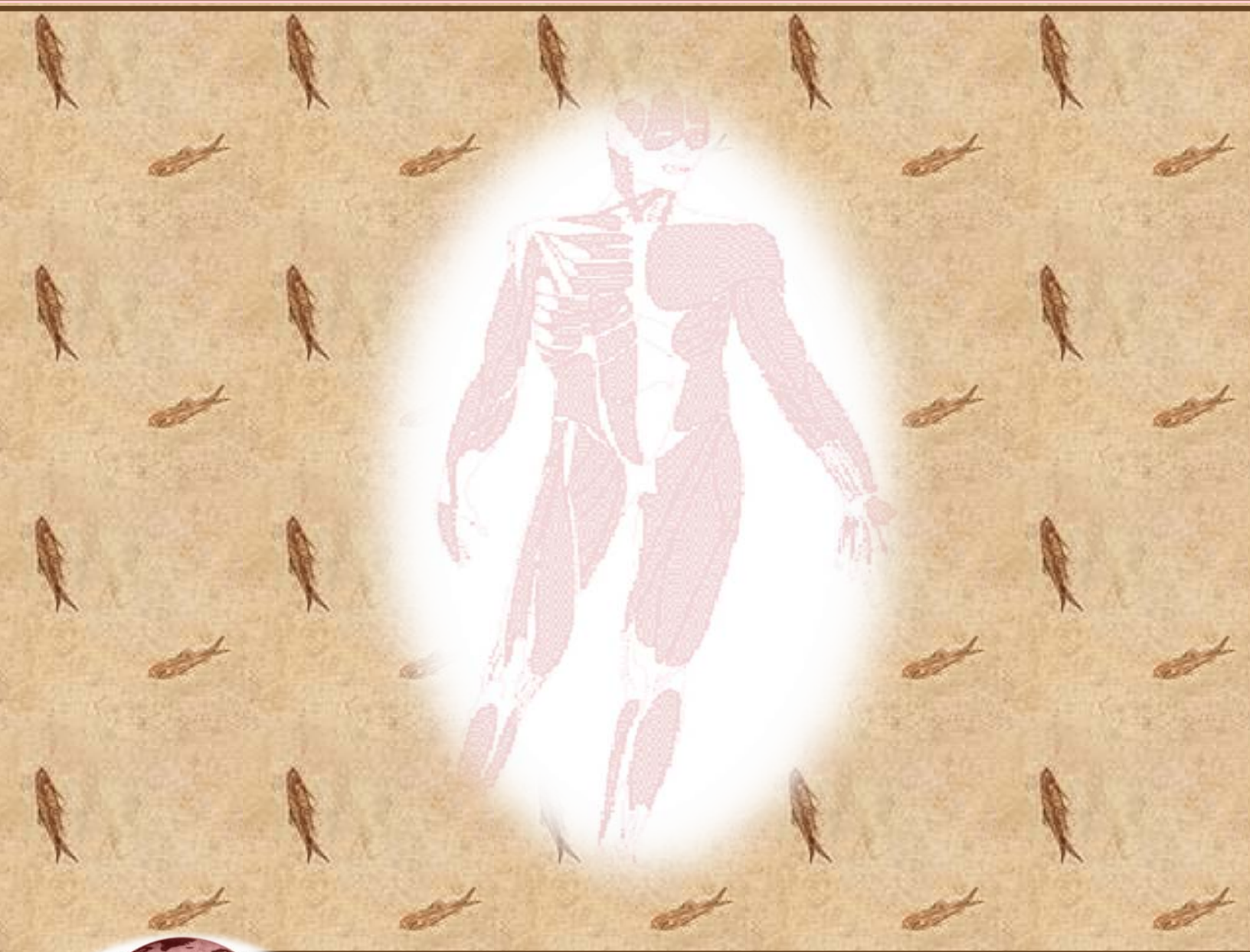
Fish, Mercury and Cardiac Health

A Review of the Current Literature

by Robert Ferguson



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A REVIEW OF THE CURRENT LITERATURE

by Robert Ferguson | March 2005

SUMMARY FOR POLICY MAKERS

In this companion to our white paper, ***How Safe Are We From the Fish We Eat?***, we offer a scientific analysis and evaluation of another serious public health scare related to fish consumption using the latest peer-reviewed literature: there is emerging evidence that trace amounts of "mercury" in fish could overwhelm the positive effects of Omega-3 fatty acids, causing cardiovascular disease (CVD), coronary heart disease (CHD) and even death in adults.

The "emerging evidence" appears to be based on two highly suspect studies.

The first is the Kuopio Ischaemic Heart Disease (KIHD) Risk Factor Study (Salonen et al. 1995, 2000) of a group of men in eastern Finland which suggested a statistical relationship linking mercury with risk of CHD and CVD. The second is a case-control study of 684 men from eight European countries and Israel (Guallar et al. 2002) concluding, "High mercury content may diminish the cardioprotective effect of fish intake."

However, it appears convincing from the literature that the claimed role of methylmercury for negatively impacting human health, including the heart, is neither clear nor direct, and often contradicted by published data. Instead, **the available evidence suggests that numerous risk factors other than methylmercury from fish** more likely explain most of the findings in Salonen et al. (1995, 2000) and Guallar et al. (2002). Also, as with the troubled Faeroe data on neurodevelopment of children, there are reasonable concerns that **the Finnish results are not directly applicable for the US population.**

At the same time, **the American Heart Association** has reviewed the benefits and risks of regular consumption of fish and fish oils. The review **concludes that fish and fish oils help prevent cardiovascular disease including fatal and non-fatal heart attacks, strokes, sudden cardiac death, and coronary artery disease (angina).**

Finally, media-fed alarmism (and lack of critical reporting) over mercury may be causing a dangerous fall off in the already inadequate levels of U.S. fish consumption.

It is no wonder that public health professionals are beginning to express concern, including new concerns that harm to public health may not be limited to nutritional deficits, but may extend to the inflated (mercury) fear itself (Ropeik, 2004) promoted by many interest groups and the EPA.

ANOTHER FALSE ALARM ABOUT MERCURY AND FISH

In the white paper ***How Safe Are We From The Fish We Eat?*** (September 2004)[1], the Center for Science and Public Policy (CSPP) surveyed the current peer-reviewed literature on mercury, fish consumption and human health. In synthesizing the findings of experts in related fields, we found that both epidemiological and clinical data suggest no credible scientific evidence that any Americans (including vulnerable groups such as pregnant women, infants and young children) have been exposed to harmful levels of mercury from consuming a wide variety of fish. Further, current levels of methylmercury (MeHg) production and aquatic bioaccumulation could simply continue – as they likely have since humans first evolved – unchanged even if all U.S. sources of atmospheric mercury emission and deposition were regulated to zero levels, yielding no reputed health benefit. However, there is significant potential harm to public health from being frightened by alarmist claims into avoiding or restricting fish nutrition. The primary reason is that fish contains the highly beneficial polyunsaturated (in contrast to saturated animal fats) omega-3 fatty acids known as the eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acids.

The environmental news outlet, *Greenwire*, recently reported that EPA officials agreed with CSPP's paper in raising "legitimate issues."[2]

In this companion paper, we offer scientific analysis and evaluation of another serious public health scare related to fish consumption: the trace amount of "mercury" in fish could overwhelm the positive effects of EPA+DHA, causing cardiovascular disease (CVD), coronary heart disease (CHD) and even death in adults.

Alan Stern of the New Jersey Department of Environmental Protection and member of the NRC (2000) MeHg committee recently revealed in Stern (2005)[3] that:

> "In 2000, the National Research Council's Committee on the Toxicological Effects of Methylmercury issued a report (NRC, 2000) in which it considered the various adverse health effects associated with the exposure to methylmercury (MeHg). Among the effects considered were cardiovascular effects. The committee concluded that 'Given the limits of the available data, neurotoxicity is the most sensitive, well-documented health endpoints. ... However, there is emerging evidence of potential effects on both the immune and cardiovascular systems at low doses of exposure. Although these effects are not well understood, emerging data underscore the need for continued research and raise the possibility of adverse effects ... at or below the current levels of concern for developmental neurotoxicity.' The committee recommended that an overall uncertainty factor of adjustment of 10 be applied to the neurodevelopmental point of departure to derive a MeHg reference dose (RfD). This uncertainty factor, in part, addressed the possibility that cardiovascular effects may ultimately prove to be a more sensitive endpoint than neurodevelopment effects. The US EPA, in its derivation of an RfD for methylmercury, followed the lead of the NRC committee in applying a similar rationale for its 10-fold uncertainty factor adjustment (US EPA 2004)."

Professor Thomas W. Clarkson from the University of Rochester, the world's leading authority on the human health effects of mercury and the most common biologically-active form methylmercury (MeHg), commented partly in response to claims like those in Stern (2005) that:[4]

> "If these [cardiac-related] findings are confirmed, two long-held dogmas may have to be abandoned, namely, that methylmercury primarily affects the central nervous system and that the prenatal period is the most susceptible part of the life cycle."

In light of the very serious implications for both human health and the actual science of methylmercury toxicity itself, the following literature reviews and critical analyses are offered for a clarification of the strengths and weaknesses of the "new" claims linking MeHg and cardiovascular health.

CLAIMS FOR LINKS OF "MERCURY" TO CARDIOVASCULAR DISEASE (CVD), CORONARY HEART DISEASE (CHD) AND DEATH

Salonen et al. (1995)[5], based on the Kuopio Ischaemic Heart Disease (KIHD) Risk Factor Study, was the first to suggest a strong statistical relationship linking non-fatty freshwater fish consumption, levels of urine and hair mercury and risk of CHD and CVD for a group of men in eastern Finland. A subsequent study by the same group in Salonen et al. (2000)[6] reported a correlation between mercury accumulation and accelerated progression of carotid atherosclerosis. The most recent results from this University of Kuopio group are reported by Virtanen et al. (2002)[7]:

> "The [KIHD] study is an ongoing population-based study designed to investigate risk factors for CHD, atherosclerosis and related outcomes in [1833 to 2005] middle-aged men from eastern Finland, **a population with one of the highest recorded rates of CHD.**[8] [Emphasis added] … The mean hair content of mercury was 1.9 ppm. The subjects were divided into quarters according to the mean hair mercury content (<0.66, 0.66-1.31, 1.32-2.50 and >2.50 ppm). The men in the highest quarter of hair mercury had almost **two times higher intake of fish** [original emphasis] than the men in the lower three quarters (68 vs. 38 grams/day …). During an average follow-up time of 12 years, 114 CVD deaths and 76 CHD deaths occurred among men free of CVD at baseline. In the Cox proportional hazards' model adjusted for age, examination years, serum HDL and LDL cholesterol and triglycerides, family history of ischaemic heart disease, systolic blood pressure, body mass index, serum selenium and intakes of saturated fatty acids, fiber, vitamin C and E and beta-carotene, **men in the highest quarter** [original emphasis] of hair mercury content (>2.5pm) had a **1.6-fold** (95% CI [confidence interval], 1.1-2.4) **risk of CVD death and 1.7-fold** (95% CI, 1.0-2.7) **risk of CHD death** [original emphasis] when compared with men in the lowest three quarters. "

But in "Epidemiology Faces Its Limits" (1995, Science, vol. 269, 164-169), the science reporter, Gary Taubes, has cautioned that most epidemiologists interviewed by the *Science* magazine suggested that for a statistical association to be taken seriously, the relative risk ratio better be at least higher than 3. [9] Thus, **it is clear that the relative risk ratios of 1.6 to 1.7 by the Finnish KIHD results of Salonen et al. (1995, 2000) are far below the statistical association standard that would be taken seriously by most epidemiologists.**

Next, Guallar et al. (2002)[10], based on a case-control study of 684 men from 8 European countries and Israel with myocardial infarction and 724 controls, reported that increasing a toenail mercury level from as low as 0.11 to 0.66 ppm (or about 0.34 to 2.03 ppm in equivalent hair mercury levels) "was directly associated" with a doubling of the risk of myocardial infarction **after adjusting for** age, DHA level, body-mass index, waist-to-hip ratio, smoking status, alcohol intake, HDL cholesterol level, diabetes, history of hypertension, family history of heart attack, blood levels of Vitamin E and beta-carotene and toenail selenium. These authors concluded that "high mercury content may diminish the cardioprotective effect of fish intake."

SCIENTIFIC CRITICISMS OF SOURCE PAPERS

It is well recognized that **CVD and CHD have multiple risk factors**[11] like age, family history, stress, dietary habits, smoking, alcohol use, diabetes and socio-economic status **that are not easily resolved or separated**. In fact, the University of Kuopio group, while examining the KIHD database, had reported many additional risk factors beyond the popularly promoted complications from mercury. These include:

(1) Hypertension[12]
(2) Mutation of hemochromatosis gene Cys282Tyr[13] (resulting in excess iron accumulation)
(3) Vodka (a whole bottle or more in 1 session) and beer (greater than 6 beers at a time) binging[14]
(4) Vitamin C deficiency[15]
(5) Low intakes of fruits, berries and vegetables[16]
(6) Low folate[17]
(7) Low intake of lycopene[18] (an antioxidant carotenoid mainly from tomatoes and tomato products)
(8) And even blood donation[19].

In this context, the primary criticisms concerning the claimed association of mercury and CVD+CHD by Salonen et al. (1995, 2000) are confirmed in the authors' own admission:

> **"Theoretically, our findings could be specific only for men in Eastern Finland, who traditionally have a high intake of meat, fish, and saturated animal fat and a low intake of selenium and vitamin C and, most likely, other vegetable-derived antioxidants."** [Emphasis added.]

Additionally, both Salonen et al. (1995) and Virtanen et al. (2002) clearly identified and confirmed that the men with the highest hair mercury group in their sample have a relatively larger proportion of rural inhabitants consuming local nonfatty fish species caught from local lakes and a significantly higher level of saturated fatty acids intake and measured LDL cholesterol (i.e., low-density lipoprotein or so-called bad cholesterol). The statistics compiled by the "Seven Countries Study" (USA, Finland, The Netherlands, Italy, former Yugoslavia, Greece and Japan) in Menotti et al. (1999)[20] shows that the **cohort from eastern Finland has the highest CHD 25-year death rates of 268/1000 deaths** when compared to 25/1000 CHD deaths for a cohort from Crete, Greece or to 30/1000 CHD deaths for a cohort from Tanushimaru, Japan where the consumption of animal fats are distinctively lower.

Coupling such information with the lack of accounting for stress— a suspected major risk factor[21]—in the KIHD study by Salonen et al. (1995), **one could indeed question the direct relevance of this result for men from eastern Finland for assessing the potential CVD+CHD vulnerability of average Americans from consuming a variety of ocean fish.**

Stern (2005) identified another major weakness of the Finnish KIHD study. In the Salonen et al. (1995) paper, it can already be noted that **as long as 9 years had elapsed between the time of collection of the hair and urine samples** (i.e., between March 1984 and December 1989, and the one-time only hair and urine mercury determination[22] was done at a much later time between May 1992 and August 1993 at the Department of Chemistry of the University of Kuopio) **and the recording of a CVD, CHD and death event** (i.e., reported until the end of 1992). An updated report of the KIHD mercury-related results in Virtanen et al. (2002) extends the problematic, long elapsed time to 16 years or so, hence **contributing to a serious exposure misclassification if there are any changes in the dietary habits or simply the amount of fish consumption during the intervening 16 years**.

Clarkson (2002) critically noted, "The highest recorded hair level of 15.7 ppm[23] was more than six standard deviations from the mean. A histogram of hair levels was not presented, but these statistics imply only a small percentage of the study group had high mercury levels. Such outlying and 'influential points' may play a major role in studies of this type. It would have been of interest to see if these correlations persisted when the very high mercury levels were excluded."[24]

Barbara V. Howard, both as chair of the American Heart Association (AHA) Nutrition Committee and president of MedStar Research Institute, cautioned:

> "These [mercury-related] results from Kuopio are intriguing, but preliminary, and should be viewed in the context of many other studies that have shown **a clear cardiovascular benefit** to consuming fish on a regular basis. It is important to note that this is an observational study, and the **conclusions do not prove a direct relationship** between the amount of mercury in hair and heart attacks. There may be factors such as the socio-economic status of the men or other dietary factors that are hard to measure, that account for the higher risk."[25] [Emphasis added.]

It is perhaps most telling that in an earlier experimental study of 62 healthy students from Kuopio, Finland, Agren et al. (1988) [26] had found that

> "**A moderate intake of fish-containing meals has some beneficial effects on plasma lipid and prostanoid metabolism, when coronary heart disease risk factors are considered.**" [Emphasis added.]

It is important to stress that the selected Kuopio students ate on average 3.7 times fish-containing meals per week for 15 weeks and that 87% of those fish meals consisted of locally caught freshwater fish (vendace, pike, perch and rainbow trout) and 13% of Baltic herring from brackish water. **The largest decrease in CHD risk was found for those 21 students that both took those Finnish freshwater fishmeals and restricted their lipid intake when compared to two other groups**.[27] In other words, for the University of Kuopio students, restricting intake of bad, saturated fatty acids and a moderate consumption of even freshwater fish from local Finnish lakes appeared to be providing beneficial health effects.

Having evaluated the problematic claims of the poorly designed KIHD study by Salonen et al. (1995, 2000), we now turn to the identified direct impact of mercury on myocardial infarction by Guallar et al. (2002).

In a rather sharp contrast to the results presented by Guallar et al. (2002) in the same issue of the *New England Journal of Medicine*, Yoshizawa et al. (2002)[28], based on a 5-year follow up of 33,737 U.S. male health professionals with no previous history of CVD or cancer, concluded that there is **no clear association** between total mercury exposure (covering measured toe nail mercury levels from about 0 to 14.56 ppm) and the risk of CVD after adjusting for age, smoking and other risk factors for CVD.

In addition to the contradictory evidence offered by Yoshizawa et al. (2002) and the clear difficulty in singling out mercury as the predominant risk factor for CVD and CHD, Plante and Babo (2003)[29] raised the following criticisms in the *New England Journal of Medicine*:

> "We find it **difficult to reconcile this [Guallar et al., 2002] finding with published data** on the cardiovascular health of highly exposed populations. **Patients with Minamata disease and hair mercury levels above 100 ppm did not have a higher rate of death from heart disease than controls, nor did they have a higher degree of arteriosclerosis. In the Minamata region of Japan, a population of approximately 50,000 with an average hair mercury level of 50 ppm did not have a higher rate of death from heart disease than a reference population of 800,000 with an average level of 9 ppm. According to data from monitoring programs in Canada, Cree Indians with an average hair mercury concentration of 10 ppm have a lower risk of death from circulatory disease than the rest of the population in Quebec, in which the average hair mercury level is 0.5 ppm**. If, as Guallar et al. suggest, mercury increases the risk of myocardial infarction by more than 100 percent when the hair mercury level reaches approximately 2 ppm, how can one explain **the absence** of significant effects at doses greater than 100 ppm? **The authors raise the possibility of modifying fish-intake recommendations on the basis of their findings. In our**

> **opinion, this suggestion is ill founded and may do more harm than good, considering the nutritional value of fish."** [Emphasis added.]

ADDITIONAL EVIDENCE QUESTIONING CLAIMED MERCURY HARM TO HEART-RELATED HEALTH

It appears convincing from the above literature that the claimed role of methylmercury in negatively impacting the human heart is neither clear nor direct. However, it could be reasonably argued and concluded from the available evidence that **numerous risk factors other than methylmercury from fish more likely explain most of the findings in Salonen et al. (1995, 2000) and Guallar et al. (2002).**

Also, as with the troubled Faeroe data concerning neurodevelopment of children or infants, there are reasonable concerns that **the Finnish results are not directly applicable for the US population**. Thus, a relevant question is whether there is additional evidence either for or against the claim of a connection between methylmercury and heart-related health that speaks more directly and appropriately to the US population (in addition to Yoshizawa et al. referenced above).

We look forward to additional results from the ongoing Center for Disease Control (CDC)'s US National Health and Nutrition Examination Survey (NHANES), such as the Vupputuri et al. (2004)[30] upcoming publication in the journal *Environmental Research*. Related to heart health, **they report another failure to find support for a direct connection between mercury and blood pressure in the NHANES database**:

> "**We found no significant association between total blood mercury and systolic and diastolic BP [blood pressure] among [the NHANES] study participants overall. … Our findings support the hypothesis that the intake of fish oils may counter the harmful effects of mercury on BP regulation.**"[31] [Emphasis added.]

Vupputuri et al. point to the support by the experimental study of omega-3 DHA fatty acids in Engler et al. (2003)[32] that "it is possible that the harmful effects of mercury exposure on BP may be offset by the consumption of fish which may reduce [i.e., rather than increase] BP and pulse pressure, as well as decrease arterial stiffness."

Similarly, Dorea et al. (2004)[33] in examining data for hair mercury and blood pressure for the Munduruku and Kayabi Indians of Amazonia found that "Hg per se was not significantly related to blood pressure [for] all ages considered [from about 15 to 80 years old]. However, as a function of age, adult individuals of the Munduruku group had a tendency toward high pressure ... which was not shown for the Kayabi [group]." **Thus, while age may be tentatively identified as a negative factor on systolic blood pressure for the Munduruku natives in the Amazon, mercury was not found to be a risk factor.**

Finally, in the July 27, 2004 publication of "Fish Intake and Risk of Incident Atrial Fibrillation" in the AHA's journal, Circulation, Mozaffarian et al. (2004)[34] found in the 12-year follow-up database for a cohort of 4,815 men and women over 65 in 4 US communities **that adults**

consuming tuna or other broiled or baked fish[35] 1 to 4 times per week had 28% lower risk of developing atrial fibrillation when compared to those who ate fish less than once per month. Those eating fish five times or more per week showed a 31% lower risk. Mozaffarian et al. (2004) concluded that "fish intake may influence risk of this common cardiac arrthymia" that affects more than 2 million individuals in the United States.

THE WONDROUS HEALTH BENEFITS OF FISH-DERIVED NUTRITION

Kris-Etherton et al. (2002)[36] and Kris-Etherton et al. (2003),[37] both in the capacity of the AHA Nutrition Committee, clearly outlined the following protective mechanisms of omega-3 fatty acids for the heart, that polyunsaturated fatty acids EPA+DHA can:

- "Decrease risk for arrhythmias, which can lead to sudden cardiac arrest.
- Decrease risk for thrombosis, which can lead to heart attack and stroke.
- Decrease triglyceride and remnant lipoprotein levels.
- Improve endothelial function.
- Slightly lower blood pressure.
- Reduce inflammatory responses."[38]

Also, CSPP independently noted and documented from the literature the following remarkable list of both life-threatening and non-life-threatening health conditions that could benefit from omega-3 polyunsaturated fatty acids available in a fish-rich diet:

(a) Cardiovascular disease (CVD) + coronary heart disease (CHD) + sudden deaths
(b) Breast cancer
(c) Prostate cancer
(d) Endometrial (inner lining of uterus) cancer
(e) Treatment of kidney disorders
(f) Alzheimer disease
(g) Rheumatoid arthritis
(h) Type 2 diabetes in women and CHD in type 2 diabetic women
(i) Pre-term delivery and low birth weights + physiological and mental development of infants and children.

AMERICANS NEED MORE, NOT LESS FISH IN THEIR DIETS

Figures 1 and 2 confirm that the U.S. population is susceptible to potential life-threatening diseases because current levels of average EPA+DHA omega-3 polyunsaturated fatty acids consumption is **already 3 to 6 times lower** than recommendations by National Institute of Health (NIH) and AHA.

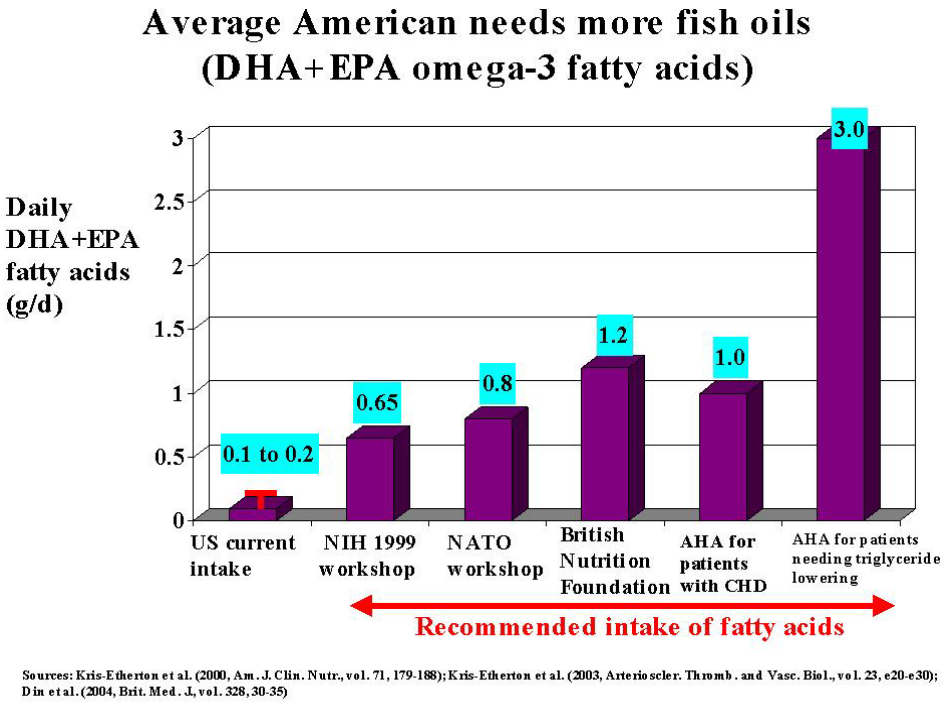

Figure 1: According to various recommended daily levels of omega-3 polyunsaturated fatty acids (DHA+EPA), the average American needs more rather than less fish consumption.

Dorea (2003)[39] and Dorea et al. (2004), who specialized in diet and health of native populations of the Amazonian rainforest, point out the critical role fish nutrition plays in human health:

> "Fish is a nutritious and important dietary staple of the people of the Amazonian rain forest. It is an abundant natural resource that is rich in high-quality protein, lysine, iodine, sulfur-containing amino acids, copper, calcium, zinc, iron, manganese, selenium, and omega-3 polyunsaturated fatty acids, among others. In the Amazonian rain forest, fish supply much needed protein and provide a balance to starchy food-staples such yam, cassava, and plantain. ... In spite of substantial amounts of metallic Hg released due to gold-mining activity, **there is no evidence** that this Hg has impacted fish Hg in the head tributaries of Rio Tapajos. Fish consumption is the only source of MMHg [MonoMethylmercury] exposure for native people who do not have access to commodity foods. For these people, to reduce dietary MMHg means reducing the consumption of fish, a dietary staple and a source of many important nutrients. **No evidence exists** that shows that freshwater Amazonian fish cause neuropathies. As an abundant natural resource, fish has been consumed for generations in large amounts by Amazonian people without any perceived problems. For these people, exposure to fish MMHg from the forest environment (nonindustrial sources) is less of an issue than endemic infectious diseases such as malaria." [Emphasis added.]

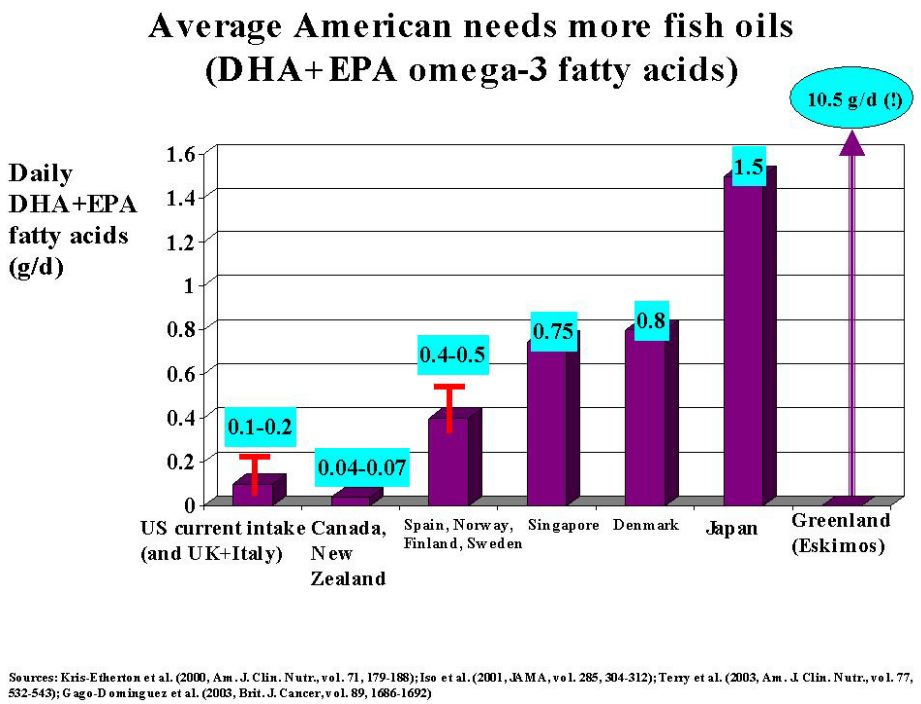

Figure 2: Americans suffer from a relatively low daily intake of omega-3 fatty acids DHA+EPA.

In the final analysis, CSPP agrees with and supports the latest AHA's recommendation and strategy in balancing the risk and benefit of fish consumption:

- **"Children and pregnant and nursing women usually have very low CVD risk but may be at higher risk of exposure to excessive mercury from fish. Avoiding potentially contaminated fish is a higher priority for these groups.**

- **For middle-aged and older men and for women after menopause, the benefits of eating fish far outweigh the risks when consuming according to the US Food and Drug Administration and Environmental Protection Agency.**[40]

- **Eating a variety of fish will help minimize any potentially adverse effects due to environmental pollutants."**[41] [Emphasis added.]

CONCLUSIONS

Media-fed alarmism over mercury is causing a dangerous fall off in already inadequate U.S. fish consumption. It is no wonder that public health professionals are beginning to express concern.

Dr. Eric Rimm, Professor of Epidemiology and Nutrition at the Harvard School of Public Health and co-author of the Yoshizawa et al. (2002) paper, expressed serious concern that:[42]

> "The message of fish being good has been lost and people are learning more about the ***hypothetical scare*** of contaminant than they are of the well-documented benefit of coronary disease reduction. **The danger of the tuna fish is not well documented compared to the potential dangers for a 50-year old male or female who are at much higher risk of coronary health."** [Emphasis added.]

The harm to public health may not be limited to nutritional deficits, but may extend to the inflated (mercury) fear itself promoted by interest groups and the EPA.

Ropeik (2004), in his evaluation of the consequences of exaggerated fear, finds that:[43]

> "[T]he cumulative load of modern threats may be creating an even greater risk that is largely overlooked: the risk that arises from misperceiving risks as higher as or lower than they actually are. As a result of some of the decisions we make when we are fearful, some of the choices we make when we are not fearful enough, and because of the ways our bodies react to chronically elevated levels of stress, the hazards of risk misperception may be more significant than any of the individual risks about which we fret. ... Most importantly, the costs of risk misperception, especially from fear and anxiety, must be included in cost-benefit analyses of risk management options."[44]

Again**, alarmism over mercury is causing a serious fall off in U.S. consumption of fish in the face of no convincing scientific evidence of dangerous threats for heart-related disease from the variety of fish available to Americans**. In contrast, there is huge potential for a public health crisis resulting from extreme precautions over hypothetical mercury health threats from fish consumption. This is so because the proven positive health benefits from fish are being compromised and de-emphasized. This negative health burden will fall disproportionately upon the poor and minority groups depending on fish for vital daily nutrition, as well as pregnant women requiring vital nutrition to support a healthy fetal development.

ENDNOTES

[1] Available at (http://ff.org/centers/csspp/pdf/mercury092804.pdf)

[2] In the September 29, 2004's *Greenwire* article, **'Sound science' group questions data used by EPA** by Marty Coyne.

[3] Stern, 2005, Environmental Research, in press (available online September 27, 2004).

[4] Clarkson, 2002, Environmental Health Perspectives, vol. 110 (supplement 1), 11-23.

[5] Salonen et al., 1995, Circulation, vol. 91, 645-655.

[6] Salonen et al., 2000, Atherosclerosis, vol. 148, 265-273.

[7] Virtanen et al., 2002, poster presentation in the April 23-26, 2002 American Heart Association, Asia Pacific Scientific Forum at Honolulu, Hawaii.

[8] The CHD mortality rate at eastern Finland is "10 times higher than in Crete in which the Mediterranean diet rich in plant foods and low in animal foods is consumed." (p. 199 of Rissanen et al., 2003, Journal of Nutrition, vol. 133, 199-204; see also Menotti et al., 1999, European Journal of Epidemiology, vol. 15, 507-515.)

[9] Taubes (1995) continued with the following important and revealing general discussion: "So what does it take to make a study worth taking seriously? ... **Sir Richard Doll of Oxford University**, who once co-authored a study erroneously suggesting that women who took the anti-hypertension medication reserpine had up to fourfold increase in the risk of breast cancer, **suggests that no single epidemiologic study is persuasive by itself unless the lower limit of its 95% confidence interval falls above a threefold increased risk.** Other researchers, such as **Harvard [Dimitrios] Trichopoulos, opt for a fourfold risk increase as the lower limit.** Trichopoulos's ill-fated paper on coffee consumption and pancreatic cancer had reported a 2.5-fold increased risk. 'As a general rule of thumb,' says [Marcia] Angell of the *New England Journal* [*of Medicine, NEJM*], 'we are looking for a relative risk of three or more [before accepting a paper for publication] [*sic.*], particularly if it is biologically implausible or if it's a brand new finding.' **Robert Temple, director of drug evaluation at the Food and Drug Administration, puts it bluntly: 'My basic rule is if the relative risk isn't at least three or four, forget it.'** But as **John Bailar, an epidemiologist at McGill University** and former statistical consultant for the NEJM, points out, there is no reliable way of identifying the dividing line. **'If you see a 10-fold relative risk and it's replicated and it's a good study with biological backup, like we have with cigarettes and lung cancer, you can draw a strong inference,' he says. If it's a 1.5 relative risk, and it's only one study and even a very good one, you scratch your chin and say maybe.'** Some epidemiologists say that an association with an increased risk of tens of percent might be believed if it shows up consistently in many different studies." [Emphasis added] **Therefore, in the best of scientific tradition and understanding of what constitutes a good epidemiologic evidence, CSPP finds that the University of Kuopio's KIHD study published by Salonen et al. (1995, 2000) has failed to pass the minimal tests outlined by some of the distinguished epidemiologists highlighted in Taube (1995).** Additional scientific criticisms of the KIHD results are presented in the main text.

[10] Guallar et al., 2002, New England Journal of Medicine, vol. 347, 1747-1754.

[11] See e.g., Bosma et al., 1998, American Journal of Public Health, vol. 88, 68-74 and Bonnet et al., 2004, Atherosclerosis, in press (accepted August 31, 2004).

[12] Lakka et al., 1999, Hypertension, vol. 34, 51-56.

[13] Tuomainen et al., 1999, Circulation, vol. 100, 1274-1279.

[14] Kauhanen et al., 1999, Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 19, 3001-3006.

[15] Nyyssonen et al., 1997, British Medical Journal, vol. 314, 634-638.

[16] Rissanen et al., 2003, Journal of Nutrition, vol. 133, 199-204.

[17] Voutilainen et al., 2000, European Journal of Clinical Nutrition, vol. 54, 424-428.

[18] Rissanen et al., 2003, American Journal of Clinical Nutrition, vol. 77, 133-138.

[19] Salonen et al., 1998, American Journal of Epidemiology, vol. 148, 445-451. See however a direct contradiction of this KIHD claim in the study of Ascherio et al. (2001, Circulation, vol. 103, 52-57) which found no significant associations of blood donation (via the lowering of body iron stores) and risk of CHD while examining the 4-year follow-up database for the 38,244 US male health professionals.

[20] Menotti et al., 1999, European Journal of Epidemiology, vol. 15, 507-515.

[21] See e.g., Bosma et al., 1998, American Journal of Public Health, vol. 88, 68-74 and Bonnet et al., 2004, Atherosclerosis, in press (accepted August 31, 2004).

[22] It is important to note that although Salonen et al. (1995) pointed out that the KIHD men's hair mercury contents show decreasing trend over the baseline examinations from 1984-1989 (with 6 annual mean values from 2.55, 2.47, 1.92, 1.51, 1.40, 1.72 ppm when those men were group annually according to the year of their

respective examinations), **there are no repeated measurements of hair mercury contents performed for the KIHD men**. All the hair samples were collected in the original baseline examinations which were conducted in two batches: first for 1166 men between March 1984 and August 1986 and next for 1516 men between August 1986 and December 1989. **This clarification is important because even an expert and a NRC (2000) committee member like Alan Stern had apparently misunderstood the KIHD results in Salonen et al. (2000)** for example in his review of the KIHD study when he said that "Salonen et al. (2000) conducted a study ... Artery wall thickness was measured in 1014 men with an average age of 51.9 years at baseline. A second measurement was obtained 4 years later. Hair for measurement of Hg concentration and data on atherosclerotic risk factors were obtained during the follow-up period" (in Stern, 2005, Environmental Research, in press [available online September 27, 2004]). Salonen et al. (2000) only made repeated measurements for the two carotid intima-media thickness variables examined in order to quantify the 4-year progression of carotid atherosclerosis. The hair samples were collected during the baseline examinations conducted 1984-1989 as noted in Salonen et al. (2000).

[23] The highest value noted in the KIHD study published by Salonen et al. (1995), but we note the highest hair mercury content was raised to 23.3 ppm in Salonen et al. (2000) **with no apparent explanation or correction offered**.

[24] pp 13-14 of Clarkson, 2002, Environmental Health Perspectives, vol. 110 (supplement 1), 11-23.

[25] From http://ww.scienceblog.com/community/older/2002/2002587.html (dated April 2002).

[26] Agren et al., 1988, Lipids, vol. 23 (No.10), 924-929.

[27] The summary provided by the commercial fish oil website at http://www.oilofpisces.com/hearthealth.html (accessed November 10, 2004) further explained that: "A 15-week experiment involving 62 students was carried out to determine if a regular diet of freshwater fish affects coronary heart disease risk factors. The students were divided into three groups: a fish eating group who made no other changes to their diet, a fish eating group who also decreased their overall fat intake and a control group (19 students) who ate a typical western diet. The special diet consisted of one fish meal a day (in addition to the regular diet) and provided about 0.25 g/day of eicosapentaenoic acid and 0.55 g/day of docosahexaenoic acid. Serum cholesterol was found to decrease in fish eaters who also decreased their lipid intake but not in the other groups. Blood triglyceride levels decreased significantly in the fish eating groups, but not in the control group. Levels of apolipoproteins A1 and B were lowered in both fish eating groups as was the formation of thromboxane B2 during incubation of whole blood. In the fish eating groups, the proportion of omega-3 fatty acids increased significantly in erythrocyte ghosts and platelets at the expense of omega-6 fatty acids. **The results of the study support the contention that moderate fish consumption has a protective effect against coronary heart disease**." [Emphasis added.]

[28] Yoshizawa et al., 2002, New England Journal of Medicine, vol. 347, 1755-1760.

[29] Plante and Babo, 2003, New England Journal of Medicine, vol. 348: 2151-2152.

[30] Vupputuri et al., 2004, Environmental Research, in press (available online July 14, 2004).

[31] Vupputuri and colleagues added that "However among those women who had not consumed fish in the previous 30 days, we observed elevated levels of systolic BP with increasing mercury exposure." It is important to point out that for those NHANES samples with low total blood mercury levels (i.e., say roughly from 0 to 4 ppb), it is known that the relative amount of methylmercury (the organic and biologically-active form of mercury associated with fish consumption) in blood declines dramatically as shown in Figure 1 of Mahaffey et al., 2004, Environmental Health Perspectives, vol. 112, 562-570. This fact points to the increasing concentration of inorganic mercury (such as those derived from dental amalgams) in blood at the low total blood mercury levels. Thus, the observed tendency for elevated levels of systolic BP with increasing mercury exposure for those specific group of 481 women that reported no fish consumption in the previous 30 days would require further clarification from the understanding of exposure risk to inorganic mercury.

[32] Engler et al., 2003, Experimental Biology and Medicine, vol. 228, 299-307.

[33] Dorea et al., 2004, Environmental Research, in press (available online about July 2004).

[34] Mozaffarian et al., 2004, Circulation, vol. 110, 368-373.

[35] In an earlier publication (Mozaffarian et al., 2003, Circulation, vol. 107, 1372-1377), Mozaffarian and colleagues pointed to the importance of types of fish meal consumed, finding that fried fish or fish sandwiches may not offer the same level of protection for the heart as broiled or baked fish.

[36] Kris-Etherton et al., 2002, Circulation, vol. 106, 2747-2757.

[37] Kris-Etherton et al., 2003, Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 23, 151-152.

[38] p. 151 of Kris-Etherton et al., 2003, Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 23, 151-152.

[39] Dorea, 2003, Environmental Research, vol. 92, 232-244.

[40] See http://www.epa.gov/waterscience/fishadvice/advice.html.

[41] p. 152 of Kris-Etherton et al., 2003, Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 23, 151-152.

[42] As quoted in the April 10, 2004's New York Times article "Fears (Real and Excessive) from Warning on Tuna" by Jennifer Lee.

[43] Ropeik, 2004, European Molecular Biology Organization Reports, vol. 5 (special issue), S56-S60.

[44] Ropeik (2004) continues that "As argued for by Matthew Adler and others (2003), the effects of fear are harmful to health, no less than the physical harm from some toxic agent or pollutant, and these can and should be measured and economically quantified to help identify the most efficient approaches to improving public health."