Current progress on understanding the impact of mercury on human health

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ABSTRACT

Mercury pollution and its impacts on human health is of 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 efforts are needed to translate the research results into management tools for health professionals and policy makers.

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1. Introduction

Mercury (Hg) is a global pollutant that affects human and ecosystem health (UNEP, 2013a, 2013b). The awareness of the health effects of Hg pollution began in the 1950s when chemical waste was released into the nearby sea by the Chisso Corporation in Minamata, Japan. This waste led to the accumulation of the more bioavailable form of Hg, i.e. methylmercury (MeHg) in fish, and as a consequence it resulted in devastating health effects to thousands of local populations who consumed the fish as their main food source (Kurland et al., 1960). It is well documented that prenatal or postnatal exposure to MeHg produces adverse neurological impacts in adults and children, now known as Minamata Disease (Harada, 1995). These patients with chronic Hg poisoning 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 the 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 billions of people

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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 these issues. For example, the United Nations Environment Programme (UNEP) has implemented a number of global projects that aim to decrease human health and environmental risk from the release of Hg, as well as to improve the understanding of international Hg emissions and their transport and fate (UNEP, 2013a). Most significantly, an international treaty (Minamata 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 which is expected to occur in 2017. Article 16 of the Convention relates to the concern on human health aspects. It encourages states to promote strategies to: 1) identify all the population affected by Hg pollution; 2) to adopt health guidelines regulating Hg exposure; and 3) to provide education about the dangers of Hg exposure. Countries should provide appropriate health-care for treatment and care for people who are already exposed to Hg compounds. It is clear that more scientific knowledge is needed to fully understand effects of Hg exposure and 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 assure all the most recent publications are included in our attempt to address these questions.

2. 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; genetics 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 (Fig. 1).

3. 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.

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

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

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

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.

4. Discussion

There were 25 review papers published during that period. The relatively high number of review papers (almost 5%) probably reflected the increased scientific interest in Hg research and the response from environmental health scientists to the call from the national and international agencies on the need for scientific evidence to support the signing of the Minamata Convention. We highlight four 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 and Kaur (2012) attempts to address the long time “mysteries” of MeHg 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.

4.1. Environmental exposure and risk assessment

The World Health Organization (WHO, 2010) recognize the importance of collecting site-specific data of Hg concentrations in fish and seafood from around the world as there is a high intraspecies 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 highlights the need for collecting local data for exposure assessment. As a result, 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 evidence relating to its impact on public health and international trade. Most papers report 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 surveys which report 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 (Rajaei et al., 2015), and Suriname (Peplow and 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 on the 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 farmed fish or shellfish, for example Delgado-Alvarez et al. (2015) reported Hg in farmed shrimp in NW Mexico and characterized the risk of exposure is low using the national consumption rate. Increasing evidence suggests 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. Hg is also widely used in cosmetic products and 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.

4.2. 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 (Hg0), divalent mercury (Hg2+), 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 is 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 is to estimate external dose by measuring concentrations in foods or air or water and multiplying this by the frequency of exposure like consumption rate or inhalation volume over time. The second method 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 report adjusted R² 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 Hg concentrations of 1866 adult participants in Korea and reported the adjusted R²=0.234. Further studies with more precise estimations of dietary Hg intake are required to evaluate the risk for Hg exposure from food and assure risk management within heavily exposed groups.

Human absorption of liquid Hg0 is minimal, and acute toxicity does not occur even when the liquid Hg 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 Hg0 is absorbed into the blood and easily passes through the BBB in its un-oxidized form, thereby reaching the brain and damaging the CNS (WHO, 1976). With time, gaseous Hg0 in the body is oxidized to Hg2+, which accumulates in the kidneys and causes damage there (UNIDO, 2008). The biological half-life of Hg absorbed from vapor into the blood is approximately 2–4 days when 90% is excreted through urine and feces. Absorption of Hg2+ through the digestive tract is comparatively low. However, a large intake of Hg2+, 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 is 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 (Se), Hg and MeHg in blue shark meat due to water loss, particularly grilling. While 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 farmed meagre compared to fresh meagre before a consistent demethylation. Carneiro et al. (2014) also found inorganic Hg 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 that 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 Hg stable isotope ratios have emerged 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 should reflect the MeHg concentration in the brain, since the brain is the major target organ. Generally, the amount of Hg retained in the body reaches a steady state 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 such steady state conditions. Therefore, Hg concentration in the blood/red blood cells is proposed to be 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 250–300-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 biomarker 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. Libera et al. (2014) measured total hair and total blood Hg concentrations in 1333 individuals from 9 First Nations communities in northern Quebec, Canada and found that 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 27 participants of a 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 may be unreliable, particularly at an 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 concentrations in fingernails and toenails at parturition have also been shown to have a strong correlation with Hg concentrations 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 and methods are used to estimate exposure. A more concerted effort is required to harmonize human biomonitoring survey design and data interpretation. For example, Smolders et al. (2015) reported the first ever such effort to harmonize biomarker data in 17 European countries.

4.3. Effects on children development

Hg 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 outcomes, with respect to low-level Hg exposure or environment dose, from the 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., 2015).

Previous studies have reported that prenatal exposure to MeHg 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 been associated with an increased risk of chronic diseases in adulthood, including metabolic syndrome (Fox et al., 2012). Thus, elucidating the associations of environmental contaminant 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 Hg, 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 MeHg in utero exhibit decreased motor function, attention span, verbal abilities, memory, and other mental functions (Grandjean et al., 1997). Overall, research from the Faroe Islands has reported that a doubling of the prenatal Hg exposure results in a developmental delay of one to two months when the child is aged seven years; that is, at the age when the child is expected to enter school. This delay corresponds to approximately 1.5 IQ points (Grandjean and Herz, 2011) and it is suggested that this observed neurocognitive impact persists into adulthood as a small effect on educational achievements was observed at age 22 years (Debes et al., 2016). No effects were found on school performance at 16 years, and only a small effect on educational achievements was observed at age 22 years (Debes et al., 2016). 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 = 1311) 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 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 Hg, PCB and lead on child behavior in 306 30 month old children and reported 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 months but not with Hg or lead (Tatsuta et al., 2014). In contrast, Kim et al. (2011) studied 921 mother-child pairs in Korea and found that the cord blood Hg concentration 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 Hg have been hypothesized to be associated with increased risk of autism spectrum disorders (ASDs) (Grandjean and 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
individuals or populations affected by MeHg exposure from adults depend on methods/strategies to identify susceptible in-

4.4. Effects on fish consumption.

A number of other studies have reported that exposure to MeHg does not play an important role in the development of ASD phenotypic behavior. For example, Yau et al. (2014) reported no significant association between ASD 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 MeHg 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 1784 children, adolescents, and young adults. No consistent association between prenatal MeHg exposure and the 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 (Ulló 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 bio-monitoring section, the use of maternal hair or blood as bio-

4.4. 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 MeHg exposure from fish consumption. There are no cases where markers of environmental MeHg exposure from fish consumption are indicators or pro-

dromes 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 705 μg/g (Koos and Longo, 1976; Harada, 1982). A recent study in Japan showed that residents who were exposed to elevated MeHg historically still show significant functional deficit decades later (Ushijima et al., 2012).

Interestingly, Amazonians who consume large amounts of fish and have Hg concentrations as high as 90.6–303.1 μg/g yet do not display the clinical symptoms of ‘Minamata disease’ (Boischo and Barbosa, 1993). Moreover, a cross-sectional study also reported no observable effects on neurological outcomes among whole meat consumers in Japan who had high Hg exposure (average hair Hg concentration of 14.9 μg/g) (Nakamura et al., 2014). The authors suggest that the high Se 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 (Dorea 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 Hg concentrations were associated with the prevalence of hypertension and that simultaneously elevated serum ferritin and Hg concentrations are related to the risk for hypertension in men in Korea. However, in a cross-sectional study of the U.S. general population, Park et al. (2013) found no association of hypertension with blood Hg but a suggestive inverse association with urinary Hg. 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 2114 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 3875 American young adults, and found that toenail Hg levels are associated with incidence of diabetes over 18 years of follow-up after adjusting for age, sex, obesity, 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 study reported that people with high Hg 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.
4.5. Health hazards of artisanal and small-scale gold mining

Liquid mercury (Hg\textsuperscript{0}) is applied in artisanal and small-scale gold mining (ASGM) to extract gold from ore. Gold containing ores are grinding, mixed with liquid Hg and panned. During this process gold binds to Hg forming an amalgam. The amalgam is then smelted; Hg being vaporized and gold remains. The panning and smelting expose the smelters and the inhabitants of the mining village to toxic Hg vapor (Hg\textsuperscript{0}) (Cordy et al., 2013; Cordy et al., 2011; De Miguel et al., 2014; Gonzalez-Carrasco et al., 2011). Once Hg is released it methylates in the aquatic food chain, and becomes bioavailable. Especially Hg polluted waters, coming from ASGM areas, can contaminate fish leading to high MeHg levels (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). Hg can accumulate in rice grown in ASGM areas and ingestion of this polluted rice contributes to the MeHg exposure of the population (Bose-O’Reilly et al., in preparation; 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 Hg\textsuperscript{0} vapor, and depending on the local situation to ingestion of MeHg from local fish and/or rice. Exposure scenarios are similar downstream and downstream from mining areas.

This exposure to Hg in ASGM areas shows high concentrations of Hg in human specimens as reported in several studies (Gibb and O’Leary, 2014; Kristensen et al., 2013). Both reviews showed that miners and their families are exposed to Hg vapor; that the exposure with inorganic Hg vapor is high, that fish contains MeHg and that the toxic effects have to be considered. Hg concentrations in any analyzed biomarker were observed to be higher compared to control groups or reference values. Smelting and panning did lead to high and very high levels of Hg, especially not only in urine, but also in blood and hair. Up to 80% of smelters were found to have typical signs of chronic Hg intoxication, mainly neurological symptoms like ataxia, tremor and coordination problems (Bose-O’Reilly et al., 2010a, 2010b; Drasch et al., 2001; Lettmeyer et al., 2010; Steckling et al., 2011, 2014). World Health Organization (WHO) is concerned about Hg 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 downstream 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 Hg intoxication ranks within the top 20 health hazards of the country (Steckling et al., 2014; Steckling et al, 2015). Hg is a serious health problem especially for children (Afandiyev et al., 2011; Bose-O’Reilly et al., 2010c). Limited evidence exists of the health hazards for children in ASGM areas (Bose-O’Reilly et al., 2008a; Grandjean et al., 1999). Children are exposed by living in ASGM areas, inhaling Hg fumes and ingesting MeHg 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 Hg (Amon et al., 2012; Kippenberg, 2011). The exposure to Hg leads to increased Hg concentrations in urine, blood and hair (Bartrem et al., 2014; Hrubá et al., 2014; Olander et al., 2013). Clinical symptoms of chronic Hg intoxication can be observed (Bose-O’Reilly et al., 2008a). Increased concentrations of Hg have been observed in breast-milk, contributing to an additional exposure pathway for breast-fed infants (Bose-O’Reilly et al., 2008b). There are concerns, that Hg in breast-milk does have a negative effect on the breast-fed child (Al-Saleh et al., 2013; Dórea, 2004, 2014). There is a lack of studies to investigate the possibility that Hg 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. Hg is a serious environmental pollutant and health hazard in ASGM areas. Data for human biomonitoring results show increased levels of Hg in certain mining areas (Baemul 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 albeit there is a scarcity of available data (Calys-Tagoe et al., 2015; Hentschel et al., 2002). The use of cyanide is not controlled or monitored and as a result possible negative health effects are likely (Donato et al., 2007; Obiri et al., 2006). Other hazards are noise and dust, cadmium, lead and arsenic pollutants (Amedofo, 2002; Bartrem et al., 2014; Basu et al., 2013; Basu et al., 2011; Burki, 2012; Chadambuka et al., 2013; Dooyema, 2010; Greig et al., 2014; Ikhasuren 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 Hg, local laboratories with appropriate equipment and trained staff are needed. Health care providers, including doctors, nurses, pharmacists and community health workers, need to be trained in order to be able to diagnose and treat chronic Hg 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 needs to be collected, analyzed and the consequences of the results need to be considered by stakeholders and policymakers. Screening programs for pregnant women, children and miners are needed to identify those intoxicated. 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 to elucidate the effects of accidents, noise, dust, cyanide, cadmium, arsenic and lead in these populations. Studies to assess the specific risk for children and infants are needed for example the investigation of birth cohorts to improve the knowledge of pre and postnatal effects of Hg exposure. The awareness, that Hg is a serious health hazard requires urgent action on all levels, from national policymakers, regional stakeholders, to health experts as well at the population level in mining areas.

4.6. Effects of dental amalgam

There remains significant concern worldwide about the potential health effects of exposure to Hg\textsuperscript{0} 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 programme 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., 2016). In addition to continued biomonitoring efforts, in recent years, a number of new paradigms in the Hg sciences have been applied to studies of dental professionals that are briefly reviewed here.

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Stable isotopes of Hg have emerged as an analytical tool to better track Hg in the ecosystem and people as well as being able to distinguish between exposure to MeHg and Hg\textsuperscript{0}. 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., $\Delta 199$Hg values) and geologically derived Hg such as Hg\textsuperscript{0} 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 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 (Echeverría et al., 2005); 3) a deletion in the SLC6A4 promoter on finger tap and hand steadiness tests (Echeverría et al., 2010a); and 4) a polymorphism in BDNF with indicators of anxiety and memory (Heyer et al., 2004).

4.7. Effects of Hg in cosmetics and in thimerosal-containing vaccines

Exposure to Hg occurs by inhalation (metallic Hg vapor/ionized Hg), ingestion (methylmercury-MeHg), through the skin in cosmetic products (skin-lightening creams), and injection (ethylmercury-EthHg). 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 EthHg (Geier et al., 2015), concerns are justifiably heightened (Dörea, 2015). When combined exposures to MeHg and EthHg 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 EthHg) exposure be identified and reduced.

4.8. 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 Hg 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 Hg, 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 Hg and Hg compounds (Landrigan et al., 2013), about 70% of atmospheric Hg emanates from natural sources and re-emissions (UNEP, 2013a, 2013b). 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, 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 Hg 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 Hg 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 Hg exposure has provided a challenge to researchers.
when devising dietary recommendations in pregnancy (Teis 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 (Myers et al., 2007). Fish are the primary source of docosahexaenic acid (DHA) which is a major lipid in the brain and essential for normal brain function (Kuratto 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 et al., 2010). Uncertainty about possible developmental effects continues to represent a challenge for devising public policies on fish consumption. As previously discussed Hg 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 Hg 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 Hg concentrations > 1 ppm 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 n-3 PUFA despite being frequent seafood consumers. Several studies have now shown that the benefits of seafood consumption during pregnancy are apparent when Hg 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 n-3 PUFA and low in Hg. 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; Myers 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-Jorgensen et al., 2007; Strain et al., 2012, 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 (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. Se is an essential nutrient that is required for normal function of enzymes that protect brain and endocrine tissues from oxidative damage (Rayman, 2012). Se has received attention as a potential protector from methylmercury toxicity in populations with high fish consumption (Berr et al., 2009; Ralston and Raymond, 2010; Carocci et al., 2014; Björklund, 2015). It is proposed that the toxicity of MeHg is related to the amount of Sewhere the formation of MeHg-selenocisteine compounds is proposed to reduce the bioavailability of Se and thus interferes with the synthesis of the Se dependent antioxidant enzymes that provide antioxidant protection to the brain (Raymond and Ralston, 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). Hg 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 Se can impair thyroid hormone production and reduce antioxidant status, which can exacerbate iodine deficiency. Consequently, there is believed to be interdependence between Se 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 MeHg through demethylation and the release of inorganic Hg (Magos and Clarkson, 2006). A study of Inuit preschool children reported an inverse relationship between the consumption of tomato products and blood Hg 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–Hg complexes (Magos and Clarkson, 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.

4.9. Genetic factors

Over the past decade, scientific studies have emerged to document that genetic and epigenetic factors may influence Hg exposure and associated health risks (reviewed by Basu et al. (2014) and 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.

Mobilizing 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 addressing exposure-outcome relationships (Woods et al., 2005; Echeverria et al., 2006, 2010b), 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 Hg 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 of developing KD (Mutter and Yeter, 2008). A study of African, Asian, Caucasian, and Hispanic children residing in the US suggests a relationship between low-dose exposure to Hg and the development of KD and that Hg exposure may 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 to Hg exposure (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 effects, 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 Liop et al. (2015).

4.10. 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 and Selin (2013) stated that most future emissions scenarios project a growth or stabilization of anthropogenic Hg 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 Hg reservoirs in the land and ocean as Hg 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; Sunderland and Selin, 2013). Seawater Hg 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, 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 and 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 PUFA with the risks of Hg among women of childbearing age. A similar risk assessment model has been applied at the national level in the US and Europe (Rheinberger and 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 Hg concentrations in different species of fish (Wenstrom, 2014). The message may not be easily communicated to the target population. Ser and 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-Hg 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 Hg 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 and 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 women without causing unwarranted anxiety and loss of nutrition benefits (Bjerregaard and Mulvad, 2012; Weihe and Joensen 2012).

5. 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 care 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, EHTg and AI, 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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