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Insights from mercury stable isotopes into factors affecting the internal body burden of methylmercury in frequent fish consumers

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Abstract

Methylmercury (MeHg) exposure can cause adverse health effects in children and adults and is predominantly from seafood consumption in the United States (U.S.). Here we examine evidence for differences in MeHg uptake and metabolism in U.S. individuals who consume three or more fish meals per week. We hypothesized based on prior research that some individuals have enhanced capacity to demethylate ingested MeHg and this will be reflected by a greater than typically observed δ^{202}Hg offset in their hair relative to consumed fish (~2 ‰). We used self-reported seafood intake data to identify individuals with hair Hg concentrations that agree extremely well with reported ingestion and those that do not. Approximately one-third of individuals in our survey population had hair Hg levels below the lower bound of probabilistic exposure modeling based on dietary intake data. The Δ^{199}Hg values measured in the hair of a subset of individuals with the highest and lowest discrepancies between modeled and measured exposures are consistent with self-reported fish intake, validating the reliability of their dietary recall information. The δ^{202}Hg offset between fish and human hair is similar for low- and high-discrepancy individuals, suggesting enhanced *in vivo* demethylation does not explain some individuals with hair Hg levels equivalent to non-fish consumers (0.10 ug/g). Using the probabilistic exposure model, we find dietary MeHg absorption efficiencies required to explain hair Hg levels in these high-discrepancy individuals are on average lower than 14% (range: 1%–72%). Exposure modeling for MeHg typically assumes a range of 91–97% and our results emphasize much greater inter-individual variability in this value.

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1. Introduction

Methylmercury (MeHg) is a potent neurotoxin that crosses the blood-brain and placental barriers, leading to developmental and neurocognitive impairment (Castoldi et al., 2001; Steuerwald et al., 2000). Seafood is the dominant source of MeHg exposure in the U.S. general population because generally more than 90% of the Hg found in higher trophic level fish is MeHg and concentrations in other foods are usually below detection (Bloom, 1992; Mergler et al., 2007; Sunderland and Tumpney, 2013). Food frequency questionnaires (FFQs)

provide information on quantities and types of consumed fish and shellfish needed to assess human exposure. However, many studies find self-reported fish and shellfish consumption can only weakly explain measured variablity in Hg concentrations in hair and blood (Golding et al., 2013; Lincoln et al., 2011; Mahaffey et al., 2004; McDowell et al., 2004). Prior studies of frequent seafood consumers in Japan (Canuel et al., 2006), France (Sirot et al., 2008), Quebec (Loranger et al., 2002; Noisel et al., 2011), and indigenous populations in northern Canada (Gosselin et al., 2006) have all reported extremely low measured concentrations of Hg in hair and blood relative to ingested MeHg and correspondingly modeled internal concentrations (mean 4–14 fold difference). Despite the consistency in these results, such discrepancies are normally attributed to dietary recall bias and imprecision in exposure biomarkers (i.e., integrated signal of MeHg exposure measured in hair) rather than differences in the pharmacokinetics of MeHg metabolism across individuals (Gosselin et al., 2006; Grandjean and Budtz-Jørgensen, 2010; Sirot et al., 2008; Tsuchiya et al., 2008; Zhang et al., 2009). Here we examine drivers of the internal body burden of MeHg in high-frequency seafood consumers across the United States (U.S.).

The dietary absorption efficency for ingested MeHg in fish is thought to be more than 90% based on limited data from two human intervention studies conducted in the 1960s with 17 individuals (Aberg et al., 1969; Miettinen et al., 1971). After being absorbed in the gastrointestinal tract, MeHg quickly enters the blood stream and is distributed throughout the human body (Clarkson et al., 2007). Demethylation is thought to occur in the gastrointestinal tract, kidneys, liver, and hair follicles (Ballatori et al., 1995; Berglund et al., 2005; Clarkson et al., 2007; Dock et al., 1994; Rowland, 1988). Most MeHg is eliminated in feces and urine after being demethylated to inorganic Hg (Clarkson and Magos, 2006). Mammals that consume marine fish such as seals and whales have evolved an enhanced capacity for demethylation of ingested MeHg (Caurant et al., 1996; Wagemann et al., 2000). By extension, Canuel et al. (2006) hypothesized some high-frequency fish consumers have developed an adaptive mechanism for more rapidly demethylating MeHg compared to low and moderate seafood consumers.

Naturally occurring stable Hg isotopes are useful for validating types of seafood consumed as well as examining differences in the metabolism of MeHg in the human body (Li et al., 2014; Sherman et al., 2013). All stable Hg isotopes undergo mass-dependent fractionation (MDF) during various environmental reactions (Estrade et al., 2009; Jiskra et al., 2012; Rodriguez-Gonzalez et al., 2009). Kritee et al. (2009) found heavier isotopes are preferentially retained when MeHg is demethylated by microorganisms following the kinetic mass-dependent fractionation law. Several studies report higher δ^{202} Hg values in human hair relative to consumed fish and a decrease in δ^{202} Hg in urine (Laffont et al., 2011; Li et al., 2014; Sherman et al., 2013). These results indicate lighter Hg isotopes are preferentially demethylated and excreted prior to MeHg accumulation in hair. Similar to other kinetic isotope reactions, the magnitude of MDF is expected to increase as the reaction proceeds (Kendall and Caldwell, 1998). In other words, individuals with enhanced *in vivo* demethylation should exhibit larger MDF between consumed fish and hair, providing a means for identifying differences in MeHg metabolism across individuals.

Mass-independent fractionation (MIF) of the odd-mass number isotopes of Hg (^{199}Hg and ^{201}Hg) is also observed in natural samples and believed to occur primarily during photochemical reactions (Bergquist and Blum, 2007; Zheng and Hintelmann, 2009, 2010). MIF is reported as the deviation of a measured isotope ratio from the ratio theoretically predicted to result from MDF. Lab and field studies suggest the MIF signature is retained during trophic transfer of MeHg, both through the aquatic food web and into human consumers (Kwon et al., 2012; Laffont et al., 2011; Li et al., 2014; Perrot et al., 2010). The MIF signature in human hair reasonably matches that of consumed seafood because this fractionation is driven by photochemical reactions that do not occur after ingestion (Laffont et al., 2011; Li et al., 2014; Sherman et al., 2013).

The main objective of this work is to better understand factors contributing to inter-individual differences in MeHg exposures. We selected individuals for hair Hg isotope analysis from a U.S. cohort of frequent seafood consumers by identifying hair Hg samples that agreed very well with reported seafood ingestion (±10%) and those that exceed predicted ranges from probabilistic human exposure modeling. We used the composition of Hg isotopes in hair from these individuals to evaluate the validity of dietary recall data and evidence for enhanced *in vivo* demethylation.

2. Methods

2.1 Study population

We recruited a cross-sectional cohort (n = 2099) of U.S. individuals who consume three or more fish meals per week (Figure 1). This corresponds to the 90th–95th percentile seafood consumer in the National Health and Nutrition Examination Survey (NHANES) (U.S. EPA, 2011). Cross-sectional data were collected in April (n = 685), July (n = 689), and September (n = 725) of 2013 to account for seasonal variability in fish consumption. Participants were selected to be statistically representative of the U.S. Census from a panel maintained by GfK Knowledge Networks (GfK), a professional organization specializing in survey research. Additional details

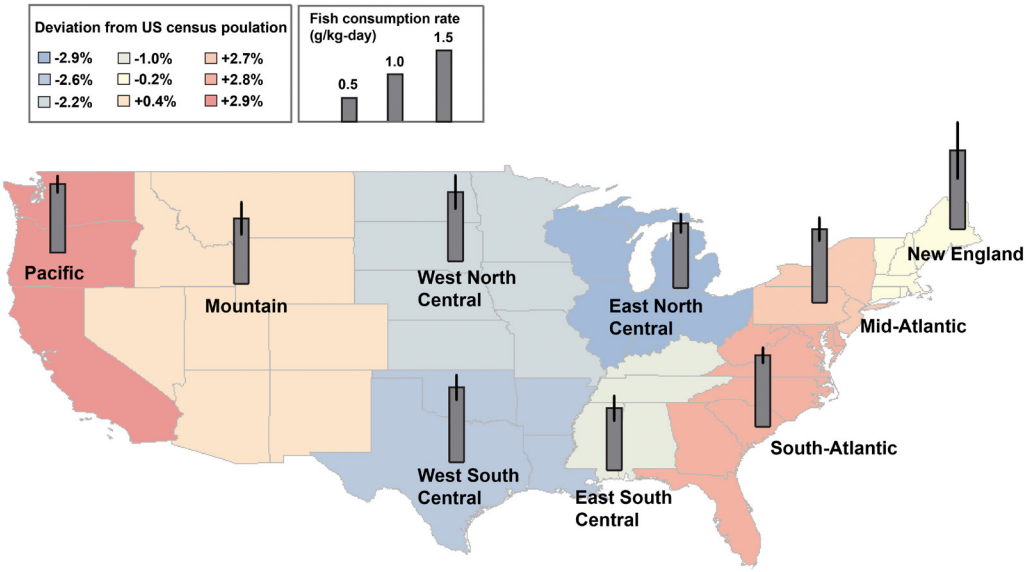

Figure 1

Distribution of high-frequency fish consumers across the U.S. relative to the Census population in 2010.

The deviation from the Census is indicated by color: blue represents relatively fewer high-frequency fish consumers and red represents relatively greater abundance. Bars denote mean seafood consumption rates for each region and 95% confidence intervals around the mean (g kg^{-1} day^{-1}). Consumption rates are not significantly different across regions.

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on recruitment and how statistical representation is ensured are provided in the Supporting Information (Text S1). Research protocols, consent procedures and the survey instrument were reviewed and approved by the Harvard T.H. Chan School of Public Health Human Subjects Committee prior to recruitment.

2.2 Hair total mercury analysis

Most (~ 91%) of the total Hg in hair of fish consumers is present as MeHg (Berglund et al., 2005). Total Hg concentrations in hair are a better indicator of exposure than direct MeHg measurements because approximately 4% is demethylated in the hair follicle (Berglund et al., 2005; Clarkson and Magos, 2006). We analyzed total Hg in the two-centimeter proximal end of hair from 304 randomly selected survey participants. Hair samples represent an exposure window of appproximately three months, which is much longer than that reflected by concentrations in blood (WHO and UNEP, 2008). Participants were mailed detailed instructions for sampling the occipital region of the scalp and returned samples within 30 days of completing the survey. Total Hg concentrations were quantified by thermal decomposition, amalgamation, and atomic absorption spectrophotometry (EPA method 7473 using a Milestone Direct Mercury Analyzer, Milestone Inc., Shelton, CT, U.S.) (U.S. EPA, 2007). The instrument was calibrated with a liquid Hg^{II} standard, with daily verifications across a range of Hg masses using two certified reference materials (CRMs: MESS-2 and TORT-3). At least one method blank and one human hair powder CRM (GBW-07601) was tested every 10 samples. Average recovery for hair CRMs was 111.7%. Precision, estimated by replicate analysis of the hair CRM and duplicate hair samples (RSD), was better than 4% and 9%, respectively.

2.3 MeHg intake and conversion to hair Hg equivalent

To convert self-reported seafood intake into a plausible range of hair Hg equivalents, we probabilistically simulate expected variability in: (1) MeHg concentrations within and across seafood types; (2) dietary absorption efficiency; (3) the fraction of absorbed dose found in blood; (4) elimination of absorbed MeHg in blood; and (5) hair-to-blood partitioning. Probabilistic exposure modeling is based on accepted ranges in MeHg concentrations from national datasets (Birch et al., 2014; Karimi et al., 2012) and inter-individual variability in pharmacokinetics (Stern, 1997). We used simulation results to capture the plausible range of hair Hg levels for each survey participant. Individuals with measured hair Hg levels that fall outside the range of modeled hair values are considered to be high-discrepancy samples and we revisit model parameters that might account for such differences.

To do this, we calculated MeHg intakes corresponding to reported ingestion of fish and shellfish over the last 30 days for all survey participants. We considered plausible concentrations of MeHg in each seafood category consumed (C_i) using data from national synthesis efforts (Birch et al., 2014; Karimi et al., 2012) and assumed a lognormal distribution with a truncated tail for Monte Carlo simulations (10,000 trials), following previous probabilistic exposure modeling (Table 1) (Xue et al., 2015; Zhang et al., 2009). This analysis was used to bracket the plausible daily MeHg dose for each survey participant:

$$D = \frac{\sum_i^n S_i \times C_i}{bw} \quad (1)$$

Table 1. Methylmercury concentrations (μg g^{-1}, wet weight) in different seafood types used to derive intake based exposure estimates

Seafood Item	Mean	SD	Min	Max
King mackerel	1.1	3.5	0.11	1.5
Swordfish	0.89	2.1	0.15	3.3
Shark	0.88	2.5	0.08	8.3
Mackerel	0.59	3.2	0.0080	1.5
Fresh tuna	0.45	1.62	0.0070	3.0
Grouper	0.42	0.80	0.035	1.1
Pike	0.40	1.3	0.25	1.3
Bluefish	0.35	0.97	0.034	0.7
Trout	0.34	1.0	0.030	0.4
Canned tuna (white or albacore)	0.33	0.96	0.16	0.59
Sea bass or monkfish	0.29	1.0	0.0050	0.65
Walleye[a]	0.27	NA	NA	NA
Freshwater bass	0.17	0.36	0.12	0.24
Haddock	0.10	0.75	0.020	0.38
Lobster	0.15	0.32	0.042	0.25
Catfish	0.12	0.59	0.0050	0.71
Canned tuna (light or skipjack)	0.12	0.30	0.047	0.40
Perch	0.12	0.42	0.010	0.55
Crab	0.098	0.45	0.0050	0.30
Other finfish[a]	0.097	NA	NA	NA
Cod	0.087	0.36	0.019	0.18
Sardines	0.079	0.20	0.010	0.33
Porgy	0.065	0.14	0.033	0.10
Breaded fish (fishsticks, etc.)	0.058	0.34	0.0050	0.70
Pollock	0.058	0.34	0.0050	0.70
Shrimp	0.053	0.21	0.0030	0.38
Salmon	0.048	0.14	0.0050	0.19
Scallops	0.040	0.15	0.0040	0.090
Crayfish	0.034	0.10	0.0210	0.21
Other shellfish[a]	0.032	NA	NA	NA
Clam	0.028	0.18	0.0050	0.30
Mussels	0.028	0.11	0.013	0.085
Oysters	0.020	0.18	0.0050	0.083
Tilapia	0.019	0.097	0.0020	0.15

[a]Denotes data from Birch et al. (2014). All other seafood categories from Karimi et al. (2012). We assume a truncated lognormal distribution for probabilistic modeling all species following previous work except those from Birch et al. due to data limitations (Xue et al., 2015; Zhang et al., 2009).

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Where, D is the daily MeHg dose (μg kg^{-1} day^{-1}); S_i is the consumption rate of each seafood category, i (g day^{-1}); C_i is the average MeHg concentration of species i (μg g^{-1}, wet weight); and bw is self-reported body weight (kg).

Ingested MeHg is standardly converted into hair equivalents using the one-compartment pharmacokinetic model developed by the U.S. Environmental Protection Agency (U.S. EPA, 2001; WHO, 1990):

$$C = \frac{(D \times A \times f \times bw)}{(b \times V)} \times R \quad (2)$$

Where, C is the modeled hair Hg concentration (μg g^{-1}); D is the daily MeHg dose from Equation (1); b is the elimination constant (day^{-1}); V is the blood volume (L) calculated from self-reported body weight (i.e., V(L) = 0.037bw (kg) + 1.43) (Stern, 1997); A is the gastrointestinal absorption factor (unitless); f is the

Table 2. Pharmacokinetic parameters used in one-compartment model to calculate hair Hg equivalents corresponding to self-reported MeHg intake

Parameter	Mean	Std. dev.	Min	Max	PDF[a]
Elimination constant (*b*), [day^{-1}]	0.014	0.003	0.006	0.016	Lognormal
Gastrointestinal absorption factor (*A*), unitless	0.940	0.016	0.910	0.970	Normal
Fraction of absorbed dose found in blood (*f*), unitless	0.059	0.008	0.048	0.093	Lognormal
Ratio of total Hg in hair to that in blood (*R*) [(μg/g)/ (μg/L)]	0.250	0.174	0.073	0.535	Lognormal

[a]PDF = probability density function used in Monte Carlo simulations. All data from Stern (1997).
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fraction of absorbed dose found in blood (unitless); and *R* is the hair-to-blood partitioning ratio [(μg g^{-1})/ (μg L^{-1})]. Table 2 lists the values for each parameter in Equation (2) and the shape of the probability density function (PDF) specified for Monte Carlo simulations.

2.4 Statistical predictors of hair Hg biomarkers

We examined statistical associations between measured hair Hg levels and predictors identified in previous dietary surveys using multivariable linear regression, including: MeHg daily intake based on self-reported seafood consumption (μg day^{-1}), age, gender, education, ethnicity, body weight, household income and geographic regions (Dong et al., 2015; Lincoln et al., 2011; Mahaffey et al., 2009; McDowell et al., 2004). We also examined predictors for the differences between modeled and measured hair Hg levels. Body mass index (BMI; calculated from self-reported height and weight) was included as an additional predictor because prior work suggests obesity influences MeHg metabolism (Rothenberg et al., 2015). We included the fraction of total seafood consumption consisting of shellfish as an additional explanatory variable because selenium (Se) is known to modify MeHg metabolism and shellfish generally have much higher molar ratios of Se:Hg than most finfish (Karimi et al., 2013; Kehrig et al., 2009; Nigro and Leonzio, 1996). Measured hair Hg levels and discrepancies between modeled and measured hair Hg were log-transformed before analysis because their distributions are skewed to the right. Residual plots were examined to ensure that standard assumptions of linearity, normality, and homoscedasticity were met. All statistical analyses were conducted using R (R Foundation for Statistical Computing, 2014).

2.5 Hair mercury isotope analysis

To identify the largest potential differences in isotope fractionation within the survey population, we targeted a subset of individuals with hair Hg levels that fell within 10% of the probabilistic model simulations (n = 8, hereon referred to as low-discrepancy individuals) and those that fell outside the bounds of probability distributions (n = 15, hereon referred to as high-discrepancy individuals). The expected mean of probabilistically modeled hair Hg levels for high-discrepancy individuals overpredicted measured hair Hg concentrations by at least 30-fold up to two orders of magnitude, as discussed in the results section.

We followed the analytical procedure outlined in prior studies (Laffont et al., 2009, 2011) for preparation of hair samples. Previous studies have found that washing human hair with deionized water, soap, acetone, or HCl does not remove Hg that is externally adsorbed to the hair (Laffont et al., 2011; Morton et al., 2002). Briefly, hair was weighed and digested at 120˚C for 6 hours using a 2 mL acid mixture ($HCl:HNO_3$ = 1:3, v:v). Certified reference materials (TORT-2 and ERM-DB001) were prepared in the same way as the samples.

Samples were analysed using a Neptune Plus multicollector inductively coupled plasma mass spectrometry (MC-ICP-MS) housed at the Wisconsin State Laboratory of Hygiene. Some hair samples from high-discrepancy individuals had total Hg concentrations that were too low for isotope analysis and were pooled to provide detectable concentrations in eight samples. Composite samples are routinely used for determining Hg exposure (WHO and UNEP, 2008).

Isotope results are reported in the delta (δ) notation relative to a standard reference material (NIST 3133):

$$\delta^{XXX}Hg = \left(\frac{^{XXX/198}Hg_{sample}}{^{XXX/198}Hg_{NIST3133}} - 1 \right) \times 10^3 \text{ ‰} \quad (3)$$

Changes in the fractionation of even-number isotope presumed to be from demethylation for hair samples are expressed using δ^{202}Hg notation. Photochemically driven changes in the odd-numbered isotopic signature are presented in the Δ^{199}Hg notation (Blum and Bergquist, 2007). The UM-Almadén standard solution (0.5 to 1.0 ng mL^{-1}, diluted in 10% aqua regia) was measured once every 10 samples. The Hg concentrations of the bracketing standard (NIST SRM 3133, diluted in 10% aqua regia) were systematically adjusted to within 10% of the sample digest. The signal for ^{202}Hg was <0.02 V for acid blanks, 0.9–1.1 V for 1 ng mL^{-1} Hg solutions, and 0.4–0.5 V for 0.4 ng mL^{-1} Hg solutions, respectively. The overall average and uncertainty

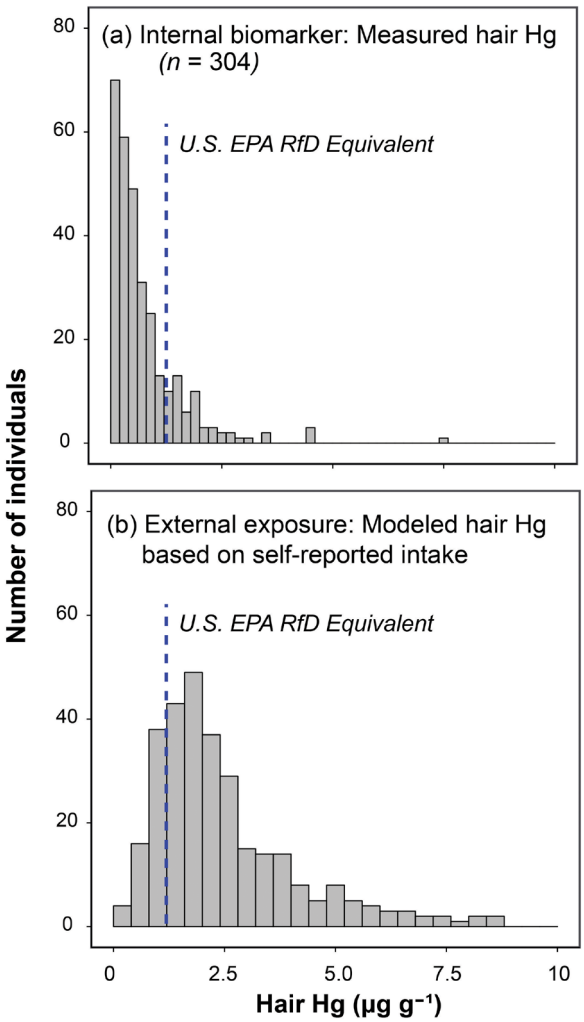

Figure 2
Distributions of hair Hg concentrations.

(a) measured concentrations; (b) modeled concentrations corresponding to self-reported exposures.

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of UM-Almadén (δ^{202}Hg: -0.52 ± 0.04‰; Δ^{199}Hg: -0.04 ± 0.03‰, σ, n = 7) and TORT-2 (δ^{202}Hg: 0.05 ± 0.02‰; Δ^{199}Hg: 0.77 ± 0.03‰; σ, n = 1) agreed well with previous studies (Kwon et al., 2014; Sherman et al., 2013). The isotope ratios of hair standard ERM-DB001 (n = 3) is 2.09 ± 0.09‰ for δ^{202}Hg and 1.14 ± 0.04‰ for Δ^{199}Hg. Mean recovery for duplicate hair samples and hair standard was 89±3% (N = 5), which is similar to prior work (Laffont et al., 2011; Sherman et al., 2013).

3. Results and discussion

3.1 Comparison of external and internal Hg exposures

Figure 2 shows exposure based on self-reported intake overestimates measured Hg levels in hair by a mean factor of 3.3 in our survey of high-frequency fish consumers. Self-reported intake of MeHg among individuals who provided hair samples (0.17 μg kg^{-1} day^{-1}) corresponds to 2.5 μg g^{-1} Hg in hair, with 85% of individuals above the reference dose (RfD) established by the U.S. EPA for MeHg. By contrast, the mean measured Hg concentration in hair was 0.76 μg g^{-1} and only 19% of individuals exceeded the level approximately equivalent to the U.S. EPA RfD (Figure 2). Similar overestimates have been observed in earlier studies on Japan, France, Quebec and indigenous populations in Northern Canada (Gosselin et al., 2006; Loranger et al., 2002; Noisel et al., 2011; Sirot et al., 2008).

Linear regression of mean measured hair Hg levels against a variety of predictors reveals significant and positive associations with MeHg intake from seafood consumption and age, and a negative association with body weight (Table 3). Participants who are Black, non-Hispanic or with an income < $20K per year have lower hair Hg compared to individuals with other ethnicities or income levels. Cumulatively, all predictors account for only 32% of the total variance in measured hair Hg concentrations. Although the r-squared value for our regression model is similar to prior work (Dong et al., 2015; Golding et al., 2013; Lincoln et al., 2011; Mahaffey et al., 2004), large remaining variability in measured exposures across individuals suggests other factors must also be important.

Table 3. Multivariate linear regression of the natural log of measured hair Hg levels (μg g^{-1})

Predictors	β-coefficient	SE	p-value
MeHg intake estimate (μg day^{-1})	0.02	0.007	<0.01[a]
Age (years)	0.01	0.004	0.02[a]
Body weight (kg)	-0.01	0.003	0.01[a]
Gender			
Female	Referent		
Male	0.2	0.1	0.1
Ethnicity			
White, Non-Hispanic	Referent		
Black, Non-Hispanic	-0.4	0.2	0.03[a]
Hispanic	0.05	0.2	0.8
Other, Non-Hispanic	0.03	0.3	0.9
2+race	0.3	0.3	0.3
Household Income			
≥100K	Referent		
$20K – <50K	-0.3	0.2	0.05
$50K – <100K	-0.3	0.2	0.09
Less than $20K	-1	0.2	<0.01[a]
Geographic regions			
East-North Central	Referent		
East-South Central	-0.9	0.3	0.01[a]
Mid-Atlantic	0.5	0.2	0.02[a]
Mountain	0.3	0.3	0.3
New England	-0.1	0.3	0.7
Pacific	0.6	0.2	0.01[a]
South Atlantic	-0.04	0.2	0.8
West-North Central	-0.01	0.3	1.0
West-South Central	-0.3	0.3	0.2

[a]Denotes statistically significant predictors. R^2 value for final model = 0.32.

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3.2 Variability in exposures due to fish MeHg and pharmacokinetics

Figure 3 shows differences between individual hair Hg levels modeled based on self-reported intake (external exposure) and measured (internal concentrations) range from negligible (±10%, n = 9) to more than 100-fold (n = 7). Many high-discrepancy individuals in our survey have hair Hg concentrations that are lower than non-fish consumers (<0.1 μg/g) (McDowell et al., 2004).

Results of probabilistic modeling indicate variability in fish MeHg concentrations (Table 1) and established ranges in the pharmacokinetics of MeHg uptake, elimination and hair-to-blood partitioning (Table 2) can account for approximately an order of magnitude difference between measured and modeled hair Hg (indicated by the solid black circles in Figure 3). However, measured hair Hg levels for 37% of individuals (open circles in Figure 3, n = 111) are well below the lower bound of simulated hair Hg levels. Thus, additional factors are required to explain low hair concentrations for more than one-third of the high-frequency fish consumers.

Previous exposure assessments for MeHg using the same one-compartment model applied here indicate it performs well for low and moderate fish consumers (Carrington and Bolger, 2002; Clarkson, 1990; Ginsberg and Toal, 2000; Jenssen et al., 2012; Zhang et al., 2009). Many studies cite the large range (0.073–0.353) in hair-to-blood partitioning (Table 2) as a major uncertainty for exposure assessments (Abe et al., 1995; Haxton et al., 1979; Kershaw et al., 1980; Phelps et al., 1980; Sherlock et al., 1982). However, recent work suggests higher partitioning to hair than earlier studies. This would result in the opposite bias as our study (higher measured hair Hg) compared to self-reported exposures (Jo et al., 2015; Yaginuma-Sakurai et al., 2012). Thus, variability in hair-to-blood partitioning of MeHg also does not provide a sufficient explanation for the observed discrepancy between measured and modeled values (Figure 3).

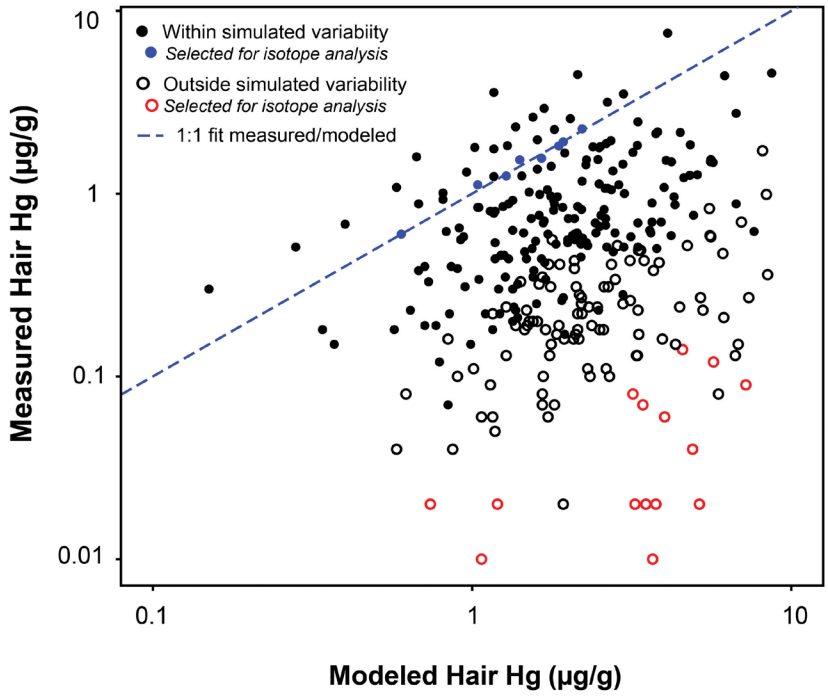

Figure 3

Individual-level comparisons of paired modeled and measured hair Hg concentrations in high-frequency consumers (n = 304).

Solid black circles denote individuals with modeled hair Hg concentrations that fall within plausible ranges anticipated due to variability in seafood MeHg concentrations (Table 1) and pharmacokinetics of MeHg in the human body (Table 2). White circles denote individuals with modeled hair concentrations that fall outside the expected range of variability based on Monte Carlo simulations. Individuals with very good (±10%) and very poor (>30-fold) agreement between modeled and measured hair Hg concentrations selected for analysis of Hg isotope composition are denoted by blue and red circles, respectively.

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3.3 Evaluation of dietary recall data using hair Hg isotope signatures

Imprecision in dietary survey data due to recall bias and mislabeling of seafood species is widely acknowledged. The signature of naturally occurring Hg isotopes in fish and hair provides a useful check on reported seafood consumption because the Δ^{199}Hg values are constant between consumed fish and human hair and δ^{202}Hg values are offset by a consistent ~2‰ (Laffont et al., 2011; Li et al., 2014; Sherman et al., 2013).

Figure 4 compares the composition of Hg isotopes in hair from low- and high-discrepancy individuals. Hair Hg concentrations in low-discrepancy individuals were higher (0.60–2.26 µg g^{-1}) than high-discrepancy individuals (all samples <0.15 µg g^{-1}, see Table S1 for additional information). The Δ^{199}Hg values for low-discrepancy individuals reasonably match their reported fish consumption, which was mainly from oceanic fish (indicated by the pie charts in Figure 4, Table S1). Two low-discrepancy individuals who received MeHg primarily from freshwater fish (e.g., trout) have higher Δ^{199}Hg, which is consistent with highly variable MIF (0.5–5.4‰) in other freshwater fish due to diverse ecosystem characteristics controlling the sources and photodegradation of MeHg (Bergquist and Blum, 2007; Kwon et al., 2012; Sherman and Blum, 2013).

High-discrepancy individuals displayed lower Δ^{199}Hg values (0.25–1.4‰) than low-discrepancy individuals and this reflects their higher reported consumption of shellfish and benthopelagic fish (e.g., cod, pollock, salmon) (Tables S1). We assume that benthopelagic fish will have a lower Δ^{199}Hg signature due to their deep foraging environments (benthic or mesopelagic) resulting in more limited photochemical degradation of MeHg (Blum et al., 2013). One high-discrepancy sample (ID 5) was a composite from two individuals reporting substantial consumption of tuna and the Δ^{199}Hg falls within the lower range of previously measured values. The Δ^{199}Hg value for sample ID 1 (Figure 4) is inconsistent with a diet that includes substantial oceanic fish but is from a woman with a child under age one. Since childbirth and/or breastfeeding in women can dramatically lower MeHg body burdens (Barbosa and Dórea, 1998; Marques et al., 2013; Marques et al., 2007), we find it plausible that unusual isotope fractionation also occurs, although this is beyond the scope of the present investigation. Apart from sample ID 1, the Δ^{199}Hg signatures in hair from high-discrepancy individuals are consistent with their predominant fish consumption patterns reported in dietary survey data. Thus, recall bias and mislabeling of seafood does not sufficiently explain their extremely low measured hair Hg levels. Table S2 contains additional details of demographic data on individuals who provided hair samples for stable Hg isotope analysis.

3.4 Mass-dependent fractionation of Hg isotopes as an indicator of MeHg demethylation

Following the hypothesis put forward by Canuel et al. (2006), an alternate explanation for extremely low hair Hg levels compared to external exposures is enhanced capacity for eliminating MeHg from blood in some individuals, thereby lowering hair concentrations. We examined the δ^{202}Hg offset between fish and human hair

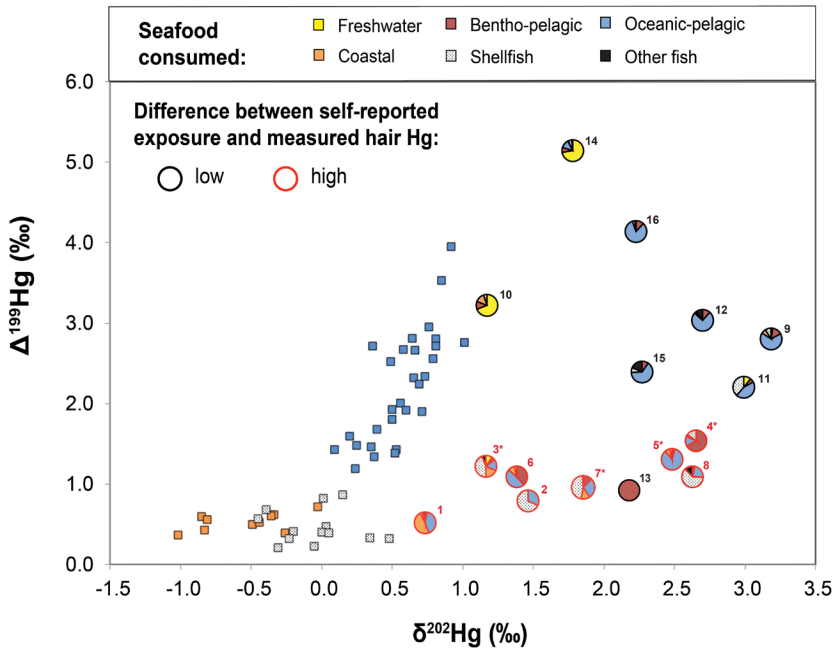

Figure 4

Stable Hg isotope ratios measured in hair samples and consumed seafood types.

Pie charts for each hair sample (circles) indicate MeHg exposure from different seafood types (squares) (Table S1). Low-discrepancy individuals with very good (±10%) agreement between modeled and measured hair Hg concentrations are denoted by black outline, while those with poor agreement (>30-fold overestimate based on self-reported consumption) are orange. Data sources for fish isotopes are compiled from prior work (Blum et al., 2013; Kwon et al., 2014; Kwon et al., 2013; Senn et al., 2010). *Indicates a composite hair sample used for analysis.

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in high- and low-discrepancy individuals. Results shown in Figure 4 indicate a similar δ^{202}Hg offset between fish and human hair across all samples, which are not consistent with enhanced *in vivo* demethylation, as we originally hypothesized.

The δ^{202}Hg offset in individuals whose hair matched their reported exposures extremely well all exhibited the expected approximately 2.0–2.5‰ offset from the oceanic fish they mainly reported consuming. In the high-discrepancy individuals, the offset in δ^{202}Hg between their hair and predominantly consumed shellfish or/and coastal fish appear to be less than 2.5‰, similar to those of low-discrepancy samples. We conclude that the δ^{202}Hg signatures in individuals with poor agreement between externally derived exposures and measured hair Hg show no evidence for enhanced demethylation of MeHg, which would have resulted in a greater offset compared to low-discrepancy individuals. Stable Hg isotope data of participants' hair samples can be found in Table S3.

3.5 Variable absorption efficiency for MeHg

By eliminating many factors that could potentially contribute to low measured hair Hg levels, our analysis points to decreased uptake of the MeHg in seafood by some individuals. Most studies assume a gastrointestinal absorption factor for MeHg that ranges between 91% and 97% (Table 2). For most high-discrepancy individuals, under the scenario of lowest species-specific Hg concentrations, smallest absorbed fraction found in blood, fastest MeHg elimination rate, and lowest hair-to-blood partitioning ratio (Table 2), we find that a lower than 14% (range: 1–72%) gastrointestinal absorption factor is still required to match their hair Hg burdens.

Both hair isotope ratios and dietary recall imply that high-discrepancy individuals obtained higher fractions of MeHg from benthopelagic and shellfish compared to low-discrepancy individuals. This suggests that the absorption efficiency of MeHg from these types of fish may be lower than that of oceanic-pelagic fish. Experimental evidence shows selenium may immobilize MeHg and poses a strong antagonistic effect on assimilation and accumulation in fish and marine mammals (Kehrig et al., 2009; Nigro and Leonzio, 1996). Experiments simulating human gastric and intestinal digestion suggest that high molar ratios of Se:Hg in fish may lower MeHg bioaccessibility (Cabanero et al., 2007). Shellfish have higher Se:Hg ratios than many other fish (Karimi et al., 2013), but we found no significant association between reported fractions of shellfish consumption and the magnitude of discrepancy between modeled and measured hair Hg levels (Table S4). Given large variability in Se:Hg ratios across species (Burger and Gochfeld, 2012), additional data are required to fully resolve a potential role of Se on observed hair Hg levels.

A variety of studies have indicated that co-ingestion of foods rich in phytochemicals (e.g., tea, fruit) are associated with reductions in MeHg absorption to less than 10% (Gagné et al., 2013; Ouédraogo and Amyot, 2011; Shim et al., 2009). Tropical fruit consumption has been associated with an over 60% reduction in Hg levels in human hair and blood (Passos et al., 2007). Animal experiments show garlic juice can reduce ~50% of mercury levels in different organs of rats (Lee et al., 1999). The exact physiological mechanism(s) for reductions in MeHg bioavailability is/are unknown and studies on the potential modifying effect of non-fish food items on MeHg bioavailability are extremely limited (Chapman and Chan, 2000). In addition,

microflora in the gastrointestinal tract that play an important role in digesting and absorbing nutrients and toxicants may also be responsible for variability in MeHg absorption efficiency (Chapman and Chan, 2000; Rowland et al., 1984). For example, Rowland et al. (1986) found a relationship between total Hg levels in mice depend and diet composition, which they attributed to differences in the metabolic activity of gut microflora.

4. Conclusion

In summary, we observed large discrepancies between modeled and measured hair Hg in 37% of high-frequency U.S. fish consumers included in our study. The Hg isotope composition of a subset of these individuals was consistent with their self-reported diet and provided no evidence for enhanced *in vivo* demethylation. No systematic source of survey bias or demographic variability can explain the extremely low hair Hg concentration observed in some high frequency fish consumers. Our analysis suggests the range in absorption efficiencies for MeHg in seafood is much larger than that previously established (91–97%) (Stern, 1997) and may be lower than 14% for some individuals. Mechanistic data on factors contributing to reduced MeHg uptake with co-ingested foods warrants additional study because it offers a potential mitigation mechanism for toxicity concerns in populations that rely on seafood for essential nutrition.

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Contributions

- Designed research and analyzed data: ML, KvS, EMS
- Performed research: ML
- Co-wrote the paper: ML, EMS
- Helped with the Monte Carlo simulation: CMR, JKM
- Assisted mercury isotope analysis: DPK, RY

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Competing interests

All individuals involved in this work declare no competing interests. The views expressed in this paper are solely those of the authors and the content of the paper does not represent the views or position of the European Chemicals Agency and U.S. Geological Survey. Any use of trade, product, or firm names in this publication is for descriptive purposes only and does not imply endorsement by the U.S. Government.

Supplemental material

- **Text S1. Survey methods and fish consumption calculations. (DOC)**
  doi: 10.12952/journal.elementa.000103.s001
- **Table S1. Contributions to MeHg exposure from different seafood types in hair samples analyzed for Hg isotopes (see Figure 4, main text). (DOC)**
  doi: 10.12952/journal.elementa.000103.s002
- **Table S2. Demographic data corresponding to hair samples analyzed for Hg isotopes. (DOC)**
  doi: 10.12952/journal.elementa.000103.s003
- **Table S3. Stable Hg isotope data for high-discrepancy (ID 1–8) and low-discrepancy (ID 9–16) hair samples. (DOC)**
  doi: 10.12952/journal.elementa.000103.s004
- **Table S4. Linear regression of the natural log of discrepancy between modeled and measured hair Hg levels (R square = 0.29). (DOC)**
  doi: 10.12952/journal.elementa.000103.s005

Data accessibility statement

The following datasets were generated:

- Hair Hg isotope data: Uploaded as online supporting information.
- Hair Hg concentration data: Summarized in main text and Figure 2 and 3.