global pollutant. At present, the study on the effects of methylmercury exposure on fetus, especially in population which consume a lot of fish, is recognized as a matter of great concern.

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Mercury chemical forms and their dynamics in environment

Fossil fuel combustion and volcanoes emit large amounts of Hg^0 and particle bond mercury. Most mercury in the air is

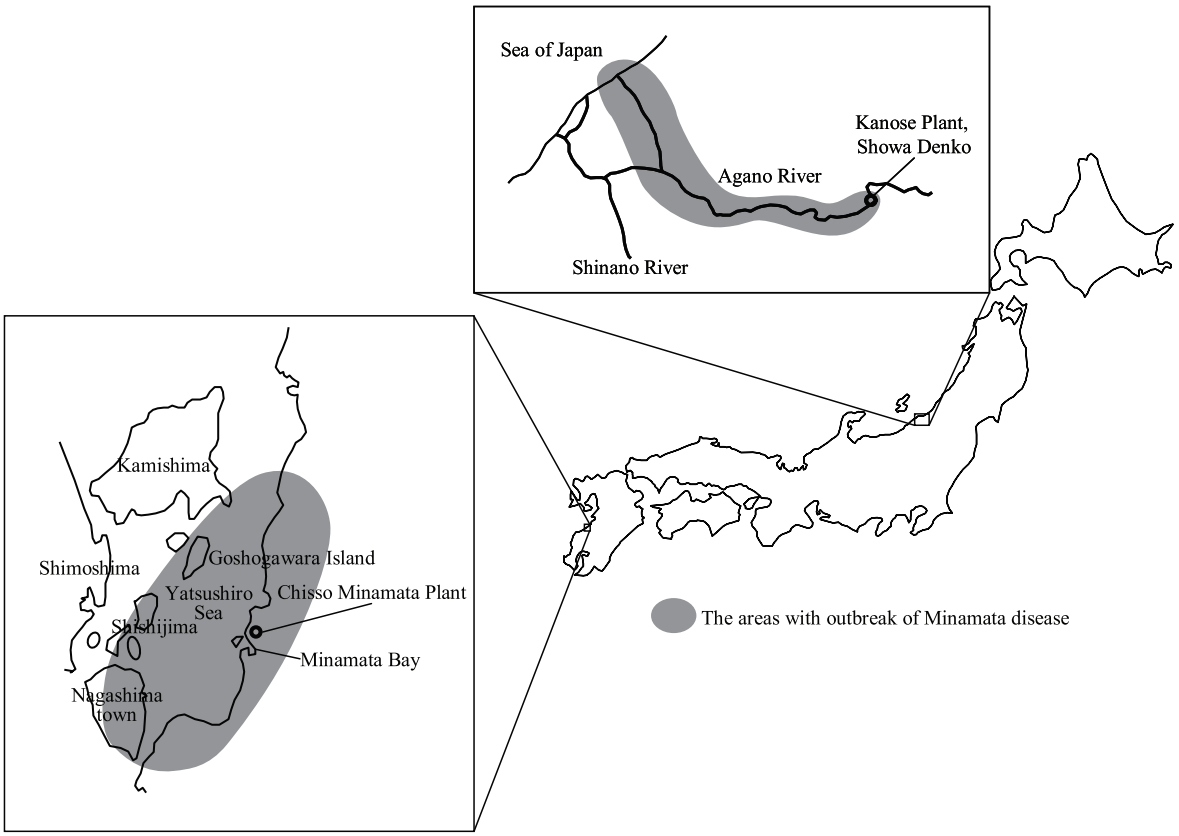

Fig. 1 Map of areas with outbreak of Minamata disease in Japan.

gaseous Hg^0 because of its much longer retention time in the atmosphere compared with other mercury forms (6). Natural mercury emission at an annual rate of about 1,000 tonnes has continued for millions of years as a result of crustal movement creating volcanic activity (6). In addition, annually about 2,600 tonnes of mercury, more than two fold natural emission amount, originates from anthropogenic sources, and more than 60% of the results from fossil fuel combustion (6). The amount of anthropogenic mercury emission in China is estimated particularly high, followed by that in the USA (6). The mercury concentration in the atmosphere of those regions is higher than that in other regions. Also, the mercury concentration in the atmosphere of the northern hemisphere is two fold higher than that of the southern hemisphere (6). These indicate that global mercury emission has increased since the industrial revolution started. The United Nations Environment Programme (UNEP) Global Mercury Assessment project was undertaken to investigate the possibility of setting international limits of mercury emission, deemed necessary because mercury concentration in superficial ice in the Arctic has increased (6).

Elemental mercury emitted into the atmosphere is oxidized and transformed into Hg^{2+}, a portion of which is methylated and enters the aquatic food chain. Species higher on the food chain tend to have higher concentrations of mercury, e.g., often above 10 μg/g in whales (toothed whale) and above 1 μg/g in sharks, pike, swordfish and tuna. Although regional pollution caused by a high concentration of MeHg such as in the aforementioned Japanese cases is not presently apparent, the mercury concentrations in fish and other seafoods are thought to be becoming higher in the sea because of the mercury emission of anthropogenic origin (6). Recently, research focusing on the global mercury cycle has been actively undertaken, particularly in Western countries, because of the emissions of Hg^0 and sulphur that polluted the Great Lakes in the USA and the lakes in Scandinavia. These have caused concern regarding a possible increase in human exposure to MeHg in the future.

Metabolism and toxicity of chemical forms of mercury

Human absorption of liquid Hg^0 is low, and acute toxicity does not occur even if the liquid Hg^0 used in thermometers is accidentally ingested. The problem is gaseous Hg^0 resulting from the heating of Hg^0, which causes acute interstitial pneumonia when inhaled at a high concentration. About 80% of inhaled gaseous Hg^0 is absorbed into the blood and easily passes through the blood-brain barrier in its unoxidized form, thereby reaching the brain and damaging the central nervous system. With time, gaseous Hg^0 in the body is oxidized to Hg^{2+}, which accumulates in the kidneys and causes kidney toxicity (2). The absorption of Hg^{2+} in the digestive tract is comparably low. However, a large intake of Hg^{2+}, such as in accidental or suicidal ingestion, causes digestive tract and kidney disorders resulting in death (2). Methylmercury is readily absorbed by the digestive tract and enters the central nervous system after passing the blood-brain barrier, thereby causing the degeneration and dysfunction of nerve cells (2–4). The symptoms of Minamata disease include sensory disorders of the four extremities, cerebellar ataxia, constriction in the visual field,

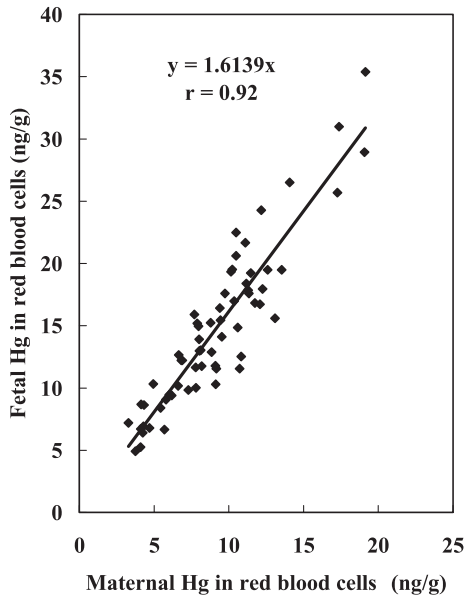

Fig. 2 Correlation between maternal and fetal mercury concentrations in red blood cells of mother-child pairs. Reprinted with permission from Maternal and fetal mercury and n-3 polyunsaturated fatty acid as a risk and benefit of fish consumption to fetus (8). Copyright 2004 American Chemical Society.

smell and hearing impairments and disequilibrium syndrome (4).

Most mercury in fish and other seafoods exists as MeHg (more than 90%). Generally, fish and other seafoods are the main sources associated with MeHg exposure in humans; note that tooth whales and tuna, which are at the top of the aquatic food chain, accumulate high concentrations of MeHg (3, 7). Methylmercury transport into tissues appears to be mediated by the formation of a MeHg-cysteine conjugate, which is transported into cells via a neutral amino acid carrier protein (3, 7). The brain of the developing fetus is very sensitive to MeHg. In addition, MeHg concentration in the blood of the fetus is about 1.5- to 2-fold higher than that of the mother because of the active transport of MeHg to the fetus through the placenta (3, 7). Figure 2 shows the correlation between maternal and fetal mercury concentrations in the red blood cells of 63 mother-fetus pairs (8). Therefore, fetuses are recognised to be a high-risk group for MeHg since the susceptibility of the developing brain itself is high and high MeHg accumulates in fetuses than mothers.

Exposure evaluation

Table 1 shows the major target organs and biomakers of mercury by chemical forms. To determine the effect of MeHg on the human body, it is preferred to use a biomarker in the body that reflects the MeHg concentration in the brain, because the major target organ is the brain. In humans, MeHg has on average a biological half-life of about 70 days (whole body) (9). Generally, its internal retention quantity becomes stable under constant MeHg exposure, which depends on dietary intake. Animal experiments indicate that the ratio of the mercury concentration in the blood to that in the brain becomes fixed in steady state conditions. Therefore, the mercury concentration in the blood is a good biomarker of the mercury concentration in the brain (7). The mercury concentration in the hair also reflects MeHg concentration in the blood during hair formation and is frequently used as biomarker for evaluating MeHg exposure (7). Generally, the mercury concentration in the hair is 250- to 300-fold higher than that in the blood, because sulphur-containing proteins in the hair bind to mercury. In addition, the mercury concentration in the umbilical cord blood or umbilical cord itself is a good biomarker for evaluating MeHg exposure of the fetus, which becomes susceptible to MeHg toxicity in the later term of pregnancy (10). The mercury concentration in the umbilical cord reflects MeHg concentration in the umbilical cord blood well (11). Traditionally in Japan, umbilical cords from each birth are kept. It has therefore become possible to evaluate MeHg exposure level of infants at birth.

Table 1 Major target organs and biomarkers of mercury by chemical forms

Chemical form of mercury		Target organ	Biomarker
Elemental (Gaseous)	Hg^0	Brain, kidney, Lung	Urine, serum
Divalent	Hg^{2+}	Kidney	Urine, serum
Methyl	CH_3-Hg^+	Brain, fetal brain	Hair, blood, umbilical cord

The major form of mercury in the urine is inorganic mercury. The mercury concentration in the urine increases with increased amounts of inorganic mercury accumulated in the kidney. Moreover, with exposure to Hg^0 and inorganic mercury, the total mercury concentration in the urine, which reflects the amount of inorganic mercury accumulated in the kidney, is a good biomarker for evaluating the mercury exposure. On the other hand, in the case of acute exposure to gaseous Hg^0 at a high concentration, the mercury causes acute toxicity conditions, e.g. respiratory distress, difficulty in breathing, bronchitis, and renal tubule damage (12). Therefore, the lungs are another target organ of high and acute exposure.

Medical professionals should refer to sampling methods for each chemical form of mercury and its preservation conditions, e.g., those presented by the Japan Public Health Association (12), and to the total mercury analysis method in the Mercury Analysis Manual published by Japanese Ministry of the Environment (13) for proper sampling and the evaluation of mercury exposure.

Normal mercury concentrations of different human biomarkers

The relative concentrations of organism tissues at steady state exposure are as follows: hair, 250; red blood cells, 2; blood plasma, 0.2, when the relative value of MeHg in whole blood is assigned 1 (7). The total mercury concentration in the hair, the biomarker used for the general populace of Japan, is generally within 1–5 μg/g, and rarely exceeds 10 μg/g; that in the blood is generally less than 50 ng/g (12, 13). However, even if the total mercury concentration exceeds these values, it does not mean that the symptoms of poisoning develop immediately. The total

mercury concentration in the hair differs depending on sex and age mainly refracting the quantity and mercury content of fish and seafood consumed. The total mercury concentration in the urine is generally less than 10 ng/ml among Japanese. The total mercury concentration in the umbilical cord is generally about 0.1 μg/g (dry weight) (14), but reached 1–3 μg/g (dry weight) in the residents of Minamata City during the Minamata epidemic (11).

Thresholds for onset of MeHg symptoms in adults

The large-scale poisoning incidents from 1972 to 1973 in Iraq were caused by wheat seed disinfected with methylmercury. These incidents afflicted more that 6,000 people and resulted in 400 deaths, and the main symptoms shown were similar to those shown in Minamata disease (7). A study on Iraqi case showed that the thresholds of mercury body burden at diagnosis of patients were as follows: abnormal sensory, about 25 mg (equivalent to a mercury concentration in blood of 250 μg/l); ataxia, about 50 mg; articulation disorders, about 90 mg; hearing loss, about 180 mg; death, more than about 200 mg. Table 2 shows the summary of the thresholds for which the first neurological symptoms appear in adults with the highest susceptibility according to the World Health Organization (WHO) (7).

Thresholds for onset of MeHg symptoms during fetal period

Grandjean et al. (10) determined the MeHg exposure levels influencing the development of children exposed to MeHg during the fetal period in a cohort study of about 900 residents of the Faroe Islands, where a large quantity of pilot whale meat with elevated mercury content is consumed. The results show a significant association of deteriorated motor function, attention, visual field, speech and language memory with mercury concentrations in the cord blood. Myers et al. (15) conducted a cohort study in the Seychelles Islands, where large quantities of fish and other seafoods are consumed and the effect of MeHg on children is a source of concern. However, in their study, no results showing a significant association between the biomarkers of MeHg exposure before and after birth were obtained. Kjellström et al. conducted a cohort study of New Zealand children (16). In their study, they estimated prenatal MeHg exposure level using maternal hair samples and dietary questionnaires. They observed adverse effects of MeHg on children development (16). A similar cohort study is ongoing in Japan (17). The effect of MeHg exposure on the fetus remains an important issue to elucidate, particularly in populations that consume high amounts of fish and seafoods.

Table 2 Various indices showing thresholds for onset of neurological symptoms in human body (level at which neurological symptoms would appear in the most susceptible adults) (7)

Index	Threshold
Average daily intake	3–7 μg/kg
Body burden	15–30 mg (50 kg body weight)
Total mercury in blood	20–50 μg/100 ml
Total mercury in hair	50–125 μg/g

Although the threshold for the onset of symptoms for MeHg is about 10 μg/g in maternal hair based on the results of studies in Iraq and the Faroe Islands, the standards for tolerable intake levels of MeHg for pregnant women are decided by each country and the authorities concerned, taking safety into consideration. The Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) calculated the threshold as 12 μg/g in maternal hair and established a provisional tolerable weekly intake (PTWI) for MeHg of 1.6 μg Hg/kg bw/week (equivalent to a hair mercury concentration of about 2.3 μg/g) using an uncertain factors 3.2 and 2. The United States Environmental Protection Agency (USEPA) set the limit to 0.1 μg Hg/kg bw/day (equivalent to a hair mercury concentration of 1.0 μg/g) as reference dose (RfD) using an uncertain factor 10. The amount of fish and other seafoods consumed by people in Japan and other Asian countries bordering the sea is higher than that consumed by most European and American people. The average mercury concentration in the hair of women of childbearing age (15–49 years) in Japan is 1.4 μg/g (18). On June 3, 2003, the Japanese Ministry of Health, Labour and Welfare issued standards for the tolerable intake of tooth whales, red snapper, swordfish, bluefin tuna and other seafoods for pregnant women, owing to the fact that a certain percentage of fish and other seafoods contain high MeHg concentration as a result of biomagnification. In August 2005, the Food Safety Commission, which was requested by the Japanese Ministry of Health, Labour and Welfare to evaluate tolerable weekly intake, established the MeHg TWI to 2.0 μg Hg/kg bw/week (19) using an uncertain factor 4, corresponding to a hair mercury concentration of about 2.8 μg/g.

Risks and benefits of fish consumption

Generally, most human exposures to MeHg are through the consumption of fish and other seafoods. Methylmercury exposure level estimated from hair mercury concentration depends on the amount, species and organs of the fish and other seafoods consumed. The developing brain in the late gestation period is most vulnerable to neurochemically disruptive exposure. Furthermore, more MeHg accumulates in fetuses than in mothers. Therefore, efforts must be made to protect fetuses from the risk of damage from MeHg exposure, particularly in populations that consume large amounts of fish and other seafoods. If human exposure to MeHg were independent of nutrition associated with fish and seafood consumption, one could aim for a close to zero exposure. However, fish and seafoods are a very important source of protein and other nutrients (20, 21), particularly for Japanese and some other Asians, as well as for people in the Arctic region and other self-sustaining people living along rivers, lakes and coasts. Docosahexaenoic acid (DHA), which is one of the most important n-3 polyunsaturated fatty acids for normal brain development and function, is mainly obtained through fish consumption. Recently, Sakamoto et al. (8) have reported a significant positive correlation between MeHg and DHA concentrations in fetal circulation (Fig. 3). This finding

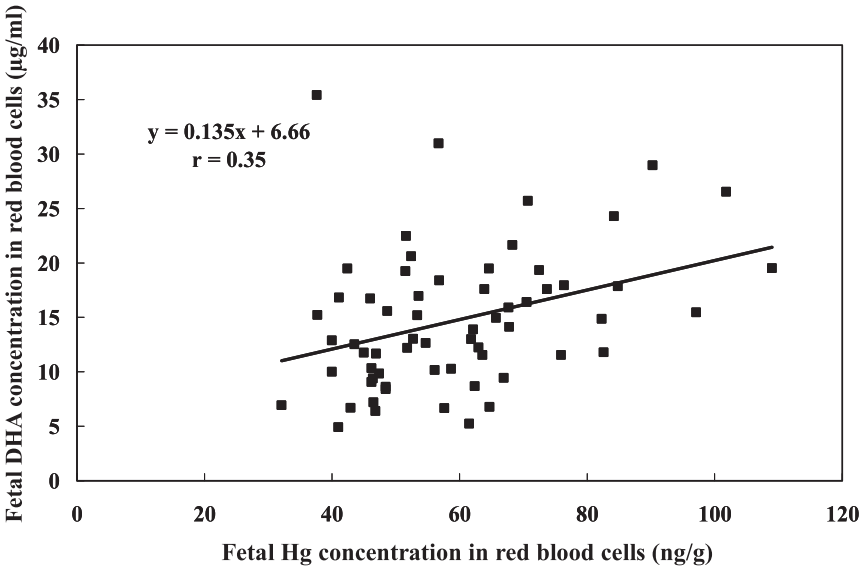

Fig. 3 Correlation between mercury concentration in red blood cells and plasma docosahexaenoic acid concentrations for 63 fetuses. Reprinted with permission from Maternal and fetal mercury and n-3 polyunsaturated fatty acid as a risk and benefit of fish consumption to fetus (8). Copyright 2004 American Chemical Society.

confirms that a decrease in fish consumption may cause a decrease in not only MeHg concentration but also DHA level. Pregnant women, in particular, should not give up eating fish and forgo its nutritional benefits. Instead, they should follow the amount of fish and other seafoods consumed for pregnant women recommended by the Pharmaceutical and Food Safety Council (22). It is important to consume smaller fish and avoid top predatory species to lower MeHg intake, thereby balancing the risks and benefits of fish consumption.

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