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Impacts of farmed fish consumption and food trade on methylmercury exposure in China

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Abstract

The global pollutant mercury (Hg), especially as methylmercury (MeHg), threatens human and ecosystem health. But major contributors of MeHg exposure to people in China remain highly debated. We developed the China Mercury Exposure Assessment (CMEA) model, which incorporates human exposure pathways for MeHg and total Hg (THg), the interregional, including international and interprovincial, food trading as well as human physiology to provide a comprehensive system that can evaluate the pathway of Hg forms to human consumers in China. Based on the CMEA model that employed the most comprehensive and recent data, we have found that the probable daily intake (PDI) of MeHg for the Chinese population was 0.057 (range: 0.036 –

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0.091 as 60% confidence interval) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, while that of THg was 0.35 (range: 0.22 – 0.55) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$. MeHg exposure was dominated by fish intake, especially by farm-raised freshwater fish due to higher consumption of these fish. In 2011, fish intake contributed to 56% to the total MeHg exposure, followed by rice (26%). Consumption of farm-raised fish reduced human exposure to MeHg by 33%. On the other hand, interregional food trading increased MeHg exposure of the Chinese population, as a whole, by 7.6%. The international and interprovincial food trades contributed to 5.1% and 22% of MeHg intake, respectively. For the whole China, fish intake related exposure to MeHg was highest for the Eastern and Northeastern populations, while Tibetans were chronically exposed to the highest MeHg from other sources. Our findings highlight the importance of farmed fish and food trade for MeHg exposure.

Keywords

Methylmercury exposure; Farmed fish; Freshwater Fish; Marine Fish; Interregional food trade; Physiologically Based Pharmacokinetic (PBPk) model

1. Introduction

The toxic element mercury (Hg) biomagnifies through food webs and poses health risks to wildlife and people (Clarkson et al., 2003; Grandjean et al., 1997; Harris et al., 2007). Although Hg occurs naturally, human activities have altered its global biogeochemical cycle in the atmosphere, hydrosphere and pedosphere (Driscoll et al., 2013; Mason and Sheu, 2002; Obrist et al., 2018). Hence, extensive research efforts on global inventories and fluxes of anthropogenic Hg among various environmental media have been carried out over the past several decades (Amos et al., 2015; Lamborg et al., 2014; Mason and Sheu, 2002; Nriagu and Pacyna, 1988; Streets et al., 2017). As one of the most toxic forms of Hg, methylmercury (MeHg) can cause developmental delays and decrement in the intelligence quotient (IQ) in children when it crosses the placenta and passes the blood–brain barrier (Clarkson et al., 2003; Debes et al., 2006; Grandjean et al., 1997; NRC, 2000). Adult exposure to MeHg may result in cardiovascular impairment (Roman et al., 2011). As a result, human exposure to MeHg has been related to a loss of workforce productivity and human impairment (Rice et al., 2010; Trasande et al., 2005).

MeHg biomagnifies in aquatic food webs, where fish are at higher trophic levels, resulting in muscle tissue concentrations that are several orders of magnitude higher than the water in their ecosystem (Stein et al., 1996). Therefore, in most cases significant human exposure to MeHg occurs via fish intake (FDA, 2000), and has been considered as the single significant dietary source of MeHg in most studies (Giang and Selin, 2016; Selin et al., 2010). For example, intake of fish products accounted for 87–95% of the total Hg (THg) exposure of adults in the U.S. and the U.S. Food and Drug Administration (U.S. FDA) stated that fish are the exclusive source of Hg to people living in the U.S. (FDA, 2000; Haxton et al., 1979; MacIntosh et al., 1996). In the 1950s and 60s, intake of MeHg contaminated fish caught in the Minamata Bay in Japan resulted in the spread of neurological disease that is now known as the Minamata disease (Harada, 1995). Since, there has been a common understanding that fish intake, especially of marine species, acts as the critical exposure pathway (dietary

exposure through different food sources) to MeHg and THg (Björnberg et al., 2003; FDA, 2000; Mahaffey et al., 2009).

As an industrial center with extensive coal powered energy production plants, China is the largest contributor to the global anthropogenic THg release (AMAP/UNEP, 2013). Overall, large quantities of THg are released to both the atmosphere (530 Mg in 2014) and aquatic ecosystems (100 Mg in 2012) (Liu et al., 2017; Liu et al., 2016b; Wu et al., 2016), accounting for 25% and 9.1% of the global releases, respectively (Kocman et al., 2017; Pirrone et al., 2010; Streets et al., 2011). While the atmospheric THg emissions in China have continued to increase (Wu et al., 2016), the direct release of THg from wastewater to aquatic environment decreased following 2004, reflecting major improvements in wastewater management (Liu et al., 2016b). However, the application of sewage sludge as a fertilizer in farmland may be a source of direct pollution to rice (Liu et al., 2017). Given the ongoing Hg pollution in China as well as the implementation of the Minamata Convention, progress towards a comprehensive assessment of Hg cycling and human health implications is needed (Hsu-Kim et al., 2018).

Despite severe environmental Hg contamination in China (Feng et al., 2007; Zhang and Wong, 2007), an independent assessment system for Hg (including MeHg and THg) in the human-environment system has not been developed. This is because in China Hg exposure pathways are diverse (Hong et al., 2016; Li et al., 2012; Zhang et al., 2010), and the required data is insufficient. Zhang et al. established the Hg exposure inventory in rural areas of Guizhou province, which included fish, grain, vegetables, livestock and water as exposure pathways, and indicated that rice was the most significant dietary contributor of MeHg exposure (Zhang et al., 2010). The study of Hong et al. and Li et al. also verified this result in the rural areas of Southwest China (Hong et al., 2016; Li et al., 2012). Other MeHg exposure sources such as poultry were also significant in some inland regions of China i.e. Guizhou (Yin et al., 2017). High Hg concentrations found in some traditional medicinal products used in China can also be exposure sources of Hg to the Chinese public (Liu et al., 2018a). Therefore, MeHg exposure pathways in China might be more intricate than in western countries such as the U.S. (FDA, 2000; MacIntosh et al., 1996; Mahaffey et al., 2009; Sunderland et al., 2018). To our knowledge, previous studies in China have ignored the potential importance of the food trade in contributing to Hg exposure. Further, despite severe Hg pollution in waters and soils (Liu et al., 2016a; Zhang et al., 2010), the environmental protection administration in China has not paid sufficient attention to the long-term human exposure to Hg (Zhang and Wong, 2007). Hence, research assessing exposure pathways, including data statistics such as per capita diet intake and food trade are very limited. Thus, it has been difficult to provide a quantitative assessment of human exposure to Hg in relation to consumption patterns, therefore hampering efforts to effectively manage Hg risks for the Chinese public. Notably, the total consumption of both marine and freshwater fish species has been increasing in China mainly due to the improved economic situation and living standards, which enables more people to afford purchasing of fish on regular basis (Cao et al., 2007; NBS, 2012). For example, in total, in 2011, freshwater fish accounted for 78% of all China-consumed freshwater and marine edible products including fish, shellfish etc., and has more than doubled since 1980 (35%; Food and Agricultural Organization, <http://www.fao.org/home/en/>). In parallel, consumption of

rice has been gradually decreasing recently as it is partly replaced by other foods e.g. pork and poultry, due to the improvement of living standards (NBS, 2012).

Therefore, the factors and trends highlighted above provide motivation for the present study. The main objective here was to establish validity of the China Mercury Exposure Assessment (CMEA) model as an effective tool to evaluate the connections between environmental Hg pollution and human exposure and to determine exposure of the Chinese public as a whole, as well as on a region specific basis. The model includes 14 main pathways and 8 regions of China and considers the impact of international and interprovincial food trade. As an effective method to quantify the transfer of a chemical in human body, we have also included the Physiologically Based Pharmacokinetic (PBPK) model into the CMEA framework to verify the validity of the modeled Hg, including MeHg and THg, exposure intake and demonstrate the relationship between concentrations in human blood Hg and exposure of the Chinese population. In the present study we have evaluated the potential exposure risk to Hg for the general population of China and provided a new tool that can be used to understand Hg exposure pathways for humans worldwide. To our knowledge, this work is the first comprehensive nationwide assessment of Hg exposure for Chinese populations, which accounts for 20% of the global human population. This novel assessment evaluates the influence of farmed fish consumption and food trade, as well as the consumption of wild fish, and other products.

2. Materials and Methods

2.1 China mercury exposure assessment model (CMEA)

The CMEA model connects the environmental Hg system, including MeHg and THg (Note: in this manuscript Hg represents both MeHg and THg), and human exposure to this Hg in China. The model includes three submodules: I. a MeHg and THg intake model based on Hg monitoring data for different kinds of foods from published peer-reviewed literature and interregional food trade information; II. international and interprovincial trades of food (Supplementary Table S1); and III. A Physiologically Based Pharmacokinetic (PBPK) model, which was used to verify Hg intake modeling results, and simulate blood Hg levels (Figure 1).

2.2 THg and MeHg intake modeling

The Probable Daily Intake (PDI) of MeHg or THg was calculated to evaluate Hg exposure on the Chinese population (EPA, 1997). A Monte Carlo simulation was incorporated to calculate the probabilistic distribution of PDI following the method described in previous studies (Liu et al., 2016a; Liu et al., 2016b). The calculation method is described below:

$$PDI(x)_{ij} = \sum_k (I_{jk} \times C(x)_{ijk}) / bw$$

where $PDI(x)_{ij}$ is the probabilistic distribution of probable daily intake of MeHg or THg in different regions in China ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, Supplementary Figure S1); I is intake rate (ingestion rate or inhalation rate, g/day) of different exposure pathways in 2011

(Supplementary Tables S2 and S3); $C(x)$ is the probabilistic distribution of MeHg or THg concentrations (ng/g) of different exposure pathways in recent years (Supplementary Material, MeHg and THg concentrations, Table S4). The following abbreviations indicate the following: bw - body weight (kg); i - MeHg or THg; j - different regions in China; k - exposure pathways, including marine fish and other seafood, freshwater fish, rice, wheat, bean, vegetables, pork, poultry, milk, eggs, water, air (through inhalation), soil (through ingestion) and traditional Tibetan medicine. A population-weighting method was used to address the overall MeHg or THg exposure risk of various Chinese populations (Supplementary Table S5). Data pertaining to THg and MeHg concentrations in the traditional Tibetan medicinal products is taken from our recent study (Liu et al., 2018a).

2.3 Food intake rates

We constructed the first inventory of main food intake rates of the Chinese population in each province, which was a pivotal tool for evaluating MeHg and THg exposure in this study. The inventory was constructed based on the *China Health and Nutrition Survey* (CHNS, Table S2) and published literature (Tables S2 and S3). Instead of food consumption data from a market survey (Zhang et al., 2010; Zhang et al., 2017), we have considered food intake information based on a real dietary survey, as this would be more useful and representative as a tool for Hg exposure. The CHNS (<http://www.cpc.unc.edu/projects/china>), which is an international collaborative project between the *University of North Carolina* and the *Chinese Center for Disease Control and Prevention*, covered 9 provinces and 3 municipalities, and 2.7 million individuals from 1989 to 2011. The survey in 2011 contained information for at least three more provinces than in other years. Thus we used the most current data, i.e. from 2011, to calculate the daily Hg exposure. Consumption diaries were used in the survey. For each household, the survey was conducted for 3- to 7-days using a multistage and random cluster sampling process (Yang et al., 2002). The survey included breakfast, lunch and dinner. Intake rate of each kind of food was calculated based on the initial food cooking mass minus the residue mass of each food.

Because CHNS covered only 12 provinces and municipalities in China, food intake data of other provinces were collected from the published literature (Table S2). Survey data of 2011 in these provinces were selected. In the absence of 2011 data for certain provinces, we restricted observations to the year 2000 and later. Due to the improvement of living standards in China, consumption of rice and wheat has decreased gradually in recent years, while consumption of fish and livestock products has increased (NBS, 2012). Therefore, data on the diverse foods for these provinces were matched to 2011, based on the variation trend of each food in other provinces in the same region in the CHNS database from 1989 to 2011 (Figure S1). In contrast to the food consumption data used in previous studies, food intake rates offer more accuracy (Li et al., 2012; Zhang et al., 2017). Literature provided food consumption rates, used to represent food intake rates that were not calculated based on real-time diet survey, were not considered in the present study. To intercalibrate the food intake data that we have derived from different sources, we compared values for provinces covered by CHNS and obtained from peer-reviewed publications with other data sets (Supplementary Figure S2). Due to absence of data, we have estimated intake rates of

certain foods in some provinces based on values of the average eastern or western regions of China (Figure S2).

For the coastal regions, we have divided the fish intake into freshwater and marine fish categories based on previously determined ratio of 42%:58%, respectively (Chan et al., 2013; Deng et al., 2016). Unlike in the previous study (Zhang et al., 2010), the intake of marine fish is considered here as a significant source of Hg to the people from the inland regions, due to high Hg concentration of marine fish (Figure S3). The ratio of marine fish to freshwater fish intake in the context of the whole of China is 24%:76% based on the fish consumption data from FAO (Food and Agricultural Organization, <http://www.fao.org/home/en/>) (Zhang et al., 2017). We used the above provided ratios to calculate the ratio of marine fish to freshwater fish intake in the inland regions. Data was weighted based on the population size. The calculated % ratio of marine fish to freshwater fish intake in the inland regions is 8.2%:91.8% in the present study.

2.4 MeHg and THg concentrations in food products

Concentrations of MeHg and THg in food products were obtained from peer-reviewed publications, as summarized in Table S4. All samples used in the publications we obtained data from were collected from markets that were locally supplied. We did not consider data from publications where the food sources were not provided. Our aim was to avoid using food MeHg and THg data from contaminated areas. Data from Hg mining areas were not considered in this study, which could lead to overestimation of Hg exposure to the general population in China. For other areas, as done in the previous study (Amos et al., 2014), we applied conservative estimates to exclude the extremely contaminated foods as they are not relevant to the large scale study such as the present one. In China, the government has set MeHg and THg concentration limits for food. Food with high concentrations of MeHg and THg is prohibited on the market (SAC, 2005). MeHg or THg concentrations exceeding the limits of *Chinese National Limits* published by the *National Health and Family Planning Commission of the People's Republic of China* such as 1,000 ng/g of MeHg for fish, 20 ng/g of THg for rice, wheat, bean and vegetables, 50 ng/g of THg for pork, poultry and eggs, and 10 ng/g of THg for milk, were not considered in this study (SAC, 2005). We also selected the median value of Hg intake modeling based on the Monte Carlo Method to avoid the influence of any extreme values. Data for food products based on the sample size < 3 or lack of QC in measurements of concentration data were not considered.

In the present study, we have included major fish species and other seafood, including carp (grass, crucian, common, bighead or black), catfish, hairtail, yellow croaker, snapper, ocean perch, crab, shrimp *etc.*, produced in China according to *China Fisheries Statistical Yearbook* (CMA, 2000–2012). Previous studies of Hg exposure in China have not considered consumption of imported high Hg fish species, such as tuna (Li et al., 2012; Zhang et al., 2010). In contrast to these studies, we have evaluated the exposure of Chinese people to Hg from different fish species including those that were produced in China and imported from other countries. Because detailed intake rates of different fish species were not available, we estimated the contributions of different aquatic products to the Hg exposure based on their production rates, as has been done in previous studies (Lavoie et al.,

2018; Sunderland et al., 2018). Unlike in the previous studies (Zhang et al., 2010; Zhang et al., 2017), both wild and aquaculture sources of fish were included in our analysis. Marine fish from the wild and mariculture accounted for 47% and 53% of the total marine fish products in China in 2011, while 8.3% and 91.7% for freshwater fish products were from wild and freshwater aquaculture, respectively (CMA, 2000–2012). Contributions of fish species from the wild and aquaculture were estimated based on their Hg concentration and production rate.

To simulate the mean value and uncertainty (P20–80 confidence interval) of food Hg concentration in each region, we applied a bootstrapping method and the sampling of each food was repeated ($\times 10,000$) for sample sizes ≥ 3 (Amos et al., 2014; Liu et al., 2016a). For areas with sample size < 3 , we assumed a coefficient of variation (CV) at 65% following previous studies (Amos et al., 2014; Liu et al., 2016a). The distribution of MeHg and THg concentrations were confirmed to be log-normal, as found previously (Larsen et al., 2002; Mangerud, 2005). Estimates for otherwise absent THg concentration data of certain food in some provinces were made similarly to the method described above. MeHg concentrations in food products in China are relatively scarce. Researchers have used the relationships between MeHg and THg to estimate the concentrations of MeHg in China and the U.S. (Giang and Selin, 2016; Zhang et al., 2017). In this study, we used the best fit between all MeHg and THg concentrations of the specific food types in published data (Table S4) to model the absent MeHg concentrations for a given food. Based on MeHg measured in products other than seafood and rice foods in China, pork, poultry, eggs and vegetables have been found to contain significant levels of this contaminant and should not be ignored (Cheng et al., 2013; Deng et al., 2016; Shao et al., 2012; Tang et al., 2015; Yin et al., 2017; Zhang et al., 2010; Zhang and Wong, 2007). The equations used for estimating concentrations for MeHg based on THg for different foods are provided below:

$$\text{wild marine fish: } C_{\text{MeHg}} = 0.85 (\pm 0.020) \times C_{\text{THg}} - 1.8 (\pm 1.9) \text{ (unit: ng/g)}$$

$$\text{farmed marine fish: } C_{\text{MeHg}} = 0.72 (\pm 0.051) \times C_{\text{THg}} - 0.31 (\pm 5.6) \text{ (unit: ng/g)}$$

$$\text{wild freshwater fish: } C_{\text{MeHg}} = 0.80 (\pm 0.026) \times C_{\text{THg}} + 0.17 (\pm 3.2) \text{ (unit: ng/g)}$$

$$\text{farmed freshwater fish: } C_{\text{MeHg}} = 0.53 (\pm 0.043) \times C_{\text{THg}} + 1.6 (\pm 1.1) \text{ (unit: ng/g)}$$

$$\text{rice: } C_{\text{MeHg}} = 0.30 (\pm 0.031) \times C_{\text{THg}} + 0.073 (\pm 1.2) \text{ (unit: ng/g)}$$

$$\text{poultry: } C_{\text{MeHg}} = 0.53 (\pm 0.12) \times C_{\text{THg}} + 0.45 (\pm 4.0) \text{ (unit: ng/g)}$$

$$\text{eggs: } C_{\text{MeHg}} = 0.53 (\pm 0.046) \times C_{\text{THg}} - 2.7 (\pm 1.3) \text{ (unit: ng/g)}$$

$$\text{vegetables: } C_{\text{MeHg}} = 0.0043 (\pm 0.00080) \times C_{\text{THg}} + 0.029 (\pm 0.017) \text{ (unit: ng/g)}$$

where the $\pm$ SE (standard error) is considered as the uncertainty of the model. Significance tests of the fitting results are provided in Figure S4. All the relationships above are statistically significant ($P < 0.01^{**}$). Published data were used to calculate the average proportion of THg as MeHg in pork (Deng et al., 2016; Tang et al., 2015; Zhang et al., 2010), which is 1.2% in this study. According to the previous studies (Giang and Selin, 2016; Zhang et al., 2017), 13% was set for the proportion of MeHg to THg for beans. MeHg in wheat and milk is not considered, since no published literature reported MeHg in wheat

and milk in China. All statistical analyses were conducted using the R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.5 Interregional trades of agricultural products and mass flow analysis

A multiregional input-output (MRIO) model has been previously applied to analyze environmental issues under the impact of interregional trade, such as the global biodiversity variation (Lenzen et al., 2012), aerosol pollution (Lin et al., 2016), and atmospheric THg emission (Chen et al., 2018; Liang et al., 2014). The core of the MRIO model is a monetary multiregional input–output table describing product exchanges among provinces. The MRIO table of China from 2010, developed by Liu et al., was matched to 2011 and applied to establish the trade relationships for food categories in this study (Liu et al., 2014; NBS, 2012). Details of the MRIO modeling method are described in previous studies (Lenzen et al., 2012; Liang et al., 2014; Lin et al., 2016).

The Hg Intake Flow Analysis (including MeHg and THg) of China was coupled with the interregional trades of agricultural products inferred from the MRIO model and the total output monetary values of each agricultural product. The process of calculation is shown below:

$$NF_{ijk} = F_{jk} \times \frac{P_{ik} + M_{ik}}{TP_k + \sum_i M_{ik}}$$

$$Per_{ijk} = \frac{NF_{ijk}}{\sum_k NF_{ijk}}$$

$$TIF(x) = \sum_{ijk} (Per_{ijk} \times I_{ij} \times C(x)_{ik})$$

where F_{jk} represents the final demand (10^2 million \$/yr) of economic sector ‘Farming, Forestry, Animal Husbandry and Fishery’ in province j from the supply of province k , which is derived from the Chinese MRIO table (Liu et al., 2014); represents the final demand (10^2 million \$/yr) of food category i in province j from the supply of province k ; represents the total output monetary values (10^2 million \$/yr) of food category i in province k , which is inferred from *China Agriculture Yearbook*; represents the total output monetary values (10^2 million \$/yr) for the sector ‘Farming, Forestry, Animal Husbandry and Fishery’ in province k , which is also inferred from *China Agriculture Yearbook*; M_{ik} represents the international imports (10^2 million \$/yr) of food category i in province k from the rest of world, and the categories include rice, wheat, bean, milk, and marine fish; Per_{ijk} is the source contribution (%) of food category i in province j from the supply of province k ; $TIF(x)$ is the probabilistic distribution of total intake flow of MeHg or THg (Mg/yr) by Chinese population; I_{ij} is the intake rate (g/day) of food category i in province j ; $C(x)_{ik}$ is the probabilistic distribution of Hg concentration (ng/g) of food category i that supplied from province k . Hg intake flows between each province of China were modeled and summed up to each region of China

(Figure S1). As was done in Lin et al. (Lin et al., 2014), the coefficient of variation (CV) is quantified to be 10% for uncertainties of economic statistics and the input–output analysis itself, and is considered in the uncertainty analysis based on the Monte Carlo method. More details of the calculation of interregional food trades based on this method is provided in Supplementary Material (Interregional trades) and Supplementary Table S1.

2.6 Association between MeHg exposure and blood MeHg level

The PBPK model of MeHg was applied to verify the validity of the exposure intake modeling (Brown et al., 1997; Clewell et al., 1999), and evaluated the relationship of MeHg exposure and the blood MeHg levels in human body in Chinese populations. A Monte Carlo simulation was incorporated in the model to analyze the uncertainty, as done previously (Clewell et al., 1999). Because MeHg can be converted to inorganic Hg (IHg) in the human body in the liver and intestine (Brown et al., 1997; Clewell et al., 1999), a toxicokinetic model was applied to connect the kinetic behavior of MeHg and IHg in the human body (Carrier et al., 2001).

In the PBPK model, the fraction of MeHg absorbed by the digestive system in human body was set as 95%, according to previous studies (Holmes et al., 2009; Zhang et al., 2010). THg inhalation was not considered in the toxicokinetic model, since the contribution of this pathway is low to the overall THg exposure in this study (<1%), and the mechanism and effectiveness of THg transfer into respiratory system of human body is still unclear (Holmes et al., 2009). For the fraction of IHg absorbed by the digestive system, the World Health Organization (WHO) presented a percentage of 20% (WHO, 2008), while EPA suggested 17% with a range of 8 – 25% (EPA, 1997). Holmes et al. compared different publications and indicated that oral absorption of IHg ranged from 2 to 38%, depending upon the form and test conditions (Holmes et al., 2009). Therefore, in this study, the fraction of IHg absorbed by the digestive system was set as 20%: with a range of 2 to 38%, and this was considered in the uncertainty analysis.

2.7 Uncertainty analysis

A Monte Carlo simulation (10,000 runs) was applied to analyze the robustness of the CMEA model. Median values and P20–80 confidence intervals of the results were calculated to quantify the uncertainties (Liu et al., 2018b; Zhang et al., 2015). Furthermore, the modeling results of blood MeHg and THg were compared with observational data from the published literature, to ensure their validity. As done above, data from the Hg mining areas Hg in human blood from these areas were excluded.

2.8 Data availability

All the databases used for the model are publicly available and are cited in the Supplementary Data.

3. Results

We have determined that in 2011, the probable daily intake (PDI) of MeHg for the Chinese population was 0.057 (range: 0.036 – 0.091 based on a 60% confidence interval, Figure S5)

$\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, while the PDI of THg was 0.35 (range: 0.22 – 0.55) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, based on the population-weighted mean values. Fish intake was the leading driving factor (56%, Figures 2a and b) of human exposure to MeHg. Importantly, intake of freshwater fish species from inland water ecosystems rather than marine species served as the major MeHg exposure pathway in China and accounted for 51% of the total fish MeHg intake. According to the published literature, collected for the purposes of the present study, MeHg concentrations of fish produced in China (primarily carp and hairtail, etc.) are relatively low, while the concentrations of imported fish (primarily tuna, etc.) are high (Figure 3). Farmed fish, especially freshwater farmed fish, have recently become a significant source of the fish consumed in China (Figure 4). Lower MeHg concentrations were found in farmed fish species, especially the freshwater species, such as carp. We have calculated that after fish intake, the second major source for MeHg intake was rice (26%), followed by eggs (10%) and poultry (5%).

Fish intake dominated the MeHg exposure in coastal (i.e. North, Northeast, East and South China) and some inland regions (i.e. Central and Southwest China) of China, and ranged from 42% to 78% of the total exposure. The MeHg exposure was high in coastal regions (Figure 2c), where fish are the most important protein source. In inland China, MeHg exposure through rice intake accounted for 36% in the Central and Southwest regions, and 46% in Northwest China, indicating that rice was an important MeHg source in the human diet.

Among different exposure pathways, fish intake was the major driving factor of THg exposure in China, accounting for 29% of the exposure (Figure 2b), and it was followed by rice (21%). Fish intake was the largest contributor of the THg exposure in North (26% of the total THg exposure), Northeast (49%), East (40%) and South China (28%), while rice intake dominated Central (39%) and Southwest China (28%), while wheat intake dominated THg exposure in Northwest China (54%). There are however other significant pathways, as depicted in Figure 2d.

In total, the intake of fish and rice contributed from 68% to 93% of the total MeHg exposure and from 13% to 64% of the total THg exposure in the above mentioned seven regions (Figures 2c and d), except for the Tibetan region, and the exposure in these regions was driven primarily by the higher MeHg and THg concentrations in fish and the substantially higher intake rate of rice compared with other foods (Supplementary Figure S3 and Table S2). These seven regions (excluding the Tibetan Region) contain most of the Chinese population (more than 1.3 billion; 99% of the total Chinese population). The cumulative frequency distributions of MeHg and THg PDIs in most regions were higher than previously reported for the U.S. and Norway (Mahaffey et al., 2004; Mangerud, 2005), but lower than Japan where fish consumption rates are higher than most of other countries in the world (Figure 5) (Food and Agricultural Organization, <http://www.fao.org/home/en/>) (Iwasaki et al., 2003).

We have simulated the average blood MeHg and THg concentrations for the general population in this study (Figure 6). Although the bioavailability of THg for the human body is still under question (Bradley et al., 2017), comparison between the results of the Hg intake

modeling and PBPK modeling shows a reasonable agreement and can therefore be used to reflect the overall Hg exposure levels of Chinese population in different regions. In the future, more detailed studies should be carried out to reduce all of the specified uncertainties involved in the exposure assessment.

In total, 2.0 Mg (range: 1.3 – 3.6) and 12 Mg (range: 7.1 – 19) of MeHg and THg, respectively, were ingested by the Chinese population in 2011. In 2011, 1.2 Mg of MeHg was taken into human bodies from fish, the primary driving factor of exposure. In China, the contribution of rice to the total MeHg intake is also substantial, amounting to 0.44 Mg for the year 2011. For MeHg, we found that 5.1% and 22% of its intake was contributed by foods derived from international and interprovincial trades, respectively (Figure 7), and lower percentages were found for THg (i.e. 1.1% and 11%, respectively; Supplementary Figure S6). In 2011, 0.10 and 0.13 Mg of the MeHg and THg intake, respectively, was contributed to the Chinese public by imported foods with highest contributions from fish (Supplementary Figure S7). On the other hand, 0.037 and 0.060 Mg of the MeHg and THg was exported from China to other countries through international food trade, and thereby decreased the possibility of exposure of the Chinese population to that amount of Hg (Figure 7).

4. Discussion

4.1 MeHg and THg exposure associated with farmed fish consumption in China

Our models suggest that, on average, fish intake was still the primary factor (56%, Figures 2a and b) of human exposure to MeHg in China, rather than rice, though the relative importance of fish as the major exposure pathway is lower in comparison to the U.S. and Europe, where fish are the exclusive source of Hg to people (FDA, 2000; Sunderland et al., 2018; Višnjevec et al., 2014). For example, intake of fish products accounted for 87–95% of THg exposure in adults inside the U.S. (MacIntosh et al., 1996). Primarily, intake of freshwater fish species (51%) rather than marine species, which was 49%, served as the major MeHg exposure pathway in China, again contrasting estimates for the U.S. and Europe where marine fish are the major exposure pathway of MeHg to human consumers (Björnberg et al., 2003; FDA, 2000; Sunderland et al., 2018). The above-stated differences in exposure between freshwater and marine fish could result from fish occupying different trophic levels. For example, the primarily consumed freshwater fish in inland China is common carp, located at a trophic level 3.1 (Froese and Pauly, 2000). Hairtail represents another commonly consumed fish species, although marine, but occupying a higher trophic level i.e. 4.2 (Froese and Pauly, 2000). Typically, fish occupying higher trophic levels are expected to have higher concentrations of MeHg (Hall et al., 1997). Significant consumption levels of farmed fish species (Figures 4a - c) further contribute to Hg exposure differences as these are mostly lower trophic level fish. In the U.S., for comparison, tuna species, which occupy high trophic levels (3.9 – 4.6) (Cox et al., 2002), have been demonstrated as the main exposure source for MeHg exposure, primarily due to their high consumption rates because of relatively low price of canned tuna (Sunderland et al., 2018). In China, farmed fish, from both freshwater as well as marine facilities, have recently become a significant source of fish (Figures 4a - c) (Cao et al., 2007; CMA, 2000–2012). Moreover, MeHg concentrations in

farmed fish have been shown to be lower, especially for farmed freshwater fish (Figures 4a - c), due to the lower species diversity and the substantially shorter food chains of the aquaculture system (Cheng et al., 2015). Proportions of MeHg to THg in wild and farmed marine fish were 92% and 79%, respectively, while they were respectively 73% and 55% for freshwater fish. Increasing the proportion of farmed fish in the human diet could therefore significantly alleviate the deleterious health impacts of MeHg in China.

Select species of farm-raised fish are a source of protein and omega-3 fatty acids, and these fish are especially important to communities of low income (Sapkota et al., 2008; Tocher, 2015). Additionally, as we have shown, the meat of freshwater-farmed fish tends to contain less MeHg, hence consumption of farm-raised freshwater fish can lower human exposure to MeHg (Figures 4a and b). However, while consumption of freshwater-farmed fish may have the benefit of lowered exposure to MeHg, aquaculture is known for its other environmental problems e.g. overall environmental degradation that otherwise negatively impacts human and environmental health (Grigorakis and Rigos, 2011). Problems of aquaculture include the unintended introduction of farmed fishes into the wild populations and their interbreeding (Dimitriou et al., 2007; Grigorakis, 2010), loss of benthic biodiversity due to the formation of dead zones caused by elevated flux of organic matter from fish pens (Soto and Norambuena, 2004), increased rate of fish disease transfer (Zlotkin et al., 1998), and chemical and organic matter contamination of aquatic ecosystems (Sapkota et al., 2008; Wu, 1995). It is worth remarking that China has a 2,000 year-long tradition of aquaculture, but this industry has been rapidly growing since the 1970s (Cao et al., 2007). Hence, in the reality of increased demand for fish products in China, a balanced approach needs to be developed for aquaculture and mariculture practices with consideration of the overall combined diverse benefits and risks of aquaculture.

The extremely high THg intake by people in Tibetan Region is higher than in any other studied location, and is related to the regular ingestion of Hg-containing traditional Tibetan medicines (Liu et al., 2018a). The East China region is the most economically developed and densely-populated area in China (Figure S1), and therefore is faced with the highest risk of MeHg exposure. The PDI of MeHg in Northwest populations was the lowest in China and more than 99% of the probability distribution was under the EPA's RfD (Figure 5). This was due primarily to the low translocation factor of Hg into wheat grains (Wang et al., 2016), which is the base diet for these Northwest populations. This means that for MeHg susceptible populations, such as the pregnant women living in mining areas, a wheat-containing food-based diet could be a better choice than rice, due to high MeHg concentration in rice produced in mining areas (Zhang et al., 2010). Because of the high Hg concentrations in the meat of swordfish, snapper and various tuna species classified collectively as tuna here (Figure 3), we suggest that pregnant women should avoid consumption of these fish species. Additionally, we have found that the PDIs of THg in the seven regions, were also higher than the U.S. and Norway, but, as in the case of MeHg, were lower than in Japan. At the individual level, food choices will obviously play a critical role in determining an individual's MeHg and THg exposure and associated risk. Thus, besides marine fish, attention should be paid in China to the other important exposure pathways, such as freshwater fish, rice and traditional Tibetan medicine (Liu et al., 2018a; Sallon et al., 2006).

4.2 MeHg and THg exposures associated with interregional food trade in China

Interregional food trade, including international and interprovincial trades, plays an important role in Hg exposure to the humans in China. Mass flow analysis of both MeHg and THg intake in the eight regions of China was constructed to gain a better understanding of sources and driving factors as well as health impacts associated with the resultant MeHg and THg exposure. We also used this analysis to demonstrate the role of humans in global Hg transport. As mentioned above, farmed fish from mariculture and freshwater aquaculture serve as substantial sources for MeHg exposure in China, due to their high consumption, even though their MeHg concentrations are lower in comparison to the wild fish.

In a global context, the Chinese population serves as a net sink in terms of both MeHg and THg transport through the international food trade. Interprovincial food trade appears to have a negative effect on the health impacts of MeHg for the exposed Chinese population. In 2011, the international food trade contributed to the highest intake flows of MeHg and THg in the population of the East China region. High intake flow of MeHg resulted directly from this being the highest human population size in the country, as well as the high MeHg intake rate driven by fish intake relative to other regions (Supplementary Figure S7). In the interregional food trades, East China, which is the most developed region of China, served as a net sink of MeHg from the global trade but a net source to other regions of China (Figure 7a). Similar trend was also observed in the Tibetan region, but it was not significant (net export from this region was 3.0×10^{-6} Mg in 2011). The vast majority of MeHg intake in the Tibetan region was contributed by the local sources (Figure 7b) (Liu et al., 2018a). However, other regions in China showed adverse trade effects for both international and interprovincial food trades, especially the North and South China regions (Figure 7b).

4.3 Implications

The overall goal of the present study was to demonstrate the connection between environmental Hg pollution, Hg levels in food and human exposure in China and this goal was achieved by using the comprehensive modeling tool, namely the CMEA. We have demonstrated how the various sources of MeHg and THg, local practices and trade together influence exposure to this toxic metal to the Chinese human population. Our results suggest a need for differential policy recommendations for the various regions in China due to the significant differences in the dietary habits in the various regions. Furthermore, results of the CMEA model indicate that fish intake is overall the dominant Hg exposure pathway in China. Freshwater fish are the more important source of MeHg in comparison to marine fish, and this is especially evident in the inland regions, which contrasts other countries.

For most regions of China, domestic food intake is the dominant MeHg and THg exposure pathway. Our results suggest that freshwater Hg pollution and the MeHg and THg levels in fish from freshwater aquaculture need further investigation. Attention should also be given to the control of Hg releases into Chinese watersheds and adjacent seas, since substantial Hg continues to be discharged from various sources including rivers and direct industrial wastewater to the various watersheds and transported to the adjacent seas in China (Liu et al., 2016a; Liu et al., 2016b). Human exposure to MeHg and THg via intake of rice and wheat however cannot be ignored, due to the large mass of rice being consumed in China.

Moreover, as discussed, transfer of Hg with the sewage sludge to the farmland (Liu et al., 2017), may increase MeHg concentrations in rice. Furthermore, although the Chinese population serves as a net sink in the global MeHg and THg transport by international food trade, a reasonable arrangement of the interregional food trades and with the increased proportions of fish farming, including mariculture and freshwater aquaculture, could alleviate MeHg exposure to the Chinese population leading to the reduction in health risks. However, as we have discussed above, aquaculture may lead to other biotoxic exposure events, and both the benefits and risks of aquaculture to public and environmental health should be further studied in consideration of determining the most sustainable practices.

The CMEA model provides a new approach to quantify global Hg transport and assess the final human health impact of intake of foods containing MeHg for the general population in China, and could be applied to further evaluate Hg release from diverse anthropogenic sources into different environmental media. As a first attempt to quantitatively link a variety of models together along the Hg exposure continuum in China, we demonstrate some major data gaps. As mentioned above, in previous studies in China, consumption of fish species with high Hg concentrations was not considered (Li et al., 2012; Zhang et al., 2010; Zhang et al., 2017). In contrast with these studies, we considered different fish species including that were produced in China (with low Hg concentrations) and imported from other countries (some with high Hg concentrations) in the present study. Data limitations, such as the lack of intake rates of different fish species, and the lack of Hg concentration data of certain fish species, might increase the uncertainties of the results. We suggest that further investigations on the Hg concentration and intake of different fish species in China should be carried out. More data of Hg levels for other foods is also needed to fill the data gap in China. For example, MeHg measurement data for pork were not sufficient to build the relationship between MeHg and THg in this study. There is no available statistics for interregional food trade in China. Investigation of detailed physical quantity information of food trade, instead of monetary values, is needed to reduce the uncertainties. In the present study, as well as in many similar studies in China and other countries like the U.S., the age and socio-economic status of people were not considered in the Hg intake modeling, because of the difficulties in obtaining such information but it could be very important as shown in some of the U.S. based studies (Giang and Selin, 2016; Li et al., 2012; Sunderland et al., 2018; Zhang et al., 2010; Zhang et al., 2017). The brain of the developing fetus is more susceptible than that of an adult to the damage induced by Hg (Clarkson et al., 2003; Ou et al., 2018). Previous studies indicated that elevated blood THg occurred more commonly for women at childbearing age, and households that have higher income, since they eat more fish (Karagas et al., 2012; Mahaffey et al., 2009). We suggest that age and socio-economic status should be considered in future studies, when more data and better proxies become available. Additionally, China is undergoing a rapid change in dietary habits, fishing activities, trade etc. The lack of data pertaining to food intake is also problematic for conducting a Hg exposure assessment in China. As many of the currently considered factors will continue to change in the future, and more data will become available to address the current knowledge gaps, the results of the present study will need to be regularly e.g. every decade, reassessed in the future.

Previous studies have evaluated the connection between the atmospheric Hg deposition levels and human and ecosystem health impacts (Giang and Selin, 2016; Harris et al., 2007). Contributions of other substantial Hg sources, such as riverine Hg discharged into the coastal seas, to the final human exposure assessment are still poorly understood (Amos et al., 2014; Kocman et al., 2017; Liu et al., 2018b). China is a large country, and as we show in the present study Hg exposure to various subpopulations is more intricate in comparison to other human populations, and therefore we should consider not only fish intake but also other exposure routes when appropriate (Giang and Selin, 2016; Selin et al., 2010). Since the intake of fish and rice represent the two dominating exposure pathways to MeHg and THg in China, some critical knowledge gaps need to be assessed as soon as possible. These knowledge gaps include (1) levels of the Hg released to the aquatic environment and soil from anthropogenic and natural sources; (2) mass of Hg that is transported in the river-ocean continuum; (3) factors determining the levels of methylation and demethylation in water and sediment/soil; (4) factors influencing the accumulation of Hg into fish and rice; transport of Hg from its sources into other agricultural products. With new information, combined modeling of Hg transport, fate, bioaccumulation and exposure as done in this paper offers a comprehensive tool to evaluate the impacts of anthropogenic Hg releases on human exposure.

5. Conclusions

Our analysis indicated that in most areas in China, MeHg and THg exposure was dominated by fish intake, especially by farmed freshwater fish, given the high consumption rates. Considering all fish sources, it was found that fish from inland water and domestic coastal ecosystems, rather than those from open ocean ecosystems, contributed most of the MeHg exposure to people in China. Eastern and Northeastern populations were more highly exposed to MeHg. MeHg exposure for the Chinese population was alleviated relatively by high proportion of farmed fish consumption, in which MeHg levels are relatively low. Interregional food trading had negative impacts on the extent of MeHg exposure for the Chinese population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- A new model evaluated methylmercury (MeHg) exposure to the Chinese public
- In China MeHg exposure was dominated by intake of farmed fish
- In China consumption of farm-raised fish results in lower human exposure to MeHg
- In China interregional food trade negatively impacted human exposure to MeHg

Figure 1.
Conceptual metamodel of the China Mercury Exposure Assessment (CMEA) model.

Figure 2. Breakdown of the MeHg and THg exposure to the Chinese population. Figures **a** and **b** show contributions of different exposure pathways to MeHg and THg across China, respectively; and **c** and **d** are regional MeHg and THg exposures, respectively. In Figures **c** and **d**, y axes are scaled to $0.13 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ and $0.25 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, respectively.

Figure 3.

Comparisons of MeHg and THg concentrations of major marine and freshwater products in China and the U.S. based on published literature (a) and contributions of different aquatic products of MeHg and THg exposures to the Chinese population (b).

Figure 4.

MeHg exposure reduced by farmed fish consumption in China. **a** is MeHg and THg concentrations measured by previous studies in wild and aquaculture marine fish, respectively; **b** is MeHg and THg concentrations measured by previous studies in wild and aquaculture freshwater fish, respectively; **c** is percentages of marine and freshwater fishes from wild and aquaculture sources in 2011, respectively; **d** is four scenarios of Probable Daily Intake (PDI) for the Chinese population: 1 - an estimate based on the available data from 2011; 2 - assuming no intake of sea-farmed fish; 3 - assuming no intake of freshwater farm-raised fish; 4 - assuming intake of wild-caught fish only. In figures **a** and **b**, error bars are standard deviations. In figure **d**, error bars are uncertainty ranges as 60% confidence intervals (CI) based on the Monte Carlo simulation.

Figure 5.

Probability distributions of PDIs of MeHg and THg in different regions of China and other countries. Blue lines are reference doses for MeHg and THg advised by United States Environmental Protection Agency (EPA). Red lines are provisional tolerable weekly intakes of MeHg and THg given by the Joint Expert Committee on Food Additives (JECFA), and have been adjusted to daily intakes. Data of different regions in China originated from the results of our modeling. Data of Japan, Norway and the U.S. were from previous studies (Iwasaki et al., 2003; Mahaffey et al., 2004; Mangerud, 2005).

Figure 6.

Comparisons of MeHg and THg concentrations in blood of Chinese people from different regions based on the model results with observational data derived from published literature (Chen et al., 2014), (Deng et al., 2016), (Ding et al., 2013), (Gao et al., 2018), (Gui et al., 2014), (Jin et al., 2014), (Li et al., 2014a), (Li et al., 2014b), (Liang et al., 2013), (Ou et al., 2015), (Shi et al., 2010), (Tian et al., 2014), (Wang et al., 2010), (Yang, 2011), (Yu et al., 2011), (Yu et al., 2012), and (Zhang and Wang, 2008). CI is confidence interval.

Concentrations of MeHg and THg in blood of Tibetan people were not simulated in the present study.

Figure 7.

MeHg intake by Chinese population in 2011 and the driving factors according to our models. **a** shows the modeled mass flow of MeHg intake driven by the international and interprovincial food trades of China. Numbers at the top of the figure show the three largest mass flows of MeHg intake by general populations in China (unit: kg/yr). **b** are modeling results of contributions of different food sources from local (blue), interprovincial (orange) and international (red) products, respectively. y axes in the figure are scaled to the largest contributor. Numbers are the increase or decrease percentages of PDI in different regions caused by interregional food trades.