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A Probabilistic Characterization of the Health Benefits of Reducing Methyl Mercury Intake in the United States

GLENN E. RICE,[†] JAMES K. HAMMITT,[‡] AND JOHN S. EVANS*[,†,§]

Department of Environmental Health, and Center for Risk Analysis, Harvard School of Public Health, Boston, Massachusetts 02115, and Cyprus International Institute for the Environment and Public Health, Laiki Bank Building, second Floor, Corner of Athinon and Nicou Xiouta Street, Limassol, Cyprus 3041

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We developed a probabilistic model to characterize the plausible distribution of health and economic benefits that would accrue to the U.S. population following reduction of methyl mercury (MeHg) exposure. MeHg, a known human developmental neurotoxicant, may increase fatal heart attack risks. Model parameters reflect current understanding of the relationships between MeHg intake, health risks, and societal valuation of these risks. The expected monetary value of the annual health benefits generated by a 10% reduction in U.S. population exposure to MeHg for one year is $860 million; 80% of this is associated with reductions in fatal heart attacks and the remainder with IQ gains. The plausible distribution of the benefits is quite broad with 5th and 95th percentile estimates of approximately $50 million and $3.5 billion, respectively. The largest source of uncertainty is whether epidemiological associations between MeHg exposure and fatal heart attacks reflect causality. The next largest sources of uncertainty concern the slope of the relationship between maternal MeHg exposure and reduced intelligence among children and whether this relationship exhibits a threshold. Our analysis suggests that the possible causal relationship between MeHg exposure and fatal heart attacks should be better characterized, using additional epidemiological studies and formally elicited expert judgment.

Introduction

Methyl mercury (MeHg), a known human developmental neurotoxicant, may also contribute to heart disease risks. Concerns about potential neurotoxicity from MeHg exposures have been the impetus for developing regulations to reduce anthropogenic mercury emissions. Proposals further reducing mercury emissions and MeHg exposures are under consideration. Critical analysis of the social benefits anticipated to flow from such proposals is vital to deliberation about their merits.

Fish consumption is the major source of MeHg intake, which averages approximately 1 μg Hg/day in the U.S. population (*1*). Because fetal neurotoxicity has been of most concern, MeHg body burden measures (i.e., blood and hair MeHg levels) have targeted women of childbearing age. Blood levels of U.S. women aged 15−44 years are lognormally distributed (median = 0.85 μg Hg/L; geometric standard deviation (GSD) = 3; Supporting Information Figure S1A) (*2*).

At exposures approximately 25 times greater than those now prevalent in the U.S., small decrements in childhood intelligence measures are associated with maternal MeHg exposures during pregnancy (*3, 4*). Such small decrements are of minor concern for individuals, but large enough to suggest that current MeHg levels in the population may lead to small but widespread IQ decrements (Supporting Information Figure S2). Also, studies in two epidemiologic cohorts (*5, 6*) suggest that MeHg exposure may increase heart attack risks among adults. However, it is not known if these associations are causal (Supporting Information S1).

Some impacts of these health effects can be valued using economic models. Part of the value of reduced intelligence can be estimated by the value of lost productivity. The incremental risk of a fatal heart attack can be valued through estimates of individual willingness to pay to reduce mortality risk. Three recent analyses have estimated the benefits of reduced MeHg exposures (*7*−*9*); each quantified the monetary benefits associated with reduced neurological decrements, but none quantified the potential cardiovascular benefits.

We estimate the economic value to the U.S. population of the public health benefits associated with a uniform 10% reduction in average daily MeHg intakes (i.e., 0.1 μg MeHg/kg-day reduction) from current levels for one year. Our model can be easily adapted to estimate the benefits of other patterns of exposure reduction. We examine the reduction in exposure; consequent reduction of health risks; and valuation of the societal benefits flowing from these risk reductions (Figure 1 and Supporting Information Figure S3). Because the underlying science is imperfect, attempts to characterize these relationships must include probabilistic characterization of the relevant parameters. In this analysis, we follow the advice of Morgan et al. (*10*) who describe current "best practices" for uncertainty characterization in policy analysis.

Materials and Methods

Model. The economic value, V, of the health improvement expected following a reduction in daily MeHg intake is the sum of the economic value of the reduced neurotoxicity, V_n, and the economic value of the reduced cardiovascular disease, V_c. We estimate the present values of the discounted streams of health benefits generated by reductions in both effects.

$$V = V_n + V_c \quad (1)$$

While both neurotoxicity and cardiovascular effects are multifaceted, we use proxies intended to capture the dominant components of these values. For neurotoxicity, we evaluate the discounted present value of the increase in earnings expected to accrue from IQ increases in an annual birth cohort,

$$V_n = B\Delta E \quad (2)$$

* Corresponding author phone: +357-22-44-92-92; fax: +357-25-00-22-01; e-mail: jevans@hsph.harvard.edu.
[†] Department of Environmental Health, Harvard School of Public Health.
[‡] Center for Risk Analysis, Harvard School of Public Health.
[§] Cyprus International Institute for the Environment and Public Health.

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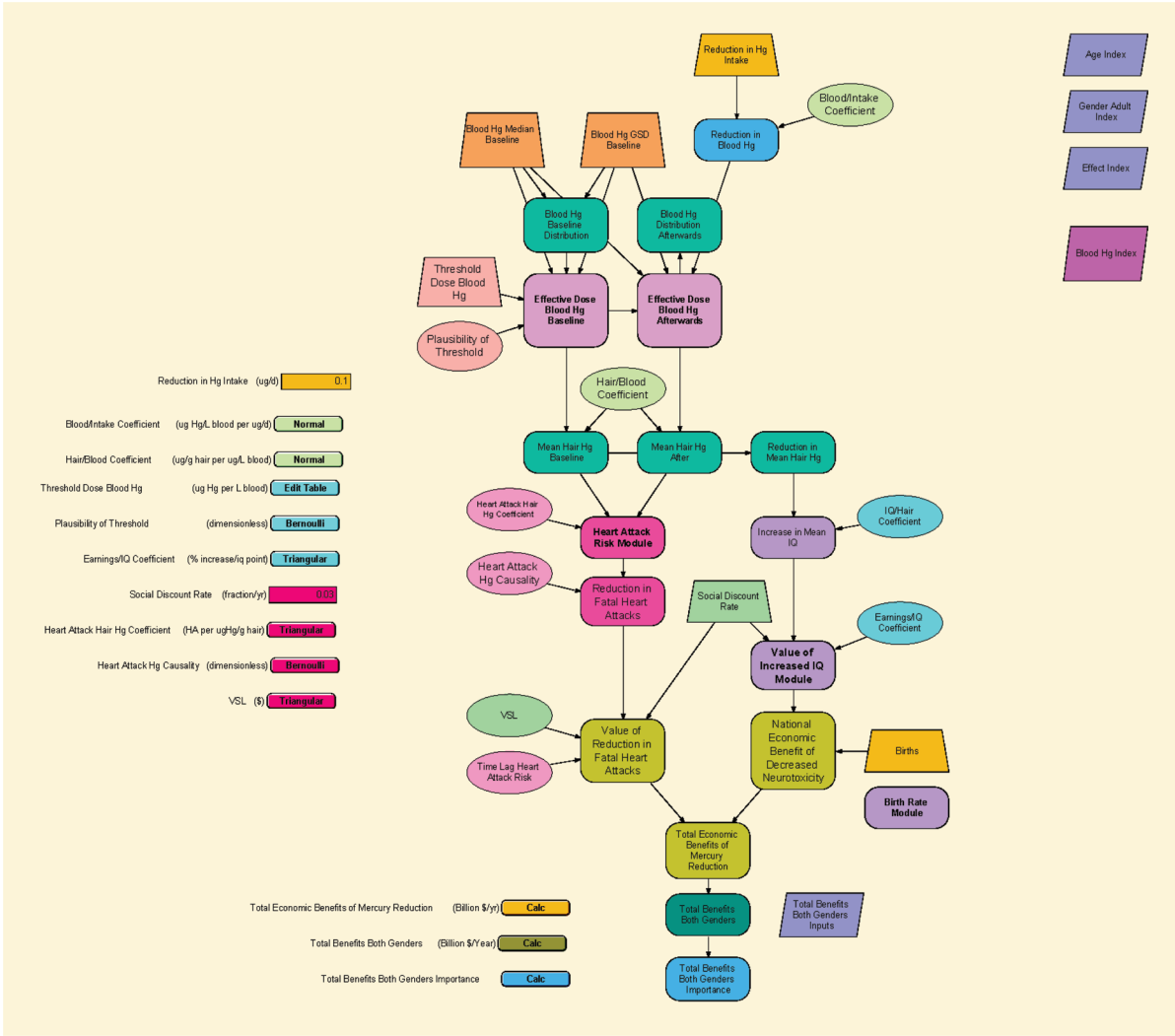

FIGURE 1. Model to estimate health benefits of reduced MeHg exposures. This figure depicts the structure of the Analytica model used to conduct the analysis. Trapezoids depict constants, rounded objects with thin lines depict variables, rounded objects with thick lines depict modules, and ovals depict chance variables.

where B is the annual number of births in the population and ΔE is the expected increase in the present value of lifetime earnings (discounted at rate ρ) of the infants born to mothers with reduced MeHg intake.

For the small changes relevant here, the relationships between the child's earnings and IQ and the mother's hair MeHg, blood MeHg, and MeHg intake are taken to be linear with slopes η, γ, λ, and β, respectively.

$$\Delta E = \eta \Delta \mathrm{IQ};\ \Delta \mathrm{IQ} = \gamma \Delta M_{\mathrm{hair}};\ \Delta M_{\mathrm{hair}} = \lambda \Delta M_{\mathrm{b}} \text{ and } \Delta M_{\mathrm{b}} = \beta \Delta I \quad (3)$$

Thus, unless there is a threshold in the relationship between maternal MeHg intake and IQ, V_{n} may be expressed as a weighted sum of the MeHg intake reduction:

$$V_{\mathrm{n}} = \sum_a b_a P_{\mathrm{women},a} \{\eta\gamma\lambda\beta\} \Delta I_{\mathrm{women},a} \quad (4)$$

where b_a is the birth rate (live births/woman/year) among women of age a, $\mathrm{P}_{\mathrm{woman},a}$ is the population of women of age a, and $\Delta I_{\mathrm{women},a}$ is the MeHg intake reduction among women of age a.

Assuming a constant MeHg intake reduction across all ages yields:

$$V_{\mathrm{n}} = \eta\gamma\lambda\beta b \Delta I \quad (5)$$

The economic value of reductions in the risk of death due to heart attacks is measured in terms of willingness to pay.

$$V_{\mathrm{c}} = \sum_g (P_g \Delta \mathrm{Cf}_g v_g) \quad (6)$$

where P_g is the number of people aged 40 years or more of gender g; $\Delta \mathrm{Cf}_g$ is the reduction in fatal heart attack risk due to reduced MeHg intake (deaths/person-year); and v_g is the value of reducing the fatal heart attack risk ($/death) in males and females.

Reduction in fatal heart attack risk is conventionally predicted using a relative risk model:

$$\Delta \mathrm{Cf}_g = \mathrm{Cf}_g(1 - \exp(-\varphi \Delta M_{\mathrm{hair}})) \quad (7)$$

where Cf_g is current risk of fatal heart attack among people aged ≥40 years of gender g (note: the current risk reflects an unobservable baseline combined with the impact of current MeHg exposure levels); ΔM_{hair} is the reduction of hair mercury expected from the MeHg intake reduction, computed as $\lambda\beta(\Delta I)$; and φ is the coefficient reflecting the relationship between hair mercury levels and fatal heart attack risks.

Because the causality of the association between hair mercury level and heart attack risk is uncertain, we include parameter, ω, the probability that the association reflects causation.

$$\Delta \mathrm{Cf}_g = \mathrm{Cf}_g \omega [1 - \exp(-\varphi \Delta M_{\mathrm{hair}})] \quad (8)$$

If there are thresholds (i.e., doses below which increased exposure does not increase risk) in either dose−response relationship, then the marginal impact of a small change in intake is found by multiplying the derivative (with respect to dose) of the integral of the product of the current distribution of dose and the dose−response function by the change in dose resulting from this change in intake. It is convenient to characterize the derivative in this expression as the effective slope, γ_{eff}, of the dose−response function. Thus, the IQ change from a small change in intake becomes

$$\gamma_{\mathrm{eff}} \lambda \beta \Delta I \quad (9)$$

We also examine the dose−response function with a population threshold for neurotoxicity, T_{n}. If the current distribution of hair mercury levels is characterized as log-normal, with density Λ, median, $\mu_{M\mathrm{hair}}$, and GSD, $\sigma_{gM\mathrm{hair}}$, then

$$\gamma_{\mathrm{eff}} = ({}^{\partial}/_{\partial \mu_{M\mathrm{hair}}})\left(\int_{T_{\mathrm{n}}}^{\infty} [\gamma(M_{\mathrm{hair}} - T_{\mathrm{n}})\Lambda(\mu_{M\mathrm{hair}}, \sigma_{gM\mathrm{hair}})\mathrm{d}M_{\mathrm{hair}}]\right) \quad (10)$$

which may be approximated numerically. Age-specific birth and heart attack rates were not used in this analysis, as a simplification.

Parameters. We provide quantitative probabilistic characterizations for the eight parameters in the model (Table 1) focusing on the hair mercury to heart attack risk coefficient and the plausibility of causal interpretation of cardiovascular risk parameters to which the model results were most sensitive. Supporting Information S2 provides additional parameter information.

The *intake to blood coefficient,* β (day/L blood), is an aggregate population parameter reflecting the marginal reduction in equilibrium blood MeHg concentration (μg Hg/L blood), averaged across the U.S. population, resulting from a small reduction in the daily MeHg intake. Most published estimates of β have been used to parametrize a one-compartment toxicocokinetic model, which estimates the equilibrium blood concentrations corresponding to specific MeHg intake rates. The following parameters comprise the model: the fraction of intake absorbed by the gut, f_{a}, the fraction of the absorbed MeHg found in the blood at equilibrium, f_{b}, the blood volume, V_{b}, and the biological half-life of MeHg in the human body, κ.

$$\beta = ((\mathrm{IBW}\mathrm{fafb})/(\mathrm{KVb}))/(\mathrm{IBW}) \text{ or } f_{\mathrm{a}} f_{\mathrm{b}}/(\kappa V_{\mathrm{b}}) \quad (11)$$

Most analysts are confident that f_{a} and f_{b} are approximately 95% and 6%, respectively. The most uncertain element in the calculation is κ. One analysis (*11*) noted that four studies, totaling 100 subjects, provide the empirical basis for estimating κ and suggested that the population average likely falls between 40 and 50 days (mode ~45 days). This analysis also suggested that the mean blood volume of pregnant women (and standard deviation) is 5.7 ($\pm$0.15) L. Using these estimates we characterize β as approximately normal with a mean of 0.6 ($\pm$0.09) μg Hg/L blood per μg Hg/day.

The *blood to hair coefficient,* λ (μg Hg per g hair/μg Hg per L blood), is an aggregate population parameter reflecting the reduction in equilibrium hair mercury concentration, averaged across the U.S. population, that would result from a unit reduction in the equilibrium blood MeHg concentration. A log-normal distribution with a median of 0.21 (GSD = 1.85) is consistent with a distribution reported in an analysis of 10 relevant studies (*12*). A subsequent analysis concluded that the central estimate of λ was 15% larger for pregnant women than nonpregnant women (*13*). Because the standard errors of the mean were less than 2% in both analyses (*12, 13*), we treat λ as constant, using different values for pregnant and nonpregnant women.

The *hair mercury to IQ coefficient,* γ (IQ points per μg MeHg/g maternal hair), estimates the IQ point increase in children resulting from a unit decrease in maternal hair mercury concentrations during pregnancy and persisting into adulthood. Three epidemiological studies—conducted in the Faroe Islands (FI), Seychelles Islands (SI), and New Zealand (NZ) (*3, 4, 14*)—provide the primary evidence for γ. While the FI and NZ studies report statistically significant associations between MeHg exposure and decreased performance on several childhood neurodevelopmental tests, coefficients from similar tests conducted in the SI showed no statistically significant effect. Two groups have synthesized the results from these three studies. Using expert judgment, Cohen (*15*) reported the central estimate of γ as 0.7 IQ points per μg MeHg/g maternal hair, with plausible values ranging from 0 to 1.5 IQ points per μg MeHg/g maternal hair. Using a Bayesian analysis, Axelrad (*16*) estimated γ to be 0.18 $\pm$ 0.10 IQ points per μg MeHg/g maternal hair. The primary difference in these two analyses stems from their treatment of the FI regression coefficients. Had Cohen used a supplementary report prepared by the FI investigators (*17*), our evaluation suggests that their results would have been comparable to those of Axelrad. Finally, neither Cohen or Axelrad explicitly consider possible confounding of the MeHg-IQ relationship by the concurrent consumption of fish fatty acids that might enhance cognitive development and bias downward the observed regression coefficient estimates from these three epidemiological studies (*18*).

We characterize γ using a log-normal distribution (median = 0.3; GSD = $\sqrt{3}$). The median is Axelrad's central estimate (0.18) multiplied by a factor of 1.5 to offset the possible downward bias from inadequate confounder control (*18*) and rounded to one digit. The lower and upper values of the 95% confidence interval of our distribution are supported by the SI and NZ study results, respectively. We note that the typical MeHg exposures in these epidemiological studies are approximately 20- or 30-fold larger than current levels of interest in the U.S. In the low dose region, our analysis includes both a linear extrapolation of these results to the origin (i.e., a no threshold model) and a population neurotoxicity threshold.

The *population threshold for neurotoxicity,* T_n (μg Hg/g hair), is based on the U.S. Environmental Protection Agency's (EPA) MeHg oral reference dose (RfD) of 0.1 μg/kg-day (*19*), which is based on the FI (*5*) and NZ studies (*4*). We find no strong biological support for this population threshold and assign 10% probability to this interpretation of the evidence and a 90% probability to the no-threshold alternative.

The *plausibility of causal interpretation of cardiovascular risk,* ω (unitless), quantifies our belief that MeHg exposure reductions decrease fatal heart attacks risks. Because fish consumption is the primary source of both MeHg and fish-derived fatty acids, we estimate ω from studies reporting the effects of MeHg alone or after controlling for fish-derived fatty acid exposures. Epidemiological studies in five cohorts met these criteria (*5, 6, 20−22*). We evaluate ω as a dichotomous variable, using five Hill causality criteria (bolded below) (*23, 24*).

Although the small number (four) of epidemiological studies limits our confidence, we conclude that there is some **consistency of results across studies.** The individual study results follow. A prospective Finnish male cohort study reported increased risks of first time heart attack (RR = 1.69,

TABLE 1. Variables Used in Methyl Mercury Benefits Model

symbol	definition	units	assumed value	central tendency	variability	references
V	economic value of improvement in health		$V_n + V_c$			n/a
V_n	economic value of reduction in neurotoxicity	$	$V_n = B\Delta E$			n/a
B	births	#/y	4 059 000			*43*
$P_{women,a}$	women of childbearing age of age a	#				U.S. Vital Statistics
b_a	birthrate for women of age a	#/p−y	see annex			U.S. Vital Statistics
P_g	number of people ≥40, gender g	#	males 55.7 million females 63.7 million			*44*
ΔE	improvement in present value of lifetime earnings of a child affected by mercury	$	$\Delta E = \eta\Delta IQ$			n/a
η	earnings-IQ parameter	percent per IQ point	normal	mean = 0.9	SD = 0.15	*35*
ΔIQ	improvement in average IQ	IQ points	$\Delta IQ = \gamma\Delta M_h$			n/a
γ	IQ-hair mercury coefficient	IQ points per μg Hg/g hair	lognormal	median = 0.3	GSD = 3	*16*
ΔM_{hair}	reduction in hair mercury level of a person	μg Hg/g hair	$\Delta M_h = \lambda\Delta\ M_b$			n/a
λ	hair-blood coefficient	μg Hg/g hair per μg Hg/L blood	pregnant women	mean = 0.21	SD = 0.0014	*12, 13*
			nonpregnant women[a]	mean = 0.18	SD = 0.0014	
ΔM_b	reduction in blood mercury level of a person	μg/L	$\Delta M_b = \beta\Delta I$			n/a
β	blood-intake coefficient	μg Hg/L blood per μg Hg/day	normal	mean = 0.6	SD = 0.09	*11*
ρ	social discount rate	fraction/yr	primary analysis sensitivity analysis	0.03 0.07		*32,33*
Mb	current distribution of blood mercury in the U.S.	μg/L	women 15−45	median = 0.85	GSD = 3	*2*
			lognormal men ≥ 40; lognormal	median = 1.1	GSD = 2.8	
T_n	neurotoxicity threshold dose	μg/kg-d OR μg/L	0.1 5.8			*19*
Ψ	plausibility of neurotoxicity threshold dose	dimensionless	dichotomous 0.1 threshold exists 0.9 no threshold			author's judgment
V_c	economic value of reduction in cardiovascular disease	$	$V_c = \sum_g (P_g\Delta Cf_g v_g)$			n/a
$\Delta Cf_{a,g}$	reduction in the risk of a fatal heart attack of a person of age a and gender g	dimensionless	$\Delta Cf_{a,g} = Cf_{a,g}(1 - \exp(-\varphi M_{hair}))$			n/a
φ	heart attack-hair mercury coefficient	risk per μg Hg/g hair	triangular	mode = 0.066	min = 0 max = 0.17	*5*
ω	plausibility of causality-heart attacks vs mercury	dimensionless	dichotomous $^1/_3$ MeHg causally associated with heart attack $^2/_3$ epidemiologic associations not causal			author's judgment
C	heart attacks in the U.S. year 2000	number	among men-520 000 among women-345 000			*29*
Cf_g	fatal heart attacks in the U.S. year 2000 by gender	number	among men-100 000 among women-92 500			*29*
v	value of reducing fatal heart attack	million U.S.$ (2000) per fatal heart attack	triangular	mode 5.5	minimum 1 maximum 10	*45−47*
τ	heart attack cessation lag	years	uniform	median 6	minimum 2 maximum 12	*38−41*
ΔI	reduction in daily mercury intake	μg/d	0.1			assumption

[a] Standard errors of the mean were less than 2% for both pregnant and nonpregnant women, so λ treated as constant. Table notes- n/a = not applicable, #/y = number per year, SD = standard deviation, GSD = geometric standard deviation.

95% CI = 1.03−2.76) and fatal coronary heart disease (RR = 1.75, 95% CI = 0.64−4.78), comparing these incidences in the highest mercury exposure tertile to those in the other tertiles (*5*). A case-control study conducted in European and Israeli males reported increased risks of first time heart attack with increased toenail mercury concentrations (OR = 2.16; 95% CI = 1.09−4.29), comparing the highest and lowest exposure quintiles (*6*). The primary multivariate analysis of a nested case-control study in American males reported a positive association between toenail mercury concentrations and incidence of coronary artery surgery, nonfatal heart attacks and fatal coronary heart disease (RR = 1.03; 95% CI = 0.65−1.65) comparing the highest and lowest exposure quintiles. Comparing these same exposure quintiles in a separate multivariate analysis that excluded subjects likely exposed occupationally to inorganic mercury showed an increased risk of these three coronary outcomes (RR = 1.70; 95% CI = 0.78−3.73) after adjusting for fish fatty acid intake (*21*). In contrast to these positive studies (*5, 6, 21*), a Swedish male prospective nested case-control study (*20*) reported decreased first time heart attack risks with increased erythrocyte mercury concentrations, comparing the highest and lowest exposure tertiles (OR = 0.43; 95% CI = 0.19−0.95). MeHg exposures in this cohort may be substantially lower than those in the Finnish cohort (Supporting Information S3; Figure S4). We also discount a second study reporting a decreased heart attack risk with increasing serum mercury concentrations because this measure disproportionately reflects inorganic mercury rather than MeHg exposures (*22, 25*).

We conclude that, overall, the **strength of the associations** is modest, noting the effect magnitudes (1.69, 1.70, and 2.16) are similar among the three positive studies (*5, 6, 21*) despite differences in study design, population, and exposure contrasts. We discount slightly the inconsistent effect magnitude of the Swedish study (OR = 0.43), because the exposure contrast appears limited.

The Finnish ($p = 0.001$) and European/Israeli ($p = 0.006$) cohorts report positive trend tests across exposure groups, providing limited evidence of a **biological gradient;** however, the U.S. study shows no trend and the Swedish study reports an inverse trend. The designs of the three positive studies suggest that MeHg exposures preceded the outcomes (**temporality**).

The Finnish study (*5, 26*) presents limited epidemiologic evidence that these cardiovascular effects of MeHg are **biologically plausible**. Hair mercury levels were statistically significantly associated with immune complexes containing oxidized low density lipoprotein, which might be related to adverse myocardial events (*5*) and were predictors of carotid artery atherosclerosis, indicating that MeHg may have a role in limiting arterial blood flow (*26*), an effect also observed in rats (*27*).

In summary, we view the evidence for causal interpretation as relatively weak, assigning ω a subjective probability of 1/3 that the epidemiological associations are causal (i.e., $\omega = 1$) and 2/3 that they are not (i.e., $\omega = 0$). We would have increased ω if there were additional cohorts reporting positive associations between MeHg and fatal heart attacks or if the existing studies reported higher effect magnitudes. While others have used similar informal approaches to evaluate plausibility of causal associations in benefits analysis (*28*), we developed this estimate knowing that formal expert elicitation would be more desirable and might reach a different conclusion.

The *hair mercury to heart attack risk coefficient,* φ (fractional increase in risk/μg Hg per g hair), reflects the reduction in the relative risk of fatal heart attack, averaged over all age groups and both genders, resulting from a unit reduction of 1 μg Hg/g hair. We selected a risk estimate from the Finnish study because it might be less confounded than those from other studies. This study population consumed several nonfatty fish species (*5*) and subjects likely were exposed to low concentrations of fish-derived fatty acids relative to other studied cohorts. The study reported an association between elevated hair mercury levels and increased heart attack risk (RR = 1.068 at 1 μg Hg/g hair, which corresponds to $\varphi = 0.066$) (*5*). Although this risk estimate is not statistically significant in the full cohort (95% CI = 0.97−1.18), it is the authors' best estimate of effect and analyses restricted to participants with greater than 2 μg Hg/g hair reported larger, statistically significant relative risks. We characterize φ using a triangular distribution with mode, minimum, and maximum values of 0.066, 0, and 0.17 (risk per μg Hg/g hair), respectively, using the Finnish study.

MeHg has been associated with increased risk of both fatal and nonfatal heart attacks in the epidemiologic literature. The distribution of φ, which yields a slope for total heart attacks, is multiplied by the percentage of all heart attacks that were fatal in men (19%) and women (27%) in the U.S. in the year 2000 (*29*), providing an estimate of the fatal heart attack risk in both genders. We note the limited evidence in women (*22*).

The *IQ to earnings coefficient,* η ($ per IQ point), quantifies the monetary benefit realized by a typical infant due to a permanent 1 point IQ increase. We use cost-of-illness models

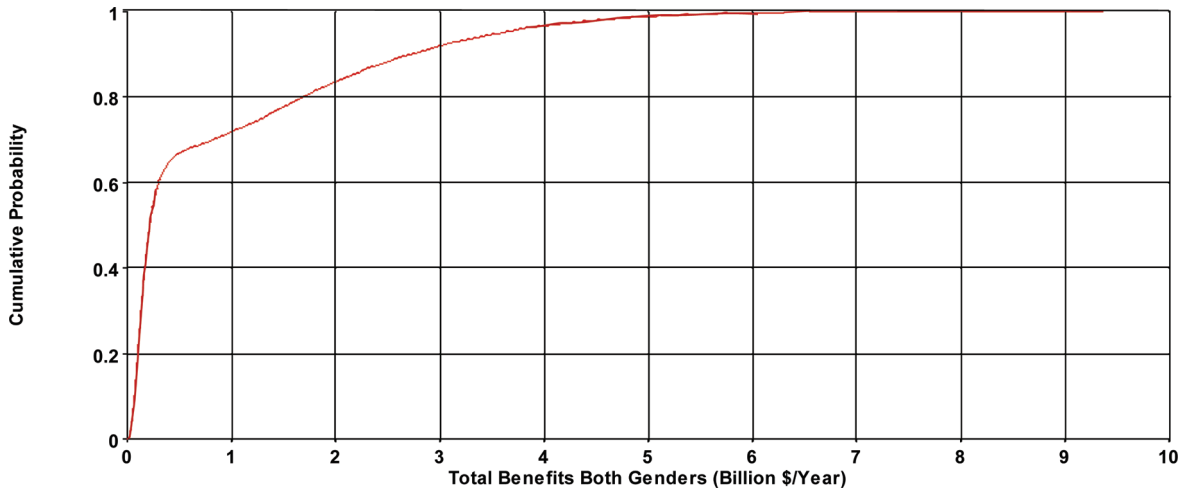

FIGURE 2. Estimate of distribution of total benefits associated with reducing U.S. MeHg exposures by 10%. Supporting Information Section S5 presents detailed model results. This figure presents the distribution of the total annual economic benefits based on increased IQ scores of the birth cohort and reduced fatal heart attacks.

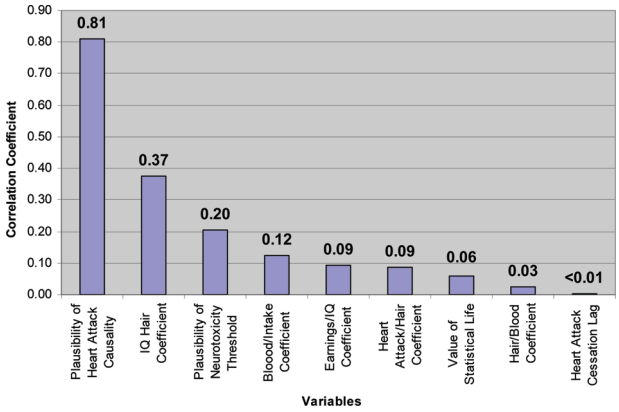

FIGURE 3. Rank correlation coefficient analysis.

(*30, 31*) to estimate the impact of a marginal change in IQ on lifetime earnings, although these models address only a subset of the welfare issues associated with IQ decrements (*32, 33*). Heckman (*34*) estimated that a 1 IQ point increase directly boosts hourly wages in men aged 30 years by 0.6%. When they included the effects of cognitive ability on educational attainment, the boost in hourly wages was 0.9%. Although their study does not evaluate women, another study (*35*) suggests this IQ effect on earnings is 30−40% larger for women than men, implying a direct impact for women of approximately 0.8% and an effect of approximately 1.2% when educational attainment is included. To characterize this parameter, we develop a triangular distribution with minimum, mode, and maximum values of 0.6, 0.8, and 1.2%, respectively. The neurocognitive deficits associated with current environmental MeHg exposure have (to date) been reported only in children up to 7 years of age (*4*); while it is not known if these are permanent, neurotoxicities associated with Minamata disease are permanent.

We converted age- and gender-specific wage estimates (*35*) to 2000$ using the CPI-U for all items and computed the present value of these earnings streams using ρ.

Value of heart attack risk reduction, υ (U.S.$ per fatal heart attack), reflects the societal value of reducing fatal heart attack risks, averaged over all age groups and both genders. This parameter is typically used to estimate the value of a change in the risk of premature death (*36*). Following one U.S. EPA approach (*37*), we characterize $\boldsymbol{\upsilon}$ as a triangular distribution with minimum, mean, and maximum values of 1, 5.5, and 10 (million U.S.$/death), respectively.

Heart attack cessation lag, τ (years), estimates the length of time between decreased MeHg intake and heart attack risk reduction, which is uncertain because the mode of action for MeHg-associated heart attacks is not well-understood. As a surrogate, studies in ex-smokers report both heart attack risks and inflammatory response markers decline to levels consistent with those of never smokers between 2 and 10 years after quitting smoking (*38*−*41*). We represent the distribution of τ as uniform with a lower and upper bounds of 2 and 10 years (Supporting Information S4).

Discount rate, ρ (fraction/year), translates future benefits to an equivalent present value. OMB (*33*) suggested discount rates of 3 and 7% per year using the social rate of time preference approach and the opportunity cost of capital approach, respectively. We present the stream of benefits and the benefit estimates using a discount rate of 3% and in a sensitivity analysis use 7%.

Final model results were developed by averaging the results of 10 individual Analytica model "runs", each run consisting of 10 000 iterations. The coefficients of variation for key outputs were less than 2% across these runs (Supporting Information S5).

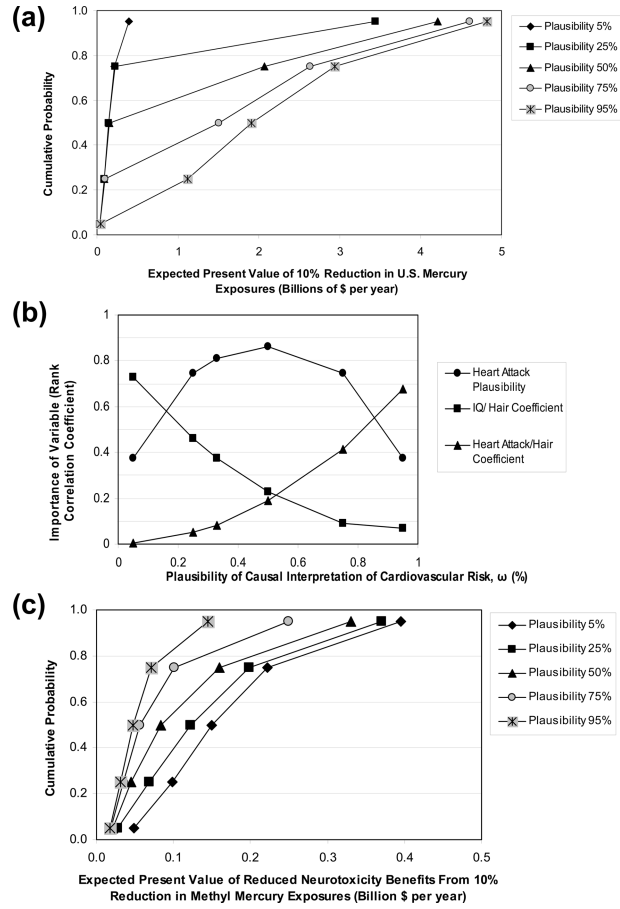

FIGURE 4. (a) Expected present value of 10% reduction in MeHg exposures varying heart attack plausibility. This figure depicts the cumulative distribution function of the predicted annual economic benefits when the heart attack plausibility parameter is allowed to vary between 5 and 95%. (b) Changes in correlation coefficient estimates based on value of heart attack plausibility parameter. This figure depicts the changes in the rank correlation coefficient estimates for three model variables, heart attack plausibility, IQ/hair coefficient and heart attack hair coefficient, when the heart attack plausibility parameter is allowed to vary between 5 and 95%. (c) Influence of the varying neurotoxicity threshold parameter on economic benefits of reduced neurotoxicity. This figure depicts the changes in the predicted annual economic benefits of reduced neurotoxicity associated with increased population IQ, when the neurotoxicity threshold plausibility parameter is varied between 5 and 95%.

Results

The median present value of the benefits stream that results from reducing daily MeHg exposures by 0.1 μg across the U.S. population for one year is estimated as $220 million, (~$0.70/person). The 5th and 95th percentile estimates are $48 million and $3.5 billion (Figure 2). The asymmetry in the benefits distribution results from our dichotomous treatment of the evidence regarding the risk of fatal heart attack due to MeHg exposure. The long tail of the cumulative distribution of benefits begins at the inflection point in the curve, the 67th percentile of the cumulative distribution function where cardiovascular benefits are included.

This skewed benefits distribution has an expected value of $860 million (~$3/person). Approximately 80% of the expected benefits ($690 million) flow from projected reductions in fatal heart attacks (~130 fewer annually). The remaining 20% of expected benefits ($170 million) is due to the increase in the mean intelligence (0.01 IQ points) of the

TABLE 2. Comparison of Recent Methyl Mercury Benefit Cost analyses[a]

analysis	$/(μg/day) per capita	primary reasons for differences
Gayer and Hahn, 2005 (*7*)	low: $1.07 high: $1.57	no consideration of cardiovascular effects, lower valuation of childhood IQ loss, low = $1200; high = $2000
U.S. EPA, 2005 (*8*)	5th $1.10 50th $4.67 95th $7.67	no consideration of cardiovascular effects, lower IQ hair mercury coefficient 0.2 IQ points per μg methyl mercury/g hair
threshold 0.1 μg/kg-day	*$1.37*	
threshold 0.2 μg/kg-day	*$0.57*	
Spadaro and Rabl, 2008 (*9*)	5th $1.07 50th $5.33 95th $26.33	no consideration of cardiovascular effects, lower IQ hair mercury coefficient 0.2 IQ points per μg methyl mercury/g hair; higher valuation of childhood IQ loss $16 000
threshold 0.1 μg/kg-day	*50th $1.56*	
this study 2010	5th $1.60 50th $7.30 95th $116	NA

[a] While both the U.S. EPA (*8*) and Spadaro and Rabl (*9*) conducted separate sensitivity analyses of a neurotoxicity risk threshold, we list these separately because neither analysis explicitly incorporates these into their benefits distribution.

4 million children annually born to mothers with reduced MeHg intakes.

Figure 3 shows the rank-correlation (R) between each independent variable and total benefits. Given the influence of fatal heart attacks on overall benefits, it is not surprising that the MeHg-heart attack causality variable is most important ($R = 0.81$). The slope of the hair mercury-IQ dose response ($R = 0.37$) and plausibility of a neurotoxicity threshold parameters ($R = 0.20$) contribute modestly to uncertainty in our benefit estimates; both variables express themselves in the region of the curve where neurotoxicity alone is responsible for benefits.

We conducted four sensitivity analyses. The first explores the sensitivity of results to the plausibility that the epidemiological evidence relating MeHg exposure to fatal heart attacks reveals a causal relationship. Through a series of cumulative distribution functions, Figure 4a shows that as the plausibility of causal interpretation increases from 0.05 to 0.95, the 50th percentile estimate of the benefits increases from $0.14 to $1.9 billion. One's interpretation of the epidemiological evidence about the link between mercury exposure and heart attack risks also affects the influence of uncertainty about other parameters on benefits. As Figure 4b indicates, for those who are skeptical about causal interpretation of this evidence, the slope of the hair mercury-IQ dose response is an important determinant of the benefits of mercury control. Among those who are persuaded that MeHg exposure increases cardiovascular disease risks, the slope of the hair mercury-IQ relationship is virtually irrelevant but the value of the slope of the hair-mercury heart attack relationship is a matter of some interest.

The second sensitivity analysis considers the influence of the assumption one makes about the plausibility of a threshold in the relationship between in utero MeHg exposure and IQ. Ignoring the cardiovascular risks, this analysis shows that as the plausibility of a neurotoxicity threshold increases from 5% to 95% the expected value of neurotoxicity benefits alone in the annual birth cohort decreases by a factor of about 3, from $180 to $60 million. As the threshold plausibility increases from 5% to 95%, the fifth percentile of the value of the IQ increase in the annual birth cohort decreases from $48 million to $17 million and the 95th percentile of the value of the IQ increase decreases from $400 million to $140 million (Figure 4c).

In the fourth sensitivity analysis, we change the social discount rate from 3% to 7%/year. The expected present value of benefits decreases from $860 to $680 million. The fifth percentile, which reflects only the change in the earnings stream due to IQ reductions, drops precipitously, from $48 million to $1.2 million. In contrast, the 95th percentile, which is dominated by reductions of heart attack fatalities (which lag the exposure reduction by only 2−10 years) drops modestly from $3.5 to $3.2 billion.

Discussion

Our estimate of the health benefits resulting from a decrease in human MeHg intake is both larger and encompasses a broader range of uncertainty than previous estimates. The larger magnitude of our estimate stems from our inclusion of cardiovascular impacts of MeHg exposures. Excluding these, our estimate of the expected national benefit of a 10% reduction in MeHg exposure drops to roughly $170 million (~$0.60/person), which is consistent with previous estimates (*7*−*9*). The large uncertainty in our estimate of national benefits stems from epistemic uncertainty about the plausibility of causal interpretation of the studies linking MeHg exposures to fatal heart attacks, from uncertainty about the true slope of the dose−response relationship linking childhood IQ decrements to maternal MeHg exposure, and from epistemic uncertainty about the presence of a neurotoxicity threshold.

Our evaluation of the evidence shows that the social value of the expected cardiovascular benefits likely exceed those associated with the reduction in neurotoxicity, as long as one assigns a subjective probability greater than 1 in 10 to a causal interpretation of the cardiovascular evidence. This occurs despite the greater confidence in the scientific evidence underlying the neurotoxicity data and the greater scientific consensus about the interpretation of these studies (*19*). The IQ MeHg exposure response function is shallow and the cost-of-illness estimates for IQ loss are small relative to the VSL. While one might argue that our use of a cost-of-illness measure could bias downward the estimated impact of population IQ gains, we note that willingness to pay estimates for children's IQ loss are smaller than the cost-of-illness measures (*42*). This suggests that benefit cost analyses that do not account for cardiovascular health impacts may substantially underestimate the benefits of reducing MeHg exposures.

Table 2 compares our benefit estimates with those of other MeHg analyses (*7*−*9*). Because these analyses assumed different exposure reductions and estimated the benefits for different populations, we estimate per capita benefits for an exposure reduction of 1 μg MeHg/day (assuming linearity).

The fifth percentile estimates of all four analyses are similar. The 50th percentile estimates (only three analyses report this) differ by less than a factor of 2; much of this difference is attributable to our hair mercury to IQ coefficient, which is ~50% greater than in the other two analyses. The largest difference among analyses occurs at the 95th percentile. Since none of the other analyses quantified the potential cardiovascular benefits, our benefits estimate at the 95th percentile is substantially larger than the alternative estimates. Our estimates also imply much greater uncertainty. The 95th and 5th percentile estimates of per capita benefits differ by factors of 7 and 25 in the U.S. EPA and Spadaro and Rabl analyses, respectively. In contrast, our estimates differ by a factor of 70, reflecting the inclusion of a neurotoxicity threshold and the possibility of a cardiovascular effect in our primary analysis.

The goal of our investigation was to characterize the benefits of reducing U.S. MeHg exposures, reflecting the current state of knowledge and major sources of uncertainty. We considered eight parameters that would be logically involved in any similar effort, critically reviewed the scientific literature and developed probabilistic characterizations of information about each parameter, and constructed an Analytica model to estimate national benefits of a 10% exposure reduction. Of these eight parameters, the uncertainty in only three—plausibility of heart attack causality, hair mercury-IQ dose response slope, and plausibility of a threshold for neurotoxicity—appreciably affected our health benefits estimate. Thus, while there is scientific interest in further study of other parameters, such investigations are unlikely to significantly affect our ability to quantify the benefits of MeHg exposure reductions. On the other hand, studies that could improve understanding of the link between MeHg exposure and cardiovascular disease would be of great value. In addition, epidemiological studies to improve estimates of the slope of the dose−response for MeHg induced neurotoxicity (including studies evaluating the persistence of childhood IQ effects into adulthood) could substantially improve these benefit estimates. Finally, more defensible characterizations of the benefits of MeHg exposure reductions could be developed by replacing our crude preliminary characterizations of model parameters with estimates based on formally elicited expert judgments from a group of experts in MeHg exposure, toxicity, effects, and valuation.

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Supporting Information Available

Epidemiologic studies that evaluate the association between MeHg and heart attacks, detailed parameter information, conversion estimates for tissue mercury measures, epidemiological evidence evaluating the lag between smoking cessation and heart attack risk reduction, and additional details of model structure and results.This material is available free of charge via the Internet at http://pubs.acs.org.

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