BNL-77474-2007-IR

BROOKHAVEN NATIONAL LABORATORY

THE COMPETITION BETWEEN METHYLMERCURY RISKS AND OMEGA-3 POLYUNSATURATED FATTY ACID BENEFITS: A REVIEW OF CONFLICTING EVIDENCE ON FISH CONSUMPTION AND CARDIOVASCULAR HEALTH

F. W. Lipfert and T. M. Sullivan

Progress Report on Mercury Health Effects
Prepared for
the U.S. Department of Energy
National Energy Technology Laboratory

October 2006

Environmental Sciences Department
Environmental Research & Technology Division

Brookhaven National Laboratory
P.O. Box 5000
Upton, NY 11973-5000
www.bnl.gov

DISCLAIMER

Abstract

The health concerns of methylmercury (MeHg) contamination of seafood have recently been extended to include cardiovascular effects, especially premature mortality. Although the fatty acids (fish oils) found in most species are thought to confer a wide range of health benefits, especially to the cardiovascular system, some epidemiological studies have suggested that such benefits may be offset by adverse effects of MeHg. This comprehensive review is based on searches of the NIH MEDLINE database and compares and contrasts 145 published studies involving cardiovascular effects and exposures to mercury and other fish contaminants, intake of fatty acids including dietary supplements of fish oils, and rates of seafood consumption. Since few of these studies include adequate simultaneous measurements of all of these potential predictor variables, we summarized their effects separately, across the available studies of each, and then drew conclusions based on the aggregated findings. It is important to realize that studies of seafood consumption encompass the net effects of all of these predictor variables, but that seafood intake studies are rarely supported by human biomarker measurements that reflect the actual uptake of harmful as well as beneficial fish ingredients. As a result, exposure measurement error is an issue when comparing studies and predictor variables. It is also possible that the observed benefits of eating fish may relate more to the characteristics of the consumers than to those of the fish.

We found the evidence for adverse cardiovascular effects of MeHg to be sparse and unconvincing. Studies of cardiovascular mortality show net benefits, and the findings of adverse effects are mainly limited to studies Finland at high mercury exposure levels. By contrast, a very consistent picture of beneficial effects is seen for fatty acids, after recognizing the effects of exposure uncertainties and the presence of threshold effects. Studies based on measured biomarker levels are seen to be the most reliable and present a convincing picture of strong beneficial effects, especially for those causes of death involving cardiac arrhythmias. This conclusion also extends to studies of fish-oil supplementation.

Studies based on fish consumption show mainly benefits from increased consumption. This finding is supported by an ecological study at the national population level, for which the lifestyle effects that might be correlated with fish consumption within a given population would be expected to "average out" across nations.

Finally, the net survival benefits resulting from eating fish are consistent with studies involving complete diets, although benefits are also seen to accrue from reduced consumption of red meat and saturated fats.

The Competition between Methylmercury Risks and Omega-3 Polyunsaturated Fatty Acid Benefits: A Review of Conflicting Evidence on Fish Consumption and Cardiovascular Health

Frederick W. Lipfert, Ph.D.
Independent Consultant
Northport, NY 11768

Terrence M. Sullivan, Ph.D.
Deputy Division Head
Environmental Research and Technology Division
Brookhaven National Laboratory
Upton, NY 11973

1. Introduction

1.1 Background

Fish and seafood have long been recognized as important components of a healthy diet, including the "Mediterranean diet" that has been widely praised (American Heart Association, 2006; Kok and Kromhout, 2004). Survival benefits have been shown at the population level by comparing international statistics, and at the individual level through cohort studies. Recently, cautions have been raised because of the potential for adverse cardiovascular effects ascribed to methylmercury (MeHg), which is present at some level in all seafood, as are the polyunsaturated fatty acids (PUFAs) thought to confer cardiovascular benefits. Salonen et al. (1995a) pointed out that "epidemiological studies have a limited ability to distinguish the effects of beneficial and harmful substances in the same foodstuff." However, the correlation (R) between blood concentrations of these two agents is not very strong (for example, R=0.35, as reported by Sakamoto et al., 2004).

The specific PUFA compounds hypothesized to confer the most cardiovascular benefits have been identified as "omega-3" or "n-3", and these hypotheses have been tested with clinical trials of dietary supplements of fish oils. In order to allow consumers to choose wisely, it is important to balance these competing aspects of a seafood diet (Morrissey, 2006), and to recognize that other contaminants may be present in seafood, especially in farmed fish (Hayward et al., 2006).

Although mercury contamination of seafood has largely been addressed as originating from air pollution, it has important distinctions from those of inhaled pollutants. Methylmercury (MeHg) exposure is essentially limited to the dietary pathway, which means that exposure is largely voluntary and that substantial variations may be expected within any given population group. Fortunately, reliable biomarkers are available for individuals, such as the Hg content of blood, hair, or toenail clippings, which is not the case for most conventional air pollutants. Biomarkers for fatty acid intake are less readily available, and sampling may involve invasive procedures.

Another important distinction for the dietary exposure pathway is the necessity to consider an individual's entire diet, not just the intake rates of specific substances of interest. For example, people who rely heavily on seafood for protein may be less likely to consume red meat (Zhang et al., 1999), which has its own adverse health effects and for which biomarkers may be less available. In most developed countries, individuals consume a variety of seafood, comprising both fatty and lean species, so that statistics on overall fish consumption may be misleading. There is also evidence that nutrition may affect mercury toxicity (Clarkson and Strain, 2003). Studies of entire populations (i.e., ecological studies) will capture the net effects of entire dietary patterns, while cohort studies must control for these dietary correlates as possible confounders, often relying on personal dietary recall. The analysis of the Nurses Health Study cohort by Fung et al. (2001) recognized this and used factor analysis to synthesize two different dietary patterns, one of which was associated with significantly lower mortality.

1.2 Findings from Previous Reviews

The literature on the general topic of diet and health is quite extensive, including the various aspects of eating seafood. A search of PubMed for papers with "fish consumption" and "cardiovascular" in their titles or abstracts, limited to English language review papers based on human subjects, yielded 33 relevant review papers, beginning in the 1980s. However, only five of them also referred to mercury or methylmercury, indicating that this notion of competing risks and benefits is relatively recent (since

~2003). By the same token, the National Research Council's 2000 monograph on the toxicological effects of methylmercury devoted only 4 of its 344 pages to human cardiovascular effects.

The epidemiological literature on Hg toxicity tends to be diverse and contradictory; Jacobson (2001) proposes some criteria for evaluating conflicting observational studies and points out that there is often "limited control over confounding and other factors." For example, only a few of the published studies on cardiovascular effects have devoted the same care to assessing exposures to both MeHg and PUFAs. Other important dietary elements and other fish contaminants have been largely neglected in observational studies. There are perhaps an order of magnitude more published papers on fatty acids in general and on marine fatty acids in particular, but only a few deal specifically with both MeHg and the fatty acids found in fish. Even fewer studies include other fish contaminants such as Pb or PCBs.

The overall conclusions of recent review papers vary. Systematic reviews and meta-analyses of dietary supplements of fish oils are discussed below (Section 3.3). Levenson and Axelrad (2006) support the cardioprotective role of n-3 fatty acids, but caution that the methylmercury in some types of fish could attenuate those benefits. They note that the literature is conflicting, but emphasize the most recent report on a cohort from eastern Finland (Virtanen et al., 2005) as "specifically designed to address this controversy." They recommend using an index of the ratio of fatty acids to mercury content as a guide to selecting the "best" fish species; salmon is the clear winner on this basis, with whiting, flounder, and pollock as much less desirable. They do not specifically discuss the fresh-water predatory fish species consumed by the Finns upon which their cautionary study is based or the importance of absolute levels of fish oil and fish contaminants in causing effects.

Virtanen et al. (2005, in press) review studies of the relationships between Hg and adverse cardiovascular disease (CVD) effects, with an emphasis on the four publications from the Finnish cohort study. The mercury intake for these subjects was primarily from fresh-water species, but no other contaminants were considered. They discuss potential cardiovascular mechanisms and call for further studies, in part to examine whether there may be other correlated CVD risk factors confounding the observed Hg effects. They discuss the possibility of a threshold for Hg-cardiovascular effects, but conclude that the extant data are not sufficient to define it. The possibility of a PUFA threshold was not mentioned.

Konig et al. (2005) performed a meta-analysis of fatty-acid benefits and derived an overall dose-response relationship for coronary heart disease mortality (CHD). However, they declined to extend this paradigm to methylmercury risks, because the "available literature was judged inadequate for quantitative analysis." Part of the reason for this conclusion was the variety of Hg exposure metrics used in the various Hg studies; they made no effort to convert these data to a common metric. There are also issues of nonlinearity (adverse effects at high doses). Subsequent correspondence on this paper raised the question of other fish contaminants, especially in farmed species such as salmon (Foran et al., 2005).

Van Oostdam et al. (2005) present an extensive review of various contaminants in the Canadian Arctic diet and conclude that cultural values must also be considered when dietary changes are recommended. However, this review did not discuss possible offsetting benefits of PUFAs. Hansen and Gilman (2005) contrasted Hg and PUFA effects but did not mention the other contaminants.

Matthan et al. (2005) reviewed selected animal studies of omega-3 supplementation and concluded that fish oils protect against arrhythmias, but that α-linolenic acid (an omega-3 PUFA derived from plants) does not.

Mahaffey (2004) discusses the benefits of fatty acids in fish and the risks of methylmercury (emphasizing neurological effects) and provides some useful data on the relative contents of each for various fish and shellfish species (marine species only). She also recommends that other fish contaminants like dioxins and pesticides be considered.

Calder (2004) reviews fatty acid and fish oil studies involving both mortality and cardiovascular events as endpoints, without discussing the potential problems of fish contaminants. This approach was also taken by the Holubs (2004). Calder discusses potential mechanisms for the benefits of fatty acids, and the Holubs point out that the average intake of fatty acids in the U.S. population is well below recommended guidelines.

Chan and Egeland (2004) emphasized studies suggesting that Hg exposure may attenuate the protective effect of fatty acids. They point out that autopsy evidence of Hg accumulation in the heart supports this hypothesis, but that some studies conflict and some suggest an Hg exposure threshold for cardiovascular effects (Frustaci et al. [1999] also reported high levels of Hg in the heart muscles of some cardiac patients).

Kris-Etherton et al. (2003) present an "American Heart Association Scientific Statement" that recommends eating oily fish at least twice a week, but urge caution with respect to contaminants like PCBs and Hg. PCB exposures can be reduced by removing the fish skin and fat before cooking. Mercury content relates to the type of fish; guidelines are available for pregnant women and young children. They conclude that "Consumption of a wide variety of species within the guidelines is the best approach to both minimizing mercury exposure and increasing omega-3 fatty acid intake."

Castoldi et al. (2003) review the neurotoxic effects of MeHg, without mentioning cardiovascular effects, and discuss oxidative stress as an important mechanism. Marckmann and Gronbaek (1999) performed a systematic review of 11 studies of coronary heart disease mortality and concluded that benefits of fish consumption were limited to high-risk populations.

Nakai and Satoh (2002) review neurological effects of fish contaminants, including an extensive discussion of PCBs, which they conclude should be considered in parallel with MeHg. PCB exposures and health effects are reviewed in detail by Carpenter (2006).

In summary, these reviews shed little light on the basic question on whether eating fish is likely to improve health and survival, in part because they do not cover the full range of exposure issues.

1.3 Measures of Effect

Burger et al. (2003) showed that the absolute quantity of Hg in fish is relatively constant during frying, but that the concentrations are higher on a dry weight (cooked) basis than for raw fish (wet weight basis). Thus, there may be uncertainties about actual intake doses when based on fish consumption frequencies alone.

Most of the extant epidemiological literature has been concerned with testing hypotheses, as to whether or not a specific agent may in fact exhibit the hypothesized effect (yes/no). For observational studies, a common approach has been to divide the observations into equally-sized groups (n-tiles. where n is usually from 3 to 6, i.e., tertiles to sextiles). Many authors then use the most-exposed group to test the hypothesis of whether the hypothesized effect exists (i.e., is statistically significant relative to the lowest exposure group), essentially ignoring the information implied by the relative risks shown for the intermediate n-tile groups. Also, it may be problematic to compare such findings across groups of studies with very different exposure levels. Since extreme exposures may be required to successfully test these "existence" hypotheses, this information may not always be relevant to less-exposed populations or situations. A dose-response relationship across all the n-tiles may thus be more useful, once the hypothesis of causality has been accepted (if only tentatively).

Comparing the observational cohort studies of seafood, MeHg, and PUFA effects requires a way to compare the various types of exposures used, which include measured levels in blood or adipose (fat) tissue as well as estimates based on diet. One way around this obstacle is to compare the slopes of dose-response functions based on logarithmic-transformed (log-log) regression models of relative risks or odds ratios across the various n-tiles. This linearization paradigm ignores the statistical significance levels of individual n-tile estimates, which are affected by sample size and the range of exposures, and focuses on the relative magnitudes of the effects across the entire range of exposures. The slope of a log-log model is independent of the units of exposure measurement and corresponds to the *elasticity* metric used by economists (Lipfert, 1994). For example, a log-log slope of 1.0 implies a directly proportional 1:1 relationship, such that the predictor accounts for all of the variability in the endpoint. A log-log slope of –0.10 indicates that for each 10% increase in the predictor variable, the dependent variable decreases by 1%. This paradigm is used to compare some of the various dose-response relationships implied by the studies considered. However, complications may arise when a threshold is observed (RRs for intermediate n-tiles = ~1.0).

By way of comparison, Stampfer et al. (2000) present n-tile risk data for the Nurses Health Study for some of the major coronary risk factors, which we converted to log-log slopes: body-mass index, 0.88 (this is an example of a predictor with a definite "background" level); smoking, about 0.31; diet score, -0.35; exercise, -0.13; and alcohol consumption, -0.074.

1.4 Plan of This Review

Table 1 depicts a somewhat tautologic outline for the evaluation of evidence relating to this topic, including the most general types of epidemiological studies (national death rates vs. national fish consumption levels, for example) as well as more specific types of cohort studies in which very detailed data on exposures and outcomes are often available. The table indicates that there are a number of possible

reasons for a false indication of "no beneficial effect" but only one general reason for a beneficial indication: confounding by correlated lifestyle or dietary factors other than eating fish. We intend to evaluate all of these alternative hypotheses in this review. Of course, in any epidemiological study, a true effect may be obscured by imprecise or inappropriate measurements. When two or more correlated causal factors are considered jointly (for example, Hg and PUFAs), those with the more accurate and precise measurements are likely to prevail (Lipfert, 1997). Thus, exposures based on measured biomarker levels would be preferable to those based on estimated dietary intake rates.

Table 1 Alternative Hypotheses for Consideration

Observation: "Is Eating Fish Indicated to Improve Health and Survival?"

A. Yes	**B. No**
A1. Other associated diet or lifestyle factors are responsible. (examples: eating less red meat, drinking alcohol, exercising more)	B1. Study has insufficient statistical power (random variation)
A2. Eating fish is truly beneficial	B2. Fish consumption data are flawed.
A2a. because of PUFAs A2b. because of other fish nutrients A2c. because other contaminants don't matter A2c1. their concentrations are too low A2c2. their effects are truly benign.	B3. Insufficient fish consumption B4. Confounding from other factors
A3. An ecological fallacy is present (ecological studies only)	B5. Inappropriate health endpoint B6. Results are limited to a specific cohort. (because of genetics or pre-existing disease)
	B7. Because of specific types of fish eaten B7a. low PUFA levels B7b. other fats (fried fish) B7c. high Hg levels B7d. other fish contaminants B7e. harmful ingredients in specific types of fish.
	B8. An ecological fallacy is present (ecological studies only

The "ecological fallacy" referred to in Table 1 is a well-known weakness of studies based on population groups rather than individuals: although a group-average risk may be associated with risk factors averaged across groups, such a relationship may not always apply to individuals within the groups.

In this paper, we summarize relevant portions of the extant literature and compute some additional statistics to facilitate comparisons across studies. We consider the literature in several categories:

- Studies of (adverse) mercury health effects (Section 2)
- Studies of (presumably beneficial) effects of fatty acids, mainly n-3 PUFAs (Section 3)
- Studies of seafood consumption per se, which presumably encompass both types of effects, including ecological studies of national populations (Section 4).
- Studies of overall diets and dietary interventions (Section 5).

The review emphasizes various cardiovascular end points including mortality, as well as mortality from any cause. The concluding discussion (Section 6) includes the overall implications with respect to the U.S. population. An Appendix defines abbreviations and notations used in the tables and text.

2. Studies of Mercury and Cardiovascular Health Effects

2.1 Definitions and Measurements

Almost all of the mercury in fish is in the form of methylmercury (MeHg), so that the exceptions in this section are identified as elemental or inorganic Hg. The preferred exposure metrics are Hg in head hair (ppm or μg/g) or blood (μg/L), to facilitate comparisons with existing data bases. The ratio between MeHg in hair (ppm) and in blood (μg/L) is about 250.

Two of the larger studies of acute events (Guallar et al., 2002, Yoshizawa et al. 2002) used toenail clippings to estimate exposures instead of the more common head hair metric. To convert the toenail values to a basis of head hair, we rely on two case-control studies of dental workers. Since such workers may be inordinately exposed to inorganic Hg from dental amalgams, we used data on the non-dentist "control" subjects in these studies. Ritchie et al. (2002) report mean toenail clipping and head hair levels of 0.24 and 0.57μg/g respectively, for a ratio of 0.42. Morton et al. (2004) report levels of 0.18 and 0.40, for a ratio 0f 0.45. We use the average of these two estimates to convert toenail Hg data to a head-hair basis (0.6 and 1.0 μg/g for the Guallar and Yoshizawa studies, respectively). For reference, the median and 95th percentile hair Hg levels in the U.S. are about 0.2 and 1.6 ppm, respectively (McDowell et al., 2004).

2.2 The Extant Literature on Cardiovascular Effects of Mercury

Table 2 summarizes eight epidemiological studies of cardiovascular health effects as a function of mercury exposures, seven of which involve European subjects. The effect estimates shown are "fully adjusted" for confounders. The paper of Ahlqvist et al. (1999) reported only *p*-values and the signs of correlations, which precludes making estimates of the avoided deaths. The only American study involved male health professionals, including dentists. This group of studies exhibits very mixed results, most of which showed non-linear responses, so that higher relative risks (RRs) were often seen at exposures greater than the mean values shown in the Table. The responses also vary by end point; the risks for non-fatal cardiac events (denoted with asterisks) tend to be positively associated with mercury exposures (negative "avoided" events) while cardiovascular mortality tends to be negatively associated (positive avoided deaths).

Table 2 also provides estimates of the "avoided deaths", defined as (1-RR)*total deaths for each cause; this facilitates consideration of the additional deaths involved in successively broader cause-of-death categories. For example, in the latest paper on the Finnish cohort study (Virtanen et al., 2005), cardiovascular causes account for all of the all-cause deaths ascribed to mercury exposure, while this is (apparently) not the case for the occupational study of Boffetta et al. (2001). We then summed these incremental death counts across studies and divided by the total deaths to provide weighted-average estimates of the mean relative risks (Table 3). The implications of the small additional risks of all-cause mortality and CVD events are unclear but could be the result of random variation (there are too few studies to permit meaningful statistical significance tests).

Boffetta et al. studied mercury mine and mill workers, whose (inorganic Hg) exposures are orders of magnitude higher than those of the general public (Kingman et al., 1998). Note the small number of hypertension deaths (Hg effects on blood pressure are discussed below) and the absence of significant cardiovascular effects in these highly exposed workers.

Table 2 Mortality and Cardiovascular Events as a Function of Mercury Exposure (RRs at mean consumption levels)

1st author, yr	period	location	cause of death	group	# subjects	# events	mean fish meals/wk	mean Hg	estimated mean RR	avoided events	remarks
Ahlqvist,1999	1974-93	Sweden	all	women	1397	253	n/a	n/a	negative correlation	n/a	
Boffetta, 2001	1950-90	Europe	all	Hg workers	7049	2749	n/a	~300U	1.08+ (1.04-1.12)	-220	not adjusted
			hypertension			49			1.4 (0.3-6)	-20	for confounders
			IHD			259			0.9 (0.5-1.6)	26	
			CVD			261			0.7 (0.4-1.4)	78	
			other heart			271			1.1 (0.6-2.0)	-27	
Guallar, 2002	1991-2	Europe + Israel	acute MI*	males	1408	684	n/a	0.26T	1.18 (0.67-2.07)	-123	
Hallgren, 2001	1985-94	Sweden	acute MI*	volunteers	234	78	~1.5	~0.6H	0.91 (0.49-1.69)	7	
Rissanen, 2000	1984-97	Finland	acute CHD*	males	1871	194	~2.0	1.82H	~1.4	-26	
Salonen, 1995	1984-89	Finland	all	males	1833	78	~2.0	1.92H	1.17 (1.006-1.39)	-13	
			CHD			18			1.44 (1.08-1.92)	-8	
			CVD			24			1.32 (1.03-1.70)	-8	
Virtanen, 2005	1984-98	Finland	all	males	1871	525	~2.0	1.8H	0.92 (0.71-1.19)	42	
			CHD			91			0.61 (0.34-1.10)	35	
			CVD			132			0.66 (0.41-1.07)	45	
			acute event*			282			1.07 (0.77-1.49)	-20	
Yoshizawa,2002	1986-91	all US	CHD cases	male health professionals	33737	470	~1.3	0.45T	0.83 (0.53-1.30)	22#	
Yoshizawa,2002	1986-91	all US	CHD cases	w/o dentists		220	~1.3	~0.33T	1.70 (0.78-3.73)	-154#	

* first-ever heart attacks (not deaths)
H = hair level, μg/g; T = toenail level, μg/g; U = urinary level (inorganic Hg), μg/L
# based on nonlinear relationship
+ Standardized mortality ratio (Hg exposure data not provided)

The study of Guallar et al. includes cohorts from 8 European countries (two from Spain), plus one from Jerusalem, Israel (from the EURAMIC study). The range of estimated individual head hair Hg levels was from 0.18 to 1.8 for the controls and 0.21 to 2.5 for heart attack patients. However, by cohort, only one showed significantly higher mean Hg exposures for patients than for controls (Malaga, Spain), which also had the highest Hg levels, and the exposures of patients were significantly higher than for controls, by 15%, after adjustment for confounders. Other EURAMIC papers provide other cohort data, for toenail Se (Kardinaal et al., 1997) and fatty acids (Guallar et al., 1999). Cross-plots of these exposure data by cohort (Figure 1a,b,c) show the Spanish Hg data to be outliers (high levels) with respect to the data for Se and for fatty acids, all of which presumably derive mainly from eating fish. Dropping the two Spanish cohorts would appear to render the Hg-heart attack relationship non-significant, on the basis of mean cohort levels. Both of the Spanish cities are on the Mediterranean Sea; perhaps other dietary components played a role (no fish consumption data were provided). Chan and Egeland (2004) also discuss this aspect of the EURAMIC cohort study. Welch et al. (2002) provide data on fish consumption for 10 European countries by type of fish and noted that consumption of fatty fish seems to follow that of total fish. Intake of fatty fish was highest in northern European coastal areas with lean fish predominating in France, Italy, and Spain.

The relative risks for mercury exposures in the Finnish cohort study (Salonen et al., 1995b; Rissanen et al., 2000; Virtanen et al., 2005) have decreased over time. The most recent paper (Virtanen et al., in press) is based on ~14 years of follow-up and shows negative mortality effects at the mean exposure levels (middle tertile), but stronger positive effects at the highest exposure levels, yielding an overall adverse effect of mercury exposure.

It is perhaps unfortunate that the only U.S. study included a high proportion of dentists (~50%); Yoshizawa et al. reported that when the dentists were excluded from the analysis, the risk of CHD associated with Hg exposure (presumably from fish) was positive but not significant (median risk level not reported). Also, the results of Yoshizawa et al. imply that controlling the Hg analysis for PUFA intake tends to slightly increase the estimated Hg risks. Excluding the dentists from the RR summary above would have resulted in a stronger adverse effect of Hg exposure on non-fatal CHD risks. This finding, together with the results of Bofetta et al. suggests major differences in the cardiovascular effects of organic (MeHg) and inorganic mercury exposures.

In summary, the main evidence for adverse effects of MeHg exposure on cardiovascular health comes from the Finnish cohort studies, which suggest a hair Hg threshold of about 2 ppm.

Table 3 Mean Relative Cardiovascular and Mortality Risks from Mercury

(Based on Table 2)

Cause of Death	Avoided deaths/ Total deaths	Avg Relative Risk
All causes (3 studies)	-101/3352	1.06
CHD, IHD mortality (3 studies)	53/368	0.86
CVD mortality (3 studies)	115/417	0.72
CVD events or cases (5 studies)	-140/1748	1.08

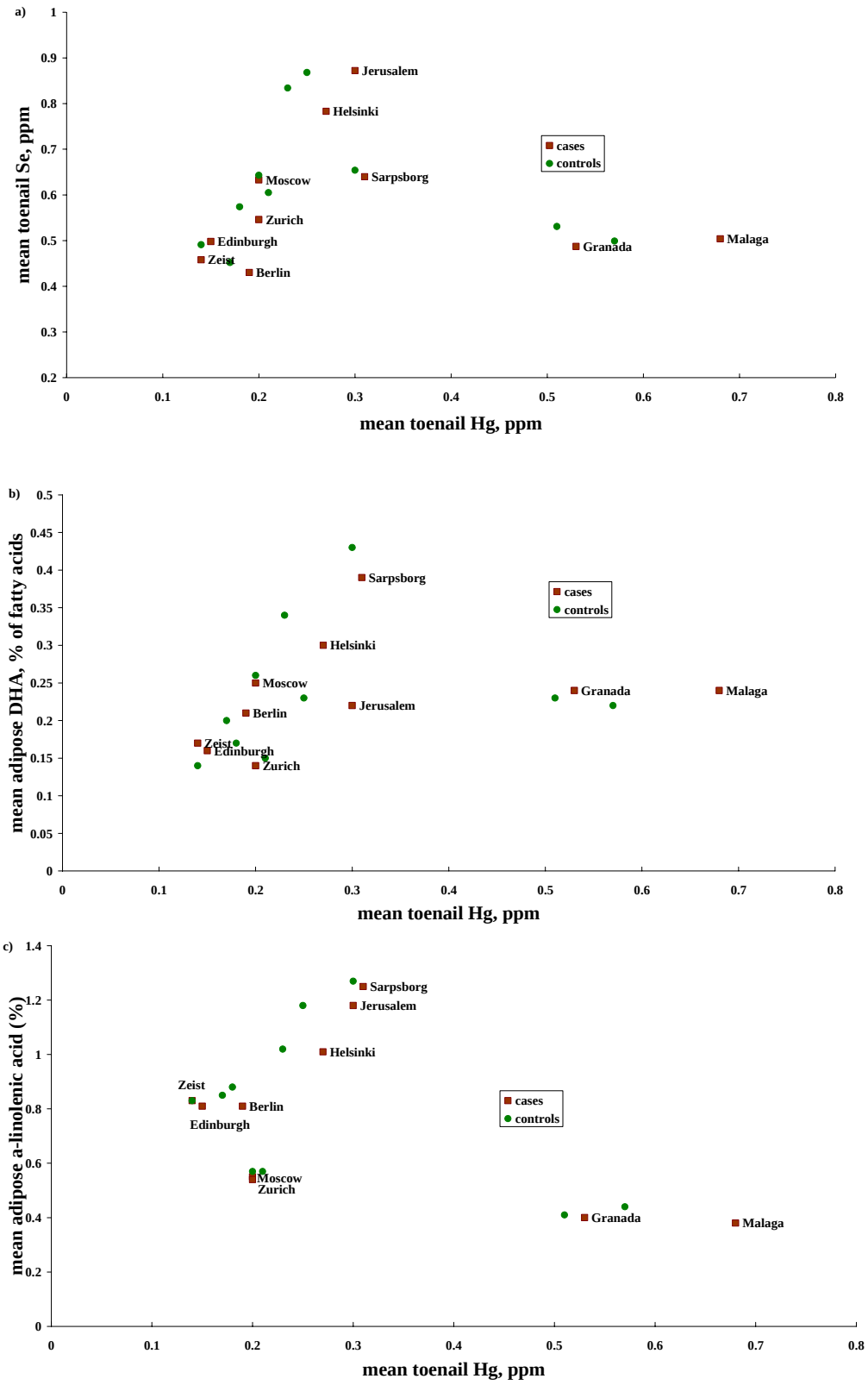

Figure 1 Biomarker data from the EURAMIC study by cohort, for cases and controls. (a) Toenail Se. vs. toenail Hg. (b) Adipose DHA vs. toenail Hg. (c) Adipose ALA vs. toenail Hg.

2.3 Other Health Effects of Methylmercury

The literature includes epidemiological studies of health endpoints other than mortality, some of which are briefly summarized in this section. However, since the extant neurological studies are well-known, only recent papers on that topic have been included.

2.3.1 Blood Pressure. Blood pressure effects have been examined in several papers. An early study of dietary fats (Margolin et al., 1991) showed that dietary supplements of both fish oil and corn oil reduced blood pressure significantly after 8 weeks of treatment in elderly hypertensive patients. However, Morris et al. (1993) found no significant effect of fish oil on 18 healthy subjects, as did Rasmussen et al. (2006) in a larger study of 162 subjects. A subsequent meta-analysis (Morris et al., 1993) confirmed that blood pressure reduction by fish oil is strongest in subjects with hypertension or coronary heart disease.

Vupputuri et al. (2005) linked NHANES mercury exposure data with blood pressure in 1240 U.S. women, by fish consumption. There were no relationships with diastolic blood pressure, but systolic pressure increased significantly with blood Hg for non-fisheaters and decreased (non-significantly) for fish consumers, with no overall association. Fish consumption per se was controlled for in the analysis of fish eaters. The authors concluded that their findings support the hypothesis that fish oils may counter the harmful effects of mercury. In this sample, 97% of the inorganic Hg samples were below the detection limit, which leaves open the question of differences between Hg compounds.

Pedersen et al. (2005) compared blood pressure and blood mercury levels in Greenlanders and Danes (n=198), over a much wider range of mercury exposures. The most consistent finding was that of a significant increase in pulse pressure (systolic less diastolic pressures) with increased blood mercury. However, Jorgensen et al. (2002) had concluded that a portion of this increase could have been due to genetic factors. The rate of increase was about the same as that reported by Vupputuri et al. for systolic pressure, which amounts to a mean blood pressure effect for the U.S. population of only a few mmHg. Pulse pressure is regarded as an indicator of arterial stiffness (de la Sierra, 2006).

Blood pressure data were obtained from native peoples in the Amazon rain forest, where fish is an important part of the diet (Dorea et al., 2005). Average hair Hg (2.5 to 12.8 ppm) increased with mean fish consumption (22 to 110 g/d), but there were no neurological indications of Hg poisoning. For the total group, hair Hg was not significantly associated with increased blood pressure, but the high Hg exposure group had a stronger blood pressure increase with age. The authors concluded that access to medical care was far more important for these populations than any effects from mercury in fish.

Barberger-Gateau (2005) reported that elderly "regular" (at least weekly) fish eaters in France were more likely to suffer from hypertension, but blood pressure data were not provided.

Sorensen et al. (1999) reported that both diastolic and systolic pressures increased with Hg exposures in 7-y old Faroese children who had been exposed prenatally, but only at the low end of the exposure scale. There was no effect above about 2 ppm maternal hair concentration; this might be another manifestation of interaction between Hg and PUFA, since the most highly exposed Faroese also consume fatty marine mammals. Grandjean et al. (2004) examined these children at age 14 and concluded that there was "no discernible effect" on blood pressure.

In summary, the evidence for increased blood pressure due to fish consumption is scant. No study has controlled for all of relevant dietary variables (such as red meat, for example). Any such adverse effects of Hg in the U.S. population are likely to be small and of doubtful clinical importance.

2.3.2 Autonomic Control. Reduced heart rate variability (HRV) is another indicator of potential cardiovascular risk. Grandjean et al. (2004) found decreases associated with prenatal Hg exposures in 14-y old Faroese children. Oka et al. (2002) examined blood pressure and HRV in 9 patients who had been diagnosed with fetal type Minamata disease, which involved very high exposures to MeHg, but probably normal levels of PUFA. They found indications of reduced HRV but also lower pulse blood pressure. Christensen (2003) reports a positive correlation between HRV and PUFA and also increases in HRV in response to supplemental PUFA. Murata et al. (2006) examined the effects of prenatal exposure to MeHg in 136 Japanese schoolchildren, age 7. Umbilical cord tissue MeHg was significantly associated with decreased HRV while current hair Hg was not. The authors concluded that postnatal exposures less than 4 ppm MeHg in hair may not influence cardiac autonomic function.

The effect of fish consumption on heart rate was examined by Dallongeville et al. (2003) in 9758 men from France and Northern Ireland. A highly significant negative association was found, after confounder control, with an average slope of –0.75 beats/min per weekly fish meal. However, according to

the Paris mortality data of Jouven et al. (1999), such a small effect corresponds to a decreased risk of sudden death of about 1% and of fatal heart attack, about 1.5%. Given the much larger relative risks seen in Table 2, there must be factors other than heart rate involved. Mozaffarian et al. (2006) also found that heart rate decreased with consumption of (non-fried) fish, with a slope of –0.5 beats/min per weekly fish meal, even though there was slightly higher prevalence of CHD among frequent fish eaters. Other electrocardiographic parameters were also reported to vary with fish consumption, some of which are consistent with improved survival.

Romieu et al. (2005) examined the effect of fish oil supplements on HRV responses to ambient $PM_{2.5}$ air pollution in Mexico City, for 50 elderly nursing home residents. Fish oil was contrasted with soy oil; both were found to be significant attenuators of air pollution effects on HRV, with fish oil somewhat better than soy oil. These findings suggest interactions between dietary and inhalation exposure pathways.

Taken together, these studies do not support adverse effects of either fish consumption or modest levels of Hg exposure on cardiac autonomic control.

2.3.3 Mercury and Development of Atherosclerosis. Salonen et al. (2000) measured carotid artery intima-media thickness in 1014 Finnish males and found a relationship with hair Hg levels in the range 2.8 - 23 ppm (but not below this level). This suggests that Hg accumulation may be associated with accelerated progression of atherosclerosis. By contrast, Erkkila et al. found that higher levels of fish intake (2004) and plasma DHA (2006, in press) were associated with less progression of atherosclerosis in postmenopausal women. Also, Sacks et al. (1995) reported no effect of fish oil supplementation for 2 y arterial narrowing, in spite of higher adipose EPA levels in the treatment group/

2.3.4 Recent Papers on Neurobehavioral Function. Debes et al. (2006) reported on the 14-y follow-up of the Faroese children, in which neurological responses were deemed to be consistent with previous evaluations where some effects were found. (The median exposure level is about 16 μg/L as maternal blood Hg.) This may imply extension of these effects into adulthood.

By contrast, Davidson et al. (2006) performed a longitudinal analysis of repeated IQ evaluations of individual Seychelles children and found no significant associations with prenatal exposures to MeHg. Their consumption of ocean fish is an order of magnitude higher than typical levels in the United States.

A new birth cohort study of 599 pregnant women has begun to produce results in Japan (Nakai et al., 2004; Suzuki et al., 2006). Among several developmental tests, infants showed adverse effects associated with maternal hair Hg levels (mean=2.2 ppm) but beneficial effects associated with maternal fish consumption (mean=69 g/d). Data on PCB exposures were also collected but have not yet been analyzed.

Weil et al. (2005) studied a random cohort of adults in Baltimore, whose median blood Hg level was 2.1 μg/L, which is at about the 80^{th} percentile of the NHANES survey child-bearing aged U.S. women (Jones et al., 2004). Neurological test results for the Baltimore cohort were mixed, and the authors concluded that their results "do not provide strong evidence that blood mercury levels are associated with worse neurobehavioral performance...". These results could then be viewed as also implying the absence of effects of childhood/prenatal exposures.

Daniels et al. (2004) examined a cohort of 7421 British children, comparing two measures of neurodevelopment (at 15 and 18 months of age) against fish consumption and umbilical cord tissue concentrations of total Hg (in a subset of 1054 children). They concluded that total Hg concentrations were low and not associated with neurodevelopment and that moderate fish intake is associated with *in*creased development. However, the umbilical cord Hg levels were about half of those seen in the Faroes (Grandjean et al., 2005), and thus are not "low" in the context of the U.S. population.

Jedrychowski et al. (2006) examined the blood mercury levels of nonsmoking mothers of 233 Polish 1-y old infants and found a significantly lower mean level in mothers of normal infants relative to mothers of infants with delayed neurocognitive performance. However, the analysis seems to focus on the mean exposure differences between the 197 infants with "normal" performance" and the 36 infants with "delayed" performance, and it is not clear if or how confounders such as maternal age (higher in the "delayed" group) or birth weight (lower in the "delayed" group) may have been controlled. The amounts of developmental delay were not discussed.

Blood Hg levels in this Polish cohort are low (0.5-0.8 μg/L). A review of the worldwide literature on "normal" levels (without occupational exposure) reported a mean blood Hg level of 2.0 μg/L based on six studies of non-fisheaters, increasing to 4.8, 8.4, and 44.4 μg/L for those consuming <2, 2-4, and >4 fish meals per week (up to 10 studies), respectively (Brune et al., 1991). For U.S. women of childbearing age,

the 1999-2000 median blood Hg levels with and without fish consumption are 0.8 and 2.3 μg/L, respectively (Vuppituri et al., 2005). This suggests that agents other than MeHg may have been involved in the Polish study.

The question of linkage between Hg exposure and adult dementia has been debated for some time. Originally, the primary suspect was inorganic Hg, in relation to dental amalgam, for example (Schurrs and de Wolff, 1997; Saxe et al., 1999; Ely, 2001; Mutter et al., 2004; Mutter and Nauman, 2005). With respect to possible contributions from MeHg, Morris et al. (2003) followed 815 elderly subjects for four years and found that the risk of developing Alzheimer's disease was 60% less in those who ate fish at least once per week, after adjusting for confounders. Engelhart et al. (2002) found no significant effects of various types of dietary fats (including n-3 PUFAs) on the risk of dementia, while Kalmijn et al. (2004) found that, among 1613 middle-aged subjects, fatty fish and the associated PUFAs were associated with decreased risks and cholesterol and saturated fats were associated with increased risk of impaired cognitive function. Barberger-Gateau (2002) also found a significant decrease in the incidence of dementia among 17674 elderly French subjects who ate fish or seafood weekly. Thus, it appears to be important to distinguish between inorganic Hg and MeHg exposures with regard to cognitive effects in adults.

In summary, a wide range of responses still characterizes the effects of prenatal exposures to MeHg, which seem to be stable over time in the affected children. However, there is no credible evidence for neurological effects of MeHg on adults.

3. Health Effects of Polyunsaturated Fatty Acids (PUFAs)

3.1 Introduction

The literature on PUFAs is quite extensive and will not be discussed in detail here (about 7000 entries in MEDLINE for omega-3 fatty acids). It includes observational studies in which PUFA intake is estimated based on consumption frequencies of foods containing PUFAs, intervention studies in which either fatty-fish diets or fish-oil supplements are instituted, and studies of PUFAs as therapy for cardiac victims. Although the totality of all studies is not unanimous in finding benefits, the weight of evidence was sufficiently convincing that the American Heart Association (Kris-Etherton et al., 2003) recommended a daily diet that contains 650 mg of PUFAs, which is considerably higher than the current level of 100-150 mg/d (Holub and Holub, 2004).

PUFAs have been associated with the following health effects:

- reduced likelihood of diabetes (Haag and Dippenaar (2005).
- a small mean increase (0.13 points) in child IQ (Cohen et al., 2005).
- triglycerides, cholesterol, platelets, inflammation, oxidative stress (Mori and Beilin, 2004).
- increased heart rate variability (Holguin et al., 2005; Christensen, 2003).
- reduced heart rate (Dallongeville et al., 2003; Mozaffarian et al., 2006).
- large reductions in the risk of sudden death (Albert et al., 2002; Marchioli et al., 2002).
- reduced mortality from various causes (Dolecek, 1992).
- reduced risk of nonfatal heart attack (Tavani et al., 2001; Lemaitre et al., 2003).
- reduced risk of fatal ischemic heart disease (Lemaitre et al., 2003).
- reduced risk of adult dementia (Engelhart, 2002; Kalmijn et al., 2004.

Other effects inferred from fish consumption include:

- reduced development of allergic diseases in childhood (Kull et al., 2006).
- reduced progression of atherosclerosis (Erkkila et al., 2004).

However, no significant effects of fish oil on ventricular tachyarrythmias and death were reported by Brouwer et al. (2006). Burr et al. (2003) reported that 3114 male angina patients showed no benefits from dietary intervention, including either fish or fish-oil capsules; the group given the capsules showed an increase in cardiac deaths. In the same research group, Ness et al. (2002) reported that, among 2033 men who had survived a previous heart attack, short-term (< 2 y) benefits from eating more fish were shown, but there was no significant long-term benefit (adjusted RR = 0.95 [0.85-1.07].

3.2 Definitions, Exposure, and Effect Estimates.

The "marine" PUFA fatty acid compounds referred to as long-chain omega-3 (n-3) include eicosapentaenoic (EPA), docosahexaenoic (DHA), and docasapentaenoic (DPA) acids, extracts of which are often called "fish oil" and are commercially available as dietary supplements. A non-marine n-3 fatty acid, α-linolenic acid, derives from vegetable oils and is an essential nutrient. Vegetable oils (corn, sunflower, soybean, and safflower oils) are enriched in omega-6 (n-6) fatty acid, known as lineolic acid, which has generally shown lesser cardiovascular benefits (Holub and Holub, 2004).

Most of the extant studies have synthesized their exposure estimates, based on food frequency data and the PUFA contents of typical foods. Others have measured PUFA levels directly, either in blood or in adipose tissue samples. Because of potential differences in metabolic processes, it would appear that the measured PUFA data would be more accurate and thus to be preferred. For randomized control trials (RCTs) of supplemental fish oils, the putative doses are known, but the degree of subject compliance with the intervention regimen during long trials may be an issue.

The available exposure data show a potentially important difference between exposures based on intake estimates and those based on biomarkers. The intake estimates are basically analogues of food (especially fish) consumption, such that the exposure of the reference or control group is essentially nil. This is also the situation with respect to RCTs of supplemental doses. However, biomarker data usually show appreciable (background?) levels of PUFAs for these reference or control groups (Welch et al., in press; Siscovick et al., 2000; Pedersen et al., 2000). Thus, questions arise as to whether the relative magnitudes of these background levels might be important and whether they in fact constitute thresholds. In the latter scenario, PUFA levels below the putative threshold could result in failure to find health benefits of fish consumption or supplemental fish oils. This hypothesis is supported by the findings of Wallace et al. (2003) of a threshold in the effect of EPA+DHA intake on decreased interleukin-6 production, of Fernandez-Jarne et al. (2002) and a threshold in the relationship between fish intake and heart attacks, and of the conclusion of Alonzo et al. (2003) that the epidemiological literature suggests threshold effects.

3.3 Observational Epidemiology Studies.

The Multiple Risk Factor Intervention Trial (MRFIT) analyzed the effects of various types of PUFAs in detail with respect to mortality from various causes in the control group (no intervention) of white middle-aged men at high risk of developing CHD (Dolecek, 1992; Dolecek and Grandits, 1991). The most consistent mortality benefits were seen with marine (n-3) PUFA compounds, which comprised only a small portion of the total PUFA intake (175 mg/d). Only the quintile with the highest intake (664 mg/d) showed significant mortality benefits, for all causes, CHD, and CVD (but not for cancer), suggesting a threshold effect. No data were provided on rates of fish consumption. As discussed above, meta-analyses of RCTs of PUFAs are sensitive to the inclusion of specific studies and to the selection of health endpoints. A more approximate but broad-based estimate of the MRFIT results may be estimated by considering the effects of the intervention group, whose coronary heart disease mortality decreased by 10.6% after 10.5 years of follow-up (MRFIT Research Group, 1990), while their intakes of PUFA increased by 33% (Gorder et al., 1986). This leads to an estimated elasticity of -0.105/0.33 = -0.32. Gorder et al. also indicated increased consumption of fish.

The EURAMIC study (discussed above with respect to Hg) also examined the effects of fatty acids on heart attack risk, based on adipose tissue samples. No protective effects were found; it was also noted that EPA levels were below the detection limit for most samples. Perhaps this indicates that marine PUFA levels were too low to register an effect (i.e., below the threshold). Also, the paper by Ascherio et al. (1995) involved the same cohort as that of Yoshizawa et al., 2002 (see Table 2), and it appears that the mean intake of fatty acids may be in the low end of the range.

Table 4 compares log-log slope estimates for selected observational cohort studies involving various (n-3) PUFAs. Some studies provided data on relative risks by n-tiles of fish consumption as well as by fatty acid level; comparing these regression slopes provides some insights as to which predictor fits the data better (for this specific modeling paradigm). If fish consumption data were to fit better, for example, we would conclude that fatty acids were serving as a surrogate agent for some other fish constituent. If the slope for fish consumption were substantially lower than that for fatty acids, we might conclude that fish consumption data also encapsulated a harmful agent such as MeHg, for example. The table is organized to show RRs based on measured PUFAs first (Table 4A), with blood data followed by adipose (fat) tissue

data. Table 4B presents the results based on PUFA intake levels, as estimated from specific food consumption frequencies.

The first impression from Table 4 is that almost all of the slopes are negative, indicating beneficial effects; the results of Pietinen et al. (Finland) are an important exception. This was a larger cohort than in the KIHD, and none of the RRs for "omega-3 fish fatty acids" were statistically significant, based on estimated daily intake rates. No data were presented on fish contaminants or on the species consumed.

The next impression is that the slopes of RR vs. PUFA levels are consistently stronger (more negative) than those based on fish consumption alone. This is the case in 14 of the 16 comparisons, and the two exceptions are based on intake estimates. Finally, the slopes based on measured PUFA levels tend to be stronger (more negative) than those based on estimated intake rates. This is the case even when baseline PUFA thresholds are assumed for the slope calculation. The correlations between intake rates and biomarker concentrations tend to be significant but modest, in the range 0.4-0.6 (Andersen et al., 1996; Kobayashi et al., 2003). If we assume that the biomarker data are the "true" indicators, then we would expect the slopes based on intake rates to be around half of the values found with biomarkers. We would also expect fewer statistically significant relationships based on intake rates, for a given sample size.

It is also interesting to note that the EURAMIC data of Guallar et al. (1999) showed very weak, nonsignificant responses to PUFA, for which (measured) concentration levels are quite low in comparison to the other studies. This is the same cohort that showed adverse CVD effects associated with toenail concentrations of Hg.

Figure 2 is a plot of relative mortality risks as a function of n-3 PUFA concentrations measured in blood, as the percentage of all fatty acids. Data from the studies of Albert et al. (2002), Siscovick et al. (2000), Pedersen et al. (2000), and Daviglus (1997) represent relative risks by n-tile of fatty acid level, taken directly from the publications. Results from the Finnish study of Virtanen et al. that combined Hg and PUFA data are based on the mean PUFA levels for each Hg tertile (as opposed to PUFA tertiles). The linear RR regression coefficients given in the paper for DHA and DPA (only) and for the subset of subjects with hair Hg < 2 ppm were then used to estimate the trend in PUFA effects. The general trends of these plots are consistent with reports of very low incidence of heart disease among the Arctic Inuit peoples and an average EPA+DPA value of about 7% (DeWailly et al., 2001). The plot is also consistent with the failure of Guallar et al. (1995) to find significant effects at relatively low levels of PUFAs.

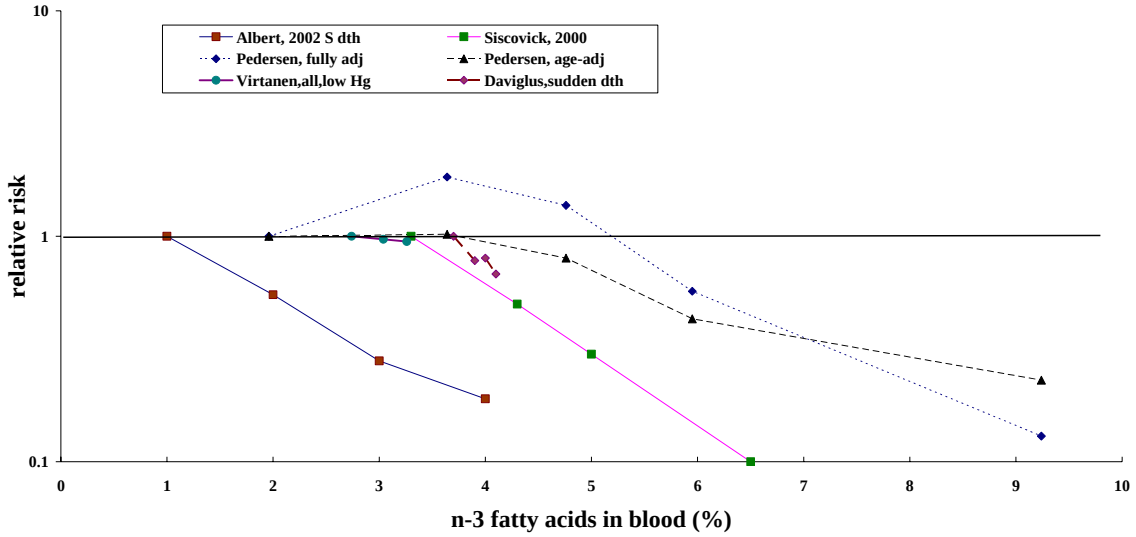

Figure 2 Results of cohort studies of mortality vs. the percentage of n-3 fatty acids in blood. Each study normalized to a relative risk of 1 at the lowest n-3 fatty acid level in that study.

Although there are substantial variations among the studies shown in Figure 2, the overall impression is one of an effect threshold at PUFA levels of about 3-5% of total fatty acids. This is also consistent with the results of Lemaitre et al. (2003), who showed levels of 3.3% and 3.8% DHA+EPA for fatal IHD cases and controls, respectively (not included in Table 4). This suggests that dietary supplements

of PUFAs may be more effective in populations whose mean baseline levels exceed the threshold. In the absence of PUFA n-tile data for the Finnish cohort, we can only speculate whether their PUFA levels might be below such a threshold. This is also the case with the study of Guallar et al., for which EPA data were not available.

Table 4A Results from Cohort Studies of Measured PUFA Effects on Cardiovascular Health

1st author	period	location	# subjects cases,controls	agent(s)	mean level	endpoint	log-log slope	remarks
Albert, 2002	1982-99	all US	94, 184	n-3 PUFA	4.8%	sudden death	-2.6 (no threshold) -0.4 to –0.9 w/thresh	
Daviglus, 1997	1957-87	Chicago	1822 men	fish	19 g/d	MI	-0.13	
				PUFA	3.9%	MI	-0.45	(threshold)
				fish	19 g/d	CHD	-0.10	
				PUFA	3.9%	CHD	-0.35	(threshold)
				fish	19 g/d	CVD	-0.065	
				PUFA	3.9%	CVD	-0.22	(threshold)
				fish	19 g/d	any death	-0.031	
				PUFA	3.9%	any death	-0.11	(threshold)
Erkkila, 2003	1995-00	Finland	415	fish	60 g/d	any death	-0.22	
				EPA	1.72%	any death	-1.0	
				DHA	0.69%	any death	-2.0	
				fish	60 g/d	CAD death	0.05	
				EPA	1.72%	CAD death	-1.1	
				DHA	0.69%	CAD death	-1.2	
Guallar, 1995	1984-89	all US	14916 men (physicians)	EPA	0.49%	heart attack	-0.03	not signficant
				DHA	2.11%	heart attack	0.11	not signficant
				EPA+DHA	2.6%	heart attack	0.31	not signficant
Rissanen, 2000	1984-97	Finland	1871 men	n-3 PUFA	2.9%	CHD event	-0.74	
				hair Hg	1.9 ppm	CHD event	0.44	joint regression
Virtanen, 2005	1984-98	Finland	1249 men	n-3 PUFA	3.0%	any death	-0.11	
				(hair Hg <2.0 ppm)		CHD death	-0.84	
			1871 men	n-3 PUFA	3.0%	any death	-0.12	
				(hair Hg = 1.9 ppm)		CHD death	-0.54	
Siscovick, 2000	1988-94	Seattle	334, 493	n-3 PUFA	0.14 g/d	cardiac arrest	-0.2	
				n-3 PUFA	4.9%	cardiac arrest	-4.4	no threshold
				n-3 PUFA	1.9%	cardiac arrest	-1.1	thresh = 3%

Guallar, 1999	1991-2	Europe + Israel	639, 700	ALA DHA (adipose)	0.8% 0.25%	1st MI 1st MI	-0.18 -0.07	(estimated quintiles)
Pedersen, 2000	1996	Norway	100, 98	n-3 PUFA (adipose)	0.68%	1st MI	-1.3	threshold at 0.7%

Table 4B Results from Cohort Studies of Estimated PUFA Effects on Cardiovascular Health

1st author	period	location	# subjects cases,controls	agent(s)	mean level	endpoint	log-log slope	remarks
Ascherio, 1995	1986-92	all US	44895 men	fish	2.2 m/wk	fatal CHD	-0.052	
				n-3 PUFA	0.24 g/d	fatal CHD	-0.005	
				fish	2.2 m/wk	any CHD	-0.007	
				n-3 PUFA	0.24 g/d	any CHD	0.043	
Dolecek, 1991	1978-85	all US	6250 men	fish oils	0.05 g/d	CHD death	-0.047	
				fish oils	0.05 g/d	CVD death	-0.046	
				fish oils	0.05 g/d	any death	-0.029	
Iso, 2006	1990-01	Japan	41578	fish	78 g/d	CHD cases	-0.16	
				n-3 PUFA	0.9 g/d	CHD cases	-0.23	
				fish	78 g/d	non fatal	-0.35	
				n-3 PUFA	0.9 g/d	non fatal	-0.52	
Jarvinen, 2006	1970-92	Finland	5220	fish	28 g/d	CHD death	-0.04	
				n-3 PUFA	0.33 g/d	CHD death	-0.001	
Pietinen, 1997	1988-93	Finland	1399 men	n-3 PUFA	0.4 g/d	CHD event	0.11	
				n-3 PUFA	0.4 g/d	CHD deaths	0.17	
Tavani, 2001	1995-9	Milan	507, 478	n-3 PUFA	~0.14 g/d	nonfatal MI	-0.45	
				fish	~1.5 m/wk	nonfatal MI	-0.21	
Yuan, 2001	1986-98	Shanghai	18244 men	fish meals	~1 m/wk	any death	-0.083	
				n-3 PUFA	0.08 g/d	fatal MI	-0.28	
				n-3 PUFA	0.08 g/d	IHD death	-0.08	

In Table 4, only Rissanen et al. (2000) considered the effects of PUFA and Hg separately, but not simultaneously. In order to estimate the combined effect, we regressed these quintile results jointly and found significant negative effects of PUFA in conjunction with positive effects of Hg. This finding needs to be corroborated with modeling of individual exposures to both agents as continuous variables.

In Table 4B, there is no apparent relationship between mean PUFA intake rates and the log-log slopes. However, the mean intake rates are often much higher than the medians shown in the table.

In summary, Table 4 shows that observational cohort studies based on measured PUFA biomarker levels provide clear evidence of the beneficial effects of these compounds. Failure to find such effects based on intake rates may well be the result of either imprecise estimates or individual variability in terms of metabolic processing.

3.3 Controlled Clinical Trials of Dietary Supplements

Studies involving dietary supplements of fish oils avoid the complications of fish contaminants (Kris-Etherton et al., 2003) and possible life-style differences that may accompany fish consumption. In 2002, Bucher et al. published a meta-analysis of 11 randomized controlled trials (RCTs) in which diets of 7951 patients were enriched with supplemental n-3 PUFAs and the risks of coronary heart disease outcomes were compared with those of 7855 unsupplemented patients in control groups. The n-3 PUFA supplemented patients had 20% fewer non-fatal heart attacks, 30% fewer fatal heart attacks, 30% fewer sudden deaths, and 20% fewer deaths overall; all of these results were statistically significant. More recently, Hooper et al. (2006) performed a more formal systematic review and meta-analysis that included many more studies and participants but that was limited to more broadly defined cardiovascular outcomes (total mortality and all cardiovascular events). Hooper et al. concluded that supplemental n-3 PUFAs provided *no* clear mortality or cardiovascular benefits; the RRs for total mortality and cardiovascular events were 0.87 (0.73-1.03) and 0.95 (0.82-1.12), respectively. No results were provided specifically for heart attacks or sudden deaths, and cohort studies showed significant benefits for mortality but not for events. Another difference between these two meta-analyses is the inclusion in the latter analysis of a large RCT for 3114 angina patients (Burr et al., 2003) that showed some *adverse* effects from supplemental fish-oil capsules. An earlier evaluation of this cohort (Burr et al., 1989) found beneficial effects. When Hooper et al. removed the Burr et al (2003) study from their data base, the relative risk of all-cause mortality agreed with that of Bucher et al. (RR=0.83 [0.75-0.91]). This illustrates the sensitivity of meta-analysis to the criteria used for study inclusion and perhaps the folly of relying too heavily on statistical significance criteria. Bucher et al.'s review was updated by Studer et al. (2005), who presented meta-analysis results with and without the Burr paper, which they found to be the main source of heterogeneity among the 14 RCTs of n-3 fatty acids. However, the effect on total mortality was about the same: 0.77 (0.63-0.94) vs. 0.80 (0.69-0.92). Wang et al. (2006), who cite neither Bucher et al nor Hooper et al. (Hooper et al cite an earlier version of Wang et al.), also present a systematic review of dietary fatty acids and selected 46 studies on CVD outcomes for detailed review. They did not perform meta-analysis, but concluded that n-3 PUFAs from fish or fish oil reduce all-cause, cardiac, sudden death, and possibly stroke mortality.

The modest correlations between PUFA intake rates and the corresponding biomarker concentrations imply that individuals may vary in terms of their metabolic processing of dietary supplements. This in turn suggests that intervention studies involving supplements should evaluate their relative outcomes in terms of biomarker levels as well as in terms of intake rates.

Finally, omega-3 fatty acids have been recommended to primary care physicians for cardiac therapy (Oh, 2005).

4. Studies of Mortality vs. Fish Consumption

4.1 Definitions and Measurements

We define "seafood" or "fish" as including both finfish and shellfish, from either marine or freshwater sources, unless otherwise specified. In converting from meals per week to g/d, we assume an average meal size of 150 g for males and 120 g for females. Where only ranges of consumption are given (e.g., 1-2 meals/wk) we assume that the midpoint of the range (e.g., 1.5 meals/wk) represents the entire category. Where open-ended ranges are given, say > 5 meals/wk, we assume an arbitrary value for this purpose and test the sensitivity of the result to this assumption.

4.2 The Extant Literature.

4.2.1 Cohort Studies. From the standpoint of risk analysis, the ultimate health endpoint is that of dietary effects on all-cause mortality ("any death"). Although effects on specific causes of death are also of great interest, for example, in hypothesizing mechanisms, there may also be misclassification problems and competing risks to consider. Such statistics reflect both direct and indirect effects, including those of confounders that might be associated with a seafood-consuming lifestyle. If the benefits of fatty acids outweigh the risks of MeHg, eating more fish should reduce mortality, in the absence of confounding effects.

Table 5 summarizes the results of ten published studies that reported mortality risks as a function of fish consumption, for various causes of death. Most of them presented their results in terms of quintiles of exposure, relative to the lowest exposure group. Table 5 presents the risks for the third quintile, which are taken to represent the mean or median risks for the entire cohort (this is tantamount to assuming a linear dose-response relationship). There is considerable diversity among these 21 results; however, all but three of them are negative (RR < 1), indicating overall survival benefits from eating fish. However, only three of them are statistically significant, in part because of small sample sizes.

Table 5 also provides estimates of the "avoided deaths", defined above. For example, in the Western Electric (Daviglus, 1997) and Iowa (Folsom, 2004) studies, there are no additional all-cause deaths ascribed to fish consumption relative to cardiovascular causes, while this is (apparently) not the case for the studies of Albert (1998) or Nakamura (2005). As in Table 3, these incremental death counts are summed across studies and divided by the total deaths to provide weighted-average estimates of the overall mean relative risks (Table 6).

Note that these estimates are based on different studies for each of these cause-of-death groupings. These cohorts are mostly male, and four of the studies are based on health professionals, who may not be representative of the general population. The study of Morris et al, which was superceded by that of Albert et al., is included for completeness, but was not used in estimating the overall relative risks listed above. The weighted-average RRs above are compatible with the hypothesis that only cardiovascular mortality is affected by eating fish.

The CHD and CVD mortality estimates are reasonably consistent with those in Table 3, even though there are far fewer deaths or events with Hg exposure measurements in Table 3. Such agreement implies equivalence between fish consumption and MeHg exposure, i.e., that considering MeHg exposure provides no additional information (at mean levels of exposure).

Table 5 shows only one result for sudden deaths (Albert et al., 1998), for which a 50% reduction in risk was reported. However, reductions in the risk of sudden death have been shown in intervention studies featuring dietary fish oil supplements. Note that the cohort studied by Albert et al. had relatively fewer sudden deaths relative to heart attacks, compared too much of the literature on cardiovascular risks. This might reflect the higher rates of average fish consumption in this cohort, relative to the U.S. general public. The implied findings of reduced mortality associated with fish consumption for causes of death other than cardiovascular imply that other lifestyle effects may be present. For example, Kromhout (1998) pointed out that the non-fish-eating reference group in the Physicians Health Study also smoked more, drank less, and exercised less than the fish-eaters and that residual confounding may have been present, even though attempts were made to control for these factors.

Table 5 Mortality as a Function of Fish Consumption (RRs at mean consumption levels)

1st author, yr	period	location	cause of death	group	# subjects	# deaths	mean fish meals/wk	estimated mean RR	avoided deaths
Albert, 1998	1984-95	all US	sudden death	male Drs.	20551	133	2.5	0.51 (0.25-1.04)	65
			heart attack			737		1.03 (0.67-1.58)	-22
			all causes			1652		0.70 (0.54-0.89)	496
Ascherio, 1995	1986-92	all US	CHD	male health professionals	44895	264	2.2	0.71 (0.41-1.21)	77
Daviglus, 1997	1957-83	Chicago	heart attack	males	1822	293	1.0	0.76 (0.52-1.12)	70
			all CHD			430		0.84 (0.61-1.17)	69
			all CVD			573		0.89 (0.67-1.19)	63
			all causes			1042		0.98 (0.79-1.22)	21
Folsom, 2004	1986-97	Iowa	all causes	females	41836	4653	2.1	0.93 (0.83-1.05)	326
			CVD			1589		0.79 (0.63-0.99)	334
			CHD			922		0.75 (0.55-1.03)	230
			stroke			313		0.90 (0.53-1.53)	31
He, 2002	1986-98	all US	stroke	male Drs.	43671	608	1.9	0.67 (0.46-0.96)	201
Kromhout, 1985	1960-80	Neth.	CHD	males	852	78	1.0	0.56 (0.27-1.15)	34
Kromhout, 1995	1971-88	Neth.	all	age 65+	272	187	0.5	0.96 (0.72-1.30)	7
			CHD			58		0.51 (0.29-0.89)	28
(Morris, 1995	*1983-8*	*all US*	*CVD*	*male Drs.*	*21185*	*121*	*1.9*	*1.7 (0.9-3.4)*	*-85*
Nakamura, 2005	1980-99	Japan	all causes	random	8879	1745	4.5	0.88 (0.76-1.0)	209
			stroke			288		0.81 (0.58-1.14)	55
			CHD			124		0.73 (0.45-1.20)	33
Oomen, 2000	1970-90	Finland	CHD	males	1088	242	~1.0	0.97 (0.68-1.38)	7
		Italy	CHD	males	1097	116		0.93 (0.53-1.63)	8
		Neth.	CHD	males	553	105		1.00 (0.59-1.68)	0
Yuan, 2001	1986-9	China	heart attack	males	18244	113	~2.0	0.72 (0.42-1.21)	32
			other IHD			74	(fish only)	0.84 (0.40-1.77)	12
			stroke			480		0.87 (0.65-1.15)	62

* superceded by the study of Albert et al., 1998

The study of middle-aged (45-64) Shanghai men by Yuan et al. (2001) provides an opportunity to contrast the effects of eating fish (only) with that of eating shellfish (only). For heart attack deaths, there was a significant negative relationship with weekly intake, regardless of the type of seafood, based on log-log regression. For other ischemic heart disease and stroke deaths, there were no significant relationships with either type of seafood. Since finfish tend to have higher MeHg levels than shellfish (Mahaffey, 2004), this study does not support an adverse cardiovascular effect of MeHg.

As reported by Yoshizawa et al. (2002), Ascherio et al.'s study of health professionals included a high proportion of dentists, who tend to have higher exposures of inorganic Hg. If Hg^0 truly had adverse effects on coronary heart disease, a stronger response to fish consumption would have been expected.

4.2.2 Gender and Race Effects. Some possible insights into socioeconomic and lifestyle factors might be inferred from the results of Gillum et al. (2000), who analyzed the mortality experience of the first National Health and Nutrition Examination Survey (NHANES I) cohort in relation to fish consumption, for a mean follow-up of 19 years beginning in the 1970s. The study involved a nationally representative sample of initially healthy adults, ages 25-74. Most of the studies summarized in Table 2 involved white males, and the white men in the NHANES-I cohort showed similar relationships: decreased mortality from all causes, CVD, and non-CVD for those eating fish at least once per week and no additional benefit for additional consumption. However, white women showed no significant mortality benefits, nor did black men. The results for black women were similar to those for white men, but failed to reach statistical significance, presumably because of the smaller sample. The combined cohort results (total of 2901 deaths) showed no effect for CVD deaths and decreasing mortality with increasing fish consumption for non-CVD deaths, with less additional benefit after about one fish meal every two weeks. These results are suggestive of lifestyle effects, since no mechanisms have been postulated for non-CVD deaths and there is no *a priori* reason to suspect gender or racial differences in the effects of fish.

4.3 Estimated Dose-Response Relationships.

Table 5 is based on responses at or near the mean exposure levels; many of the authors' conclusions are based on risks at the highest exposure levels. In this section, we examine dose-response relationships across the range of each study, assuming a linear response. Some studies appear to show a significant difference between people who eat no fish and those who eat various amounts, with no trend according to the rate of consumption. We would interpret such findings as showing a difference between types of *subjects*, perhaps because of lifestyle differences, rather than an effect of fish consumption per se (Hypothesis A1). The data appear to indicate that high-consumers of fish may tend to be of higher socioeconomic status (SES) in developed countries than in poorer countries.

Table 6 Relative Mortality Risks from Fish Consumption
(Based on Table 5)

Cause of Death	Avoided deaths/ Total deaths	Relative Risk
All causes	1061/9279	0.886
Coronary Heart Disease (CHD)	528/3300	0.840
Stroke	349/1689	0.793

The meta-analysis of Konig et al. (2005) produced a linear dose-response function for CHD mortality in which the major effect was between those who did not eat fish and those who ate fish in any amount:

$$RR = 0.83 - 0.039 * \text{fish meals per week} \qquad (R^2 = 0.23) \qquad [4\text{-}1]$$

This relationship is roughly in agreement with those derived from meta-analyses of randomized control trials of supplementary fish oil discussed above. Such a relationship is also compatible with a log-log model with a slope of about –0.09. This implies that a 10% increase in fish consumption (at any level) is

associated with a decrease in CHD mortality of ~0.9%. A slightly stronger CHD relationship was found by He et al. (2004) based on 13 cohorts, over 220,000 individuals, and about 12 years of follow-up:

$$RR = 0.94 - 0.048*\text{fish meals per week.} \qquad (R^2 \text{ across quintiles} = 0.91) \qquad [4\text{-}2]$$

The log-log slope is –0.105 and the trend is highly significant. Whelton et al. (2004) pooled data from 14 observational and 5 case-control studies and found a relative risk for fatal CHD of 0.83, for any fish consumption vs. "little or no" consumption. A similar relationship was found for fatal and non-fatal CHD combined. However, the authors referred to fish consumption as a "component of lifestyle modification", suggesting that other factors may be involved (Hypothesis A1 in Table 1). Osler et al. (2000) reported a RR of 0.74 for ischemic heart disease mortality in Denmark, for persons at high risk.

Bouzan et al. found a much weaker (not significant) meta-relationship for stroke mortality:

$$RR = 0.88 - 0.02*\text{fish meals per week} \qquad (R^2 = 0.034) \qquad [4\text{-}3]$$

He et al. (2004) also performed a meta-analysis of cohort studies of stroke mortality and found striking differences between the two major types of strokes. Ischemic stroke mortality was reduced by about 35% at all levels of fish consumption, while mortality from hemorrhagic strokes increased dramatically at small rates of fish consumption. The net result of a log-log regression of all types of strokes combined (by weighted average) was a slope of –0.09 (highly significant trend; R^2 across quintiles = 0.94).

Based on U.S. age-adjusted mortality rates for 2004 and assuming no contributions form non-CVD causes, the combination of [4-1] and [4-3] would result in a relationship for all-cause mortality of

$$RR = 0.95 - 0.012*\text{fish meals per week} \qquad [4\text{-}4]$$

This relationship [4-4] implies an all-cause mortality RR of 0.866 for daily consumption of fish.

An unweighted regression analysis of the data in Table 4 based on the mean or median fish consumption in each study produced a negative but nonsignificant relationship between all-cause mortality and fish consumption very similar to [4-4], and a log-log relationship for CHD mortality with a slope of –0.096 after deleting two apparent outliers (the Kromhout studies in the Netherlands).

In summary, the association of fish consumption with reduced mortality seems quite clear (Hypothesis A in Table 1), even though there is no apparent physiological justification for a log-log relationship in which most of the benefit is obtained at relatively low levels of fish consumption. However, the relative roles of other dietary and lifestyle factors that may be correlated with eating fish remain to be defined (Hypothesis A1 in Table 1).

4.4 An Ecological Mortality Study

Ecological studies of average national population risk vs. national averages of risk factors have the disadvantage of lacking data on individuals and are thus subject to the "ecological fallacy", in which the individuals having the risk factor in question may have health outcomes that differ significantly from the average outcome for the entire group. However, relative to the generally preferred cohort studies, ecological studies have the advantage of the absence of subject selection bias (health professionals, for example) and of representing much larger and more diverse populations. Also, cohort studies have the potential problem of early depletion of the most sensitive subjects; for example, the early beneficial effect reported by Burr et al. (1989) was based on a difference of only 36 deaths, while 8 years later, the mortality increment in this cohort had decreased to 23 deaths and become non-significant (Ness et al., 2002). Conclusions based on such small samples are inherently problematic.

Zhang et al. (1999) used data from 36 (mainly developed) countries, including the United States and Canada, to investigate the relationship between fish consumption and mortality. Dietary data back to 1961 were obtained from the United Nations Food and Agriculture Organization (FAO), for fish consumption, animal protein (less fish), animal fat-fish fat, alcohol consumption, and cigarette sales (incomplete data). The dietary variables were expressed as percentages of total energy intake; on this basis, fish consumption ranged from 0.23% (Hungary) to 10.4% (Iceland). Annual mortality rates by sex were standardized to ages 45-74 for all causes, ischemic heart disease (IHD), and cerebrovascular causes (CVA). Eastern Europe had the highest mortality rates; Japan and Iceland, the lowest. The authors concluded that

"fish consumption is associated with reduced risk from all-cause, ischemic heart disease, and stroke mortality at the population level."

We reanalyzed the tabulated data, with and without the Eastern European countries (Hungary, Poland, Czech Republic, Bulgaria, Romania), in order to remove any effects of deprivation that might have remained from their prior membership in the Soviet block. We found that log-log models fit the data better, as did Zhang et al. Surprisingly, cigarette consumption was not a significant predictor in the subset of countries with data, perhaps because lagged consumption data should have been used to account for the latency periods involved. Fish intake showed a negative (beneficial effect); animal-fish fat, positive (harmful) for IHD and negative for stroke; and alcohol was significantly beneficial for IHD mortality, harmful for stroke, with no effect on all-cause mortality. Figure 3 is a scatter plot of all-cause mortality vs. fish consumption. Without the five Eastern European countries, the all-cause, log-log regression coefficients were -0.077 for males and –0.061 for females. These estimates are not significantly different from the –0.09 to –0.11 values reported above for cohort studies. For all-cause mortality, fish consumption was the most important predictor; for IHD deaths, animal-fish fats (positive); for stroke, animal-fish fats (negative).

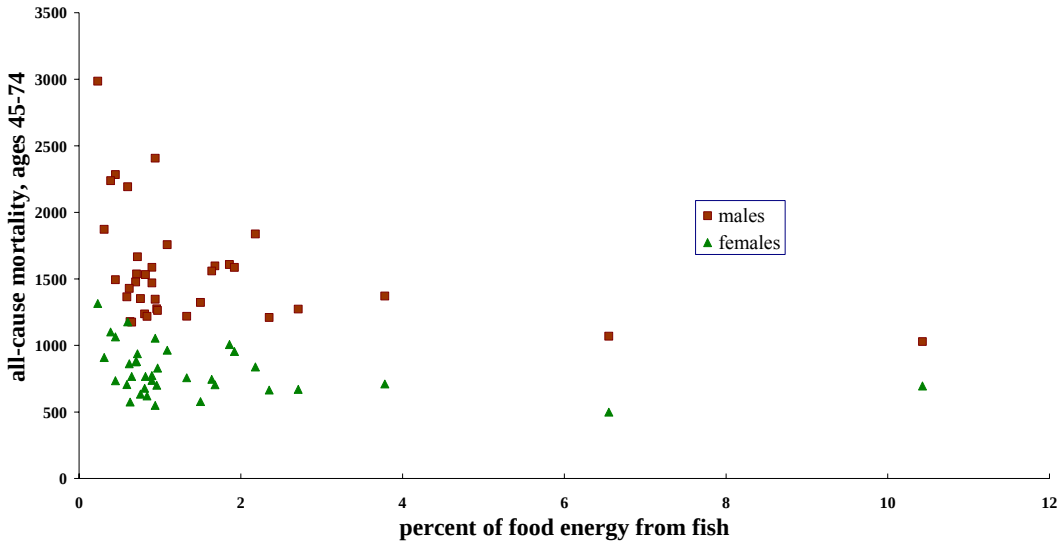

Figure 3 Scatter plot of national population data from Zhang et al. (1999), showing all-cause mortality rates as a function of fish consumption.

We used these relationships to derive a simulated dose-response function for IHD mortality vs. fish consumption, to demonstrate how the benefit levels off at high levels of fish consumption (Figure 4). (For reference, the mean fish consumption value for the United States is 0.7% of daily energy intake.) However, this is not the case with the (harmful) effects of animal fat (Figure 5), for which the US level is 20.5% of energy intake.

In a similar study, Zhang et al. (2000) reported showed significant reductions in male lung cancer mortality associated with fish consumption in countries with high rates of smoking or consumption of animal fats.

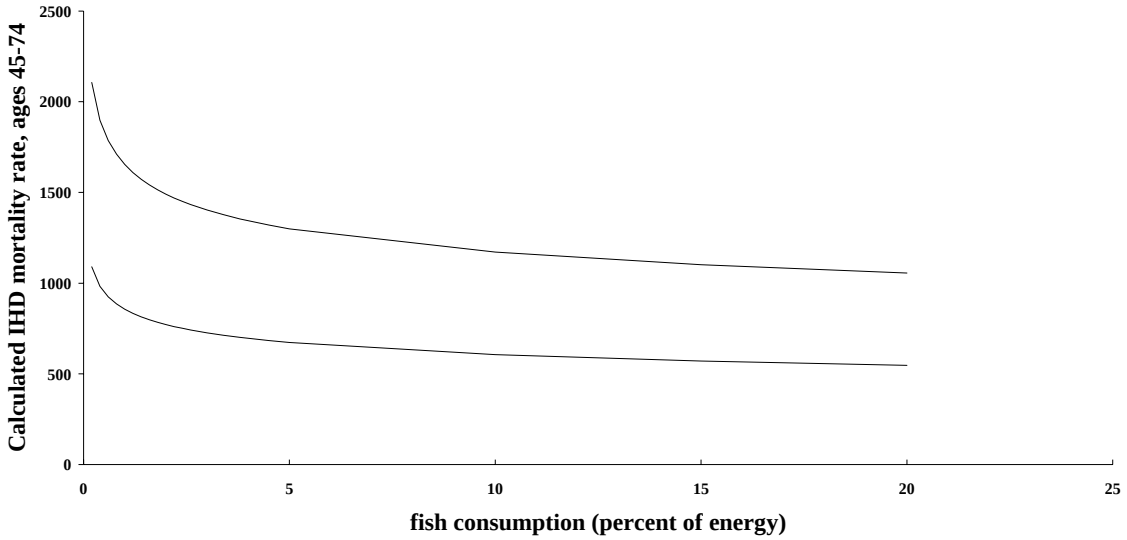

Figure 4 Dose-response functions based on log-log regression models of the data of Zhang et al. (1999).

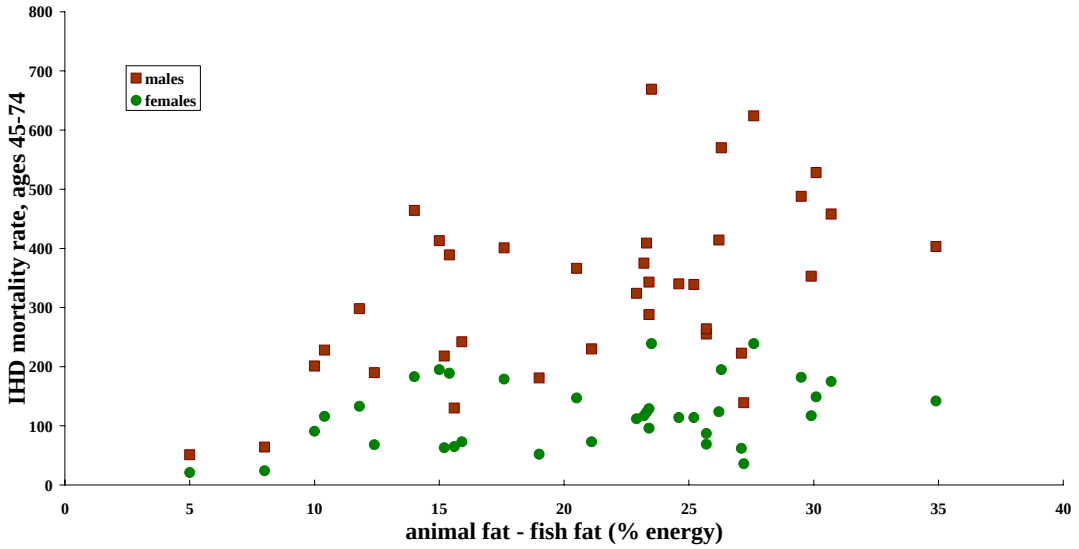

Figure 5 Scatter plot of national population data from Zhang et al. (1999), showing ischemic heart disease mortality rates as a function of net animal fat consumption.

5. Results from Studies of Specific Diets

5.1 Studies of Various Complete Diets.

Observational studies involving complete diets rather than selected constituents offer the opportunity to examine interactions among major food groups. Since diet may be considered a "zero-sum" game, such interactions may be important. For example, Barberger-Gateau et al. (2005) showed that French fish consumers tended to have higher education and income levels, eat more fruits and vegetables, consume more alcohol, and to feel better about their health. However, there was a significant positive association between fish and meat consumption, and the physical health status of fish eaters was no better.

Fung et al. (2001) used data from the Nurses Health Study (n = 69017 females) to synthesize two model dietary patterns. The "prudent" diet pattern was characterized by higher intakes of fruits, vegetables, legumes, fish, poultry, and whole grains. The "Western" pattern included more meat, sweets, french fries, and refined grains. Each individual in the cohort was given a score for each of the patterns, and they were

grouped into quintiles. Proportional hazard modeling was then used to define associations of each quintile with new cases of CHD. Figure 6 shows the relative CHD risks associated with each quintile (taken separately); the benefits of the "prudent" diet are seen to level off at an RR of 0.76, while the increased risks of the "Western" diet continue to rise. This suggests that dietary benefits may be limited, while dietary harm is apparently not.

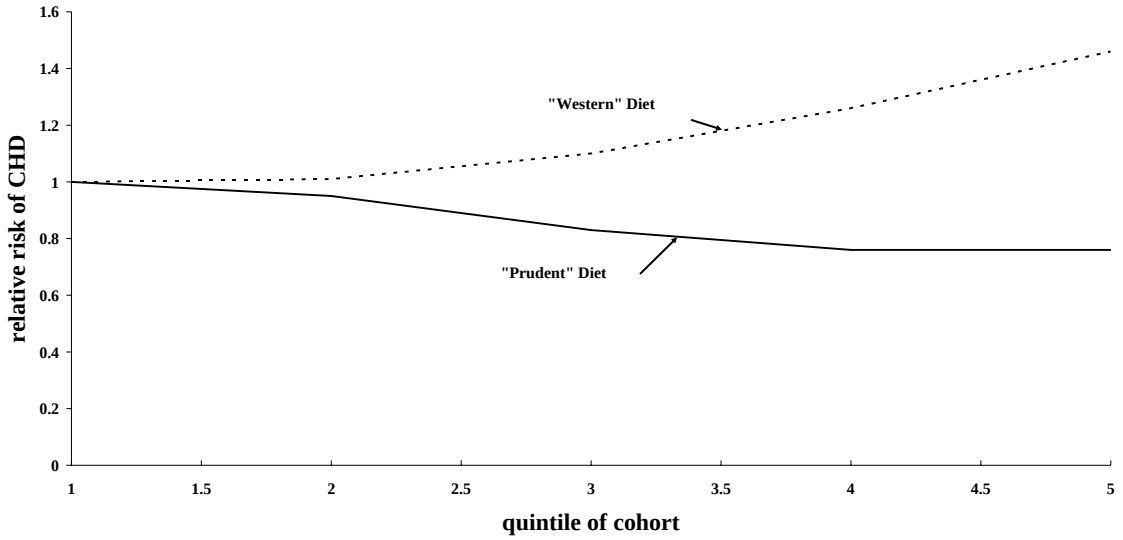

Figure 6 Quintile relative risks from the Nurses Health Study (Fung et al., 2001) for two synthesized diets.

Fung et al. also analyzed the two factors jointly in order to examine interactions, providing 16 estimates of various combinations of the two diets (the highest 2 quintiles were combined). This showed that for diets with high "western" scores, additional use of the prudent diet had little benefit (Figure 7), while at the highest levels of the "prudent" diet, only the highest "western" group reduced the "prudent" benefit. Finally, Fung et al. provided data on the major constituents of the two diets, which we used in additional regression analysis. The best predictor of relative risk of CHD was the difference between meat and fish consumption (servings per day), for which the correlation was about 0.6 (n=10). Other "healthy" diet constituents (fruits, vegetables, whole grains) made little improvement (Figure 8). In a personal communication (September, 2006), Dr. Fung confirmed that red meat seemed to be the most important factor in this study.

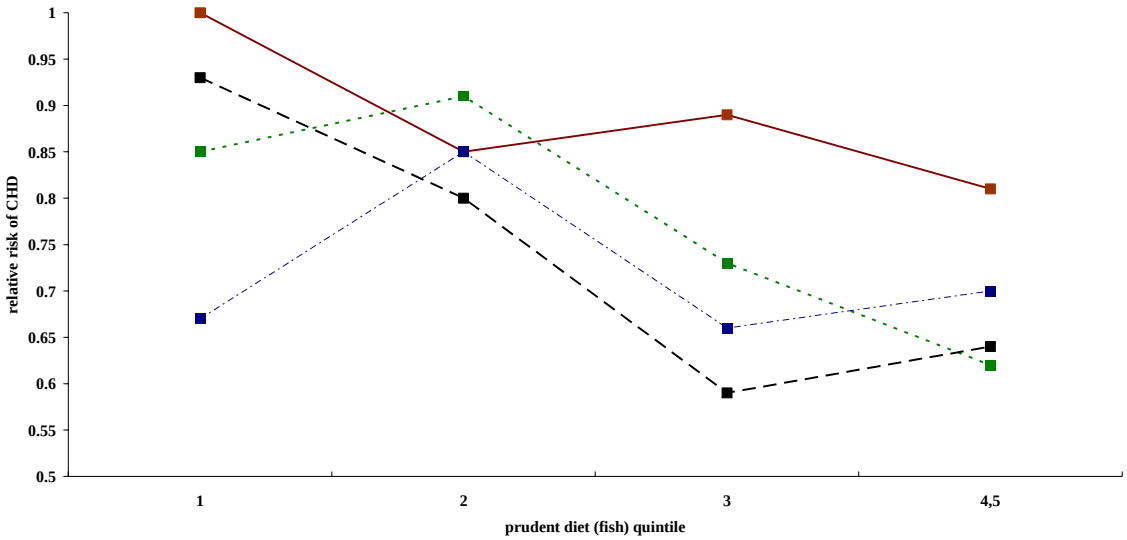

Figure 7 Quintile relative risks from the Nurses Health Study (Fung et al., 2001) showing the interactions among adherents to two synthesized diets.

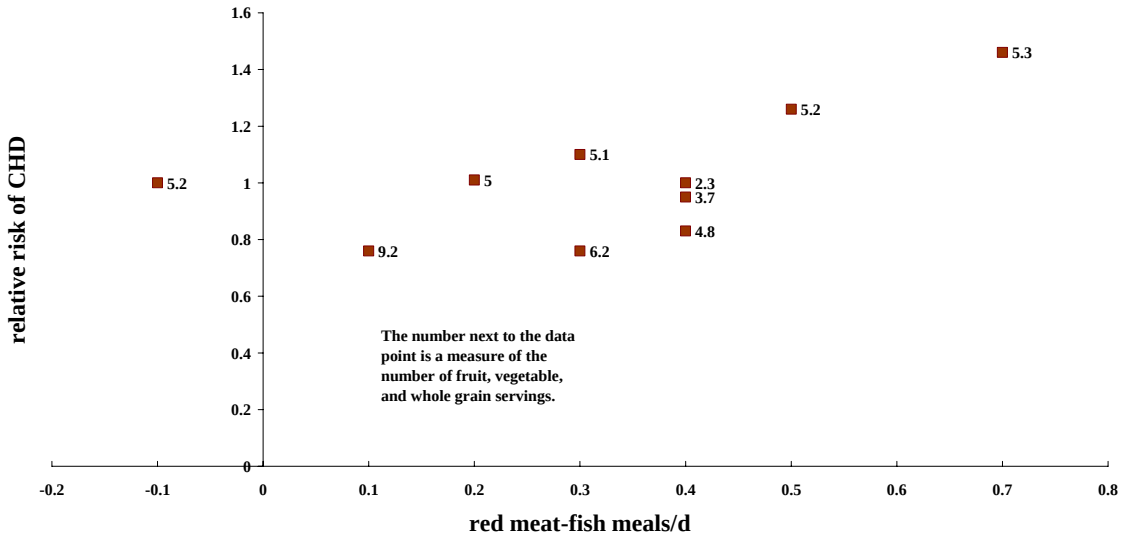

Figure 8 Relative risks of coronary heart disease from the Nurses Health Study (Fung et al.2001) showing the relative importance of meat consumption and other "healthy" foods.

5.2 Studies of the "Mediterranean Diet"

The so-called "Mediterranean Diet" has received a great deal of attention in the literature. MEDLINE lists 420 English language papers for which this phrase appears in the title or abstract, of which 128 are classified as review papers. This diet features olive oil, red wine, fruits and vegetables, cereals, nuts, fish and chicken, and only small amounts of red meat, dairy products, or eggs (American Heart Association, 2006). Serra-Majem et al. (2006) reviewed 43 papers on various aspects of this diet.

Several intervention studies have involved the Mediterranean diet. For example, Knoops et al. (2004) reported a 23% lower mortality rate (RR=0.77) for elderly individuals who adhered to this diet for 10 years. The relative risk for CHD was 0.61. Adherence to this diet in combination with moderate alcohol consumption, not smoking, and physical activity produced a RR of 0.35 in this cohort. The separate contribution of fish consumption was not identified.

Kok and Kromhout (2004) identified a variant of this diet in a cohort from Crete and reported a RR of 0.3 for all-cause and cardiac mortality. This diet included 18 g/d of fish (about 1 meal/wk). In a much larger study of about 75,000 elderly residents of 9 European countries, Trichopoulou et al. (2005) reported an overall all-cause RR of 0.83 for those who adhered most closely to a modified Mediterranean diet that included about 37 g/d of fish. The RRs were lowest for residents of Greece and Denmark (0.69, 0.71).

6. Concluding Discussion

The evidence for adverse cardiovascular effects of MeHg is sparse and unconvincing. The studies of CVD, IHD, and CVD mortality show net benefits (Table 3); there are no plausible rationales for adverse effects on other major causes of death. The finding of adverse effects in Finland at high Hg exposure levels requires replication in another setting prior to use for policy purposes. There is no convincing evidence for adverse Hg effects on blood pressure or heart rate, and the Hg effects on heart rate variability and atherosclerosis are mixed.

By contrast, a very consistent picture of beneficial effects is seen for omega-3 PUFAs, after recognizing the effects of exposure uncertainties and the presence of thresholds in the baseline range of 3-5% of total fatty acids (Figure 2). Studies based on measured biomarker levels are seen to be the most reliable and present a convincing picture of strong beneficial effects, especially for those causes of death involving arrhythmias. This conclusion extends to studies of fish-oil supplementation, for which measurements of biomarker levels are also needed.

Studies based on fish consumption per se are expected to display the net effects of (potentially) adverse effects of MeHg and the beneficial effects of n-3 PUFAs. This distinction is difficult to study separately, since the two factors tend to be positively correlated within a population (they are linked by variations in the rates of fish consumption). These cohort studies show net benefits from increased fish consumption (Table 6), for all-cause, CHD, and CVD mortality. This finding is supported by an ecological study at the population level (Figure 4), for which the lifestyle effects that might be correlated with fish consumption within a given population would be expected to "average out."

Finally, the net survival benefits resulting from eating fish are consistent with studies involving complete diets, although benefits are also seen to accrue from reducing consumption of red meat and saturated fats.

7. Acknowledgments

This research was supported by the U.S. Department of Energy; Pierina Noceti is the project Officer. However, the content of this report is solely the responsibility of the authors. A preliminary version of this material was presented at the "Air Quality V" conference in Arlington, VA, September 2005.

8. References

Ahlqvist M., Bengtsson C., Lapidus L., Bergdahl I.A., and Schutz A.; Serum Mercury Concentration in Relation to Survival, Symptoms, and Diseases: Results From the Prospective Population Study of Women in Gothenburg, Sweden. Acta Odontol Scand 1999;57:168-174

Albert C.M., Hennekens C.H., O'Donnell C.J., Ajani U.A., Carey V.J., Willett W.C., Ruskin J.N., and Mason J.E.; Fish Consumption and Risk of Sudden Cardiac Death. JAMA 1998;279:23-8

Albert C.M., Campos H., Stampfer M.J., Ridker P.M., Manson J.E., Willett W.C. and Ma J.; Blood Levels of Long-Chain n-3 Fatty Acids and the Risk of Sudden Death. N Engl J Med 2002;346:1113

Alonso A., Martinez-Gonzalez M.A., Serrano-Martinez M.; Fish Omega-3 Fatty Acids and Risk of Coronary Heart Disease. Med Clin (Barc) 2003;121(1):28-35

American Heart Association, downloaded from website 08/29/2006 www.americanheart.org/presenter.jhtml?identifier=4644.

Anderson L.F., Solvoll K., Drevon C.A.; Very-long-chain n-3 Fatty Acids as Biomarkers for Intake of Fish and n-3 Fatty Acid Concentrates. Am J Clin Nutr 1996;64(3):379-80

Ascherio A., Rimm E.B., Stampfer M.J., Giovannucci E.L. and Willett W.C.; Dietary Intake of Marine n-3 Fatty Acids, Fish Intake, and the Risk of Coronary Disease Among Men. N Engl J Med 1995;332(15):997-82

Barberger-Gateau P., Letenneur L., Deschamps V., Peres K., Dartigues J-F., and Renaud S.; Fish, Meat, and Risk of Dementia: Cohort Study. BMJ 2002;325:932-3

Barberger-Gateau P., Jutand M-A., Letenneur L., Larrieu S., Tavernier B. and Berr C.; Correlates of Regular Fish Consumption in French Elderly Community Dwellers: Data From the Three-City Study. Eur J Clin Nutr 2005:1-9

Boffetta P., Sallsten G., Garcia-Gomez M., Pompe-Kirn V., Zaridze D., Bulbulyan M., Caballero J-D., Ceccarelli F., Kobal A.B., and Merler E.; Mortality From Cardiovascular Diseases and Exposure to Inorganic Mercury. Occup Environ Med 2001;58:461-466

Bouzan C., Cohen J.T., Connor W.E., Kris-Etherton P.M., Gray G.M., Going A., Lawrence R.S., Savitz A., and Teutsch S.M.; A Quantitative Analysis of Fish Consumption and Stroke Risk. Am J Prev Med 2005;29(4):347-352

Brouwer I.A., Zock P.I., Camm A.J., Bocker D., Hauer R.N.W., Wever E.F.D., Dullemeijer C., Ronden J.E., Katan M.B., Lubinski A., Buschler H., Schouten E.G.; Effect of Fish Oil on Ventricular Tachyarrhythmia and Death in Patients With Implantable Cardioverter Defibrillators: The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) Randomized Trial. JAMA 2006;295(22):2613-19

Brune D., Nordberg G.F., Vesterberg O., Gerhardsson L., Wester P.O.; A Review of Normal Concentrations of Mercury in Human Blood. Sci Total Environ 1991;100:235-282

Bucher H.C., Hengstler P., Schindler C. and Meier G.; N-3 Polyunsaturated Fatty Acids in Coronary Heart Disease: A Meta-analysis of Randomized Controlled Trials. Am J Med 2002;112:298-304

Berger J., Dixon C., and Boring C.S.; Effect of Deep-Frying Fish on Risk From Mercury. J Toxi Environ Health, Part A. 2003;66:817-828

Burr M.L., Gilbert J.F., Holliday R.M., Elwood P.C., Fehily A.M., Rogers S., Sweetnam P.M. and Deadman N.M.; Effects of Changes in Fat, Fish, and Fibre Intakes on Death and Myocardial Reinfarction: Diet and Reinfarction Trial (DART). The Lancert, 1999; September 30

Burr M.L., Ashfield-Watt P.A., Dunstan F.D., Fehily A.M., Breay P., Ashton T., Zotos P.C., Haboubi N.A., and Elwood P.C.; Lack of Benefit of Dietary Advice to Men with Angina: Results of a Controlled Trial. Eur J Clin Nutr 2003;57(2):193-200

Calder P.C.; n-3 Fatty Acids and Cardiovascular Disease: Evidence Explained and Mechanisms Explored. Clin Sci (Lond) 2004;107(1):1-11

Carpenter D.O.; Polychlorinated Biphenyls (PCBs): Routes of Exposure and Effects on Human Health. Rev Environ Health 2006;21(1):1-23

Castoldi A.F., Coccini T. and Manzo L.; Neurotoxic and Molecular Effects of Methylmercury in Humans. Rev Environ Health 2003;18(1):19

Chan H.M and Egeland M.; Fish Consumption, Mercury Exposure, and Heart Diseases. Nut Rev 2004;62(2):68-72

Christensen J.H.; n-3 Fatty Acids and the Risk of Sudden Cardiac Death: Emphasis on Heart Rate Variability. Dan Med Bull 2003;50(4):347-67

Clarkson T.W. and Strain J.J.; Nutritional Factors May Modify the Toxic Action of Methyl Mercury in Fish-Eating Populations. Am Soc Nutr Sci 2003;133:1539S-1543S

Cohen J.T., Bellinger D.C., Connor W.E. and Shaywitz B.A.; A Quantitative Analysis of Prenatal Intake of n-3 Polyunsaturated Fatty Acids and Cognitive Development. Am J Prev Med 2005;29(4):366-374

Dallongeville J., Yarnell J., Ducimetiere P., Arveiler D., Ferrieres J., Montaye M., Luc G., Evans A., Bingham A., Hass B., Ruidavets J-B., and Amouyel P.; Fish Consumption Is Associated with Lower Heart Rates. Circulation 2003;108:820-825

Daniels J.L., Longecker M.P., Roland A.S., Golding J.; Fish Intake During Pregnancy and Early Cognitive Development of Offspring. Epidemiology 2004;15:394-402

Davidson P.W., Myers G.J., Cox C., Wilding G.E., Shamlaye C.F., Huang L.S., Cernichiari E.; Methylmercury and Neurodevelopment: Longitudinal Analysis of the Seychelles Child Development Cohort. Neurotoxicol Teratol 2006; Jun 29

Daviglus M.L., Stamler J., Orencia A.J., Dyer A.R., Liu K., Greenland P., Walsh M.K., Morris D., and Shekelle R.B.; Fish Consumption and the 30-Year Risk of Fatal Myocardial Infarction. N Eng J Med 1997;336:1046-53

Dewailly E., Blanchet C., Lemieux S., Sauve L., Gingras S., Ayotte P., and Holub B.J.; n-3 Fatty Acids and Cardiovascular Disease Risk Factors Among the Inuit of Nunavik. Am J Clin Nutr 2001;74:464-73

Debes F., Budtz-Jergensen E., Weihe P., White R.F., and Grandjean P.; Impact of Prenatal Methylmercury Exposure on Neurobehaviuoral Function at
Age 14 Years. Neurotoxicol Teratol 2006;28(3):363-375

de la Sierra A.; Value of Pulse Pressure as a Cardiovascular Risk Marker. Med Clin (Barc) 2006;126(10):384-8

Dolecek T.A.; Epidemiological Evidence of Relationships Between Dietary Polyunsaturated Fatty Acids and Mortality in the Multiple Risk Factor Intervention Trial. Soc Experi Bio Med 1992;92:9727-37

Dolecek T.A. and Grandits G.; Dietary Polyunsaturated Fatty Acids and Mortality in the Multiple Risk Factor Intervention Trial (MRFIT). World Rev Nutr Diet 1991;66:205-216

Dorea J.G., de Souza J.R., Rodrigues P., Ferrari I. and Barbosa A.C.; Hair Mercury (signature of Fish Consumption) and Cardiovascular Risk in Munduruku and Kayabi Indians of Amazonia. Environ Res 2005;97(2):209-19.

Ely J.T.; Mercury Induced Alzheimer's Disease: Accelerating Incidence? Bull Environ Contam Toxicol 2001;67(6):800-6

Engelhart M.J., Geerlings M.I., Ruitenberg A., Van Swisten J.C., Hofman A., Witteman J.C. and Breteler M.M.; Diet and Risk of Dementia: Does Fat Matter?: The Rotterdam Study. Neurology 2003;60(12):2020-1

Erkkila A.T., Lehto S., Pyorala K. and Uusitupa M.; n-3 Fatty Acids and 5-y Risks of Death and Cardiovascular Disease Events in Patients with Coronary Artery Disease. Am J Clin Nutr 2003;78-65-71

Erkkila A.T., Lichtenstein A.H., Mozaffarian D. and Herrington D.M.; Fish Intake is Associated with a Reduced Progression of Coronary Artery Atherosclerosis in Postmenopausal Women with Coronary Artery Disease. Am J Clin Nutr 2004;80:626-32

Erkkila A.T., Matthan N.R., Herrington D.M. and Lichtenstein A.H.; Higher Plasma Docosahexaenoic Acid is Associated with Reduced Progression of Coronary-Artery Atherosclerosis in Women with Established Coronary Artery Disease. J Lipid Res 2006 (in press).

Fernandez-Jarne E., Alegre G.F., Alonso G.A., de la Fuente A.C., and Martinez-Gonzalez M.A.; Dietary Intake of n-3 Fatty Acids and the Risk of Acute Myocardial Infarction: A case-Control Study. Med Clin (Barc) 2002;118(4):121-5

Folsom A.R. and Demissie Z.; Fish Intake, Marine Omega-3 Fatty Acids, and Mortality in a Cohort of Postmenopausal Women. Am J Epidemiol 2004;160:1005-1010

Foran J.A., Carpenter D.O., Hamilton M.C., Knuth B.A. and Schwager S.J.; Risk-based Consumption Advice for Farmed Atlantic and Wild Pacific Salmon Contaminated with Dioxins and Dioxin-like Compounds. Environ Health Perspect 2005;113(5):552-6

Frustaci A., Magnavita N., Chimenti C., Caldarulo M., Sabbioni E., Pietra R., Cellini C., Possati GF, Maseri A.; Marked Elevation of Myocardial Trace Elements in Idiopathic Dilated Cardiomyopathy Compared with Secondary Cardiac Dysfunction. J Am Coll Cardiol 1999;33(6):1578-83

Fung T.T., W.C.Willett, Stampfer M.J., Manson J.E. and Hu F.B.; Dietary Patterns and the Risk of coronary Heart Disease in Women. Arch Intern Med 2001;161:1857-1862

Gillum R.F., Mussolino M. and Madans J.H.; The Relation Between Fish Consumption, Death From All Causes, and Incidence of Coronary Heart Disease: the NHANES I Epidemiologic Follow-up Study. J Clin Epidem 2000;53:237-244

Gorder D.D., Dolecek T.A., Coleman G.G., Tillotson J.L., Brown H.B., Lenz-Litzow K., Bartsch G.E. and Grandits G.; Dietary Intake in the Multiple Risk Factor Intervention Trial (MRFIT): Nutrient and Food Group Changes Over 6 Years. J Am Diet Assoc 1986;86(6):744-51

Grandjean P., Murata K., Budtz-Jergensen E. and Weihe P.; Cardiac Autonomic Activity in Methylmercury Neurotoxicity: 14-year Follow-up of a Faroese Birth Cohort. J Pediatr 2004;144:169-76

Grandjean P., Budtz-Jergensen E., Jergensen P.J. and Weihe P.; Umbilical Cord Mercury Concentration as Biomarker of Prenatal Exposure to Methylmercury. Environ Health Perspect 2005;113:905-908

Guallar E., Hennekens C.H., Sacks F.M., Willett W.C. and Stampfer M.J.; A Prospective Study of Plasma Fish Oil Levels and Incidence of Myocardial Infarction in U.S. Male Physicians. JACC 1995;25:387-94

Guallar E., Aro A., Jimenez F.J., Martin-Moreno J.M., Salminen I. van't Veer P., Kardinaal A.F.M., Gomez-Aracena J., Martin G.C., Kohlmeier L., Kark J.D., Mazaev V.P., Ringstad J., Guillen J., Riemersma R.A., Huttunen J.K., Thamm M. and Kok F.J.; Omega-3 Fatty Acids in Adipose Tissue and Risk of Myocardial Infarction: The EURAMIC Study. Arterioscler Thromb Vasc Biol 1999;19:1111-1118

Guallar E., Sanz-Gallardo I., van't Veer P., Bode P., Aro A., Gomez-Aracena J., Kark J.D., Riemersma R.A., Martin-Moreno J.M. and Kok F.J.; Mercury, Fish Oils, and the Risk of Myocardial Infarction. N Engl J Med 2002;347:1747-54

Haag M. and Dippenaar N.G.; Dietary Fats, Fatty Acids and Insulin Resistance: Short Review of a Multifaceted Connection. Med Sci Monit 2005;11(12):359-367

Hallgren C.G., Hallmans G., Jansson J.H., Marklund S.L., Huhtasaari F., Schutz A., Stromberg U., Vessby B. and Skerfving S.; Markers of High Fish Intake are Associated with Decreased Risk of a First Myocardial Infarction. Br J Nutr 2001;86(3):397-404

Hansen J.C. and Gilman A.P.; Exposure of Artic Populations to Methylmercury from Consumption of Marine Food: An Updated Risk-Benefit Assessment. Int J Circumpolar Health 2005;64(2):121-136

Hayward D., Wong J. and Krynitasky A.J.; Polybrominated Diphenyl Ethers and Polychlorinated Biphenyls in Commercially Wild Caught and Farm-raised Fish Fillets in the United States. Environ Res 2006 Jun 9

He K., Rimm E.B., Merchant A., Rosner B.A., Stampfer M.J., Willett W.C. and Ascherio A.; Fish Consumption and Risk of Stroke in Men. JAMA 2002;288(24):3130-6

He K., Song Y., Daviglus M.L., Liu K., Van Horn L., Dyer A.R. and Greenland P.; Accumulated Evidence on Fish Consumption and Coronary Heart Disease Mortality: A Meta-Analysis of Cohort Studies. Circulation 2004;109:2705-2711

Holguin F., Tellez-Rojo M.M., Lazo M., Mannino D., Schwartz J., Hernandez M., and Romieu I.; Cardiac Autonomic changes Associated with Fish Oil vs. Soy Oil Supplementation in the Elderly. CHEST 2005;127:1102-1107

Holub D.J. and Holub B.J.; Omega-3 Fatty Acids from Fish Oils and Cardiovascular Disease. Mol Cell Biochem 2004;263:217-225

Hooper L., Thompson R.L., Harrison R.A., Summerbell C.D., Ness A.R., Moore H.J., Worthington H.V., Durrington P.N., Higgins P.T., Capps N.E., Riemersma R.A., Ebrahim S.B.J., and Smith G.D. Risks and Benefits of Omega 3 Fats for Mortality, Cardiovascular Disease, and Cancer: Systematic Review. BMJ 2006;10:1136

Iso H., Kobayashi M., Ishihara J., Sasaki S., Okada K., Kita Y., Kokubo Y., and Tsugane S.; Intake of Fish and n-3 Fatty Acids and Risk of Coronary Heart Disease Among Japanese: The Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation 2006;113:195-202

Jacobson J.L.; Contending with Contradictory Data in a Risk Assessment Context: The Case of Methylmercury. NeuroTox 2001;22:667-675

Jarvinen R., Knekt J.R., Rissanen P. and Reunanen A.; Intake of Fish and Long-chain n-3 Fatty Acid and the Risk of Coronary Heart Mortality in Men and Women. Br J Nutr 2006;95(4):824-9

Jedrychowski W., Jankowski J., Flak E., Skarupa A., Mroz E., Sochacka-Tatara E., Lisowska-Miszczyk I., Szpanowska-Wohn A., Rauh V., Skolicki Z., Kaim I. and Perera F.; Effects of Prenatal Exposure to Mercury on Cognitive and Psychomotor Function in One-Year-Old Infants: Epidemiologic Cohort Study in Poland. Ann Epidemiol 2006;16:439-447

Jones R.L., Sinks T., Schober S.E., Pickett M.; Blood Mercury Levels in Young Children and Childbearing-Aged Women – United States, 1999-2002. Morbidity and Mortality Weekly Report 2004;53:1018-1020.

Jorgensen M.D., Pedersen M.B., Siggaard C., Sorensen T.B., Mulvad G., Hansen J.C., Skjoldborg H., and Pedersen E.B.; Twenty-four-hour Blood Pressure Among Greenlanders and Danes: Relationship to Diet and Lifestyle. Scand J Clin Lab Invest 2002;62(6):413-22

Jouven X., Desnos M., Guerot C., and Ducimetiers P.; Predicting Sudden Death in the Population: The Paris Prospective Study I. Circulation 1999 99;(15):1978-83

Kalmijn S., van Boxtel M.P., Ocke M., Verschuren W.M., Kromhout D. and Launer L.J.; Dietary Intake of Fatty Acids and Fish in Relation to Cognitive Performance at Middle Age. Neurology 2004 62;(2):275-80

Kardinaal A.F.M., Kok F.J., Kohimeier L., Martin-Moreno J.M., Ringstad J., Gomez-Aracena J., Mazaev V.P., Thamm M., Martin B.C., Aro A., Kark J.D., Delgado_Rodriguez M., Riemersma R.A., van't Veer, P. and Huttunen J.K.; Association Between Toenail Selenium and Risk of Acute Myocardial Infarction in European Men. Am J Epidemiol 1997;145:373-9

Kingman A., Albertini T., and Brown L.J.; Mercury Concentrations in Urine and Whole Blood Associated with Amalgam Exposure in a US Military Population. J Dent Res 1998;77(3):461-71

Knoops K.T.B., de Groot L., Kromhout D., Perrin A-E., Moreiras-Varela O., Menotti A. and van Staveren W.; Mediterranean Diet, Lifestyle Factors, and 10-Year Mortality in Elderly European Men and Women. JAMA 2004;292:1433-1439

Kobayashi M., Sasaki S., Kawabata T., Hasegawa K., and Tsugane S.; Validity of a Self-Administered Food Frequency Questionnaire Used in the 5-year Follow-up Survey of the JPHC Study Cohort I to Assess Fatty Acid Intake: Comparison with Dietary Records and Serum Phospholipid Level. J Epidemiol 2003;13(1 Suppl):S64-81

Kok F.J. and Kromhout D.; Atherosclerosis: Epidemiological Studies on the Health Effects of a Mediterranean Diet. Eur J Nutr 2004;(Suppl 1)43:1/2-1/5

Konig A., Bouzan C., Cohen J.T., Connor W.E., Kris-Etherton P.M., Gray G.M., Lawrence R.S., Savitz D.A., and Teutsch S.M.; A Quantitative Analysis of Fish Consumption and Coronary Heart Disease Mortality. Am J Prev Med 2005;29(4):335-346

Kris-Etherton P.M., Harris W.S., and Appel L.J.; Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease. Arterioscler Thromb Vasc Biol 2003;23:e20-e31

Kromhout D., Bosschieter E.B. and Coulander C.L.; The Inverse Relation Between Fish Consumption and 20-Year Mortality From Coronary Heart Disease. N Engl J Med 1985;312:1205-9

Kromhout D., Freskens E.J. and Bowles C.H.; The Protective Effect of a Small Amount of Fish on Coronary Heart Disease Mortality in an Elderly Population. Int J Epidemiol 1995;24(2):340-5

Kromhout D.; Fish Consumption and Sudden Cardiac Death. JAMA 1998;279:65

Kull I., Bergstrom A., Lilja G., Pershagen G. and Wickman M.; Fish Consumption During the First Year of Life and Development of Allergic Diseases During Childhood. Allergy 2006;61:1009

Lamaitre R.Nl, King I.B., Mozaffarian D., Kuller L.H., Tracy R.P. and Siscovick D.S.; n-3 Polyunsaturated Fatty Acids, Fatal Ischemic Heart Disease, and Nonfatal Myocardial Infarction in Older Adults: The Cardiovascular Health Study. Am J Clin Nutr 2003;77:319-25

Levenson C.W. and Axelrad D.M.; Too Much of a Good Thing? Update on Fish Consumption and Mercury Exposure. Nutr Rev 2006;64:139-14

Lipfert F.W.; Air Pollution and Community Health, Van Nostrand Reinhold, New York 1994

Lipfert F.W., Estimating Exposures to Methylmercury: Effects of Uncertainties, Water, Soil, Air Poll 1997; 97:119-145

MRFIT Research Group; Mortality Rates After 10.5 Years for Participants in the Multiple Risk Factor Intervention Trial. Findings Related to a Priori Hypotheses of the Trial. The Multiple Risk Factor Intervention Trial Research Group. JAMA 1990;263:1795-801

Mahaffey K.R.; Fish and Shellfish as Dietary Sources of Methylmercury and the ω-3 Fatty Acids, Eicosahexaenoic Acid and Docosahexaenoic Acid: Risks and Benefits. Environ Res 2004;95:414-428

Marchioli R., Barzi F., Bomba E., Chieffo C., DiGregorio D., DiMascio R., Franzosi M.G., Geraci E., Levantesi G., Maggioni A.P., Mantini L., Marfisi R.M., Mastrogiuseppe G., Mininni N., Nicolosi G.L., Santini M., Schweiger C., Tavazzi L., Tognoni G., Tucci C., Valagussa F.; Early Protection Against Sudden Death by n-3 Polyunsaturated Fatty Acids After Myocardial Infarction Time-Course Analysis of the Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897-1903

Margolin G., Huster G., Glueck C.J., Speirs J., Vandegrift J., Illig E., Wu J., Streicher P., Tracy T.; Blood Pressure Lowering in Elderly Subjects: A Double-Blind Crossover Study of Omega-3 and Omega-6 Fatty Acids. Am J Clin Nutr 1991;53:562-72

Matthan N.R., Jordan H., Chung M., Lichtenstein A.H., Lathrop D.A. and Lau J.; A Systematic Review and Meta-Analysis of the Impact of ω-3 Fatty Acids on Selected Arrhythmia Outcomes in Animal Models. Metabol Clin Exper 2005;54:1557-1565

McDowell M.S., Sillon C.F., Osterloh J., Bolger P.M., Pellizzari E., Fernando R., Montes de Oca R., Schober S.E., Sinks T., Jones R.L. and Mahaffey K.R.; Hair Mercury Levels in U.S. Children and Women of Childbearing Age: Reference Range Data From NJANES 1999-2000. Environ Health Perspect 2004;112:1165-71

Mori T.A. and Beilin L.J.; Omega-3 Fatty Acids and Inflammation. Curr Atheroscler Rep 2004;6:461-7

Morris M.C., Sacks F. and Rosner B.; Does Fish Oil Lower Blood Pressure? A Meta-Analysis of Controlled Trials. Circulation 1993;88:523-33

Morris M.C., Manson J.E., Rosner B., Buring J.E., Willett W.C. and Hennekens C.H.; Fish Consumption and Cardiovascular Disease in the Physicians' Health Study: A Prospective Study. Am J Epidemiol 1995;142:166-75

Morris M.C., Evans D.A., Bienias J.L., Tangney C.C., Bennett D.A., Wilson R.S., Aggarwal N. and Schneider J.; Consumption of Fish and n-3 Fatty Acids and Risk of Incident Alzheimer Disease. Arch Neurol 2003;60:923-4

Morrissey M.T.; The Good, the Bad, and the Ugly: Weighing the Risks and Benefits of Seafood Consumption. Nutr Health 2006;18:193-7

Morton J., Mason H.J., Ritchie K.A. and White M.; Comparison of Hair, Nails and Urine for Biological Monitoring of Low Level Inorganic Mercury Exposure in Dental Workers. Biomarkers 2004;9:47-55

Mozaffarian D., Prineas R.J., Stein P.K. and Siscovick D.S.; Dietary Fish and n-3 Fatty Acid Intake and Cardiac Electrocardiographic Parameters in Humans. J Am Coll Cardiol 2006;48:478-84

Murata K., Sakamoto M., Nakai K., Dakeishi M., Iwata T., Liu X.J. and Satoh H.; Subclinical Effects of Prenatal Methylmercury Exposure on Cardiac Autonomic Function in Japanese Children. Int Arch Occup Environ Health 2006;79:379-86

Mutter J. and Naumann J.; Blood Mercury Levels and Neurobehavior. JAMA 2005;294:679-80

Mutter J., Naumann J., Sadaghiani C., Schneider R. and Walach H.; Alzheimer Disease: Mercury as Pathogenetic Factor and Apolipoprotein E as a Moderator. Neuro Endocrinol Lett 2004;25:331-9

Nakai K., Suzuki K., Oka T., Murata K., Sakamoto M., Okamura K., Hosokawa T., Sakai T., Nakamura T., Saito Y., Kurokawa N., Kameo S. and Satoh H.; The Tohoku Study of Child Development: A Cohort Study of Affects of Perinatal Exposures to Methylmercury and Environmentally Persistent Organic Pollutants on Neurobehavioral Development in Japanese Children. Tohoku J Exp Med 2004;202:227-37

Nakai K. and Satoh H.; Developmental Neurotoxicity Following Prenatal Exposures to Methylmercury and PCBs in Humans from Epidemiological Studies. Tohoku J Exp Med 2002;196:89-98

Nakamura Y., Ueshima H., Okamura T., Kadowaki T., Hayakawa T., Kita Y., Tamaki S., Okayama A.; Association Between Fish Consumption and All-cause and Cause-specific Mortality in Japan: NIPPON DATA80, 1980-99. Am J Med 2005;118:239-245

National Research Council; Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology Commission on Life Sciences. National Academy Press, Washington DC 2000

Ness A.R., Hughes J., Elwood P.C., Whitley E., Smith G.D., Burr M.L.; The Long Term Effect of Dietary Advice in Men With Coronary Disease: Follow–up of the Diet and Reinfarction Trial (DART). Eur J Clin Nutr 2002;56:512-518

Oh, R.; Practical Applications of Fish Oil (Ω-3 Fatty Acids) in Primary Care. J Am Board Fam Pract 2005;18:28-36

Oka T., Matsukura M., Okamoto M., Harada N., Kitano T., Miike T., Futatsuka M.; Autonomic Nervous Functions in Fetal Type Minimata Disease Patients: Assessment of Heart Rate Variability. Tohoku J Exp Med 2002 Dec;198(4):215-221

Oomen C.M., Feskens E.J.M., Rasanen L., Fidanza F., Nissinen A.M., Menotti A., Kok F.J., Kromhout D.; Fish Consumption and Coronary Heart Disease Mortality in Finland, Italy, and the Netherlands. Am J Epidemiol 2000;151:999-1006

Osler M., Godtfredsen J., Gronbaek M.N., Marckmann P., Overvad O. K.; A Quantitative Assessment of the Impact of Diet on the Mortality of Heart Disease in Denmark. Estimation of Etiologic Fraction. Ugeskr Laeger 2000 Sep 11;162(37):4921-5

Pedersen J.I., Ringstad J., Almendingen K., Haugen T.S., Stensvold I., Thelle D.S.; Adipose Tissue Fatty Acids and Risk of Myocardial Infarction – a Case-Control Study. Eur J Clin Nutr 2000;54:618-625

Pedersen E.B., Jorgensen M.E., Pedersen M., Siggaard C., Sorensen T.B., Mulvad G., Hansen J.C., Asmund G., Skjoldborg H.; Relationship Between Mercury in Blood and 24-H Ambulatory Blood Pressure in Greenlanders and Danes. Am J Hypertens 2005;18:612-618

Pietinen P., Ascherio A., Korhonen P., Hartman A.M., Willett W.C., Albanes D., Virtamo J.; Intake of Fatty Acids and Risk of Coronary Heart Disease in a Cohort of Finnish Men. Am J Epidemiol 1997;145:876-87

Rasmussen B.M., Vessby B., UusitupaM., Berglund L., Pedersen E., Riccardi G., Rivellese A.A., Tapsell L., Hermansen K.; Effects of Dietary Saturated, Monosaturated and N-3 Fatty Acids on Blood Pressure in Healthy Subjects. Am J Clin Nutr 2006 Feb;83(2):221-226

Rissanen T., Voutilainen S., Nyyssonen K., Lakka T., Salonen J.T.; Fish Oil Derived Fatty Acids, Docosahexaenoic Acid and Docosapentaenoic Acid, and the Risk of Acute Coronary Events. Circulation 2000;102:2677-2679

Ritchie K.A., Gilmour W.H., MacDonald E.B., Burke F.J., McGowan D.A., Dale I.M., Hammersley R., Hamilton R.M., Binnie V., Collington D.; Health and Neuropsychological Functioning of Dentists Exposed to Mercury. Occup Environ Med 2002 May;59:287-93

Romieu I., Tellez-Rojo M.M., Lazo M., Manzano-Patino A., Cortez-Lugo M., Julien P., Belanger M.C., Hernandez-Avila M., Holguin F.; Omega-3 Fatty Acid Prevents Heart Rate Variability Reductions Associated With Particulate Matter. Am J Resp Crit Care Med 2005; 172:1534-1540

Sacks E.M., Stone P.H., Gibson C.M., Silverman D.I., Rosner B., Pasternak R.C.; Controlled Trial of Fish Oil for Regression of Human Coronary Altherosclerosis. J Am Coll Cardiol 1995 Jun;(7):1492-1498

Sakamoto M., Kubota M., Liu X.J., Murata K., Nakai K., Satoh H.; Maternal and Fetal Mercury and n-3 Polyunsaturated Fatty Acids as a Risk and Benefit of Fish Consumption to Fetus. Environ Sci Technol 2004 Jul 15;38(14):3860-3863

Salonen J.T., Nyyssonen K., Salonen R.; Fish Intake and the Risk of Coronary Disease. N Engl J Med 1995; 333(14): 937

Salonen J.T., Seppanen K., Nyyssonen K., korpela H., Kauhanen J., Kantola M., Tuomilehto J., Esterbauer H., Tatzber F., Salonen R.; Intake of Mercury from Fish, Lipid Peroxidation, and the Risk of Myocardial Infarction and Coronary, Cardiovascular and Any Death in Eastern Finnish Men. Circulation 1995;91:645-655

Salonen J.T., Seppanen K., Lakka T.A., Salonen R., Kaplan G.A.; Mercury Accumulation and Accelerated Progression of Carotid Atherosclerosis: A Population Based Prospective 4-Year Follow-Up Study in Men in Eastern Finland. Atherosclerosis 2000 Feb;148(2):265-273

Saxe S.R., Wekstein M.W., Kryscio R. j., Henry R.G., Cornett C.R., Snowdon D.A., Grant F.T., Schmitt F.A., Donegan S. J., Wekstein D.R., Ehmann W.D., Markesbery W.R.; Alzheimer's Disease, Dental Amalgam and Mercury. J Am Dent Assoc 1999 Feb;130(2):191-199

Schurrs A.H., deWolffe F.A.; Relation Between Mercury and Alzheimer's Disease. Ned Tijdschr Tandheelkd 1997 Jun;104(6):219-222

Serra-Majem L., Roman B., Estruch R.; Scientific Evidence of Interventions Using the Mediterranean Diet: A Systematic Review. Nutr Rev 2006 Feb;64(2 pt 2):S27-47

Siscovick D., Raghunathan T.E., King I., Weinman S., Bovbjerg V.E., Kushi L., Cobb L.A., Copass M.K., Psaty B.M., Lemaitre R., Retzlaff B., Knopp R.; Dietary Intake of Long Chain n-3 Polyunsaturated Fatty Acids and the Risk of Primary Cardiac Arrest. Am J Clin Nutr 2000;71(suppl):208S-12S

Sorensen N., Murata K., Budtz-Jorgensen E., Weihe P., Grandjean P.; Prenatal Methylmercury Exposure as a Cardiovascular Risk Factor at Seven Years of Age.
Epidemiology 1999 Jul;10(4):370-375

Stampfer M.J., Hu F.B., Manson J.E., Rimm E.B., Willett W.; Primary Prevention of Coronary Heart Disease in Women Through Diet and Lifestyle. N Engl J Med 2000;343:16-22

Studer M., Briel M., Leimenstoll B., Glass T., Bucher H.C.; Effect of Different Antilipidemic Agents and Diets on Mortality. Arch Intern Med 2005;165:725-730

Suzuki K., Nakai K., Ohba T., Murata K., Sakamoto M., Satoh H.; Tohoku Study of Child Development, a Cohort Study to Examine the Effects of Perinatal Exposure to Methylmercury, PCBs or Dioxins on Child Development; the Association of Neonatal Neurobehavioral Status with Maternal Hair Mercury Concentration and Fish Intake. NIMD Forum 20 Feb 2006:97

Tavani A., Pelucchi C., Negri E., Bertuzzi M., LaVecchia C.; n-3 Polyunsaturated Fatty Acids, Fish, and Nonfatal Acute Myocardial Infarction. Circulation 2001;104:2269-2272

Trichopolou A., Orfanos P., Norat T., Bueno-de Mesquita B., Ocke M., Peeters P., van der Schouw Y.T., Boeing H., Hoffmann K., Boffetta P., Nagel G., Masala G., Krogh V., Panico S., Tumino R., Vineis P., Bamia C., Naska A., Benetou V., Ferrari P., Slimani N., Pera G., Martinez-Garcia C., Navvarro C., Rodriguez-Barranco M., Dorronsoro M., Spencer E., Key T., Bingham S., Khaw K.T., Kesse E., Clavel-Chapelon F., Boutron-Rualt M.C., Berglund G., Wirfalt E., Hallmans G., Johansson I., Tjonneland A., Olsen A., Overvad K., Hundborg H., Riboli E., Trichopolous D.; Modified Mediterranean Diet and Survival: EPIC-Elderly Prospective Cohort Study. BMJ 2005;330(7498):991-994.

Van Oostdam J., Donaldson S.G., Feeley M., Arnold D., Ayotte P., Bondy G., Chan L., Dewaily E., Furgal C.M., Kuhnlein H., Loring E., Muckel G., Myles E., Receveur O., Tracy B., Gill U., Kalhok S.; Human Health Implications of Environmental Contaminants in Arctic Canada: A Review. Sci Total Environ 2005;351-352:165-246.

Virtanen J.K., Voutilainen S., Rissanen T.H., Mursu J., Tuomainen T-P., Korhonen M.J., Valkonen V-P., Seppanen K., Laukkanen J.A. and Salonen J.T.; Arterioscler Thromb Vasc Biol 2005;25:228-233

Virtanen J.K., Rissanen T.H., Voutilainen S. and Toumainen T-P.; Mercury as a Risk Factor for Cardiovascular Disease. J Nutr Biochem 2006 (in press).

Vupputuri S., Longnecker M.P., Daniels J.L., Guo X. and Sandler D.P.; Blood Mercury Level and Blood Pressure Among US Women: Results from the National Health and Nutrition Examination Survey 1999-2000. Environ Res 2005;97:195-200

Wallace F.A., Miles E.A. and Calder P.C.; Comparison of the Effects of Linseed Oil and Different Doses of Fish Oil on Mononuclear Cell Function in Healthy Human Subjects. Br J Nutr 2003;89:679-89

Wang C., Harris W.S., Chung M., Lichtenstein A.H., Balk E.M., Kupelnick B., Jordan H.S. and Lau J.; n-3 Fatty Acids from Fish or Fish-oil Supplements, but Not α-linolenic Acid, Benefit Cardiovascular Disease Outcomes in Primary- and Secondary-prevention Studies: A Systematic Review. Am J Clin Nutr 2006;84:5-17

Weil M., Bressler J., Parsons P., Bolla K., Glass T. and Schwartz B.; Blood Mercury Levels and Neurobehavioral Function. JAMA 2005;293:1875-82

Welch A.A., Lund E., Amiano P., Dorronsoro M., Brustad M., Kumle M., Rodriguez M., Lasheras C., Janzon L., Jansson J., Luben R., Spencer E.A., Overvad K., Tjonneland A., Clavel-Chapelon F., Linseisen J., Klipstein-Grobusch K., Benetou V., Zavitsanos X., Tumino R., Galasso R., Bueno-De-Mesquita H.B., Ocke M.C., Charrondiere U.R., Silmani N.; Variability of Fish Consumption within the 10 European Countries Participating in the European Investigation into Cancer and Nutrition (EPIC) Study. Public Health Nutr 2002;5(6b):1273-85

Welch A.A., Bingham S.A., Ive J., Friesen M.D., Wareham N.J., Riboli E., Khaw K.T.; Dietary Fish Intake and Plasma Phospholipid n-3 Polyunsaturated Fatty Acid Concentrations in Men and Women in the UK EPIC-Norfolk Cohort. Am J Clin Nutr (in press)

Whelton S.P., He J., Welton P.K. and Muntner P.; Meta-analysis of Observational Studies on Fish Intake and Coronary Heart Disease. Am J Cardiol 2004;93-1119-23

Yoshizawa K., Rimm E.B., Morris J.S., Spate V.L., Hsieh C-C., Spiegelman D., Stampfer M.J. and Willett W.C.; Mercury and the Risk of Coronary Heart Disease in Men. N Engl J Med 2002;347:1755-60

Yuan J-M. Ross R.K., Gao Y-T. and Yu M.C.; Fish and Shellfish Consumption in Relation to Death from Myocardial Infarction Among Men in Shanghai, China. Am J Epidemiol 2001;154;809-16

Zhang J., Sasaki S., Amano K. and Kesteloot H.; Fish Consumption and Mortality from All Causes, Ischemic Heart Disease, and Stroke: An Ecological Study. Preventive Med 1999;28:520-529

Zhang J., Temme E. and Kesteloot H.; Fish Consumption Is Inversely Associated with male Lung Cancer Mortality in Countries with High Levels of Cigarette Smoking or Animal Fat Consumption. Int J Epidemiol 2000;29:615-621

Appendix List of Abbreviations and Acronyms

ALA	α-linolenic acid (a PUFA found in plants)
AMI	acute myocardial infarction (heart attack)
CHD	coronary heart disease
CVD	cardiovascular disease (CHD + strokes)
DHA	docosahexaenoic acid |
DPA	docasapentaenoic acid | PUFAs found in fish
EPA	eicosapentaenoic acid |
EURAMIC	European Multicenter Case-Control Study on Antioxidants, Myocardial Infarction, and Cancer of the Breast
Hg	mercury
Hg^0	elemental mercury
HRV	heart rate variability
IHD	ischemic heart disease (a subset of CHD)
IMT	intima media thickness
IQ	intelligence quotient
KIHD	Kuopio (Finland) Ischemic Heart Disease Risk Factor Study
MeHg	methylmercury
MI	myocardial infarction (heart attack)
MRFIT	Multiple Risk Factor Intervention Trial
NHANES	National Health and Nutrition Examination Survey
omega-3	molecular structure notation for PUFAs (also denoted n-3)
OR	odds ratio (the ratio of cases to controls)
p-value	the probability of differing from zero
PCB	polychlorinated biphenyl
Pb	lead
PUFA	polyunsaturated fatty acid
R	correlation coefficient (R^2 = the proportion of variance explained by the relationship)
RBC	red blood cells
RCT	randomized controlled trial
RR	relative risk (the ratio of outcomes with the factor in question to those without) RRs > 1 represent "positive" relationships; RRs < 1 represent "negative" relationships
Se	selenium
(xxx-yyy)	95% confidence intervals