

Fish Consumption, Mercury Exposure, and Heart Diseases

There is increasing concern regarding methylmercury exposure in populations that consume large amounts of fish. This situation poses a dilemma for those who choose to consume fish for its beneficial effects on heart disease risk. Recent evidence suggests that high mercury content in fish may diminish the cardioprotective effect of fish intake. We explore the current knowledge of Hg toxicity on the heart and evaluate the epidemiologic evidence to date.

Key words: mercury, fish consumption, cardiovascular disease

© 2004 International Life Sciences Institute
doi: 10.1301/nr.2004.janr.68-72

Many but not all studies have found beneficial effects of fish consumption on coronary heart disease (CHD) risk.¹ Numerous factors may contribute to the discrepancies in the results observed, most notably differences in the *n*-3 fat content of the fish consumed, the extent of variability in fish consumption in the population, background risk, and the nature of the endpoints examined.¹ Scientists recently suggested that methylmercury exposure through fish consumption may provide another explanation for the discrepant results observed in the epidemiologic studies.^{2,3}

Mercury (Hg), a metallic element that occurs naturally in the environment, has long been recognized as toxic. Human activities, especially the burning of fossil fuels (coal) and municipal waste incineration, increase the amount of total Hg released into the atmosphere. In air, elemental mercury (Hg⁰) is the most abundant form (98%).⁴ Hg⁰ is highly volatile and can travel great distances before being oxidized to inorganic mercury, primarily in the mercuric (Hg¹⁺) or, to a lesser extent, the mercurous (Hg²⁺) state, at which point it is deposited onto surface soil or water.⁴ Inorganic Hg can undergo methylation, catalyzed by sulfate-reducing bacteria in aquatic sediment, which produces the most toxic form of mercury: methylmercury (MeHg).⁵ Flooding due to deforestation and building of dams increases MeHg in the aquatic ecosystem. MeHg is highly absorbable (95–100%) compared with inorganic Hg (5–10%) and can both bioaccumulate and biomagnify within aquatic food webs.⁶ Almost all of the Hg found in biologic systems has therefore been absorbed in the form of MeHg.⁷

This review was prepared by Hing Man Chan, Ph.D., and Grace M. Egeland, Ph.D., Centre for Indigenous Peoples' Nutrition and Environment and School of Dietetics and Human Nutrition, McGill University, 21,111 Lakeshore Rd., Ste-Anne-de-Bellevue, QC, Canada H9X 3V9.

Long-term exposure to either inorganic or organic Hg can permanently damage the brain, kidneys, and developing fetus.⁸ Prenatal poisoning with high-dose MeHg causes mental retardation and cerebral palsy. Recent data from the Faroe Islands study showed subtle developmental, dose-related deficits with chronic prenatal exposure.⁹ Based on these results, the U.S. Environmental Protection Agency established a reference dose for MeHg of 0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$,¹⁰ and the World Health Organization lowered their provisional tolerable weekly dose from 3.3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{week}^{-1}$ to 1.6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{week}^{-1}$.¹¹ Fish at higher trophic level as such walleye, pike, swordfish, tuna, and shark have higher levels of MeHg because of bioaccumulation and biomagnification. People who frequently consume these fish species are regarded as being at relatively high risk.

In addition to the concern of developmental toxicity and neurotoxicity, there is also evidence that Hg may increase risk of cardiovascular disease. The heart is one of the target organs of Hg in addition to the brain, kidney, and liver. Matsuo et al.¹² measured Hg in autopsy samples from 46 Japanese subjects and found that levels of total Hg in heart were similar to those in the cerebrum and cerebellum; approximately 80% of this was in the form of MeHg. The health implications of Hg accumulation in the heart are not fully characterized, and the mechanisms of Hg cardiotoxicity are not known. Multiple mechanisms are plausible, however, including altered cardiac sodium handling and Hg-modified response to viral infections. Hg can disrupt cardiac function by forming a sulfur-Hg-sulfur bridge that blocks the Na-channel in myocytes.^{13,14} Hg can also block Na-K-ATPase by a ligand-dependent and reversible mechanism.¹⁵ MeHg has been shown to potentiate myocarditis caused by Coxsackie virus type B3 (CB3) in a rat model.¹⁶ Similar toxicity was found for inorganic Hg, and the severity of Hg-modified viral infection was further enhanced in a selenium-deficient mice model,¹⁷ which suggests the possibility of complex mineral-mineral interactions.

Effects of MeHg on heart development have been reported in a rat model. Bartolome et al.¹⁸ showed that MeHg treatment in rats from birth to 21 days of age produced sustained elevations of ornithine decarboxylase activity, an early index of perturbation of cellular maturation in heart, and was associated with tissue hypertrophy throughout the preweaning stage. These findings suggest that prenatal exposure to MeHg may affect cardiac development. However, inconsistent cardiovascular effects of Hg have been observed in other animal experiments.^{19–26}

Similarly, there is mixed evidence relating occupa-

tional mercury exposure among miners and millers to cardiovascular mortality.²⁷ In a study of workers in four mercury mines (Almaden in Spain, which mines one-third of the world's Hg; Abbadia San Salvatore in Italy; Irtzi in Slovenia; and Nikitovka in the Ukraine), workers in the mines in Spain and the Ukraine had significantly elevated risk of hypertension (Standardized Mortality Ratio (SMR) = 2.78 and 9.38, respectively), but only workers in the mine in Spain had an increased risk of cerebrovascular disease (SMR = 1.17, 95% confidence interval [CI], 1.01–1.35). Workers in Slovenia had an increased risk of ischemic heart disease (SMR = 1.66, 95% CI, 1.35–2.02), while workers in the three other mines had statistically significantly lower rates of ischemic heart disease. Nephritis and nephrosis were elevated significantly in the miners in Spain (SMR = 1.69, 95% CI, 1.18–2.34), and non-significantly elevated in the miners in Slovenia (SMR = 1.6, 95% CI, 0.4–4.1). Although the study offers some evidence of an association between long-term inorganic mercury exposure in miners and millers and various groupings of cardiovascular mortality endpoints, the inconsistencies suggest that there may be other causal factors contributing to the findings. For example, miners in Spain and Slovenia were also exposed to crystalline silica (silica is a known nephrotoxin), and smoking was excessive in the one center in which smoking data were available.

In a case-control study of Minamata disease, patients developed neurological symptoms associated with Hg exposure in Minamata, Japan, there was no elevated rate of death from heart disease and no elevated risk of arteriosclerosis among cases with hair mercury levels above 100 $\mu\text{g/g}$.^{28,29} In a life-table analysis of mortality and MeHg exposures in Japan, the Minamata region did not have a higher rate of death from heart disease than a reference population: average exposures were considerably higher in the Minamata region (average hair Hg of 50 $\mu\text{g/g}$) compared with that of the reference population (9 $\mu\text{g/g}$).³⁰

In a study conducted in eight European countries and Israel, toenail mercury levels were associated with an elevated risk of non-fatal myocardial infarction (MI) in men.² The study population of 684 cases and 724 controls (frequency matched for age) were part of the European Multicenter Case-Control Study on Antioxidants, Myocardial Infarction and Cancer of the Breast (EURAMIC).³¹ Age-adjusted analyses presented by center shows average toenail mercury levels that were not statistically different between cases and controls with only one exception: Málaga, Spain, where the ratio of the average toenail mercury levels of cases and controls reached statistical significance with a case:control ratio of 1.33 (95% CI, 1.08–1.63). With all centers in the analysis and adjusting for center, the multivariate ad-

justed ratio of average toenail mercury levels for cases versus controls was 1.15 (1.05–1.25). When the Málaga center was excluded from the analyses, the adipose docosahexaenoic acid-adjusted case:control ratio of mercury levels was reduced to 1.08 (95% CI, 1.01–1.15); the multivariate adjusted ratio was not presented.³¹

In further analyses examining the odds ratios for a first non-fatal MI by quintile of toenail Hg level, a positive relationship between toenail Hg level was observed, with a multivariate adjusted relative risk of 2.16 (95% CI, 1.09–4.29) comparing the highest to the lowest quintiles of toenail Hg levels (average toenail Hg for the highest and lowest quintiles was 0.66 and 0.11 $\mu\text{g/g}$, respectively). Also, a significant trend was observed over quintiles of exposure. However, the authors do not report the results excluding the Málaga center from the analyses. The interquartile ranges of toenail Hg by center suggest that the magnitude of the odds ratios for a first non-fatal MI by quintile of Hg may be highly influenced by the inclusion of patients from the Málaga center. The upper 75th percentile value of toenail Hg in all centers but the two centers in Spain ranged from 0.19 to 0.49 $\mu\text{g/g}$. In contrast, the upper 75th percentile value in Granada and Málaga, Spain, was 0.77 and 1.09, respectively, for cases and 0.85 and 0.80, respectively, for controls. Exclusion of the Málaga center from the analyses would have been helpful in determining the reproducibility of the magnitude of the associations across the spectrum of exposures.

In additional analyses, a Hg effect on CHD risk masked a protective effect of adipose DHA, with a clear protective DHA dose-response gradient observed for a first non-fatal MI when toenail Hg levels were adjusted for in the analyses.

The above findings are compatible with research findings suggesting a Hg effect on acute MI, lipid peroxidation, and carotid atherosclerosis in population-based, prospective, follow-up studies of men in Eastern Finland.³² Fish intake (the majority being non-fatty local freshwater fish) and hair Hg were associated with an increased risk of acute MI, and death from CHD, cardiovascular disease, and all-cause mortality.³² Men in the highest tertile (>2.0 $\mu\text{g/g}$) of hair Hg levels had a twofold relative risk of acute MI and a 2.9-fold relative risk of CVD death compared with those with lower hair Hg levels. Associations remained significant after adjustment for multiple risk factors.

In a subsequent study from the same region in Finland, high hair Hg content was associated with accelerated progression of carotid atherosclerosis, determined by ultrasonographic assessment of common carotid intima-media thickness (IMT), based upon a 4-year, prospective, follow-up study of 1014 men aged 42 to 60 years that were recruited between 1984 and 1989. In

linear regression models adjusting for other atherosclerotic risk factors, high hair mercury content was among the strongest predictors of the 4-year increase in the mean IMT. In analyses in which hair Hg levels were examined in quintile groupings, those in the highest quintile of hair Hg (>2.81 – $23.3 \mu\text{g/g}$) had a 0.034 mm (32%) greater increase in the IMT over a period of 4 years than those with lower hair Hg levels. Increases in mean IMT did not differ among the four lowest quintiles of hair Hg levels, suggesting a possible threshold effect.

Finnish lakes and soil have low selenium content³² and the Finnish population had exceptionally low dietary intake of selenium prior to 1987.³³ Selenium deficiency in Eastern Finland has been related to acute MI, CHD, and cardiovascular deaths,³⁴ lipid peroxidation,³⁵ and accelerated progression of carotid atherosclerosis.³⁶ It is plausible that Hg's effects may be more pronounced in a population with very low selenium intake because mercury forms an insoluble complex with selenium (mercury selenide), binding selenium into an inactive form and thereby reducing its bioavailability.

By contrast to the European and Finnish studies, a North American study of men participating in the Health Professionals Follow-up Study found no evidence of a mercury effect on CHD mortality.³⁷ Sixty-five percent of the original cohort of 51,529 men, aged 40 to 75 years, sent in toenail clippings to the research center in 1987; during a 5-year follow-up period, a total of 470 men developed CHD. A nested case-control study was conducted selecting one control per CHD case matching for age, smoking, and the date of returning the toenail clippings. Fifty-seven percent of the original cohort consisted of dentists. When the highest and lowest quintiles of toenail Hg were compared (0.87 – $14.56 \mu\text{g/g}$ vs. 0.13 – $0.21 \mu\text{g/g}$), the multivariate relative risk of CHD was 0.97 (95% CI, 0.63–1.50). When dentists were removed from the analyses, a non-significant positive association was found between toenail mercury levels and 220 CHD events. Comparing the highest ($0.84 \mu\text{g/g}$) with the lowest quintile ($0.13 \mu\text{g/g}$) of toenail mercury exposures, the multivariate adjusted relative risk was 1.27 (95% CI, 0.62–2.59, p -trend = 0.43). The Health Professional Study group could further evaluate the association of Hg (through fish consumption) and CHD by recruiting more controls per case to improve statistical power and by limiting their study to non-dentists.

Two Swedish studies have found no evidence of a mercury effect on CHD risk.^{38,39} In Northern Sweden, a population-based prospective study of more than 36,000 individuals enabled the evaluation of erythrocyte mercury concentrations (Ery-Hg) and risk of a first MI in a nested, case-control design of 78 cases and 156 controls.³⁸ In this study, Ery-Hg levels and polyunsaturated fatty acid concentrations showed a protective association

with MI in multivariate analyses taking into account traditional risk factors. Whereas there is no reason to believe Hg exposures would be in themselves beneficial, both Ery-Hg and polyunsaturated fatty acids are reliable indicators of fish intake. The Hg exposures in this cohort were relatively low, with an average of 4.44 ng of Hg/g erythrocytes for cases and 5.42 ng/g for controls (corresponding levels would be 0.6 and 0.7 μg Hg/g hair, respectively).

In another prospective Swedish study of 1462 women, who were 38 to 60 years of age at baseline examination (1968–1969), baseline total serum Hg concentrations were not related to an increased risk of MI, stroke, and many other outcomes within a 20-year follow-up period.³⁹

In summary, there is currently highly contradictory and insufficient evidence to suggest that mercury is associated with CHD risk. However, the findings to date and the plausible biologic mechanisms certainly warrant additional research in this arena. The magnitude of the associations observed in the EURAMIC study was likely to have been highly influenced by one center, whereas the Health Professionals Study had weak statistical power for examining mercury's effects among non-dentists. The conflicting findings may indicate that high mercury intake may have an effect on cardiovascular health but that the consequences of exposure may vary among populations owing to various modifying factors.

Concomitant exposures that can act as effect modifiers or confounders either mitigating or exacerbating effects deserve careful attention in future research and may help explain the highly contradictory findings observed to date in studies examining the effects of mercury on cardiovascular morbidity and mortality.

Disparities may be due to the heterogeneous nutrient and Hg composition of fish and differences in dietary composition between study populations. To illustrate, in addition to differences in n -3 fatty acid content of fish, non-fatty fish is usually cooked differently from that of fatty fish, and cooking procedures may dramatically alter the fat content and modify the health benefits of eating an otherwise low-fat source of protein. Socioeconomic and cultural preferences in cooking procedures of non-fatty fish may vary from a heart-healthy approach of baking the fish in olive oil to frying it in sources of saturated fat and *trans*-fatty acids, such as lard, butter, and hard margarines. High intake of saturated fat and *trans*-fatty acids are risk factors for CHD.^{40,41}

Dietary fiber provides another illustration of the complexities of nutrition and environment interactions in epidemiologic research. Individuals consuming similar amounts of fish but varying amounts of fiber would be expected, to a certain extent, to have different body burdens of MeHg, because MeHg is bound to dietary

fiber and excreted in the feces.⁴² The majority of dietary studies that have examined dietary fiber find that high fiber intake is related to low CHD risk.^{43,44} In one study, for example, men in the highest one-third of dietary fiber consumption experienced approximately one-third the risk of CHD during a 20-year period.⁴⁵ Dietary selenium intake may also contribute to differences observed between study populations, as it is plausible that a mercury effect on heart disease may be more pronounced in populations with exceptionally low selenium intake.

Whereas further evaluation of the putative Hg and heart disease association is highly warranted, public health advice should continue to be based upon the full weight of the existing scientific information on fish consumption and CHD benefits.¹ Currently, the American Heart Association (AHA) Dietary Guidelines recommend that fish be consumed at least two times per week with an emphasis on fatty fish. For patients with CHD, AHA now recommends an intake of 1 g/day of eicosapenoic acid and docosapentaenoic acid.¹ Indigenous populations often bear a heavy burden associated with restrictive fish consumption advisories,⁴⁶ and it would be premature to issue additional fish consumption advisories based upon the available and conflicting data on Hg and CHD. It is noteworthy, for example, that among the James Bay Cree of Quebec, that a period of high MeHg exposures through fish consumption was related to a period of low CHD risk.^{47,48} Given the ubiquitous nature of Hg exposures, the uncertainties of risk, and the many benefits of fish consumption, research further clarifying the role of mercury in heart disease should be a high priority.

1. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106:2747–2757.
2. Guallar E, Sanz-Gallardo MI, van't Veer P, et al. Mercury, fish oils, and the risk of myocardial infarction. *N Engl J Med*. 2002;347:1747–1754.
3. Salonen JT, Seppänen K, Lakka TA, Salonen R, Kaplan GA. Mercury accumulation and accelerated progression of carotid atherosclerosis: a population-based prospective 4-year follow-up study in men in eastern Finland. *Atherosclerosis*. 2000;148:265–273.
4. Jackson TA. Long-range atmospheric transport of mercury to ecosystems, and the importance of anthropogenic emissions—a critical review and evaluation of the published evidence. *Environ Rev*. 1997;5:99–120.
5. Westcott K, Kalff J. Environmental factors affecting methylmercury accumulation in zooplankton. *Can J Fish Aqua Sci*. 1996;53:2221–2228.
6. Wolfe MF, Schwarzbach S, Sulaiman RA. Effects of mercury on wildlife: a comprehensive review. *Environ Toxicol Chem*. 1998;17:146–160.
7. Watras CJ, Back RC, Halvorsen S, Hudson RJM, Morrison KA, Wentz SP. Bioaccumulation of mer-

- cury in pelagic freshwater food webs. *Sci Total Environ*. 1998;219:183–208.
8. ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological profile for mercury. Available at: <http://www.atsdr.cdc.gov/toxprofiles/tp46.html>. Accessed January 29, 2004.
9. Grandjean P, Weihe P, White R, et al. Cognitive deficit in 7-year old children with prenatal exposure to methylmercury. *Neurotox Teratol*. 1997;19:418–428.
10. USNRC (United States National Research Council). Toxicological effects of methylmercury. Washington, DC: National Academic Press; 2000, 344.
11. WHO. Joint FAO/WHO Expert Committee on Food Additives. Sixty-first meeting, Rome, 10–19 June 2003. Available at: <ftp://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf>. Accessed January 27, 2004.
12. Matsuo N, Suzuki T, Akagi H. Mercury concentration in organs of contemporary Japanese. *Arch Environ Health*. 1989;44:298–303.
13. Kurata Y, Hisatome I, Tsuboi M, et al. Effect of sulfhydryl oxidoreduction on permeability of cardiac tetrodotoxin-insensitive sodium channel. *Life Sci*. 1998;63:1023–1035.
14. Hisatome I, Kurata Y, Sasaki N, et al. Block of sodium channels by divalent mercury: role of specific cysteinyl residues in the P-loop region. *Biophys J*. 2000;79:1336–1345.
15. Anner BM, Moosmayer M, Imesch E. Mercury blocks Na-K-ATPase by a ligand-dependent and reversible mechanism. *Am J Physiol*. 1992;262:F830–F836.
16. Ilback NG, Lindh U, Wesslen L, Fohlman J, Friman G. Trace element distribution in heart tissue sections studied by nuclear microscopy is changed in Cocksackie virus B3 myocarditis in methyl mercury-exposed mice. *Biol Trace Element Res*. 2000;78:131–147.
17. South PK, Morris VC, Levander OA, Smith AD. Mortality in mice infected with an amyocarditic coxsackievirus and given a subacute dose of mercuric chloride. *J Toxicol Environ Health Part A*. 2002;63:511–523.
18. Bartolome J, Chait EA, Trepanier P, Whitmore WL, Weigel S, Slotkin TA. Organ specificity of neonatal methyl mercury hydroxide poisoning in the rat: effects of ornithine decarboxylase activity in developing tissues. *Toxicol Lett*. 1982;13:267–276.
19. Rhee HM, Choi BH. Hemodynamic and electrophysiological effects of mercury in intact anesthetized rabbits and in isolated perfused hearts. *Exp Mol Pathol*. 1989;50:281–290.
20. Massaroni L, Rossoni LV, Amaral SM, et al. Haemodynamic and electrophysiological acute toxic effects of mercury in anaesthetized rats and in langendorff perfused rat hearts. *Pharmacol Res*. 1995;32:27–36.
21. Rossoni LV, Amaral SM, Vassallo PF, et al. Effects of mercury on the arterial blood pressure of anesthetized rats. *Braz J Med Biol Res*. 1999;32:989–997.
22. Carmignani M, Boscolo P, Artese L, et al. Renal mechanisms in the cardiovascular effects of chronic exposure to inorganic mercury in rats. *Br J Indust Med*. 1992;49:226–232.

23. Massaroni L, Oliveira EM, Stefanon I, Vassallo DV. Effects of mercury on the mechanical and electrical activity of the Langendorff-perfused rat heart. *Braz J Med Biol Res.* 1992;25:861-864.
24. Oliveira EM, Vassallo DV, Sarkis JJ, Mill JG. Mercury effects on the contractile activity of isolated heart muscle. *Toxicol Appl Pharmacol.* 1994;128:86-91.
25. Halbach S, Schonsteiner G, Vierling W. The action of organic mercury compounds on the function of isolated mammalian heart muscle. *Eur J Pharmacol.* 1989;167:255-264.
26. Halbach S. Mercury compounds: lipophilicity and toxic effects on isolated myocardial tissue. *Arch Toxicol.* 1990;64:315-319.
27. Boffetta P, Sallsten G, Garcia-Gomez M, et al. Mortality from cardiovascular diseases and exposure to inorganic mercury. *Occup Environ Med.* 2001;58:461-466.
28. Tamashiro H, Akagi H, Arakaki M, Futatsuka M, Roht LH. Causes of death in Minamata disease: analysis of death certificates. *Occup Environ Health.* 1984;54:135-146.
29. Oyanagi K, Furuta A, Ohama E, Ikuta F. Does methylmercury intoxication induce arteriosclerosis in humans? A pathological investigation of 22 autopsy cases in Niigata, Japan. *Acta Neuropathol.* 1992;83:217-227.
30. Tamashiro H, Fukutomi K, Lee ES. Methylmercury exposure and mortality in Japan: a life table analysis. *Arch Environ Health.* 1987;42:100-107.
31. Kardinaal AFM, Kok FJ, Ringstad J, et al. Antioxidants in adipose tissue and risk of myocardial infarction: the EURAMIC study. *Lancet.* 1993;342:1379-1384.
32. Salonen JT, Seppänen K, Nyssönen K, et al. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and death in Eastern Finnish men. *Circulation.* 1995;91:645-655.
33. Alfthan G. Effects of selenium fertilization on the human selenium status and the environment. *Nor J Agric Sci.* 1993;11:175-181.
34. Salonen JT, Alfthan G, Huttunen JK, Pikkakainen J, Puska P. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. *Lancet.* 1982;2:175-179.
35. Salonen JT, Ylä-Herttala S, Yamamoto R, et al. Autoantibody against oxidized LDL and progression of carotid atherosclerosis. *Lancet.* 1992;339:883-887.
36. Salonen JT, Nyssönen K, Korpela H, Tuomilehto J, Seppänen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men. *Circulation.* 1992;86:803-811.
37. Yoshizawa K, Rimm EB, Morris JS, et al. Mercury and the risk of coronary heart disease in men. *N Engl J Med.* 2002;347:1755-1760.
38. Hallgren CG, Hallmans G, Jansson JH, et al. Markers of high fish intake are associated with decreased risk of a first myocardial infarction. *Br J Nutr.* 2001;86:397-404.
39. Ahlqvist M, Bengtsson C, Lapidus L, Gergdahl IA, 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.
40. Willett WC, Stampfer MJ, Mason JE, et al. Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet.* 1993;341:581-585.
41. Renaud S, Lanzmann-Petithory D. Dietary fats and coronary heart disease pathogenesis. *Curr Atheroscler Rep.* 2002;4:419-424.
42. Chapman L, Chan HM. The influence of nutrition on methylmercury intoxication. *Environ Health Perspect.* 2000;108:29-56.
43. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect: potential in the prevention of cardiovascular disease. *Br J Nutr.* 2002;88:S263-S271.
44. Ludwig DS, Pereira MA, Kroenke CH, et al. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA.* 1999;282:1539-1546.
45. Morris JN, Marr JW, Clayton DG. Diet and heart: a postscript. *BMJ.* 1977;2:1307-1314.
46. Egeland GM, Middaugh JP. Balancing fish consumption benefits with mercury exposure. *Science.* 1997;278:1904-1905.
47. Robinson E. The health of the James Bay Cree. *Can Fam Physician.* 1988;34:1606-1613.
48. Plante M, Babo S. Mercury and the risk of myocardial infarction. *N Engl J Med.* 2003;348:2151-2152.