Current progress on understanding the impacts of mercury on human health

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Abstract

Mercury pollution and its impacts on human health are global concern. The authors of this paper were members of the Plenary Panel on Human Health in the 12th International Conference on Mercury as a Global Pollutant held in Korea in June 2015. The Panel was asked by the conference organizers to address two questions: what is the current understanding of the impacts of mercury exposure on human health and what information is needed to evaluate the effectiveness of the Minamata Convention in lowering exposure and preventing adverse effects. The authors conducted a critical review of the literature published since January 2012 and discussed the current state-of-knowledge in the following areas: environmental exposure and/or risk assessment; kinetics and biomonitoring; effects on children development; effects on adult general populations; effects on artisanal and small-scale gold miners (ASGM); effects on dental workers; risk of ethylmercury in Thimerosal-containing vaccines; interactions with nutrients; genetic determinants and; risk communication and management. Knowledge gaps in each area were identified and recommendations for future research were made. The Panel concluded that more knowledge synthesis effort is needed to translate the research results into management tools for health professionals and policy makers.

Key words: Critical Review; Environmental Exposure; Environmental Pollutants; Humans; Mercury; Methylmercury; Toxicity; Health; Advisory

Introduction

Mercury (Hg) is a global pollutant that affects human and ecosystem health (UNEP 2013). The awareness of health effects of Hg pollution began since the 1950s when chemical waste was released into the nearby sea by the Chisso Corporation in Minamata, Japan. The waste led to the accumulation of the more bioavailable form of Hg, i.e. methylmercury (MeHg) in fish, and consequent devastating thousands of local populations who had consumed the fish as their main food source (Kurland et al. 1960). It is well documented that prenatal or postnatal exposure to MeHg can produce adverse neurological impacts in adults and children, now known as Minamata Disease (Harada 1995). These patients with chronic Hg poisoning continue to complain of distal paresthesias of the extremities and the lips even 30 years after cessation of exposure to MeHg (Ekino et al. 2007). Moreover, more recent evidence showed that even general population exposed to MeHg in Minamata who were not certified Minamata Disease patients showed increased risk of psychiatric symptoms (e.g., impairment of intelligence and mood and behavioral dysfunction) (Yorifuji et al. 2011). With increasing awareness of environmental stewardship, an incidence of acute Hg poisoning from industrial pollution like Minamata has become rare. However, the scale of chronic exposure to a lower dose of Hg as a result of global pollution or occupational hazard has grown. For example, the Food and Agriculture Organization (FAO)/World Health Organization (WHO) identified that hundreds of millions of peoples worldwide who rely on fish as their major source of protein in their diet are at risk of increased exposure to MeHg (FAO/WHO 2011). Artisanal and small-scale gold mining is another major contributor to mercury consumption and emissions into the environment affecting millions of people particularly in low- and middle-income countries (Veiga et al. 2006).

These growing concerns have led to the initiation of numerous international efforts to address the issues. For example, the United Nations Environment Programme (UNEP) has implemented a number of global projects that aimed at decreasing human health and environmental risk from the release of Hg, as well as improving the understanding of international Hg emissions and their transport and fate (UNEP, 2013a). Most significantly, an international treaty (Minimata Convention on Mercury) was signed in October 2013 to control the global release of Hg to the environment (UNEP, 2013b). The objective of the Minamata Convention, as indicated in Article 1, is "to protect the human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds" (UNEP, 2013b). The Convention recognizes that anthropogenic emissions are a serious threat to human and environmental health and each signing nation will make a commitment to reduce the emission and use of Hg to protect human and environmental health. By the end of 2015, the Minamata Convention has been signed by 128 countries and ratified by 20 countries. It will go into effect after 50 countries have deposited their instruments of ratification, acceptance, approval, or accession that is expected to be in 2017. Article 16 of the Convention stated the concern on human health aspects. It encourages states to promote strategies to: 1) identify all the population affected by mercury pollution; 2) adopt health guidelines regulating mercury exposure; and 3) provide education about dangers of mercury exposure. Countries should provide appropriate health-care for treatment and care for people who are already exposed to mercury compounds. It is clear that more scientific knowledge is needed to fully understand effects of Hg emission reduction on environmental concentrations and identify other factors leading to reduced human exposure and resulting in prevention of adverse outcome. Moreover, integration of science with national and international

policy efforts is needed to target efforts in the implementation of the intervention and evaluate the effectiveness of the Convention on improving health.

The authors of this paper were invited by the organizing committee of the 12th International Conference on Mercury as a Global Pollutant held in Korea in June 2015 to be members of the Plenary Panel on Human Health. The Panel was challenged to prepare presentations to address two questions: what is the current understanding of the impacts of mercury exposure on human health and what information is needed to evaluate the effectiveness of the Minamata Convention in lowering exposure and preventing adverse effects. This review paper is prepared based on the presented materials and discussions at the Conference. In addition, a systemic review of the literature was conducted to assured all the most recent publications are included in our attempt to address these questions.

Methods

A literature search was conducted in OVID Medline (January 2012-present) and Toxline (January 2012-present). The search strategy combined terms for mercury, methylmercury, human, and health. The rationale for the choice of inclusion period was based on the publication of the latest review paper of this nature by Driscoll et al. (2013) that cited bibliography published until the end of 2011. The included papers were grouped into the following 10 major areas: environmental exposure and/or risk assessment; kinetics and biomonitoring; effects on children development; effects on adult general populations; effects on artisanal and small-scale gold miners; effects on dental workers; risk of vaccination; interactions with nutrients; genetic determinants and; risk communication and management. Selected publications were included in this critical review in the context of addressing the two questions posed to the Panel (Figure 1).

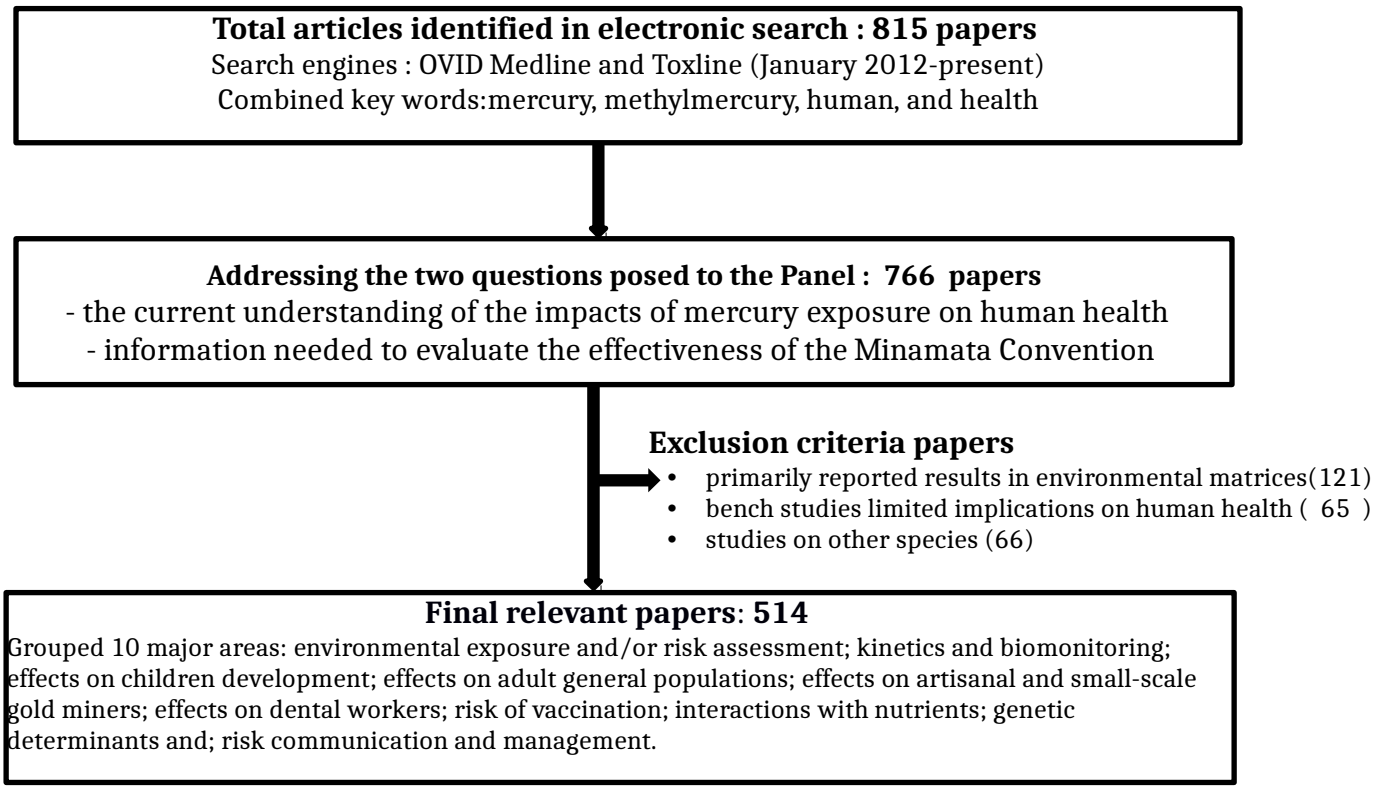

Figure 1. Flow chart of literature search for the impacts of mercury on human health

Results

The literature search found a total of 815 papers published between Jan 1, 2012 to present. A screening found that 514 are relevant (Table 1). The others primarily reported results in environmental matrices, bench-based studies that have limited immediate implications on human health, or studies on other species.

Table 1. Results of the literature search of papers published related to Hg health effects.

Areas	**Number of publications (%)**
Review papers	25 (5)
Environmental exposure and risk assessment	108 (21)
Kinetics and Biomarkers	66 (13)
Effects on children development	75 (15)
Effects on fish consuming adults	72 (14)
Health hazards of artisanal and small-scale gold mining	14 (3)
Effects of Dental Amalgam	22 (4)
Effects of Hg in Thimerosal-containing vaccines	4 (1)
Nutrient interactions	59 (11)
Genetic Factors	20 (4)
Risk communication and Policy	49 (10)
Total	514(100)

The relative number or percentages of publications in the 10 different areas of Hg research may reflect the recent research focus. It is not surprising that the highest number of papers (21%) was on environmental monitoring and exposure assessment. This is the first step of hazard identification in many regions around the world. There was almost an equal number of studies reporting effects of Hg on maternal-child health (15%) and adult fish consuming populations (14%). There were 11% of papers reporting results on the interactions between nutrients and Hg effects. The risk of Hg exposure on artisanal and small-scale gold miners (3%) and effects of dental amalgam (4%) have been intensive areas of research. The potential risk of Thimerosal-

containing vaccines (1%) remains to be a concern and studied. Genetic polymorphisms (4%) have been identified to be important modifiers or confounding factors affecting the toxicokinetics and effects of Hg. Almost 10% of the papers are on risk communications and policy, again showing the growing challenge among public health professionals to educate the public on the complex issues of risks and benefits. The following sections will discuss the state of the knowledge and knowledge gaps in each of these areas.

Discussion

There were 25 review papers published during that period. The relatively high number of review papers (almost 5%) of the publications probably reflected the increase scientific interests in the Hg research and the response among of the environmental health scientists to the call from the national and international agencies on the need for scientific evidence support for the signing of the Minamata Convention. We highlighted 4 papers of review papers below. Rice et al. (2014) reviewed the systemic pathophysiology of individual organ systems including cellular, cardiovascular, hematological, pulmonary, renal, immunological, neurological, endocrine, reproductive, and embryonic toxicological effects. The review by Syversen & Kaur (2012) attempted to address the long time " mysteries" of methylmercury neurotoxicology related to the cellular selectivity and the delayed onset of symptoms and presented some suggestions towards explaining these observations. Bernhoft (2012) focused his review on the diagnosis of Hg clinical toxicity and therapeutic treatments. Sheehan et al. (2014) was the first systematic review on the relationship between MeHg exposure from seafood consumption and risk of developmental neurotoxicity. Their review included 164 studies of women and infants from 43 countries. They found that the fish-consuming populations living along rivers near small-scale

gold mining and consumers of marine mammals in Arctic regions had MeHg intake several times higher than the FAO/WHO reference. In a comment letter, Myers et al. (2015) highlighted the importance of including the benefits of nutrients in fish into the risk assessment, particularly among the low- and middle- income countries where fish consumption is high and resources are limited.

Environmental Exposure and Risk Assessment

The World Health Organization (WHO 2010) recognized the importance of collecting site-specific data of Hg concentrations in fish and seafood around the world as there is a high intra-species variation that is determined by the local environment. The report also identified the lack of data for many areas of the world outside of Europe, the US and Japan. This highlight the need for collecting local data for exposure assessment and there is a current effort by the Global Environmental Monitoring System - Food Contamination Monitoring and Assessment Programme (GEMS/Food) of WHO to collect contaminant data from foods, including Hg in fish, data from all countries for the assessment of their contribution to total human exposure, and significance with regard to public health and international trade.

Most of the papers reported measured Hg concentrations in food or other matrices and estimate human exposure using dietary survey information or biomonitoring results. There are ongoing total diet studies or national health and nutritional examination survey which reported food concentrations and/or biomonitoring of contaminants including Hg in the general populations at the national level, e.g. in France (Arnich et al. 2012) and in Korea (Park et al. 2014). More

importantly, there is an increasing number of data coming from developing countries, e.g. Nepal (Thapa et al. 2014), Peru (Diringer et al. 2015; Ashe 2012), Ghana (Rajaee et al., 2015), and Suriname (Peplow & Augustine 2012), etc. Also, more studies were designed to target the specific sub-populations that have a different cultural background or a local fish-heavy diet. For example, the Caribbean immigrant community in Brooklyn, New York (Geer et al. 2012) or the women of childbearing age in Duval County, Florida (Traynor et al. 2013). There were also reports studying potential exposure from known hot spots such as the historically polluted area in southern Italy (Bonsignore et al. 2013). As aquaculture is expected to gain global prominence in seafood supplies, it is important to monitor Hg levels in farm fish or shellfish, e.g. Delgado-Alvarez et al. (2015) reported Hg in farmed shrimp in NW Mexico and characterized the risk of exposure is low using national consumption rate. Increasing evidence is showing that rice can be an important source of Hg among certain populations in China and other Asian countries (Li et al. 2012; Li et al. 2014; Zhang et al. 2014) but this has yet to be studied in other geographic regions. It has been known that Hg is widely used in cosmetic products but the scale of human exposure from hand cream use was recently reported (Hamann et al. 2014). This can be a major source of Hg in many populations and the exposure can be avoided by stricter regulation and education/communication.

Kinetics and biomarkers

In order to assessment the effects of Hg on health, it is important to establish a quantitative dose-response relationship. It is particularly challenging for Hg as Hg can exist in different forms including elemental mercury (Hg^0), divalent mercury (Hg^{2+}) and organic mercury (mainly as

methylmercury, MeHg). Exposure sources, target organs, toxicity, and metabolism differ with each chemical form. For example, most MeHg exposure comes from consuming fish and seafood. MeHg has the highest bioavailability compared to the other forms and easily absorbed by the digestive tract, entering the central nervous system (CNS) after passing the blood-brain barrier (BBB). The result is permanent injury to the CNS, particularly in the developing fetus (UNEP 2008). Elemental Hg exposure mainly results from dental amalgam restorations. Additionally, workers at artisanal and small-scale gold mining (ASGM) sites also experience high exposures to elemental mercury. Target organs here include the brain and kidneys (UNIDO 2008). There are two ways to assess exposure or dose. The first one is to estimate external dose by measuring concentrations in foods or air or water and multiplied by the frequency of exposure like consumption rate or inhalation volume over time. The second one is to estimate Hg body burden by measuring Hg concentrations in tissues such as hair, urine, blood, nails, cord tissues or blood, and placenta. Both approaches involve challenges and uncertainty. Therefore, most studies reported adjusted R(2) of less than 0.5 when comparing estimated dietary exposure to blood Hg concentration using regression analysis. For example, You et al. (2014) performed multiple regression analysis on dietary estimate and blood concentrations of 1,866 adult participants in Korea and reported the adjusted R(2) = 0.234. Further studies with more precise estimation of dietary mercury intake are required to evaluate the risk for Hg exposure by foods and assure risk communication with heavily exposed groups.

Human absorption of liquid Hg^0 is minimal, and acute toxicity does not occur even when the liquid mercury used in thermometers is accidentally ingested (WHO, 1976). The problem arises when liquid mercury vaporizes into the gaseous phase, which causes acute interstitial pneumonia

when inhaled at a high concentration. Approximately 80% of inhaled gaseous Hg^0 is absorbed into the blood and easily passes through the blood-brain barrier in its un-oxidized form, thereby reaching the brain and damaging the central nervous system (WHO, 1976). With time, gaseous Hg^0 in the body is oxidized to Hg^{2+}, which accumulates in the kidneys and causes damage there (UNIDO 2008). The biological half-life of Hg absorbed from vapour into the blood is approximately 2-4 days when 90% is excreted through urine and feces. Absorption of Hg^{2+} through the digestive tract is comparatively low. However, a large intake of Hg^{2+}, such as in accidental or suicidal ingestion, causes digestive tract and kidney disorders resulting in death (WHO, 1990). The major source of MeHg is through fish and shellfish consumption and MeHg was thought to be readily absorbed by the digestive tract. Animal studies indicate that the efficiency of gastrointestinal absorption is usually in excess of 90% of the oral intake (WHO, 1990). Risk assessors often assumed that 100% of Hg in fish is MeHg and its absorption rate is also 100% (NRC 2000). Recent studies showed that these assumptions are not necessarily true. Matos et al. (2015) found that cooking increased the concentrations of selenium, Hg and MeHg in blue shark meat due to water loss, particularly by grilling. While selenium (Se) bioaccessibility (the amount that is free for absorption) was above 83% in grilled samples, Hg and MeHg bioaccessibility was lower in grilled samples with values near 50%. Afonso et al. (2015) reported that cooking meagre by grilling decreased the bioaccessibility for both Se and Hg; Se bioaccessibility was decreased up to 82% in grilled farm meagre compared to only up to 54% for bioaccessibility for Hg and up to 64% bioaccessibility for MeHg. Jadán-Piedra et al. (2016) also reported a lower bioaccessibility for Hg in cooked swordfish (between 14 and 92%) than selenium. Most of the solubilization took place in the gastric step, with acidic pH and higher pepsin concentration but the bioaccessibility of Hg decreased in the presence of bile salts. Wang

et al. (2013) measured 10 freshwater and 10 marine fish collected from markets in Hong Kong and reported bioaccessibilities of Hg and MeHg ranging from 21.4 to 51.7% (mean 37.4%) and 19.5 to 59.2% (mean 43.7%), respectively. These results clearly show that the conservative approach of assuming Hg in fish to be 90-100% bioavailable can over-estimate intake by 50%. More research is needed to characterize the absorption rate of different species of fish before a consistent correction factor can be adopted for future risk assessment.

MeHg 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 (NRC, 2000; WHO, 1990). The extent of biotransformation of MeHg in the gastrointestinal tract varies resulting in variability in MeHg absorption rate. MeHg elimination from the human body occurs slowly with a half-life approximately 70 days and is a major determinant of the Hg body burden resulting from fish consumption (WHO, 1990). Two recent human trials provided some insight on the variability. Yaginuma-sakurai et al. (2012) estimated that the half-life of T-Hg was calculated from raw data to be 94 ± 23 days for blood and 102 ± 31 days for hair, but the half-life recalculated after subtracting the background levels from the raw data was found to be 57 ± 18 based on blood concentrations measured in 27 healthy adults through fish consumption for 14 weeks, followed by a 15-week washout period after the cessation of exposure in Japan. However, the half-life was estimated to be 64 ± 22 days when hair concentrations were used. Rand et al. (2015) measured MeHg elimination rates in eight individuals following the consumption of 3 fish meals in two 75-day trials separated by a 4-month washout period in the United States and estimated that the half-life ranged from 42.5 to 128.3 days. They also found that the ratio of MeHg and inorganic g (I-Hg) in feces varied widely among individuals

suggesting that faster MeHg elimination is associated with a higher %I-Hg in feces indicating a more complete de-methylation. Carneiro et al. (2014) also found inorganic mercury in plasma originated endogenously through a demethylation reaction in a population exposed to MeHg. Moreover, age displayed a direct linkage with inorganic Hg levels in plasma. Using a one-compartment model, Jo et al. (2015) estimated that the mean MeHg half-life was 81.6 ± 8.4 days for men and 78.9 ± 8.6 days for women. Moreover, a recent systemic review concluded modelling studies estimated the half-life of inorganic Hg in the brain to be very long at 27.4 years, which are consistent with autopsy findings (Rooney, 2014). A number of factors including ethnicity, genetics and diet may influence the variability MeHg disposition and its half-life and more studies are needed. In addition, naturally occurring mercury stable isotope ratios have emerged recently as a powerful tool to further distinguish among different forms of Hg and better understand its toxicokinetics (Sherman et al., 2013; Sherman et al., 2015).

The preferred biomarker reflects the MeHg concentration in the brain since the brain is the major target organ. Generally, the amount retained in the body becomes stable under constant MeHg exposure and depends on dietary intake. Animal experiments indicate that the ratio of the Hg concentration in the blood to that in the brain becomes fixed under steady state conditions. Therefore, the Hg concentration in the blood/red blood cells is a good biomarker (WHO, 1990). The Hg concentration in the hair also reflects blood MeHg concentration during hair formation and is frequently used as a biomarker for evaluating MeHg exposure (WHO, 1990). Generally, the Hg concentration in the hair is 250 to 300-fold higher than that in the blood, because sulfur-containing proteins rich in the hair bind to MeHg. To compare results of different studies using either blood or hair as biomarkers, the World Health Organization (WHO) recommends Hg hair-

to-blood ratio of 250 for the conversion of Hg hair levels to those in whole blood. This encouraged the selection of hair as the preferred analyte because it minimizes collection, storage, and transportation issues. In spite of these advantages, there is concern about inherent uncertainties in the use of this ratio. Liberda et al. (2014) measured total hair and total blood Hg concentrations in 1,333 individuals from 9 First Nations communities in northern Quebec, Canada and found that their hair-to-blood ratios spanning 3 to 2845. Yaginuma-sakurai et al. (2012) also reported the mean hair-to-blood ratio to be 344 ± 54 (S.D.) for the 27 participants of the fish consumption study. Therefore, using the constant ratio hair-to-blood ratio of 250 recommended by WHO to convert hair Hg concentrations to blood concentrations could be unreliable, particularly at the individual level. Therefore, future Hg exposure assessment should refer to blood measurements when there are human health concerns. Also, the use of singular hair concentrations and a standard hair-to-blood concentration conversion should be avoided for individual health risk assessment.

The organ targeted by MeHg exposure during gestation is the fetal brain. For this reason, biomarkers reflecting the MeHg exposure level in the fetus during the gestation are very important for predicting the effects of MeHg on child development. In addition, the MeHg concentration in the fetal blood reaches approximately 2-fold higher than that of the mother, because of active MeHg transport across the placenta (NRC, 2000; WHO, 1990). Therefore, umbilical cord blood is the most desirable biomarker for estimating pre-natal exposure. Concentrations of Hg in cord blood were reported for various population in China, the United States and Spain (Wu et al. 2013; King et al. 2013; Garcia-Esquinas et al. 2013). Hg concentrations in umbilical cord tissue and placenta have been shown to be useful biomarkers to determine fetal MeHg exposure levels (Sakamoto et al. 2012; Garcia-Esquinas et al. 2013; Jin et

al. 2013; Chen et al. 2014). Maternal Hg levels in fingernails and toenails at parturition also showed strong correlations with those in cord blood and can be used as biomarkers (Sakamoto et al. 2015).

In summary, it is still a challenge to compare Hg exposure between populations as different biomarkers or methods to estimate exposure were used. More concerted effort to harmonize human biomonitoring survey design and data interpretation is needed. For example, Smolders et al. (2015) reported the first ever such effort to harmonize biomarker data in 17 European countries.

Effects on children development

Mercury enters the fetus' body through the placenta (NRC 2000). Therefore, the fetus is very susceptible to Hg exposure during organogenesis, a fact that has drawn great attention toward women's health issues worldwide. In the last three decades, many studies have reported negative health outcome corresponds with low-level Hg exposure or environment dose through dietary consumption of seafood (Karagas et al. 2012). In the European Union, it was estimated that more than 1.8 million children were born every year with MeHg exposures above the limit of 0.58 μg/g, and about 200,000 births exceed a higher limit of 2.5 μg/g proposed by the World Health Organization (WHO) (Bellanger et al. 2013).

Previous studies have reported that prenatal exposure is associated with low birth weight, delayed neurodevelopment, and growth and development of children (Grandjean et al. 2010). Suboptimal fetal growth has been adversely associated with neurodevelopment in childhood and

it has even shown an increased risk of chronic diseases in adulthood, such as metabolic syndrome (Fox et al. 2012). Thus, elucidating the associations of environmental contaminants with health and development outcomes is of the utmost importance. As noted by a World Health Organization expert committee (World Health Organization, 2006), addressing such gaps in knowledge requires the design and implementation of prospective longitudinal cohort studies of pregnant women, infants, and children with assessment of their exposure at critical windows of development, along with sensitive health endpoints across the full continuum of development. Several such studies have been conducted to date to assess the effects of prenatal exposure to mercury, PCBs, and lead since these widespread environmental contaminants are known for their adverse effects on neurodevelopment (Grandjean and Landrigan, 2006).

Cohort studies in the Faroe Islands conducted since the 1980s have demonstrated that children exposed to methylmercury in utero exhibit decreased motor function, attention span, verbal abilities, memory, and other mental functions (Grandjean et al., 1997). Overall, the Faroe study found that a doubling of the prenatal mercury exposure for a child resulted in a developmental delay of one to two months at the age of seven years; that is, at the age when the child is expected to enter school. This delay corresponds to about 1.5 IQ points (Grandjean and Herz, 2011) and the neurocognitive impacts persist into adulthood as a small effect on educational achievements was observed at age 22 years (Debes et al., 2013). No effects were found on school performance at age 16 years, and only small effect on educational achievements was observed at age 22 years (Debes et al., 2013). In the Faroese birth cohort study, additional statistical analyses have shown that post-natal MeHg as shown by the child's current blood Hg concentration at age 7 contributed to neurobehavioral delays observed that were mainly

determined by pre-natal exposure, particularly in regard to visuospatial processing and memory (Grandjean et al. 2012). Similar to the Faroese study, a cohort study conducted on 94 Inuit mother-infant pairs in Arctic Canada who were exposed to elevated of Hg from their marine-mammal based diet found that prenatal exposure to MeHg was associated with poorer performance on A-not-B test, which depends on working memory and is believed to be a precursor of executive function, among infants at 6.5 and 11 months (Boucher et al. 2014).

Julvez et al. (2013) studied a subsample (n = 1,311) of the Avon Longitudinal Study of Parents and Children conducted in Bristol, UK, and found that the prenatal exposure to Hg was low but was positively associated with IQ, which attenuated after adjustment for nutritional and sociodemographic cofactors. They conclude that in this population with a low level of MeHg exposure, there were only equivocal associations between MeHg exposure and adverse neuropsychological outcomes. They suggested that heterogeneities in several relevant genes in the studied population might confound their results. Genetic polymorphism as a disposition for Hg toxicity was reported in a cohort study started in 2006 in Korea (Lee BE et al. 2010) in which maternal and cord blood Hg levels were associated with lower birth weight for mothers with both GSTM1 and GSTT1 null genotype. The importance of genetic factor of Hg toxicity research will be discussed in details in a later section.

As Japan and Korea are two major fish consuming countries in the world, results from the cohort studies conducted in these two countries attracted worldwide interests. The cohort study in Japan investigated the effects of prenatal exposure to PCB, Hg and lead on child behavior in 306 30-month-old children from pregnancy and found that internalizing behavior in the children was

significantly correlated with PCB (r=0.113), but showed no significant correlation with either Hg or lead (Tatsuta et al. 2012). A similar association between intelligence and achievement and PCB was observed among the children at 42-month-old but not with Hg or lead (Tatsuta et al. 2014). In contrast, Kim BM et al. (2011) studied 921 mother-child pair samples in Korea and found that the cord blood mercury level was negatively associated with the infants' attained weight over the first 24 months of age (β=−0.36. p=0.01). A more detailed comparison of these two cohort studies may be useful in future risk assessment for other fish consuming nations.

Prenatal and early-life exposures to mercury have been hypothesized to be associated with increased risk of autism spectrum disorders (ASDs) (Grandjean & Landrigan 2014). A cross-sectional study examined the potential correlation between hair Hg concentrations and ASD severity among participants (n = 18) using the Childhood Autism Rating Scale (CARS) in a prospective cohort of participants diagnosed with moderate to severe ASD (Geier et al. 2012). Increasing hair Hg concentrations were found to be significantly correlated with increased ASD severity. This study provides biological plausibility for the role of Hg exposure in the pathogenesis of ASDs. Sagiv et al. (2012) conducted a population-based prospective birth cohort recruited in New Bedford, Massachusetts (1993-1998). In multivariable regression models, Hg exposure was associated with inattention and impulsivity/hyperactivity. On the other hand, there was a protective association for fish consumption (>2 servings per week) with ADHD-related behaviors, particularly impulsive/hyperactive behaviors. Their results show that even at low-level, prenatal mercury exposure was associated with a greater risk of ADHD-related behaviors, but fish consumption during pregnancy or maternal fatty acid status is protective of these behaviors (Steenweg-de Graaff et al. 2015). These findings underscore the difficulties of

balancing the benefits of fish intake with the detriments of low-level mercury exposure in developing dietary recommendations in pregnancy. The importance of nutrient interactions on Hg toxicity will be discussed in a later section.

A number of other studies show that exposure to methylmercury does not play an important role in the development of ASD phenotypic behavior. For example, Yau et al. (2014) reported no significant association between ASDs and levels of total Hg measured in maternal serum from mid-pregnancy and infant blood shortly after birth in a study on children with ASD (n=84), children with intellectual disability or developmental delay (DD) (n=49), and general population controls (GP) (n=159). van Wijngaarden et al. (2013) evaluated the association between prenatal methylmercury exposure and ASD phenotype in children and adolescents in the Republic of Seychelles, where fish consumption is high. The Social Communication Questionnaire was administered to parents of a cohort of 1,784 children, adolescents, and young adults. No consistent association between prenatal methylmercury exposure and ASD screening instrument was found. Taken together, this evidence suggests that the role of Hg may be minor and inconsistent and can be masked by the nutritional benefits from fish consumption.

In the next few years, there will be an explosion of data generated by over 10 cohort studies being conducted around the world; e.g. Canada (Thomas et al. 2015), Italy (Deroma et al. 2013), Norway (Veyhe et al. 2015), Spain (Llop et al. 2012), Poland (Polanska et al. 2013), Amazonia, Brazil (Marques et al. 2013), France (Chan-Hon-Tong et al. 2013), Massachusetts, USA (Kalish et al. 2014), Mexico (Basu et al., 2014), and the Seychelles (Strain et al., 2015). We would expect to obtain more conclusive data on the dose-response relationship between pre-natal

exposure and a better understanding of the confounding factors including the nutritional and genetic factors. However, as discussed in the biomonitoring section, the use of maternal hair or blood as biomarkers for fetal exposure can generate uncertainty when the dose of different studies was compared. Moreover, the use of different evaluation tools at different age of the infants or children also make the inter-study comparison of effects challenging. More harmonization efforts are needed to integrate the future database for risk assessment purposes.

Effects on fish consuming adults

Current challenges regarding the effects of fish consumption on adults depend on methods/strategies to identify susceptible individuals or populations affected by fish-methylmercury (MeHg) exposure. There are no cases where markers of environmental MeHg exposure from fish consumption are indicators or prodromes of clinical conditions. Because of the complex interaction between fish-related constituents, both covariates, health-promoting and toxic substances, are not always taken into account; furthermore, confounding (constitutional) factors and/or accompanying effect modification in statistical models have frequently produced apparently contradictory or confusing results (Choi et al, 2008). The effects of toxic substances on adults are difficult to disentangle from the functional characteristics of fish consumption. Since the Minamata environmental disaster, human studies have focused mainly on MeHg contamination of fish. The extraordinary circumstances in post-war Japan and the highly polluted Minamata Bay contaminated fish to a level not found elsewhere, with Hg concentration reaching in excess of 20 μg/g fish (Clarkson, 1998). These special circumstances turned ordinary fish consumption into a tragic and emblematic environmental disaster. Hair-Hg concentrations of fish consumers during the `Minamata disease` outbreak ranged from 191 μg/g to 705μg/g (Koos and Longo, 1976; Harada, 1982). A recent study in Japan showed that residents who were exposed to elevated MeHg historically still showed significant functional deficit decades later (Ushijima et al. 2012).

However, Amazonians who consumed large amounts of fish showed Hg concentrations as high as 90.6 to 303.1 μg/g without displaying the clinical symptoms of ‘Minamata disease’ (Boischio and Barbosa, 1993). Moreover, a cross-sectional study also reported no observable effects on

neurological outcomes among whale meat consumers in Japan who had high mercury exposure (average hair Hg concentration of 14.9 ug/g) (Nakamura et al. 2014). The authors suggest that the high selenium intake offered a protective effect against the Hg toxicity. Fillion et al. (2013) reported color vision loss increased with hair Hg and decreased with plasma Se and % of omega-fatty acids among residents in the Brazilian Amazon. More details on nutrient interactions will be discussed in a later section.

It has been over 10 years since the association of tissue Hg concentrations and cardiovascular outcomes were suggested (Guallar et al, 2002) but inconsistent outcomes are still reported. A study of Amazon tribes suggested that fish consumption (hair-Hg) is inversely associated with age-related increases in blood pressure (Dórea et al., 2005); however, an opposite conclusion was reached by Fillion et al. (2006) with non-Amerindian populations. Choi et al. (2015) also showed that blood serum ferritin and mercury concentrations were associated with the prevalence of hypertension and that simultaneously elevated serum ferritin and mercury concentrations are related to the risk for hypertension in men Korea. However, in a cross-sectional study of the U.S. general population, Park et al. (2013) found no association of hypertension with blood mercury but a suggestive inverse association with urinary mercury. Nevertheless, some authors suggested a dose-response between Hg exposure and cardiovascular health (Roman et al. 2011). It seems that the cause-effect relationship is far from conclusive and future prospective studies are warranted.

There is emerging evidence on the positive relationship between Hg exposure and metabolic syndrome. In a cross-sectional study, the blood Hg concentrations of 2,114 healthy adults in Korea (geometric mean of 3.90 μg/L) showed a positive association with body mass index, waist circumference, diastolic blood pressure, total cholesterol, and triglyceride after adjustment for covariates (Eom et al. 2014). Also, Hg exposure was significantly associated with metabolic syndrome and their components such as obesity and increased fasting glucose. These results show that Hg exposure is influenced by sociodemographic factors and individual lifestyles including dietary habits and is associated with metabolic syndrome. Moreover, He et al. (2013) conducted a prospective cohort of 3,875 American young adults, and found that toenail mercury levels are associated with incidence of diabetes over 18 years of follow-up after adjusting for age, sex, ethnicity, study center, education, smoking status, alcohol consumption, physical activity, family history of diabetes, intakes of long-chain n-3 fatty acids and magnesium. The hazard ratio (95% CI) of incident diabetes compared the highest to the lowest quintiles of mercury exposure was 1.65 (1.07-2.56; P for trend = 0.02). This is the first time an epidemiological studying showing that people with high mercury exposure in young adulthood may have elevated the risk of diabetes later in life. Future studies should collect more information on the potential effects of Hg on metabolic syndrome.

Health hazards of artisanal and small-scale gold mining

Liquid mercury (Hg^0) is applied in artisanal and small-scale gold mining (ASGM) to extract gold from ore. Gold containing ores are grinded, mixed with liquid mercury and panned. During this process gold binds to mercury forming an amalgam. The amalgam is then smelted; mercury being vaporized and gold remains. The panning and smelting expose the smelters and the

inhabitants of the mining village to toxic mercury vapor (Hg^0) (Cordy et al., 2013; Cordy et al., 2011; De Miguel et al., 2014; Gonzalez-Carrasco et al., 2011). Once mercury is released it methylates in the aquatic food chain, and becomes bioavailable. Especially mercury-polluted waters, coming from ASGM areas, can contaminate fish leading to high methylmercury levels (MeHg) (Barbieri et al., 2009; Castilhos et al., 2006; De Miguel et al., 2014; Diringer et al., 2015; Dórea, 2008; Frery et al., 2001; Niane et al., 2015). Mercury can accumulate in rice grown in ASGM areas and ingestion of this polluted rice contributes to methyl-mercury exposure of the population (Bose-O'Reilly et al., 2016; Feng et al., 2008; Krisnayanti et al., 2012; Li et al., 2015; Li et al., 2014; Rothenberg et al., 2014). Miners and community members in ASGM areas are constantly exposed to elemental mercury vapor, and depending on the local situation to ingestion of MeHg from local fish and/or rice. Exposure scenarios are similar downwind and downstream from mining areas.

The exposure to mercury in ASGM areas shows high levels of mercury in human specimens as several studies showed (Gibb and O'Leary, 2014; Kristensen et al., 2013). Both reviews showed, that miners and their families are exposed to mercury vapor; that the exposure with inorganic mercury vapor is high, that fish contains MeHg; and that toxic effects have to be considered. Mercury levels in any analyzed biomarker were higher compared to control groups or reference values. Smelting and panning did lead to high and very high levels of mercury, especially in urine, but also in blood and hair. Smelters showed in up-to 80% typical signs of chronic mercury intoxication, mainly neurological symptoms like ataxia, tremor and coordination problems (Bose-O'Reilly et al., 2010a; Bose-O'Reilly et al., 2010b; Drasch et al., 2001; Lettmeier et al., 2010; Steckling et al., 2011; Steckling et al., 2014).

World Health Organization (WHO) is concerned about mercury as a health risk for miners and population in ASGM areas: "*Mercury exposure in ASGM communities is associated with adverse health effects including kidney dysfunction, autoimmune dysfunction, and neurological symptoms*" (World Health Organization, 2013).

ASGM affects approximately 15 million miners globally, as well as other community members, and the population downwind and downstream of mining areas, causing a serious public health problem (Spiegel et al., 2005; Wade, 2013). A burden of disease study for Zimbabwe showed that chronic mercury intoxication ranks within the top 20 health hazards of the country (Steckling et al., 2014; Steckling et al., 2015). Mercury is a serious health problem especially for children (Afandiyev et al., 2011; Bose-O`Reilly et al., 2010c). The health hazards for children in ASGM areas are less known, only a few publications exist (Bose-O'Reilly et al., 2008a; Grandjean et al., 1999). Children are exposed by living in ASGM areas, inhaling mercury fumes and ingesting mercury from fish and/or rice. Even worse off are children working in ASGM areas, performing all different kind of child labor, including handling, inhaling and ingesting toxic mercury (Amon et al., 2012; Kippenberg, 2011). The exposure to mercury leads to increased mercury levels in urine, blood and hair (Bartrem et al., 2014; Hruba et al., 2012; Ohlander et al., 2013). Clinical symptoms of chronic mercury intoxication can be observed (Bose-O'Reilly et al., 2008a). Increased levels of mercury can be found in breast-milk, contributing to an additional exposure pathway for breast-fed infants (Bose-O'Reilly et al., 2008b). There are concerns, that mercury in breast-milk does have a negative effect on the breast-fed child (Al-Saleh et al., 2013; Dórea, 2004; Dórea, 2014). There is a complete lack of studies to investigate the possibility that

mercury exposure during pregnancy in ASGM areas might have a negative effect on the pregnancy outcome.

Mining activities do have a negative effect on the health of miners and the community members. Mercury is a serious environmental pollutant and health hazard in ASGM areas. Data for human biomonitoring results show increased levels of mercury in certain mining areas (Baeuml et al., 2011; Kristensen et al., 2013). Data for health effects are rare (Gibb and O'Leary, 2014). Other possible health hazards due to mining are accidents in tunnels, shafts, and open pits, available data is rare (Calys-Tagoe et al., 2015; Hentschel et al., 2002). The use of cyanide is not controlled or monitored, even so possible negative health effects are likely (Donato et al., 2007; Obiri et al., 2006). Other hazards are noise and dust, cadmium, lead and arsenic (Amedofu, 2002; Bartrem et al., 2014; Basu et al., 2015; Basu et al., 2011; Burki, 2012; Chadambuka et al., 2013; Dooyema, 2010; Greig et al., 2014; Lkhasuren et al., 2007; Ono et al., 2012). The baseline data for these hazards is insufficient to estimate the real risk for the health of miners and community members in ASGM areas. To obtain more data integrated assessments are necessary (Basu et al., 2015). To analyze mercury laboratories with appropriate equipment and trained staff are needed. Health care providers, including doctors, nurses, pharmacists and community health workers, need the training to be able to diagnose and treat chronic mercury intoxication (Bose-O’Reilly et al., 2008c). Intoxicated people need proper treatment with detoxifying medication (chelating agents). The available drugs need to be licensed and made available by the respective national authorities. Appropriate health care centers in ASGM areas have to be set up and funded. Health data from ASGM areas requests to be collected, analyzed and consequences of the results need to be taken by stakeholders and policymakers. Screening programs for pregnant women, children

and miners are needed to identify intoxicated people. Regular human-biomonitoring should be established to be able to identify hot spots, and to evaluate intervention programs. To reduce knowledge gaps studies are needed - accidents, noise, dust, cyanide, cadmium, arsenic and lead need to be urgently assessed. Studies to assess the specific risk for children and infants are needed, like birth cohorts to improve the knowledge of per- and postnatal effects of mercury. The awareness, that mercury is a serious health hazard, is the key to required urgent actions and needs to be increased on all levels, from national policymakers, regional stakeholders, to health experts and the population in mining areas.

Effects of Dental Amalgam

There remains significant concern worldwide about the potential health effects of exposure to mercury vapour (Hg0) that may be released from dental amalgam restorations. This form of restoration has been used for over 100 years, and most standard formulations contain approximately 50% elemental Hg. Expert panels from across Europe, United States, Canada, and Australia among others have concluded that there is no strong scientific evidence to make a causal link between dental amalgam restorations and adverse health outcomes except for some rare cases of hypersensitivity in some people (Brownawell et al., 2005). Nonetheless research continues in this area. Foremost is that Hg exposures have been steadily declining among dental professionals in many regions. For example, through a biomonitoring program run by the American Dental Association on their membership, researchers have shown a decrease of nearly 10-fold in the urinary Hg values between 1975 and 2012 (Goodrich et al., 2015). In addition to

continued biomonitoring efforts, in recent years, a number of new paradigms in the Hg mercury sciences have been applied to studies of dental professionals that are briefly reviewed here.

Stable isotopes of Hg have emerged as an analytical tool to better track Hg in the ecosystem and people as well as distinguish between exposure to MeHg and Hg0. Characterization of mass-independent fractionation of Hg stable isotopes in human biomarkers (blood, hair, urine) can be used to differentiate between exposure to MeHg derived from seafood (with high positive mass-independent fractionation; i.e., Δ199Hg values) and geologically derived Hg such as Hg0 inhaled from dental amalgams (exhibits no mass-independent fractionation). In contrast to mass-independent fractionation, mass-dependent fractionation of the isotopes can be used to understand processes occurring in the body such as MeHg demethylation. Sherman et al. (2013) characterized Hg stable isotopes in hair and urine samples from a small group of 11 dental professionals and drew two main conclusions. First, the stable isotope results confirmed that Hg measured in hair largely originates from seafood ingestion, which is an observation made by many others. Second, a large percentage of Hg in urine may be derived from the ingestion and demethylation of MeHg that is derived from seafood. This contradicts a widely held assumption that Hg in urine is derived from exposure to inorganic sources of Hg. This assumption held true from those individuals who had more than 10 personal amalgams but for participants with less than 10 personal amalgams, >70% of the urinary Hg was estimated to be derived from seafood. This finding raises important questions about how Hg exposure assessments are performed in dental populations but also the general public. Since the publication of this work by Sherman et al. (2013), other stable isotope studies have been performed with human populations that are deepening our understanding of how people handle Hg (Li et al., 2014; Sherman et al., 2015).

Genetic polymorphisms have emerged to help us better identify biomarkers, sensitive sub-groups, and life stages. This is particularly important for research on dental amalgams given the rare cases of hypersensitivity that occur. It begs the question whether genetic susceptibilities to Hg exist thus rendering some individuals hypersensitive. Studies involving dental professionals have documented a role of genetics in terms of modifying the relationship between Hg exposure and adverse health outcome for the following: 1) a polymorphism in CPOX4 and altered porphyrin excretion (Woods et al., 2005); 2) a polymorphism in BDNF and performance on neurobehavioral tests such as hand steadiness and finger tapping, both of which are critical to dental professionals (Echeverria et al., 2005); 3) a deletion in the SLC6A4 promotor on finger tap and hand steadiness tests (Echeverria et al., 2010); and 4) a polymorphism in BDNF with indicators of anxiety and memory (Heyer et al., 2004).

Effects of Hg in cosmetics and in Thimerosal-containing vaccines

Exposure to mercury occurs by inhalation (metallic Hg vapor/ionized mercury), ingestion (methylmercury-MeHg), through the skin in cosmetic products (skin-lightening creams), and injection (ethylmercury-EtHg). Skin-lightening creams are used by pregnant and lactating mothers (Al Saleh, 2016) and Thimerosal-containing vaccines are given to pregnant mothers, newborns, neonates, and children (Marques et al, 2016) in less developed countries. We do not have established criteria for neurologic diagnosis due to low doses of these types of Hg exposure. Because of the vulnerability of young humans to the intellectual disabilities provoked by MeHg (Cohen et al, 2005) and EtHg (Geier et al, 2015), concerns are justifiably heightened (Dórea, 2015). When combined exposures to MeHg and EtHg are evaluated, increases in neurodevelopmental delays may occur (Marques et al, 2016). Currently, only less developed

countries use pediatric Thimerosal-preserved vaccines. In these populations, the exposure to both forms of organic Hg is associated to fish (MeHg in an important food source) and vaccine (an essential item of modern medicine to prevent infectious diseases). Concerns about any one single chemical form of exposure are compounded when we consider the cumulative total Hg load. Therefore, to safeguard neurological development in children, it is important that all forms of Hg, inorganic or organic (not only environmental MeHg but also iatrogenic EtHg) exposure be identified and reduced.

Nutrients reported to modulate MeHg toxicity

Research on the developmental effects of MeHg exposure from fish consumption with background contamination has been extensive albeit, there is still substantial scientific uncertainty about the consequences, if any, of low-level MeHg exposure and the safety or risk of fish consumption. It is, however, clear that metabolism and/or toxicity of MeHg are modulated by intake of dietary nutrients including those concomitantly eaten with fish (Gagné et al, 2013). The mechanisms underlying the potential protective effect of foods on mercury exposure and toxicity are not fully understood albeit is an area of growing scientific interest (Donaldson et al., 2010; Deroma et al, 2013, Choi et al, 2014, Strain et al, 2015).

Several nutrients and foods have been associated with modulating MeHg including n-3 polyunsaturated fatty acids (PUFA), selenium, iodine, tomatoes fruit and antioxidants such as lycopene proanthocyanidins and tea polyphenols (Liu et al., 2014; Yang et al., 2012; Gagné et al, 2013). More recently the impact of the GUT microbiome has received attention for its role in the excretion of MeHg (Rothenberg et al, 2016; Rand et al, 2016). With respect to inorganic

mercury, animal studies have identified antioxidants, including lycopene, as potential protective factors against toxicity induced by MeHg (Deng et al., 2012).

The primary route of MeHg in the human diet is from consumption of fish with the species and age of the fish impacting on the amount of MeHg. Fish is an important source of nutrition worldwide being the primary source of protein for approximately four billion people (FAO 2012). While the recently-ratified Minamata Treaty will reduce future anthropogenic releases of mercury and mercury compounds (Landrigan et al. 2013), about 70% of atmospheric Hg emanates from natural sources and re-emissions (UNEP 2013). Therefore, exposure to MeHg from fish consumption will continue to pose a potential risk to child development. Contrary to this, the ALSPAC study reported that the contribution of seafood (white fish, oily fish, and shellfish) accounted only for an estimated 6.98% of the variation in blood mercury levels in the pregnant women included in the analysis (Golding et al, 2013). In this study, herbal teas were unexpected dietary predictors of total blood mercury. It must be noted that self-reported dietary data is challenged by misreporting and care should be taken when using such data to inform health policy (Hebert et al, 2014). Furthermore, that this study does not take into account variability in absorption or the metabolism of Hg. More recently exposure to MeHg from foods sources other than fish has received much-needed attention. Exposure to MeHg from the consumption of rice contaminated as a result of inorganic mercury pollution has given concern as rice is a stable food for billions especially in East and Southeast Asia (Barrett, 2010; Lin et al, 2012). In some Hg mining regions of China, the MeHg concentrations of rice is much higher than the national limit of Hg in food (Meng et al., 2014). Similarly, vegetables and meat produced in these regions have been shown to contribute largely to the total mercury exposure.

Rice lacks the nutrients which are proposed to offset the neurotoxicity of MeHg (Barrett, 2010) therefore research is needed to determine the effects of consuming rice and other foods contaminated with MeHg on health effects especially during pregnancy and child development.

Balancing the benefits of fish intake with the detriments of low-level mercury exposure has provided a challenge to researchers when devising dietary recommendations in pregnancy (Teisl et al. 2011). Fish contain nutrients essential for maternal and fetal health, including long-chain polyunsaturated fatty acids (PUFA), selenium, vitamin E, and other nutrients (Myres et al, 2007). Fish are the primary source of docosahexaminic acid (DHA) which is a major lipid in the brain and essential for normal brain function (Kuratko et al. 2013) therefore limiting fish consumption during pregnancy could adversely affect child development. Guidelines from Australia, Europe, and the USA all encourage pregnant women, those who may become pregnant, breastfeeding mothers and young children to eat more fish and to eat a variety of fish from a choice that is lower in mercury. A recent joint report from the FAO/WHO recommended that the neurodevelopmental benefits of consuming fish be explicated (FAO/WHO, 2010). Nevertheless, it has been proposed that the present fish consumption advisories have led to a decline in fish intake by pregnant women with no clear indication that this trend has benefitted children's health (Bloomingdale, 2010). Uncertainty about possible developmental effects continues to represent a challenge for devising public policies on fish consumption. As previously discussed mercury is a powerful neurotoxin harmful to the developing brains of the fetus and young children. The Environmental Working Group (EWG) in the USA recommend that more advice is needed for pregnancy women on the type of fish they should consume as the current advice may result in exposure to high mercury and low omega-3 fatty acids (Lunder, 2016). The EWG conducted a

study on pregnant women who were frequent consumers of seafood and observed that some 30% and 60% had hair mercury concentrations >1ppm and >0.58 ppm respectively; values reported to be associated with negative outcomes to the developing fetus (Grandjean et al, 2012).

Furthermore, few of the pregnant women within this study met the dietary intake recommendations for omega-3 fatty acids despite being frequent seafood consumers. Several studies have now shown that the benefits of seafood consumption during pregnancy are apparent when mercury concentrations are low (Oken et al, 2008; Sagiv et al, 2012). The EWG propose that pregnancy women should be provided with more advice by the FDA and EPA on seafood which is a rich source of omega-3 fatty acids and low in mercury. Studies have revealed that the association between maternal fish consumption and child development outcomes is far more complex than initially thought. Results from prospective mother-child cohorts in the United Kingdom, Spain and the Republic of Seychelles have shown no adverse associations between prenatal MeHg exposure and children's subsequent development (Davidson et al, 1998; Myres et al, 2003; Daniels et al, 2004; Davidson et al, 2008; Strain et al, 2008; Strain et al 2015; Llop et al, 2012) whilst studies from New Zealand, the Faroe Islands, and the United States have reported adverse developmental influences of prenatal MeHg exposure (Crump et al, 1998; Grandjean et al, 1997; Sagiv et al, 2012; Debes et al, 2016). Variability in study designs, populations, genetic susceptibility and nutrition may explain some of the inconsistencies between studies. Research on fish consumption during pregnancy indicates that allowing for PUFA present in fish in statistical analysis may influence whether or not neurocognitive associations with MeHg are found (Budtz-Jørgensen et al., 2007; Strain et al 2012; Strain et al, 2015). The n-3 PUFA in fish has been increasingly identified as having health benefits (Karimi et al, 2014).

The toxic effects of MeHg on the developing brain is considered to be mediated by oxidative damage, which in turn causes inflammation (do Nascimento et al, 2008). Maternal PUFA status, a putative indirect marker of inflammation, is suggested to modify MeHg associations with psychomotor development (Strain et al, 2012). The relative amounts of n-3 PUFA available in the diet are important for determining the physiologic n6/n3 balance and the maternal inflammatory milieu. Incorporation of the less pro-inflammatory n-3 PUFA, may reduce any possible inflammatory insults following MeHg exposure in the brain and subsequently benefit child development (Janssen et al, 2013; Strain et al, 2015).

It is well known that fish are also rich in a number of micronutrients such as selenium and iodine which are nutrients known to enhance neurodevelopment. Selenium (Se) is an essential nutrient that is required for normal function of enzymes that protect brain and endocrine tissues from oxidative damage (Rayman, 2012). Selenium has received attention as a potential protector from methylmercury toxicity in populations with high fish consumption (Berr et al, 2009; Ralston & Raymond, 2010; Carocci et al, 2014; Bjørklund, 2015). It is proposed that the toxicity of MeHg is related to the amount of selenium where the formation of MeHg-selenocisteine compounds is proposed to reduce the bioavailability of selenium and thus interferes with the synthesis of the selenium-dependent antioxidant enzymes that provide antioxidant protection to the brain (Raymond & Ralson, 2009). Nevertheless the role of Se in MeHg intoxication remains to be confirmed due to inconsistencies in animal studies along with a lack of evidence from epidemiological studies (Farina et al, 2011). Fish is also the major dietary source of iodine which is a component of the thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3) and essential for neurodevelopment (Pearce, 2013). Mercury has been found to be inversely associated with

thyroid hormone concentrations in adults and immunotoxic mechanisms have been suggested (Chen et al, 2012). Dietary iodine is taken up by the thyroid for synthesis of these hormones, stimulated by thyroid stimulating hormone (TSH) in a pathway which also requires selenoprotein iodothyronine deiodinase (DIO) enzymes (Skeaff, 2011). It is proposed that Hg accumulates in the thyroid, reduces iodide uptake at the sodium/iodide symporter and inhibits DIO activity (Chen et al, 2011). Furthermore, insufficient selenium can impair thyroid hormone production and reduce antioxidant status, which can exacerbate iodine deficiency. Consequently, there is believed to be interdependence between selenium and iodine in their effects on thyroid function and neurodevelopment and these nutrients may modify the effects of MeHg albeit much research is needed to fully elucidate these relationships.

Research carried out in the Brazilian Amazon identified fruit consumption as having a protective effect against MeHg exposure (Passos et al., 2007) and propose that the soluble dietary fibre and prebiotic nutrients found in fruit could be impacting on MeHg metabolism in the GUT. The gut flora plays a predominant role in the excretion of methylmercury through demethylation and the release of inorganic mercury (Clarkson and Magos, 2006). A study of Inuit preschool children reported an inverse relationship between the consumption of tomato products and blood mercury concentrations (Gagné et al, 2013). Along with having putative effects on the GUT microflora impacting on demethylation rates, they also suggest that a good supply of dietary antioxidants, including lycopene in tomatoes, would preserve glutathione enabling it to bind MeHg and contribute to its secretion into bile as glutathione–mercury complexes (Clarkson and Magos, 2006). Silva de Paula et al. (2016) found protective effects of niacin (rich in fish) against MeHg-induced genotoxicity and alterations in antioxidant status in rats. It is clear that some nutrients

consumed concomitantly with MeHg in the diet may ameliorate its toxicity albeit much more research is needed to fully investigate the mechanisms of action.

Genetic factors

Over the past decade, scientific studies have emerged to document that genetic and epigenetic factors may influence mercury exposure and associated health risks (reviewed by Basu et al., 2014; Llop et al., 2015). The results of these studies are helping to increase our understanding of Hg's mechanisms of actions, and in turn, this knowledge is expected to help us better identify biomarkers, sensitive sub-groups, and life stages. Further, the outcome of these studies may help reduce uncertainty in our risk assessments and thus improve decision-making.

As background, several biological pathways (e.g., DNA repair, chemical biotransformation) have evolved to help protect the human body from environmental insults. The genes in these pathways are often referred to as environmentally responsive genes, and these genes may have variant forms to help living organisms cope with a changing environment. Environmentally responsive genes important to how the human body handles Hg can include those involving glutathione (e.g., glutathione s-transferases), proteins that bind and transport Hg (e.g., metallothioneins), and xenobiotic transporters (e.g., solute carriers). Polymorphisms in these environmentally responsive genes are ubiquitous across populations, and thus may influence the absorption, distribution, metabolism, and elimination of Hg.

Cross-sectional, hypothesis-driven studies from across the world are beginning to show that

genetic polymorphisms in selected environmentally responsive genes can be associated with the main effect (i.e., carriers of wildtype and variant forms have different Hg biomarker levels) and gene-environment interactions (i.e., exposure-biomarker relationships are different between carriers of the wildtype and variant form). Such observations have been made on studies involving, for example, dentists (Goodrich et al., 2011; Yang et al., 2012; Parajuli et al., 2016), students (Gundacker et al., 2007; Gundacker et al., 2009), riverine populations (Barcelos et al., 2013; Barcelos et al., 2015) and gold miners (Custodio et al., 2005; Harari et al., 2012; Engstrom et al., 2013). The work to date has largely focused on adults and much less is known about early-life exposure situations. Further, most of the studies have focused on populations exposed mainly to inorganic sources of Hg, and the MeHg exposures are generally within background levels.

Moving beyond the influence of genetic polymorphisms on Hg exposure biomarkers (i.e., toxicokinetics), there are a handful of studies showing that genes are important in the toxicodynamics of Hg. A study from Korea documented that the Hg-associated risk of low birth weight in newborns was greater in carriers with deletion polymorphisms of GSTM1 and GSTT1 (Lee et al., 2010). A series of studies involving dental professionals documented the importance of considering genetic polymorphism information when address exposure-outcome relationships (Woods et al., 2005; Echeverria et al., 2006; Echeverria et al., 2010), and these are elaborated upon later in this paper. There are relatively few health studies that have considered genetics and much more work is needed in this area particularly in terms of expanding the number of polymorphisms studied and how they are selected, and involving cohort studies with large sample sizes.

Early life mercury exposure was found to increase the ethnic risk of developing Kawasaki disease (KD), a condition that causes inflammation in the walls of medium-sized arteries throughout the body, including the coronary arteries, which supply blood to the heart muscle. East Asian children are 20 times at risk to develop KD (Mutter & Yeter 2008). A study conducted in the US showed that African, Asian, Caucasian, and Hispanic children in the US having increasing low-dose exposure to Hg may induce KD or contribute to its later development in susceptible children (Yeter et al. 2016). More research is needed to study this disease caused by gene-environmental interactions.

Epigenetics refers to heritable factors that affect gene expression but occur outside of direct changes to the DNA sequence (Head et al., 2012). Such epigenetic factors can be influenced by stimuli such as contaminants but also by psychosocial stress and nutritional status. Epigenetic marks (e.g., DNA methylation, histone modification) left by such stimuli can persist in the absence of the initial stressor, and this supports the notion that exposures to stressors in early life can lead to adverse health outcomes later in life. Epigenetic mechanisms are likely very relevant for Hg (reviewed by Basu et al. 2014) as the contaminant is an established developmental toxicant that can have a long latency period between exposure and disease. There is some emerging evidence from both animals (Pilsner et al., 2010; Basu et al., 2013) and humans (Hanna et al., 2012; Goodrich et al., 2013) to suggest that Hg is epigenetically active, and these studies provide a foundation to explore the matter deeper.

The risk assessment of Hg is challenged because of great inter-individual variability that can

exist in its exposure and health effect, and the latencies exposure and health effect can range from weeks to years (Canuel et al., 2006; Basu et al., 2014). Variation has largely been addressed by trying to account for biological or environmental factors such as age, sex, accuracy of dietary surveys, and the measurement of other toxicants and nutrients yet the inclusion of such factors has been met with limited success. There is growing evidence that consideration of genetic polymorphisms and epigenetic processes may help better resolve underlying mechanisms, identify susceptible sub-populations, and ultimately improve risk assessments and decision making. Genes recommended for future studies are outlined in recent reviews by Basu et al. (2014) and Llop et al. (2015).

Risk communication and Policy

It is expected the global inventory of Hg will decrease and will subsequently lead to a reduction in Hg exposure and health risk when the Minamata Convention is ratified and implemented. However, Sunderland & Selin (2013) stated that most future emissions scenarios project a

growth or stabilization of anthropogenic mercury releases relative to present-day levels. Analyses that only consider changes in primary anthropogenic emissions are likely to underestimate the severity of future deposition and concentration increases associated with growth in mercury reservoirs in the land and ocean as mercury already in the environment can be re-emitted via processes in the natural cycle, resulting in a longer lag time before pollution reduction can have a demonstrable effect on the food chain. (Bender et al. 2014; Elsie M Sunderland & Selin 2013). Seawater mercury concentration trajectories in areas such as the North Pacific Ocean that supply large quantities of marine fish to the global seafood market are projected to increase by more than 50% by 2050 (Sunderland et al. 2009). Therefore, much research is needed to characterize the physical-chemical-biological interactions in the environment, as well as impacts of environmental management before a direct relationship between anthropogenic emission and exposure among human populations, can be established. Chan & Jacobs (2013) used a dynamic model to simulate such a complex problem in a stream basin in Kentucky, USA. This example illustrates that it is possible to manage the environmental issues at a local scale if sufficient scientific data are available.

In the near term, health professionals need to implement effective risk management and risk communication programs to minimize exposure risks. The importance of including the nutritional benefits in the risk assessment of Hg exposure from fish consumption is discussed in the earlier section. The FAO and WHO held an Expert Consultation workshop in 2011 (FAO/WHO 2011) to address the dilemma of fish consumption and proposed an integrative approach that balances the benefits of n-3 polyunsaturated fatty acids with the risks of Hg among women of childbearing age. Similar risk assessment model has been applied at the national level

in the US and Europe (Rheinberger & Hammitt 2012; EFSA Scientific Committee 2015) and at regional levels such as the Canadian Arctic (Laird et al. 2013).

However, issuing dietary advisory may not necessarily lower Hg exposure. One of the reasons is because of the complicated message of different consumption rate for different species of fish (Wenstrom 2014). The message may not be easily communicated to the target population. (Ser & Watanabe 2012) reported that the public awareness of the fish advisory was very low in both USA. Herdt-Losavio et al. (2014) conducted a cross-sectional study with 421 adults and 207 children (171 adult-child pairs) examining the generational differences in fish consumption and knowledge of benefits/warnings of fish consumption among parents and children. They found that in 71% of parent-child pairs, both the parent and the child knew of benefits of consuming fish; but only 31% knew of warnings. Parental consumption of high or moderately-high-mercury fish was related to the child's consumption of fish in the same category. Parents and children need additional education to make better choices about fish consumption. Education should target the family and include specifics about benefits and risks.

On the other hand, one must caution that there is a possibility that a strong emphasis on mercury toxicity may drive the general population towards a trend of lower fish consumption. This may lead to an unnecessary loss of nutritional benefits among the portion of populations that were not at risk of over Hg exposure. A delicate balance and clear communication messages need to be developed. The challenge on issuing fish consumption advice was comprehensively discussed by Nesheim & Nestle (2014) including the importance to consider the sustainability of fishery stocks globally. Successful cases have been demonstrated in Greenland and Faroe Island that

with effective communication programs/messages, dietary advisory can result in lowering Hg burden among pregnant without causing unwarranted anxiety and loss of nutrition benefits (Bjerregaard & Mulvad 2012; Weihe & Joensen 2012).

Conclusion

This critical review has made an attempt to highlight the most important findings in the understanding of health issues related to Hg exposure. A number of knowledge gaps have been identified in each of the areas discussed. Researchers and health professionals need to work closely together to conduct strategic research to address these knowledge gaps so that policy makers can formulate intervention policy based on the best science. Extra efforts are needed to harmonize the research design and methodology so that integrated data can be generated to provide more conclusive evidence. Finally, more resources are needed to devote to knowledge synthesis.

The following is a summary of recommendations from the Panel members:

- Using unvalidated instruments for dietary assessment often resulted in high degree of uncertainty in exposure assessment. Improvement on the accuracy of dietary exposure, for example, using stable isotopes, are needed.

- Potential new sources of exposure such as rice consumption and skin cream use have not been fully assessed. Research results from multiple countries are needed to assess the scope of the problem nationally and internationally.
- Combined effects of co-exposure with other contaminants e.g. MeHg and PCBs, MeHg and Pb, MeHg and As, EtHg and Al, from seafood consumption, will be important for future studies.
- Continuing research efforts on effects of low-dose MeHg exposure on children's health is needed. Future studies need to make an effort to harmonize the parameters measured, for example, the biomarkers used for dose and the neuro-performance assessment tools used for effects.
- Effects of Hg on metabolic syndrome and delayed long-term effects among adults need to be characterized.
- Hg exposures in ASGM communities are amongst the highest worldwide though relatively few health studies have been conducted, and of these, few have accounted for the multiple public health hazards that exist in such communities.
- Potential effects of nutrient interactions needed to be considered in all Hg health studies and more research is needed to quantify the protective effects of food or nutrients to establish effective public health guidelines.
- Genetic research is beginning to show that polymorphisms may help explain inter-individual differences in exposure and health effects, though only a handful of genes have been investigated thus far and thus more work is needed to expand the number of targets studied.
- Effective communication messages need to be developed to increase awareness and lower exposure among the seafood consumers, and the ASGM communities.
- Researchers and health professionals should assist policy makers at the national level to implement the Minamata Convention to restrict the use of Hg and establish national policy based on precautionary prevention strategy.

- National monitoring programs to ensure the safety of food and nutritional and health surveillance to ensure healthy diet and lifestyles among vulnerable groups.

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