Environmental Science & Technology

Policy Analysis

pubs.acs.org/est

Risk Trade-Offs in Fish Consumption: A Public Health Perspective

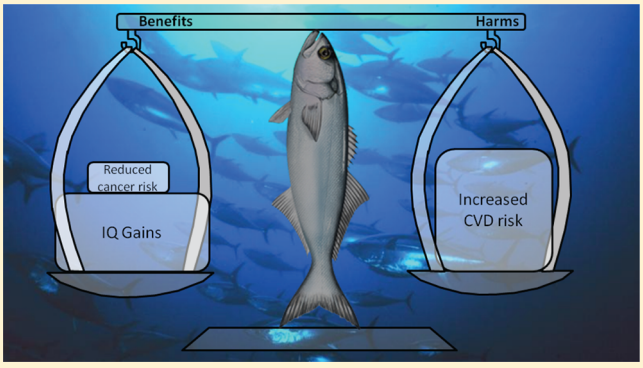
Christoph M. Rheinberger[†,*] and James K. Hammitt[†,‡]

[†]LERNA-INRA, Toulouse School of Economics, 1 Rue des Amidonniers, 31000 Toulouse, France

[‡]Center for Risk Analysis, Harvard School of Public Health, Boston, Massachusetts

Supporting Information

ABSTRACT: Fish consumption advisories instruct vulnerable consumers to avoid high mercury fish and to limit total fish intake to reduce neurotoxic risk. Consumption data from the U.S. suggest that nontarget consumers also respond to such advice. These consumers reduce exposure to mercury and other toxicants at the cost of reduction in cardioprotective fatty acids. We present a probabilistic model to assess these risk trade-offs. We use NHANES consumption data to simulate exposure to contaminants and nutrients in fish, employ dose–response relationships to convert exposure to health end points, and monetize them using benefit transfer. Our results suggest that newborns gained on average 0.033 IQ points from their mothers' compliance with the prominent FDA/EPA advisory. The welfare gain for a birth cohort is estimated at $386 million. This gain could be fully offset by increments in cardiovascular risk if 0.6% of consumers aged 40 and older reduced fish intake by one monthly meal until they reached the age of 60 or if 0.1% of them permanently reduced fish intake.



INTRODUCTION

Fish is considered a healthful food. It is rich in proteins, vitamins, minerals, and long chain n-3 polyunsaturated fatty acids (n-3 PUFAs). Physicians and nutritionists encourage fish consumption because of the cardioprotective effects of n-3 PUFAs.[1,2] Moreover, n-3 PUFAs have been found to enhance the development of the infant brain and nervous system.[3,4] Fish are thus an important nutrient source during pregnancy.[5]

However, fish is also the primary source of human exposure to methylmercury (MeHg).[6] MeHg impairs neurodevelopment in fetuses and infants[7,8] and may promote cardiovascular diseases (CVD).[9] In most aquatic systems MeHg is present in low concentrations but accumulates along the food chain to potentially harmful concentrations in large predator fish.

Fish raised in aquaculture farms or industrially polluted waters may be contaminated with dioxin-like compounds (DLCs).[10,11] Long-term exposure to these pollutants may inhibit hormonal action, alter the regulatory function of immune, nervous, and endocrine systems, impair brain development, and cause some forms of cancer.[12] Because DLCs deposit in fatty tissues whereas MeHg concentrates in muscle tissue and viscera, fish rich in n3-PUFAs tend to have higher DLC concentrations.[13]

These complications make it difficult to distinguish between "good" and "bad" fish. Consumers make implicit risk trade-offs when they decide whether, how much, and which fish to eat. Smart species selection may help minimize risk from contaminants while maximizing benefits from healthful nutrients.[5,14]In 2001, the U.S. Food and Drug Administration (FDA) released a consumption advisory that grouped fish into low, medium, and high mercury categories, to inform consumers' choices. The advisory instructed households with pregnant women and young children to avoid high mercury fish and to eat no more than 340 g (12 oz.) of fish per week. A 2004 update published jointly with the U.S. Environmental Protection Agency (EPA) further advised limiting consumption of albacore tuna to 170g (6 oz.) per week.

Empirical evidence suggests the advisory reduced fish consumption of target consumers.[15,16] Yet it is unclear whether the campaign improved or impaired public health because some nontarget consumers reduced fish consumption.[17] While these consumers benefited by reducing their exposure to contaminants, they were harmed by reduced intake of cardioprotective n-3 PUFAs.[18]

Such confounding of beneficial and detrimental health effects poses a dilemma for government agencies and consumer organizations. Can consumers appropriately balance the risks associated with fish consumption? What are the consequences if consumers do not respond as expected to the advisory? We investigate these questions by analyzing the effect of changes in the mixture and amount of fish consumed on selected health end points in the U.S. population. Using probabilistic simulations and comparing them to baseline consumption recorded by the National Health and Nutrition Examination

Received: July 1, 2012
Revised: October 11, 2012
Accepted: October 30, 2012
Published: October 30, 2012

ACS Publications © 2012 American Chemical Society

Survey (NHANES),[19] we model the population health effects of two scenarios of policy relevance.

The *compliance* scenario assumes that target consumers who became aware of the EPA/FDA advisory altered their fish intake. Women of childbearing age restricted weekly fish intake to 340 g, the intake of albacore tuna to 170 g, and avoided eating high mercury fish. The *overcompliance* scenario presumes that, in addition, a fraction of nontarget consumers decreased fish intake in response to the advisory. In the simulation, we assume these overcomplying consumers reduced fish intake on average by 20% (one monthly meal), approximating the per-capita consumption decline among target households after FDA's 2001 advisory.[16]

Using these scenarios, we analyze whether adverse effects of reduced fish intake by nontarget consumers can offset beneficial effects for target consumers, and if so, what fraction of nontarget consumers could have responded to the advisory without eliminating the population benefits. Effects of consumers' exposure to MeHg, n-3 PUFAs, and DLCs on selected health end points are estimated using established dose−response relationships. Effects on mortality, morbidity, and labor productivity are monetized using benefit-transfer functions.[20]

Unlike earlier studies,[21,22] we quantify the most detrimental health effects of DLCs ingested through fish including cancer in adults[12] and neurotoxicity in infants.[23] This extension is of interest since there has been fierce debate about whether organic pollutants in some fish detract significantly from health benefits.[10,24−27] The dearth of congener-specific PCB measurements in fish[11] and limited understanding of the health effects of various PCB mixtures constrain our analysis.

The following section describes materials and methods. We present simulation results for two response scenarios, derive welfare estimates of population health effects, and report sensitivity to uncertain parameters. We discuss our findings in light of the debate over the effectiveness of fish consumption advisories.[28]

■ MATERIALS AND METHODS

Our assessment integrates four submodels. The *consumption* model assesses daily fish intake by the U.S. population. The *exposure* model uses empirical concentration data to simulate exposure to MeHg, n-3 PUFAs, and DLCs from fish. The *dose−response* model converts exposure into selected health end points. The *valuation* model aggregates welfare effects.

Consumption Model. We model daily fish intake using food recall data from three waves (2003−2008) of NHANES.[19] These data report consumption of 26 types of fish and shellfish. We disaggregate "other fish" and "other shellfish" categories based on market shares of fish species not reported in NHANES.[29]

The consumption model randomly samples cohorts of target consumers (women aged 16−40) and nontarget consumers (women and men aged 40 or older) from the universe of NHANES participants. Consumer-specific daily fish intake (g/day) is simulated by multiplying each cohort member's reported monthly fish meals by an average meal size, modeled as a truncated log-normal distribution. This implies meal sizes of 10−300 g (400 g) for women (men) with a grand average of 120 g (160 g) per meal (SI, Figure S1).

Exposure Model. We adapt a well-established model to quantify nutrient and contaminant exposure.[30] We first estimate species-specific concentration distributions (SI, Table S1) using available concentration data for MeHg, n-3 PUFAs, and DLCs measured in terms of dioxin-toxic equivalents (TEQs).[31] This modeling approach captures interfish variability in contamination and, consequently, variability in exposure of consumers eating the same types of fish from the same water bodies.

The exposure model takes random draws from the empirical concentration distributions for every fish meal reported by a cohort member. The generated concentrations are averaged across meals and multiplied by the simulated average meal size to simulate the cohort member's daily doses. The exposure model hence captures between-person differences in types and sizes of fish meals.

Dose−Response Model. A recent FAO/WHO expert report[32] summarizes the health end points frequently associated with fish consumption. These include fetal neurodevelopment, heart attacks, and strokes. We additionally estimate lifetime excess cancer risk, but emphasize that the selected end points are not exhaustive.

We note that the relationship between body burden and daily intake differs between agents. Mercury has a half-life of 40−50 days in the human body.[33] Hence, body burden equilibrates to a changed intake within a few months. Unlike mercury, DLCs persist for years in the human body. The average background body burden in U.S. adults is about 18 pg TEQ/g body lipid.[34] Using EPAs central half-life estimate of 7.1 years for the TEQ-reference congener 2,3,7,8-TCDD, short-term changes in body burden, ΔBB (pg TEQ/g LW), are approximated by

$$\Delta \mathrm{BB} = \frac{1-\exp(-\kappa \mathrm{ED})}{\kappa}\left[\left(\mathrm{BB}+\frac{D^1}{\mathrm{LW}}\right)-\left(\mathrm{BB}+\frac{D^0}{\mathrm{LW}}\right)\right] = \frac{\Delta D}{\mathrm{LW}}\frac{1-\exp(-\kappa \mathrm{ED})}{\kappa} \quad (1)$$

where LW denotes lipid weight, typically assumed to be 25% of total body weight; ED is the exposure duration of interest; κ is the elimination rate constant corresponding to a 7.1 year half-life; D^0 and D^1 denote the absorption-adjusted average daily doses of TEQs (pg/day) ingested before and after the dietary change. (Following EPA,[34] we take the absorption rate to be 80%.)

Equation 1 can be modified to yield the cumulative TEQ dose, AUC (pg TEQ/g LW × years), which is a standard exposure metric for cancer risk assessment.[35] Changes in AUC resulting from a dietary change can be calculated by integrating changes in the daily dose over the period of exposure (from age t' through t'') and beyond (from age t'' through the end of life at t'''):[36]

$$\Delta \mathrm{AUC}(t''', t') = \int_{t'}^{t''} \frac{\Delta \mathrm{D}}{\mathrm{LW}} \exp[-\kappa(\tau - t')]\mathrm{d}\tau + \int_{t'}^{t''} \exp[-\kappa(\tau - t'')]\frac{\Delta \mathrm{D}}{\mathrm{LW}} \frac{1-\exp[-\kappa(t''-t')]}{\kappa}\mathrm{d}\tau \quad (2)$$

Modeling Neurocognitive Risk. We focus on neurocognitive effects to unborn children because few infants in the NHANES data ate fish in sufficient amounts to be harmful. In utero, the developing brain is particularly sensitive to both neurotoxins[37] and fatty acids.[38] However, dose−response relations between maternal n-3 PUFA intake during pregnancy and cognitive development in utero are unknown. Following Cohen et al.,[4]

Table 1. Definition of parameters Used in the Dose−Response Model

symbol	definition	units	distributional form	central tendency	variability[a]	source
λ	blood to hair mercury parameter	μg Hg/g hair per μg MeHg/L blood	lognormal	median = 0.21	GSD = 1.85	44
γ	hair mercury to IQ parameter	IQ points lost per μg MeHg/g maternal hair	lognormal	median = 0.3	GSD = $\sqrt{3}$	20
β	MeHg intake to blood parameter	μg MeHg/L blood per μg MeHg/day	normal	mean = 0.6	SD = 0.09	20
ι	n-3 PUFA to IQ parameter	IQ points gained per 100 mg DHA intake/day	normal	mean = 0.13	SD = 0.025	4
ψ	PCB and PCCD/Fs to IQ parameter	IQ points lost per pg TEQ/g LW	triangular	mode = 0.2	min = 0.1, max = 0.3	41
ϕ_{DHA}	fraction of DHA in n-3 PUFA from fish	percent	discrete value	62%		40
$\phi_{MI,g}$	fraction of myocardial infarctions from total CVD incidences in gender g	percent	discrete value	males: 65% females: 40%		45
$\phi_{SI,g}$	fraction of stroke incidences from total CVD incidences in gender g	percent	discrete value	males: 35% females: 60%		45
$\sigma_{CVD}(\tau)$	survival chance of CVD incidence at age τ	percent	exponential	$1-0.0224e^{0.0318\tau}$		45
$\sigma_{CA}(\tau)$	survival chance of cancer diseases at age τ	percent	exponential	$1-0.0543\ e^{0.0275\ \tau}$		46
δ	cumulative TEQ to cancer risk parameter	increase in fatal cancer risk per pg TEQ/g LW	triangular	mode = 6.3×10^{-6}	min = 8.8×10^{-7}, max = 1.3×10^{-5}	35
ζ	n-3 PUFA to heart attack risk parameter	decrease in heart attack risk per mg n-3 PUFA intake/day	triangular	mode = 1.02×10^{-3}	min = 6×10^{-4}, max = 1.2×10^{-3}	22
ξ	n-3 PUFA to stroke incident risk parameter	decrease in stroke risk per mg n-3 PUFA intake/day	triangular	mode = 6.4×10^{-4}	min = 2×10^{-4}, max = 9×10^{-4}	22
φ	hair mercury to heart attack risk parameter	increase in heart attack risk per μg Hg/g hair	triangular	mode = 6.6×10^{-2}	min = 0, max = 1.7×10^{-1}	20
ω_ζ	plausibility of mercury to heart attack relationship	dimensionless	Bernoulli	mean = 1/3		20
ω_ξ	plausibility of n-3 PUFA to stroke relationship	dimensionless	Bernoulli	mean = 0.5		
ω_φ	plausibility of n-3 PUFA to heart attack relationship	dimensionless	Bernoulli	mean = 0.95		

[a]SD = standard deviation; GSD geometric standard deviation.

we use observations on infants to approximate cognitive benefits of maternal n-3 PUFA intake in terms of full scale IQ.

Assuming nonzero background exposure, we take the dose−response relationships between a child's IQ response (ΔIQ) to maternal intake of n-3 PUFAs (ΔP), MeHg (ΔM), and the incremental body burden (ΔBB) to be linear with slope parameters ι, γ, and ψ:

$$\begin{aligned}\Delta IQ &= \iota(\phi_{DHA}\Delta P) - \gamma\Delta M_H - \psi\Delta BB;\ \Delta M_H \\ &= \lambda\Delta M_B;\ \Delta M_B \\ &= \beta\Delta M \end{aligned} \tag{3}$$

where M_B and M_H denote the equilibrium mercury concentrations in blood and hair, respectively. (ΔIQ is not the most sensitive measure of cognitive effects but provides a common denominator for assessing and valuing the joint effect of exposure to n-3 PUFAs, MeHg, and DLCs.)

Table 1 summarizes probabilistic characterizations of the conversion parameters β and λ, and the slope parameters. The hair mercury to IQ parameter γ describes the effect of a unit change in maternal hair mercury concentration on IQ in the offspring. This relationship has been analyzed in prospective studies of high fish consumers.[7,8] However, parameter estimates from these studies are likely to be too small as they neglect confounding of detrimental and beneficial effects.[39] Following Rice et al.,[20] we multiply the central estimate of the existing studies by a factor of 1.5 to offset the downward bias.

There is less uncertainty about the fatty acids to IQ parameter ι because confounding effects of toxicants can be controlled in clinical trials. A meta-analysis of eight randomized controlled trials in children receiving n-3 PUFA supplementation indicates that a daily intake of 100 mg of docosahexaenoic acid (DHA) by mothers-to-be increases average IQ of the offspring by 0.13 points.[4] Since dose−response relations are available only for DHA, we assume IQ is independent of other n-3 PUFAs and use species-specific ratios of DHA to total n-3 PUFA content (ϕ_{DHA}) derived from USDA's nutrient databank.[40]

Previous studies consistently report a negative association between prenatal PCB exposure and measures of cognitive functioning in infancy.[23] However, IQ impairments have been observed only at substantial maternal body burdens. In a cohort of children born to Great Lakes fish consumers, a negative effect of total PCBs was found only when body burdens were larger than 0.45 μg/g LW.[41] A threshold near this value would be equivalent to a TEQ-based body burden (TBB) of 11.6 pg TEQ/g LW.[42] As there is little biological support for a threshold dose (TD),[43] we assume dose linearity (DL) in the reference model and apply the IQ decrement parameter ψ by Stewart et al.[41]

We test the implications of a threshold at 11.6 pg TEQ/g LW in an alternative model. For this purpose, we analyze PCB exposure data of the 2003−2004 NHANES wave[19] in which roughly one-third of women of child-bearing age exceeded the TBB. Based on these exposure data, we simulate each consumer's TBB to which we add the incremental body burden, ΔBB, from the dietary change in fish consumption. We quantify ΔBB by eq 1, assuming mothers-to-be change fish consumption at conception, that is, ED = 274 days.

Table 2. Definition of Parameters Used in the Valuation Model

symbol	definition	units	distributional form	central tendency	variability	source
ρ	discount rate	percent	discrete value	3%		20
N_0	newborns in the U.S. in 2009	cohort size	discrete value	4 131 019		55
$N_{g,\tau}$	U.S. population of gender g and age τ	age cohort size	discrete values	females:	males:	63
			40−44	10 487 466	10 504 139	
			45−49	11 535 568	11 295 524	
			50−54	11 083 544	10 677 847	
			55−59	9 770 360	9 204 666	
			60−64	8 234 990	7 576 933	
			65−69	6 273 156	5 511 164	
			70 and over	16 473 874	11 312 396	
P	penetration rate of the advisory	percent	discrete value	80%		54
Θ_{IQ}	fraction of female fish consumers aged 16−40	percent	discrete value	33.7%		19
$\Theta_{g,\tau}$	fraction of fish consumers of gender g and age τ	percent	discrete value	females:	males:	19
			40−44	78.8%	79.6%	
			45−49	83.9%	79.6%	
			50−54	84.0%	81.1%	
			55−59	86.5%	79.2%	
			60−64	86.7%	80.5%	
			65−69	79.1%	79.3%	
			70 and over	76.2%	75.5%	
E	discounted lifetime earnings	$ per average working life	discrete value	918,583 (2009$)		56
η	IQ to earnings parameter	percent per IQ point	triangular	mode = 0.8%	min = 0.6%, max = 1.2%	20
VSLY(τ)	age-specific value of statistical life year	$ per life year of age τ	polynomial[a]	$-6.78\tau^3 + 6.25 \times 10^2\tau^2 - 8.96 \times 10^3\tau + 1.2 \times 10^5$ (2009$)		60
VMI	value of myocardial infarction	$ per avoided heart attack	discrete value	120,000 (2009$)		61
VSI	value of stroke incidence	$ per avoided stroke	discrete value	35,000 (2009$)		61
VCA	value of nonfatal cancer	$ per avoided cancer case	discrete value	150,000 (2009$)		62

[a]Minimum of $100,000 per life year, see text.

Modeling Cardiovascular Risk. The assessment of cardiovascular end points includes heart attacks and ischemic and hemorrhagic strokes. Since there is no evidence DLCs increase CVD risk,[34] we model relative CVD risk as a function of changes in hair mercury (ΔM_H) and n-3 PUFA intake (ΔP):

$$\mu^1_{CVD}(\tau) = \mu^0_{CVD}(\tau)\exp(\Delta M_H(\omega_\varphi\varphi + \omega_\varsigma\varsigma) - \Delta P(\omega_\zeta\zeta + \omega_\xi\xi))\leftrightarrow \quad (4a)$$

$$\Delta\mu_{CVD}(\tau) = \mu^0_{CVD}(\tau)[\exp(\Delta M_H(\omega_\varphi\varphi + \omega_\varsigma\varsigma) - \Delta P(\omega_\zeta\zeta + \omega_\xi\xi)) - 1] \quad (4b)$$

where $\mu^0_{CVD}(\tau)$ is baseline CVD mortality risk at age τ;[45] $\mu^1_{CVD}(\tau)$ is CVD mortality risk at age τ after the dietary change; φ (ς) represents the hair mercury to heart attack (stroke) risk per additional μg Hg/g hair; ζ (ξ) represents the n-3 PUFA to heart attack (stroke) relationship per additional mg n-3 PUFA (Table 1).

Some of these relationships are controversial and require subjective judgment. We include Bernoulli distributed causality parameters of the form $\omega \sim B(\theta)$ to reflect our interpretation of the scientific evidence of a causal association between mercury exposure and risk of heart attacks (ω_φ) or strokes (ω_ς), and between n-3 PUFA intake and risk of heart attacks (ω_ζ) or strokes (ω_ξ). In the main analysis we assign subjective probabilities as explained below, but test the implications of these assumptions on the resulting distributions of population health effects.

Rice et al.[20] reviewed six studies that analyzed a potentially causal association between MeHg exposure and heart attack risk. They concluded the strength of association found in three of six studies is modest and assigned a probability of causality θ_φ = 33%. We maintain this assumption, noting that two recent studies provide new evidence for[47] and against[48] causality.

There is much stronger evidence of causality between n-3 PUFA intake and heart attacks[18,49] to which we assign a probability θ_ζ = 95%. For stroke, two meta-analyses[50,51] support a causal relationship, but a recent cohort study from Sweden[52] does not. Given the mixed evidence, we assign a probability θ_ξ = 50%. There is no support for a causal association between MeHg exposure and stroke risk.[48,52] Hence we assign a zero probability to θ_ς.

Modeling Cancer Risk. The cancer risk assessment draws on a dose−response function found in a meta-analysis of three large cohort studies of 2,3,7,8-TCDD exposure.[35] Excess risk is modeled as

$$\mu^1_{CA}(\tau) = \mu^0_{CA}(\tau)\exp(\Delta AUC(\tau, t')\delta)\leftrightarrow \quad (5a)$$

$$\Delta\mu_{CA}(\tau) = \mu^0_{CA}(\tau)[\exp(\Delta AUC(\tau, t')\delta) - 1] \quad (5b)$$

where δ denotes the cancer slope factor; $\mu^1_{CA}(\tau)$ is the cancer mortality risk of a consumer who changed diet at age t'; $\mu^0_{CA}(\tau)$ is the consumer's background cancer mortality risk capturing the age-specific prevalence;[53] $\Delta AUC(\tau, t')$ is the advisory-induced change in the cumulated TEQ dose of a consumer aged τ.

While the carcinogenicity of DLCs is established, there is disagreement on whether cancer is caused at any dose[34] or only above a threshold.[32] The latter position is based on the observation that dioxins do not act directly on DNA, but by binding to a receptor site. It is possible that dioxins have no adverse low dose effects. To account for this possibility, we estimate a version of eq 5b wherein δ is set to zero whenever the simulated background body burden is smaller than 34.4 pg TEQ/g LW. This TD corresponds to the FAO/WHO provisional tolerable monthly intake dose of 70 pg TEQ/kg bodyweight.

Valuation Model. The valuation model quantifies the expected welfare implications of altered population fish consumption in monetary terms. We estimate the net present value (NPV) of the population health effects under the compliance and the overcompliance scenarios. Changes in neurotoxicity are valued by their effect on labor productivity and changes in CVD and cancer risk by their effects on longevity (Table 2). We account for the fractions of consumers who do not eat fish and those unaware of the advisory.

Valuation of Neurocognitive Effects. The effects of neurotoxicity for an annual birth cohort are valued by the present value of the change in lifetime earnings expected from a change in IQ:

$$NPV_{IQ} = P\Theta_{IQ}N_0[\Delta IQ\int_{\underline{t}=20}^{\bar{t}=65} \exp(-\rho\tau)\eta E d\tau] \tag{6}$$

where P is the penetration rate of the advisory;[54] Θ_{IQ} is the share of target consumers who eat fish;[19] N_0 is the number of newborns who survive infancy;[55] ΔIQ is the change in IQ points expected from changes in fish consumption; η is the percentage change in lifetime earnings from a permanent one-point IQ change in a typical child. We assume a typical work life of 45 years and use CPU-adjusted average annual earnings E from Grosse et al.[56] At a discount rate of ρ = 3%, present value lifetime earnings are about $920,000 and the value per IQ point is $7,350.

Valuation of Cardiovascular and Carcinogenic Effects. We combine an excess lifetime risk model[57] with common benefit-transfer values for the selected health end points to assess the present value of changes in cancer and CVD risk from a dietary change in consumers aged 40 and older. We start by estimating each consumer's survivor function before and after the presumed dietary change at age t':

$$S^0(t''', t') = \exp[-\int_{t'}^{t''} \mu^0(\tau)d\tau] \tag{7a}$$

$$S^1(t'', t') = \exp[-\int_{t'}^{t''} \mu^1(\tau)d\tau] = \exp[-\int_{t'}^{t''} \mu^0(\tau) + \Delta\mu_{CVD}(\tau) + \Delta\mu_{CA}(\tau)d\tau], \text{ and} \tag{7b}$$

$$S^1(t''', t'') = \exp[-\int_{t'}^{t''} \mu^0(\tau)d\tau]\exp[-\int_{t'}^{t''} \Delta\mu_{CVD}(\tau) + \Delta\mu_{CA}(\tau)d\tau] \tag{7c}$$

where t'' is the age at which the consumer returns to initial consumption; t''' denotes life expectancy at age t', which coincides with t'' in case of a permanent dietary change; $\mu^0(\tau)$ and $\mu^1(\tau)$ are age-specific mortality rates before and after the dietary change. Changes in fatal risk from CVD, $\Delta\mu_{CVD}(\tau)$, and cancer, $\Delta\mu_{CA}(\tau)$, are defined in eqs (4−5). Parameterized forms of these hazard functions are derived from population statistics (SI, Table S2).

We monetize the gender-specific change in life expectancy caused by the dietary change from age t' through age t''' by:

$$\Delta L_g(t''', t') = \int_{t'}^{t''} \exp[\rho(t' - \tau)]VSLY(\tau) [S^1_g(\tau, t')I_{\tau\le t''} + S^1_g(\tau, t'')I_{\tau>t''} - S^0_g(\tau, t')]d\tau \tag{8}$$

where $I_\bullet$ are binary indicators. Gains or losses in life expectancy are valued by the age-dependent value per statistical life year, VSLY ($/year), expressing the consumer's willingness-to-pay to reduce mortality risk.[58,59] Aldy and Viscusi[60] estimate age-dependent VSLY adjusted for the effect of increasing income by cohort. Since their best estimate gives unreasonably low values for people above retirement age, we bound VSLY from below at $100,000 per life year.

To value reductions in nonfatal cancers, strokes, and heart attacks, we modify eq 8 to determine a lower bound on changes in the likelihood of suffering a nonfatal incident:

$$\Delta R_g(t''', t') = \int_{t'}^{t''} \exp[\rho(t' - \tau)] \left[\begin{array}{l}(\phi_{SI,g}VSI + \phi_{MI,g}VMI) \\ \dfrac{\mu^1_{CVD}(\tau)\{S^1_g(\tau, t')I_{\tau\le t''} + S^1_g(\tau, t'')I_{\tau>t''}\} - \mu^0_{CVD}(\tau)S^0_g(\tau)}{\sigma_{CVD}(\tau)} \\ VCA\dfrac{\mu^1_{CA}(\tau)\{S^1_g(\tau, t')I_{\tau\le t''} + S^1_g(\tau, t'')I_{\tau>t''}\} - \mu^0_{CA}(\tau)S^0_g(\tau)}{\sigma_{CA}(\tau)}\end{array}\right] d\tau \tag{9}$$

$\phi_{SI,g}$ and $\phi_{MI,g}$ denote weights capturing gender differences in the relative frequency of strokes and myocardial infarctions; $\sigma_{CVD}(\tau)$ and $\sigma_{CA}(\tau)$ are the survival chances (estimated based on recent CVD and cancer incidence data)[45,46] of a consumer aged τ who suffers an acute cardiac disease or cancer. Values per statistical nonfatal stroke (VSI), heart attack (VMI) and cancer (VCA) are taken from the Clean Air Act assessment.[61,62]

Finally, we aggregate nonfatal and fatal risks over the affected population of fish consumers aged 40 or older to obtain a welfare estimate for the two overcompliance scenarios:

$$NPV_{CVD+CA} = \tilde{P}\sum_g\sum_\tau \Theta_{g,\tau}N_{g,\tau}[\Delta L_g(t''', t'_\tau) + \Delta R_g(t''', t'_\tau)] \tag{10}$$

with $\tilde{P}$ denoting the unknown fraction of nontarget consumers who reduced fish intake in response to the advisory; $\Theta_{g,\tau}$ is a gender and age-specific correction for the share of people who do not eat fish;[19] $N_{g,\tau}$, is the number of individuals of gender g and age τ.[63]

Simulation. Simulations are based on a tailored routine written in R.[64] Each simulation run comprised 10 000 random

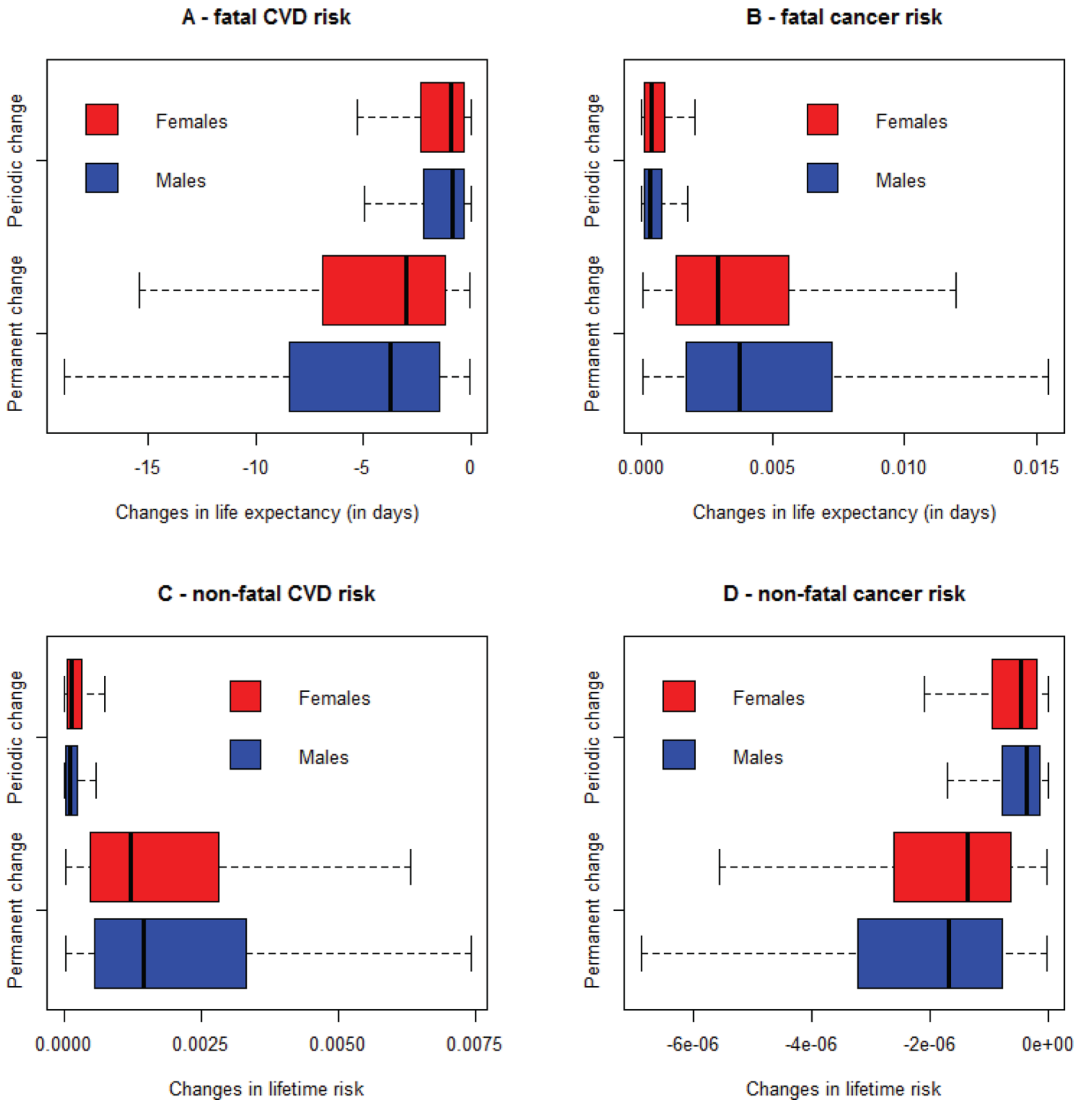


Figure 1. Box plots show the expected effects on fatal and nonfatal health end points in nontarget consumers caused by a 20%-decrease in fish consumption. Under the permanent change scenario, fish consumption is reduced for the rest of life; under the periodic change scenario, fish consumption is reduced until age 60.

draws from the NHANES consumption survey and repeated the probabilistic assessment of the health effects for each of the virtual consumers 100 times. Each model was run ten times to test its sensitivity to the random selection of NHANES respondents.

RESULTS

About one-third of the target consumers surveyed in NHANES ate fish in compliance with the advisory. Children born to mothers who changed their fish intake to comply with the advisory gained on average 0.033 IQ points (5th/50th/95th percentiles: 0.0003, 0.011, 0.163 IQ points). Fewer than 1% of these children faced a net harm from their mother's compliance with the advisory. About 90% of the IQ gains were due to reductions in MeHg exposure; the remaining 10% to reduced exposure to DLCs. These gains were partly offset by the reduced intake of n-3 PUFAs, which lowered IQ gains by about 20%. Assuming a TD for neurotoxicity of DLCs, the expected IQ gain from compliance was 22% smaller and the fraction of children harmed by the advisory-induced consumption change increased to 2.5%.

The welfare effect of compliance with the advisory for an annual birth cohort amounts to $386 million (5th/50th/95th percentiles: $5 million, $130 million, $1930 million) assuming DL, and $306 million (5th/50th/95th percentiles: $3 million, $114 million, $1448 million) assuming a TD on neurotoxicity of DLCs. These estimates reflect the shares of mothers who already comply with the advisory in the base case, those never eating fish, and those unaware of the advisory.

Shimshack and Ward[16] found that target consumers reduced fish consumption in response to FDA's 2001 advisory by 20% on average. For the overcompliance scenario, we assume nontarget consumers also reduced fish intake by 20% (uniformly across species). To allow for variability in the reduction, we use a symmetric triangular distribution between 5 and 35%. Below, we present results of two variants of overcomplying behavior. The first variant assumes a permanent reduction in fish consumption; the second variant makes the somewhat more realistic assumption that overcompliers return to their preadvisory consumption level once they pass the age of 60, and face increased cardiovascular risk. We call this a periodic dietary change.

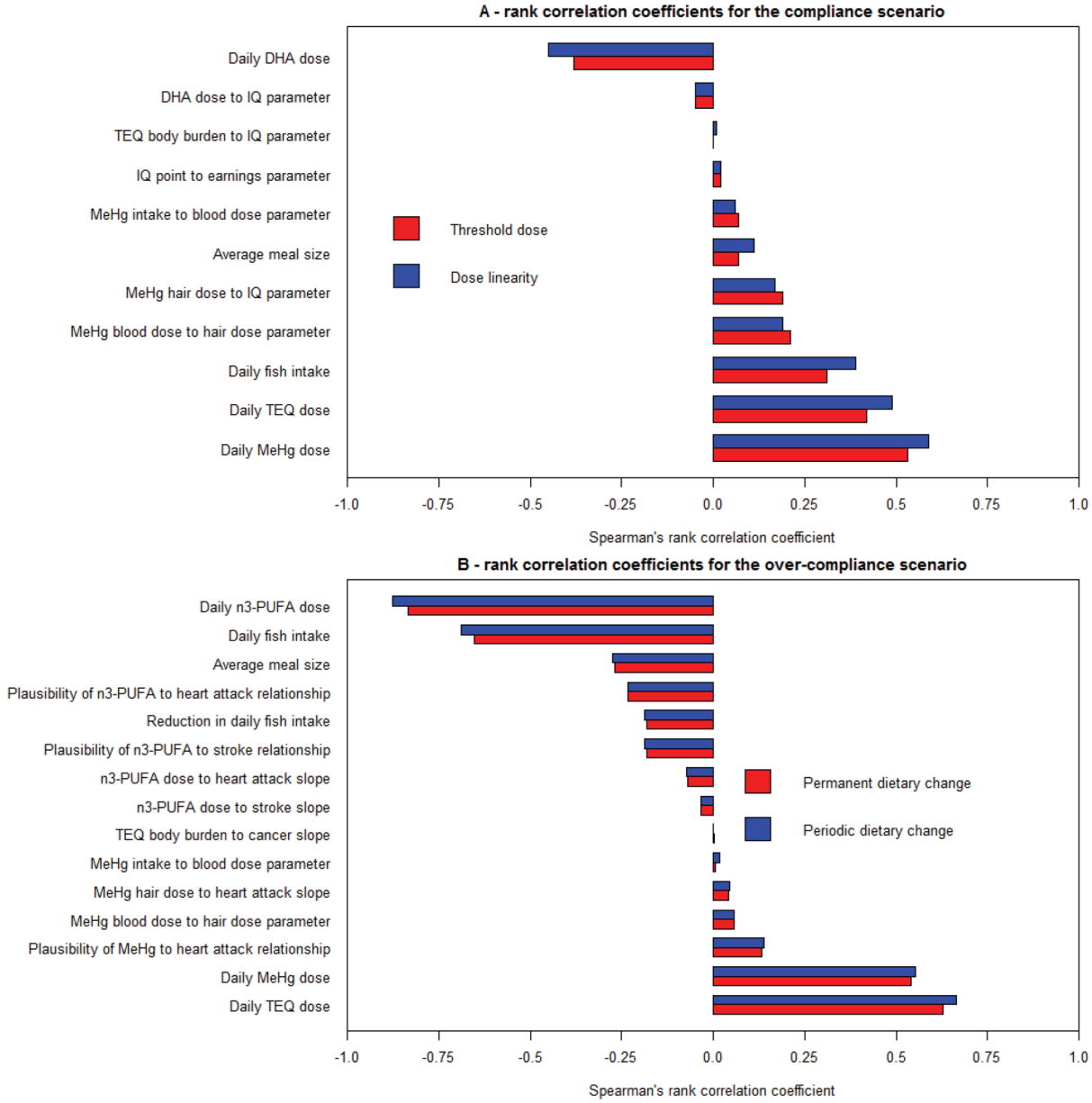


Figure 2. Rank correlation coefficients for the compliance (Panel A) and overcompliance scenario (Panel B).

Figure 1 shows individual risk changes expected under both variants. Panels A and B depict the expected changes in life expectancy for women and men aged 40 and older, whereas Panels C and D depict changes expected changes in lifetime risk for nonfatal health end points. In both cases, the cancer risk assessment assumes DL. (Figure S6 in the SI contrasts cancer risk under the linearity and threshold assumption.) For all end points considered, periodic changes in fish consumption result in median risks that are about four times smaller than for permanent changes.

The harm from overcompliance can be characterized as the sum of a stock and flow effect. The stock effect results because an unknown number of nontarget consumers reduced their fish consumption when the advisory was issued and have/will continue their lower consumption path for some time, perhaps the rest of their lives. The flow effect results if new cohorts that age into the nontarget group consume less fish than if the advisory had not been issued.

These two effects are to be balanced against the neurocognitive benefits to each annual birth cohort. The stock effect is potentially large as the population aged 40 and older is large compared with a birth cohort. The flow effect is much smaller because the population cohort aging into the nontarget category is of the same order of magnitude as a birth cohort. In the long run, the net effect of a permanent advisory is determined by the two flow effects, as the numbers of newborns and new nontarget consumers eventually overwhelm the initial population of nontarget consumers.

If every member of a cohort aging into the nontarget group overcomplies, then the annual flow value would be between \$4222 million (for periodic dietary changes) and \$9107 million (for permanent dietary changes). The flow effect is proportional to the unknown fraction of nontarget consumers who reduce their fish consumption in response to the advisory. We calculate that the lifetime harm to consumers turning 40 would equal the lifetime benefit to newborns if 4.2% (5th/50th/95th percentiles: 0.05%, 1.4%, 21.2%) to 9.1% (5th/50th/95th

percentiles: 0.1%, 3.1%, 45.7%) of them overcomply. These calculations assume the probability of overcompliance is independent of age and sex and neglect possible changes in cohort size over time.

We estimate the stock effect as \$70.1−\$315.7 billion for periodic and permanent dietary changes, respectively. This suggests that the harm if all current nontarget consumers overcomply would not be offset until approximately 182−818 birth cohorts had benefited. Alternatively, the harm to existing nontarget consumers would equal the benefit to one birth cohort if 0.12% (5th/50th/95th percentiles: 0.002%, 0.04%, 0.61%) to 0.55% (5th/50th/95th percentiles: 0.007%, 0.19%, 2.75%) of nontarget consumers reduce fish consumption in response to the advisory.

Obviously, the welfare estimates are fraught with uncertainty. Rank correlation coefficients (Figure 2) suggest our welfare estimates are only modestly sensitive to assumptions about the dose−response parameters but highly sensitive to intake and to contaminant and nutrient levels in consumed fish. Under the TD assumption, correlation coefficients for the compliance scenario are somewhat smaller than under the DL assumption (Panel A). The plausibility parameters assigned to causal relationships between MeHg exposure and heart attack risk, and between n-3 PUFA intake and heart attack or stroke risk, have limited effect on overall welfare estimates (Panel B) and differences between correlation coefficients for permanent and periodic dietary change are small. The SI provides further sensitivity and plausibility checks.

DISCUSSION

We have developed an integrated model to assess the welfare implications of fish consumption advisories. The model allows us to explore how relevant health end points change across the U.S. population if target and nontarget consumers adjust their fish consumption to comply with the current fish consumption advisory. Unlike earlier studies, we provide monetary values of population health effects to compare the benefits of additional IQ points and the harms of increased CVD and cancer risk induced by the advisory policy.

Our results suggest there is a modest benefit to newborns whose mothers shift consumption to comply with the current EPA/FDA advisory. Nearly all of this benefit can be attributed to reductions in MeHg; reductions in DLCs have marginal impact. The potential harm to nontarget consumers who misunderstand the advisory is large compared with this benefit. If little more than 0.1% of these consumers reduce fish consumption by 20% (uniformly across species), their expected harm equals the expected benefits for one birth cohort. In the long run, the advisory is likely to provide a positive public health effect so long as the fraction of consumers aging into the nontarget category who misinterpret the advisory is less than 5 to 9%.

Individual effects of changes in fish consumption are small. Each child born to a mother who reduces her fish consumption to comply with the advisory gains on average 0.033 IQ points. Each nontarget consumer who reduces fish intake by 20% faces a loss of life expectancy of about 5 days due to increased risk of fatal cardiovascular disease. As cancer risk from PCB levels commonly found in fish is small, the corresponding gain in life expectancy is of the order of five to ten minutes.

What do these findings imply? From a public health perspective they reconfirm that health authorities should not focus solely on the potential harms associated with a particular food, but also on the misunderstanding of health warnings and the consequent risk of non action.[28] Conveying the appropriate message is challenging, all the more because consumers seem to be more alert to the possible harms of toxicants than to the possible harms of malnutrition.[65] Our results show that effective communication can eventually pay off.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is provided on the consumption model, the exposure model, the dose−response model, and the valuation model. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone: +33-5-6163-5783; fax: +33-5-6112-8520; e-mail: crheinbe@toulouse.inra.fr.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was sponsored by an INRA Scientific Package. C.M.R. acknowledges additional funding from the Swiss National Science Foundation under fellowship grant no. PBEZP1-131130. J.K.H. acknowledges support from the European Research Council (FP7/2007-2013, grant no. 230589).

ABBREVIATIONS

AUC	area under the serum lipid concentration curve
CVD	cardiovascular diseases
DHA	docosahexaenoic acid
DCLs	dioxin-like compounds
DL	dose linearity
MeHg	methylmercury
NHANES	National Health and Nutrition Survey
n-3 PUFAs	long-chain n-3 polyunsaturated fatty acids
PCBs	polychlorinated biphenyls
SI	Supporting Information
TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
TD	threshold dose
TEQ	toxic equivalents (WHO 1998 standard)
VCA	value per avoided cancer case
VMI	value per avoided myocardial infarction
VSLY	value per statistical life year
VSI	value per avoided stroke incidence

REFERENCES

(1) Kris-Etherton, P. M.; Harris, W. S.; Appel, L. J. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* **2002**, *106*, 2747−2757.

(2) Lee, J. H.; O'Keefe, J. H.; Lavie, C. J.; Harris, W. S. Omega-3 fatty acids: Cardiovascular benefits, sources and sustainability. *Nat. Rev. Cardiol.* **2009**, *6*, 753−758.

(3) Hibbeln, J. R.; Davis, J. M.; Steer, C.; Emmett, P.; Rogers, I.; Williams, C.; Golding, J. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): An observational cohort study. *Lancet.* **2007**, *369*, 578−585.

(4) Cohen, J. T.; Bellinger, D. C.; Connor, W. E.; Shaywitz, B. A. A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. *Am. J. Prev. Med.* **2005**, *29*, 366−374.

(5) Mahaffey, K. R.; Sunderland, E. M.; Chan, H. M.; Choi, A. L.; Grandjean, P.; Marien, K.; Oken, E.; Sakamoto, M.; Schoeny, R.; Weihe, P.; Yan, C. H.; Yasutake, A. Balancing the benefits of n-3 polyunsaturated fatty acids and the risks of methylmercury exposure from fish consumption. *Nutr. Rev.* **2011**, *69*, 493−508.
(6) NRC (National Research Council). Committee on the Toxicological Effects of Methylmercury. *Toxicological Effects of Methylmercury*; National Academy Press: Washington, DC, 2000.
(7) Cohen, J. T.; Bellinger, D. C.; Shaywitz, B. A. A quantitative analysis of prenatal methyl mercury exposure and cognitive development. *Am. J. Prev. Med.* **2005**, *29*, 353−365.
(8) Axelrad, D. A.; Bellinger, D. C.; Ryan, L. M.; Woodruff, T. J. Dose-response relationship of prenatal mercury exposure and IQ: An integrative analysis of epidemiological data. *Environ. Health Perspect.* **2007**, *115*, 609−615.
(9) Roman, H. A.; Walsh, T. L.; Coull, B. A.; Dewailly, E.; Guallar, E.; Hattis, D.; Mariën, K.; Schwartz, J.; Stern, A. H.; Virtanen, J. K.; Rice, G. Evaluation of the cardiovascular effects of methylmercury exposures: Current evidence supports development of a dose-response function for regulatory benefits analysis. *Environ. Health Perspect.* **2011**, *119*, 607−614.
(10) Hites, R. A.; Foran, J. A.; Carpenter, D. O.; Hamilton, M. C.; Knuth, B. A.; Schwager, S. J. Global assessment of organic contaminants in farmed salmon. *Science* **2004**, *303*, 226−229.
(11) Judd, N.; Griffith, W. C.; Faustman, E. M. Contribution of PCB exposure from fish consumption to total dioxin-like dietary exposure. *Regul. Toxicol. Pharmacol.* **2004**, *40*, 125−135.
(12) Crisp, T.; Clegg, E.; Cooper, R. Environmental endocrine disruption: An effects assessment and analysis. *Environ. Health Perspect.* **1998**, *106*, 11−56.
(13) Sioen, I.; Van Camp, J.; Verdonck, F.; Verbeke, W.; Vanhonacker, F.; Willems, J. L.; De Henauw, S. Probabilistic intake assessment of multiple compounds as a tool to quantify the nutritional-toxicological conflict related to seafood consumption. *Chemosphere* **2008**, *71*, 1056−1066.
(14) Burger, J.; Stern, A. H.; Gochfeld, M. Mercury in commercial fish: Optimizing individual choices to reduce risk. *Environ. Health Perspect.* **2005**, *113*, 266−271.
(15) Oken, E.; Kleinman, K. P.; Berland, W. E.; Simon, S. R.; Rich-Edwards, J. W.; Gillman, M. W. Decline in fish consumption among pregnant women after a national mercury advisory. *Obstet. Gynecol.* **2003**, *102*, 346−351.
(16) Shimshack, J. P.; Ward, M. B. Mercury advisories and household health trade-offs. *J. Health Econ.* **2010**, *29*, 674−685.
(17) Shimshack, J. P.; Ward, M. B.; Beatty, T. K. M. Mercury advisories: Information, education, and fish consumption. *J. Environ. Econ. Manage.* **2007**, *53*, 158−179.
(18) Mozaffarian, D.; Rimm, E. B. Fish intake, contaminants, and human health. *JAMA, J. Am. Med. Assoc.* **2006**, *18*, 1885−1896.
(19) NCHS (National Health and Nutrition Examination Survey), *NHANES 2003−2008 dietary data*. http://www.cdc.gov/nchs/nhanes (accessed April 24, 2012).
(20) Rice, G.; Hammitt, J. K.; Evans, J. S. A probabilistic characterization of the health benefits of reducing methyl mercury intake in the united states. *Environ. Sci. Technol.* **2010**, *44*, 5216−5224.
(21) Cohen, J. T.; Bellinger, D. C.; Connor, W. E.; Kris-Etherton, P. M.; Lawrence, R. S.; Savitz, D. A.; Shaywitz, B. A.; Teutsch, S. M.; Gray, G. M. A quantitative risk-benefit analysis of changes in population fish consumption. *Am. J. Prev. Med.* **2005**, *29*, 325−334.
(22) Guevel, M.-R.; Sirot, V.; Volatier, J.-L.; Leblanc, J.-C. A risk-benefit analysis of french high fish consumption: A QALY approach. *Risk Anal.* **2008**, *28*, 37−48.
(23) Schantz, S. L.; Widholm, J. J.; Rice, D. C. Effects of PCB Exposure on neurosychological function in children. *Environ. Health Perspect.* **2003**, *111*, 357−376.
(24) Lund, E.; Engeset, D.; Alsaker, E.; Skeie, G.; Hjartaker, A.; Lundebye, A. K.; Niebor, E. Cancer risk and salmon intake. *Science* **2004**, *305*, 477−477.
(25) Rembold, C. M. The health benefits of eating salmon. *Science* **2004**, *305*, 475−475.
(26) Tuomisto, J. T.; Tuomisto, J.; Tainio, M.; Niittynen, M.; Verkasalo, P.; Vartiainen, T.; Kiviranta, H.; Pekkanen, J. Risk-benefit analysis of eating farmed salmon. *Science* **2004**, *305*, 476−476.
(27) Weaver, D. E. Contaminant levels in farmed salmon. *Science* **2004**, *305*, 478−478.
(28) Oken, E.; Choi, A. L.; Karagas, M. R.; Mariën, K.; Rheinberger, C. M.; Schoeny, R.; Sunderland, E.; Korrick, S. Which fish should i eat? Perspectives influencing fish consumption choices. *Environ. Health Perspect.* **2012**, *120*, 790−798.
(29) NMFS (National Marine Fisheries Service). *Fisheries of the United States 2008.*; NOOA Fisheries Statistics and Economics Division: Silver Spring, MD, 2008.
(30) Carrington, C. D.; Bolger, M. P. An exposure assessment for methylmercury from seafood for consumers in the United States. *Risk Anal* **2002**, *22*, 689−699.
(31) Van den Berg, M.; Birnbaum, L.; Bosveld, A. T.; Brunström, B.; Cook, P.; Feeley, M.; Giesy, J. P.; Hanberg, A.; Hasegawa, R.; Kennedy, S. W.; Kubiak, T.; Larsen, J. C.; van Leeuwen, F. X.; Liem, A. K.; Nolt, C.; Peterson, R. E.; Poellinger, L.; Safe, S.; Schrenk, D.; Tillitt, D.; Tysklind, M.; Younes, M.; Waern, F.; Zacharewski, T. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ. Health Perspect.* **1998**, *106*, 775−792.
(32) FAO/WHO. *Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption, Rome 2010*; World Health Organization (WHO): Geneva, 2011.
(33) Stern, A. H. A revised probabilistic estimate of the maternal methyl mercury intake dose corresponding to a measured cord blood mercury concentration. *Environ. Health Perspect.* **2005**, *113*, 155−163.
(34) USEPA. *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*; U.S. Environmental Protection Agency: Washington, DC, 2003.
(35) Crump, K. S.; Canady, R.; Kogevinas, M. Meta-analysis of dioxin cancer dose response for three occupational cohorts. *Environ. Health Perspect.* **2003**, *111*, 681−687.
(36) Flesch-Janys, D.; Steindorf, K.; Grun, P.; Becher, H. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ. Health Perspect.* **1998**, *106*, 655−662.
(37) Myers, G. J.; Davidson, P. W. Does methylmercury have a role in causing developmental disabilities in children? *Environ. Health Perspect.* **2000**, *108*, 413−420.
(38) Crawford, M. A. Placental delivery of arachidonic and docosahexaenoic acids: Implications for the lipid nutrition of preterm infants. *Am. J. Clin. Nutr.* **2000**, *71*, 275S−284S.
(39) Stern, A. H.; Korn, L. R. An approach for quantitatively balancing methylmercury risk and omega-3 benefit in fish consumption advisories. *Environ. Health Perspect.* **2011**, *119*, 1043−1046.
(40) USDA (U.S. Department of Agriculture). *National Nutrient Database for Standard Reference*. http://ndb.nal.usda.gov (accessed 12 December, 2011).
(41) Stewart, P. W.; Lonky, E.; Reihman, J.; Pagano, J.; Gump, B. B.; Darvill, T. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. *Environ. Health Perspect.* **2008**, *116*, 1416−1422.
(42) Bhavsar, S. P.; Hayton, A.; Reiner, E. J.; Jackson, D. A. Estimating dioxin-like polychlorinated biphenyl toxic equivalents from total polychlorinated biphenyl measurements in fish. *Environ. Toxicol. Chem.* **2007**, *26*, 1622−1628.
(43) Crawford, M.; Wilson, R. Low-dose linearity: The rule or the exception? *Hum. Ecol. Risk Assess.* **1996**, *2*, 305−330.
(44) Shipp, A. M.; Gentry, P. R.; Lawrence, G.; Van, L. C.; Covington, T.; Clewell, H. J.; Gribben, K.; Crump, K. Determination of a site-specific reference dose for methylmercury for fish-eating populations. *Toxicol. Ind. Health.* **2000**, *16*, 335−438.

(45) Lloyd-Jones, D.; Adams, R. J.; Brown, T. M.; Carnethon, M.; Dai, S.; De Simone, G.; Ferguson, T. B.; Ford, E.; Furie, K.; Gillespie, C.; Go, A.; Greenlund, K.; Haase, N.; Hailpern, S.; Ho, P. M.; Howard, V.; Kissela, B.; Kittner, S.; Lackland, D.; Lisabeth, L.; Marelli, A.; McDermott, M. M.; Meigs, J.; Mozaffarian, D.; Mussolino, M.; Nichol, G.; Roger, V. L.; Rosamond, W.; Sacco, R.; Sorlie, P.; Stafford, R.; Thom, T.; Wasserthiel-Smoller, S.; Wong, N. D.; Wylie-Rosett, J.; American Heart Association Stat Comm, S.. Heart disease and stroke statistics-2010 update A report from the american heart association. *Circulation* **2010**, *121*, E46−E215.

(46) NCI (National Cancer Institute). *Probability of Developing or Dying of Cancer Software, Version 6.6.0*; Statistical Research and Applications Branch, National Cancer Institute, 2011.

(47) Choi, A. L.; Weihe, P.; Budtz-Jørgensen, E.; Jørgensen, P. J.; Salonen, J. T.; Tuomainen, T. P.; Murata, K.; Nielsen, H. P.; Petersen, M. S.; Askham, J.; Grandjean, P. Methylmercury exposure and adverse cardiovascular effects in faroese whaling men. *Environ. Health Perspect.* **2009**, *117*, 367−372.

(48) Mozaffarian, D.; Shi, P.; Morris, J. S.; Spiegelman, D.; Grandjean, P.; Siscovick, D. S.; Willett, W. C.; Rimm, E. B. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. *N. Engl. J. Med.* **2011**, *364*, 1116−1125.

(49) He, K.; Song, Y.; Daviglus, M. L.; Liu, K.; Van Horn, L.; Dyer, A. R.; Greenland, P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation* **2004**, *109*, 2705−2711.

(50) Bouzan, C.; Cohen, J. T.; Connor, W. E.; Kris-Etherton, P. M.; Gray, G. M.; König, A.; Lawrence, R. S.; Savitz, D. A.; Teutsch, S. M. A quantitative analysis of fish consumption and stroke risk. *Am. J. Prev. Med.* **2005**, *29*, 347−352.

(51) He, K.; Song, Y. Q.; Daviglus, M. L.; Liu, K.; Van Horn, L.; Dyer, A. R.; Goldbourt, U.; Greenland, P. Fish consumption and incidence of stroke—A meta-analysis of cohort studies. *Stroke.* **2004**, *35*, 1538−1542.

(52) Wennberg, M.; Bergdahl, I. A.; Stegmayr, B.; Hallmans, G.; Lundh, T.; Skerfving, S.; Stromberg, U.; Vessby, B.; Jansson, J.-H. Fish intake, mercury, long-chain n-3 polyunsaturated fatty acids and risk of stroke in northern Sweden. *Br. J. Nutr.* **2007**, *98*, 1038−1045.

(53) American Cancer Society. *Cancer Facts & Figures 2009*; American Cancer Society: Atlanta, http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-and-figures-2010 (accessed 20 October, 2011).

(54) Lando, A. M.; Zhang, Y. Awareness and knowledge of methylmercury in fish in the United States. *Environ. Res.* **2011**, *111*, 442−450.

(55) Hamilton, B. E.; Martin, J. A.; Ventura, S. J. *Births: Preliminary Data for 2009*; National Center for Health Statistics: Hyattsvile, MD, 2010.

(56) Grosse, S. D.; Matte, T. D.; Schwartz, J.; Jackson, R. J. Economic gains resulting from the reduction in children's exposure to lead in the United States. *Environ. Health Perspect.* **2002**, *110*, 563−569.

(57) Vaeth, M.; Pierce, D. A. Calculating excess lifetime risk in relative risk models. *Environ. Health Perspect.* **1990**, *87*, 83−94.

(58) Hammitt, J. K. Valuing changes in mortality risk: Lives saved vs. life years saved. *Rev. Environ. Econ. Policy.* **2007**, *1*, 228−240.

(59) Hammitt, J. K. Valuing mortality risk: Theory and practice. *Environ. Sci. Technol.* **2000**, *34*, 1396−1400.

(60) Aldy, J. E.; Viscusi, W. K. Adjusting the value of a statistical life for age and cohort effects. *Rev. Econ. Stat.* **2008**, *90*, 573−581.

(61) USEPA. *Health and Welfare Benefits Analyses to Support the Second Section 812 Benefit-Cost Analysis of the Clean Air Act*; U.S. Environmental Protection Agency: Washington, D.C., 2011.

(62) USEPA. *Air Toxics Case Study—Health Benefits of Benzene Reductions in Houston, 1990−2020*; U.S. Environmental Protection Agency: Washington, DC, 2008.

(63) U.S. Census Bureau, Annual Estimates of the Resident Population by Sex and Five-Year Age Groups for the United States: April 1, 2000 to July 1, 2009 (NC-EST2009-01). http://factfinder.census.gov (accessed 24 May, 2011).

(64) R Development Core Team, R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria., 2011. http://www.R-project.org (accessed 12 December 2011).

(65) Verbeke, W.; Sioen, I.; Pieniak, Z.; Van Camp, J.; De Henauw, S. Consumer perception versus scientific evidence about health benefits and safety risks from fish consumption. *Public Health Nutr.* **2005**, *8*, 422−429.