EXPOSURE OF ARCTIC POPULATIONS TO METHYLMERCURY FROM CONSUMPTION OF MARINE FOOD: AN UPDATED RISK-BENEFIT ASSESSMENT

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ABSTRACT

Recent and powerful epidemiological studies have been used as a basis for revising international and domestic guidelines for human exposure to mercury. Long-range transport of mercury into the Arctic makes some Arctic peoples consuming traditional marine foods, especially newborns, children and pregnant women, very vulnerable to harmful exposures.

The WHO, the USEPA and Health Canada have all recently revised their mercury intake guidelines as a result of neurological effects reported in children exposed in utero and adults. Guidance values are equivalent to 0.23 µg/kg-bw/d, 0.1 µg/kg-bw/d and 0.2 µg/kg-bw/d respectively. Differences between the numbers represent slight differences in the uncertainty factors applied, rather than in toxicological interpretation. More recent findings suggest that mercury may also be a factor in ischemic heart disease, which could lower guidance values in the future.

Considering the benefits of marine fatty acids (n–3 fatty acids) and guidance that populations consume 300-400g fish/week, consumers face a reality that most open ocean and relatively ‘un-polluted’ fish species contain levels of mercury that would lead to exposures at current guidance levels. Clearly, there is no more room for further mercury pollution and there is an urgent need for international action to reduce mercury emissions.

Concomitantly, while there may be a need for public health authorities to provide consumption advisories to some highly exposed populations, such as in the Arctic, there remains a need to better understand the interactions and benefits associated with marine foods that may reduce health risks associated with low-level mercury exposure. (Int J Circumpolar Health 2005;64(2):121-136.)

Key words: diet, benefits, mercury, n-3 fatty acids, risk assessment, Arctic populations, selenium
INTRODUCTION

Mercury has been an element of significant global economic importance for centuries. Historically, it has been used extensively to extract gold from mineral ores. It has also been used as a medicine, in pesticide formulations, in jewellery, in laboratory equipment, and in electrical applications. Over the last 65 years, public health officials have come to understand that exposure to mercury is very injurious to health. The widespread poisonings reported in Minamata, Japan, in the 1950s, and in Iraq in the 1970s, have led to even greater public health focus on the neurotoxic effects of mercury and methylmercury on adults and their exposed offspring.

National and international agencies have developed and redeveloped guidance values for maximum safe exposure levels as more and more detailed research studies have been reported. The U.S. EPA has based its latest risk assessment on large epidemiological studies that had become available since 1995. The methods used and the rationale for this assessment are described by Rice et al. (1). These guidance values are used by governments and public health agencies to develop advice for locally exposed populations. New and powerful cohort studies in several countries have lead to recent re-evaluations of the guidance values issued by a variety of jurisdictions. Some of the recently suggested guidance values are now so low that they may have implications for many populations (e.g. in the Arctic) that normally consume large amounts of fish and marine mammals as a principal part of their diet. The overall problems related to the health-environment interactions in an Arctic context have recently been reviewed by Suk et al. (2).

Local public health officials must develop advice for locally exposed populations based on a variety of medical, dietary, social and cultural factors that weigh the risks of mercury exposure against the benefits of traditional and highly nutritious diets and life-styles. This paper briefly examines the basis for these new guidance values. It also discusses their implications for current risk characterization with emphasis on Arctic populations and public health.

MERCURY IN THE ENVIRONMENT

Mercury exists in various physical and chemical forms. From a toxicological point of view, the metallic form (also called elemental mercury) and an organic form (methylmercury) are the most important. Elemental mercury (Hg\textsuperscript{0}) is released from the earth’s crust by volcanic and other geothermal activities, giving rise to natural background concentrations, which have been present in the environment through the ages. In addition to these natural background levels, some mercury enters the environment as a result of anthropogenic activities. The primary global anthropogenic source comes from the combustion of fossil fuel; however, some industrial activities and the use of mercury-based pesticides have added to global mercury pollution and caused extensive local pollution episodes (3). Since elemental mercury vapourises at environmental temperatures, it enters the atmosphere from both natural and anthropogenic sources as mercury vapour. In the atmosphere, it undergoes photochemical reac-

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tions, whereby it is oxidised and transformed to an ionised state, making it hydrophilic and enabling its deposition on the earth surface via precipitation. A relatively new phenomenon called a 'mercury depletion event' (MDE) was recently reported in the Canadian high Arctic by Schroeder et al. (4). These authors observed that, each year at polar sunrise, the atmospheric mercury concentration dropped sharply, concurrent with a depletion of ozone in surface air. MDEs have been demonstrated in both the Arctic and the Antarctic regions; they are likely the result of photochemical reactions in which elemental mercury is oxidised to a form of reactive gaseous mercury as ozone is destroyed. Models for mercury transport and deposition, which take MDEs into consideration, have shown that the amount of mercury deposition in the Arctic is more than twice the estimate made without including these spring-time depletion events (5).

In the terrestrial environment, deposited mercury can be reduced by soil micro-organisms to volatile compounds, which are recycled to the atmosphere. For this reason mercury pollution is generally not a problem in the terrestrial environment and in surface soils. However, mercury deposited into the aquatic environment can be methylated by micro-organisms in sediments and is subsequently ingested by biota. Once absorbed, methylmercury (which has a high affinity for sulphur ligands) binds to the sulphur-containing amino acid cysteine. Through this reaction, it loses some of its lipophilic character, but, bound to amino acids, it enters the protein pool. Due to its long biological half-life, methylmercury bioaccumulates in marine and fresh-water organisms (i.e., the older the animal, the higher the mercury concentration) and also biomagnifies (i.e., the higher an organism is placed in the food chain, the higher its trophic level and the higher its mercury concentration). As a consequence, the main source of human exposure to mercury occurs through the consumption of species from the freshwater and marine environments, where the food chains tend to be longer than in the terrestrial environment, and where biomagnification of mercury is greatest. Populations with a very high intake of top-of-the-food-chain fish species and marine mammals will have the highest exposure levels. Methylmercury, as a moderately lipophilic substance, readily crosses biological membranes. In humans, about 95% of the methylmercury ingested in fish muscle is absorbed (6, 7). Methylmercury also crosses the placenta and is accumulated by the foetus.

**TOXICITY OF METHYLMERCURY**

**High dose exposure**

The toxic effects of methylmercury were originally described by Hunter et al. (8). A poisoned adult patient develops paraesthesia in the fingers, the tongue and the face (particularly around the mouth). Later on, disturbances occur in motor functions, resulting in ataxia and dysphasia. The visual field is decreased and, in severe cases, the result may be total blindness. Impaired hearing may also occur and progress to complete deafness.

Identical symptoms were reported among cases in Minamata, Japan, where consumed fish were severely contaminated by effluents from a local chemical factory (3). The methylmercury poisoning episode in Minamata,
which took place between 1953 and 1960, involved 628 cases. The overall prevalence of neurological and mental disorders in the Minamata region was 59%. Among the patients, 78 deaths occurred and hair concentrations of mercury ranged from 50 to 700 µg/g.

In 1971, an unknown number of people in Iraq were exposed to methylmercury-treated seed grain that was used to make home-baked bread. Toxicity was observed in many adults and children who had consumed this bread over a period of three months. The sub-population that showed greatest sensitivity was that of the offspring of women who ate contaminated bread during pregnancy. The mothers experienced paraesthesia and other sensory disturbances, but at higher doses than the dosages causing the same effects in their children exposed in utero (7, 9).

Experiences from these two episodes of high-dose exposure have indicated that the earliest effects of methylmercury in adults, such as paraesthesia, seem to appear at maternal hair concentrations above 50 µg/g, which correspond to blood concentrations above 200 µg/l (7).

The foetus is much more susceptible to the toxic effect of methylmercury than the mature adult. Congenital methylmercury poisoning can result in a cerebral palsy syndrome, even though the mothers remain healthy, or experience only minor symptoms due to the exposure (10).

Low dose exposures
Two major studies, one in the Faroe Islands and one in the Seychelles Islands, have recently been conducted to assess the impact of environmental dietary exposures on the foetal brain. Both studies have compared biomarkers of methylmercury exposure of the mother and foetus with neuropsychological and other endpoints of pre-school-age children.

The Faroe Island population was exposed to methylmercury mainly from the consumption of pilot whale meat, which had a relatively high concentration of methylmercury, i.e., around 2 µg/g (11). This study of about 900 children showed that prenatal exposure resulted in measurable neuropsychological and neurophysiological deficits at 7 years of age (12). It also included objective measurements, such as evoked visual and auditory potentials, which are less susceptible to confounding. The most vulnerable brain functions seemed to be attention, memory and language, while motor speed, visuo-spatial function and executive function showed less robust decrements with increased mercury exposure. Mercury concentration in the cord blood of newborns appeared to be the best indicator of future risk. Developmental delays were found to be significantly associated with hair mercury concentrations below 10 µg/g. Calculations based on these data suggested that the lower 95% confidence limit for a doubling of a 5% abnormality response occurred at maternal hair levels of approximately 10 µg/g and at a corresponding cord blood concentration of 58 µg/l (13). Each doubling of the prenatal methylmercury exposure level was associated with a developmental delay of 1-2 months. On an individual basis, the effects could be viewed as minor. However, they may have more severe implications on a population basis if a broad segment of the youth previously exposed to methylmercury in utero are functioning below their expected capability.
In the other prospective study, conducted in the Seychelles Islands, the exposure level was similar to that reported by the Faroese, but it originated from the consumption of fish. The pregnant women typically ate 10-15 fish meals per week (14). The main study started in 1989 and followed about 700 mother-child pairs. Maternal hair concentrations (with a mean of about 7 µg/g) and child hair concentrations were used as markers of exposure in this study. No effects on child developmental tests were found to be associated with maternal hair concentration up to 5.5 years of age (15-19). If anything, the results suggested a beneficial effect from increased fish consumption, which parallels increased mercury exposure. At 9 years of age, the children were re-examined with the same result, i.e., there were no associations between effects and prenatal exposure (56).

In addition to the two large studies discussed above, there is a study from New Zealand which suggests an effect of mercury on the mental development of children at the ages of 4 and 7 years (27, 28). The raw data from this study have been used for benchmark calculations. The benchmark dose limits (BMDLs) range from 7.4 to 10 µg/g maternal hair and are similar to BMDL values calculated using the the Faroe Island study data.

There is controversy about what constitutes an ‘acceptable’ level of exposure to methylmercury, primarily because different scientific groups chose different dose–response models, different uncertainty factors, and may emphasize one data set over another (32). The discrepancy between the results from the three studies, and the possible reasons for the conflicting results, have been discussed vigorously and an in-depth analysis has been completed by the US National Research Council (32). This body did not reach a definitive conclusion, although all three studies were considered to be of a high scientific standard with no serious methodological flaws.

The benchmark calculations from the Seychelles study were similar to those calculated from the Faroe Island and New Zealand studies. A reanalysis using raw scores rather than age-standardized scores showed similar results. Recent correspondence in the Lancet (57) claims that the large confidence intervals do not allow the Seychelles study data to be used to refute the hypothesis of an effect similar to the one found in the Faroe Islands.

Apart from the discussions of the differences in methodology between the studies, there has been speculation on other possible explanations for the differences in the reported data, such as potential interactions between nutrients and methylmercury. From animal experiments, selenium is known to reduce mercury toxicity and, even though the protective effects of selenium for humans are still considered to be controversial (7), it is likely that some of the same protection is present in humans. Other nutrients, such as vitamin E and fatty acids of the n-3 family, have also been discussed as possible candidates for explaining the different population responses. However, the reported results have been inconsistent. For a full review of these interactive factors, see reports by Chapman and Chan (20) and the European Commission (21).

Other possibilities for the different findings from the Faroese and Seychelles studies include interactions between methylmercury and other environmental contaminants, such as
polychlorinated biphenyls (PCBs). These compounds are generally found in higher concentrations in the Northern hemisphere than in the Southern hemisphere (58). Bemis and Seegal (22, 23) have reported a synergistic effect between methylmercury and PCBs in experiments with rats. The Faroese exposure to methylmercury originates from the consumption of top-of-the-food-chain predatory pilot whale, while the source of the dietary exposure in the Seychelles is fish, which has a lower level of PCBs than pilot whale meat. While analyses of the Faroese data do not support a direct interaction between mercury and PCB (32), it cannot be excluded that a population with a concomitant high exposure to PCBs is more susceptible to effects from methylmercury than a population with a low PCB exposure.

The neurotoxic effect of methylmercury has mainly been studied in children with prenatal exposure, while the specific effects of adult low-dose exposures have been less well documented. However, in a cross-sectional study conducted on the Cuiaba River, Brazil, Yokoo et al. (24) have demonstrated that relatively low hair-mercury concentrations (mean 4.2 ± 2.4 µg/g) were associated, in a dose-dependent manner, with detectable decrements of performance in tests of fine motor speed, dexterity and concentration. Some aspects of verbal learning and memory were also found to be affected. The effects observed in adults are similar to some of those reported in children with prenatal exposure (24).

The data from the studies of mercury exposure through consumption of marine species in the Faroe Islands and the Seychelles opens up a new dimension in risk assessment for mercury, i.e., the need for an integrated evaluation of the toxicological data from animal studies, epidemiology data from high-dose and low-dose exposures, and the possible beneficial influences of local, or regional diets. As a consequence, international guidelines for maximum intakes of mercury should only be considered as ‘guides’ for local public health authorities, which should decide for themselves on the appropriate safety factor to be applied following a risk-benefit analysis in the local community. This aspect has been discussed by Odland et al. (25) and in the most recent AMAP Human Health Report (26).

GUIDELINES FOR MERCURY EXPOSURE SUGGESTED BY DIFFERENT HEALTH AGENCIES

In spite of the discrepancies between the two major low-dose exposure studies mentioned above, several internationally respected agencies have used a variety of data from these and other studies for risk assessment purposes. Some risk assessments have also included the consideration of results provided in the smaller study of exposed New Zealanders (27, 28).

The World Health Organization and the Food and Agriculture Organization

In 1999, the Joint Expert Committee on Food Additives (JECFA) of the FAO and the WHO (29) decided to maintain the provisional tolerable weekly intake (PTWI) value for mercury of 3.3 μg/kg-bw (equivalent to 0.47 μg/kg-bw/d). The Committee considered data on intake, the quantitative relationship between daily intake of methylmercury and concentrations
in blood and hair, and ongoing epidemiological
studies. The available information was consid-
ered by the Committee "to be insufficient for
evaluation of the neuro-developmental effects
on offspring of mothers with low intakes of
methylmercury". The committee noted that
"fish (the major source of methylmercury in
the diet) contribute importantly to nutrition, es-
pecially in certain regional and ethnic diets".
They recommended that "the nutritional ben-
efits be weighed against the possible harm,
when consideration was being given to setting
limits on both methylmercury concentrations
in fish for human consumption and on amounts
of fish for human consumption". In 2003, the
WHO lowered its PTWI for methylmercury to
1.6 µg/kg-bw (30). The new PTWI corresponds
to a daily intake of 0.23 µg/kg-bw. This value,
with the uncertainties included, differs little
from the ‘Reference Dose’ developed by the
US-EPA (see below).

United States
The US EPA defines a Reference Dose (RfD)
as an estimate of a daily exposure of the human
population (including sensitive subgroups) that
is likely to be without appreciable risk of dele-
terious effects during a lifetime (31). The RfD
is an important risk-characterisation tool that is
broadly used as a measure of the "acceptabili-
ty" of population exposure levels. It is used to
guide risk-management decisions and regula-
tory policies in the United States, ranging from
fish consumption advisories to air-emission
permits (32).

The RfD is calculated from the Benchmark
Dose Limit (BMDL). The BMDL is the 95%-
lower confidence limit on the maternal hair
concentration corresponding to a 10% extra
risk level (33). The US EPA uses 11 µg/g ma-
ternal hair as the BMDL. Hair concentrations
can be converted to blood concentrations using
the ratio 250:1 (34). Thus 11 µg/g hair corre-
spond to 44 µg/l blood. Using this information,
and applying the following equation (34), the
daily intake is calculated to be 1.1 µg/kg-bw:

\[
\text{d} = \frac{\text{C} \times \text{b} \times \text{V} \times \text{f} \times \text{bw}}{\text{A} \times \text{x} \times \text{bw}}
\]

\(\text{d} = \text{daily dietary intake in } \mu\text{g/kg-bw}\)
\(\text{C} = \text{concentration in blood } \mu\text{g/L}\)
\(\text{b} = \text{elimination constant (0.014 days-1)}\)
\(\text{V} = \text{volume of blood in the body (L)}\)
\(\text{A} = \text{absorption factor (expressed as a unit-less}\)
\(\text{decimal fraction of 0.95)}\)
\(\text{f} = \text{fraction of daily intake taken up by blood}\)
\(\text{(unit-less 0.05)}\)
\(\text{bw} = \text{body-weight default value of 60 kg for}\)
\(\text{an adult woman.}\)

To derive the RfD, an uncertainty factor of 10
was used to account for human population
variability. An uncertainty factor of at least 10
is recommended by the Committee on the Tox-
icological Effects of Methylmercury (32).
Hence, the current RfD for methylmercury de-
veloped by the US EPA is 0.1 µg/kg-bw/d.

The US National Research Council (32) re-
cently reviewed the research studies evaluated
by the US EPA and found the basis for the RfD
to be scientifically justifiable for the protection
of health. The NRC agreed that the RfD should
be derived from an analysis of data from the
Faroe Islands study instead of data from Iraq,
which was used previously. The NRC review
and the studies were re-reviewed by an external
expert panel, before the US EPA evaluation was finally presented in 2001 (11).

In contrast to the US EPA´s use of the Faroese study, the Agency for Toxic Substances and Disease Registry (ATSDR) (35) developed its proposed minimum risk level (MRL) for methylmercury of 0.3 µg/kg-bw/d from the Seychelles child development data.

The European Union

A European expert group recently suggested that the US-EPA RfD (0.1 µg/kg-bw/day) is appropriate for use by the European Union (21). After further evaluation, the European Food Safety Authority (EFSA) concluded that the epidemiological evidence is not sufficient to distinguish between the US EPA RfD and the new JECFA PTWI of 1.6 µg/kg bw (corresponding to a daily intake of 0.23 µg/kg) and both guidelines are recognized. (54).

Canada

In 1998, Health Canada proposed a revised interim Tolerable Daily Intake value (pTDI) for methylmercury of 0.2 µg/kg-bw for pregnant women, women of childbearing age and infants. (Feely. pers. com.). This value took account of the Seychelles data up to the evaluation of children at 29 months of age and the Faroese data for 7-year-old children. These two studies demonstrated measurable effects in children born to mothers with methylmercury hair concentrations above 12 µ/g and 10 µ/g, respectively. Based on a no-observed-adverse-effect-level of 10 µ/g methylmercury in maternal hair as the approximate benchmark dose, dividing this level by 250 to convert the total hair mercury concentration to a blood methylmercury concentration and, using this value in the US-EPA Integrated Risk Information System equation for converting blood methylmercury concentrations to dietary methylmercury intake level (34), the benchmark dose of dietary intake was calculated to be 58.95 µg/person/d, or 0.98 µg/kg-bw/d (rounded to 1 µg/kg-bw/d). Canada applied a 5-fold uncertainty factor to this benchmark dose to create their interim tolerable daily intake (TDI) of 0.2 µg/kg-bw/d and cautioned that this should be regarded as a temporary measure, because the 66-month (last interval) evaluation of the Seychelles studies had yet to be completed.

IMPLICATIONS OF NEW RESEARCH RESULTS ON RECENTLY PROPOSED GUIDELINES

While risk assessments of methylmercury have been based primarily on neurotoxic effects, recent studies have indicated that methylmercury may also be cardio-toxic. Salonen et al. (36) compared dietary intake of fish and mercury concentrations in human hair and urine with the prevalence of acute myocardial infarction (AMI) and deaths from coronary heart disease, or cardiovascular disease, in a cohort of 1,833 Finnish men. Dietary mercury intakes ranged from 1.1 to 95.3 µg/day, with a mean of 7.6 µg/day. Over a 7-year period, men in the highest tertile of hair mercury concentration (equal to, or greater than, 2 µg/g in hair, corresponding to a blood concentration of 8 µg/l and a daily intake of 0.18 µg/kg-bw in a 70 kg person) had a two-fold higher risk (1.2-3.1) of AMI than men in the two lowest tertiles. Thus, the lower limit for the highest tertile corresponds
to a daily intake that is only 80% higher than the EPA RfD of 0.1 µg/kg-bw/d. A later follow-up study (37) showed a protective role of n-3 fatty acids with respect to acute coronary disease, although this effect was less evident in those with high hair mercury concentrations. The authors concluded that high mercury content in fish could attenuate the protective effect of the n-3 fatty acids. A recent study by Sorensen et al. (38) showed an association between prenatal exposure to methylmercury and cardiovascular function at age 7 in children from the Faroe Islands. Diastolic and systolic blood pressures increased by 13.9 and 14.6 mmHg, respectively, as cord blood concentrations rose from 1 µg/l to 10 µg/l. The cord blood concentration corresponding to the EPA RfD is 5.8 µg/l.

In an international case-control study, Guallar et al. (39) found an independent and graded association between relatively low toe nail mercury levels (<1 µg/g) and the risk of myocardial infarction. Furthermore, they found that mercury masked an inverse association between DHA (docosahexaenoic acid) levels and the risk of myocardial infarction that became evident only after adjustment for the mercury level. Yoshizawa and coworkers (59) also investigated a possible relationship between toe nail mercury levels and the risk of coronary heart disease in men. In this study, no increased risk was observed in relation to mercury exposure and this finding was not changed after adjustment for intake of n-3 fatty acids. The major differences between the two studies are that (a) the study group used by Yoshizawa et al. consisted of a large number of dentists (greater than 50 percent) who had an additional exposure to metallic mercury, and that (b) the intake of n-3 fatty acids was estimated from food questionnaires, while Guallar et al. (39) measured the n-3 fatty acids in fat biopsies. When the dentists in the study group were excluded, Yoshizawa et al. (59) found a non-significant association between effect and toe nail mercury. However, they concluded that a weak relation between mercury exposure (particular from fish consumption) and coronary heart disease could not be excluded.

In a study among Greenlanders, Pedersen (pers. com) found a significant positive correlation between blood mercury concentrations and ‘pulse pressure’ (the difference between systolic and diastolic blood pressure). Pulse pressure (PP) has been found to be not only an independent predictor of coronary mortality in elderly females, but also a better predictor than systolic, or diastolic pressure alone (40).

Both the Kuopio ischemic heart disease risk factor study (36–37) and the study by Guallar et al. (39) conclude that DHA is inversely correlated with the risk of ischemic heart disease (IHD) and that mercury is positively correlated. In the Kuopio study, the level of methylmercury was found to be a strong predictor of oxidized low-density lipoprotein (ox-LDL). Under physiological conditions, native LDL is protected from oxidation by HDL, partly by the anti-oxidative enzyme paraoxonase 1 (PON1) associated with HDL.

In vitro studies of human liver cells have shown that mercury compounds, at biologically relevant concentrations, are powerful inhibitors of PON1. Mercury blocks a free sulphhydryl group in, or near to, the catalytic centre of PON. The ability of mercury to block the sulphhydryl group is reversible after addition of a thiol-containing reagent (41, 42), suggesting
that ox-LDL inactivation of PON involves the interaction of oxidized lipids in ox-LDL with the free sulphydryl group of PON. In this way, mercurials may block the PON-mediated regeneration of ox-LDL to non-oxidized LDL (43). If this effect of mercury also takes place in vivo, it may explain the role of mercury in cardiovascular disease, which has been indicated in the Kuopio ischemic heart disease risk factor study (37) and in a case-control study carried out in eight European countries and Israel (39). Both studies conclude that DHA is inversely correlated to the risk for IHD, and that mercury is positively correlated. The hypothesized effect of mercury on the PON/HDL complex is supported by a Norwegian study, which demonstrated a strong negative relationship between the dietary intake of mercury and HDL ($r = -0.76$, $p < 0.01$) in a group consuming large amounts of fish (44). The possible influence of mercury may also explain the inconsistency of the epidemiological findings of the relationship between n-3 fatty acids and coronary heart disease, as the two are supplied through the same types of food, but at varying levels according to the trophic level of the preferred food, i.e., the fatty acid level will be more or less the same at different trophic levels, while mercury, in the form of methylmercury, is biomagnified in the marine foodwebs.

Methylmercury can induce endothelial lesions and has been associated with the acceleration of atherosclerotic processes (45). The pathology may be based on an enhancement of lipid peroxidation and reduction of the anti-oxidative capacity, leading to oxidative stress, which is the initial event in the development of metabolic syndrome, obesity, type 2 diabetes, and cardiovascular disease. It has been suggested that these pathologies may be counteracted by polyunsaturated fatty acids of the n-3 family which, together with mercury, are supplied through a marine diet. In this way, benefits from a diet rich in healthy marine foods might be overruled by concomitant exposure to mercury. These newer findings could indicate an even lower RfD than that used by the USEPA if the cardiac effects were used as endpoints in risk assessments (1). These findings also imply that the consumption of fish containing current global concentrations of methylmercury is associated with a certain degree of risk. On the one hand, they emphasize the importance of reductions of anthropogenic emissions of mercury into the environment and, on the other hand, the need for further studies of interactions between methylmercury and nutrients to understand the beneficial aspects of fish consumption.

**INTERPRETATION OF THE US EPA REFERENCE DOSE IN A PUBLIC HEALTH CONTEXT**

In order to investigate the public health implications of exposure to mercury, a margin-of-exposure (MOE) analysis can be applied (32) to examine the margin of safety between available estimates of population exposure and the Benchmark Dose Limit (BMDL). The MOE is the ratio of the BMDL to the estimated population exposure level. The smaller the ratio determined in this analysis, the greater the cause for concern. Because the BMDL is not adjusted for uncertainty factors, MOEs of less than 10 indicate that population exposures might be approaching levels of public health concern (32).
As an example, a hypothetical population is reported to have a mean blood mercury concentration of 5.5 µg/l, with a range from 1.6 µg/l to 14.3 µg/l. Using the US EPA equation, the mean daily mercury intake would be estimated at 0.14 µg/kg-bw (range 0.04 to 0.39 µg/kg-bw). The MOE would therefore be 7.9 (1.1: 0.14) for the mean intake and between 27.5 (1.1 : 0.04) and 2.8 (1.1 : 0.39) for the range. For those at the high end of the population exposure distribution, the MOE indicates that the margin of safety for the most highly exposed is below 10. In other words, the exposure levels of the high-end consumers in this example are close to those at which adverse neuro-developmental impacts have been observed in epidemiological studies.

HEALTH BENEFITS FROM CONSUMPTION OF FISH

The question of the health benefits of fish consumption is extremely complicated. The following is in no way complete, but deals with some of the aspects which have gained most interest.

Intake of polyunsaturated fatty acids (PUFA) of both the n-6 and the n-3 family has been related to the prevention of coronary heart disease (CHD). These two families of PUFAs have different functions and animal studies suggest that the ratio of n-6 to n-3 is of importance (46). Wijendran and Hayes (46) suggest a ratio of approximately 6:1 as adequate, while a ratio of 2.3:1 is recommended by Kris-Etherton et al. (51). As the current mean estimated ratio in the United States is 12:1, an increased consumption of fish, which are an excellent source of n-3 PUFAs, seems to be warranted to further accelerate the decline in both the incidence and the mortality rates observed during the latest decennia in the United States (62) and in the rest of the western world. The beneficial effect of fish consumption is reflected in a substantial number of cohort and case-control studies i.e., dietary intake of n-3 fatty acids reduces the risk of cardiovascular mortality (reviewed by Calder (61)).

Marine oils might also be of importance to public health for reducing the onset of autoimmune diseases (47). Black and Sharpe (47) suggested that socio-cultural and regional differences in the prevalence of autoimmune diseases may be associated with differences in the consumption of PUFAs, such as eicosapentaenoic acid (EPA). While linoleic acid is the precursor of arachidonic acid, which can be converted to prostaglandin E2 (PGE2), EPA inhibits the formation of PGE2. PGE2 is known to act on T-lymphocytes, reducing the formation of interferon-gamma (IFN-gamma), without affecting the formation of interleukin-4 (IL-4). This may lead to the development of allergic sensitisation, since IL-4 promotes the synthesis of immunoglobulin E, whereas IFN-gamma has the opposite effect. Therefore, it has been suggested that changes in the diet could explain the increased prevalence of allergic diseases observed during the last few decades (47). This is, however, still hypothetical and no epidemiological evidence has been provided so far.

Obesity is another major area of public health concern where the intake of n-3 fatty acids may be of importance. A dramatic increase in obesity and the resulting type 2 diabetes have been observed in the western world
over the last 20 years, especially in Arctic and northern indigenous peoples. The major reasons for this are a more sedentary life-style (including less hunting of traditional foods) and higher intakes of substitute foods that are high in carbohydrates and have a high glycemic index. A contributing factor may also be a relatively low intake (i.e. a high n-6 to n-3 ratio) of highly unsaturated fatty acids (found abundantly in traditional foods), which have been found to lead to a repartitioning of hepatic fatty acids away from triglyceride synthesis and toward fatty acid oxidation, or thermogenesis (48). Mori et al. (49) found that the incorporation of a daily fish meal into a weight-loss regimen was more effective than a weight-loss regimen alone at improving glucose-insulin metabolism and dyslipidemia. Cardiovascular risk is likely to be substantially reduced in overweight hypertensive patients with a weight-loss programme incorporating fish meals rich in n-3 fatty acids.

In recent years, the optimal level of n-3 fatty acids in the diet has been the focal point of intense scientific scrutiny. In the United States, this has resulted in recommendations from scientists to increase consumption of the highly unsaturated n-3 fatty acids, especially EPA and DHA, from 0.1-0.2 g/d to 0.65 g/d (50). This, however, has not yet been established as an official dietary recommendation. A weekly consumption of approximately 300-400 grams of fish can provide an adequate intake of n-3 fatty acids. Alternative strategies for increasing intake of n-3 fatty acids may be developed through the use of supplementary fish-oil capsules, food enrichment and the biotechnological manipulation of the EPA, DHA and linoleic acid (ALA) contents of some items in the food supply.

In a future perspective, the FAO (60) has stated that, on a global scale, fish consumption per capita will increase in the next three decades. This will, however, depend on development of fish farming, as the world’s natural fisheries have by now reached, or even exceeded, the limit of sustainability. There will also be regional and local differences in fish consumption patterns that are not reflected by the global perspective taken by the FAO.

RISKS AND BENEFITS: MERCURY TOXICITY VERSUS BENEFICIAL NUTRIENTS

Fish can be a significant component of diet for both adults and children in the Arctic. It is also a rich source of proteins, vitamins (E and D) and trace elements (selenium, fluoride, and iodine), and can be one of the most important sources of essential n-3 fatty acids. For this reason, alternative strategies to increase the intake of n-3 fatty acids alone through the use of supplements, or fortified foods, may not be the ideal solution from an Arctic public health point of view.

Based on the findings in the Seychelles Islands, a high consumption of fish, which has a relative low level of mercury, appears to create a balance between the benefits and the risks. Under other and less balanced dietary regimes, mercury may cause subtle symptoms at the same level of exposure as in the Seychelles. Nutrients and contaminants may interact directly via the same mechanism, or they may affect the same outcome via different mechanisms. This suggests that studies designed to better understand the relative impacts of nutrients on pollutant effects should have a high priority.
Since the National Research Council evaluated the US EPA RfD of 0.1 µg/kg-bw/d to be scientifically justified, and as it is now also suggested to be appropriate for Europe, this exposure level should be seriously considered by local public health authorities when they give dietary advice, especially to pregnant women.

If the optimal amount of fish is consumed (300-400 g/week), the mercury level in the fish muscle should not exceed 0.12 to 0.16 mg/kg, a level commonly reported in ‘unpolluted’ oceanic fish. Taking this calculation into account, it seems clear that there is no room for any further mercury pollution. Because of the beneficial effects of fish consumption, the long-term aim is not to replace fish in the diet by other less nutritious foods, but to reduce the methylmercury concentrations in the fish to natural background levels. If this is not possible, dietary advice should be provided to girls over the age of 12 and to pregnant women, in order to reduce their consumption of fish with high levels of methylmercury and to seek nutritious substitutes. Both the USA and Canada have issued similar consumption advisories pertaining to large oceanic fish species for women of childbearing age, pregnant women and children (52, 53). The Faroese Health authorities have recommended that "Women who intend to be pregnant during the three next months, women who are pregnant, or those who are breast-feeding, should not eat any whale meat at all. Liver and kidneys of whale should not be eaten at all" (55). This is a prudent approach, considering the recent reports of mercury-induced cardio-toxicity, which could lead to further reductions in international guidance levels for mercury exposure.

CONCLUSION

The main source of human exposure to methylmercury is through the consumption of fish and meat (muscle and organs) from marine mammals. As an element naturally found in the earth’s crust and the environment, mercury is present in background concentrations in muscle tissue from 0.1 to 1 mg/kg, depending on the trophic level and age of the fish/mammalian species examined.

Recent benchmark calculations based on neuro-physiological endpoints have demonstrated effects at a daily intake as low as 1.1 µg/kg-bw. The present US EPA Reference Dose of 0.1 µg/kg-bw/d is derived from this benchmark by applying an uncertainty factor of 10. If other endpoints were used, e.g. cardiac effects, an even lower benchmark dose might appear. From this, it can be concluded that the consumption of relatively unpolluted fish can be associated with negative effects due to mercury.

Fish and marine mammals are the most important sources of essential n-3 fatty acids, protein and many micronutrients. Reductions in the consumption of marine food may constitute an important etiological cofactor for the increasing worldwide prevalence of a number of diseases, such as autoimmune disorders, diabetes type-2, obesity, and cardiovascular diseases. Much of the Arctic population relies on traditional foods from the freshwater and marine environments and is at risk of excessive exposure to mercury. Some communities have shifted in their food consumption patterns and may now have reduced intakes of beneficial n-3 fatty acids and too much intake of replacement foods containing carbohydrate and saturated fats.
Thus, there is an incompatibility between the toxicological and the nutritional basis for dietary advice regarding fish consumption. It is clear that prompt political action to reduce mercury pollution is needed. At a minimum, this should include immediate ratification and implementation of international protocols designed to reduce human emissions of mercury, and local and regional planning to reduce sources of mercury, which are contributing to human exposure. The development of comprehensible and relevant dietary advice, especially to women of child-bearing age, is also warranted under some circumstances. This advice should be provided on a case-by-case basis for affected populations, taking into account both cultural and social factors in the communities. Consumption advisories for sub-populations in specific communities, or regions, should always be prepared in co-operation with appropriate local public health practitioners.

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