Fish Intake, Contaminants, and Human Health
Evaluating the Risks and the Benefits

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Context Fish (finfish or shellfish) may have health benefits and also contain contaminants, resulting in confusion over the role of fish consumption in a healthy diet.

Evidence Acquisition We searched MEDLINE, governmental reports, and meta-analyses, supplemented by hand reviews of references and direct investigator contacts, to identify reports published through April 2006 evaluating (1) intake of fish or fish oil and cardiovascular risk, (2) effects of methylmercury and fish oil on early neurodevelopment, (3) risks of methylmercury for cardiovascular and neurologic outcomes in adults, and (4) health risks of dioxins and polychlorinated biphenyls in fish. We concentrated on studies evaluating risk in humans, focusing on evidence, when available, from randomized trials and large prospective studies. When possible, meta-analyses were performed to characterize benefits and risks most precisely.

Evidence Synthesis Modest consumption of fish (eg, 1-2 servings/wk), especially species higher in the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduces risk of coronary death by 36% (95% confidence interval, 20%-50%; $P<.001$) and total mortality by 17% (95% confidence interval, 0%-32%; $P=.046$) and may favorably affect other clinical outcomes. Intake of 250 mg/d of EPA and DHA appears sufficient for primary prevention. DHA appears beneficial for, and low-level methylmercury may adversely affect, early neurodevelopment. Women of childbearing age and nursing mothers should consume 2 seafood servings/wk, limiting intake of selected species. Health effects of low-level methylmercury in adults are not clearly established; methylmercury may modestly decrease the cardiovascular benefits of fish intake. A variety of seafood should be consumed; individuals with very high consumption (≥5 servings/wk) should limit intake of species highest in mercury levels. Levels of dioxins and polychlorinated biphenyls in fish are low, and potential carcinogenic and other effects are outweighed by potential benefits of fish intake and should have little impact on choices or consumption of seafood (women of childbearing age should consult regional advisories for locally caught freshwater fish).

Conclusions For major health outcomes among adults, based on both the strength of the evidence and the potential magnitudes of effect, the benefits of fish intake exceed the potential risks. For women of childbearing age, benefits of modest fish intake, excepting a few selected species, also outweigh risks.

JAMA. 2006;296:1885-1899 www.jama.com

SINCE THE PUBLICATION OF PIONEERING studies demonstrating low rates of death from coronary heart disease (CHD) among Greenland Eskimos,[1] fish (used herein to refer to finfish or shellfish) has been considered a healthy food. During ensuing years, evidence from several research paradigms—including animal-experimental, observational, and clinical studies—further supported this hypothesis and identified 2 long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as the likely active constituents.[2-20] DHA also appears important for neurodevelopment during gestation and infancy.[21-26] Conversely, concern has arisen over potential harm from mercury, dioxins, and polychlorinated biphenyls (PCBs) present in some fish species.[27-34] The public is faced with seemingly conflicting reports on the risks and benefits of fish intake, resulting in controversy and confusion over the role of fish consumption in a healthy diet.[35,36] To elucidate the relative risks and benefits, we reviewed the scientific evidence for adverse and beneficial health effects of fish consumption.

EVIDENCE ACQUISITION

Identification of Studies

A myriad of exposures and outcomes have been related to fish consumption; we focused on populations and topics for which evidence and concern are greatest. We searched MEDLINE, governmental reports, and systematic reviews and meta-analyses to identify reports published through April 2006 evaluating (1) intake of fish or fish oil and risk of cardiovascular events and mortality, (2) effects of methylmercury and fish oil on early neurodevelopment, (3) risks of methylmercury for cardiovascular and neurologic outcomes in adults, and (4) health risks of dioxins and PCBs in fish.

MEDLINE search terms were (*Fish* or *n-3 PUFA* or *omega-3*) and (*coronary* or *cardiac* or *cardiovascular* or *mor-*

See also Patient Page.

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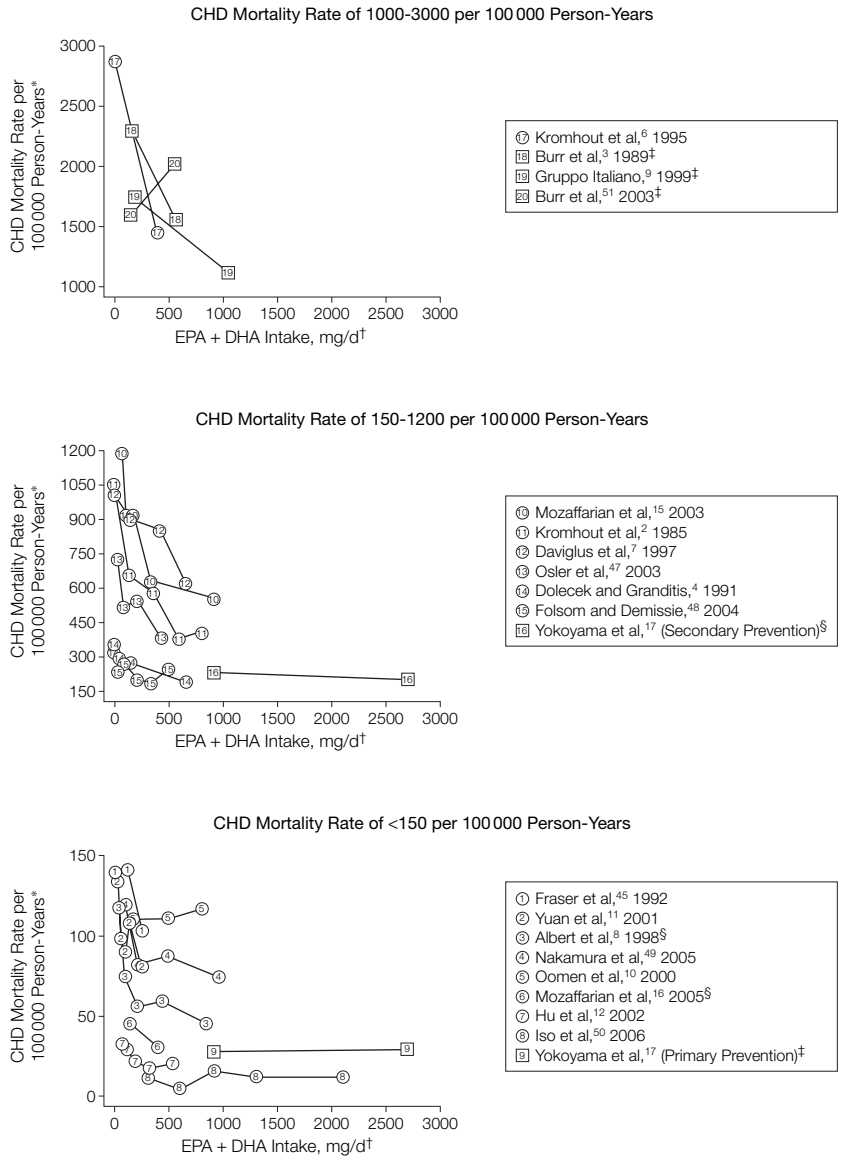
Clinical Review Section Editor: Michael S. Lauer, MD. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Michael S. Lauer, MD, at lauerm@ccf.org.

Figure 1. Relationship Between Intake of Fish or Fish Oil and Rates of CHD Death in Prospective Cohort Studies and Randomized Clinical Trials



Circular data markers indicate prospective studies; square data markers, randomized trials. Absolute coronary heart disease (CHD) mortality rates vary more than 100-fold across different populations (due to differences in age, prior CHD, and other risk factors), but the relative effects of intake of fish or fish oil are consistent, whether for primary or secondary prevention, for cohort studies or randomized trials, or for comparing populations at higher or lower absolute risk. Compared with little or no intake, modest consumption (≈250-500 mg/d eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]) is associated with lower risk of CHD death, while at higher levels of intake, rates of CHD death are already low and are not substantially further reduced by greater intake. For instance, populations with very high fish intake (Yokoyama et al[17] [secondary prevention; square 16]) already have much lower CHD death rates than otherwise comparable populations (Gruppo Italiano[9] [square 19]), and additional intake of fish or fish oil produces little further reduction in CHD mortality. Only 1 study (Burr et al[51] [square 20]) found results markedly divergent from this pattern. One study[46] was not included due to limited events data and limited multivariable adjustment.

*Rates in the control and intervention groups (for randomized trials) or rates in the reference group and multivariable-adjusted relative rates (for cohort studies).

†Reported data or estimated from similar populations.

‡Populations with prior CHD (secondary prevention).

§Rates of sudden death, not CHD death.

tality) and (*clinical trial* or *prospective* or *meta-analysis*); (*fish* or *n-3 PUFA* or *omega-3* or *docosahexaenoic* or *mercury* or *methylmercury*) and (*cognitive* or *neurologic* or *neurodevelopment*) and (*clinical trial* or *prospective* or *meta-analysis*); (*mercury* or *methylmercury*) and (*coronary* or *cardiac* or *cardiovascular* or *cognition* or *neurologic*) and (*clinical trial* or *prospective* or *meta-analysis*); (*dioxin* or *polychlorinated biphenyl* or *PCB*) and (*fish* or *seafood*). MEDLINE searches were restricted to identify only English-language reports, studies in humans, and adult or child populations (as appropriate) and were supplemented by searches of related articles of relevant identified manuscripts as well as by hand reviews of references from identified reports and direct contact with investigators.

Study Selection

One author (D.M.) screened all identified studies, and the final articles included were selected by both authors by consensus. Because fish intake is related to exposure to many different compounds, including n-3 PUFAs, mercury, and PCBs and dioxins, as well as to multiple different health outcomes, including cardiovascular diseases, neurologic outcomes, and cancer, a systematic quantitative review of every possible combination was beyond the constraints of this report. We concentrated on studies evaluating or estimating risk in humans, focusing on the evidence, when available, from randomized clinical trials and large prospective studies. Metabolic studies and animal-experimental evidence were also considered to elucidate potential mechanisms of effect. The evidence for risks and benefits was considered overall and among different at-risk populations. When possible, pooled or meta-analyses were performed to characterize effects most precisely.[37-39] Other potential benefits of fish intake (eg, for cognitive decline or dementia,[40] depression or neuropsychiatric disor-

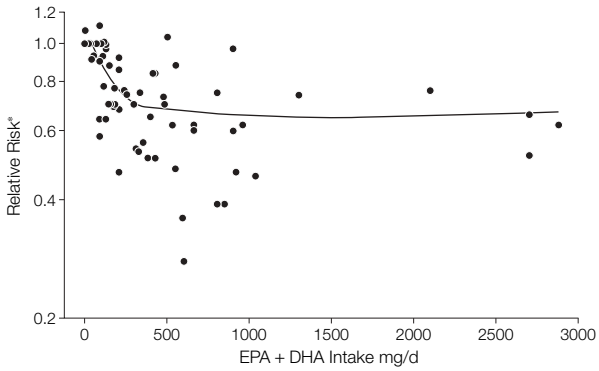
ders,[41,42] and asthma or inflammatory disorders[43,44]) were not reviewed in this report.

EVIDENCE SYNTHESIS

Benefits of Fish Intake

Cardiovascular Outcomes. Death from CHD—ie, documented or suspected fatal myocardial infarction—and sudden death—ie, a sudden pulseless condition of presumed cardiac etiology—are clinically defined entities often sharing the final common pathway of ventricular arrhythmia, often ischemia-induced ventricular fibrillation. The evidence from prospective studies and randomized trials[2-4,6-17,45-51] suggests that consumption of fish or fish oil lowers risk of CHD death and sudden death (**FIGURE 1** and **FIGURE 2**). Across different studies (Figure 1), compared with little or no intake, modest consumption (≈250-500 mg/d of EPA and DHA) lowers relative risk by 25% or more. Higher intakes do not substantially further lower CHD mortality, suggesting a threshold of effect.[52] Pooling all studies, this pattern was clearly evident (Figure 2). At intakes up to 250 mg/d, the relative risk of CHD death was 14.6% lower (95% confidence interval [CI], 8% to 21%) per each 100 mg/d of EPA and DHA, for a total risk reduction of 36% (95% CI, 20% to 50%). At higher intakes, little additional risk reduction was present (0.0% change per each 100 mg/d; 95% CI, −0.9% to +0.8%). This threshold effect explains findings among Japanese populations,[17,50] in whom high background fish intake (eg, median 900 mg/d of EPA and DHA[50]) is associated with very low CHD death rates (eg, 87% lower than comparable Western populations[9,17]), and additional n-3 PUFA intake predicts little further reduction in CHD death; thus, most of the population is already above the threshold for maximum mortality benefits. Comparing different types of fish, lower risk appears more strongly related to intake of oily fish (eg, salmon, herring, sardines), rather than lean fish (eg, cod, catfish, halibut).[10,15] Fish intake may modestly affect other cardiovascular outcomes, but evidence is not as robust as for CHD death (**TABLE 1**).[17,50,53-66]

Figure 2. Relationship Between Intake of Fish or Fish Oil and Relative Risks of CHD Death in Prospective Cohort Studies and Randomized Clinical Trials



The relationship between intake of fish or fish oil and relative risk of coronary heart disease (CHD) death in a pooled analysis of the prospective studies and randomized trials shown in Figure 1, evaluated nonparametrically using restricted cubic splines[38,39] and adjusted for each within-study relationship. Given the much higher reference group intakes in some studies, the reference relative risk was scaled by 0.7 for studies with reference group intakes between 150-500 mg/d of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) (n=5) and by 0.6 for studies with reference group intakes >500 mg/d (n=1) based on spline relationships prior to including these studies; exclusion of these studies, or of the few groups with intakes >1000 mg/d, had little effect on the pooled spline relationship. A significant threshold effect ($P<.001$) was evident at intake of 250 mg/d: between 0 and 250 mg/d, mortality risk was lower by 14.6% (95% confidence interval [CI], 8% to 21%) per each 100-mg/d greater intake (total risk reduction, 36%; 95% CI, 20% to 50%; $P<.001$), while at higher intakes, risk was not further lowered (0.0% change per each 100 mg/d; 95% CI, −0.9% to 0.8%; $P=.94$). *Relative risks in the control and intervention groups (for randomized trials) or relative risks in the reference group and multivariable-adjusted relative risks in the comparison groups (for cohort studies).

n-3 PUFAs influence several cardiovascular risk factors.[18,19,43,49,50,60-75,79-84] Effects occur within weeks of intake and may result from altered membrane fluidity and receptor responses following incorporation of n-3 PUFAs into cell membranes[76,77] and direct binding of n-3 PUFAs to intracellular receptors regulating gene transcription.[78] The heterogeneity of the effects of fish or fish oil intake on cardiovascular outcomes is likely related to varying dose and time responses of effects on the risk factors (**FIGURE 3**). At typical dietary intakes, antiarrhythmic effects predominate, reducing risk of sudden death and CHD death within weeks. At higher doses, maximum antiarrhythmic effects have been achieved, but other physiologic effects may modestly impact other clinical outcomes (possibly requiring years to produce clinical benefits). For instance, nonfatal myocardial infarction may not be significantly affected by lower doses or shorter durations of intake but may be modestly reduced by higher doses or prolonged intake (eg, 1.8 g/d for 5 years[17]).

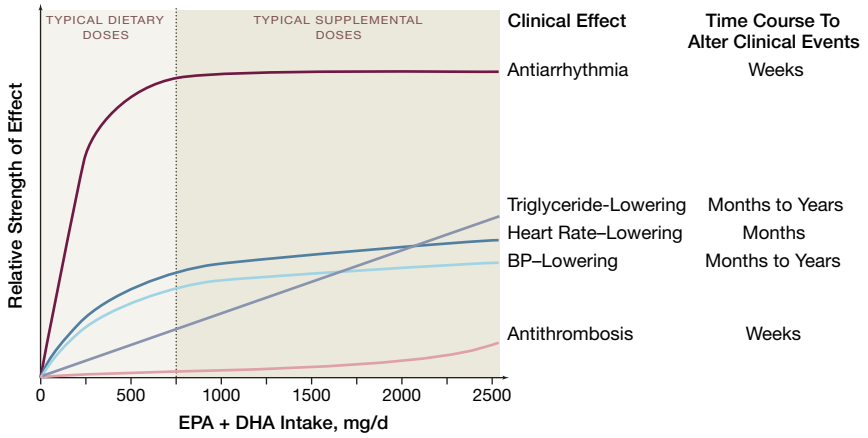
Heterogeneity of clinical effects may also be related to differing pathophysiologies of the clinical outcomes. For instance, disparate pathophysiologies of primary ventricular fibrillation (often ischemia-induced) vs recurrent ventricular tachyarrhythmias (ectopic or reentrant) may explain stronger effects of n-3 PUFAs on the former. Similarly, biological differences in development of atherosclerosis vs acute plaque rupture/thrombosis vs arrhythmia would account for heterogeneous effects of n-3 PUFAs on plaque progression vs nonfatal myocardial infarction vs CHD death. Consumption of fish may displace that of other foods, such as meats or dairy products, in the diet. However, this likely accounts for little of the observed health benefits, because foods replaced would be highly variable among individuals and across cul-

Table 1. Summary of Evidence for Effects of Consumption of Fish or Fish Oil on Cardiovascular Outcomes

Outcome	Clinical Effect	Strength of Evidence	Comment
CHD mortality			
CHD death	≈ 35% decrease	Strong	Probable threshold of effect—most risk reduction occurs with modest intake (≈ 250 mg/d EPA + DHA), with little additional benefit with higher intakes[2-4,6-17,45-51]*
Sudden death	≈ 50% decrease	Strong	
Ischemic stroke	≈ 30% decrease	Moderate	Strong evidence from prospective cohort studies[53,54]; no RCTs
Nonfatal CHD			
Nonfatal MI	Modest benefit?	Equivocal	Possible benefits at very high intakes (≈ 2 g/d n-3 PUFAs)[17,50]
Progression of atherosclerosis	Modest benefit?	Equivocal	Mixed results in cohort studies[55] and RCTs[56-58]
Postangioplasty restenosis	Modest benefit?	Equivocal	Possible benefits in a meta-analysis of RCTs[59]
Recurrent ventricular tachyarrhythmias	Modest benefit?	Equivocal	Mixed results in 3 RCTs[60-62]
Atrial fibrillation	≈ 30%+ decrease	Limited	Mixed results in 2 cohort studies[63,64]; benefit in 1 RCT[65]
Congestive heart failure	≈ 30% decrease	Limited	Benefit in 1 prospective cohort study[66]

Abbreviations: CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infraction; n-3 PUFA, n-3 polyunsaturated fatty acid; RCT, randomized clinical trial.
*See Figure 1.

Figure 3. Schema of Potential Dose Responses and Time Courses for Altering Clinical Events of Physiologic Effects of Fish or Fish Oil Intake



The relative strength of effect is estimated from effects of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) on each risk factor and on the corresponding impact on cardiovascular risk.[70-72,79-84] For example, dose response for antiarrhythmic effects is initially steep with a subsequent plateau, and clinical benefits may occur within weeks, while dose response for triglyceride effects is more gradual and monotonic, and clinical benefits may require years of intake. At typical Western levels of intake (eg, <750 mg/d EPA + DHA), the physiologic effects most likely to account for clinical cardiovascular benefits include (1) modulation of myocardial sodium and calcium ion channels, reducing susceptibility to ischemia-induced arrhythmia;[18,19] and (2) reduced left ventricular workload and improved myocardial efficiency as a result of reduced heart rate, lower systemic vascular resistance, and improved diastolic filling.[67-72,80] At higher levels of intake seen with fish oil supplementation or in Japanese populations[49,50] (>750 mg/d EPA + DHA), maximum antiarrythmic effects have been achieved and clinically relevant effects occur on levels of serum triglycerides[79] and possibly, at very high doses, thrombosis.[75] Potentially important effects on endothelial,[73] autonomic,[74] and inflammatory[43] responses are not shown because dose responses and time courses of such effects on clinical risk are not well established. Effects are not necessarily exclusive: eg, antiarrythmic effects may be partly mediated by effects on blood pressure (BP) or heart rate.

tures, and modest intake of such foods is not associated with CHD risk.[85]

Total Mortality. n-3 PUFAs most strongly affect CHD death[5,9,14-16,18] and are unlikely to affect appreciably other causes of mortality. Effects on total mortality in a population would therefore depend on the proportion of deaths due to CHD, ranging from one quarter of deaths in middle-age populations[86] to one half of deaths in populations with established CHD.[9] Thus, given a ≈36% reduction in CHD death (Figure 2), intake of fish or fish oil would reduce total mortality by between ≈9% (36% reduction × 25% CHD deaths) to ≈18% (36% reduction × 50% CHD deaths), or an average of ≈14% in mixed populations. This is consistent with a meta-analysis of randomized trials through 2003[3,9,51,56,57,87-93] that found a nonsignificant 14% reduction in total mortality with n-3 PUFAs (pooled relative risk, 0.86; 95% CI, 0.70 to 1.04).[94] When we added additional placebo-controlled, double-blind, randomized trials[60-62] performed since 2003, marine n-3 PUFAs reduced total mortality by 17% (pooled relative risk, 0.83; 95% CI, 0.68 to 1.00; $P = .046$) (FIGURE 4). This can be compared to effects of statins on total mortality—a 15% reduction—in a meta-analysis of randomized trials (pooled relative risk, 0.85; 95% CI, 0.79 to 0.92).[95]

Neurologic Development. DHA is preferentially incorporated into the rapidly developing brain during gestation and the first 2 years of infancy, concentrating in gray matter and retinal membranes.[26] Infants can convert shorter-chain n-3 fatty acids to DHA,[96] but it is unknown whether such conversion is adequate for the developing brain in the absence of maternal intake of DHA.[22,25]

Effects of maternal DHA consumption on neurodevelopment have been investigated in observational studies and randomized trials, with heterogeneity in assessed outcomes (visual acuity, global cognition, specific neurologic domains) and timing of DHA intake (gestational vs nursing). In a meta-analysis of 14 trials, DHA supplementation

improved visual acuity in a dose-dependent manner.[23] Results for cognitive testing are less consistent, possibly due to differences in neurologic domains evaluated[21,25,26]; a quantitative pooled analysis of 8 trials estimated that increasing maternal intake of DHA by 100 mg/d increased child IQ by 0.13 points (95% CI, 0.08 to 0.18).[24] Most trials evaluated effects of maternal DHA intake during nursing, rather than pregnancy. In a trial among 341 pregnant women, treatment with cod liver oil from week 18 until 3 months postpartum increased DHA levels in cord blood by 50% and raised mental processing scores, a measure of intelligence, at age 4 years.[97] This is consistent with observational studies showing positive associations between maternal DHA levels or fish intake during pregnancy and behavioral attention scores, visual recognition memory, and language comprehension in infancy.[98-100] Thus, while dose responses and specific effects require further investigation, these studies together indicate that maternal intake of DHA is beneficial for early neurodevelopment.

Risks of Mercury

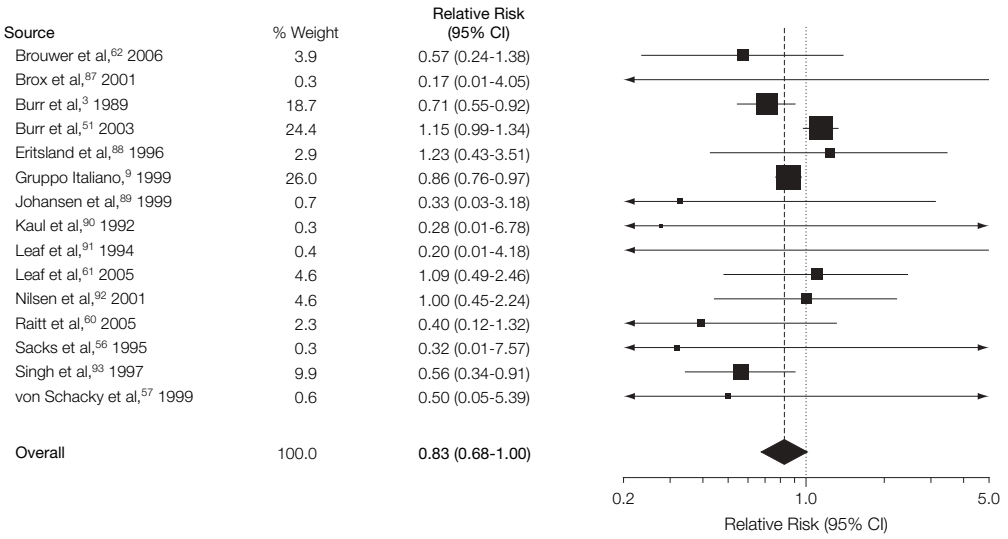
Mercury is a reactive heavy metal emitted from natural sources (volcanoes) and human sources (coal-fired electric power plants, gold mining, institutional boilers, chlorine production, and waste incineration).[101] From the atmosphere, mercury cycles from rainwater into lakes and oceans, where it is converted by microbial activity into organic methylmercury. Inorganic mercury is poorly absorbed following ingestion, and elemental mercury does not readily cross tissue barriers. In contrast, methylmercury is readily absorbed and actively transported into tissues.[27] Thus, methylmercury bioaccumulates in aquatic food chains and has greater potential toxicity than inorganic mercury.[27,28,30] Concentrations of methylmercury in aquatic species depend on levels of environmental contamination and on the predatory nature and lifespan of the species. Larger, longer-living predators (eg, swordfish, shark) have higher tissue concentrations, while smaller or shorter-lived species (eg, shellfish, salmon) have very low concentrations (TABLE 2).[122] Preparation methods have little impact on methylmercury content.[27]

Health effects of very high mercury exposure following occupational or industrial accidents are well documented, including paresthesias, ataxia, and sensory abnormalities in adults, and delayed cognitive and neuromuscular development following in utero exposure.[27,131] Toxicity appears related to binding of methylmercury to sulfhydryl groups of enzymes, ion channels, and receptors, resulting in inhibition of antioxidant systems and production of free radicals and reactive oxygen species.[27,29] Health effects of chronic low-level mercury exposure—ie, that seen with fish consumption—are less well established. The public is aware of the potential harm from mercury in fish but lacks clear understanding of who is at risk or which seafood species contain mercury.[35,36] We review the evidence for health effects below.

Methylmercury and Neurodevelopment

Methylmercury crosses the placenta, and fetal exposure correlates with maternal

Figure 4. Risk of Total Mortality Due to Intake of Fish or Fish Oil in Randomized Clinical Trials



The size of the shaded squares indicates each trial's contribution (inverse-variance weight) to the pooled estimate (dotted line) and 95% confidence interval (CI; diamond), determined by random effects meta-analysis.[37] Intake of fish or fish oil reduced total mortality by 17% ($P=.046$), with evidence for heterogeneity between trials ($P=.04$ for heterogeneity). If 2 trials with methodologic concerns[51,93] were excluded, the pooled relative risk was 0.83 (95% CI, 0.74-0.92; $P<.001$) with little evidence for heterogeneity ($P=.75$). A recently reported trial of fish oil among Japanese individuals[17] was not included in the primary analysis due to very high fish intake in the reference group (estimated eicosapentaenoic acid + docosahexaenoic acid intake, 900 mg/d) which would obviate mortality benefits of additional fish oil intake. When this trial was added to the secondary analysis, the pooled relative risk was 0.87 (95% CI, 0.76-0.99; $P=.048$; $P=.29$ for heterogeneity).

exposure.[132] Marked neurodevelopmental abnormalities occur in children following very high gestational exposure,[27,131] such as from maternal consumption of highly contaminated fish (10-30 ppm mercury) from industrially polluted Minimata Bay, Japan, in the 1950s, or of contaminated grain in Iraq in 1971 (maternal intake, 710-5700 ug/kg per day; 18-598 ppm mercury in maternal hair). More typical methyl mercury exposures are substantially lower: among US women of childbearing age, median (10th-95th percentiles) levels of mercury in hair were 0.19 (0.04-1.73) ppm overall and 0.34 (0.09-2.75) ppm among women consuming 3 or more servings of fish per month.[133]

Table 2. Levels of n-3 Fatty Acids and Contaminants in Commonly Consumed Fish, Shellfish, and Other Foods*

	EPA + DHA, mg/serving (Serving Size†)	EPA + DHA, mg/100 g (3.5 oz)	Selenium, µg/g (ppm)	Mercury, µg/g (ppm)	PCBs, ng/g (ppb)	Dioxins, TEQ pg/g (ppt)‡
FDA action level[33,102]	NA	NA	NA	1.0	2000	None§
Fish						
Anchovy	1165 (2 oz)	2055	0.68	<0.05		0.35 (1997-1998)[103]
Catfish, farmed	253 (5 oz)	177	0.15	<0.05	<50 (1997)[104]	0.53 (1995-1997)[105] 0.51 (1996)[106] 2.09 (1995-1996)[107] 1.65 (1995)[108]
Cod, Atlantic	284 (6.3 oz)	158	0.38	0.10		0.05 (1995-1997)[105] 0.15 (1995-1996)[107]
Fish burger, fast food	337 (2.2 oz)	546	0.17‡	<0.05	8 (2001)[109]	0.01 (2001)[110] 0.11 (2001)[109]
Fish sticks, frozen	193 (3.2 oz)	214	0.17	<0.05		0.04 (2001)[110]
Golden bass (tilefish), Gulf of Mexico	1358 (5.3 oz)	905	0.52	1.45		
Golden bass (tilefish), Atlantic	1358 (5.3 oz)	905	0.52	0.14		
Halibut	740 (5.6 oz)	465	0.47	0.25		1.00 (1995-1997)[105]
Herring, Atlantic	1712 (3 oz)	2014	0.47	<0.05		0.97 (1995-1998)[105]
Mackerel, Atlantic	1059 (3.1 oz)	1203	0.52	0.05		0.87 (1997-1998)[103] 0.32 (1995-1998)[105]
Mackerel, King	618 (5.4 oz)	401	0.47	0.73		
Mahimahi	221 (5.6 oz)	139	0.47	0.15		
Pollock, Alaskan	281 (2.1 oz)	468	0.43	<0.05		0.01 (1998)[105] 0.24 (1998)[111]
Salmon, farmed‖	4504 (6 oz)	2648	0.41	<0.05	21 (2001-2003)[112] 15 (2002)[113] 40 (2002)[115]¶ 26 (2001)[110] 25 (2001)[116] 51 (1999-2000)[117]¶ 38 (1999)[116]	0.50 (2001-2003)[112] 0.87 (2002)[114] 0.45 (2002)[115] 0.33 (2001)[110] 0.50 (1997)[105]
Salmon, wild‖	1774 (6 oz)	1043	0.46	<0.05	3 (2002)[115]¶ 0.5 (2002)[113] 5 (2000)[117]¶	0.03 (2002)[115] 0.34 (2002)[114]
Sardines	556 (2 oz)	982	0.53	<0.05	57 (2001-2003)[112] 22 (2002)[118]	0.44 (2001-2003)[112] 0.18 (2002)[118] 0.60 (1995)[105]
Shark	585 (3 oz)	689	0.34	0.99		
Snapper	546 (6 oz)	321	0.49	0.19		
Swordfish	868 (3.7 oz)	819	0.62	0.98		
Trout	581 (2.2 oz)	935	0.15	0.07	11 (2002)[113]	0.56 (2002)[113]# 0.32 (2002)[114] 0.74 (1998-2000)[119] 0.35 (1998)[105]
Tuna, light (skipjack)‖	228 (3 oz)	270	0.80	0.12	45 (2001)[110]	0.02 (1995-1998)[105]
Tuna, white (albacore)‖	733 (3 oz)	862	0.66	0.35	100 (2001-2003)[112]	0.23 (2001-2003)[112]

(continued)

Table 2. Levels of n-3 Fatty Acids and Contaminants in Commonly Consumed Fish, Shellfish, and Other Foods* (cont)

	EPA + DHA, mg/serving (Serving Size†)	EPA + DHA, mg/100 g (3.5 oz)	Selenium, µg/g (ppm)	Mercury, µg/g (ppm)	PCBs, ng/g (ppb)	Dioxins, TEQ pg/g (ppt)‡
Shellfish						
Clams	241 (3 oz)	284	0.64	<0.05	3 (2001-2003)[112] 2 (2002)[118]	0.05 (2001-2003)[112] 0.05 (2002)[118] 0.10 (1997-1998)[103]
Crab	351 (3 oz)	413	0.40	0.09	6 (2002)[113]	0.55 (2002)[113]# 1.05 (1998)[111]
Lobster	71 (3 oz)	84	0.43	0.31		0.69 (1998)[111] 0.12 (1997-1998)[103]
Mussels	665 (3 oz)	782	0.90	<0.15	7 (2001-2003)[112] 0.8 (2002)[113] 2 (2002)[118]	0.09 (2001-2003)[112] 0.11 (2002)[113]# 0.07 (2002)[118] 0.39 (1998)[105] 0.45 (1995-1996)[107]
Oysters	585 (3 oz)	688	0.77	<0.05	17 (2001-2003)[112] 0.8 (2002)[113]	0.46 (2001-2003)[112] 0.19 (2002)[113]#
Scallops	310 (3 oz)	365	0.28	<0.05		0.16 (1998)[111]
Shrimp	267 (3 oz)	315	0.40	<0.05	2 (2002)[118] 0.2 (2002)[113]	0.06 (2002)[113]# 0.11 (2002)[118] 0.06 (2001)[110] 0.19 (1995-1997)[105] 0.08 (1995-1996)[107]
Other Foods						
Beef	0	0	0.19	0	22 (2001)[110]	0.13 (2001)[110] 0.27 (1995)[120]
Bologna	0	0	0.14	0		0.16 (2001)[110] 0.29 (1995)[120]
Butter, regular	0	0	<0.05	0	70 (2001)[110]	0.22 (2001)[110] 0.31 (1995-1996)[107] 0.66 (1995)[120]
Cheese	0	0	0.22	0		0.25 (2001)[110] 0.77 (1998)[111] 0.34 (1995)[120]
Chicken	0	0	0.23	0	32 (2001)[110]	0.02 (2001)[110] 0.20 (1995)[120]
Eggs	22 (1 egg)	43	0.23	0	19 (2001)[110]	0.05 (2001)[110] 0.52 (1998)[111] 0.31 (1995)[120]
Milk, whole	0	0	0.02	0		0.01 (2001)[110] 0.12 (1995-1996)[107] 0.13 (1995)[120]
Pork	0	0	0.34	0	18 (2001)[110]	0.10 (2001)[110] 0.23 (1995)[120]

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDA, US Food and Drug Administration; NA, not applicable; PCB, polychlorinated biphenyl; ppb, parts per billion; ppm, parts per million; ppt, parts per trillion; TEQ, toxic equivalence.

*Based on data from US Department of Agriculture (USDA),[121] Food and Drug Administration (FDA),[110] Environmental Protection Agency,[122] and other[103-109,111-120,123-126] sources. These values may vary due to methodologic, geographic, temporal, and fish-to-fish differences. Levels of PCBs and dioxins may overestimate current levels because contaminant levels in most foods, including fish species, are decreasing over time[33,110,112,127,128] (eg, TEQs decreased by 33%-81% in meats[127] and 66%-77% in salmon and tuna fish[112] between 1995 and 2003); year of sampling is given in parenthesis.

†Based on USDA serving sizes: 2 oz anchovies or sardines; 1 fillet catfish, cod, mackerel, mahimahi, snapper, or trout; ½ fillet halibut, king mackerel, pollock, or golden bass; 6 oz salmon; 3 oz herring, shark, shellfish, or tuna; 1 piece (3.75 oz) swordfish.[121]

‡The sum of dibenzodioxins (PCDDs) + debenzofurans (PCDFs) (nondetects = 1/2 LOD when multiple estimates available).

§Due to "numerous questions and uncertainties regarding scientific data on and analysis of dioxin risk."[129]

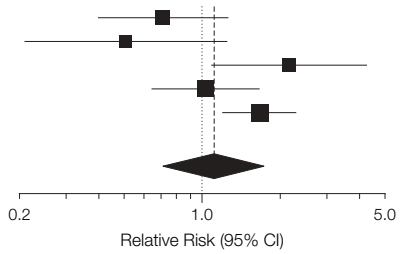
||For the same specific species, there are minimal differences in nutritional or contaminant content of canned vs fresh salmon or tuna. However, different species are typically canned vs sold fresh. For salmon, differences between species are small compared with differences between farmed and wild salmon. For tuna, canned light (skipjack) tuna and fresh yellowfin/ahi tuna are more similar overall, while canned white (albacore) tuna and fresh bluefin tuna are more similar overall.

¶Measured including the fish skin; levels may be lower in the edible portion.[130]

#Includes dioxin-like PCBs.

Figure 5. Multivariate Risk of Incident Coronary Heart Disease (CHD) With Higher Levels of Mercury Exposure

Source	Study Design	No. of Events	Relative Risk (95% CI)
Ahlqwist et al,[144] 1999	Prospective	87	0.71 (0.4-1.26)
Hallgren et al,[145] 2001	Prospective	78	0.51 (0.21-1.24)
Guallar et al,[146] 2002	Retrospective	684	2.16 (1.09-4.29)
Yoshizawa et al,[147] 2002	Prospective	470	1.03 (0.65-1.65)
Virtanen et al,[148] 2005	Prospective	282	1.66 (1.2-2.29)
Overall			1.12 (0.71-1.75)



Relative risk and 95% confidence intervals (CIs) are shown comparing the highest to the lowest quantile of mercury exposure after adjustment for other risk factors. In 2 studies in Sweden, higher mercury levels were associated with trends toward lower risk,[144,145] but findings may have been limited by relatively few numbers of events. In 2 larger European studies, positive associations between mercury levels and CHD risk were reported.[146,148] A large US study observed no association,[147] but most participants were dentists, in whom mercury levels in part represented occupational exposure to inorganic mercury,[149] which may be less toxic than methylmercury in fish.[27,28,30] The overall pooled relative risk (dotted line) and 95% CI (diamond), estimated using inverse-variance random-effects meta-analysis,[37] was 1.12 (95% CI, 0.71-1.75; $P=.62$), with significant heterogeneity between studies ($P=.008$).

These exposure levels do not produce symptomatic neurodevelopmental deficits, but several prospective studies have evaluated whether subclinical effects, detectable with specialized testing, might occur.[98,100,134-140] Among children from the Faroe Islands,[134,135] New Zealand,[136,137] and Poland,[138] higher gestational exposure to mercury was associated with lower scores on some neurologic tests (eg, finger tapping, naming tests) but not others. In contrast, higher gestational exposure to mercury was associated with higher scores on some neurologic tests among Seychellois children.[139,140] In a US cohort, gestational maternal fish intake was positively associated with, but mercury levels in hair were negatively associated with, visual recognition memory scores in infancy,[98] indicating possible opposing effects of overall fish consumption (ie, providing DHA) and methylmercury exposure. In a British cohort, gestational mercury exposure was not associated with, but maternal and infant fish intake was associated with, improved neurodevelopmental scores.[100] Other studies did not detect consistent associations between gestational exposure to mercury and neurologic test scores during childhood.[141]

Comparisons across studies are limited by heterogeneity of study designs (prospective vs cross-sectional), mercury assessment methods, neurologic tests used, timing of assessment (infancy vs childhood), and statistical methods. Some analyses are also limited by multiple statistical testing (eg, ≥30 neurologic variables) or incomplete adjustment for other potential risk factors. Randomized trials to test effects of reducing low-level methylmercury exposure during gestation have not been performed. Nevertheless, given associations with some lower neurologic test scores in some studies, and clinical neurotoxicity of methylmercury following high-level accidental exposures, it is prudent to conclude that subclinical neurodevelopmental deficits may occur at lower exposure levels.

Based on this, the Environmental Protection Agency determined a reference dose, ie, the allowable upper limit of daily intake, for methylmercury of 0.1 ug/kg per day (≈50 µg/wk for a 70-kg woman, calculated from the lower 95% confidence limit at which gestational exposure to mercury may produce abnormal neurologic test scores, multiplied by a 10-fold uncertainty factor)[132] and published a focused advisory for women of childbearing age, nursing mothers, and young children.[142] The advisory specifically advises such individuals to avoid shark, swordfish, golden bass, and king mackerel (each containing >50 µg methylmercury per serving) (Table 2); to eat up to 12 oz/wk (2 average meals) of a variety of fish and shellfish lower in mercury, including up to 6 oz/wk of albacore tuna (30 µg methylmercury per serving); and to consult local advisories for locally caught freshwater fish. This advisory was not intended for the general population, because the importance of this reference dose to health effects in adults was unclear.[143] We review the evidence for such effects below.

Health Effects of Methylmercury in Adults

Cardiovascular Disease. Several studies[144-148] have evaluated the relationship between mercury exposure and incidence of cardiovascular disease (FIGURE 5). The conflicting results provide inconclusive evidence for cardiovascular toxicity of mercury. Notably, in the 2 studies observing higher risk with higher mercury levels, the net effect of fish consumption was still beneficial: greater mercury exposure lessened the benefit associated with consumption of fish or n-3 PUFAs but did not increase overall risk.[146,148,150] Thus, the principal question may not be whether consumption of mercury-containing fish increases cardiovascular risk but whether consumption of such fish would decrease risk even further if mercury were not present. This would be most true for oily fish species containing higher amounts of n-3 PUFAs (ie, most mercury-containing ocean fish), compared with lean freshwater fish. This is an important public

health issue, which requires balancing potentially attenuated benefits of fish intake due to presence of mercury with the costs and practicality of reducing mercury contamination in fish species. Nevertheless, this should not obscure evidence for net cardiovascular benefits of fish consumption, particularly fish richer in n-3 PUFAs.

Neurologic Outcomes. Very high methylmercury exposure from accidents (eg, Minimata)[27,151] or prolonged high intakes of mercury-containing fish (eg, 1-2 fish servings/d, including species high in mercury, for >10 years[152]) can produce sensorimotor symptoms in adults, most commonly paresthesias, which are often reversible when mercury exposure is reduced. Whether lower exposures produce neurologic abnormalities in adults is not clear. Cross-sectional studies have evaluated associations between mercury levels in hair or blood and subclinical neurologic function in adults. Among Amazon basin and Quebec Cree individuals, both positive and inverse associations were seen between mercury levels and some neurologic measures,[153-155] but findings were limited by minimal adjustment for other risk factors and multiple testing (typically ≥20-30 neurologic tests or participant subgroups). Among US adults, mercury levels were associated with lower visual memory scores ($P=.01$) but better motor and manual dexterity scores ($P=.02$) among 20 different outcomes evaluated.[156] Among elderly Swedish adults, no associations were found between mercury levels and cognitive function.[157] Thus, it is unclear whether low-level methylmercury affects subclinical neurologic outcomes in adults and, if so, what quantities or durations of exposure are necessary. Conversely, a growing body of evidence suggests that fish consumption may favorably affect clinical neurologic outcomes in adults, including ischemic stroke,[53] cognitive decline and dementia,[40] and depression and other neuropsychiatric disorders.[41,42]

Possible Mercury-Selenium Interaction. Health effects of mercury may partly result from selenoprotein inactivation, which might be mitigated by adequate intake of selenium, an essential dietary trace element.[158-161] Selenium also may reduce tissue accumulation of mercury in fish[162] and humans.[163] Seafood species are rich dietary sources of selenium.[121] A protective effect of selenium may partly account for conflicting results of studies of mercury exposure and neurodevelopmental indices in children[160] and of mercury exposure and risk of CHD.[164] A potential selenium-mercury interaction would have important public health implications, and additional investigation is warranted.

Risks of PCBs and Dioxins

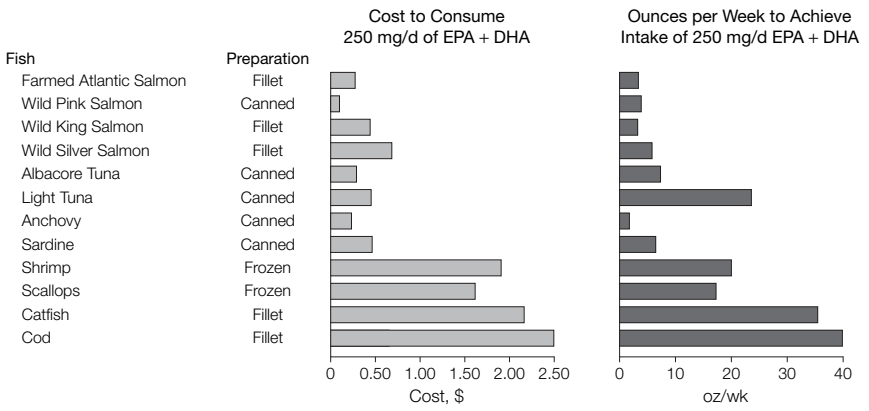
PCBs are synthetic organochlorine compounds previously used in industrial and commercial processes.[34] Dioxins—commonly referring to dibenzodioxins and dibenzofurans—are organochlorine by-products of waste incineration, paper bleaching, pesticide production, and production of polyvinyl chloride plastics.[33] Manufacture and processing of PCBs was prohibited in 1977,[34] and regulatory and industry efforts have reduced dioxin emissions by more than 90% since 1987.[33] Nevertheless, these contaminants persist for long periods in the environment, and thus while levels are steadily declining,[33,110,112,127,128] PCBs and dioxins continue to be present in low concentrations in many foods (Table 2).

Cancer Risks. Animal experiments and some evidence in humans indicate that PCBs and dioxins are carcinogenic, possibly related to effects on the aryl hydrocarbon receptor, a transcription factor affecting gene expression.[32,165] Multiple congeners (structural variants) of PCBs and dioxins exist. Potential toxicities of foods are calculated using toxic equivalence (TEQ): the sum of each congener's level in the food multiplied by that congener's toxic equivalency factor (standardized against 2,3,7,8-tetrachlorodibenzo-p-dioxin). In the United States, PCBs comprise 28% and dioxins 72% of total TEQ exposure.[120] Among adults, major dietary sources of PCBs and dioxins are beef, chicken, and pork (34% of total TEQ); dairy products (30%); vegetables (22%); fish and shellfish (9%); and eggs (5%).[120] Dietary sources are similar for children.[120]

Although major sources of exposure to PCBs and dioxins are meats, dairy products, and vegetables, considerable attention has been given to fish sources (Table 2). When PCBs and dioxins were measured in farmed and wild salmon,[115,166] levels were similar to those in several other foods (Table 2). Farmed and wild salmon also contained substantial levels of n-3 PUFAs: 4504 and 1774 mg of EPA and DHA per 6 oz, respectively.[166] Cancer risks and CHD benefits were evaluated in a quantitative risk-benefit analysis, assuming regular farmed or wild salmon intake to provide 1000 mg/d of EPA and DHA over a 70-year lifetime.[167,168] Per 100 000 individuals, consumption of farmed vs wild salmon would result in 24 vs 8 excess cancer deaths, respectively, while consumption of either farmed or wild salmon would result in 7125 fewer CHD deaths.[167] We further evaluated age-specific estimates, based on allocation of lifetime cancer risks[167] (adjusted for competing risks) by age-specific cancer mortality[169] and 25% reduction in age-specific CHD mortality.[169] For all ages evaluated (25-34 to ≥85 years), CHD benefits outweighed cancer risks by 100- to 370-fold for farmed salmon and by 300- to more than 1000-fold for wild salmon.

Notably, estimated CHD benefits are based on prospective studies and randomized trials in humans (Figures 1 and 2); estimated cancer risks include a 10-fold safety factor and are based on animal-experimental data and limited studies in humans at high doses.[168] Cancer estimates also assumed lifetime salmon consumption to provide 1000 mg/d of EPA and DHA (eg, four 6-oz servings of wild salmon every week for 70 years). However, CHD mortality reduction may be achieved with lower intake: ≈250 mg/d (Figures 1 and 2), or one 6-oz wild salmon serving per week. At this intake, CHD benefits would be

Figure 6. Estimated Costs of Consuming the equivalent of 250 mg/d EPA + DHA From Fish



Costs were calculated for commonly consumed seafood species, based on retail prices (averaging the most commonly sold items in each of 6 US cities in the east, midwest, and south from a national online grocery store[181] or, for wild king and silver salmon, from online retailers[182-184]) and on species-specific eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) content.[121] Least expensive was canned pink salmon (9 cents/250 mg of EPA + DHA); the average cost per 250 mg of EPA + DHA for these 12 types of seafood was 92 cents. The corresponding ounces per week needed to achieve 250 mg/d of EPA + DHA is also shown.

largely unchanged (≈7125 fewer CHD deaths), while lifetime cancer risk would decrease by ≈75% (6 and 2 estimated deaths per 100 000 lifetimes for farmed and wild salmon, respectively). Consistent with these very low cancer risks, prospective studies in humans have seen little evidence for effects of fish intake on cancer risk.[170]

Other Risks. PCBs and dioxins may have noncancer risks in adults, such as immune system or neurologic effects.[32-34] Conversely, fish consumption may also have other benefits, possibly lowering risk of other cardiovascular outcomes (Table 1), dementia,[40] neuropsychiatric disorders,[41,42] and inflammatory disorders.[43,44] If present, such additional possible risks would have to exceed additional possible benefits by more than 100-fold to meaningfully alter the present estimates of risks vs benefits. PCB content in fish can be reduced 12% to 40% by trimming belly and back fat during filleting and by not consuming the skin.[130] Also, contaminant levels are typically measured in unprepared foods, and cooking may reduce PCB and dioxin content.[106]

Prenatal (but not postnatal) exposure to PCBs and dioxins has been associated with childhood neurodevelopmental deficits in several,[171-177] though not all,[178,179] studies. Because most exposure (>90%) generally comes from meat, dairy, and vegetable sources,[120,180] this concern is not specific to fish consumption, particularly since fish also contains potentially beneficial DHA. However, women consuming 1 or more servings/d of commercial freshwater fish or consuming locally caught freshwater fish from highly contaminated inland sources may be more greatly exposed to PCBs and dioxins[180] and should consult regional advisories.

Related Considerations

Costs. We evaluated potential costs of consuming 250 mg/d of EPA and DHA from fish (FIGURE 6). The daily cost was as low as 9 cents, or 63 cents/wk. For combinations of different types of salmon; salmon and tuna; or salmon, tuna, anchovies, and sardines, the average cost was 37 cents/d ($2.59/wk) or less. Actual (net) costs would be lower because intake of fish would replace intake of other foods.

Supplements. Fish oil capsules contain 20% to 80% of EPA and DHA by weight (200-800 mg/g[185,186]), little to no mercury,[187] and variable levels of PCBs (0-450 ng/g,[116,188]) and dioxins (0.2-11 TEQ pg/g[114,189]). Given small amounts of fish oil consumed (1-3 g/d), exposure to PCBs and dioxins from fish oil intake is low. "Functional foods" supplemented with EPA and DHA (eg, dairy products, salad dressings, cereals) can also provide reasonable intake to individuals not consuming seafood.[190] Compared with supplements, fish intake also provides potentially beneficial protein, vitamin D, and selenium.[121]

Commercial Preparation. Commercially-prepared fried fish meals from fast food restaurants or supermarket frozen sections[123,124] are often made using white-meat fish (lower in n-3 PUFAs)[27,123] and prepared with partially hydrogenated oils (containing *trans* fats) or oils reused for multiple frying cycles (introducing oxidative/deteriorative products[191]). Higher cardiovascular risk seen with fried fish intake[15,54,63,66] may relate to this unfavorable balance of benefit vs harm (lower levels of EPA and DHA; higher levels of *trans* fats/deteriorative products) or to residual confounding from other lifestyle factors. While further research is needed, it appears unlikely that most commercially prepared fried fish meals lower cardiovascular risk.

n6:n3 Ratio. Ecologic studies and limited animal-experimental data suggest that linoleic acid (18:2n-6) may counteract potential benefits of n-3 fatty acids,[192,193] but this hypothesis has not been supported by clinical trials or prospective studies in humans.[16,194] A much greater change in the dietary ratio of n-6 fatty acids to n-3 fatty acids can be practically achieved by increasing intake of n-3s (eg, going from no intake of oily fish to 1 serving/wk) compared with lowering intake of n-6s (which are widely consumed in cooking oils, salad dressings, and prepared foods). Thus, for most populations, attention to relative intakes of n-6 vs n-3 fatty acids may be less important than simply increasing n-3 intake.

Aquaculture. Concerns exist about sustainability of some aquaculture and

commercial fishing practices.[195-197] Conversely, aquaculture contributes to global fish production,[198] and sustainability concerns are not unique to aquaculture or fishing but also exist for agricultural, forestry, freshwater, atmospheric, and energy resources.[195,199,200] Some progress has been made, such as changes in fish feeds to reduce dependence on fish meal or oil.[195] Given the importance of n-3 PUFAs for health, balance must be achieved between environmental and economic concerns to allow sustainable, financially viable aquaculture and commercial fishing.[195,196,199]

Plant Sources. Alpha-linolenic acid (ALA) (18:3n-3) is an n-3 fatty acid present in flaxseed, canola, soybeans, and walnuts.[121] In humans, ALA is converted to EPA in small quantities (in women more than men); further conversion to DHA is very limited.[201] Consumption of ALA (eg, 2-3 g/d) may reduce cardiovascular risk[202] or affect neurodevelopment, but benefits are less established compared with those for EPA and DHA.

Optimal Intakes

Optimal intake of n-3 PUFAs may vary depending on population and outcome of interest. In the general population, 250 mg/d of EPA and DHA is a reasonable target intake to reduce CHD mortality. Because dietary n-3 PUFAs persist for weeks in tissue membranes,[203] this can be converted to a weekly intake of ≈1500-2000 mg. This corresponds to one 6-oz serving/wk of wild salmon or similar oily fish, or more frequent intake of smaller or less n-3 PUFA–rich servings (Table 2). For individuals with CHD, 1000 mg/d of EPA and DHA is currently recommended to reduce CHD mortality.[204,205] Our analysis suggests that lower doses may be sufficient, but given this population's higher risk and that most data are from primary prevention studies, a target intake of 500 to 1000 mg/d—consistent with the largest secondary prevention trial to date[9]—appears reasonable. This could be approximated by one 6-oz serving/wk of fish richest in n-3 PUFAs (eg, farmed salmon, anchovies, herring), more frequent consumption of other fish (Table 2), or supplements. Optimal intake levels for other clinical outcomes are not well established.

The effects, if any, of low-level methylmercury exposure in adults are not established; mercury may modestly reduce the cardiovascular benefits of fish intake. One can minimize concerns by choosing fish higher in n-3 PUFAs and lower in mercury or by simply consuming a variety of different seafood. Individuals with high consumption (≥5 servings/wk) should limit intake of selected species highest in mercury (Table 2).

DHA appears important for early neurodevelopment. Women who are or may become pregnant and nursing mothers should avoid selected species (shark, swordfish, golden bass, and king mackerel; locally caught fish per local advisories) and limit intake of albacore tuna (6 oz/wk) to minimize methylmercury exposure.[31,142] However, emphasis must also be placed on adequate consumption—12 oz/wk—of other fish and shellfish to provide reasonable amounts of DHA[31,142] and avoid further decreases in already low seafood intake among women (74% of women of childbearing age and 85% of pregnant women consume <6 oz/wk).[206,207]

Continued efforts to limit environmental contamination from organochlorine compounds are appropriate. However, levels of PCBs and dioxins in fish are low, similar to those in several other foods, and the magnitudes of possible risks in adults are greatly exceeded by benefits of fish intake and should have little impact on individual decisions regarding fish consumption (for locally caught freshwater fish, women of childbearing age should consult regional advisories).

CONCLUSIONS

Potential risks of fish intake must be considered in the context of potential benefits. Based on strength of evidence and potential magnitudes of effect, the benefits of modest fish consumption (1-2 servings/wk) outweigh the risks among adults and, excepting a few selected fish species, among women of childbearing age. Avoidance of modest fish consumption due to confusion regarding risks and benefits could result in thousands of excess CHD deaths annually and suboptimal neurodevelopment in children.

Author Contributions: Dr Mozaffarian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design; acquisition of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content: Mozaffarian, Rimm.
Analysis and interpretation of data; statistical analysis; obtained funding: Mozaffarian.
Administrative, technical, or material support; study supervision: Rimm.
Financial Disclosures: Dr Rimm reports that he has received research funding from Merck, Pfizer, and GlaxoSmithKline, and that he has received payment or honoraria for presentations about food and diets from the US Environmental Protection Agency, the US Food and Drug Administration, the Institute of Medicine, the Culinary Institute of America, the International Chefs Association, and academic conferences funded by Bunge and Unilever. Dr Mozaffarian reported no financial disclosures.
Funding/Support: This study was supported by National Heart, Lung, and Blood Institute, National Institutes of Health grant K08-HL-075628.
Role of the Sponsor: The National Heart, Lung, and Blood Institute had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.
Acknowledgment: We thank Ingeborg Brouwer, PhD, Wageningen Centre for Food Sciences, Wageningen, the Netherlands, for providing mortality results from the Study on Omega-3 Fatty Acids and Ventricular Arrythmia trial; Calle Bengtsson, MD, PhD, Cecilia Björkelund, MD, PhD, Lauren Lissner, PhD, and Valter Sundh, BSc, The Sahlgrenska Academy at Göteborg University, Gothenburg, Sweden, for providing results from their analysis of mercury and coronary heart disease in Sweden; and Walter Willett, MD, DrPH, Meir Stampfer, MD, DrPH, and Russ Hauser, MD, ScD, Harvard School of Public Health, Boston, Mass, for insightful comments. None of those acknowledged received compensation for their contributions.

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prevented the development of protective immunity. In another murine model, protective immunity was also inhibited by azithromycin.[9] Brunham et al[10] observed that while chlamydial sexually transmitted infections in Vancouver decreased substantially over a few years after an azithromycin treatment program began, they estimated that annual risk of re-infection increased by 4.6% thereafter.

Personal hygiene and environmental improvements have already eliminated blinding trachoma in developed and some developing countries. Emphasis should be placed on all SAFE components with further evaluation of the antibiotic component, longitudinal assessments of efficacy, and vaccine development for sustainability.

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Financial Disclosures: None reported.

1. West SK, Munoz B, Mkocha H, et al. Infection with *Chlamydia trachomatis* after mass treatment of a trachoma hyperendemic community in Tanzania: a longitudinal study. *Lancet*. 2005;366:1296-1300.
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CORRECTIONS

Citation Error: In the Original Contribution entitled "Impact of Annual Targeted Treatment on Infectious Trachoma and Susceptibility to Reinfection" published in the September 27, 2006, issue of *JAMA* (2006;296:1488-1497) page 1493 contained an error in the use of a citation. The sentence "Since the immune response to *C trachomatis* is usually sustained for only 1 to 4 months,[24] we reasoned that individuals with resolved infection (conversion of PCR-positive result to negative at a subsequent time point) would be susceptible to infection at the next time point, 6 months later" should read "Since the duration of *C trachomatis* infection is reduced in older age groups, presumably as a result of acquired immunity,[24] we reasoned that if the immune response is usually sustained for only 1 to 4 months, individuals with resolved infection (conversion of PCR-positive result to negative at a subsequent time point) would be susceptible to infection at the next time point, 6 months later."

Omitted Financial Disclosure Information: In the Clinical Review entitled "Fish Intake, Contaminants, and Human Health" published in the October 18, 2006 issue of *JAMA* (2006;296:1885-1899), financial disclosure information was omitted. The disclosure for Dr Mozaffarian should have read: Dr Mozaffarian reported that he has received honoraria for presentations or articles about fish or *trans* fat consumption & cardiovascular health from the Institute of Food Technologists, the Danish Nutrition Council, the American Oil Chemists' Society, Project Syndicate, and several academic medical centers.