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Development and Evaluation of a Dynamic Model that Projects Population Biomarkers of Methylmercury Exposure from Local Fish Consumption

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Abstract

A dynamic model was developed to project Hg concentrations in common biomarkers of exposure in response to changes in Hg concentrations in predatory fish from local waters. The model predicts biomarkers in susceptible populations for intake rates representing the mean, 90th, 95th, and 99th percentiles of populations of interest. The biomarkers the model calculates are blood methylmercury, total hair Hg, and fetal blood methylmercury. Decision makers can use the model to determine the degree of reduction in fish tissue Hg levels necessary to protect the health of susceptible populations. Biomarker output was calibrated with literature sources. Output was then compared to additional literature sources to evaluate model function. Projected biomarkers were not different from literature sources. The model can be used as a tool to understand the impact of local fish consumption on susceptible populations.

Keywords

Mercury exposure; Fish consumption; Susceptible populations; Dynamic modeling

INTRODUCTION

Human exposure to mercury (Hg) has been shown to cause a number of adverse health outcomes, predominantly neurological effects. The largest source of Hg exposure for the

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SUPPLEMENTAL DATA

Supplemental Data. Model equations and documentation.

general population is through consumption of contaminated fish. The developing fetus is most susceptible, and even low levels of exposure have been shown to produce nervous system deficits. The 1999 to 2002 US National Health and Nutrition Examination Study found that 6% of women of childbearing age had blood Hg levels indicative of exposure at or above the US Environmental Protection Agency (USEPA) reference dose of 5.8 µg/L (CDC 2004). Further analysis of this same data found that 16.59% of women of childbearing age in the “other” racial or ethnic group category had blood Hg levels that exceeded the USEPA reference dose (Hightower et al. 2006). The “other” category includes several groups, such as Asians, Pacific Islanders, and Native Americans, who are known to consume fish at higher rates than the general population. These studies suggest a significant portion of the fetal population is exposed to methylmercury above the level deemed protective by the USEPA and that certain populations may be disproportionately impacted by these exposures (USEPA 2009a).

The Clean Water Act requires states to set water quality criteria to protect specific uses of US waterways. One such use is the consumption of fish. The problem of Hg contamination is widespread, with 27 states issuing statewide advisories that limit fish consumption by number of meals for a given time period. Many of these states have more stringent advisories for specific water bodies, reflecting higher Hg levels in those systems. Only Alaska and Hawaii have issued no advisories on any water body for Hg (USEPA 2009b).

The primary source of elevated Hg levels in fish tissue comes from emissions into the atmosphere, with subsequent deposition and transport of Hg into waterways (USEPA 2009a). In addition to women of childbearing age and children, subsistence fishers and their families who live near these emission sources may be disproportionately affected. Individuals with low socioeconomic status may rely on fishing as an affordable source of protein and consequently bear a greater burden of exposure than less disadvantaged populations. Unfortunately, educating susceptible populations of the need to limit consumption has had limited effectiveness, perhaps due to inability to reach the target population, an economic need to supplement the diet, or a misperception of risk (Burger 1998). In order to protect populations at risk and to meet water quality criteria, fish tissue levels of Hg must be reduced through management strategies or decreased loading to ecosystems from anthropogenic sources.

Because Hg emissions into the atmosphere can travel great distances, opponents of regulations have argued that regulations to limit Hg emissions must take place at the international level to effectively protect human health (Stimola 2005). However, research has demonstrated that environmental Hg contamination can be much greater near emission sources (Volz et al. 2007; NADP 2008). Because efforts to regulate Hg emissions by the US government have been unsuccessful, some states have begun implementing their own regulations to reduce Hg emissions (The Heartland Institute 2004; Milford and Pienciak 2009; Minnesota Pollution Control Agency 2010). States cannot regulate outside their borders and so must demonstrate that local reductions in emissions would result in reduced levels of Hg in local waterways with a subsequent reduction in risk to susceptible populations.

A number of models have been developed that simulate Hg fate and transport in the environment. These models have been used to develop total maximum daily loads, to explore the effectiveness of various management scenarios, or to gain a better understanding of the dynamics of Hg in an ecosystem (Henry et al. 1995; Diamond 1999; MacLeod et al. 2005; Hope 2006). However, the central problem of Hg contamination in the environment is its impact on populations. These models do not attempt to quantify the effect of environmental Hg levels on susceptible populations.

This project was designed to develop a multitiered model that would predict the reduction in human biomarkers of exposure that could be obtained by regulations or management strategies implemented at the state level. The completed model will follow Hg from emission sources, through environmental compartments and into the biota, with bioaccumulation in fish and subsequent consumption of fish from local waters as the path to human exposure. The first step of this project was to project biomarkers of exposure in susceptible populations by relating fish consumption from local waters to internal exposure. The model predicts biomarkers of exposure in susceptible populations for the intake rates representing the mean, 90th, 95th, and 99th percentiles of populations of interest. The biomarkers the model calculates are blood methylmercury, total hair Hg, and fetal blood methylmercury. The blood Hg levels can be compared to the USEPA reference dose of 5.8 µg/L, the level deemed to be protective of the fetal population (USEPA 2009a). Decision makers can use the model to determine the degree of reduction in fish tissue Hg levels necessary to protect the health of susceptible populations. This article describes the development, calibration, and evaluation of the model, and includes a discussion of its strengths and limitations.

MODEL DEVELOPMENT

The model was developed using STELLA, version 9.0.3 (isee systems, Lebanon, NH). STELLA is an icon-based modeling program that graphically represents components of systems and how they interact (isee systems 2010). In this model (Figure 1), stocks, shown as rectangles, represent compartments in which Hg accumulates, and flows, the arrows, show the movement of Hg from one compartment to another or out of the system. Each flow is controlled by an equation that can be affected by multiple variables, called “converters,” which are represented by circles in the model (Figure 1). The model uses a monthly time scale with a 100-y run and a time step of 0.25. Euler’s method was used for integration.

The structure of the modeled system controls the dynamics of storage and movement through the human system. Initial values for all stocks, equations for the flows, and values or equations for converters are given in the Supplemental Data. The user chooses the population to be modeled on the interface page of the model (Figure 2). The distribution of intake rates is represented as an array in the model, so that biomarker values are calculated for the mean, 90th, 95th, and 99th percentiles for the chosen population. These percentiles were chosen to give decision makers some flexibility in choosing a level of protection for populations. Intake rates and population descriptions are given in Table 1. For this portion of the model, the fish tissue concentration is also input by the user on the interface page. Fish tissue Hg concentration can be adjusted before or during a model run. The default value is

equal to the USEPA criterion for methylmercury in fish tissue of 300 µg/kg (0.3 mg/kg) (USEPA 2008). During a model run, graphical output is produced on the interface page for the 3 biomarkers: blood methylmercury, hair total Hg, and fetal blood methylmercury.

Intake rates for populations of interest were taken from the literature. The *Exposure Factors Handbook* provided the intake rates for all but 2 of the populations modeled and gave ingestion of freshwater fish in grams per day (USEPA and NCEA 1997). The 2 exceptions include the Anglers 2 population and the Subsistence Fishers 1 population (Table 1). The Anglers 2 intake rates were taken from Connelly et al. (1996) and describe the consumption patterns of Lake Ontario sport fishers. The Subsistence Fishers 1 intake rates were calculated from summary statistics given in Burger et al. (1999) and represent a rural southern subsistence population. Although several populations were described in the Burger et al. (1999) study, the distribution of intake rates used in this study was calculated for the population with income under US\$ 20 000. The standard error was used instead of the standard deviation as the variance parameter in the calculation of the lognormal distribution, in order to give a more accurate estimate of fish ingestion.

Methylmercury ingestion is calculated from the fish tissue concentration and the distribution of intake rates of the population selected by the user. Miettinen et al. (1971) reported that approximately 95% of ingested methylmercury is absorbed into the bloodstream. The model flow “MeHg Absorption” calculates the amount of methylmercury that is absorbed into the bloodstream. “BLOOD MeHg” is both a clearinghouse for the disposition of methylmercury throughout the body and the stock from which the biomarker, methylmercury blood concentration, is calculated. Pathways leading from “BLOOD MeHg” include removal by defecation, transfer to tissue, excretion in hair, and the fetal pathway.

The methylmercury defecation pathway includes the “MeHg defecated” flow, which is calculated as a fraction of “BLOOD MeHg.” Defecation is thought to account for approximately 80% to 90% of Hg loss (Smith et al. 1994). However, it is unclear what portion is lost through demethylation by gut fauna (Clarkson et al. 2007) or through transformation to inorganic Hg in the tissues and subsequent transport to the gut for defecation (Farris et al. 1993). Because no consensus was found in the literature, both processes are simulated. The relative portion that is converted to inorganic Hg in the tissue versus that which is converted in the gut does not affect the purpose of the model, namely, to accurately forecast biomarkers on the basis of intake rates. Therefore, the rate of conversion to inorganic Hg in the tissue was adjusted on the basis of accurately predicting biomarkers and matching literature values for reaching the steady state and half-life of ingested methylmercury.

The pathway of methylmercury in hair includes the “Excretion in Hair” and “Outgrowth” flows, and the “MeHg in 1 CM HAIR” stock. Total Hg in hair is a commonly used biomarker of exposure. The converters “hair to blood ratio,” “mass of 1 cm hair,” and “MeHg blood conc” are used to calculate the mass of methylmercury that moves through the “Excretion in Hair” flow. The “monthly hair MeHg” converter calculates the amount of Hg in 1 cm of hair (from the entire scalp) based on the ratio of hair concentration to blood concentration. This is multiplied by 0.8, because only a portion of hair Hg is organic. The

inorganic portion is excreted separately through the inorganic pathway (Bakir et al. 1973; Phelps et al. 1980).

The stock “MeHg IN 1 CM HAIR” is used to calculate MeHg concentration in hair, which is the organic fraction of the biomarker of interest. The “Outgrowth” flow moves the methylmercury out of the stock at a monthly rate, simulating the constant growth of hair, and with it, the methylmercury that is excreted in hair. Total hair Hg is calculated by adding the organic and inorganic fractions in hair.

The fetal pathway includes the stock “FETAL MeHg” and the flows “Placental Transfer” and “Birth.” This pathway simulates fetal exposure, and the biomarker of interest is cord blood concentration. For this model, a pregnancy is generated at 5-y intervals. When a population of children is selected, the fetal pathway is switched off. The mass of Hg needed in the fetus is calculated from the maternal methylmercury blood concentration (“MeHg blood conc”) and the ideal fetal blood concentration (“ideal fetal conc”). This concentration is then converted to mass by the “fetal bl vol” converter. The Hg is transferred to the fetus over a 9-month interval. Literature values are not available for cord blood throughout the course of pregnancy; thus, as a biomarker, cord blood concentration represents exposure for the full-term neonate. Fetal body weight (“fetal bw”) is set at 3.25 kg and is divided by 9 for linear growth to the full-term neonate. Fetal blood volume is also divided by 9 for linear growth to full term. The “Birth” flow empties the “FETAL BLOOD MeHg” stock after 9 months. A limitation of this flow is that emptying occurs over a 1-month time period when in reality, it is instantaneous in vivo. Over the time scale modeled, this slowing of Hg loss through this pathway does not affect the accuracy of the modeled biomarkers.

The primary pathway methylmercury follows out of “BLOOD MeHg” is to “TISSUE MeHg” (“Bl to Tissue MeHg Transfer” flow). A set of converters is used to calculate the amount of methylmercury that needs to move from “BLOOD MeHg” to “TISSUE MeHg,” or vice versa, in order to maintain or attain the expected steady-state ratio between blood and tissue published in the literature. The literature reports that the ratio between tissue and blood ranges from 5:1 to 10:1 (Cernichiari et al. 2007), so an expected ratio of 7.5:1 is applied. Ingested methylmercury moves from absorption into blood and then to tissue in less than a month. The monthly time scale of the model requires that each movement from one stock to another takes a minimum of 1 month. In order to circumvent this limitation and more closely model the rapid movement of methylmercury from ingestion into tissue, a fraction of the “MeHg Absorption” flow is added to the fraction taken from the “BLOOD MeHg” stock in the calculation for the flow “Bl to Tissue MeHg Transfer.” This streamlining of movement enabled attainment of steady-state ratios in a more realistic time frame. The process of calculating the movement of methylmercury between the blood and tissue methylmercury stocks is described in detail in the Supplemental Data.

Two converters, “MeHg blood conc” and “MeHg tissue conc,” are tools for the user. Stocks give the mass of methylmercury, but the literature primarily reports concentrations in various compartments. “MeHg blood conc” reports the biomarker maternal blood concentration. It is the mass of methylmercury in the “BLOOD MeHg” compartment divided by the volume of blood. The “MeHg tissue conc” is not a biomarker. However, calculating this value

facilitated the calibration process by determining whether the model was giving the expected ratio in the disposition of methylmercury between tissue and blood.

Conversion to inorganic Hg occurs through the “Converted to IHg” flow. This process moves Hg from the “TISSUE MeHg” stock into the “TISSUE IHg” stock. The “TISSUE IHg” stock represents inorganic Hg in all compartments of the body. It should be noted that some tissues, such as kidney, concentrate inorganic Hg, whereas other tissues may have lower concentrations. The converter “rate constant convert to IHg” determines the fraction of tissue methylmercury that is converted to inorganic Hg. This conversion rate was not determined by literature values, but by adjusting the rate so that the half-time in the body and the ratio between blood methylmercury and tissue methylmercury came closest to matching literature values. Three pathways flow out of “TISSUE IHg” and represent losses to the system. These are the flows “fecal loss of IHg,” “IHg loss in urine,” and “IHg in hair.”

The biomarkers of interest do not specifically look at inorganic Hg; however, the hair Hg biomarker typically measures total Hg, approximately comprising 80% methylmercury and 20% inorganic Hg (Phelps et al. 1980). Therefore, the pathway of inorganic Hg in hair is simulated and used in the calculation of total Hg concentration in hair. Similar to the pathway of methylmercury excretion in hair, this pathway consists of the flows “Inorganic Hair Exc” and “Outgrowth of IHg in Hair,” and the stock “IHg in 1 CM HAIR.” Monthly hair inorganic Hg is calibrated to be a fraction of “TISSUE IHg.” This fraction, 0.0296 in the “IHg hair fraction” converter, was determined by back-calculating the portion of “TISSUE IHg” that would be required to make the 20% of inorganic Hg in hair necessary to attain the desired ratio of hair total Hg to blood methylmercury. The remainder of this pathway replicates the pathway of methylmercury in hair. Total concentration in hair (“total conc in hair”) is calculated by adding “IHg conc in hair” and “MeHg conc in hair.”

The flow “IHg Defecation” simulates the loss of inorganic Hg through the feces. This loss, along with loss of methylmercury through defecation, combines to achieve the percent of total Hg lost through this pathway found in the literature. “IHg defecation rate” sets the fraction of “TISSUE IHg” that is lost due to defecation.

The loss of inorganic Hg in the urine pathway is simulated by the flow “Urine IHg loss.” The kidneys tend to accumulate inorganic Hg and slowly release the Hg into the urine (Young et al. 2001; Passos et al. 2007). Because these rates are not well-documented in the literature, the loss through this pathway balances the 80% to 90% loss through feces with the losses through the hair and fetal pathways.

CALIBRATION

The model was calibrated to literature sources to maximize biomarker accuracy. Literature sources for calibration were chosen on the basis of how comprehensive the study was in looking at the relationship being examined. The relationship between ingestion of methylmercury and blood methylmercury level was calibrated according to Sherlock et al. (1984). Instead of estimating dose, this study measured fish intake with known methylmercury levels over a period of time to relate ingestion to blood methylmercury levels

at steady state. The results found a steady-state blood methylmercury concentration of 0.8 µg/L for every 1 µg/d ingested. Because children weigh less than adults, this figure is unlikely to hold true for the modeled populations of children. No literature source was found that related ingestion to steady-state methylmercury concentrations in children, so the assumption was made that disposition between blood, hair, and tissue in children was the same as in adults, and the ratio was derived from model output. The ratio for children was found to be 1.3 µg/L for every 1 µg/d ingested.

The ratio between hair Hg and blood methylmercury shows a greater degree of variation between individuals than do other biomarkers (Phelps et al. 1980; Budtz-Jorgensen et al. 2004; Cernichiari et al. 2007). A ratio of 250 µg/kg total hair Hg to 1 µg/L blood methylmercury, which is the most commonly used ratio in epidemiology studies (Clarkson et al. 2007), was selected for use in this model.

Stern and Smith (2003) did a meta-analysis of studies measuring the relationship between maternal and cord blood. Their analysis reported ratios from studies that looked at methylmercury only, total Hg only, and combined studies of both methylmercury and total Hg. They reported that studies measuring methylmercury only produced a higher ratio (mean ratio of 1.9) than the meta-analysis that combined both methyl and total Hg (mean ratio of 1.7). They recommended the ratio from all studies combined be used because of uncertainty in the source of inorganic Hg and the small difference it produced in ratios. This model was calibrated with the ratio from the methylmercury-only analyses (1.9). The model structure shows movement of methylmercury from maternal blood to the fetal blood compartment, with no inflow of inorganic Hg. Although inorganic Hg does cross the placenta, it does not concentrate in fetal blood like methylmercury. Vahter et al. (2000) reported a mean ratio of 0.9 for the relationship of cord blood to maternal blood inorganic Hg. Because maternal blood volume is greater than fetal blood volume, the inclusion of inorganic Hg in the measurements to determine the ratio between fetal and maternal blood levels lowers this ratio. Methylmercury is thought to be more toxic to the fetus and crosses the placental barrier with greater ease than inorganic Hg. Use of the higher ratio for decision making is more protective of the fetus.

Consistency of model output was examined across the distribution of intake rates for all biomarkers. Chi-squared analyses were conducted using PASW Statistics 18 software (SPSS Inc.), comparing the expected values from literature sources to the observed model output. In addition, scatter plots were generated for a visual assessment of the comparisons.

Table 2 shows the outcomes from the distribution of ingestion rates from various populations. Model output is similar for all biomarkers to values predicted from literature sources. Table 3 shows the *p* values from chi-squared analyses. There were no significant differences between model output and the literature values (all *p* values > 0.05). Scatter plots of predicted versus observed values demonstrate that, although not significantly different, the model appears to slightly overestimate biomarker concentrations at the highest ingestion rates (Figure 3A to C).

EVALUATION

The model was evaluated by comparing the model projections to additional literature sources to further strengthen confidence in the output. Table 4 lists the literature sources that were used to evaluate the relationships between ingestion and blood methylmercury, blood methylmercury and total hair Hg, and maternal and fetal blood methylmercury concentrations. Scatter plots were generated to visually assess if model output differed from these sources. In addition, the mean and 95% confidence interval of the slopes of the literature sources for each biomarker were compared to the slope of the model output.

For the literature values that measure the relationship between intake and steady-state blood concentrations of methylmercury, values were generated from the equations taken from the 7 literature sources listed in Table 3 from the WHO (1976) and Kershaw et al. (1980). A range of intake rates were selected (25, 50, 75, and 100 µg/d) and entered into the regression equation from each literature source to generate steady-state blood concentrations. For comparison to ingestion rates from the model, the daily intake rates were converted to monthly rates, and new regression equations were determined.

For evaluation of the relationship between maternal and fetal blood, the summary statistics reported from 5 literature sources were used as data points to generate regression equations. These summary statistics included the mean for all studies and the range or the 95% confidence interval. In addition, some studies also reported the median or a range of percentiles. The slope of the regression for each literature source was then determined.

The relationship between blood methylmercury and hair total Hg was evaluated by comparing the slope of model output to the slopes of 9 literature sources that studied 11 populations. Summary statistics were used to generate a regression equation for 5 literature sources. For the remaining 6 sources, regression equations were reported and a range of blood methylmercury concentrations were input into the equations to generate hair concentrations for the scatter plot. The regression equations for 5 of these sources were reported in Table 1 from the WHO (1976).

Figure 3D compares the model output to 8 literature sources for the relationship between ingestion and blood Hg levels. The mean and 95% confidence interval of the slope for the literature values was 0.024 (0.008–0.040). The slope for model output was 0.028 and was not significantly different from literature values.

The relationship between blood methylmercury and total hair Hg concentrations for model output and the results of 9 literature sources that reported on 11 populations is shown in Figure 3E. Model output falls within the range of measurements found in the literature. The mean of the slopes for the literature values was 283 with a 95% confidence interval of 235 to 331. The slope of model output, 250, falls within that range, reflecting no difference between model output and literature sources.

The relationship between maternal and fetal blood methylmercury for 5 literature sources and model output is shown in Figure 3F. The slopes of literature sources had a mean and

95% confidence interval of 2.06 (1.49–2.62). The slope of model output was 1.89 and falls within the range of literature sources.

UNCERTAINTY ANALYSIS

The model uses epidemiological means for many variables. These variables include the distribution of intake rates for populations of interest, ratios between various compartments in the model, and physiological characteristics such as body weight and blood volume. Natural variability is inherent in all systems, and a range of values are possible for each input. To measure the reliability of model predictions, an uncertainty analysis was performed to determine the importance of differing parameters on the output of the model. Population means typically have lower variability when compared with individual-level outcomes. Therefore, using the plausible ranges for population means was considered sufficient. Qualitative methods were used to determine if the results obtained from our model were at risk or threatened, within these plausible ranges. The model output was not sensitive to any component or parameter in the model within plausible ranges.

DISCUSSION

The purpose of the overall model will be to provide information that can be used by decision makers in the process of determining reasonable regulations or management strategies to protect populations of interest. This phase of model development projects exposures to various populations on the basis of fish tissue concentrations that are input by the user. Subsequent development of the model will include Hg movement from local emission sources, through environmental compartments and bioaccumulation in the food web, to the point where local fish tissue concentrations directly inform this human exposure model. Although models are available that focus on different compartments of this system, combining all these compartments will facilitate the decision-making process by directly connecting environmental contamination to the exposure of susceptible populations.

In the development of any model, a balance is sought between generating an accurate forecast with the simplest representation of the system, while remaining transparent. Enough details of the system must be included for the model to be accurate for a variety of scenarios. Simplicity calls for breaking a system down to its most basic components so that it is easier to understand. The balance between simplicity and inclusion of enough details can be difficult to judge. Transparency refers to a clear understanding of the model by both peer reviewers and the actual users of the model. The ideal balance for these 3 competing goals depends on the purpose of the model (NRC 2007). Because the purpose of this model is to be a tool for regulatory decision makers who may need to explain policy or management recommendations to law-makers or stakeholders who have limited scientific background, the goal is to accurately forecast population outcomes with the greatest simplicity in a format that could be understood by the educated layperson. When the model is expanded to include the environmental components of the system, the stock and flow diagram will further enable these stakeholders to understand the parts of the system that may aid or hinder the reaching of human health goals, and the need for regulatory or management strategies that may not be intuitive.

The use of STELLA as a modeling tool has been successful in helping lay stakeholders understand complex systems in the process of developing policies that require stakeholder support for implementation (Stave 2003). Stave (2003) developed a STELLA model to simulate the dynamics of water supply and use in Las Vegas, Nevada, USA. The model was used to analyze the impact of various policy options in order to maximize water supply over time. An important component of the policy analysis was to garner public support for the final policy recommendation. The STELLA model was successful in creating an understanding of the system without overwhelming the stakeholders with complicated technical equations. This understanding of the system was instrumental in implementing a water conservation policy that required stakeholder cooperation.

It is important to distinguish between projected biomarkers of exposure and risk of an adverse effect (ECETOC 2005). The USEPA set the reference dose for methylmercury at 5.8 µg/L in cord blood for protection of the developing fetus and includes a safety factor of 10 (USEPA 2010). The reference dose is often applied to maternal blood but was established with the assumption that the ratio between fetal and maternal blood methylmercury was unity. Fetal blood concentrations of methylmercury are approximately 90% higher than that in maternal blood, so a corresponding maternal blood level would be expected to be lower than the reference dose (Stern and Smith 2003). Decisions made from interpreting biomarkers of exposure must consider the uncertainty surrounding the relationship between biomarker levels and adverse effects as well as the natural variability of the pharmacokinetics of methylmercury in individuals and populations (ECETOC 2005). With the long-term objective of linking proposed Hg regulations or management strategies to the protection of human populations, it is important to remember that this model does not simulate changes in an individual over a lifetime, but progressive changes in Hg levels in a population over 100 y. In analyzing population biomarkers, Hg disposition in individuals representing the distribution of intake rates for a given population are simulated. Although the most accurate method of forecasting effects would be to model the movement of Hg through these individuals, the literature provides conflicting information on exactly how Hg is transported and transformed within the human body. A simplification of the dynamics of Hg disposition in the body was used to simulate common biomarkers and loss to the human system. Because of this simplification, this model should not be used to predict Hg concentrations in individuals or specific tissues. The model only forecasts the central tendency of certain biomarkers for a distribution of intake rates of defined populations.

The human disposition model forecasts blood methylmercury, fetal blood methylmercury, and total hair Hg concentrations in response to the intake rates of freshwater fish for various populations. The distribution of intake rates gives the user the opportunity to project what portion of the population would fall below the USEPA reference dose if fish tissue concentrations of Hg are reduced by a given amount. By limiting the intake to freshwater fish, the model more accurately simulates exposure from local sources. However, many populations consume larger amounts of marine or store-bought freshwater fish from nonlocal waters, and exposures for those populations are likely to be underestimated by this model. Subsistence fishers and anglers are likely to have the greatest portion of their fish intake from local sources, and therefore this model is expected to characterize Hg exposure

in these higher risk populations more accurately than populations that ingest fish from other sources.

Table 1 describes 10 population choices that are available for users. Regulatory decision makers should choose the population whose fish intake most closely resembles the population of concern. With a basic understanding of STELLA modeling, a user could alter the model to include the intake rates for any population of interest. Although it seems counterintuitive that angler populations have lower intake rates at the highest percentiles than the general population, sampling methods and the frequency of fish meals affect the intake rates. With the exception of the angler and subsistence fisher populations, intake rates were derived from a national survey that asked subjects about fish meals over the past 3 d (USEPA and NCEA 1997). Consumers were those who reported any fish consumption during those 3 d. Because fish meals may be infrequent, a 3-d diary may have overestimated daily intake when extrapolated to a monthly rate. Both angler populations and the Subsistence 2 population used a 1-y assessment of fish consumption (CRITFC 1994; Connelly et al. 1996; USEPA and NCEA 1997). The Subsistence 1 population was assessed over an 8-month period (Burger et al. 1999). Many anglers fish more frequently during certain seasons, and therefore fish intake may be much higher at certain times of the year. A longer assessment period for those who consume fish seasonally would result in a lower daily intake rate than if the assessment was taken during the highest consumption period. These methods may have resulted in a bias toward higher daily intake rates for the more general populations and lower daily intake rates for the angler and subsistence fisher populations.

The user inputs the fish tissue concentration into the model. Although the concentration of fish tissue can be adjusted during the model run, it cannot be adjusted to simulate the variability of tissue concentrations found in various fish species. Anglers often prefer to fish for the predatory fish, such as largemouth bass and walleye, that tend to have the highest levels of Hg contamination. Subsistence fishers and children may consume more panfish because they are easier to catch. Panfish are typically lower on the food chain and subsequently have lower Hg concentrations. Because local consumers typically do not limit themselves to one species, the user may conservatively choose to enter the fish tissue concentration of the sport fish of highest concentration, or, less conservatively, adjust the fish tissue concentration by weighting to reflect the intake of various species from a particular waterway.

Perhaps the greatest challenge to the development of this model originates from varying time scales. Mercury movement through environmental compartments occurs on a slower time scale than Hg movement through the human body. Although changes in steady-state levels in environmental compartments may take years or decades, changes within the human body can occur relatively quickly. In STELLA, a single time scale must be chosen for the entire model. The time scale of months was chosen to allow for simulation of seasonal changes in environmental compartments and to allow a 100-y model run without encountering memory problems. However, for human disposition, this time scale introduces complications. Movement from one stock to another takes at least 1 month, whereas in vivo, this movement may occur in hours or days. In order to minimize this limitation, the human sector of the

model is as streamlined possible. This streamlining was achieved by consolidating certain pathways, such as the enterohepatic shunt. The model structure shows only the loss of methylmercury through defecation instead of representing the entire pathway, which also includes methylmercury removal from blood by the liver and subsequent secretion into the gut where most is reabsorbed into the blood and the remainder is lost through defecation.

Because of the monthly time scale, the time to reach the steady state and the half-life of Hg in the system is slower than what is found in the literature. The literature suggests that the steady state for a new intake rate of Hg is reached in approximately 1 y (Sherlock et al. 1984). For this model, the steady state takes almost 3 y to be attained. Similarly, the half-life of Hg in the body is approximately 2.5 months (Miettinen et al. 1971). The half-life of Hg in the model is approximately 12 months. When projecting changes over the short term, these differences are unacceptable. However, when examining change in populations over decades along with the uncertainty associated with Hg movement through environmental compartments, the imprecision of reaching a steady state in 3 y instead of 1 y would have a negligible effect on regulatory decision making.

The notion of steady-state Hg levels in blood and other human compartments is somewhat misleading. Exposure to Hg occurs through periodic meals of contaminated fish and is therefore intermittent. After a meal, blood Hg levels peak after several hours and then have a biphasic decline. An initial rapid drop in Hg levels is followed by a much slower decline with a half-life of approximately 2.5 months (Miettinen et al. 1971; Kershaw et al. 1980). For individuals who only occasionally eat fish, use of a steady-state ratio to predict a biomarker of exposure could be misleading, because the actual concentration in any sample would be highly dependent on the amount of time that had passed since the last meal. For individuals and populations that consume fish on an almost daily basis, the assumption that a steady-state concentration has been attained is more reasonable. Mercury concentration in blood would still be close to peak levels when the next exposure occurred. The question of biological relevance for projected biomarkers that have been derived by assuming a steady-state ratio for individuals with intermittent exposures depends on whether acute or chronic exposure to Hg is responsible for adverse effects in the developing fetus. That question has not yet been answered, but these values based on steady-state intake give some approximation for the amount of exposure. The steady-state assumption is more accurate for populations that eat frequent fish meals. These populations are more likely to have the highest exposures to Hg and subsequently are at greater risk for adverse effects.

To investigate whether the values obtained from the model developed in this study are similar to the expected values based on previous literature, traditional chi-squared techniques were employed. These techniques test for differences between observed and expected values. Model output values were not significantly different than the calibration sources over a wide range of exposure levels. That is, the values obtained from the model were expected based on previous research. It should be noted, however, that the model slightly overestimates biomarkers at the highest ingestion rates. At these levels, the variation in sampled populations is also at its greatest. The slight overestimation of biomarkers was shown to be negligible and insignificant when compared to population variability, as shown by evaluation of the model, and does not threaten the validity of our model.

Evaluation of the model consisted of comparing the model's parameter estimates (e.g., regression coefficients) with parameter estimates observed in the pertinent, relevant literature. The relationship between ingestion and blood methylmercury was validated using parameter estimates observed in 8 studies (Table 4). The parameter estimates from these studies varied somewhat, perhaps reflecting variability in the populations sampled or bias from sampling methods. The current model's parameter estimates were similar to the mean of parameter estimates from the previous 8 studies and fell within the range of parameter estimates from all 8 studies. This comparison established that the model produces valid and reliable estimates for blood methylmercury levels based on a given consumption rate of contaminated fish.

Similarly, parameter estimates for the model for fetal blood methylmercury relative to maternal blood methylmercury also fell within the range of literature sources. Unfortunately, only summary statistics from the literature were available for comparison. The use of summary statistics, instead of actual measurements or the regression equation derived from actual data, may introduce a limitation for this comparison. The variation could theoretically be greater for one of the comparison groups (maternal or fetal blood). Therefore, when the mean, range, or other markers of the sample are compared, this may bias the ratio between the 2 data sets. However, because these are summary statistics and several data points were used, the effect of possible outliers is likely minimized but may need to be studied in more sophisticated studies in the future.

The relationship between blood methylmercury and hair total Hg was compared to 9 literature sources describing 11 populations. No difference was found between model output and these sources. Hair is frequently preferred as a biomarker for Hg exposure because it is easy to collect, is highly correlated with blood methylmercury, and shows the history of exposure over time (Cernichiari et al. 2007). However, hair Hg levels are more variable than blood methylmercury levels for a given exposure. This model was designed to give the central tendency after a given exposure, and thus users need to be cognizant that hair Hg concentrations in individuals from a given population will vary widely with an identical exposure.

The results suggest the developed model accurately projects the central tendency of biomarkers of exposure based on ingestion rates and fish tissue concentrations for populations of interest. It is a first step in linking environmental Hg levels to effects on nearby populations. With knowledge of the Hg concentration in fish from local waters, decision makers can use the model to assess the portion of a population that is at risk and subsequently determine the decrease in fish tissue concentration needed to protect susceptible populations. The STELLA model depicts the disposition of Hg after ingestion in a simplified, yet understandable format, balancing accuracy, simplicity, and transparency. The model can be used as a tool to understand the impact of local fish consumption on local susceptible populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The STELLA model shows the movement of Hg from ingestion to loss from the human system. MeHg = methylmercury; THg = total Hg; IHg = inorganic Hg; childr = children; cons = consumers; sub = subsistence; bw = body weight; conc = concentration; def = defecation; vol = volume; bl = blood.

Figure 2.

The interface page of the model is shown. The user selects the population and inputs the fish tissue concentration from this page. Model output is in the form of a graph for each of the biomarkers.

shown are between **(D)** ingestion and blood methylmercury, **(E)** blood methylmercury and total hair Hg, and **(F)** blood methylmercury and fetal blood methylmercury.

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Table 1

Distribution of intake rates (g/d) of freshwater fish for populations

Population	Percentile				Source ^a	Description
	Mean	90th	95th	99th		
General	4.7	12.6	32.2	82.5	1	US population
Consumers only	68	170.8	224.8	374.7	1	US population that consumes fish
Women (ages 15–44 y)	5.3	10.9	28.8	70.9	1	All women of childbearing age
Women (ages 15–44 y) consumers	61.4	148.8	185.4	363.6	1	Women of childbearing age who consume fish
Children (ages 0–14 y)	1.9	1.3	13.9	40.8	1	Children ages 0 to 14
Children (ages 0–14 y) consumers	45.7	108.4	136.2	214.6	1	Children ages 0 to 14 who consume fish
Anglers 1	7.4	20.6	24.6	41.1	1	Wisconsin sport anglers
Anglers 2	17.9	13.2	17.9	39.8	2	Lake Ontario sport fishers
Subsistence fishers 1	55.5	150	200	338	3	Subsistence fishers on the Savannah River
Subsistence fishers 2	58.7	110	170	389	1	4 Native American tribes in Washington State

^aSource: 1 = USEPA and NCEA (1997); 2 = Connelly et al. (1996); 3 = Burger et al. (1998).

Table 2

Model outcome compared to predicted outcome for the distribution of ingestion rates for various populations^a

Population	Blood concentration, µg/L				Hair concentration, µg/kg				Fetal blood concentration, µg/L				
	Mean	90th	95th	99th	Mean	90th	95th	99th	Mean	90th	95th	99th	
General	Predicted	1.3	3	7.7	19.8	325	750	1925	4950	2.5	5.7	14.6	37.6
	Model output	1.2	3.2	8.2	21	300	804	2053	5262	2.3	6.1	15.5	39.8
Consumers	Predicted	16.3	41	53.9	90	4075	10 250	13 475	22 500	31	77.9	102.4	171
	Model output	17.3	43.6	57.3	95.6	4337	10 895	14 339	23 901	32.5	82.5	108.5	180.9
Women (15–44 y)	Predicted	1	2.6	6.9	17	250	650	1725	4250	1.9	4.9	13.1	32.3
	Model output	1.1	2.8	7.3	18.1	274	695	1836	4520	2.1	5.3	13.9	34.2
Women (15–44 y) consumers	Predicted	14.7	35.7	44.6	87.3	3675	8925	11 150	21 825	27.9	67.8	84.7	165.9
	Model output	15.7	38	47.4	92.8	3916	9490	11 857	23 191	29.6	71.8	89.6	175.3
Children (0–14 y)*	Predicted	0.7	0.5	5	14.7	175	125	1250	3675	–	–	–	–
	Model output	0.7	0.5	5.4	15.7	170	116	1241	3644	–	–	–	–
Children (0–14 y) consumers*	Predicted	16.4	39	49	77.2	4100	9750	12 250	19 300	–	–	–	–
	Model output	17.6	41.8	52.5	82.8	4082	9683	12 166	19 169	–	–	–	–
Anglers 1	Predicted	1.8	4.9	5.9	19.7	450	1225	1475	4925	3.4	9.3	11.2	37.4
	Model output	1.9	5.3	6.3	21	472	1313	1569	5242	3.6	9.9	11.9	39.6
Anglers 2	Predicted	1.2	3.2	4.3	9.5	300	800	1075	2375	2.3	6.1	8.2	18.1
	Model output	1.2	3.4	4.6	10.2	312	842	1141	2537	2.4	6.4	8.6	19.2
Subsistence fishers 1	Predicted	12.8	48.7	52	57.6	3200	12 175	13 000	14 400	24.3	92.5	98.8	109.4
	Model output	13.6	51.8	55.3	61.2	3399	12 949	13 823	15 309	25.7	98	104.6	115.8

Population	Blood concentration, µg/L				Hair concentration, µg/kg				Fetal blood concentration, µg/L			
	Mean	90th	95th	99th	Mean	90th	95th	99th	Mean	90th	95th	99th
Subsistence fishers 2	14.1	26.4	40.8	93.4	3525	6600	10 200	23 350	26.8	50.2	77.5	177.5
Model output	15	28.1	43.4	99.2	3744	7016	10 842	24 811	28.2	53	82	187.6

^aFish tissue concentration for all samples was 0.3 mg/kg. Predicted values for blood concentration are based on Sherlock et al. (1984). Predicted hair concentrations were calculated based on Clarkson (2007). Predicted fetal blood concentrations were based on Stern and Smith (2003).

Table 3Chi-squared analysis p values of predicted versus observed model output

Ingestion rate	Blood	Hair	Fetal blood
Mean	0.500	0.456	0.450
90	0.524	0.395	0.450
95	0.395	0.395	0.382
99	0.395	0.395	0.382

Table 4

Literature sources for evaluation

Literature source
Ingestion and blood MeHg
As cited in Table 3 of WHO (1976)
Kershaw et al. (1980)
Blood MeHg and hair THg
Abdelhouahab et al. (2008)
Björnberg et al. (2005)
Johnsson et al. (2005)
Berglund et al. (2005)
CDC (2001)
As cited in Table 1 of WHO (1976)
Blood MeHg and fetal blood MeHg
Vahter et al. (2000)
Tsuchiya et al. (1984)
Ong et al. (1993)
Lee et al. (2010)
Soria et al. (1992)
Hansen et al. (1990)

MeHg = methylmercury; THg = total mercury.