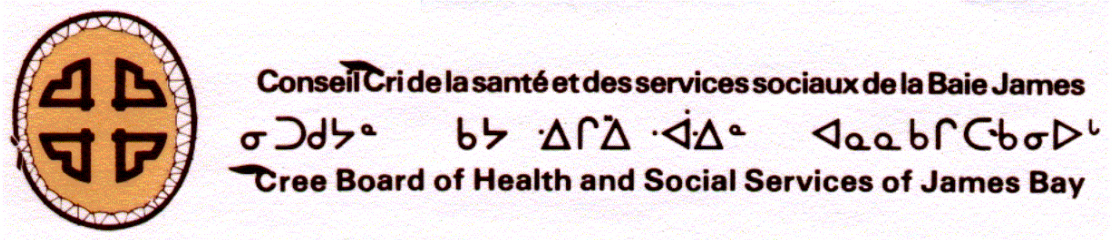
The Health Effects of Methylmercury:

A literature review

Deborah Schoen, MPH, Eng

September, 2004

Miyupimaatisiwin aa uhchi pimipiyihtaakinuwich utih iiyiyuu aschiihch
Direction de santé publique de la région des Terres cries de la Baie James
Public Health Department of the James Bay Cree Territory



Acknowledgements : we would like to thank Dr. Marc Rhainds, of the Institut National de Santé Publique du Québec, for reviewing this document. However, he is not responsible for any errors remaining in the text.

Miyupimaatisiwin aa uhchi pimipiyihtaakinuwich utih iiyiyuu aschiihch
Direction de santé publique de la région des Terres cries de la Baie James
Public Health Department of the James Bay Cree Territory
Telephone: Chisasibi office (819) 855-9001 ext 5363; fax (819) 855-9031
Montreal office (514) 861-2352; fax (514) 861-2681

Legal deposit :
Bibliothèque nationale du Québec
National Library of Canada
ISBN:

Table of contents

List of Tables

Executive Summary

Methylmercury – the form of mercury that occurs in fish – is a potent toxin at high doses. It is the cause of Minamata Disease, a debilitating and in some cases fatal neurological disease, named after the first major epidemic of methylmercury poisoning in Minamata, Japan in the late 1950s. That epidemic, caused by heavy industrial pollution in Minamata Bay, led to very high levels of methylmercury in fish, over 2000 cases of the disease in residents of the area, and over 140 deaths.

The tragedy of Minamata was repeated in two other epidemics – in Niigata, Japan in the early 1960's, again as a result of methylmercury discharged to fishing waters, and in Iraq in the early 1970s as a result of the consumption of flour milled from seed containing a methylmercury fungicide (Marsh 1987). Epidemiological studies on the populations affected by these epidemics have greatly increased knowledge of the health effects of methylmercury.

Methylmercury exposure, however, is not limited to isolated poisoning incidents. As all fish contain some level of methylmercury, moderate exposures are typical of subsistence fishing populations around the world, even when local industrial mercury pollution is absent. For the last two decades, scientists have been asking what the significance of these long-term exposures are for adults, for children, and in particular, for pregnant women and their babies. The resulting scientific literature regarding the health effects of methylmercury is extensive.

This report on the health effects of methylmercury presents an overview of the literature, particularly with respect to issues important to risk assessment and the development of consumption advice. The intention is to provide a general synthesis of the current knowledge, and interpret this information in the context of the Cree of Eeyou Istchee, and their exposure to methylmercury through the consumption of local freshwater and coastal fish.

Health effects in adults

The relationship between exposure and effects in adults at high doses of methylmercury has been established primarily on the basis of data gathered on the Iraqi epidemic, which resulted from consumption of flour milled from methylmercury-treated grain. Data from the Niigata epidemic have also contributed to establishing this relationship, although the methods of analysis for mercury exposure during the Niigata epidemic were not as sensitive as the methods used in the Iraqi investigations (Marsh 1987). In these two epidemics, severe exposures (up to 1000 ppm in hair) were associated with Minamata disease. The onset of symptoms was observed to occur at exposures corresponding to approximately 100 to 200 ppm mercury in hair. The first symptom observed is paraesthesia (numbness in fingers), which at increasingly higher doses is followed by more severe effects, including constriction of visual field, ataxia, hearing loss, and death.

On the basis of statistical analysis of the Iraqi data, the World Health Organization (WHO) estimated that an exposure of 50 ppm mercury in hair corresponding to a 5% increase in risk of paraesthesia. However, this estimate was sensitive to error in estimating the background population frequency of the condition, which was not well known for the Iraqi population (IPCS-WHO 1990). The validity of this estimate was

further investigated by Kosatsky and Foran (1996) with regard to exposures in subsistence fishing populations. In such populations, moderately high exposures have resulted from consumption of large amounts of fish with low to moderate levels of mercury.

Kosatsky and Foran noted that two studies for which dose-response could be assessed showed evidence of neurologic dysfunction with rising blood mercury levels in the range of 60 to120 ppb (15 to 30 ppm in hair). A third study "provided good evidence that chronic whole blood mercury levels up to 20 ppb [5 ppm in hair] are without apparent neurologic effect." Considering all studies together, among 57 fish eaters with a blood mercury level greater than 200 ppb (50 ppm in hair), mild neurological effects consistent with methylmercury exposure were found in as few as six individuals (11%) and as many as 15 (31%)[1] (Kosatsky and Foran 1996).

Since 1990, cross-sectional epidemiological studies investigating the neurological effects of mercury exposure in adults have been carried out in the Amazon (Tapajós and Pantanal regions of Brazil). In these regions fish consumption is widespread, with mean hair mercury levels in the range of approximately 5 to 10 ppm, and maximum levels in the Tapajós above 30 ppm (Dolbec, Mergler et al. 2000; Yokoo, Balente et al. 2003). Associations between neurologic impairment have been reported in these investigations, although the specific domains of impairment (different motor and cognitive tests) vary. The studies have not allowed for the determination of a threshold for methylmercury neurotoxicity.

The Health Canada and former World Health Organization (WHO) guidelines for adults, established in the early 1990s, recommend a maximum exposure of 20 ppb in blood (6 ppm in hair). A recent revision of the World Health Organization guideline by the Joint Expert Committee on Food and Agriculture (JECFA)[2] set the recommended weekly intake at 1.6 µg/kg bw/ week. However, this new guideline was derived on the basis of epidemiological evidence for effects in children exposed *in utero*, and not on the basis of effects in adults. The applicability of the revised WHO guideline to adults is not addressed in the document supporting the guideline revision.

Health effects in children exposed *in utero*

In the Iraqi and Niigata epidemics, severe effects in children exposed prenatally (blindness, deafness, and mental retardation) were associated with exposures above 100 ppm in the mother's hair. At levels of 10 to 20 ppm in maternal hair, no clinical effects were found, but analysis of data for developmental milestones (walking, talking) suggested a population threshold of approximately 10 ppm for delayed walking. This determination created considerable concern in the international public health community, as such exposures are common among frequent fish consumers.

Thus, beginning in the late 1970s, a second generation of epidemiological study investigating the effects of prenatal methylmercury exposure in fishing populations began. One such investigation was the McGill Methylmercury Study (see section 2.4.2), carried out in four Cree communities. The most important of the prenatal exposure investigations, with regard to establishing dose-response relationships between

[1] The range of 11 to 31 % reflects uncertainty with respect to the level of exposure (in 6 cases) or the presence of other health conditions affecting the diagnosis (3 cases).
[2] See p18-22 of 61st meeting of JECFA, Rome, 10 to 19 June, 2003 Summary and Conclusions http://www.who.int/pcs/jecfa/Summary61.pdf,

mercury exposure and effects, were carried out in the Seychelles and the Faroe Islands. These were large prospective studies for which the children's development was followed over time.

In the Faroe Islands study, reduced performance on language, attention, and memory tests was associated with increasing methylmercury exposure. However, in the Seychelles study, no neurodevelopmental effects were observed in the more highly exposed children. The contradictory nature of the findings of the two studies, both considered to be of high quality, has challenged regulatory authorities charged with setting guidelines. Several solutions to the conundrum have been applied by Health Canada, JECFA of the World Health Organization, and the National Research Council of the US National Academy of Sciences, among others. These have all led to the estimation of a critical dose of approximately 10 to 15 ppm in maternal hair, reflecting prenatal exposures that would be without appreciable effects for children in the populations investigated.

In the determination of guidelines for dietary intake of methylmercury, the critical dose, expressed as a maternal hair mercury level, is converted to an intake and divided by uncertainty factors, which vary from agency to agency. For example Health Canada estimates the critical dose at 10 ppm in maternal hair and divides by an uncertainty factor of 5 to derive a recommended exposure of 2 ppm in maternal hair or approximately 0.2 µg/kg bw/ d. The WHO estimates the critical dose at 14 ppm and divides by an uncertainty factor of 6.4 to derive a recommended intake of 1.6 µg/kg bw/ week or 0.23 µg/kg bw/ d (or maternal hair level of approximately 2 ppm).

Evaluation of the methylmercury exposures of the Cree of Eeyou Istchee

How do mercury exposures in the Cree of Eeyou Istchee compare with the different agency guidelines and with the levels at which adverse effects are observed?

The most recent general survey of mercury exposure was in 1993/94. In that year, 1772 individuals were tested. The median mercury hair level was 2.5 ppm, and the maxumum level was 42.2 ppm. Over 10 % of the individuals exceeded the Health Canada guideline of 6 ppm. Older individuals generally had higher exposures (median of 4.4 ppm) compared to the younger generation. There was also considerable variation among communities, with the highest mercury hair levels recorded for Whapmagoostui (median for all individuals of 3.6 ppm, maximum of 42.1).

Among women of childbearing age, in the 1993/94 survey approximately 10 % had mercury exposures above 3 ppm . The maximum level recorded within this group was 12.8 ppm. Among pregnant women in this time period, exposures were generally at or below the detection limit of 2.5 ppm (Dumont, Noel et al. 2002), which corresponds approximately to the Health Canada guideline for women of childbearing age.

In general, the exposures of women of childbearing age in the Cree communities in 1993/94 were lower than the exposures of mothers in the Seychelles and Faroes Islands studies (studies on which the Health Canada guideline is based). As previously noted, in the Seychelles study no neurodevelopmental effects were associated with mercury exposure. In the Faroe Islands study, reduced performance on language, attention, and memory tests was associated with a maternal hair mercury level of approximately 12 ppm and above (NRC 2000).

The findings of the Seychelles study, and indeed the results of the Faroe Islands study, suggest that Cree women can continue to eat local fish from natural lakes, as they did in 1994, during pregnancy and when breastfeeding, without harm to the development of their children. Nonetheless, there remain unresolved issues that contribute to the uncertainty associated with such a conclusion. Are the results for the Seychelles and Faroes Islands population applicable to other populations with very different diets, environments, and lifestyles? How variable are individuals in their sensitivity to the toxic effects of mercury? Were the tests administered in the two studies sufficiently sensitive to detect subtle effects of mercury toxicity? Such questions lead regulators to apply safety or uncertainty factors in their derivation of public health guidelines. This uncertainty drives the recommended dietary limits towards exposures that are much lower than the exposures at which adverse effects are documented.

One factor that may affect the magnitude of the safety factor is the weight given to the benefits derived from fish consumption. Many guidelines do not explicitly factor in such benefits, but rather assume that a population will be able to maintain a moderate level of fish consumption while reducing mercury exposure by choosing fish species that are very low in mercury. Such a strategy appears realistic for the general North American population, which does not generally consume large amounts of fish, and which has access to a wide range of species delivered to fish markets and grocery stores (NRC 2000). However, for fishing populations, reducing mercury exposure may mean reducing fish consumption. In this case, the health, economic, and social benefits of fishing and fish consumption should be considered in the development of a dietary guideline.

1.0 INTRODUCTION

Methylmercury – the organic form of mercury that occurs in fish – is a potent toxin at high doses. It is the cause of Minamata disease, a debilitating and in some cases fatal neurological disease, named after the first major epidemic of methylmercury poisoning in Minamata, Japan in the late 1950s. That epidemic was caused by heavy industrial pollution in Minamata Bay, which led to very high levels of methylmercury in local fish. Over 2000 cases of the disease were identified in the nearby fishing villages, and over 140 people died. During the Minamata epidemic, some women exposed to methylmercury during their pregnancy gave birth to children with severe neurological disabilities, including cerebral palsy and mental retardation (Tsubaki and Irukayama 1977; Igata 1993).

The tragedy of Minamata was repeated in two other epidemics – in Niigata, Japan in the early 1960's, again as a result of methylmercury discharged to fishing waters, and in Iraq in the early 1970s as a result of the consumption of flour milled from seed containing a methylmercury fungicide (Marsh 1987). These epidemics greatly increased awareness within the public health community of the serious dangers of organic methylmercury pollution. However, little attention was paid to the more widespread occurrence of inorganic mercury pollution. Then, in 1975, surprisingly high levels of methylmercury in fish were discovered in the Saint-Clair River (Ontario) downstream from a chemical plant discharging inorganic mercury (Grieg and Seagran 1970).

In addition to the St. Clair River case, other instances of high levels of methylmercury in fish were discovered throughout Canada in the 1970s, related to inorganic mercury discharges from chlor-alkali plants operating with pulp and paper mills. In northern Ontario, in the English and Wabigoon Rivers, fish were caught with mercury levels reportedly up to 24 mg/kg (24 ppm), and in northern Quebec, in the Bell River, fish mercury levels reached 4 ppm. In both cases the high mercury levels were measured in fish downstream from a chlor-alkali plant (Health Canada 1999). These levels can be compared with the limit for commercial sale of fish of 0.5 ppm mercury[3].

It was thus discovered that the mercury discharged to lakes and rivers in industrial effluent is transformed to methylmercury by microorganisms in the water and subsequently incorporated into the food web of the aquatic ecosystem. Plankton and other aquatic invertebrates ingest and concentrate the methylmercury and, in turn, insect-eating fish further concentrate the substance. Predatory fish, such as pike and walleye, accumulate the highest concentrations of methylmercury, with the older larger fish more highly contaminated than the younger fish of the same species.

[3] In the present review, mercury concentration in fish is generally expressed in ppm, equivalent to mg mercury per kg fish.

While no case of Minamata disease has ever been conclusively documented in Canada, high mercury exposures in subsistence fishing populations have been recorded (Health Canada 1999), including among the Cree of Eeyou Istchee (James Bay), and particularly in the early screening programs carried out in the 1970s.

Hydroelectric development in Eeyou Istchee has also led to increased levels of methylmercury in fish in the hydroelectric reservoirs and in river sections downstream. The release of mercury from the soil during flooding, its transformation to methylmercury, and its bioaccumulation in the food chain result in fish mercury levels three to seven times greater than fish of the same size and species in natural lakes. For example, lake whitefish – an insect-eating fish – reached peak levels greater than 0.5 ppm (400 mm length) in the Robert-Bourassa reservoir (LG-2) as compared to a natural level of less than 0.2 ppm, while northern pike – a predatory fish – reached peak levels greater than 4.0 ppm (700 mm length), as compared to a natural level of approximately 0.5 ppm. The mercury levels in reservoir fish reach their peak in the 5 to 13 years after impoundment. The levels then decline gradually, appearing to reach natural levels in 10 to 25 years after impoundment, in the case of the non-predatory fish (e.g. lake whitefish and longnose sucker), and in 20 to 30 years in the case of predatory fish (e.g. northern pike, walleye, and lake trout) (Schetagne and Verdon 1999).

Today, direct industrial discharges of mercury into lakes and rivers in Canada are largely controlled. However, even in wilderness lakes in Eeyou Istchee, remote from pollution sources and unaffected by hydroelectric development, predatory fish still accumulate moderately high levels of methylmercury. The sources of mercury in the water are the naturally-occurring mercury in the soil and sediments and the mercury transported in the atmosphere from near or distant pollution sources, volcanic eruptions, or forest fires (Nriagu 1989). The resulting levels of methylmercury in species such as pike, walleye, and lake trout are far below the levels in fish during the Japanese and Iraqi epidemics of Minamata disease, and well below the peak levels in reservoir fish. However, the mercury levels are sufficiently high that regular consumption of these species of fish could lead to a moderately high exposure, as measured by the level of mercury in an individual's blood or hair.

For the last two decades, scientists have been asking what the significance of these long-term moderately high exposures are for adults, for children, and in particular, for pregnant women and their babies. The resulting scientific knowledge regarding the health effects of methylmercury is extensive.

This report on the health effects of methylmercury presents an overview of the scientific literature on the human health effects of methylmercury. The intention is to provide a general synthesis of the current knowledge, and interpret this information in the context of the exposure of the Cree of Eeyou Istchee to methylmercury through the consumption of local freshwater and coastal fish.

2.0 METHODOLOGY

The literature on the health effects of methylmercury is large, with over 4000 references indexed on the Toxline (US National Library of Medicine) database alone. Two constraints were placed on the literature review in order to make the task manageable. First, several authoritative and comprehensive reviews[4] of the pre-2000 literature allowed us to summarize part of the literature on the basis of those reviews. We thus limited our searches to the period 1999 to 2003. However, in some instances key articles published prior to 1999 articles were also reviewed and are included in the present discussion.

Second, while all the retrieved references were consulted (either articles or abstracts), the selection of articles for discussion favoured studies directly relevant to the Cree situation and the process of risk assessment. Emphasis is therefore on epidemiological (human population) studies and on investigations into effects at the level of exposures typically associated with fish consumption. Animal studies are reviewed in relation to their impact on risk assessment assumptions.

Certain references were not consulted either because they were not available from Montreal research libraries or because they appeared in journals in a language other than English or French. Nonetheless, all the retrieved references have been copied into reference management files. A complete bibliography is included in Appendix A.

In researching the recent literature, a literature search methodology for identifying articles and compiling the references in EndNote (reference management software) has been developed and documented. Thus key articles and reports can be retrieved on a periodic basis, using this methodology, and brief summaries prepared as needed. The literature search methodology is included in Appendix B.

[4] ATSDR (1999). Toxicological Profile for Mercury (Update). Atlanta, Georgia, USA, US Department of Health & Human Services, Agency for Toxic Substances and Disease Registry**:** 617 pp. + app

NRC (2000). Toxicological Effects of Methylmercury. Washington, DC, National Research Council, National Academy of Sciences**:** 344 pp

Shipp, A., M., P. R. Gentry, et al. (2000). "Determination of a site-specific reference dose for methylmercury for fish-eating populations." Toxicology and Industrial Health **16**: 335-438.

3.0 BACKGROUND

Certain preliminary notions are presented here as background for the discussion of the health effects of methylmercury. The National Research Council's "Toxicological Effects of Methylmercury" and the ATSDR's "Mercury Update" were selected as the primary references for this discussion. The reader should consult the two reviews for further detail and for the original citations.

3.1 Chemical forms of mercury

Mercury occurs in different forms in the environment. Best known is the metal, otherwise known as quick silver. Cinnabar, the ore from which the metal is extracted, is primarily mercuric sulfide, an inorganic ionic form of mercury. Most of the mercury in fish occurs as methylmercury, an organic compound (ATSDR 1999).

Exposure to methylmercury is ordinarily limited to consumption of fish and, in certain populations, to consumption of fish and marine mammals. Metallic mercury, on the other hand, is widely distributed in the environment, used extensively in the past in thermometers, thermostats, alkaline batteries, and other consumer items and industrial equipment. Individuals could be exposed to this mercury if it was accidentally released to the home or workplace environment and they were to breathe in mercury vapours. Metallic mercury is also used in dental amalgam. Individuals with fillings inhale a low but measurable amount of mercury, the amount varying with the number of fillings and individual habits such as teeth grinding or chewing gum. Mercury in the ionic form can be measured in ambient air and water, but at extremely low levels. In certain occupational settings, however, exposure to the mercuric ion may be significant (ATSDR 1999).

The toxic effects of metallic mercury and methylmercury are distinct, in that the primary exposure routes and metabolism of the two substances in the body are very different. However, both contribute to the level of total mercury in the brain and other tissues, and there may be potential overlap and interactions between the two with regard to their toxic effects. Both methylmercury and metallic mercury are recognized neurotoxins, although the set of characteristic symptoms of acute intoxication is distinct for each chemical form. The summary of health effects presented in sections 4.0, 5.0 and 6.0 is specific to methylmercury exposure.

3.2 Toxicokinetics of methylmercury

Toxicokinetics refers to the study of the absorption and distribution of methylmercury in the body over time. In the present case, researchers ask the question: for a given amount of methylmercury ingested in a fish meal, what will be the concentration in the blood, brain, hair, kidneys, and other organs and tissues after one hour, one day, one month, or longer. The study of toxicokinetics serves to relate a given intake to concentrations in target organs such as the brain, and to concentrations in the tissues used to measure exposure, including blood and hair.

This type of data, where it exists for both humans and different animal species, helps in the interpretation of the results of animal experiments, specifically with respect to extrapolating dose-response data to humans.

Approximately 95% of the methylmercury in fish ingested by an individual is absorbed from the gastrointestinal tract into the bloodstream, where over 90% binds to the hemoglobin in red blood cells. Methylmercury will appear in the blood within 15 minutes and peak in 3 to 6 hours following a meal (NRC 2000).

The amount of methylmercury in the body at a given time is referred to as the body burden. About 10% of the body burden is found in the brain, where it is slowly transformed to inorganic mercuric ion; approximately 5 % is in the blood, and approximately 1% of the body burden is excreted daily in the feces. The whole-body half-life (time for half of the methylmercury to be eliminated from the body) is estimated at 70 to 74 days, while the half-life for blood and hair is 50 days (NRC 2000).

Methylmercury crosses the placenta and enters the fetal brain. Thus, the fetus is exposed prenatally to the methylmercury ingested by the mother during pregnancy. Exposure in infancy would result from the methylmercury in the breast milk of a mother who consumes fish (NRC 2000).

3.3 Biological variability

Different people respond differently to the same exposure to methylmercury. For example, uptake and distribution rates differ from one individual to another, as do rates of transformation and excretion. In general, a wide range of physiological and nutritional factors may affect an individual's susceptibility to toxic effects of a substance, including genetic predisposition, age, gender, health status, and the intake of other nutrients or toxins that would modify a substance's toxicity. These factors as they relate to methylmercury toxicity, are discussed below.

3.3.1 Age-related variability

Distinct changes in methylmercury toxicity with age were observed during the Minamata poisoning epidemic in Japan. In the case of prenatal exposure, methylmercury interfered with brain development, as demonstrated in the cases of cerebral palsy-type disorders and mental retardation, while in adults, more specific neurological functions were affected. The sensitivity of the fetus to the toxic effects of mercury is also greater. During the Minamata epidemic, and in subsequent poisonings in Japan and Iraq as well, mothers with no apparent symptoms themselves gave birth to babies who were severely affected (NRC 2000).

The neurotoxic effects from methylmercury are generally documented either through clinical examinations or through scoring individual performance on a battery of neurological tests. Age can also affect this neurological assessment process (NRC 2000). For example, there is considerable variability in the age at which children reach developmental milestones such as

walking and talking, and because the children are developing rapidly, the timing of the testing can influence the results of a study and its conclusions. In the elderly, the effects of age on neurological performance are also significant, and highly variable from one individual to another. This natural biological variability, in both the young and the old, can reduce the sensitivity of a particular neurological test to detect methylmercury-specific effects.

3.3.2 Variability due to gender and genetic factors

Individual human and animal studies have reported gender-related differences in the deposition, metabolism, and excretion of methylmercury, as well as in the susceptibility to toxic effects, but there has been little consistency in the observations. Animal studies generally show that females exhibit a higher body burden of mercury for the same ingested dose, but the degree to which one sex will be more affected than the other varies between strains and species of the animals tested (NRC 2000).

With respect to genetic predisposition, it is possible that certain human genetic polymorphisms (different forms of the same gene) exist that can modify the toxicity of methylmercury. However, no such polymorphisms have as yet been identified (NRC 2000).

3.3.3 Nutrition and methylmercury health effects

Diet can affect the toxicity of methylmercury through different mechanisms. Poor health, because of a diet deficient in essential nutrients, may increase an individual's susceptibility to the toxic effects of methylmercury, and may also, in and of itself, contribute to the adverse effects that might be attributed to methylmercury (e.g. developmental delays, poorer performance on neurological tests, immunological deficiencies). Other contaminants in fish, such as polychlorinated biphenyls (PCBs), may also add to or exacerbate the effects of methylmercury. At the same time, the nutritional benefits of fish – rich in protein, in important nutrients, and low in saturated-fat – may reduce susceptibility to the toxic effects of methylmercury (NRC 2000). These aspects are currently the focus of both epidemiological and toxicological research, and are discussed further in section 9.0.

3.4 Measurement of exposure to methylmercury

Methods of measuring exposure to methylmercury fall into two categories: dietary assessments and direct measurement of methylmercury in blood, hair, or in some instances, toenails (biomarkers of exposure).[5]

[5] Mercury in blood is generally expressed in µg/l or ppb; mercury in hair is generally expressed in µg/g or ppm; blood mercury levels and hair mercury levels can also be expressed in nmol/l or nmol/g, respectively. Note that 1 µg Hg is equivalent to 5 nmol Hg (molecular weight of mercury is 200.59.)

Dietary assessment methods include duplicate sampling of food consumed during meals, food diaries, and questionnaires based on recall. Duplicate diet data gives the most accurate evaluation of methylmercury exposure, but is considerably more demanding of study participants than food diaries or questionnaires. Food diaries, completed on a daily basis, generally estimate fish consumption better than do questionnaires based on recall (NRC 2000). Both of these methods require the researcher to characterize the methylmercury concentrations that are typical of the foodstuffs consumed in order to estimate exposure.

Uncertainties in recall, in identification of fish species, and in estimating the true methylmercury concentration based on typical values contribute to the overall uncertainty associated with exposure estimates based on food diaries or dietary recall. Given this uncertainty and the complexity of the duplicate food sampling method, most epidemiological studies evaluate exposure using biomarkers. Nonetheless, as the NRC review emphasizes, dietary data on all sources of exposure to mercury (including vaccines and amalgams) are essential to understanding the effects of environmental exposures on outcomes. The data also serve to identify possible confounding factors in epidemiological studies, such as other contaminants or nutrients that occur in greater concentrations in fish (NRC 2000). Thus these methods provide qualitative and quantitative information that can assist in the interpretation of exposure data derived from biomarkers.

3.4.1 Total mercury and methylmercury in blood

Exposure to methylmercury can be assessed through measurements of total mercury (inorganic mercury plus methylmercury) or methylmercury in blood. In a population with little or no fish consumption, where the total mercury in the blood results from exposure to inorganic sources such as dental amalgam, the mean mercury in blood has been reported to be about 2 µg/l. Regular fish consumers generally have total mercury blood levels far higher than this, due to the contribution of methylmercury. Thus, for fish eaters, total blood mercury is generally a good surrogate measure for methylmercury.

The mean half-life of methylmercury in blood is approximately 50 days. Blood mercury concentrations therefore reflect relatively short-term exposures. In the case of occasional consumers of fish, blood mercury can be highly variable, whereas regular frequent consumers, who on average ingest as much methylmercury as they excrete, can achieve an approximately steady concentration of blood mercury.

Researchers sometimes assess prenatal exposure by measuring total mercury in the cord blood. The advantages of measuring cord blood are that it is non-invasive (sample taken at delivery), and it gives a closer physiological measure of the amount of methylmercury to which the fetus has been exposed, as compared to the maternal blood or hair. It is often assumed that the concentration of mercury in cord blood is approximately eqaual to the concentration in maternal blood. However, a recent review of cord blood mercury data estimated the central tendency of the ratio of cord blood to maternal blood concentrations at 1.7 (Stern and Smith 2003).

Given the half-life of methylmercury in the blood of 50 days, the amount of methylmercury in the cord blood at delivery reflects exposure generally over the last trimester of the pregnancy. The extent to which the fetal brain is sensitive to methylmercury toxicity in this period is not well known. Brain structure is generally established at this time, and so gross abnormalities resulting from methylmercury exposure are less likely. However, toxic effects on specific functions might occur at this stage (NRC 2000). The period of gestation associated with the greatest risk of neurological effects is discussed in more detail in section 9.0.

3.4.2 Total mercury and methylmercury in hair

Among non fish eaters, whose hair mercury concentrations reflect primarily exposure to inorganic mercury, hair mercury is in the range of 0.2 to 0.8 µg/g (ppm). In frequent and regular fish consumers the total hair mercury levels are an order of magnitude higher, and most of the mercury is in the form of methylmercury. Thus, as in the case of blood, total mercury in hair of regular fish consumers is an acceptable surrogate for methylmercury in hair (NRC 2000).

Hair, as a biomarker, integrates exposure to mercury over a time period of several or many months, depending on the length of the sample taken. The growing hair shaft incorporates mercury from the circulating blood in proportion to the concentration in the blood. The hair shaft then grows at a fairly constant rate (estimated at approximately 1.1 cm per month). This feature is particularly relevant to prenatal exposure studies in that the maternal exposure can be tracked during many months of the pregnancy, provided that an adequately long hair sample is available.

The hair samples are normally segmented, often in lengths of 1 cm (30 days) and the individual segments analyzed. Such analysis will reflect peak exposures in an attenuated fashion. For example, a doubling of the background blood mercury level in a single peak exposure over 30 days will result in a 50 % increase in the hair mercury level in the 1-cm segment that includes the peak exposure. A more accurate profile of peak exposures can be obtained through continuous single-strand hair analysis using X-ray fluorescence. In this method, mercury levels are determined on 2 mm segments, corresponding to a period of about 6 days (NRC 2000).

The NRC review notes several caveats, however, with respect to hair as a biomarker. First there is significant inter-individual variability in hair-growth rates (0.6 to 1.5 cm per month). Second, during pregnancy hair growth slows and this variability among individuals increases. Third, a proportion of hair strand follicles (10 to 30 %) are in a “terminal resting phase” rather than a growth phase. Mercury is not incorporated during the resting phase, such that these strands will not reflect the most recent exposure (NRC 2000). This third problem would be of greatest concern for the continuous analysis method of a single strand, if the objective is to match exposure with particular time periods, such as stages in pregnancy.

3.4.3 Comparison of biomarkers

Total mercury measured in hair or blood is an acceptable surrogate for the measurement of methylmercury in hair or blood among those individuals who consume fish regularly.

The measurement of mercury in hair has certain advantages over the measurement in blood. It is non-invasive and relatively simple to sample. Field workers without previous medical training can be trained in the proper sampling technique. Hair mercury levels reflect exposure over weeks and months (depending on the length of the sample). Segmenting the hair into short segments will allow greater detection of peak exposures.

Blood mercury levels reflect recent exposures more accurately than hair mercury levels, but do not provide information on long-term exposure. Cord blood samples, taken at the time of delivery, can accurately reflect fetal exposure towards the end of gestation.

3.5 Toxicokinetic variability and interpretation of biomarkers

As discussed in section 3.3, many factors can potentially contribute to variability among individuals in the levels of methylmercury in the tissues – factors such as age, gender, and diet. This is referred to as toxicokinetic variability. Understanding toxicokinetic variability is of particular importance in risk assessments of methylmercury because of the importance of hair and blood concentrations for characterizing exposure.

Epidemiological studies identify the hair and blood mercury levels at which effects are first observed to occur. These critical exposures must then be translated into intakes (expressed as µg/kg body weight/day), a process referred to as dose reconstruction. However, because of toxicokinetic variability, the dose corresponding to a given hair or blood mercury level will be different for different individuals. In order to reconstruct the doses to include the most sensitive individuals (i.e. individuals who absorb and retain methylmercury at higher rates), risk assessors need to evaluate the degree of toxicokinetic variability among individuals.

Two models are currently widely used to describe the uptake of methylmercury, its distribution to various tissues (including the biomarkers hair and blood), and its elimination from those tissues: the one-compartment pharmacokinetic model, and the more complex model referred to as a physiologically based pharmacokinetic model (PBPK). In the latter case, separate compartments are assumed for each of the major tissues and organs involved in the toxicokinetics of methylmercury, giving the model greater flexibility and biological coherency but requiring far more information for the evaluation of the different parameters (see for example (Carrier, Bouchard et al. 2001; Carrier, Brunet et al. 2001).

The NRC review compares the results of three analyses evaluating toxicokinetic variability, two based on the one-compartment model, and the third based on the PBPK model. All three analyses use the distribution of values for each input parameter and a Monte Carlo analysis to generate the distribution of doses that correspond to a hair level of 1 ppm and a blood level of 1

ppb. While the three analyses result in different estimates for the 50th percentile dose, they are nonetheless fairly consistent with regard to the degree of variability. This variability, expressed as the ratio between the 50th percentile dose and the 5th percentile dose is estimated between 1.5 and 2.1 for hair, and between 1.4 and 2.1 for blood (NRC 2000).

These measures of variability are critical to the selection of uncertainty factor, as part of the uncertainty relates to the problem of protecting the great majority of the population, including sensitive individuals, and not just the "typical" individuals. This issue is discussed further in section 10.0 (Comparison of Methylmercury Intake Guidelines).

A critique of the use of hair and blood mercury levels as measures of methylmercury exposure was carried out by Young and colleagues (2001), as part of an analysis of methylmercury disposition in humans using a PBPK model. The authors stress the importance of considering inorganic forms of mercury in the different tissues, including the brain, even when the exposure is to methylmercury alone. They argue that the prediction of methylmercury, inorganic mercury, or total mercury levels in the whole body, or any specific organ or tissue, would be inaccurate based on total blood or hair values, due to the differing decay characteristics of each chemical in each of the organs, tissues, and fluids. They conclude that future studies in human or animal species "must include measurements for both organic and inorganic mercury for extended times to be able to clearly define the disposition of this environmental toxicant (Young, Wosilait et al. 2001).

4.0 HEALTH EFFECTS OF METHYLMERCURY FROM ACUTE HIGH-DOSE EXPOSURES: THE POISONING EPIDEMICS

The health effects of high doses of methylmercury, particularly the neurotoxic effects, have been documented through investigation of large poisoning epidemics in Japan, in Minamata and Niigata in the 1950s and early 1960s respectively, and in Iraq in the early 1970s. Smaller-scale poisoning events involving individuals or families have been recorded as well. The different health effects of acute high exposures are described in this section, with much of the information taken from the recent NRC and ATSDR reviews, as well as the 1990 WHO-IPCS review. Some recent articles related to these epidemics are discussed as well.

4.1 Neurotoxicity in adults: Japanese and Iraqi epidemics

The diagnosis of Minamata Disease during the Minamata epidemic was made on the basis of a characteristic combination of symptoms, which included paresthesia (e.g. numbness in fingers and toes), dysarthria (slurred speech), tremor, cerebellar ataxia (incoordination), gait disturbance, visual-field constriction and disturbed ocular movements, hearing loss, as well as subjective symptoms of malaise. In the worst cases, the patients went into a coma and died (IPCS-WHO 1990). The first symptoms to appear were paraesthesia and malaise.

In the adult, methylmercury poisoning is characterized by damage to specific anatomical areas of the brain (e.g. visual cortex, granule layer of the cerebellum, axon degeneration associated with the sensory branch of the peripheral nerve). This is in contrast to the diffuse and widespread damage observed in the developing brain of severely exposed fetuses (Castoldi, Coccini et al. 2001).

There is a marked latent period between exposure to methylmercury and the appearance of symptoms, which was observed to be several weeks in the Iraqi epidemic and several months or years in Niigata, Japan (IPCS-WHO 1990). The mechanism for this latent period is largely unexplained (Clarkson 2002).

Based primarily on the Iraqi data, the WHO estimated, as a LOAEL (lowest observed adverse effect level) a risk of 5% of paraesthesia at a blood mercury level of approximately 200 ppb, or a corresponding hair mercury level of 50 ppm (Marsh 1987; IPCS-WHO 1990). Exposures of 125 to 1000 ppm of mercury in hair, documented in the Iraqi and Niigata outbreaks, were clearly associated with increasingly serious and neurological effects in an increasing proportion of cases (Marsh 1987).

Efforts to clean up the polluted Minamata Bay were carried out in the 1970s and 1980s, such that a 1995 survey found a normal methylmercury content (< 0.17 ppm) in fish from the Bay. Following that environmental survey, a cross-sectional study was carried out among fishermen and their families living in the mercury-polluted area (Harada, Nakanishi et al. 1998). Of the 186 subjects, all but six showed a “normal” total mercury level in hair, which the researchers define

as less than 10 ppm. An earlier survey of normal male Japanese subjects found a mean value for total mercury in hair of 4.6 ppm (SD 2.4 ppm). For all five areas surveyed, mean hair mercury levels ranged from 1.9 to 3.7 ppm.

In spite of the relatively low mercury in hair, the subjects appeared to show various neurological symptoms at a very high rate, although these symptoms did not seriously disrupt their daily lives (Harada, Nakanishi et al. 1998). More than 85% had one or more of the following subjective symptoms, in order of frequency: numbness, forgetfulness, pain in the extremities, focal cramps, headaches, motor disturbance, hardness of hearing, speech impediment, disturbance of gait, vertigo, and tinnitus. With regard to routine neurological testing, sensory disturbances were found in 75% of the cases. Subjects also manifested hyposmia (14.4 %), taste disturbance (11.7 %), balance disturbances (11.7 %), constriction of visual fields (5.9 %), tremor (7.4 %), and ataxia (6.4 %).

Based on the age distribution of the subjects, a majority would have been potentially exposed to methylmercury-contaminated fish at the peak of the poisoning epidemic as children or young adults, if in fact they were residents of the area at the time. Some may have been exposed prenatally. However, information on individual histories is not given, such that it is unclear what proportion of the population was affected by the poisoning epidemic. Details on the selection of subjects are not given; no matched control group appears to have been examined. The authors conclude that the symptoms are considered the sequelae of the former heavy mercury pollution for the following reasons: “(1) the subjects had eaten the contaminated fish and shellfish for a long time; (2) their hair mercury levels now appeared t be within the normal range for frequent fish eaters; and (3) the clinical symptoms bore no definite relation to the hair mercury levels” (Harada, Nakanishi et al. 1998).

Other health endpoints (e.g. different cancers, diabetes) have also been investigated in the follow-up studies of Minamata Bay area residents. These are considered in section 4.3

4.2 Neurotoxicity in children: Japanese and Iraqi epidemics

Severe neurological abnormalities in children exposed to methylmercury *in utero* were observed during the large-scale poisoning epidemics in Minamata, Japan in the late 1950s, in Niigata, Japan in the early 1960s, and in Iraq in the early 1970s. The signs and symptoms of the disease, referred to as congenital Minamata disease (CMD), included mental retardation, primitive reflexes, ataxia (loss of balance), disturbances in physical growth, dysarthria (slurred, slow speech), and limb deformities, as well as, in some cases, hyperactivity, hypersalivation, seizures, and strabismus (wandering eye). Moreover, the incidence of cerebral palsy among children born during the Minamata epidemic in the affected villages was considerably higher than the national incidence (9% vs. 0.2 to 2.3 %). Although some signs and symptoms of CMD decreased over time, others, including mental retardation, did not (NRC 2000).

Severe *in utero* exposure, as noted in section 4.1, results in diffuse and widespread damage to the developing brain. In the Japanese cases, disorganization of the cerebral cortex cellular

architecture was observed. In the cerebellum, severe atrophy of the folia of the hemispheres, characterized by disappearance of granule cells and reduction of Purkinje cells has also been observed. White matter astrocytosis was a typical feature of both Japanese and Iraqi epidemics (Castoldi, Coccini et al. 2001).

Hair and blood mercury levels in the mothers of CMD cases in Japan were not measured until several years after the epidemic had passed. However some umbilical cord tissue samples had been preserved from these years, and these were analyzed for mercury concentration. Using data on the correspondence between umbilical cord tissue and maternal hair mercury levels, the mean maternal-hair mercury concentration for CMD cases was estimated to be 41ppm, with a range of 3.8 to 133 ppm. This estimate, however, is considered to be highly uncertain (NRC 2000).

In Iraq, the levels of methylmercury exposure were documented through the analysis of hair samples that included growth during the epidemic period. For mothers who were pregnant at the time of the epidemic, peak maternal hair concentrations ranged from 1 to 674 ppm (NRC 2000). Epidemiologists were thus able to examine the neurological health of the children exposed *in utero*, and investigate the dose-response relationships to an extent that was not possible for the Japanese cases. A variety of neurological outcomes were measured, including developmental outcomes such as the ages when the child fist began walking and talking.

Severe effects similar to the signs and symptoms of CMD were observed among the most highly exposed Iraqi children. However, because of the documented range of exposures, the researchers were able to model the dose-response curve over a greater dose range, and estimate a threshold for neurological effects. Using a variety of statistical models, a population threshold of approximately 10 ppm for delayed walking was estimated. However, the uncertainty associated with this estimate was substantial. For example, the estimate was highly influenced by the assumed value for the background prevalence of delayed walking in the Iraqi population, a value that was unknown. Moreover, the ages at which children first walked or talked were determined through interviews with the mothers. As the Iraqi mothers did not attach a good deal of importance to birth date, their estimates at what age their children achieved particular milestones were uncertain approximations (NRC 2000).

Two important observations with regard to methylmercury toxicity emerged from the study of the Iraqi epidemic. First, there was extensive variability among the responses in children exposed *in utero*. Many children of mothers with mercury hair levels above 100 ppm had normal neurological scores and achieved milestones at the expected ages. Second, many of the women who had very high hair mercury levels and who gave birth to infants with neurological disabilities, experienced themselves only mild and transient signs or symptoms of methylmercury toxicity (NRC 2000). This finding, observed in the Minamata epidemic as well, is the basis for the long-standing belief that the developing fetus is more sensitive to the toxic effects of methylmercury than the adult.

In a recent retrospective study of birth records from the Minamata City region for the period of 1955 to 1969, Sakamoto et al (2001) observed that significantly lower numbers of male offspring

were born in Minamata City in the period of 1955 to 1959, when the pollution was thought to be most severe. This association held when the data was examined for the area with the greatest number of Minamata disease cases, when fishing families were examined (most exposed occupational group), and when Minamata disease cases alone were considered. The proportion of male stillborn fetuses in Minamata City was examined for the periods 1952 to 1954, 1955 to 1959, and 1960 to 1964. In the period 1955 to 1959, a significantly greater proportion of the fetuses were male, as compared to the preceding and subsequent periods, and compared to a control population, in which the proportions of male and female fetuses among the stillborns were approximately equal. The authors suggest that the male fetuses were more susceptible to the toxic effects of methylmercury, leading to a greater proportion of male stillborns, and a lower proportion of male live births (Sakamoto, Nakano et al. 2001).

4.3 Other toxic effects observed in poisoning epidemics

While most investigations into methylmercury toxicity in relation to the poisoning epidemics have focused on neurological effects, there has been some research into other endpoints, as well.

In Iraq, an evaluation of the clinical symptoms and outcomes of over 6000 exposed citizens found a 79 % reduction in pregnancies among the exposed population, suggesting that methylmercury has an effect on reproduction (NRC 2000).

Investigation of cancer rates in populations near Minamata Bay did not show an association between methylmercury exposure and overall cancer rates. A comparison of death rates between a population thought to be more exposed during the Minamata epidemic – as compared to a nearby population – showed no overall increase in cancer mortality. However, an increase in liver cancer death rates, as well as the prevalence of chronic liver disease, were observed in the population thought to be more exposed. The authors noted that a difference in hepatitis B infection rates and alcohol consumption could have contributed to the difference between the two populations. The impact of the findings was also limited by the lack of characterization of individual methylmercury exposures (NRC 2000).

A health examination survey was conducted for 1500 subjects, aged 40 years and older, in Tsunagi Town, next to Minamata City, every summer since 1984. Tsunagi Town is located in a methylmercury polluted-area and there are 36.9 certified Minamata disease patients per 1000 population. A case-control study using survey data and investigating the role of various risk factors, including methylmercury exposure, found no increase in the risk of diabetes mellitus, liver disease, and renal disease, as compared to other areas in Japan (Futatsuka, Kitano et al. 1996; Futatsuka, Kitano et al. 2000).

An analysis of 64 subjective complaints, comparing a population living in the methylmercury-polluted areas near Minamata to a nearby non-exposed population found that the population from the polluted area had more various complaints than the control population. Complaints were grouped into four factors – nonspecific, sensory, arthritic, and muscular – and a factor analysis carried out. Each of the four factor scores was significantly higher in the population in

the polluted area. The authors concluded that "*it is possible that not only neurological subjective complaints but also nonspecific complaints of the population in the polluted area might be influenced by past methylmercury exposure*" (Fukuda, Ushijima et al. 1999).

5.0 HEALTH EFFECTS FROM MODERATE EXPOSURE THROUGH FREQUENT FISH CONSUMPTION: EFFECTS IN ADULTS

This section presents studies that have been carried out in fishing populations. The fish consumed by fishing populations are, in general, much less contaminated than the fish eaten in the Japanese epidemics. Nonetheless, the high frequency of fish consumption in fishing populations has led to exposures that are moderately high when compared with non-fish eaters.

Neurotoxic effects are considered first, followed by a summary of the literature pertaining to non-neurotoxic health effects in adults.

5.1 Neurotoxic effects (frequent fish consumption)

Kosatsky and Foran (1996) reviewed pre-1990 investigations regarding neurotoxic effects among adults consuming fish on a long-term basis. Their objective was to fully weigh the existing evidence for the LOAEL of 50 ppm corresponding to a 5% increase in paraesthesia, as proposed by the WHO (see section 4.1). Thirteen relevant studies were identified and six studies retained, on the basis of study design and numerical analyses, to assess dose-response relationships. The authors also tabulated the number of long-term fish consumers, among the 13 studies, with whole blood mercury concentrations above 200 ppb (corresponding to a hair mercury level of 50 ppm) who had been clinically examined for signs of neurotoxicity (Kosatsky and Foran 1996).

No case of classic Minamata disease was described in the 13 studies. Two studies among the Cree of Eeyou Istchee, for which dose-response could be assessed, showed evidence of increasing neurologic dysfunction with rising blood mercury concentrations in the range of 60 to 120 ppb (corresponding to 15 to 30 ppm in hair). A third study showed no evidence of neurologic impairment in groups with blood mercury of 10 to 20 ppb (2.5 to 5 ppm). Among 50 fish eaters with an equivalent blood mercury level greater than 200 ppb, identified in the 13 different studies, neurologic dysfunction consistent with methylmercury exposure was found in as few as six (11 %) and as many as 15 (31 %). The authors conclude that “the oft-cited LOEL for methylmercury of 200 ppb in blood is not supported by these studies” (Kosatsky and Foran 1996). Note that three of the studies reviewed by Kosatsky and Foran were carried out in part or exclusively among the Cree (Department of National Health and Welfare 1979; McKeown-Eyssen and Ruedy 1983; Spitzer, Baxter et al. 1988). The reader is directed to the document *Mercury and Health in Eeyou Istchee*[6] for more details on these investigations.

Since 1990, most of the investigations regarding the neurotoxic effects of long-term fish consumption have been carried out among fish populations in the Brazilian Amazon, such as those near the Tapajós River, an important gold mining region. Gold is extracted from the soil or river sediments through amalgamation with metallic mercury, which is then discharged to the

[6] Mercury and Health in Eeyou Istchee, Report prepared for the CBHSSJB by Deborah Schoen, June 2003.

river. Deforestation has also been implicated in the increase in inorganic mercury in the region (Dolbec, Mergler et al. 2000).

Lebel conducted two investigations in the Tapajós region, which are summarized in Table 1. In the first preliminary study, 29 young adults (15 to 35 years) with a mean hair concentration of 14 ppm underwent a battery of quantitative behavioural, sensory, and motor tests. Three individuals with hair mercury levels above 24 ppm demonstrated reduced contrast sensitivity, and individuals with levels above 20 ppm tended to demonstrate reductions in peripheral visual fields. More highly exposed women tended to have lower scores than low-exposed women on both manual dexterity and grip strength (Lebel, Mergler et al. 1996).

The findings and conclusions of the Lebel et al (1996) study were reviewed in the literature survey conducted by Shipp et al (2000). They remark that the findings for visual effects were not subject to statistical testing, and that similar testing in fish-eating populations with higher methylmercury exposures showed no impact on visual field. For example, in a Peruvian population, a total of 190 subjects were examined, with ages ranging from 1.4 to 82, and a mean of 25.4. Hair levels reached a maximum of 52 ppm, and no observed visual field effects could be attributed to methylmercury exposure (Turner et al. 1980 as reported in (Shipp, Gentry et al. 2000). In the Iraqi population, visual changes were not observed until blood levels reached 7500 ppb (approximately 125 ppm). The literature review also notes that the potential confounding from metallic mercury exposure in two individuals who had worked at the gold mines (mercury hair levels not mentioned) and the small sample size limit the study findings as evidence for a relationship between methylmercury exposure and fish consumption (Shipp, Gentry et al. 2000).

A second study by Lebel et al (1998), recruited 91 individuals (15 to 81 years), representing approximately 40% of the adult population of the study village. Individuals with hair mercury levels (either mean or peak, total or methylmercury alone) above 50 ppm were excluded from the study ; the mean hair mercury level was 13 ppm. The same battery of sensory, motor, and visual tests administered in the earlier study was used (see Table 1), and a clinical neurological examination was administered to 59 individuals selected randomly. The examination included the Branches Alternate Movement Task (BAMT – imitation of a prescribed sequence of hand movements). The authors state that «for the most part, clinical examinations were normal. » Abnormal performance on the BAMT was significantly associated with all measures of mercury exposure (p 0.05 or 0.01) and abnormal visual fields were associated with mean hair mercury and peak mercury concentrations ($p \leq 0.05$). Increased hair mercury levels were also associated with poor scores on the intermediate and higher frequencies of near visual-contrast sensitivity ($p \leq 0.05$) , with poor scores on the manual dexterity test ($p \leq 0.05$), and with increased muscular fatigue ($p \leq 0.10$). In women, but not in men, grip strength was reduced with increasing peak mercury concentration ($p \leq 0.10$) (Lebel, Mergler et al. 1998).

A cross-sectional study carried out by the same research team in May 1996 in a different village (Cametá) on the Tapajós River, surveyed 84 participants aged between 15 and 79 years, with regard to the mercury concentrations in blood and hair and their motor performance. Psychomotor performance was evaluated using the Santa Ana manual dexterity test, the

Grooved Pegboard Fine motor test, and the finger tapping motor speed test. Grip and pinch strengths were measured by dynamometry (Dolbec, Mergler et al. 2000).

The mean hair mercury level was 9.5 ppm, with a maximum level above 35 ppm. Multivariate analysis of variance indicated that hair mercury was inversely associated with overall performance on the psychomotor tests, with $p \leq 0.01$ (see Table 1). This relationship was not significant for blood mercury. No relationship was observed between methylmercury exposure and the performance on tests for grip or finger strength (Dolbec, Mergler et al. 2000).

In the Tapajós region fish consumption is widespread, and so it was not possible to recruit a control group without exposure. The dose-effect relationship showed diminishing psychomotor performance with increasing mercury concentrations. However, the authors emphasize that this may be related to previous rather than current mercury levels (Dolbec, Mergler et al. 2000).

A Japanese research team with experience in examining Minamata disease cases in Japan, carried out a medical survey in the Tapajós River region, in the villages of Barreiras, Rainha, Sao Luiz do Tapajós, over 200 km down-stream of gold mining areas (Harada, Nakanishi et al. 2001). A total of 132 subjects (fishermen and family members, ages 1 to 67) were surveyed as to their hair mercury levels. The mean levels in the three villages ranged from 14.1 to 20.8 ppm (max level recorded: 71.5 ppm). Medical examinations and a questionnaire regarding subjective symptoms were administered to 50 subjects who had hair mercury levels above 20 ppm (see Table 1).

With respect to the questionnaire, 14 subjective symptoms were reported (numbness, vertigo, headache, lassitude, irritability, loss of memory, insomnia, reduction in hearing) in proportions ranging from 8 to 34 %, with numbness, vertigo, headache, and lassitude being the most frequent complaints. The seven objective effects occurred at the following frequencies: sensory disturbance (32 %), disturbance in balance (12 %) and coordination (10 %), tremor (8 %), hyperreflexia (8 %), dysarthria (2 %), gingivitis (0 %) (Harada, Nakanishi et al. 2001).

This study consisted exclusively of medical examinations of subjects. Examiners appear to have been aware of the extent of subjects' methylmercury exposure. No statistical analysis of the dose-response relationship was conducted. The research team diagnosed three subjects with mild Minamata disease (a 56 year-old fisherman with a hair mercury level of 41.8 to 71.5 ppm, an 18 year-old fisherman/farmer with a hair mercury level of 16 to 27.1 ppm, and a 23 year-old fisherwoman with a hair mercury level of 30 to 35.6 ppm) and identified three cases of suspected Minamata disease (hair mercury between approximately 15 and 30 ppm). The case studies are described in detail in the article. The main symptoms of the six cases were disturbance in coordination, glove-and-stocking type sensory disturbance, reduction in manual dexterity, numbness, failure in two-point discrimination, and tremor, although other symptoms were reported as well (Harada, Nakanishi et al. 2001).

Recently, an investigation into neuropsychological function in adults and methylmercury exposure was conducted in the Pantanal region of Brazil, an area that is also subject to the environmental effects of gold-mining (see Table 1). A cross-sectional study, using a battery of

tests similar in nature to those used in the Seychelles and Faroe Islands investigations (see section 6.0) was conducted in six fishing communities on the Cuiaba River; the study included 129 men and women older than 17 years of age. Hair mercury levels were used to indicate methylmercury exposure. The mean hair mercury level was 4.2 ppm, with a range of 0.56 to 13.6 ppm (Yokoo, Valente et al. 2003).

The neurological screening included memory, IQ, and concentration tests, as well as tests of mechanical ability and profile of mood states. For each test, multiple regression analysis was used to adjust for sex, age, educational level, smoking, and alcohol intake. Hair mercury levels were associated decreased performance on tests of fine motor speed and dexterity, and concentration. In addition, correlations between 4 of 15 submeasures of memory and intelligence tests and hair mercury level were statistically significant. The observed effects were dose-dependent, increasing in magnitude with increasing hair mercury level (Yokoo, Valente et al. 2003).

Mergler reports on neurobehavioural testing carried out for fish-eaters from the Upper St-Lawrence Ri (Quebec). The study group was initially composed to investigate manganese neurotoxicity, and data on fish consumption from the St. Lawrence were gathered in order to adjust for fish consumption as a confounder. Multiple regression analyses, including age, educational level, smoking, and alcohol consumption as co-variates, revealed no differences between fish-eaters and non-fish-eaters on tests of sensory function, visual memory and recognition, fine motor performance, and some motor tests. Fish-eaters, as a group, performed significantly more poorly on tests requiring cognitive flexibility, word naming, auditory recall, and more complex motor tasks, when compared with non fish-eaters. However, no dose-effect relations were observed between the bioindicators of exposure to methylmercury and the neurological outcomes (Mergler 2002).

The NRC review also describes the studies published by Anne Beuter and colleagues regarding tests administered to 21 Cree subjects with respect to tremor, hand-eye coordination, and rapid alternating movements. A group of six individuals with higher exposures (annual maximum hair mercury level > 24 ppm), over a period of 25 years, was compared with a lower-exposure group of six age-matched individuals (hair mercury levels of 6 to 12 ppm). The authors found statistically significant group differences with respect to the three endpoints (NRC 2000).

The Beuter study was originally conducted as a pilot project to investigate the most appropriate tests for reliably detecting neurological differences between individuals in an eventual large-scale epidemiological study of the Cree population, and not as a test of the association between performance on neurological tests and methylmercury exposure. The larger, epidemiological study did not take place.

Most recently a small pilot study among fishermen in Carloforte, Italy (island off the southwest coast of Sardinia) suggested that the performance of heavy consumers of fresh tuna was significantly worse on several cognitive and motor tests as compared to the performance of administrative clerks of the same age (Carta, Flore et al. 2003). However, the number of

participants was limited (22 subjects, 22 controls) and mercury in blood or hair were only measured in ten subjects, and not at all in the controls. Planning for a larger study is underway.

5.2 Other health effects in adults (frequent fish consumption)

Two endpoints, other than neurological function, have been investigated through epidemiological investigation of frequent fish consumers – cardiovascular effects and genotoxicity.

5.2.1 Cardiovascular effects

Certain cardiovascular effects have been observed following acute intoxications – in patients hospitalized during the Iraqi poisoning epidemic, and in a family who consumed ethylmercury-contaminated pork. In the latter case tow deaths were attributed to cardiac arrest, with autopsies revealing myocarditis (NRC 2000). More recently the question of potential cardiovascular effects of methylmercury exposure has been investigated in fishing populations.

The first such investigation was carried out by Salonen and colleagues compared the prevalence of acute myocardial infarction (AMI) and death from coronary disease with mercury concentrations in hair and urine in a cohort of 1833 Finnish men. Daily fish intake ranged from 0 to 619.2 g and hair mercury concentrations ranged from 0 to 15.67 ppm. Over a seven-year observation period, men above the 66th percentile in hair mercury level (> 2ppm) had a two-fold greater risk of AMI than men below the 66th percentile. Men who consumed at least 30 g of fish per day had a 2.1-fold higher risk of AMI. For each additional 10 g of fish consumed, there was an increment of 5% in the 5-year risk (NRC 2000). Numerous studies examining cardiovascular disease risk and fish consumption indicate protective effects of fish consumption for cardiovascular health (NRC 2000) and, thus, these results are surprising.

Two investigations (Guallar, Sanz-Gallardo et al. 2002; Yoshizawa, Rimm et al. 2002) explore the question of whether mercury from fish increases the risk of heart disease, and if so, whether this increased risk outweighs the benefits of nutrients such as omega-3 fatty acids, particularly present in fatty fish and fish oils. For both studies, mercury levels were measured in men's toenails. Guallar and colleagues (European study) also measured the levels of an omega-3 fatty acid (DHA) in the men. They found that men exposed to the highest levels of mercury had the highest risk of heart attacks, and that this result was even stronger when the effect of the omega-3 fatty acid was adjusted for.

Guallar and his colleagues concluded that men with greater amounts of mercury in their diet have a greater risk of heart attacks. They recommend that people eat fish with low mercury levels in order to benefit from the protective effects of the omega-3 fatty acids while reducing the harmful effects of mercury (Guallar, Sanz-Gallardo et al. 2002).

In a US study, researchers found that exposure to higher levels of mercury did not raise the risk of heart disease. However, many of the study participants were dentists with exposure to

mercury in their work. The authors speculate that occupational exposure might have raised the levels of mercury in the dentists' toenails without necessarily affecting their risk of heart disease. As the clinical and pathological manifestations of elemental and methylmercury differ, the authors note that, conceivably, the two forms might also influence the risk of cardiovascular disease differently. Exclusion of dentists from the analysis resulted in a slight association between toenail mercury and heart disease, which was not statistically significant (Yoshizawa, Rimm et al. 2002).

The apparently conflicting results from different investigations with regard to fish consumption and the risk of heart disease may be related to the types of fish consumed and their respective levels of nutrients and/or contaminants. Or the different findings may arise from other risk factors, varying between populations but not measured and adjusted for in the studies. Clarkson and colleagues, writing with regard to the studies associating adverse cardiovascular effects with methylmercury exposure, state, « *Thus, firm conclusions about cause and effect cannot be yet made, since cardiovascular disease has multiple risk factors (e.g. family history, stress, dietary habits, smoking, alcohol use, diabetes, and socioeconomic status). The researchers themselves recognize this complication and use extensive statistical measures to correct for these factors. Prospective studies are needed to settle this issue*» (Clarkson, Magos et al. 2003).

In a letter in response to the Guallar study, Plante and Babo question the validity of the results of the investigation. They note, for example, that monitoring from the 1980s show that the Cree have a lower risk of dying from heart disease and stroke as compared to the rest of the Quebec population, even though their mercury exposure levels were approximately 20 times higher (Plante and Babo 2003).

5.2.2 Genotoxicity

There is limited investigation into the genotoxicity of methylmercury in humans. The NAS reports on a study by Skerfving and colleagues, which observed a positive correlation between blood mercury concentration and chromosomal aberrations in the lymphocytes of 23 people who consumed methylmercury-contaminated fish. However, these findings have been questioned because of several experimental problems, including a failure to identify smokers (NRC 2000).

More recently, genotoxicity in residents of Brasilia Legal was investigated, in conjunction with the investigations into neurological effects in that population, as described in 5.1 (Amorim, Mergler et al. 2000). A total of 98 adults (ages 15 to 81 years) participated in the study. The median hair mercury level was 13.5 ppm (22.2 ppm for the 75^{th} percentile). Women had significantly lower levels (median10.8 ppm as compared to 17.1 ppm for men).

The genotoxicity endpoints investigated included mitotic index, polyploides, and chromatid breaks. The authors found that all three types of genetic damage were statistically associated with increasing hair mercury levels. Mitotic index decreased with increasing methylmercury,

indicating impairment of lymphocyte proliferation under culture conditions. Polyploidal aberrations were observed to increase in frequency with increasing hair mercury levels above 7.25 ppm. Only 14 % of subjects showed chromatid breaks in their lymphocytes. Those subjects with chromatid breaks had significantly higher hair mercury levels compared to those without.

The authors conclude that “this is the first report showing clear cytotoxic effects of long-term exposure to methylmercury. Although the results strongly suggest that, under the conditions examined here, methylmercury is both a spindle poison and a clastogen, the biological significance of these observations are as yet unknown” (Amorim, Mergler et al. 2000).

6.0 HEALTH EFFECTS FROM MODERATE EXPOSURE THROUGH FREQUENT FISH CONSUMPTION: EFFECTS FROM PRENATAL EXPOSURE

The dose-response analysis of the Iraqi data for prenatal exposure (delay in achieving developmental milestones at exposures corresponding to 10 to 20 ppm in maternal hair) created a high degree of concern in the international public health community, as such exposures are common among frequent fish consumers. This concern resulted in a second generation of epidemiological study – investigating the effects of prenatal methylmercury exposure in fishing populations (NRC 2000).

The NRC (2000) reports on nine different epidemiological studies investigating neurodevelopmental effects in children whose mothers consumed large amounts of fish during pregnancy. Three of these studies (Seychelles, Faroes, New Zealand), in particular, form the basis for many of the current guidelines for dietary intake of methylmercury and these are discussed in greater detail. The exposures in these studies are low in comparison to the poisoning episodes in Japan and Iraq. They are nonetheless relatively high compared to the general North American population in which fish is consumed infrequently by the majority of individuals.

6.1 Seychelles Child Development Study (SCDS)

In the Seychelles, a country made up of over 100 islands in the Indian Ocean, people eat fish frequently – on average 12 fish meals per week – such that their mercury exposures are much higher than most North Americans (mean hair mercury of 6 ppm in Seychelles women compared to levels below 1 ppm in US women). The Seychellois are generally healthy, with low alcohol and tobacco consumption and a good health care delivery system. The population is highly literate and is characterized by minimal immigration and emigration (ATDSR 1999). The majority of the population lives on one island, from which the study cohort of 779 mother-infant pairs was drawn (NRC 2000). A total of 29 children were then excluded either because of the presence of known risk factors for neurological disabilities, including maternal illness during pregnancy (e.g. diabetes) and low birth weight or because of insufficient maternal-hair samples. Six twins were also excluded from the study cohort.

To assess the *in utero* exposure of the Seychelles children, samples of maternal hair were taken during pregnancy and at birth. Total mercury was measured in the maternal hair in the single longest hair segment corresponding to growth during pregnancy. Associated research studies in the Seychelles had shown that levels of total mercury in the mother's hair correlate well with their blood levels of methylmercury, and with the total mercury levels in the fetal brain, as determined through autopsy following fetal or infant death (Davidson, Myers et al. 1998). Postnatal mercury exposure of older children (> five years) was assessed in the 1-cm hair segment nearest the child's scalp, taken at the time of neurological and developmental assessments. Neurodevelopmental outcomes of the children were assessed through age-appropriate tests administered at 6 months (Marsh, Clarkson et al. 1995), 19 months and 29

months(Davidson, Myers et al. 1995), five years (Davidson, Myers et al. 1998) and 9 years (Myers, Davidson et al. 2003).

At every stage of the Seychelles children's development, no adverse effects were associated with either prenatal or postnatal exposure to methylmercury. These results are summarized in Table 1. A more detailed description of the tests used in the Seychelles and the Faroes Islands (see section 4.1.1.3) studies is included in Appendix C.

In preparation for the main Seychelles study, a pilot study, consisting of 789 mother-infant pairs, examined when the children were 5 to 109 weeks. Later a subset of 217 children at 5 years old and a subset of 87 children at 9 years old were examined, in order to evaluate the test batteries for older children. When the children were tested both as infants and as older children, certain statistically significant associations, both positive and negative, between neurological effects and methylmercury exposure were observed. Some of these associations depended on the statistical treatment of the data, and in particular, the inclusion of outliers. The authors stated that the results of the pilot study should be interpreted cautiously, and that the main study, designed to evaluate a greater number of confounding variables, provided a more sound basis for evaluating the health risks of methylmercury exposure (Myers, Davidson et al. 1995; Myers, Marsh et al. 1995; Davidson, Palumbo et al. 2000).

Following publication of the results of each stage of the SCDS (cohort assessed at 6 mo, 19 mo., 29 mo., 5 yr, 9 yr), questions and criticisms concerning the data analyses were raised in the scientific literature. This led to several re-analyses of the data. These criticisms and re-analyses are described below:

6.1.1 Role of effect modification by social and environmental factors

In recent years there has been an effort in epidemiology to distinguish between study confounders and effect modifiers. A confounder biases results because it is correlated with the exposure of interest and causally related to the outcome. Thus, for example, in a study investigating if heavy coffee drinkers are more likely to develop lung cancer, smoking is a confounder, as it is associated with drinking large amounts of coffee and is also causally related to lung cancer. In contrast effect modification refers to the phenomenon that, given a group of people, the effects of a causal exposure factor will be greater in the more sensitive individuals (Bellinger 2000). An example given by Bellinger is the association between alcohol consumption and blood pressure, which varies in strength depending on an individual's age, gender, and smoking status. Effect modification is a true characteristic of the association between an exposure and an endpoint and, unlike confounding, is not related to the study design. It is included in data analysis by including an interaction term in a regression model (e.g. effect modifier x exposure of interest).

Davidson and colleagues re-analysed the data from the SCDS for effect modification by social and environmental factor, using the data from the evaluation of the cohort at 29 months (Davidson, Myers et al. 1999a). In the original analyses, an interactive effect for gender had

been included, but social and environmental factors had been treated as independent variables – assumed to influence the children's test scores but not influence the degree to which methylmercury influenced the test scores. In the re-analysis for effect modification, interactive effects for social and environmental factors, as well as gender, were included in the regression model. However, none of these factors were observed to influence the association between methylmercury exposure and developmental outcomes. Thus the re-analysis did not alter the authors' original conclusion of a lack of association between prenatal methylmercury exposure and adverse developmental effects in Seychelles children.

6.1.2 Analysis of outcome according to subscores on behavioural tests rather than composite scores

In the original analysis of the test scores of the Seychelles cohort at age 5 years, the researchers analyzed the relationship between prenatal methylmercury exposure and the overall score on the Child Behaviour Checklist. However, such a checklist includes specific behaviors that relate to different functional domains of the brain. If methylmercury exposure affects only specific domains, then an overall score may not be sufficiently sensitive to detect such effects (Myers, Davidson et al. 2000). The subscales of the behaviour checklist included: (i) withdrawn; (ii) somatic complaints; (iii) anxious/depressed; (iv) social problems; (v) thought problems; (vi) attention problems; (vii) delinquent behaviour; and (viii) aggressive behaviour.

Following this secondary analysis on the basis on subscale scores, no association between prenatal or postnatal methylmercury exposure and any of the eight behaviour measures was found (Myers, Davidson et al. 2000).

6.1.3 Evaluation of nonlinear relationships between methylmercury exposure and neurological test scores

In the original analysis of the neurological test scores of the Seychelles children at age 5 years, linear regression model was used to investigate the relationship between methylmercury exposure and test score. However, this is not the most appropriate model if the relationship between exposure and outcome (test score) is nonlinear. Thus, the data for six primary neurodevelopmental outcomes (see Table 1, 5 year study) were re-analysed using Generalized Additive Models (GAM) (Axtell, Cox et al. 2000), which do not assume linearity (i.e. same constant increase in test score with increasing methylmercury exposure).

The results of this re-analysis are complex, and appear contradictory. For example, the authors found some evidence for a nonlinear relationship between prenatal exposure to methylmercury and the PLS Total Language score. In one model (2 degrees of freedom), the score declines by 0.8 as prenatal exposure increases from 1 to 10 ppm, and then increases by 1.3 as the exposure level increases above 10 ppm. Prenatal exposure was also marginally significant for the overall behaviour score (Child Behavior Checklist), using the GAM. In one of the models (4 degrees of freedom) a one-point increase (lower performance) in the CBCL score was observed as the exposure increased from 1 to 15 ppm, and then declined four points (improved score) as

prenatal exposure increased from 15 to 20 ppm. No evidence was found for a nonlinear relationship between prenatal exposure and the other four endpoints (Axtell, Cox et al. 2000).

With respect to postnatal exposure (mercury in child's hair at age 5 years), there was evidence for a nonlinear relationship between exposure and the McCarthy GCI. In one model (4 degrees of freedom) showed an increase of 3.9 points in the GCI as postnatal exposure increased from one to 10 ppm, followed by a decline of 5.5 points as exposure increased from 10 to 20 ppm. Nonlinear effects were not observed for the other five endpoints and postnatal exposure (Axtell, Cox et al. 2000).

The authors discussed the significance of these observations of nonlinear effects with respect to the assumption that the relationship between methylmercury exposure and neurological test score is monotone. A relationship that is monotone implies a curve, which may not be linear (i.e. slope of curve is changing), but which never changes direction (e.g. positive slope does not become a negative slope). Thus, if prenatal methylmercury exposure adversely affects neurodevelopment, and the relationship is monotone, there should not be a range or exposure at which methylmercury results in beneficial effects. The fact that non-monotonal relationships were found suggested to the authors that the nutritional benefits of fish consumption may be affecting the neurodevelopmental outcomes (Axtell, Cox et al. 2000). Since a nutritional assessment was not carried out within the Seychelles Child Development Study, the data were not analysed with regard to this factor. The authors further conclude that nonlinear modeling of data relating methylmercury exposure and developmental outcome may be appropriate. However, the use of complex models to fit the data should be grounded in a clear biological rationale (Axtell, Cox et al. 2000).

6.1.4 Re-analysis of results for 5-year old cohort, in response to National Academy of Science (NAS) panel criticisms

In a review of the Seychelles Child Development Study (5-year old cohort results), the NAS suggested a re-analysis using raw test scored instead of standardized score[7], including the child's age at testing as an additional covariate in the analysis, and adjustment for which of the three staff members administered the test battery. On the basis of the re-analysis, incorporating these modifications, the authors reiterated their conclusion of no evidence of adverse effects related to exposure to methylmercury. However, they did continue to find positive, statistically significant associations between methylmercury exposure (prenatal and postnatal) and certain neurological outcomes, suggesting dietary benefits of fish consumption on neurodevelopment (Davidson, Kost et al. 2001).

[7] Standardized test scores inherently control for small differences in age at testing.

6.1.5 Re-analysis of McCarthy Scales of Children's Abilities (MSCA)

In response to criticisms that the original analyses were not sufficiently sensitive to effects on specific neurological functions, the authors re-analysed the test scores of the Seychelles children at 5 years of age in relationship to prenatal methylmercury exposure, on the basis of the subscores. This was designed to make the analysis more sensitive, and at the same time more comparable to other investigations, notably from the Faroe Islands and New Zealand (Palumbo, Cox et al. 2000).

In the re-analysis, no adverse associations between neurological endpoints and methylmercury exposure. However, a positive association between postnatal methylmercury exposure and performance on the MSCA nonverbal memory subscale was found. The authors conclude that, while this result may have arisen by chance alone, it also suggests the hypothesis that the neurodevelopmental benefits gained from consuming fish may outweigh the risks from methylmercury exposure (Palumbo, Cox et al. 2000).

6.1.6 Evaluation of the impact of error in measuring exposure

The exposure metric used in the SCDS is maternal hair mercury level during pregnancy (analyzed over longest available section corresponding to gestational period), and data was not collected for other biomarkers of exposure (e.g. maternal blood, cord blood). This exposure marker has been criticized as not being an accurate reflection of the level of mercury in the fetal circulation (Grandjean and White 1999). In response, researchers carrying out the SCDS have argued that hair is a widely used biomarker for methylmercury exposure and correlates well with developing brain levels, the exposure of primary interest (Davidson, Myers et al. 1999b). To further explore the validity of maternal hair as an appropriate measure of prenatal exposure, the SCDS researchers investigated the degree of bias introduced by measurement error through the use of measurement error models (MEM) (Huang, Cox et al. 2003). These models can be used in the statistical analysis to correct bias from exposure error, and therefore better approximate the true outcome-exposure relationship.

The application of MEM requires information on the variance of measurement errors. The SCDC researchers relied on previous data on levels in maternal hair and infant brain, which they had used to validate the use of maternal hair as a biomarker for prenatal exposure. This enabled the re-analysis of the data from the testing of the SCDS cohort at the age of five years, with the inclusion of measurement error terms with respect to exposure. In this re-analysis, the researchers found no evidence of adverse neurodevelopmental effects related to methylmercury exposure (Huang, Cox et al. 2003).

6.2 Faroe Island studies

The population of the Faroe Islands, located in the North Atlantic, between Scotland and Iceland, relies heavily on fish and marine mammals (especially pilot whale) for protein in their

diet. A large prospective study investigating the neurodevelopmental effects in Faroese children associated with prenatal methylmercury exposure was initiated in 1986 and has included evaluations of the birth cohort up to seven years of age (Grandjean and Weihe 1993) with respect to neurological test performance, and more recently, with regard to blood pressure. In addition, a second cohort has been examined in relation to neurological health at 2 weeks and in relation to growth measured from birth to 42 months. Studies related to neurodevelopment are presented below, whereas the studies concerning cardiovascular effects are discussed in section 6.6.

In a 21-month period during 1986-87, 1022 children born at three different Faroese hospitals were recruited to the study. Mercury exposure was determined both through analysis of cord blood and maternal hair. A midwife administered a questionnaire that sought information regarding the course of the pregnancy, nutritional habits (frequency of fish or pilot whale meals), and alcohol and tobacco use during pregnancy. Routine obstetrical information was available from the infants' medical records. The results of the nutrition questionnaire indicated an adult daily consumption of seafood of 72 g fish, 12 g whale muscle, 7 g whale blubber. The average mercury concentrations in cod fish, the most commonly consumed fish, was about 0.07 ppm; whale muscle contained an average concentration of 3.3 ppm of total mercury, and approximately half of this was methylmercury. Whale blubber is a significant source of PCBs, typically about 30 ppm (Weihe, Grandjean et al. 1996).

The authors conducted an evaluation of the different factors that might have influenced the composition of the study cohort. They found that high cord blood mercury levels were associated with greater birth weight, presumably because other constituents of a seafood-rich diet prolonged the gestation period. While exposure to alcohol was generally limited in the study population, there was an association between lower methylmercury concentration in the cord blood and increased alcohol consumption by the mother during pregnancy. The authors concluded that the effect of these two factors was to bias the results of the study towards the null hypothesis (no association between neurodevelopmental outcomes and prenatal methylmercury exposure) (Grandjean and Weihe 1993).

The Faroese birth cohort was evaluated for different neurodevelopmental outcomes at two different stages: 12 months and at 7 years. The findings of these two evaluations are summarized in Table 2.

The assessment at 12 months investigated the achievement of certain developmental milestones (sitting, crawling, and standing) in relation to prenatal methylmercury exposure. The researchers found that the ages of achieving these milestones were not associated with methylmercury exposure, as measured by maternal hair or cord blood level; however an inverse association with the mercury level in child's hair at one year and age of attaining the milestone was observed (i.e. more highly exposed children sat, crawled and stood earlier, on average, than less exposed children). The authors attributed this inverse association to the beneficial effects of breastfeeding, with methylmercury exposures higher in children breastfed over a longer period (Grandjean, Weihe et al. 1995; NRC 2000).

The assessment at seven years included two test batteries – one neurophysiological (4 endpoints) and one neuropsychological (11 endpoints). Descriptions of the tests are included in Appendix C. The authors concluded that neurophysiological testing did not show clear abnormalities associated with methylmercury exposure; however, they observed decrease in performance in CPT*, Boston naming, and California verbal learning (particularly short recall) with increasing methylmercury exposure, as indicated by cord blood. When data analyzed by an alternative approach for confounder adjustment (Peters-Belson method), decreased performance with increasing exposure observed, as well, for the WISC-R block designs and Bender Gestalt (copy errors) (Grandjean, Weihe et al. 1997; NRC 2000).

A second cohort of 182 Faroese infants (all singleton and born at 36 weeks or more) was assessed for neurological optimality score (NOS) at age two weeks (Steuerwald, Weihe et al. 2000). The NOS reflects an infant's functional abilities, reflexes, responsiveness, and stability of state (NAS 2000). Two additional subscores were generated as well—muscle tone and reflexes. Exposure biomarkers included cord blood mercury and maternal hair mercury concentration (first 3 cm from the scalp). Measurements were also made of 18 pesticides and 28 PCB cogeners in maternal serum and breast milk, selenium in cord blood, and phospholipids in cord serum (two omega-3 fatty acids – eicosapentaenoic and docosahexaenoic – and one omego-6 fatty acid – arachidonic).

Steuerwald and colleagues found that the NOS score was significantly associated with gestational age, but not with birth weight. The cord-blood mercury concentration showed a negative association with the NOS, with a 10-fold increase in mercury associated with a NOS decrease of 2 points. This association did not hold for maternal hair mercury level. A shortening of gestational age by 3-weeks was associated with a decrease in NOS similar to the one related to a 10-fold increase in cord blood mercury level. The NOS subscores for muscle tone and reflexes showed no clear associations with any of the biomarkers studied (Steuerwald, Weihe et al. 2000). These findings are summarized in Table 2.

Other data analyses showed that the mercury/selenium ration in cord blood showed only a slightly improved association with the outcome of NOS. Removing the infant with the lowest NOS had only a small effect on the association between increased mercury exposure and decreased NOS. Concentrations of organic contaminants showed weak positive associations with the NOS. Fatty acids and thyroid variables were also poorly associated with the overall NOS (Steuerwald, Weihe et al. 2000).

The authors do not discuss the interaction, if any, between methylmercury exposure, omega-3 concentration in the cord blood, and gestational age. In their initial study of the cohort from 1986 and 87 (see Table 2), Grandjean and Weihe observed an association between higher exposure to methylmercury, as measured in the cord blood, and birth weight, presumably linked to a longer gestational period. They suggested that other constituents of a marine seafood diet contributed to this prolongation of pregnancy (Grandjean and Weihe 1993).

As was seen in the case of the Seychelles Child Development Study, publication of the findings from the Faroe Islands study cohort, following the one-year and the 7-year assessments,

generated a number of criticisms and questions regarding the results. These specific issues have been addressed through additional published analyses, and are summarized below.

6.2.1 Appropriate exposure measure

In the original analysis of the data (Grandjean, Weihe et al. 1997) from the neurodevelopmental assessment of the cohort at 7 years, cord blood mercury was the primary exposure indicator. With regard to maternal hair mercury level, the secondary exposure indicator, it appears that a limited length of scalp hair was analysed, although the published literature is not clear on this point. In a second analysis of the same 7-year-old assessment data (Grandjean, Budtz-Jorgensen et al. 1999), the maternal hair indicator of exposure appears to have been based on a re-analysis of the entire length of hair estimated to correspond to pregnancy. When this exposure measure is used, results of the finger tapping tests indicate that decreased performance is associated with increasing methylmercury exposure, as indicated by the maternal hair level, but not by the cord blood level. In addition, significant associations were found between increasing maternal hair mercury level and reduced performance on the Boston Naming Test and subtest of the California Verbal Learning Test, although the associations with cord blood level were stronger (Grandjean, Budtz-Jorgensen et al. 1999).

There has been considerable debate in the scientific literature concerning whether prenatal exposure is best characterized by the level of mercury in the mother's hair during pregnancy or by the level of mercury in cord blood collected at the delivery (Grandjean and White 1999; Davidson, Myers et al. 1999b).

The Faroe Island researchers argue that the developing nervous system is particularly vulnerable to effects from neurotoxicants during the second and third trimesters of pregnancy and during the early postnatal period. As methylmercury has a half-life of approximately 45 days in blood, the mercury level in a cord-blood sample taken at delivery should mainly reflect the exposure during the third trimester (Grandjean, Budtz-Jorgensen et al. 1999). In the Faroe Islands study, both cord-blood and maternal hair mercury levels (at delivery) were measured. Cord-blood level better predicted dysfunctions in the domains of language, attention, and memory, as compared to the maternal hair level. Thus, the authors argue that cord-blood mercury concentration is the main risk indicator for neurodevelopmental effects (Grandjean, Budtz-Jorgensen et al. 1999). The authors add that "decrements in fine motor coordination seemed better reflected by the maternal hair concentration at parturition, i.e., probably the methylmercury exposures during the second trimester" (Grandjean, Budtz-Jorgensen et al. 1999).

The authors comment that "according to the *a priori* hypothesis, the cord-blood mercury concentration was expected to be the best predictor for neurobehavioral decrements in the children" (Grandjean, Budtz-Jorgensen et al. 1999). Elsewhere (Budtz-Jorgensen, Keiding et al. 2002), the researchers have argued that the maternal hair mercury concentration may be affected by "hair color, hair treatment and other parameters that do not increase the variability of the cord blood concentration." Nonetheless, there appears to be a certain degree of circular

logic in the argument that cord blood mercury level is a better measure of prenatal exposure than maternal hair because that measure was associated with observations of increased neurological abnormalities and maternal hair levels were not. The Faroe Islands study findings would be more convincing if the biomarker of cord-blood mercury concentration were validated through independent studies (epidemiological, clinical, or experimental animal) as a measure that accurately reflects the amount of mercury reaching the fetal brain at the sensitive periods of fetal development, and then used as the exposure measure to investigate the association between methylmercury exposure and neurodevelopmental disabilities.

6.2.2 Risks associated with low levels of methylmercury exposure

A sub-analysis of the Faroe Islands data involved the identification of a case group of 112 children whose mothers had a hair mercury concentration of 10 to 20 ppm, corresponding to the range of exposures that had previously been identified as an approximate threshold for prenatal effects (IPCS-WHO 1990). These children were matched to children with exposures (indicated by maternal hair) below 3 ppm, using age, sex, time of examination, and mother's score on Raven's Progressive Matricies (cognitive function) as matching criteria. On six neuropsychological test measures, in the domains of motor function, language, and memory, the case group showed mild decrements relative to the control group, when measured with a one-tailed P-value of 0.05. The set of endpoints for which effects were found were somewhat different as compared to the main analysis (e.g. decreased performance found for the finger tapping test, which was not found in the main analysis (Grandjean, Weihe et al. 1998). The authors concluded that "a null hypothesis that exposures corresponding to maternal hair mercury concentrations of 10 to 20 ppm represent a ' no observed adverse effects level' must therefore be rejected."

6.2.3 Re-analysis of the findings on evoked potentials

A study of 7-year old children from a fishing village in Madeira, Portugal, carried out by a team that included the principal Faroe Island researchers, suggested that latencies of evoked potentials[8] may be delayed because of increased exposures to methylmercury during development. This provoked a re-examination of the Faroese data on evoked potentials in 7-year olds. In the main analysis (see Table 2) no association had been found between methylmercury exposure and abnormal performance on the two tests: brainstem auditory and reversal visual evoked potentials. In the assessment of Faroese 7-year olds, different instruments were used for the half of the cohort examined in 1993 and the half examined in 1994. Moreover, there were technical difficulties in 1994. In the re-analysis, the researchers compared 1993 and 1994 scores and found significant differences between the two years. They then re-analysed the data excluding all 1994 measurements. Regression analyses

[8] Evoked potentials are very small electrical voltage potentials, originating from the brain and measured in the scalp, resulting from a sensory or auditory stimulus (i.e. sound) or from a mental event.

showed significant associations between methylmercury exposure, as indicated by both cord blood and maternal hair levels but not child's hair level, and delays of the peak III latency and the I-III interpeak latency of the auditory brainstem evoked potentials. The authors conclude that, in agreement with the findings from Madeira, a delay of the peak III latency of the brainstem auditory evoked potentials appears to serve as a marker of prenatal methylmercury toxicity from contaminated seafood (Murata, Weihe et al. 1999).

6.2.4 Impact of contrast sensitivity performance on neurobehavioural tests

The Faroe Islands researchers investigated the effect of visual contrast sensitivity on the results of test that depended on reading a computer screen. Contrast sensitivity was found to be associated with the child's performance on the computer-assisted Continuous Performance Test, but also with the child's performance on traditional pencil-and-paper tests (Bender Gestalt and WISC-R block design). Contrast sensitivity was not associated with prenatal mercury exposure, and adjusting for contrast sensitivity had a negligible effect on the results of the main analysis for the cohort at age seven years (Grandjean, White et al. 2001).

6.2.5 Re-analysis of test data from the assessment at age seven years using structural equations

Structural equation models can be applied to the multiple regression analyses to correct for measurement error in exposure variables, and incorporate multiple outcomes and incomplete cases. The eleven neurobehavioural outcomes of the main analysis (see Table 2) were grouped into motor function and verbally-mediated function. The mercury effect on the two functions was similar to the strongest effects seen for individual test scores of motor function and verbal skill in the primary analysis. Adjustment for PCB exposure changed the estimates marginally, but the mercury effect could be reduced to non-significance by assuming a large measurement error for the PCB biomarker (Budtz-Jorgensen, Keiding et al. 2002).

6.2.6 Investigation of the effect of variable dose

The apparent contradiction between the findings in the Faroe Islands and the Seychelles has led several observers to comment that different patterns of exposures in the two populations may explain the differing results. Specifically, the Faroese mothers, because of their occasional consumption of more highly contaminated pilot whale meat, may be exposed to higher peak doses than the Seychelles mothers who, although they have a higher total exposure to methylmercury, are exposed through regular consumption of less contaminated fish.

In the original data collection for the main Faroe Islands study (1986/87 birth cohort) maternal hair samples collected at delivery, and corresponding to the pregnancy period, were analysed for methylmercury. In a subsequent investigation, a segment close to the scalp (2 cm) was analyzed in order to document exposures closer to the birth date. There was generally a high agreement between the two samples, suggesting a relatively stable exposure during pregnancy.

The researchers found that 62 of 614 mothers had variable exposure, as indicated when the lower level was less than 60% of the higher level. Their children were then excluded from the data analysis. Regression analysis was carried out for the outcomes at seven years of age (see Table 2). In 8 of 16 tests of the main study, poorer neuropsychological test performance was significantly associated with increasing methylmercury exposure, as indicated by cord-blood levels. The findings were similar to those obtained form the complete cohort. The authors conclude that the reported associations between methylmercury exposure and neurodevelopmental deficits observed for the Faroese cohort do not appear to be related to variable exposure (Grandjean, White et al. 2003).

The above investigation addressed in part the issue of variable exposure during pregnancy, through the comparison of the average hair mercury level over pregnancy and the hair mercury level corresponding to approximately the 2 months previous to delivery, and then by analyzing the outcome data only for children exposed to stable levels of mercury. However, the study did not specifically address the effect of peak exposures through a single large dose occurring at different stages of pregnancy. The cord blood mercury level would be expected to reflect only very recent large doses. Hair mercury levels would reflect such peaks only with an analysis such as continuous single-strand hair analysis using X-ray fluorescence, described in section 3.4.2.

6.3 Comparison of Seychelles and Faroe Islands studies

In a peer-review workshop convened in Raleigh, NC in November 1998, a five-member panel, supported by five working groups, identified five key differences between the Seychelles investigation and that of the Faroe Islands (see 4.1.1.3) that might explain the conflicting results of these two studies (Jacobson 2001). These differences were:

- Use of different biomarkers of exposure (cord-blood mercury in the Faroes, maternal hair mercury in longest segment corresponding to pregnancy in the Seychelles);
- Type of neuropsychological tests (domain-specific in the Faroes vs. global in the Seychelles);
- Difference in age at assessment (7 years in Faroes vs. 5.5 years in Seychelles);
- Sources and timing of the exposure (steady fish diet in the Seychelles vs. a steady fish diet with intermittent higher mercury pilot whale meals in the Faroes);
- Effect of PCBs in the diet (negligible PCB exposure in the Seychelles vs. considerable PCB exposure in Faroe Islands);

Researchers associated with both the Faroe Islands and Seychelles investigations have conducted secondary analyses, as reviewed above, that attempt to clarify the effects of these differences in the initial investigations. Specifically the differences in neuropsychological tests and the difference in age at assessment no longer hold, as the Seychelles cohort has now been

tested at age nine years using a battery of tests similar to that of the Faroe Islands investigation. The effects of PCBs in the Faroe Island findings have been adjusted for statistically, but this has not settled the question of the extent to which PCBs might be responsible for the observed neurological effects[9].

The potential influence of peak exposures from whale meat consumption has been answered partially by the Faroe Island investigators, but may nonetheless still be considered a factor leading to the different findings for the two populations (see 6.2.6). The controversy over the appropriate biomarker remains unresolved (see 6.2.1).

6.4 New Zealand study

In the early 1980s, Kjellström and colleagues conducted a prospective study investigating the effects of prenatal exposure to methylmercury among New Zealand mothers eating three or more fish meals per week. The results of the study were published in reports submitted to the New Zealand government, but were not published at the time in the scientific literature. The study did not therefore undergo a formal peer review process at the time of publication. However, following the publication of the Faroe Islands and Seychelles studies, the New Zealand study was extensively reviewed by the NRC panel (NRC 2000).

In the New Zealand study, exposure information (maternal hair samples and dietary questionnaires) was collected for nearly 11,000 women. Of this number, nearly 1000 were eating fish more than three times per week during pregnancy. The researchers then selected 73 women with hair mercury concentrations greater than 6 ppm. The 74 children of these women were designated as the “high-mercury group”. These children were each matched to a reference child on the basis of maternal ethnicity, hospital of birth, maternal age, and child age. Follow-up evaluations were completed when the children were four years old. A total of 38 exposed and 36 reference children were tested, including 30 matched pairs.

The primary measure of neurological function was the Denver Developmental Screening Test (DDST). A total of 52% of the children in the high-mercury group had an abnormal or questionable result compared with 17% of the children in the control group ($p < 0.05$). This corresponded to an odds ratio (indicator of relative risk) of 5.3. Results were similar when pairs that were poorly matched on ethnicity were excluded. The evaluation of the children by the DDST was a global assessment of neurodevelopment and did not allow identification of specific developmental domains in which performance was most strongly associated with maternal hair mercury concentrations (NRC 2000).

The New Zealand cohort was followed up again at six years of age. In that phase of the study, three controls were matched to each high mercury exposure child on the basis of ethnicity, sex, maternal age, maternal, smoking, area of maternal residence, and the duration of maternal

[9] For example of ongoing debate see Clarkson, T. W., L. Magos, et al. (2003). "The toxicology of mercury-Current exposures and clinical manifestations." The New England Journal of Medicine **349;18**: 1731-1737..

residence in New Zealand. One of the controls for each subject had a maternal hair mercury concentration of 3 to 6 ppm, whereas the other two controls had maternal hair mercury concentrations < 3 ppm. This resulted in 57 fully matched groups of four children, four incomplete sets, and a total of 237 children. In the high mercury exposure group, the mean maternal hair concentration was 8.3 ppm, with a range of 6 to 86 ppm and with all but 16 between 6 and 10 ppm. Information on possible confounding factors (e.g. social class, medical history, and nutrition) was collected (NRC 2000).

In the six-year old evaluation a battery of 26 psychological and scholastic tests was administered, assessing general intelligence, language development, fine- and gross motor coordination, academic attainment, and social adjustment. Multiple regression analyses of five primary end points were carried out: Test of Language Development (spoken language quotient), Weschler Intelligence Scale for Children-Revised performance and full-scale IQ, McCarthy Scales of Children's Abilities perceptual-performance scale, and the McCarthy Scales motor scale. Analyses were adjusted for an expanded list of potential confounders – social class, alcohol use, primary language, siblings, sex, birth weight, fetal maturity, Apgar score, and duration of breast feeding). In the robust regressions (giving less weight to outliers), maternal-hair mercury was associated with poorer scores (p values ranging from 0.0034 to 0.074) on full-scale IQ, language development, visual-spatial skills, and gross-motor skills. The poorer mean scores of the children in the high-mercury exposure group appeared to be largely attributable to the children whose mothers had hair mercury concentrations above 10 ppm (mean average hair mercury concentration of 13 to 15 ppm and a mean of peak monthly hair segments of 25 ppm). Maternal hair mercury concentrations accounted for relatively small amounts of variance in the outcome measures and generally accounted for less than covariates such as social class and ethnic group (NRC 2000).

In additional analyses of the data set, Crump found that when maternal-hair mercury was expressed as a continuous rather than a binary variable, none of the five primary end points studied by Kjellström and colleagues were associated with mercury at $p < 0.10$. This analysis was strongly influenced by the data for one child with a maternal hair-Hg level of 86 ppm (more than four times the next highest concentration). When the data for this child were excluded, scores on the McCarthy perceptual-performance scale were inversely associated with maternal hair mercury level at $p < 0.05$, using the full set of covariates. This reanalysis confirmed that the most important explanatory variables were ethnicity, education, mother's age, and child's sex, rather than mercury exposure (Shipp, Gentry et al. 2000).

6.5 Other neurodevelopmental studies

Other neurodevelopmental studies in fishing populations have been conducted, but because of limited size of the study population or other limitations in the study design, their findings are given less weight than those of the Seychelles, Faroe Islands, and New Zealand studies.

In a 1976/78 study of Cree children (12 to 30 months old) 247 mother-child pairs from Mistissini, Waswanipi, Whapmagoostui, and Chisasibi were examined. Exposure was assessed by the

maximum concentration in maternal hair for the period one month before conception to one month after delivery. Mean exposure was 6 ppm in maternal hair, with 6% of mothers having an exposure >20 ppm. The maximum exposure was 24 ppm (McKeown-Eyssen, Ruedy et al. 1983).

The neurologic examination of children assessed such variables as motor development, tendon reflexes, muscle tone, the Babinski reflex, coordination, special senses (myopia), cranial nerves, as well as any other sensory abnormalities. The researchers found that abnormality of muscle tone or reflexes in boys was positively associated with the index of prenatal MeHg exposure. No other measure of neurologic function or development was significantly associated with exposure, in a direction indicating an adverse effect, either before or after adjustment for confounding variables. However, incoordination in girls was negatively associated with prenatal MeHg exposure, although this relationship was not found to be statistically significant. The authors concluded that the abnormality of muscle tone was mild in severity and of doubtful clinical importance (McKeown-Eyssen, Ruedy et al. 1983).

In Mancoura, Peru, in a preliminary study, prenatal exposure of 194 children was assessed through maternal hair sampling. The children were then assessed for such characteristics as birth weight, head circumference, height, measures of infant development (age of sitting, standing, walking, and talking. The researchers concluded that there was no increase in the frequency of neurodevelopmental abnormalities in the early childhood of children exposed to methylmercury pre- and postnatally in the diet (Marsh et al. 1995a, as reported in NRC 2000)

Some cross-sectional studies among children in fishing populations have been conducted, in which exposure is measured on the basis of the child's hair or blood mercury level at the time of assessment, or on the mothers' hair at the time of assessment as a surrogate for the maternal hair mercury level during pregnancy. These cross-sectional studies are considered less convincing than prospective studies such as those of the Seychelles, Faroe Islands, and New Zealand, primarily because the researchers do not know if the outcomes they are measuring are related to exposures at the time of assessment, or to much earlier exposures, including prenatal, that might have affected the child's development.

In three regions of French Guiana, differing with respect to dietary dependence on fish, an investigation of neurological status was carried out for 378 children varying in age from 9 months to 6 years (Cordier, Garel et al. 2002). The concentration of mercury in samples of hair collected from children's mothers at the time of the study were used as a surrogate for exposure during pregnancy (assuming stable exposure patterns during and after pregnancy). The median concentration was 6.6 ppm (range of 2.6 to 17.8 ppm).

No major neurological abnormalities were observed in the children examined except for two children who began to walk late in one village (Camopi, selected for moderate mercury exposure levels). Among children two years of age and older, the prevalence of increased reflexes was significantly higher with increased mercury concentrations in maternal hair, with the association stronger in boys than girls. However, when 10 children who were found to have

increased reflexes were re-examined 9 months later by a different examiner, only three were considered to have increased reflexes (Cordier, Garel et al. 2002).

The children over five years of age were administered a battery of neuropsychological tests, including finger tapping, Stanford-Binet block designs, copying designs, and bead memory, and two subsets from the McCarthy scales – numerical memory and coordination. With adjustment for potential confounders, increased mercury concentrations were associated with copying-design score, especially in boys. When only the high-exposure region is considered, and the analyses are stratified by sex, increased mercury concentrations were associated with poorer leg coordination in boys and poorer block-design scores in girls (NRC 2000). The lack of consistency in the results, as well as the questionable reliability of assessing prenatal exposure on the basis of postnatal maternal hair concentrations, limit the interpretation of this study's findings.

In a cross-sectional study, 149 children attending first grade in a Madeiran fishing community (Portugal) were evaluated. All children were born in 1988, and were 6 or 7 years at time of testing. Methylmercury exposure was measured both through the child's hair mercury level and that of the mother, as a surrogate for the measure of prenatal exposure. Hair mercury in children ranged from 0.4 to 26 ppm, with a geometric mean of 3.82 ppm. In the mothers, hair mercury levels were generally higher, varying from 1.1 to 54.4 ppm, with a geometric average of 9.64 ppm (Murata, Weihe et al. 1999).

Children were assessed for brainstem auditory evoked potentials, and administered a battery of tests from the Neurobehavioural Evaluation System 2, including finger-tapping, hand-eye coordination test, continuous performance test, two subtests of the Weschsler Intelligence Scale for Children-revised: digit spans and block designs, and the Stanford-Binet Bead Memory test. Increased exposures to methylmercury, as measured in maternal hair were associated with delays in evoked-potential latencies for seven of twelve submeasures of brainstem auditory evoked potential latencies, and three of twelve submeasure of visual evoked potential latencies. Increased latencies are thought to reflect decreased nerve conduction velocity, depression of cortical activity, and/or reduced vigilance. These associations did not hold when the evoked potential test results were analysed in relation to the children's hair mercury levels. Moreover, the results of the neuropsychological testing did not show any clear association with mercury exposure (child or maternal hair) or with major confounders (Murata, Weihe et al. 1999)..

In a cross-sectional study of 351 children, aged 7 to 12 years, from three Tapajòs River villages (Amazon, Brazil), neuropsychological tests of motor function, attention, and visuospatial performance showed decreased performance associated with the children's hair mercury levels. The geometric mean of the children's hair mercury levels was 11 ppm. There was a close association between current maternal and child exposure levels, such that it was not possible to separate the effects of prenatal and postnatal exposures to methylmercury (Grandjean, White et al. 1999).

Two other population studies should be mentioned but are not reviewed here, as they focused on children living in gold-mining areas and thus exposed potentially to both mercury vapours

from the mining operations, and from methylmercury through the ingestion of contaminated fish. Associations between blood mercury levels and auditory effects were found in children in the Nambija gold-mining area of Ecuador (Counter, Buchanan et al. 1998). A health assessment for mercury exposure among schoolchildren residing near a gold processing, showed exposure likely to have come primarily through fish consumption. However, based on a survey of the area, investigators surmised that the children could be exposed to mercury vapours during the process of torching and refining the mercury-gold amalgam (Akagi, Castillo et al. 2000).

6.6 Non-neurological health effects from prenatal exposure

A recent study of the Faroe Islands cohort of 1000 children showed an association between prenatal exposure to methylmercury and cardiovascular risk factors at age seen. Specifically, diastolic and systolic blood pressures in the children increased by 13.9 and 14.6 mm Hg, respectively, as cord-blood mercury concentrations rose from 1 to 10 ppb. Above 10 ppb no further increase was seen. In addition, in boys, heart-rate variability, a marker of cardiac autonomic control, decreased by 47% as cord-blood mercury concentration increased from 1 to 10 ppb. The authors conclude that “these findings suggest that prenatal exposure to methylmercury may affect the development of cardiovascular homeostatsis” (Sorensen, Murata et al. 1999).

7.0 EXPERIMENTAL ANIMAL STUDIES

A large number of experimental animal studies, investigating the effects of prenatal, postnatal, and adult methylmercury exposure, have been carried out in monkeys, rats, mice, rabbits, guinea pigs, and cats. These studies are summarized below, on the basis of the reviews that have been carried out by the NRC (2000), the ATSDR (1999) and Shipp, Gentry et al. (2000).

7.1 Non-neurotoxic effects identified in animal studies

Carcinogenicity is generally not considered to be a sensitive endpoint from methylmercury toxicity. Renal tumours have been observed in male mice, but only at or above the maximum tolerated dose. Mercury has been shown to cause chromosomal damage and aneuploidy in a number of *in vivo* and *in vitro* systems. The International Agency for Research on Cancer (IARC) has classified methylmercury as a possible human carcinogen (NRC 2000).

Studies in rats and mice have demonstrated immunotoxic effects of methylmercury through both prenatal and postnatal exposure. According to the NRC review, the findings suggest that exposure to methylmercury could increase human susceptibility to infectious diseases and autoimmune disorders by damaging the immune system (NRC 2000).

Reproductive effects have been observed in monkeys, rats, and mice, including decreased conception rates, early fetal losses, and stillbirths (NRC 2000, Shipp, Gentry et al. 2000).

Several animal studies (in rats and mice) have demonstrated renal effects from methylmercury exposure. However, the kidney is considered to be less sensitive to methylmercury toxicity than the central nervous system (NRC 2000).

Studies in monkeys and rats have demonstrated cardiovascular effects, including cerebrovascular changes, polyarteritis nodosa, calcification of arterial wall, hypertension and decreased heart rate (NRC 2000).

7.2 Neurotoxic effects identified in animal studies and critical exposures

Much of the experimental animal research of the last 30 years has focused on prenatal exposure. Investigations have been carried out in monkey, rats, and mice. In general, the studies have reported a range of toxic effects similar to those reported in studies of humans exposed to methylmercury, including impaired vision, impaired memory, motor problems, impaired learning, and abnormal visual-evoked potentials (NRC 2000).

In adult experimental animals, observed neurological effects have included ataxia, tremor, constriction of visual field, and blindness (in monkey), hindlimb crossing (rat), hindlimb weakness and paralysis (mice), decreased muscle tone and reduced splay reflex (rabbit), and ataxia and impaired hopping (cat) (NRC, 2000)

The experimental animal studies generally support the conclusion that the central nervous system is the most sensitive target for the toxic effects of methylmercury, particularly during fetal development (Shipp, Gentry et al. 2000; NRC 2000). The prenatal exposure investigations have generally led to the identification of a LOAEL (lowest observed adverse effects level). In monkeys a LOAEL has 0.05 mg/kg/d (in utero exposure) for neurodevelopmental effects (impaired memory) has been observed. For adult monkeys a NOAEL (no observed adverse effects level) of 0.05 mg//kg/d and a LOAEL of 0.09 mg/kg/d from exposure to methylmercury over 177 to 392 days was observed for neurological effects, including ataxia, tremor, and blindness. In other experimental animal species, the observed NOAELs and LOAELs are higher.

The LOAELs and NOAELs observed in animal studies are generally higher than the intakes (expressed as mg/kg/d) associated with observed effects in humans. However, if the animal LOAELs and NOAELs were used for the purpose of risk assessment (i.e. to establish a reference dose or tolerable daily intake) they would likely result in reference values as low or lower than those determined on the basis of epidemiological studies (see section 10.0) because of the greater uncertainty associated with animal dose-response data.

Certain animal experiments have been conducted to investigate specific questions regarding methylmercury exposure (e.g. influence of nutrition, effects of coexposure with inorganic mercury), rather than with the objective of determining a NOAEL or LOAEL. This type of study is discussed in section 9.0 (Other relevant issues) in relation to the research question.

Recently the chemical form of methylmercury, as it occurs in fish, was investigated, and the findings are relevant to the interpretation of animal experiments. Methylmercury in fish appears to be methylmercury cysteine (or a structurally related species). In animal experiments, methylmercury is administered as methylmercury chloride. This form is more hydrophobic than methylmercury cysteine and may therefore cross membranes at a greater rate, thus leading to greater toxicity (Harris, Pickering et al. 2003).

8.0 SUMMARY OF DOSE-RESPONSE RELATIONSHIP FOR METHYLMERCURY

The epidemiological investigations discussed in section s 4.0, 5.0, and 6.0 are summarized in Table 4, which compares approximate exposure levels to methylmercury with effects and possible effects. The table considers both children exposed prenatally (expressed as the maternal blood or hair mercury level during pregnancy) and adults. The reader should refer to the accompanying text in those sections, or to the original papers, for details.

In Table 4, approximate ranges are given for the exposures related to certain effects, as most of the epidemiological investigations did not allow for the determination of a threshold level. Moreover, as the exposures decrease, the uncertainty associated with the exposure-effects relationship increases.

Exposures may be reported as hair or as blood mercury levels. Hair levels have been converted to blood levels, or vice versa, using the conversion factor of 1: 4 for hair (ppm): blood (ppb). This conversion is approximate, and two important qualifications should be noted. First, blood and hair are not equivalent biomarkers. Blood concentrations represent recent exposure while hair concentrations reflect long-term exposure, with each cm of hair corresponding to approximately 1 month of growth. Second, there is considerable interindividual variation in the ratio of hair and blood mercury, for a given pattern of methylmercury exposure.

9.0 OTHER RELEVANT ISSUES

9.1 Exposures of Cree and other populations to methylmercury

Exposure levels to methylmercury among the Cree of Eeyou Istchee for the period 1970 to 1995 is summarized in the document *Mercury studies among the Cree of Eeyou Istchee*.[10] In general, exposure levels among the Cree have been decreasing since the 1970s in all age groups. For example, in the 1970s, during the federal screening program, methylmercury levels above 100 ppb (the level defined as "at risk" by the Medical Services Branches of the Department of Health and Welfare) were relatively common, with 5 % of individuals tested having this level of exposure (Department of National Health and Welfare 1979). The highest blood mercury levels recorded in the 1970s were in the 600 ppb range (e.g.(Barbeau, Nantel et al. 1976; Wheatley, Barbeau et al. 1979).

The most recent general survey of all Cree communities took place in 1993 and 1994, with the inland communities surveyed in 1993 and the coastal communities surveyed in 1994. In all communities, and in all age groups, exposures were lower than in 1988, which in turn were lower than exposures measured in 1984 (Dumont, Girard et al. 1998). For example the proportion of the Cree population with hair mercury levels in excess of 15 ppm declined from 14.2 % in 1988 to 2.7 % in 1993/94.

In September and October 2002, an environmental health survey was carried out within the communities of Oujé-Bougoumou and Nemaska, in response to concerns regarding the contamination from mine tailing operations near the community of Oujé-Bougoumou (Dewailly and Nieboer 2003). Exposures to mercury in both communities were measured and these can be compared with corresponding data from 1993. As exposure varies considerably from one age group to another, it is important to ensure that the groups compared are similar. Different authors present their data in different formats, and thus it is not always possible to compare findings directly, without reprocessing the original data. Thus, in the comparison for Oujé-Bougoumou and Nemaska, 2002 vs. 1993, comparable results were identified for two groups: (1) men and women over the age of 40 years, and (2) women of reproductive age (15 to 39 years). The results from the two surveys are presented in Table 5. As shown, methylmercury exposures have generally declined in the period 1993 to 2002. For example, in Oujé-Bougoumou, the median exposure to methylmercury in 1993 was 8.2 ppm (hair mercury level) whereas in 2002 the level was 3.9 ppm. A similar decline occurred in Nemaska over this period.

Population exposure data from five geologically diverse coastal districts in Japan (Yasutake, Matsumoto et al. 2003), is included in Table 5, to illustrate the levels one might expect in a country in which fish traditionally forms an important part of the diet. While the sampling techniques were not identical to those used in surveys among the Cree, the results are

[10] Mercury studies among the Cree of Eeyou Istchee. Report prepared for the CBHSSJB by Deborah Schoen, M.P.H., Eng. 2004.

approximately comparable, as they represent surveys of the general population, and do not target individuals likely to have high exposures. Exposures in the Japanese adult population are similar to the Cree of Oujé-Bougoumou over 40 years of age, with similar median exposure levels documented.

The Oujé-Bougoumou and Nemaska 2002 surveys included measurements of mercury levels in blood, in addition to hair mercury levels, which allows for the comparison with other populations for which only blood mercury levels are available. These comparisons are presented in Table 6. Generally speaking, the Cree of Oujé-Bougoumou and Nemaska have higher blood mercury levels when compared to the southern Quebec population or that of the United States. However, their blood mercury levels are lower than those measured for three Inuit communities.

9.2 Vulnerable periods during gestation with respect to methylmercury exposure

A detailed analysis of the question of developmental vulnerability to methylmercury, with respect to the timing of exposure, can be found in the review by Choi (1989). This paper summarizes the effects of methylmercury on the developing brain, on the basis of Japanese and Iraqi poisoning data and the results of experimental animal investigations.

Methylmercury neurodevelopmental toxicity at the cellular level can occur by several potential mechanisms, such as mitotic interference, chromosomal effects, enzyme inhibition, or altered energy sources, and the extent to which each mechanism predominates can vary during gestation. With respect to timing, a toxic insult during the embryonic period (up to 7 weeks) would likely lead to gross organ defects and death, whereas a toxic insult during the functional maturation in the late fetal period might only result in subtle abnormalities, discernible only in the postpartum or adult period (Choi 1988).

Based on the Japanese and Iraqi data, Choi concludes that methylmercury disrupts neuronal migration and cortical differentiation, and notes: “As the late embryonic period and fetal periods represent the periods of active neuronal migration and cortical differentiation in the developing human brain, it appears reasonable to regard these periods to be the periods of greatest vulnerability to the far-reaching consequences of prenatal methylmercury poisoning” (Choi 1988).

Grandjean and colleagues have argued that the developing fetal brain is most susceptible to methylmercury toxicity leading to subtle disabilities towards the end of gestation. They argue that the associations between cord blood mercury level and diminished performance on certain learning and memory tests, which did not hold for maternal hair mercury level, indicate that the period towards the end of gestation, rather than earlier in gestation, represents a window of vulnerability of the fetus to methylmercury toxicity (Grandjean, Budtz-Jorgensen et al. 1999). The researchers add, however, “that decrements in fine motor coordination seemed better reflected by the maternal hair concentration at parturition, i.e., probably the methylmercury exposures during the second trimester” (Grandjean, Budtz-Jorgensen et al. 1999).

A recent investigation in mice, exposed to methylmercury prenatally found that the timing of exposure did significantly affect the type of developmental impairment observed (Doré, Goulet et al. 2001). Methylmercury chloride was administered in the diet at doses of 4 or 6 ppm, during days 7 to 9 of gestation (GD7-9 groups) or during days 12 to 14 of gestation (GD12-14 groups). Motor coordination on the rotarod (balance rod) and visual discrimination learning were not affected in any of the methylmercury-exposed animals. However, overall, the GD12-14 groups showed reduced locomotor activity and impaired memory as compared to the GD7-9 groups.

9.3 Diet and Methylmercury Toxicity

The relationship between methylmercury toxicity and diet is not well defined; however, the NRC does describe research concerning certain dietary factors, and this is summarized below. A more detailed compilation of moderating factors of methylmercury toxicity has been initiated and is available upon request.

Selenium

The relationship between selenium intake and methylmercury intake has been investigated in a number of animal and human investigations over the last two decades. In animal studies, selenium appears to influence the deposition of methylmercury in the body and protect against its toxic effects. No such association has been confirmed in humans, however (NRC 2000).

Garlic

Garlic has been shown in some animal studies to play a protective role, possibly through the action of thiol compounds. Garlic also contains selenium. However, the doses of garlic that were administered to the laboratory animals were well above the amount of garlic used in even the most garlic-intense cooking (NRC 2000).

Omega-3 fatty acids

This type of polyunsaturated fatty acid is essential to brain development in the fetus. Docosagexaenoic acid (DHA) accumulated in membrane phospholipids of the nervous system, and deficiency in DHA has been shown to impair leaning and memory in rats (NRC 2000).

Fish, and particularly oily fish, are rich in omega-3 fatty acids. However, the extent to which omega-3 fatty acids protect against the toxic effects of methylmercury has not been sufficiently investigated to allow a more precise characterization of this relationship (NRC 2000).

Protein

The amount of protein, and the types of amino acids that form these proteins, may influence methylmercury uptake and distribution. For example, in one study low protein intake was associated with increased mercury levels in the brain of mice. Sulfur amino acid ingestion may increase blood, renal, and liver mercury concentrations. Cysteine appears to promote transport

of methylmercury to the brains of rodents. Leucin may inhibit methylmercury uptake and methionine may stimulate its uptake (NRC 2000).

Alcohol

Animal studies have provided evidence that alcohol, when ingested with methylmercury, acts to increase the toxic effects of methylmercury (NRC 2000). In epidemiological studies, alcohol consumption is generally treated as a confounder, and is controlled for with statistical techniques through elimination of subjects with high alcohol intake. The NRC report does not identify any epidemiological studies explicitly investigating the relationship between alcohol intake and methylmercury toxicity

Vitamin E

Vitamin E (α-tocopherol) has been shown to be protective against methylmercury toxicity in rodent studies. Researchers have hypothesized that the antioxidant effect of vitamin E is related to the prevention of neuronal degeneration.

Other foods and nutrients affecting methylmercury uptake and toxicity

A study in rodents found an increased retention of methylmercury with the addition of evaporated milk to the diet. On the other hand, there are indications that wheat bran, when consumed at the same time as methylmercury, may reduce mercury concentrations in the brain. This effect has been attributed in part to binding of the mercury to bran, thereby reducing its absorption form the gastrointestinal tract. A second hypothesis is that bran increased the demethylation of methylmercury, and thus its absorption into the bloodstream (NRC 2000).

Other nutrients have been associated with the promotion of methylmercury toxicity in animal studies include vitamin C, excess iron, and ß-carotene. (NRC 2000). Note, however, that deficiencies in iron during pregnancy may also interfere with the proper development of the fetus

Contaminants

Other contaminants in fish and mammals, such as PCBs or DDT, may contribute to methylmercury toxicity, additively or synergistically (NRC 2000)[11]. The interaction between methylmercury and PCBs is discussed in section 6.2 in regard to the epidemiological studies in the Faroe Islands, where mothers have significant co-exposures to methylmercury and PCBs through their consumption of pilot whale meat.

[11] Two contaminants are said to act synergistically when the effects of the two contaminants ingested together are greater than the sum of the effects of the two contaminants acting alone.

10.0 COMPARISON OF METHYLMERCURY INTAKE GUIDELINES

The guidelines for the recommended maximum daily intake of methylmercury vary considerably between different national and international agencies. This section compares the guidelines from Health Canada, the Food and Agriculture Organization/ World Health Organization (FAO/WHO), the US Environmental Protection Agency (US EPA), and the Agency for Toxic Substances and Disease Registry (ATSDR), and identifies the basis for the differences between them. In addition, the assessments carried out by the US National Research Council (NRC) and The K. S. Crump Group, Inc., a private consulting group, have been included. The comparisons illustrate the range of values that may be derived, using the same scientific literature but with different interpretations of the scientific evidence and alternative methodologies in the application of uncertainty factors.

The comparison of different agency guidelines raises a number of issues with respect to the appropriate guideline for the Cree of Eeyou Istchee. These issues are discussed in section 10.2.

10.1 How guidelines for recommended maximum daily intake are determined

Generally, there are three major steps in establishing a guideline for allowable or maximum consumption (ATSDR 1999; NRC 2000), as described below:

a) Critical Effect:

The first step is to identify adverse effects observed in different studies through a complete review of the available health literature, including epidemiological, clinical, and animal toxicity studies. Among the studies judged to be of high quality, different adverse effects are identified at different levels of exposure. The critical effect is that associated with the lowest exposure. For example, in the case of the NRC methylmercury evaluation, the critical effect is the poorer performance on a word-naming test among children with higher prenatal methylmercury exposures in the Faroe Islands. The corresponding critical dose is the exposure at which the critical effect is first observed (12 ppm Hg in maternal hair in the Faroe Island example). The critical dose is then used as the point of departure for calculating the final guideline value[12].

The critical dose may be in the form of a NOAEL (No Observed Adverse Effects Level), a LOAEL (Lowest Observed Adverse Effects Level), or a BMDL (benchmark dose, lower bound). The benchmark dose represents a specified increase (usually 1, 5, or 10 %) in the frequency of the number of people with an effect (for example, abnormal result on the word-naming test) as compared to the background frequency. The BMDL is the lower 95% confidence limit in the estimation of the benchmark dose.

[12] An integrative analysis, in which several neuropsychological test endpoints define the critical effect, was used by the US EPA in its determination of its Reference Dose (see Table 1).

b) Critical Dose → Intake:

The critical dose (often in units of ppm Hg in hair or ppb Hg in blood) is converted into an intake, in units of µg Hg/kg bw/d where bw is the weight of the individual. Generally agencies use a one-compartment model for this conversion, with similar values for the variables representing absorption and elimination of mercury in the body. However, a more complex physiological-based pharmacokinetic (PBPK) model can be used as well.

c) Intake → Guideline Value:

The intake is divided by an uncertainty factor to derive the guideline value. Part of the uncertainty factor may account for individual biological variability. For example, two individuals will ingest different amounts of methylmercury and achieve the same critical hair or blood mercury levels. This is generally referred to as toxicokinetic variability. A factor of 2 to 3 is used to adjust for this variability, such that more sensitive individuals (those that achieve the critical dose with a smaller intake) are protected.

Uncertainty factors are also applied to account for uncertainty in the scientific understanding, and vary according to the nature of the data set (e.g. animal vs. human studies, unresolved scientific issues related to exposure patterns or sensitivity of tests measuring effects). In comparison to the uncertainty due to biological variability, scientific uncertainty is much more difficult to quantify. However, certain default values are applied with some consistency. For example, if the critical dose is based on an animal study, a factor of ten will be applied to account for the extrapolation of animal study findings to a human population.

The methodology used by the KS Crump Group differs from that described above in that an uncertainty factor with respect to scientific uncertainty was applied directly to the critical dose (BMDL). This value was then converted to a range of acceptable intakes using a Monte Carlo analysis, which integrated the statistical distributions of the parameters of a more complex physiologically-based pharmacokinetic model. A value representing the lower 10^{th} percentile of the resulting intake range was proposed as appropriate for the protection of public health. In other words, this analysis incorporates individual differences in the way in which mercury is absorbed, distributed, and eliminated into its calculation of the intake rate, such that a further uncertainty factor to account for toxicokinetic variability is unnecessary. (Shipp, Gentry et al. 2000).

Table 7 presents different agency guidelines. The different steps of the process of determining a recommended guideline (critical dose, uncertainty factors, etc.) are identified. Some agencies have established different consumption guidelines for adults and pregnant women, in order to address the greater sensitivity of the developing fetus to methylmercury toxicity. In other instances (e.g. US EPA, ATSDR), a single guideline has been issued based on the effects of prenatal exposure to methylmercury.

10.2 Issues in the determination of a guideline for methylmercury

Table 7 raises a number of issues related to the determination of a guideline for a maximum recommended intake of methylmercury in the context of a fishing population such as the Cree of Eeyou Istchee. These issues are discussed below.

10.2.1 One guideline or two?

Animal and human studies have shown that the developing fetus is more sensitive to methylmercury toxicity than the adult. For this reason some agencies, such as Health Canada, provide separate guidelines on methylmercury intake for adults and pregnant women.

The US EPA and the ATSDR, on the other hand, have derived a single guideline for methylmercury intake based on the effects in the most sensitive group (pregnant women). This is consistent with the two agencies' general approach to developing guidelines for hazardous substances on the basis of the most sensitive individuals.

The one-guideline approach is often used in situations where the health guideline is used to justify regulatory action limiting industrial emissions of the hazardous substance. In this case, a public health agency will strive to regulate emissions so as to protect the most sensitive individuals in the population. In the case of the US EPA, reference doses are, generally speaking, used to guide both risk management decisions and regulatory permits (NRC 2000). However, if regulatory considerations have played a role in the US EPA determination of the RfD, they have not been explicitly stated.

Given the different levels of risk documented for different segments of the population, some public health professionals working in fishing populations have argued against the establishment of a single guideline for the intake of methylmercury. This issue is particularly important when the single guideline, if followed, would severely restrict or eliminate fish from the diet (Wheatley, Chan, and Receveur 2001).

10.2.2 What is the difference between and RfD, and MRL, PTDI and a TDI?

These four guidelines are analogous, in that they recommend an intake of mercury that is unlikely to increase an individual's risk of adverse effects. However, there are some important practical differences in the way in which the guidelines are used. For example, the Health Canada Tolerable Daily Intake (TDI) and the FAO/WHO Provisional Tolerable Weekly Intake (PTWI) are dietary recommendations for an individual fish consumer, whereas the US EPA Reference Dose (RfD) serves both as a dietary recommendation and as a basis for further regulatory action with respect to eliminating industrial emissions of mercury. In the case of the ATSDR, the Minimal Risk Limit (MRL) is intended as a screening tool, to help ATSDR assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites (ATSDR 1999).

10.2.3 Which study should be used as the critical study?

Up until recently, critical doses, for both adult and prenatal exposure, were based on investigations carried out in the 1970s following a methylmercury poisoning epidemic in Iraq. In 1998 and 1999, the results of the Seychelles and Faroe Islands studies, two large investigations into the neurodevelopmental effects of prenatal mercury exposure, were published. Most guidelines today have been revised in light of the findings of these two studies.

There has been some controversy among US experts and agencies as to which study – the Seychelles or the Faroe Islands – should be used for the development of a dietary guideline. Both are recent and follow approximately 700 children exposed prenatally to methylmercury. In the Seychelles, this exposure is through fish consumption, while in the Faroe Islands the exposure in through the consumption of fish and pilot whale meat.

The ATSDR uses the Seychelles study, in which researchers found no increase in neurological abnormalities among children in the high prenatal exposure group, for the following reasons (ATSDR 1999):

- The Seychellois regularly consume a large quantity of ocean fish, with an average of 12 fish meals per week. Their exposure to methylmercury is significant and year-round;
- The mean methylmercury concentration in fish consumed by the Seychellois ranged from 0.004 to 0.75 ppm across the 25 species sampled. These levels are similar to typical concentrations in fish consumed by North Americans, and are not particularly elevated. Thus the high methylmercury exposure in the Seychellois comes from high fish consumption, not from consuming particularly contaminated fish;
- The concentrations of other potential fish contaminants, such as PCBs, are low;

The NRC and the US EPA, on the other hand, justify the selection of the Faroe Islands with the following arguments (NRC 2000):

- The traditional approach to establishing an RfD is to select a study that has been well-conducted and resulted in the lowest adverse effect level. While both the Seychelles and Faroe Island studies were judged to be well-conducted, the Faroe Island study showed an increased risk of adverse effects (decreased performance of neurodevelopmental tests) while the Seychelles study did not.
- The Faroe Islands population was also exposed to PCBs through the ingestion of pilot whale meat, which also had a relatively high average methylmercury concentration of 3.3 ppm. However, the NRC concluded that the statistical analysis had adequately adjusted for any potential confounding from PCB exposure.

10.2.4 Intake corresponding to critical dose

In order to calculate the intake rate that corresponds with the critical dose, the critical dose, expressed as mercury concentration in hair (ppm) is converted to mercury concentration in blood (ppb). Generally, the hair concentration (ppm) is multiplied by 4 to obtain the blood concentration (ppb), although a factor of 3.3 has also been used, most notably by Health Canada. For the purpose of the present comparison, a factor of 4 is used in all instances.

The following equation is generally used to convert the critical dose to a dietary intake:

$$d = (C_{Hg\text{-}blood} \times b \times V) / (A \times f \times bw)$$

where d = dietary intake (µg MeHg / kg d);

$C_{Hg\text{-}blood}$ = mercury exposure (e.g. critical dose), expressed in terms of concentration of mercury in blood (ppb or µg/l)

b = elimination constant (0.014 d^{-1});

V = volume of blood in body (5l);

A = absorption factor (0.95);

f = fraction of daily intake taken up by blood (0.05);

bw = body weight (assumed to be 60 kg for an adult woman).

The methodology used by the K.S. Crump Group Inc. involves a more detailed pharmacokinetic model and a Monte Carlo analysis that uses the statistical distributions of the different physiological parameters (rather than single values) to convert an exposure represented by a hair mercury level into a range of intakes within a population (Shipp, Gentry et al. 2000). The reader should consult the original reference for details.

10.2.5 How large should the uncertainty or safety factor be?

As can be see in Table 1 the choice of an uncertainty or safety factor plays a determining role in the calculation of the recommended consumption guideline. At the same time, this step of the risk characterization process is the least supported by scientific evidence.

There are two components of scientific uncertainty associated with a value for mercury intake derived from the critical dose of an epidemiological study: (1) the uncertainty associated with the variability between individuals in a population as to their susceptibility to toxic effects, and (2) the uncertainty associated with an inadequate scientific understanding of the problem. The first kind of uncertainty can be quantified through scientific investigation, but the second is not measurable. Thus the selection of a value to represent this second type of uncertainty is necessarily a policy decision – not one based solely on scientific evidence.

The NRC (2000) chose an uncertainty factor of 10, to adjust for interindividual variability in the translation of hair mercury levels into intake rates (uncertainty type 1), as well as data base insufficiency (uncertainty type 2). The NRC recognizes the inherent problem with the process of determining this factor in the following statements:

« There is no consistent approach in the application of uncertainty factors across the various regulatory and public health agencies. The selection and application of uncertainty factors represents a scientific policy judgment that has a major influence on the determination of the RfD or other risk-management guidance numbers. »

« The selection of an uncertainty factor value for database insufficiency is inherently uncertain. »

10.2.6 Should the benefits of a diet including fish be factored into the consumption guideline?

None of the guidelines presented in Table 7 explicitly factor in the benefits of a diet that includes fish, despite the fact that all agencies recognize these benefits in their supporting documentation. Wheatley, Chan, and Receveur (2001) provide an illustration of how the positive benefits of eating fish and marine mammals could be integrated into the calculation of a guideline value for maximum mercury intake. Their approach is to use a minimal level of fish consumption, based on nutritional benefits, as a starting point in the development of a mercury intake limit. They then evaluate the risk of such a fish consumption for different segments of the population and in the context of existing guidelines. This approach is illustrated below (Wheatley, Chan et al. 2001):

- The nutritional benefits of eating at least one to two fish servings per week (approximately 250 g per week or 35.7 g /d)[13] have been demonstrated by 11 of 16 research articles published since 1985. In light of the other socio-economic and cultural benefits of fish consumption, this minimum intake is used as a point of departure in the determination of an appropriate mercury guideline;

- There are different levels of risk for different segments of the population, with the greatest risk for the foetus and the lowest for the older population. One possible

[13] A serving size of fish is often considered to be approximately 250g. However, typical serving sizes vary tremendously, and may be considerably greater for the Cree.

breakdown of the population, for the purpose of mercury intake guidelines, is: (1) women of child bearing age, (2) sport anglers and adult males, and (3) older First Nations and Inuit peoples;

- In the case of a women of child bearing age (average body weight of 60 kg) eating 250 g/wk of fish, she must select fish species that have a mercury concentration below 0.34 ppm in order to remain within the Health Canada guideline of 0.2 µg/kg-d. Many freshwater fish will be below that level, but some – such as pike and walleye – will not. In contrast, in order to respect the US EPA guideline, a woman eating 250 g/wk of fish would have to consume species with an average mercury concentration of 0.17 ppm. Given that most freshwater species are above this level, such a guideline would be difficult to achieve while still consuming one to two fish meals per week ;

- In the case of adult men (average body weight of 70 kg), including sport fishermen, eating 250 g/wk of fish, they must select fish species with an average mercury concentration of 0.92 ppm, to remain within Health Canada's guideline for adults. This is entirely feasible, provided the fishermen are not consuming only large piscivorous fish such as pike and walleye from lakes known for high mercury concentrations in these species.

  Adult men can also increase the number of fish meals they consume to 3 to 4 servings per week, and stay within Health Canada limits, provided that they chose species that, on average, have a mercury concentration below 0.45 ppm. This will include most commercially available fish, and many sport fish;

- As many aboriginal people, especially older individuals, eat fish on most days, their mercury intake can greatly exceed the recommended guidelines. For example, if a 70 kg man eats 7 fish meals per week with an average fish mercury level of 0.5 ppm, he will consume 0.89 µg Hg/kg bw/d. To reduce the intake to the Health Canada limit of 0.47 µg Hg/kg bw/d would require selecting fish that had an average level of 0.28 ppm. In the case of subsistence fishing, this would be difficult to achieve.

The authors conclude that "given the uncertainty factors included in all risk calculations, flexibility and recognition of the realities of subsistence living and cultural norms must be part of the risk management discussions with First Nations and Inuit peoples."

The underlying perspective of this approach is that the development of limits on mercury intake, in particular with regard to the selection of uncertainty factors, should strike balance between the benefits of fish consumption and the health risks of mercury exposure. At a minimum, these limits should allow for consumption of one to two fish meals per week.

10.2.7 How do mercury exposures in the Cree of Eeyou Istchee compare with the different agency guidelines and with the levels at which adverse effects are observed?

The most recent general survey of mercury exposure was in 1993/94. In that year, 1772 individuals were tested. The median mercury hair level was 2.5 ppm, and the maximum level was 42.2 ppm. Over 10 % of the individuals exceeded the Health Canada guideline of 6 ppm. Older individuals generally had higher exposures (median of 4.4 ppm) compared to the younger generation. There was also considerable variation among communities, with the highest mercury hair levels recorded for Whapmagoostui (median for all individuals of 3.6 ppm, maximum of 42.1).

Among women of childbearing age, in the 1993/94 survey, approximately 10 % had mercury exposures above 3 ppm . The maximum level recorded within this group was 12.8 ppm. Among pregnant women in this time period, exposures were generally at or below the detection limit of 2.5 ppm (Dumont, Girard et al. 1998), which corresponds approximately to the Health Canada guideline for women of childbearing age.

In general, the exposures of women of childbearing age in the Cree communities in 1993/94 were lower than the exposures of mothers in the Seychelles and Faroes Islands studies (studies on which the Health Canada guideline is based). In the Seychelles study, no neurodevelopmental effects were associated with mercury exposure. In the Faroe Islands study, reduced performance on language, attention, and memory tests was associated with a maternal hair mercury level of 12 ppm (NRC 2000).

The findings of the Seychelles study, and indeed the results of the Faroe Islands study, suggest that Cree women can continue to eat fish as they did in 1994, during pregnancy or when breastfeeding, without harm to the development of their children. Nonetheless, there remain unresolved issues that contribute to the uncertainty associated with such a conclusion. Are the results for the Seychelles and Faroes Islands population applicable to other populations with very different diets, environments, and lifestyles? How variable are individuals in their sensitivity to the toxic effects of mercury? Were the tests administered in the two studies sufficiently sensitive to detect subtle effects of mercury toxicity? Such questions lead regulators to apply uncertainty factors in their derivation of public health guidelines. As was noted in the previous sections, this uncertainty drives the recommended dietary limits in Table 7 towards exposures that are much lower than the exposures at which adverse effects are observed.

10.2.8 Comments on the CBHSSJB intervention thresholds

During the Mercury Agreement (1986 to 1996), the CBHSSJB set intervention thresholds at 30 ppm (hair mercury concentration) for adults and 15 ppm for women of child bearing age. These were based on a consideration of the adverse effects, as reported in the literature available at the time (not including Seychelles and Faroe Island studies), balanced with the recognition that "*fishing is important among the Cree, economically as well as socially and culturally, [and that] placing restrictions on fishing poses its own threats to health* (Dumont, Noel et al. 1998).

The above guidelines are thus based on both scientific and policy considerations. Given that the body of scientific knowledge on the health effects of mercury and the health effects of fish consumption has evolved considerably in the past ten years, and that the health, economic, and cultural context has changed, a re-evaluation of these guidelines is appropriate.

Table 1 Neurotoxic effects in adults: studies in Brazil

Study population	Methylmercury exposure	Neurological tests	Comments/ Reference
Tapajós River (Amazon): Brasilia Legal, Ponta das Pedras; 29 young adults (15 to 35 years, 14 men, 15 women) Preliminary study	Hair mercury, varying length of hair; Geometric mean of 14 ppm; range of 5.6 to 38.4 ppm.	Colour vision; Contrast sensitivity ; Grip strength; Fatigue; Santa Ana (manual dexterity)	Villages located 250 and 375 km downstream from gold mining operations; 3 individuals with hair Hg levels > 24 ppm demonstrated reduced contrast sensitivity, and individuals with levels above 20 ppm tended to demonstrate reductions in peripheral visual fields (no statistical anaylsis) More highly exposed women tended to have lower scores than lower-exposed women on both manual dexterity and grip strength (Lebel, Mergler et al. 1996).
Tapajós River (Amazon): Brasilia Legal; 91 individuals, 15 to 81 years old	Hair mercury: 4 measures used, because of seasonal variation: mean of total Hg over entire strand, Hg in first cm from scalp, Hg peak, methylHg in first cm.	Colour vision; contrast sensitivity; Grip strength; fatigue; Santa Ana (manual dexterity); Clinical neurological examination with Branches Alternate Movement Task (BAMT).	Abnormal performance on BAMT significantly associated with all measures of mercury exposure ($p \leq 0.05$ or 0.01); abnormal visual fields associated with mean hair Hg and peak Hg levels($p \leq 0.05$). Increased hair Hg levels also associated with poor scores on the intermediate and higher frequencies of near visual-contrast sensitivity ($p \leq 0.05$), with poor scores on the manual dexterity test ($p \leq 0.05$), and with increased muscular fatigue ($p \leq 0.10$). Grip strength in women reduced with increasing peak mercury concentration ($p \leq 0.10$). (Lebel, Mergler et al. 1998)

Table 1 continued. Neurotoxic effects in adults, studies in Brazil			
Study population	**Methylmercury exposure**	**Neurological tests**	**Comments/ Reference**
Brasilia Legal 98 adults (ages 15 to 81 years)	Hair mercury: median 13.5 ppm (22.2 ppm for the 75th percentile). Women had significantly lower levels, median10.8 ppm, as compared to men, 17.1 ppm.	Mitotic Index Polyploides Chromatid breaks	All three types of genetic damage were statistically associated with increasing hair mercury levels. Mitotic index decreased with increasing hair Hg, indicating impairment of lymphocyte proliferation under culture conditions. Polyploidal aberrations were observed to increase in frequency with increasing hair mercury levels above 7.25 ppm. Only 14 % of subjects showed chromatid breaks in their lymphocytes. Those subjects with chromatid breaks had significantly higher hair mercury levels compared to those without. (Amorim, Mergler et al. 2000).

Table 1 continued. Neurotoxic effects in adults, studies in Brazil			
Study population	**Methylmercury exposure**	**Neurological tests**	**Comments/ Reference**
Tapajós River (Amazon), village of Cametà, N= 84, 16 excluded for other health conditions, occupational exposure to Hg. 41 women, 27 men.	Hair and blood Hg levels: mean hair Hg level of 9.5 ppm, max > 35 ppm.	Santa Ana (manual dexterity); grooved pegboard; finger tapping; Strength tests: grip and pinch.	Hair mercury level was inversely associated with overall performance on the psychomotor tests ($p \leq 0.01$). This relationship not significant for blood mercury. No relationship was observed between methylmercury exposure and the performance on tests for grip or finger strength. (Dolbec, Mergler et al. 2000)
Tapajós River (Amazon), villages of Barreiras, Rainha, Sao Luiz do Tapajós, over 200 km down-stream of gold mining areas. 132 subjects (fishermen and family members, ages 1 to 67).	Hair mercury, Mean of 23.6 ppm; Range of 5.1 to 42.7 ppm.	Clinical examination of 50 subjects with hair mercury levels greater than 20 ppm; questionnaire regarding subjective symptoms. 14 subjective symptoms reported (e.g. numbness, vertigo, lassitude, headache, irritability, loss of memory, insomnia);7 objective effects reported: sensory disturbance (32 %), disturbance in balance (12 %) and coordination (10 %), tremor (8 %), hyperreflexia (8 %), dysarthria (2 %), gingivitis (0 %).	Medical examinations of subjects: no blinding of examiners with regard to mercury exposure of subjects; no statistical analysis of dose-response relationship. 3 subjects diagnosed with mild Minamata disease; 3 cases with suspected Minamata disease. Case studies described in detail in article. Main symptoms reported: disturbance in coordination, glove-and-stocking type sensory disturbance, reduction in manual dexterity, numbness, failure in two-point discrimination, tremor; other symptoms were reported as well (Harada, Nakanishi et al. 2001)

Table 1 continued. Neurotoxic effects in adults, studies in Brazil

Study population	Methylmercury exposure	Neurological tests	Comments/ Reference
Cross-sectional study; subjects from 6 fishing villages, Cuiaba River of the Pantanal region of Brazil. 129 men and women older than 17 years of age.	Hair mercury levels (2cm near scalp); mean of 4.2 ppm, range of 0.56 to 13.6 ppm	Weschler Memory Scale: orientation, mental control, logical memory, digit span, visual reproduction, paired associate learning tests. Wechsler Adult Intelligence Scale: Digit Symbol Subtest. Manual ability of Leon Walter's Tests of Mechanical Ability. Concentrated Attention Test of the Toulouse Pierron Factorial Battery. Profile of Mood States (general measure for assessing mood, anxiety, and general distress).	Pantanal region of Brazil subject to environmental effects of gold mining. Battery of tests similar in nature to those used in the Seychelles and Faroe Islands investigations. Hair mercury levels were used to indicate methylmercury exposure. Hair mercury levels associated with decreased performance on tests of fine motor speed, dexterity, and concentration. Correlations between 4 of 15 submeasures of memory and intelligence tests and hair mercury level were statistically significant. The observed effects were dose-dependent (Yokoo, Valente et al. 2003).

Table 2 Seychelles Child Development Study

Age of children	Maternal Exposure			Post-natal exposure, ppm	Endpoints	Results/ Reference
	Median, ppm	IQR, ppm	Range, ppm			
6.5 months n=779	5.9	6.0	0.5 to 26.7	Not measured.	Overall neurological exam; Fagan test of visual recognition memory; Denver Developmental Screening Test-Revised	After adjusting for covariates (confounders) no association between maternal hair Hg level and adverse outcomes were identified (Myers, Marsh et al. 1995)
19 months n=738	5.9	6.0	0.5 to 26.7	Not measured.	Bayley Scales of Infant Development Raven Standard Progressive Matrices Interim health history Age of walking Age of talking	No association between maternal hair Hg level and cognitive developmental outcomes; Children walked at 10.7 ± 1.9 mo. (females), 10.6 ± 2.0 mo. (males); Children talked at 10.5 ± 2.6 mo. (females), 11.0 ± 2.9 mo. (males). No association between achievement of these milestones and Hg level; mean ages for achieving milestones somewhat younger compared to the mean ages for US children (Davidson, Myers et al. 1995; Myers, Davidson et al. 1997).

Table 2 continued. Seychelles Child Development Study

Age of children	Maternal exposure			Child's exposure, ppm	Endpoints	Results/ Reference
	Median, ppm	IQR, ppm	Range, ppm			
29 months n=736	5.9	6.0	0.5 to 26.7	Not measured.	Bayley Scales of Infant Development Bayley Infant Behavior Record Interim health history	No association between maternal hair Hg level and cognitive development; statistically significant association between decreased activity (subjective measure) in boys and increased prenatal Hg exposure. Significance of association unclear. Authors recommend further testing with older children; (Davidson, Myers et al. 1995)
5 years (66 months) n=711	5.9	6.0	0.5 to 26.7	Mean : 6.5 Range : 0.8 to 25.8	McCarthy Scales of Children's Abilities Preschool Language Scale Woodcock-Johnson Applied Problems and Letter and Word Recognition Tests of Achievement Bender Gestalt test Child Behavior Checklist Pure tone hearing threshold	No association between maternal hair Hg level and cognitive, hearing, or behavioural development; postnatal exposure associated with a small increased performance on several tests; quality of the home environment, gender, and caregiver IQ all found to influence performance scores, increasing authors' confidence in the sensitivity of tests. No detectable PCBs in the serum of 49 children tested; (Davidson, Kost et al. 2001)

Table 2 continued. Seychelles Child Development Study

Age an number of children	Maternal exposure			Child's exposure, ppm	Endpoints	Results/ Reference
	Median, ppm	IQR, ppm	Range, ppm			
9 years (107 months) n=717	5.9	6.0	0.5 to 26.7	Not reported.	Weschsler intelligence scale for children III. Woodcock-Johnson Applied Problems and Letter and Word Recognition Tests of Achievement. California verbal learning tests and memory tests; Boston naming test. Motor functions (finger tapping, trailmaking, grooved pegboard, Buininks-Oseretsky test of motor proficiency) Visual –motor integration (2 different tests) Connor's continuous performance test (sustained attention) Behavior, assessed through the Connor's teacher rating scale and the parent-child behaviour checklist.	Two of 21 endpoints associated with prenatal Hg exposure : (1) diminished performance of the grooved pegboard non-dominant hand, in males only; (2) improved score on hyperactivity index of the Connors teacher rating scale. Distribution of p-values for all results indicate that both of these outcomes are probably due to chance. (Myers, Davidson et al. 2003)

Table 3 Faroe Islands studies of children exposed prenatally to methylmercury

Age and number of children	Maternal hair Hg level (ppm)	Cord blood Hg level (ppb)	Postnatal hair Hg level in child at 12 mo. (ppm)	Endpoints	Comments/ Reference
1 year, n=583	Full cohort: Geometric mean: 4.27 IQR* of 2.6 to 7.7 15% > 15 Measured at delivery;	Full cohort: Geometric mean: 22.9 IQR* of 14.4 to 41.3 * Interquartile range	Geometric mean: 1.12 IQR* of 0.69 to 1.88 Max: 8.8	Developmental milestones: - Sits without support; - Creeps (crawls) ; - Gets up to standing position without support.	Age at achieving milestone not associated with methylmercury exposure as measured by maternal hair or cord blood level; inverse association with Hg level in child's hair at one year; Authors attribute inverse association to the beneficial effects of breastfeeding (methylmercury exposures higher in children breastfed over a longer period). Grandjean Weihe et al 1995; NAS 2000

Table 3 continued. Faroe Islands studies

Age and number of children	Maternal hair Hg level (ppm)	Cord blood Hg level (ppb)	Child's hair Hg level (ppm), at 7 yr.	Endpoints	Comments/ Reference
7 years, n=917	Full cohort: Geometric mean: 4.27 IQR* of 2.6 to 7.7 Measured at delivery, segment	Full cohort: Geometric mean: 22.9 IQR* of 13.4 to 41.3 Note: PCB concentration determined for 435 children: Geometric mean: 1.12 ppb IQR* of 0.57 to 1.55 ppb *Interquartile range	Geometric mean: 2.99 IQR of 1.7 to 6.1	4 neurophysiological endpoints: Reversal visual evoked potentials; brain stem auditory-evoked potentials; postural sway; autonomic nervous system function; 11 neuropsychological endpoints : Finger tapping; NES hand eye coordination; tactual performance; NES continuous performance test (CPT); Wechsler intelligence scale-revised (WISC-R): digit spans, similarities, block designs; Bender Gestalt (copy errors); California verbal learning (short recall and delayed (20 min) recall; Boston naming; nonverbal analogous profile of mood states.	Grandjean, Weihe et al (1997) concluded that neurophysiological testing did not show clear abnormalities associated with methylmercury exposure; however, they observed decrease in performance in CPT**, Boston naming, and California verbal learning (particularly short recall) with increasing methylmercury exposure. When data analyzed by an alternative approach for confounder adjustment (Peters-Belson method), decreased performance with increasing exposure observed, as well, for the WISC-R block designs and Bender Gestalt. Questions raised regarding confounding from PCB exposure (see text) ** Data for one-half of the cohort rejected because of changed test conditions. Association not observed for rejected data.

Table 3 continued. Faroe Islands studies

Age and number of children	Maternal hair Hg level (ppm)	Cord blood Hg level (ppb)	Endpoints	Comments/ Reference
182 2 weeks	Geometric mean: 4.08 IQR* of 2.45 to 7.35 Total range of 0.36 to 16.3	Geometric mean: 20.4 IQR* of 11.8 to 40.0 Total range of 1.90 to 102	Neurologic Optimality Score (NOS) Subscores for muscle tone and reflexes	The cord-blood mercury concentration showed a negative association with the NOS, with a 10-fold increase in mercury associated with a NOS decrease of 2 points. This association did not hold for maternal hair mercury level. NOS score was significantly associated with gestational age, but not with birth weight. The NOS subscores for muscle tone and reflexes showed no clear associations with any of the biomarkers studied A shortening of gestational age by 3-weeks was associated with a decrease in NOS similar to the one related to a 10-fold increase in cord blood mercury level. (Steuerwald, Weihe et al. 2000)

Table 4 Approximate exposure-effect relationships: neurological effects of methylmercury on adults and on the developing fetus

Effects in children (maternal exposure during pregnancy)	Mercury concentration in blood (µg/l or ppb)	Mercury concentration in hair (ppm)	Adults	Comments/Reference
Severe neurological abnormalities in children, including blindness, deafness and mental retardation; in Iraq epidemic, infant death occurred at a mean maternal hair concentration of 359 ppm.	1000 to 8000	250 to 2000	Exposures in Iraqi outbreak clearly associated with neurological effects: paresthesia (first symptom), constriction of visual field, ataxia, hearing loss, and death; increasing exposure associated with increased frequency and severity of symptoms.	Iraqi epidemic resulted from consumption of flour milled from methyl mercury-treated grain; acute exposure over a period of several months (winter 1971-72). (Marsh 1987)
Onset of severe clinical abnormalities in children as documented in the Iraqi epidemic.	400 to 800	100 to 200	Estimated onset of symptoms (paresthesia) in Niigata and Iraqi poisoning epidemics;	Considerable uncertainties in dose-response data from Niigata epidemic, as methods of analysis were not as sensitive as compared to later methods (Marsh 1987).

Table 4 continued. Approximate exposure-effects relationships

Effects in children (maternal exposure during pregnancy)	Mercury concentration in blood (µg/l or ppb)	Mercury concentration in hair (ppm)	Effects in Adults	Comments / Reference
	200	50	5 % risk of paresthesia, based on Iraqi poisoning epidemic. Review of all evidence suggests mild neurological effects occur in 11 to 31 % of adults with blood mercury level above 200 ppb Kosatsky and Foran 1996).	Estimation of exposure corresponding to onset of increased risk is sensitive to error in estimating background population frequency of condition. (IPCS-WHO 1990).
	40 to 200	10 to 50	Possible neuromotor and visual effects (see Amazon studies) Fine motor and tremor effects observed in exploratory study with 36 Cree participants (6 in high exposure group, 6 in low exposure group);	Suggestive evidence based on studies of limited size; also, considerable uncertainty regarding appropriate exposure index as observed effects might be related to earlier high exposure or to prenatal exposure. (Beuter and Edwards 1998; Lebel, Mergler et al. 1998; Beuter, Geoffroy et al. 1999a; Beuter, de Geoffroy et al. 1999b; Dolbec, Mergler et al. 2000).

Table 4 continued. Approximate exposure-effects relationships

Effects in children (maternal exposure during pregnancy)	Mercury concentration in blood (µg/l or ppb)	Mercury concentration in hair (ppm)	Effects in Adults	Comments / Reference
No clinical effects on children (Iraqi epidemic). Reduced performance on language, attention, and memory tests for Faroese children, but no neurological effects observed among Seychelles children.	40 to 80	10 to 20		(Marsh 1987) (Davidson, Myers et al. 1995; Myers, Marsh et al. 1995; Davidson, Myers et al. 1998; Myers, Davidson et al. 2003) Grandjean, Weihe et al. 1997.
Possible increase in diastolic and systolic blood pressure with increasing mercury at very low prenatal exposures; no further effect for exposures > 2 ppm (maternal hair) (Sorensen, Murata et al. 1999)	1 to 10 (cord blood)	1 to 2	Increased risk of myocardial infarction observed in two studies (Salonen, Seppanen et al. 1995; Guallar, Sanz-Gallardo et al. 2002)	Other studies indicate cardiovascular benefits of fish consumption, or are neutral with regard to risk of myocardial infarction and mercury exposure (NRC 2000)

Table 5 Methylmercury exposure levels (hair mercury level)

	Hair Mercury (ppm) Percentiles				
Group	10th	50th	90th	Max	Comments/ Reference
Women 15 to 39 yr Oujé-Bougoumou, **2002** (n=78)	<DL	0.70	2.80	7.40	(Dewailly and Nieboer 2003), Table 56
Women 15 to 39 yr Oujé-Bougoumou, **1993** (n=60)	-	2.5	4.0	8.8	(Dumont, Noel et al. 1998)
Men and women > 40 yr, Oujé-Bougoumou, **2002** (n=51)	0.90	3.90	10.8	13.9	(Dewailly and Nieboer 2003) Table 56
Men and women > 40 yr, Oujé-Bougoumou, **1993** (n=56)	-	8.2	21.4	28.1	(Dumont, Noel et al. 1998)
Women 15 to 39 yr Nemaska, **2002** (n=42)	<DL	0.20	1.10	2.70	(Dewailly and Nieboer 2003) Table 56
Women 15 to 39 yr Nemaska, **1993** (n=69)	-	2.5	4.3	11.9	(Dumont, Noel et al. 1998)
Adults> 40 yr, Nemaska **2002** (n=13)	0.70	2.80	6.50	8.80	(Dewailly and Nieboer 2003) Table 56
Adults > 40 yr, Nemaska **1993** (n=69)	-	8.2	17.3	23.4	(Dumont, Noel et al. 1998)
Japan : 5 districts Men (n=2020) Women (n=1666)		 ≈2.5 ≈1.5	 ≈ 8 ≈ 4	 26.8 25.7	(Yasutake, Matsumoto et al. 2003)

DL: detection limit, 0.2 ppm in Oujé-Bougoumou/ Nemaska surveys.

Table 6 Methylmercury exposure levels (blood mercury level)

Population	Mean Blood Hg Level (ppb)	Range (ppb)	Comments/ Reference
Adults			
Oujé-Bougoumou, 2002 (≥ 15 yr) (n=169)	7.48	0.4 to 75.2	(Dewailly and Nieboer 2003) Table 34
Nemaska, 2002 (≥ 15 yr) (n=71)	7.07	<DL to 108	(Dewailly and Nieboer 2003)Table 34
Southern Quebec (≥ 15 yr) (n=470)	1.03	<DL to 10.03	(Dewailly and Nieboer 2003)Table 34
Chippewa (Wisconsin) Random (n=175) and non-random (n=152) selection of participants;	No mean given; 20 % of individuals > 5 ppb	<1 to 33	(Peterson, Kanarek et al. 1994)
Southwest Quebec, Upper St. Lawrence region (n=289)	1.1	0.1 to 4.81	Random selection of participants (Mahaffey and Mergler 1998)
Women of childbearing age			
Oujé-Bougoumou, 2002 (women aged 15 to39) (n=78)	4.11	0.6 to 21.9	(Dewailly and Nieboer 2003)Table 34
Nemaska, 2002 (women aged 15 to39) (n=43)	2.70	<DL to 21.1	(Dewailly and Nieboer 2003)Table 34
Southern Quebec (women aged 15 to39) (n=103)	0.96	<DL to 4.61	(Dewailly and Nieboer 2003)Table 34

Table 6 continued. Methylmercury exposure levels (blood mercury level)			
Women of childbearing age			
Pregnant women from Puvirnituq (51.8%), Inukjuaq (29.7%), Kuujjuaraapik (8.5%) (n=135)	11.8	3.4 to 44.2	Women invited to participate following 1st prenatal visit.(Muckle, Ayotte et al. 2001)
US women (16 to 49), 1999 to 2000 (n=1709)	1.02	<DL to 7.13 (95th percentile)	Random sample for this age group, within the National Health and Nutrition Examination Survey (NHANES) (Schober, Sinks et al. 2003)

Table 7 Derivation of guidelines for recommended maximum intake.

Agency or Organization	Critical dose (NOAEL, LOAEL or BMDL)	Intake corresponding to critical dose	Uncertainty Factor	Recommended maximum intake of methylmercury (hair Hg concentration for a 60-kg person)	Comments
Health Canada, Bureau of Chemical Safety, Food Directorate, 27/04/98(Health Canada 1998)	Adults: LOAEL 0.2 ppm in blood (50 ppm in hair) based on the findings of Iraqi investigations Prenatal exposure: maternal hair 10 ppm, based on Faroe Islands study findings, and in light of results from Seychelles.	4.3 µg/kg bw-d 1 µg/kg bw-d	10 5	Tolerable daily intake (TDI)**: 0.47 µg/kg bw-d** for adults **(~5 ppm)**[14]. Provisional TDI of **0.2 µg/kg bw-d** for women of reproductive age, infants, young children **(~2 ppm)**.	The determination of uncertainty factor for the prenatal exposure guideline is not explained.
Environmental Protection Agency (US EPA 2002)	BMDL[15] of 46 to 79 ppb in maternal blood, based on measurement of several verbal and attention tests.	0.957 to 1.472 µg/kg bw-d	Total : 10, for toxicokinetic variability and for population differences.	Reference dose (RfD): **0.1 µg/kg bw-d** for everyone **(~1 ppm)**	The guideline is considered to apply to all members of the population.

[14] Health Canada commonly translates the TDI to a mercury exposure of 6 ppm in hair.
[15] The benchmark dose corresponds to an estimated 5% increase in the risk of obtaining an abnormally low score on a neuropsychological test (i.e. an estimated increase of 5% in the number of individuals obtaining an abnormally low score); the BMDL is the lower 95% confidence limit of the benchmark dose.

Agency or Organization	Critical dose (NOAEL, LOAEL or BMDL)	Intake corresponding to critical dose	Uncertainty Factor	Recommended maximum intake of methylmercury (hair Hg concentration for a 60-kg person)	Comments
National Research Council (NRC) of the National Academy of Sciences NRC (2000)	Critical dose based on developmental neurotoxic effects: BMDL of approximately 12 ppm maternal hair, from the results of Faroe Islands study (NRC 2000);	Approximately 1 µg/kg bw-d	10 to adjust for toxicokinetic variability and database insufficiency.	Reference dose (RfD): **0.1µg/kg bw-d**; RfD applies to everyone **(~1 ppm)**.	RfD : estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure (including sensitive individuals) that is likely to be without an appreciable risk of deleterious effects during a lifetime (NRC 2000).
FAO/WHO (IPCS-WHO 1990)	Critical dose (LOAEL) for adults is 200 ppb in blood (50 ppm in hair) based on analysis of data from the Iraq epidemic in 1971-72.	4.3 µg/kg bw-d	10	Permissible tolerable daily intake (PTDI): **0.47 µg/kg bw-d** for adults **(~5 ppm)**;	At the time of the evaluation (1990) data was judged to be insufficient to derive a permissible tolerable daily intake for pregnant women.
FAO/WHO, 2003 revision; based on summary of 61st meeting of the Joint Expert Committee on Food Additives (FAO/WHO 2003)	Critical dose of 14 ppm in maternal hair; composite value based on both Seychelles and Faroe Islands studies.	1.5 µg/kg bw-d	UF of 6.4	Permissible tolerable weekly intake (PTWI) of **1.6 µg/kg bw-wk** Permissible tolerable daily intake (PTDI) of **0.23 µg/kg bw-d (~2.5 ppm)**	At time of writing, only the Summary and Conclusions of the 61st meeting of JECFA were available. Guideline applies to all members of the population, even though it is based on effects from prenatal exposure (pers. comm. Mark Feeley, Health Canada).

Agency or Organization	Critical dose (NOAEL, LOAEL or BMDL)	Intake corresponding to critical dose	Uncertainty Factor	Recommended maximum intake (hair Hg concentration for a 60-kg person)	Comments
Agency for Toxic Substances and Disease Control (ATSDR) (ATSDR 1999)	Critical dose of 15.3 ppm in maternal hair based on the NOAEL of the Seychelles study (average maternal hair Hg level among high exposure mothers)	1.3 µg/kg/d	4.5 for intra-human variability, and possibility that a different testing protocol might have detected subtle effects in the Seychelles cohort.	Chronic minimal risk level (MRL) **0.3 µg/kg-d** applies to everyone (**~3 ppm)**.	The chronic minimal risk level: « an estimate of the daily human exposure that is likely to be without appreciable risk of adverse noncancer health effects over extended periods »(> 1yr). One guideline only.
KS Crump Group, Inc. (Shipp, Gentry et al. 2000)	BMDL of 21 ppm form the Seychelles study.	--	UF of 3, in consideration of the findings of positive effects in other studies (Faroe Islands and New Zealand). This gives a “no effects” level of 7 ppm.	Range of acceptable intakes: 0.3 to 1.1 µg/kg bw-d; RfD based on the 10th percentile of range, or **0.4 µg/kg-d (~4 ppm)**	The range of intakes was derived by a Monte Carlo analysis, which incorporates the statistical distributions of physiological parameters.

References

Akagi, H., E. S. Castillo, et al. (2000). "Health assessment for mercury exposure among schoolchildren residing near a gold processing and refining plant in Apokon, Tagum, Davao del Norte, Philippines." Sci Total Environ 259(1-3): 31-43.

Amorim, M. I., D. Mergler, et al. (2000). "Cytogenetic damage related to low levels of methyl mercury contamination in the Brazilian Amazon." An Acad Bras Cienc 72(4): 497-507.

ATSDR (1999). Toxicological Profile for Mercury (Update). Atlanta, Georgia, USA, US Department of Health & Human Services, Agency for Toxic Substances and Disease Registry: 617 pp. + app.

Axtell, C. D., C. Cox, et al. (2000). "Association between methylmercury exposure from fish consumption and child development at five and a half years of age in the Seychelles Child Development Study: an evaluation of nonlinear relationships." Environ Res 84(2): 71-80.

Barbeau, A., A. Nantel, et al. (1976). Etude sur les effets médicaux et toxicologiques du mercure organique dans le nord-ouest québécois. Montréal, Ministère des Affaires sociales du Québec: 278 pp.

Bellinger, D. C. (2000). "Effect modification in epidemiologic studies of low-level neurotoxicant exposures and health outcomes." Neurotoxicology & Teratology. 22(1): 133-40.

Beuter, A., A. de Geoffroy, et al. (1999b). "Analysis of rapid alternating movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits." Environmental Research Section A 80: 64-79.

Beuter, A. and R. Edwards (1998). "Tremor in Cree subjects exposed to methylmercury: a preliminary study." Neurotoxicology and Teratology 20(6): 581-589.

Beuter, A., d. Geoffroy, et al. (1999a). "Quantitative analysis of rapid pointing movements in Cree subjects exposed to mercury and in subjects with neurological deficits." Environmental Research Section A 80(50-63).

Budtz-Jorgensen, E., N. Keiding, et al. (2002). "Estimation of health effects of prenatal methylmercury exposure using structural equation models." Environmental Health: A Global Access Science Source 1(2): 22pp.

Carrier, G., M. Bouchard, et al. (2001). "A toxicokinetic model for predicting the tissue distribution and elimination of organic and inorganic mercury following exposure to methyl mercury in animals and humans. II. Application and validation of the model in humans." Toxicol Appl Pharmacol 171(1): 50-60.

Carrier, G., R. C. Brunet, et al. (2001). "A toxicokinetic model for predicting the tissue distribution and elimination of organic and inorganic mercury following exposure to methyl mercury in animals and humans. I. Development and validation of the model using experimental data in rats." Toxicol Appl Pharmacol 171(1): 38-49.

Carta, P., C. Flore, et al. (2003). "Sub-clinical neurobehavioral abnormalities associated with low level of mercury exposure through fish consumption." Neurotoxicology 24: 617-623.

Castoldi, A. F., T. Coccini, et al. (2001). "Neurotoxicity and molecular effects of methylmercury." Brain Res Bull 55(2): 197-203.

Choi, B. H. (1988). "The effects of methylmercury on the developing brain." Progress in neurobiology 32: 447-470.

Clarkson, T. W., L. Magos, et al. (2003). "The toxicology of mercury-Current exposures and clinical manifestations." The New England Journal of Medicine 349;18: 1731-1737.

Clarkson, T. W. (2002). "The three modern faces of mercury." Environ Health Perspect 110 Suppl 1: 11-23.

Cordier, S., M. Garel, et al. (2002). "Neurodevelopmental investigations among methylmercury-exposed children in French Guiana." Environ Res 89(1): 1-11.

Counter, S. A., L. H. Buchanan, et al. (1998). "Blood mercury and auditory neuro-sensory responses in children and adults in the Nambija gold mining area of Ecuador." Neurotoxicology 19(2): 185-96.

Davidson, P. W., J. Kost, et al. (2001). "Methylmercury and neurodevelopment: reanalysis of the Seychelles Child Development Study outcomes at 66 months of age." Journal of the American Medical Association 285(10): 1291-3.

Davidson, P. W., D. Palumbo, et al. (2000). "Neurodevelopmental outcomes of Seychellois children from the pilot cohort at 108 months following prenatal exposure to methylmercury from a maternal fish diet." Environ Res 84(1): 1-11.

Davidson, P. W., G. J. Myers, et al. (1999a). "Association between prenatal exposure to methylmercury and developmental outcomes in Seychellois children: effect modification by social and environmental factors." Neurotoxicology 20(5): 833-41.

Davidson, P. W., G. J. Myers, et al. (1999b). "Effects of methylmercury exposure on neurodevelopment, In reply." Journal of the American Medical Association 281(10): 897.

Davidson, P. W., G. J. Myers, et al. (1998). "Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment." Journal of the American Medical Association: 701-707.

Davidson, P. W., G. J. Myers, et al. (1995). "Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months." Neurotoxicology. 16(4): 677-88.

Department of National Health and Welfare (1979). Methylmercury in Canada. Exposure of Indian and Inuit Residents to Methylmercury in the Canadian Environment. Ottawa, Canada, Medical Services Branch, Department of National Health and Welfare: 200pp.

Dewailly, E. and E. Nieboer (2003). Exposure and Preliminary Health Assessments of the Oujé-Bougoumou Cree Population to Mine Tailings Residues. Québec, INSPQ-CHUQ, McMaster University.

Dolbec, J., D. Mergler, et al. (2000). "Methylmercury exposure affects motor performance of a riverine population of the Tapajos river, Brazilian Amazon." Int Arch Occup Environ Health 73(3): 195-203.

Doré, F. Y., S. Goulet, et al. (2001). "Neurobehavioral changes in mice treated with methylmercury at two different stages of fetal development." Neurotoxicol Teratol 23: 463-472.

Dumont, C., M. Girard, et al. (1998). "Mercury levels in the Cree population of James Bay, Quebec, from 1988 to 1993/94.[comment]." CMAJ Canadian Medical Association Journal. 158(11): 1439-45.

Dumont, C., F. Noel, et al. (1998). James Bay Mercury Agreement (1986) Health Component. 1987-1997 Activity Report. Chisasibi, Quebec, Canada, Cree Board of Health and Social Services of James Bay: 62pp. + app.

FAO/WHO (2003). Joint FAO/WHO Expert Committee on Food Additives, Summary and Conclusions of the 61st Meeting, Rome, 10-19 June 2003.

Fukuda, Y., K. Ushijima, et al. (1999). "An analysis of subjective complaints in a population living in a methylmercury-polluted area." Environ Res 81(2): 100-7.

Futatsuka, M., T. Kitano, et al. (2000). "Health surveillance in the population living in a methyl mercury-polluted area over a long period." Environ Res 83(2): 83-92.

Futatsuka, M., T. Kitano, et al. (1996). "An epidemiological study on diabetes mellitus in the population living in a methyl mercury polluted area." J Epidemiol 6(4): 204-8.

Grandjean, P., R. F. White, et al. (2003). "Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood." Ambul Pediatr 3(1): 18-23.

Grandjean, P., R. F. White, et al. (2001). "Impact of contrast sensitivity performance on visually presented neurobehavioral tests in mercury-exposed children." Neurotoxicol Teratol 23(2): 141-6.

Grandjean, P. and R. F. White (1999). "Effects of methylmercury exposure on neurodevelopment." Journal of the American Medical Association 281(10): 896; author reply 897.

Grandjean, P., E. Budtz-Jorgensen, et al. (1999). "Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years." Am J Epidemiol 150(3): 301-5.

Grandjean, P., R. F. White, et al. (1999). "Methylmercury neurotoxicity in Amazonian children downstream from gold mining." Environ Health Perspect 107(7): 587-91.

Grandjean, P., P. Weihe, et al. (1998). "Cognitive performance of children prenatally exposed to "safe" levels of methylmercury." Environmental Research 77(2): 165-172.

Grandjean, P., P. Weihe, et al. (1997). "Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury." Neurotoxicol Teratol 19(6): 417-28.

Grandjean, P., P. Weihe, et al. (1995). "Milestone development in infants exposed to methylmercury from human milk." Neurotoxicology. 16(1): 27-33.

Grandjean, P. and P. Weihe (1993). "Neurobehavioral effects of intrauterine mercury exposure: potential sources of bias." Environmental Research. 61(1): 176-83.

Grieg, R. A. and H. L. Seagran (1970). Survey of mercury concentrations in fishes of Lakes St.Clair, Erie, Huron. Environmental Mercury Contamination. R. Hartung and B. Dinman. Ann Arbor, MI, Ann Arbor Science Publishers Inc.

Guallar, E., M. I. Sanz-Gallardo, et al. (2002). "Mercury, fish oils, and the risk of myocardial infarction." N Engl J Med 347(22): 1747-54.

Harada, M., J. Nakanishi, et al. (2001). "Mercury pollution in the Tapajos River basin, Amazon: mercury level of head hair and health effects." Environ Int 27(4): 285-90.

Harada, M., J. Nakanishi, et al. (1998). "The present mercury contents of scalp hair and clinical symptoms in inhabitants of the Minamata area." Environ Res 77(2): 160-4.

Harris, H. H., I. J. Pickering, et al. (2003). "The chemical form of mercury in fish." Science 301: 1203.

Health Canada (1999). Methylmercury in Canada. Exposure of First Nations and Inuit Residents to Methylmercury in the Canadian Environment, Volume 3. Ottawa, Canada, Medical Services Branch, Health Canada: 73pp.

Health Canada (1998). Provisional Tolerable Daily Intake for Methylmercury. Ottawa, Health Canada Bureau of Chemical Safety, Food Directorate.

Huang, L.-S., C. Cox, et al. (2003). "Using measurement error models to assess effects of prenatal and postnatal methylmercury exposure in the Seychelles Child Development Study." Envrionmental Research 93: 115-122.

Igata, A. (1993). "Epidemiological and clinical features of Minamata disease." Environmental Research 63: 157-169.

IPCS-WHO (1990). Environmental Health Criteria 101, Methylmercury. Geneva, International Programme on Chemical Safety, World Health Organization: 144pp.

Jacobson, J. L. (2001). "Contending with contradictory data in a risk assessment context: the case of methylmercury." Neurotoxicology 22(5): 667-75.

Kosatsky, T. and P. Foran (1996). "Do historic studies of fish consumers support the widely accepted LOEL for methylmercury in adults?" Neurotoxicology 17(1): 177-86.

Lebel, J., D. Mergler, et al. (1998). "Neurotoxic effects of low-level methylmercury contamination in the Amazonian Basin." Environ Res 79(1): 20-32.

Lebel, J., D. Mergler, et al. (1996). "Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury." Neurotoxicology 17(1): 157-67.

Mahaffey, K. R. and D. Mergler (1998). "Blood levels of total and organic mercury in residents of the upper St. Lawrence River basin, Quebec: association with age, gender, and fish consumption." Environ Res 77(2): 104-14.

Marsh, D. O. (1987). Dose-response relationships in humans: methyl mercury epidemics in Japan and Iraq. The toxicity of Methyl Mercury. C. U. Eccles and Z. Annau. Baltimore, MD, The Johns Hopkins University Press: 45-53.

Marsh, D. O., T. W. Clarkson, et al. (1995). "The Seychelles study of fetal methylmercury exposure and child development: introduction." Neurotoxicology. 16(4): 583-96.

McKeown-Eyssen, G. E. and J. Ruedy (1983). "Methylmercury exposure in northern Quebec: I. Neurologic findings in adults." Am J Epidemiol 118: 461-469.

McKeown-Eyssen, G. E., J. Ruedy, et al. (1983). "Methylmercury exposure in northern Quebec: II. Neurologic findings in children." Am J Epidemiol 118: 470-479.

Mergler, D. (2002). "Review of neurobehavioral deficits and river fish consumption from the Tapajos (Brazil) and St. Lawrence (Canada)." Environmental Toxicology and Pharmacology 00 (2002): 1-7.

Muckle, G., P. Ayotte, et al. (2001). "Prenatal exposure of the northern Quebec Inuit infants to environmental contaminants." Environ Health Perspect 109(12): 1291-9.

Murata, K., P. Weihe, et al. (1999). "Evoked potentials in Faroese children prenatally exposed to methylmercury." Neurotoxicol Teratol 21(4): 471-2.

Murata, K., P. Weihe, et al. (1999). "Delayed evoked potentials in children exposed to methylmercury from seafood." Neurotoxicol Teratol 21(4): 343-8.

Myers, G., P. W. Davidson, et al. (2003). "Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study." The Lancet 361: 1667-8; 1686-92.

Myers, G. J., P. W. Davidson, et al. (2000). "Secondary analysis from the Seychelles Child Development Study: the child behavior checklist." Environ Res 84(1): 12-9.

Myers, G. J., P. W. Davidson, et al. (1997). "Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles Child Development Study." Neurotoxicology 18(3): 819-29.

Myers, G. J., P. W. Davidson, et al. (1995). "Summary of the Seychelles child development study on the relationship of fetal methylmercury exposure to neurodevelopment." Neurotoxicology. 16(4): 711-16.

Myers, G. J., D. O. Marsh, et al. (1995). "A pilot neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet." Neurotoxicology. 16(4): 629-38.

Myers, G. J., D. O. Marsh, et al. (1995). "Main neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: outcome at six months." Neurotoxicology. 16(4): 653-64.

NRC (2000). Toxicological Effects of Methylmercury. Washington, DC, National Research Council, National Academy of Sciences: 344 pp.

Nriagu, J. O. (1989). "A global assessment of natural sources of atmospheric trace metals." Nature 338: 47-49.

Palumbo, D. R., C. Cox, et al. (2000). "Association between prenatal exposure to methylmercury and cognitive functioning in Seychellois children: a reanalysis of the McCarthy Scales of Children's Ability from the main cohort study." Environ Res 84(2): 81-8.

Peterson, D. E., M. S. Kanarek, et al. (1994). "Fish consumption patterns and blood mercury levels in Wisconsin Chippewa Indians." Archives of Environmental Health. 49(1): 53-8.

Plante, M. and S. Babo (2003). "Mercury and the risk of myocardial infarction.[comment]." New England Journal of Medicine. 348(21): 2151-4; author reply 2151-4.

Sakamoto, M., A. Nakano, et al. (2001). "Declining Minamata male birth ratio associated with increased male fetal death due to heavy methylmercury pollution." Environ Res 87(2): 92-8.

Salonen, J. T., K. Seppanen, et al. (1995). "Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men - response." Circulation 92(8): 2355-2356.

Schetagne, R. and R. Verdon (1999). Post-impoundment evolution of fish mercury levels at the La Grande Complex, Québec, Canada (from 1978-1996). Mercury in the Biogeochemical Cycle. Natural Environments and Hydroelectric Reservoirs of Northern Québec. M. Lucotte, R. Schetagne, N. Thérien, C. Langlois and A. Tremblay. Berlin, Springer-Verlag: 235-258.

Schober, S. E., T. H. Sinks, et al. (2003). "Blood mercury levels in US children and women of childbearing age, 1999-2000." Journal of the American Medical Association 289(13): 1667-74.

Shipp, A., M., P. R. Gentry, et al. (2000). "Determination of a site-specific reference dose for methylmercury for fish-eating populations." Toxicology and Industrial Health 16: 335-438.

Sorensen, N., K. Murata, et al. (1999). "Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age." Epidemiology 10(4): 370-5.

Spitzer, W. O., D. W. Baxter, et al. (1988). "Methylmercury and the health of autochthons in northwest Quebec." Clinical & Investigative Medicine 11(2): 71-97.

Stern, A. H. and A. E. Smith (2003) “An assessment of the cord blood:maternal blood methylmercury ratio: Implications for risk assessment.” Environmental Health Perspectives 111(12)1465-1470.

Steuerwald, U., P. Weihe, et al. (2000). "Maternal seafood diet, methylmercury exposure, and neonatal neurologic function." J Pediatr 136(5): 599-605.

Tsubaki, T. and K. Irukayama (1977). History and Background. Minamata Disease, Methylmercury poisoning in Minamata and Niigata, Japan. T. Tsubaki and K. Irukayama. Amsterdam, Elsevier Scientific Publishing Co.: 317pp.

Weihe, P., P. Grandjean, et al. (1996). "Health implications for Faroe islanders of heavy metals and PCBs from pilot whales." Sci Total Environ 186(1-2): 141-8.

Wheatley, B., A. Barbeau, et al. (1979). "Methylmercury poisoning in Canadian Indians -- the elusive diagnosis." Le Journal canadien des sciences neurologiques 6(4): 417-422.

Wheatley, B., L. Chan, et al. (2001). Methylmercury in Fish and Sea Mammals: Risk-Benefit Assessment. Part 4: Risk-Benefit Assessment: Summary and Recommendations., Eco-Anth Consulting, Centre for Indigenous Peoples' Nutrition and Environment of McGill University, University of Montreal.

Yasutake, A., M. Matsumoto, et al. (2003). "Current hair mercury levels in Japanese: survey in five districts." Tohoku J Exp Med 199(3): 161-9.

Yokoo, E. M., G. Valente, et al. (2003). "Low level methylmercury exposure affects neuropsychological function in adults." Environmental Health: A Global Access Science Source 2(8): 11pp.

Yoshizawa, K., E. B. Rimm, et al. (2002). "Mercury and the risk of coronary heart disease in men." N Engl J Med 347(22): 1755-60.

Young, J. F., W. D. Wosilait, et al. (2001). "Analysis of methylmercury disposition in humans utilizing a PBPK model and animal pharmacokinetic data." J Toxicol Environ Health A 63(1): 19-52.

Appendices

Appendix A: Complete bibliography

Appendix B: Methodology for methylmercury literature search

Appendix C: Description of neuropsychological tests used in the Seychelles and Faroe Islands studies.

Bibliography[16]

Akagi, H., E. S. Castillo, et al. (2000). "Health assessment for mercury exposure among schoolchildren residing near a gold processing and refining plant in

Apokon, Tagum, Davao del Norte, Philippines." Sci Total Environ **259**(1-3): 31-43.

Amler, R. W., J. A. Lybarger, et al. (1994). "Adoption of an adult environmental neurobehavioral test battery." Neurotoxicology & Teratology. **16**(5): 525-30.

Amorim, M. I., D. Mergler, et al. (2000). "Cytogenetic damage related to low levels of methyl mercury contamination in the Brazilian Amazon." An Acad Bras Cienc **72**(4): 497-507.

Anger, W. K., R. Letz, et al. (1994). "Neurobehavioral test methods for environmental health studies of adults." Neurotoxicology & Teratology. **16**(5): 489-97.

Anonymous (2000). "Current practices for assessing risk for developmental defects and their limitations." Scientific Frontiers in Developmental Toxicology and Risk Assessment: 26-57.

Archibald, C. P. and T. Kosatsky (1991). "Public Health Response to an Identified Environmental Toxin: Managing Risks to the James Bay Related to Cadmium in Caribou and Moose." Canadian Journal of Public Health **82**(January/February): 22-26.

Aschner, M. (2001). "Mercury toxicity." J Pediatr **138**(3): 450-1.

ATSDR (1999). Toxicological Profile for Mercury (Update). Atlanta, Georgia, USA, US Department of Health & Human Services, Agency for Toxic Substances and Disease Registry**:** 617 pp. + app.

Auger, N., O. Kofman, et al. (2002). "Low-level methylmercury exposure as a risk factor for neurologic abnormalities in adults." unpublished (as of April/2003).

Axtell, C. D., C. Cox, et al. (2000). "Association between methylmercury exposure from fish consumption and child development at five and a half years of age in the Seychelles Child Development Study: an evaluation of nonlinear relationships." Environ Res **84**(2): 71-80.

Babi, D., M. Vasjari, et al. (2000). "Some results on Hg content in hair in different populations in Albania." Sci Total Environ **259**(1-3): 55-60.

Barbeau, A., A. Nantel, et al. (1976). Etude sur les effects médicaux et toxicologiques du mercure organique dans le nord-ouest québécois. Montreal, Ministère des Affaires sociales du Québec**:** 278 pp.

Barnes, D. G. and M. Dourson (1988). "Reference dose (RfD): description and use in health risk assessments." Regulatory Toxicology & Pharmacology. **8**(4): 471-86.

Bartell, S. M., R. A. Ponce, et al. (2000). "Human variability in mercury toxicokinetics and steady state biomarker ratios." Environ Res **84**(2): 127-32.

Bellavance, F. (1998). Study of the relationship between the mercury exposure of the head of a household and the other members of the family. Montreal,
Department of Epidemiology and Biostatistics, McGill University.

Belles-Isles, M., P. Ayotte, et al. (2002). "Cord blood lymphocyte functions in newborns from a remote maritime population exposed to organochlorines and methylmercury." J Toxicol Environ Health A **65**(2): 165-82.

Bellinger, D. C. (2000). "Effect modification in epidemiologic studies of low-level neurotoxicant exposures and health outcomes." Neurotoxicology & Teratology. **22**(1): 133-40.

Bellinger, D. C. (2003). "Perspectives on incorporating human neurobehavioral end points in risk assessments." Risk Anal **23**(1): 163-74.

[16] The bibliography includes all articles retrieved and consulted during the literature searches; these may or may not be cited in the present report.

Health Effects of Methylmercury, Appendix A

Berry, M. R. (1997). "Advances in dietary exposure research at the united states environmental protection agency national exposure research laboratory." Journal of Exposure Analysis and Environmental Epidemiology **7**(1): 3-16.

Beuter, A. (1997). Validation of measures evaluating the neuromotor system following chronic exposure to methylmercury. Montreal, Centre for Nonlinear Dynamics in Physiology and Medicine, Department of Physiology, McGill University.

Beuter, A., G. A. de, et al. (1999). "Analysis of rapid alternating movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits." Environ Res **80**(1): 64-79.

Beuter, A., G. A. de, et al. (1999). "Quantitative analysis of rapid pointing movements in Cree subjects exposed to mercury and in subjects with neurological deficits." Environ Res **80**(1): 50-63.

Beuter, A. and R. Edwards (1998). "Tremor in Cree subjects exposed to methylmercury: a preliminary study." Neurotoxicology and Teratology **20**(6): 581-589.
Blanchet, C., E. Dewailly, et al. (2000). "Contribution of selected traditional and market foods to the diet of Nunavik Inuit women." Journal of the Canadian Dietetic Association **61**(2): 50-59.

Boischio, A. A. and D. Henshel (2000). "Fish consumption, fish lore, and mercury pollution--risk communication for the Madeira River people." Environ Res **84**(2): 108-26.

Boischio, A. A. and D. S. Henshel (1996). "Risk assessment of mercury exposure through fish consumption by the riverside people in the Madeira Basin, Amazon, 1991." Neurotoxicology **17**(1): 169-75.

Boischio, A. A. and D. S. Henshel (2000). "Linear regression models of methyl mercury exposure during prenatal and early postnatal life among riverside people along the upper Madeira river, Amazon." Environ Res **83**(2): 150-61.

Brent, J. (2001). "Toxicologists and the assessment of risk: the problem with mercury (commentary)." J Toxicol Clin Toxicol **39**(7): 707-10.

Buck, G. M., G. P. Tee, et al. (2003). "Maternal fish consumption and infant birth size and gestation: New York State angler cohort study." Environmental Health: A Global Access Science Source **2**(7): 9pp.

Budtz-Jorgensen, E., N. Keiding, et al. (2002). "Estimation of health effects of prenatal methylmercury exposure using structural equation models." Environmental Health: A Global Access Science Source **1**(2): 22pp.

Burger, J. (2002). "Consumption Patterns and Why People Fish." Environmental Research Section A **90**: 125-135.

Burger, J., C. Dixon, et al. (2003). "Effect of deep-frying fish on risk from mercury." Journal of Toxicology and Environmental Health, Part A **66**: 817-828.

Burger, J. and L. Waishwell (2000). "Are we reaching the target audience? Evaluation of a fish fact sheet." The Science of the Total Environment **277**: 77-86.

Carrier, G., M. Bouchard, et al. (2001). "A toxicokinetic model for predicting the tissue distribution and elimination of organic and inorganic mercury following exposure to methyl mercury in animals and humans. II. Application and validation of the model in humans." Toxicol Appl Pharmacol **171**(1): 50-60.

Carrier, G., R. C. Brunet, et al. (2001). "A toxicokinetic model for predicting the tissue distribution and elimination of organic and inorganic mercury following exposure to methyl mercury in animals and humans. I. Development and validation of the model using experimental data in rats." Toxicol Appl Pharmacol **171**(1): 38-49.

Carrington, C. D. and M. P. Bolger (2002). "An exposure assessment for methylmercury from seafood for consumers in the United States." Risk Anal **22**(4): 689-99.

Carta, P., C. Flore, et al. (2003). "Sub-clinical neurobehavioral abnormalities associated with low level of mercury exposure through fish consumption." Neurotoxicology **24**: 617-623.

Castoldi, A. F., T. Coccini, et al. (2001). "Neurotoxicity and molecular effects of methylmercury." Brain Res Bull **55**(2): 197-203.

Chakrabarti, S. K., H. D. Durham, et al. (1997). Development of biological markers for monitoring neurotoxicity due to methylmercury exposure. Montreal, Département de médecine du travail et hygiène du milieu, Faculté de médecine, Université de Montréal.

Chan, H. M., C. Kim, et al. (1995). "Assessment of dietary exposure to trace metals in Baffin Inuit food." Environmental Health Perspectives. **103**(7-8): 740-6.

Health Effects of Methylmercury, Appendix A

Chan, H. M., M. Trifonopoulos, et al. (1999). "Consumption of freshwater fish in Kahnawake: risks and benefits." Environ Res **80**(2 Pt 2): S213-S222.

Chapman, L. and H. M. Chan (2000). "The influence of nutrition on methyl mercury intoxication." Environ Health Perspect **108 Suppl 1**: 29-56.

Chevalier, G., C. Dumont, et al. (1997). "Mercury in northern Québec: role of the Mercury Agreement and status of research and monitoring." Water, Air, and Soil Pollution **97**: 75-84.

Choi, B. H. (1988). "The effects of methylmercury on the developing brain." Progress in neurobiology **32**: 447-470.

Clarkson, T. (1998). "Methylmercury and fish consumption: weighing the risks." Cmaj **158**(11): 1465-6.

Clarkson, T. W. (2002). "The three modern faces of mercury." Environ Health Perspect **110 Suppl 1**: 11-23.

Clarkson, T. W., L. Magos, et al. (2003). "The toxicology of mercury-Current exposures and clinical manifestations." The New England Journal of Medicine **349;18**: 1731-1737.
Clarkson, T. W. and J. J. Strain (2003). "Nutritional factors may modify the toxic action of methyl mercury in fish-eating populations." Journal of Nutrition **133**(5 Suppl 1): 1539S-1543S.

Clément, D. (1992). The Cree, Fish and Mercury. Report on a case study conducted at Chisasibi. Montreal, Canada, Castonguay, Dandenault, and Associates, Inc.**:** 166pp.

Clewell, H. J., J. M. Gearhart, et al. (1999). "Evaluation of the uncertainty in an oral reference dose for methylmercury due to interindividual variability in pharmacokinetics." Risk Anal **19**(4): 547-58.

Committee, J. B. a. N. Q. N. H. R. (1982). The Wealth of the Land. Wildlife Harvests by the James Bay Cree, 1972-73 to 1978-79. Quebec City, Canada, James Bay and Northern Quebec Native Harvesting Research Committee**:** 342pp. + app.

Cordier, S., M. Garel, et al. (2002). "Neurodevelopmental investigations among methylmercury-exposed children in French Guiana." Environ Res **89**(1): 1-11.

Counter, S. A. (2003). "Neurophysiological anomalies in brainstem responses of mercury-exposed children of Andean gold miners." J Occup Environ Med **45**(1): 87-95.

Counter, S. A., L. H. Buchanan, et al. (1998). "Blood mercury and auditory neuro-sensory responses in children and adults in the Nambija gold mining area of Ecuador." Neurotoxicology **19**(2): 185-96.

Crump, K. S., L. C. Van, et al. (2000). "Benchmark concentrations for methylmercury obtained from the Seychelles Child Development Study." Environ Health Perspect **108**(3): 257-63.

Dallaire, F., E. Dewailly, et al. (2002). "Temporal trends of organochlorine concentrations in umbilical cord blood of newborns from the Lower North Shore of the St. Lawrence River (Québec, Canada)." Environ Health Perspect **110**(8): 835-838.

Davidson, P. W., J. Kost, et al. (2001). "Methylmercury and neurodevelopment: reanalysis of the Seychelles Child Development Study outcomes at 66 months of age." Jama **285**(10): 1291-3.

Davidson, P. W., G. J. Myers, et al. (1998). "Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment." Journal of the American Medical Association: 701-707.
Davidson, P. W., G. J. Myers, et al. (1999b). "Effects of methylmercury exposure on neurodevelopment, In reply." Journal of the American Medical Association **281**(10): 897.

Davidson, P. W., G. J. Myers, et al. (1995). "Neurodevelopmental test selection, administration, and performance in the main Seychelles child development study." Neurotoxicology. **16**(4): 665-76.

Davidson, P. W., G. J. Myers, et al. (1995). "Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months." Neurotoxicology. **16**(4): 677-88.

Davidson, P. W., G. J. Myers, et al. (1999a). "Association between prenatal exposure to methylmercury and developmental outcomes in Seychellois children: effect modification by social and environmental factors." Neurotoxicology **20**(5): 833-41.

Davidson, P. W., D. Palumbo, et al. (2000). "Neurodevelopmental outcomes of Seychellois children from the pilot cohort at 108 months following prenatal exposure to methylmercury from a maternal fish diet." Environ Res **84**(1): 1-11.

Health Effects of Methylmercury, Appendix A

Davidson, P. W., B. Weiss, et al. (2000). "Evaluation of techniques for assessing neurobehavioral development in children." Neurotoxicology **21**(6): 957-72.

Daviglus, M. L., J. Stamler, et al. (1997). "Fish consumption and the 30-year risk of fatal myocardial infarction." New England Journal of Medicine **336**(15): 1046-1053.

Dellinger, J. A. (2003). "Limiting health risks from fish consumption by GL tribal members." unpublished (as of April/2003).

Department of National Health and Welfare (1979). Methylmercury in Canada. Exposure of Indian and Inuit Residents to Methylmercury in the Canadian Environment. Ottawa, Canada, Medical Services Branch, Department of National Health and Welfare**:** 200pp.

Department of National Health and Welfare (1984). Methylmercury in Canada. Exposure of Indian and Inuit Residents to Methylmercury in the Canadian Environment, Volume 2. Ottawa, Canada, Medical Services Branch, Department of National Health and Welfare**:** 164pp.

Dewailly, E., C. Blanchet, et al. (2002). "Cardiovascular disease risk factors and n-3 fatty acid status in the adult population of James Bay Cree." American Journal of Clinical Nutrition. **76**(1): 85-92.

Dewailly, E. and E. Nieboer (2003). Exposure and Preliminary Health Assessments of the Oujé-Bougoumou Cree Population to Mine Tailings Residues. Québec, INSPQ-CHUQ, McMaster University.

Dolbec, J., D. Mergler, et al. (2001). "Sequential analysis of hair mercury levels in relation to fish diet of an Amazonian population, Brazil." The Science of the Total Environment **271**: 87-97.

Dolbec, J., D. Mergler, et al. (2000). "Methylmercury exposure affects motor performance of a riverine population of the Tapajos river, Brazilian Amazon." Int Arch Occup Environ Health **73**(3): 195-203.

Doré, F. Y., S. Goulet, et al. (2001). "Neurobehavioral changes in mice treated with methylmercury at two different stages of fetal development." Neurotoxicol Teratol **23**: 463-472.

Dorea, J. G. (2003). "Fish are central in the diet of Amazonian riparians: should we worry about their mercury concentrations?" Environmental Research **92**: 232-244.

Dorea, J. G. and A. C. Barbosa (2003). "Maternal mercury transfer: Letter to the editor." Envrionmental Research **93**: 113-114.

Dourson, M. L., A. E. Wullenweber, et al. (2001). "Uncertainties in the reference dose for methylmercury." Neurotoxicology **22**(5): 677-89.

Drexler, H. and K. H. Schaller (1998). "The mercury concentration in breast milk resulting from amalgam fillings and dietary habits." Environ Res **77**(2): 124-9.

Dumont "Seuil de toxicité et choix du seuil d'intervention."

Dumont, C., M. Girard, et al. (1998). "Mercury levels in the Cree population of James Bay, Quebec, from 1988 to 1993/94.[comment]." CMAJ Canadian Medical Association Journal. **158**(11): 1439-45.

Dumont, C., M. Girard, et al. (1998). "Mercury levels in the Cree population of James Bay, Quebec, from 1988 to 1993/94.[comment]." CMAJ Canadian Medical Association Journal. **158**(11): 1439-45.

Dumont, C., F. Noel, et al. (1998). James Bay Mercury Agreement (1986) Health Component. 1987-1997 Activity Report. Chisasibi, Quebec, Canada, Cree Board of Health and Social Services of James Bay**:** 62pp. + app.

Egeland, G. M. and J. P. Middaugh (1997). "Balancing fish consumption benefits with mercury exposure." Science **278**(5345): 1904-5.

Endo, T., Y Hotta, K Haraguchi, M Sakata (2003). "Mercury Contamination in the Red Meat of Whales and Dolphin Marketed for Human Consumption in Japan." Environmental Science and Technology **37**: 2681-2685.

EPA, Methylmercury - IRIS Summary, US EPA. **2003**.

EPA, (2001). Methylmercury, Integrated Risk Information System. **2003**.

FAO/WHO (2003). Joint FAO/WHO Expert Committee on Food Additives, Summary and Conclusions of the 61st Meeting, Rome, 10-19 June 2003.

Faubert, J. (1997). Evaluation of visual changes as a consequence of long-term ingestion of methylmercury among the James Bay Cree. Montreal.

Faustman, E. M., Gilbert S Omenn (2001). Chapter 4 - Risk Assessment. Casarett and Doull's Toxicology, 6th edition. C. D. Klaassen. New York, McGraw Hill.

Faustman, E. M., R. A. Ponce, et al. (2002). "Investigations of methylmercury-induced alterations in neurogenesis." Environ Health Perspect **110 Suppl 5**: 859-64.

Fowler, B. A. (2001). "Porphyrinurias induced by mercury and other metals." Toxicol Sci **61**(2): 197-8.

Francoeur, L.-G. (2003). Santé et écosystèmes sont intimement liés. Le Devoir. Montreal.

Fredriksson, A., L. Denker, et al. (1996). "Prenatal coexposure to metallic mercury vapour and methylmercury produce interactive behavioural changes in adult rats." Neurotoxicol Teratology **18**(2): 129-134.

Fukuda, Y., K. Ushijima, et al. (1999). "An analysis of subjective complaints in a population living in a methylmercury-polluted area." Environ Res **81**(2): 100-7.

Futatsuka, M., T. Kitano, et al. (2000). "Health surveillance in the population living in a methyl mercury-polluted area over a long period." Environ Res **83**(2): 83-92.

Futatsuka, M., T. Kitano, et al. (1996). "An epidemiological study on diabetes mellitus in the population living in a methyl mercury polluted area." J Epidemiol **6**(4): 204-8.

Gehle, K., Kristina Larson, Cherryll Ranger (2002). Appendix B: Important Issues Regarding Mercury. Pediatric Environmental Health. A. f. T. S. a. D. Registry and D. o. H. E. a. Promotion, US Department of Health and Human Services**:** 69-71.

Ginsberg, G. L. and B. F. Toal (2000). "Development of a single-meal fish consumption advisory for methyl mercury." Risk Anal **20**(1): 41-7.

Girard, M. and C. Dumont (1995). "Exposure of james bay cree to methylmercury during pregnancy for the years 1983-91." Water, Air, & Soil Pollution **80**(1-4): 13-19.

Girard, M., F. Noel, et al. (1996). "Varying mercury exposure with varying food source in a James Bay Cree community." Arctic Medical Research **55**: 69-74.

Goldman, L. R. and W. H. Farland (1998). "Methylmercury risks." Science **279**(5351): 640-1; author reply 641.

Goulet, S., F. Y. Dore, et al. (2003). "Neurobehavioral changes in mice chronically exposed to methylmercury during fetal and early postnatal development." Neurotoxicol Teratol **25**: 335-347.

Grandjean, P., E. Budtz-Jorgensen, et al. (2003). "Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls." Faseb J **17**(6): 699-701.

Grandjean, P., E. Budtz-Jorgensen, et al. (1999). "Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years." Am J Epidemiol **150**(3): 301-5.

Grandjean, P., Canice Nowlan (1997). Neurological development of seven-year-old children shows subtle delays from mercury in mothers' diet during pregnancy. **2003**.

Grandjean, P., P. J. Jorgensen, et al. (1994). "Human Milk as a Source of Methylmercury Exposure in Infants." Environ Health Perspect **102**(1): 74-7.

Grandjean, P., Stephen Gosden (1999). Exposure to mercury before birth may cause high blood pressure, Europa. **2003**.

Grandjean, P. and P. Weihe (1993). "Neurobehavioral effects of intrauterine mercury exposure: potential sources of bias." Environmental Research. **61**(1): 176-83.

Grandjean, P., P. Weihe, et al. (1992). "Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead." Archives of Environmental Health. **47**(3): 185-95.

Grandjean, P., P. Weihe, et al. (1995). "Milestone development in infants exposed to methylmercury from human milk." Neurotoxicology. **16**(1): 27-33.

Grandjean, P., P. Weihe, et al. (1999). "Health effects related to prenatal exposure to methylmercury." Toxicol Lett **109**(Suppl 1): 7.

Grandjean, P., P. Weihe, et al. (1998). "Cognitive performance of children prenatally exposed to "safe" levels of methylmercury." Environmental Research **77**(2): 165-172.

Health Effects of Methylmercury, Appendix A

Grandjean, P., P. Weihe, et al. (1997). "Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury." Neurotoxicol Teratol **19**(6): 417-28.

Grandjean, P. and R. F. White (1999). "Effects of methylmercury exposure on neurodevelopment." Jama **281**(10): 896; author reply 897.

Grandjean, P., R. F. White, et al. (1999). "Methylmercury neurotoxicity in Amazonian children downstream from gold mining." Environ Health Perspect **107**(7): 587-91.

Grandjean, P., R. F. White, et al. (2001). "Impact of contrast sensitivity performance on visually presented neurobehavioral tests in mercury-exposed children." Neurotoxicol Teratol **23**(2): 141-6.

Grandjean, P., R. F. White, et al. (1996). "Neurobehavioral epidemiology: Application in risk assessment." Environmental Health Perspectives **104**(SUPPL. 2): 397-400.

Grandjean, P., R. F. White, et al. (2000). "Methodological issues in assessing neurobehavioral effects of prenatal exposure to neurotoxicants." Neurotoxicology **21**(5): 888.

Grandjean, P., R. F. White, et al. (2003). "Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood." Ambul Pediatr **3**(1): 18-23.

Grieg, R. A. and H. L. Seagran (1970). Survey of mercury concentrations in fishes of Lakes St.Clair, Erie, Huron. Environmental Mercury Contamination. R.
Hartung and B. Dinman. Ann Arbor, MI, Ann Arbor Science Publishers Inc.

Guallar, E., M. I. Sanz-Gallardo, et al. (2002). "Mercury, fish oils, and the risk of myocardial infarction." N Engl J Med **347**(22): 1747-54.

Guggisberg, M., P. A. Hessel, et al. (2003). "Respiratory symptoms and exposure to wood smoke in an isolated northern community." Canadian Journal of Public Health **94**(5): 372-375.

Hallgren, C. G., G. Hallmans, et al. (2001). "Markers of high fish intake are associated with decreased risk of a first myocardial infarction." Br J Nutr **86**(3): 397-404.
Hamada, R., K. Arimura, et al. (1997). "Maternal-Fetal Mercury Transport and Fetal Methylmercury Poisoning." Met Ions Biol Syst **34**(0): 405-420.

Hansen, J. C. and G. Danscher (1997). "Organic mercury: an environmental threat to the health of dietary-exposed societies?" Rev Environ Health **12**(2): 107-16.

Harada, M., S. Nakachi, et al. (1999). "Monitoring of mercury pollution in Tanzania: relation between head hair mercury and health." Sci Total Environ **227**(2-3): 249-56.

Harada, M., J. Nakanishi, et al. (1998). "The present mercury contents of scalp hair and clinical symptoms in inhabitants of the Minamata area." Environ Res **77**(2): 160-4.

Harada, M., J. Nakanishi, et al. (2001). "Mercury pollution in the Tapajos River basin, Amazon: mercury level of head hair and health effects." Environ Int **27**(4): 285-90.

Harris, H. H., I. J. Pickering, et al. (2003). "The chemical form of mercury in fish." Science **301**: 1203.

Hayeur, G. (2001). Summary of Knowledge Acquired in Northern Environments from 1979 to 2000. Montreal, Hydro-Québec.

Health Canada (1999). Methylmercury in Canada. Exposure of First Nations and Inuit Residents to Methylmercury in the Canadian Environment, Volume 3. Ottawa, Canada, Medical Services Branch, Health Canada**:** 73pp.

Health Canada (1998). "Manuel sur la santé et l'environnement à l'intention des professionels de la santé."

HealthCanada (2002). Mercury and Human Health, Health Canada. **2003**.
Hightower, J. M. and D. Moore (2003). "Mercury levels in high-end consumers of fish." Environmental Health Perspectives **111**(4): 604-608.

Hoey, J. and B. Postl (1998). "Determinants--and determination.[comment]." CMAJ Canadian Medical Association Journal. **158**(11): 1467-8.

Hoover, S., R. Hill, et al. (1997). "Estimating risks from exposure to methylmercury: Application to first nations people in Canada." Water, Air and Soil Pollution **97**: 107-118.

Huang, L.-S., C. Cox, et al. (2003). "Using measurement error models to assess effects of prenatal and postnatal methylmercury exposure in the Seychelles Child Development Study." Envrionmental Research **93**: 115-122.
Igata, A. (1993). "Epidemiological and clinical features of Minamata disease." Environmental Research **63**: 157-169.

IPCS-WHO (1990). Environmental Health Criteria 101, Methylmercury. Geneva, International Programme on Chemical Safety, World Health Organization**:** 144pp.

Jacobson, J. L. (2001). "Contending with contradictory data in a risk assessment context: the case of methylmercury." Neurotoxicology **22**(5): 667-75.

Jones, K. and H. Klein (1999). "Lessons from 12 years of comparative risk projects." Annual Review of Public Health **20**: 159-172.

Kimmel, C. A. (2000). "The ability of EPA's testing guidelines to predict potential human developmental neurotoxicity." Neurotoxicology **21**(1-2): 252.

Kofman, O., D. Simard, et al. (1979). "Mercury intoxication of the nervous system in Canada (chronic Minamata Disease)." Le Journal canadien des sciences neurologiques **6**(3): p. 397.

Korogi, Y., M. Takahashi, et al. (1998). "MR findings of Minamata disease--organic mercury poisoning." J Magn Reson Imaging **8**(2): 308-16.

Kosatsky, T. and P. Foran (1996). "Do historic studies of fish consumers support the widely accepted LOEL for methylmercury in adults?" Neurotoxicology **17**(1): 177-86.

Krasnegor, N. A., D. A. Otto, et al. (1994). "Neurobehavioral test strategies for environmental exposures in pediatric populations." Neurotoxicology & Teratology. **16**(5): 499-509.

Larison, J. R., G. E. Likens, et al. (2000). "Cadmium toxicity among wildlife in the Colorado Rocky Mountains." Nature **406**(13 July 2000): 181-183.

Lebel, J., D. Mergler, et al. (1998). "Neurotoxic effects of low-level methylmercury contamination in the Amazonian Basin." Environ Res **79**(1): 20-32.

Lebel, J., D. Mergler, et al. (1996). "Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury." Neurotoxicology **17**(1): 157-67.

Lebel, J., M. Roulet, et al. (1997). "Fish diet and mercury exposure in a riparian Amazonian population." Water, Air and Soil Pollution **97**: 31-44.

Lipfert, F. W. (1997). "Estimating exposure to methylmercury: Effects of uncertainties." Water Air And Soil Pollution **97**(1-2): 119-145.
Lucchini, R., S. Calza, et al. (2003). "Application of a latent Variable Model for a Multicenter study on early effects due to mercury exposure." NeuroToxicology **24**: 605-616.

Lyketsos, C. G. (2003). "Should pregnant women avoid eating fish? Lessons from the Seychelles.[comment]." Lancet. **361**(9370): 1667-8.

MacIntosh, D. L., P. L. Williams, et al. (1997). "Evaluation of a food frequency questionnaire-food composition approach for estimating dietary intake of inorganic arsenic and methylmercury." Cancer Epidemiol Biomarkers Prev **6**(12): 1043-50.

Mahaffey, K. R. (1999). "Methylmercury: a new look at the risks." Public Health Rep **114**(5): 396-9, 402-13.

Mahaffey, K. R. (2000). "Recent advances in recognition of low-level methylmercury poisoning." Current Opinion in Neurology. **13**(6): 699-707.

Mahaffey, K. R. and D. Mergler (1998). "Blood levels of total and organic mercury in residents of the upper St. Lawrence River basin, Quebec: association with age, gender, and fish consumption." Environ Res **77**(2): 104-14.

Malm, O., P. Grandjean, et al. (1999). "Methylmercury toxicity in riverine children downstream from gold mining in the Amazon Basin, Brazil." Frontiers in Fetal Health **1**(6): 12-3.

Marien, K. (2002). "The importance of weight-normalized exposure data when issuing fish advisories for protection of public health." Environ Health Perspect **110**(7): 671-7.

Marien, K. and G. M. Patrick (2001). "Exposure analysis of five fish-consuming populations for overexposure to methylmercury." J Expo Anal Environ Epidemiol **11**(3): 193-206.

Health Effects of Methylmercury, Appendix A

Marsh, D. O. (1987). Dose-response relationships in humans: methyl mercury epidemics in Japan and Iraq. The toxicity of Methyl Mercury. C. U. Eccles and Z. Annau. Baltimore, MD, The Johns Hopkins University Press**:** 45-53.

Marsh, D. O., T. W. Clarkson, et al. (1995). "The Seychelles study of fetal methylmercury exposure and child development: introduction." Neurotoxicology. **16**(4): 583-96.

McGill University Methylmercury Study Group (1979). Epidemiological study of the effects of exposure to methylmercury on the health of individuals living in certain areas of the Province of Quebec, Final Report to the Steering Committee. Montreal, Canada, McGill University**:** Vol 1:93pp; Vol 2:221pp; Vol 3:338pp.
McKeown-Eyssen, G. E. and J. Ruedy (1983). "Methylmercury exposure in northern Quebec: I. Neurologic findings in adults." Am J Epidemiol **118**: 461-469.

McKeown-Eyssen, G. E. and J. Ruedy (1983). "Prevalence of neurological abnormality in Cree Indians exposed to methylmercury in northern Quebec."
Clinical & Investigative Medicine **6**(3): 161-169.

McKeown-Eyssen, G. E., J. Ruedy, et al. (1983). "Methylmercury exposure in northern Quebec: II. Neurologic findings in children." Am J Epidemiol **118**: 470-479.

Mergler, D. (2002). "Review of neurobehavioral deficits and river fish consumption from the Tapajos (Brazil) and St. Lawrence (Canada)." Environmental Toxicology and Pharmacology **00 (2002)**: 1-7.

Mergler, D., S. Belanger, et al. (1998). "Preliminary evidence of neurotoxicity associated with eating fish from the upper St. Lawrence River lakes." Neurotoxicology **19**(4-5): 691-702.

Mergler, D. and J. Dolbec (1998). Methylmercury exposure and neurotoxic effects in the Brazilian Amazon, Methylmercury Workshop Report, Response to questions by the study team for the Amazon studies.

Mirault, M.-E. (2003). TSRI # 286 - PERINATAL EXPOSURE TO MIXTURES OF POLYCHLORINATED BIPHENYLS AND METHYLMERCURY: EFFECTS ON BRAIN CELL DIFFERENTIATION AND NEUROBEHAVIORAL DEVELOPMENT, Health Canada - Toxic Substances Research Initiative. **2003**.

Montague, P. (1998). "Mercury: How much is safe?" Rachel's Environment & Health Weekly.

Muckle, G., P. Ayotte, et al. (2001). "Determinants of polychlorinated biphenyls and methylmercury exposure in Inuit women of childbearing age." Environ Health Perspect **109**(9): 957-63.

Muckle, G., P. Ayotte, et al. (2001). "Prenatal exposure of the northern Quebec Inuit infants to environmental contaminants." Environ Health Perspect **109**(12): 1291-9.

Murata, K., E. Budtz-Jorgensen, et al. (2002). "Benchmark dose calculations for methylmercury-associated delays on evoked potential latencies in two cohorts of children." Risk Anal **22**(3): 465-74.

Murata, K., P. Weihe, et al. (1999). "Evoked potentials in Faroese children prenatally exposed to methylmercury." Neurotoxicol Teratol **21**(4): 471-2.
Murata, K., P. Weihe, et al. (1999). "Delayed evoked potentials in children exposed to methylmercury from seafood." Neurotoxicol Teratol **21**(4): 343-8.

Myers, G., P. W. Davidson, et al. (2003). "Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study." The Lancet **361**: 1667-8; 1686-92.

Myers, G. J. and P. W. Davidson (1998). "Prenatal methylmercury exposure and children: neurologic, developmental, and behavioral research." Environ Health Perspect **106 Suppl 3**: 841-7.

Myers, G. J. and P. W. Davidson (2000). "Does methylmercury have a role in causing developmental disabilities in children?" Environ Health Perspect **108 Suppl 3**: 413-20.

Myers, G. J., P. W. Davidson, et al. (2000). "Twenty-seven years studying the human neurotoxicity of methylmercury exposure." Environ Res **83**(3): 275-85.

Myers, G. J., P. W. Davidson, et al. (1995). "Neurodevelopmental outcomes of Seychellois children sixty-six months after in utero exposure to methylmercury from a maternal fish diet: pilot study." Neurotoxicology. **16**(4): 639-52.

Myers, G. J., P. W. Davidson, et al. (1995). "Summary of the Seychelles child development study on the relationship of fetal methylmercury exposure to neurodevelopment." Neurotoxicology. **16**(4): 711-16.

Myers, G. J., P. W. Davidson, et al. (2000). "Secondary analysis from the Seychelles Child Development Study: the child behavior checklist." Environ Res **84**(1): 12-9.

Myers, G. J., P. W. Davidson, et al. (1998). "A review of methylmercury and child development." Neurotoxicology **19**(2): 313-28.

Myers, G. J., P. W. Davidson, et al. (1997). "Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles Child Development Study." Neurotoxicology **18**(3): 819-29.

Myers, G. J., D. O. Marsh, et al. (1995). "A pilot neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet." Neurotoxicology. **16**(4): 629-38.

Myers, G. J., D. O. Marsh, et al. (1995). "Main neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: outcome at six months." Neurotoxicology. **16**(4): 653-64.

Myers, R. A. and B. Worm (2003). "Rapid worldwide depletion of predatory fish communities." Nature **423**(15 May 2003): 280-283.

Nakagawa, R. (1995). "Concentration of mercury in hair of diseased people in Japan." Chemosphere **30**(1): 135-140.

Nakagawa, R. (1995). "Concentration of mercury in hair of Japanese people." Chemosphere **30**(1): 127-133.

Nakagawa, R., Y. Yumita, et al. (1997). "Total mercury intake from fish and shellfish by Japanese people." Chemosphere **35**(12): 2909-13.

Nakai, K. and H. Satoh (2002). "Developmental neurotoxicity following prenatal exposures to methylmercury and PCBs in humans from epidemiological studies." Tohoku J Exp Med **196**(2): 89-98.

Neumann, C. M., K. W. Kauffman, et al. (1997). "Methylmercury in fish from Owyhee Reservoir in southeast Oregon:scientific uncertainty and fish advisories." The Science of the Total Environment **204**: 205-214.

Nilsson, R., M. Tasheva, et al. (1993). "Why different regulatory decisions when the scientific information base is similar?--Human risk assessment." Regulatory Toxicology & Pharmacology. **17**(3): 292-332.

NRC (1996). Science and Judgment in Risk Assessment. Washington, D.C., National Academy of Sciences**:** 338 pp.

NRC (2000). Toxicological Effects of Methylmercury. Washington, DC, National Research Council, National Academy of Sciences**:** 344 pp.

Nriagu, J. O. (1989). "A global assessment of natural sources of atmospheric trace metals." Nature **338**: 47-49.

Oka, T., M. Matsukura, et al. (2003). "Autonomic nervous functions in fetal type Minamata disease patients: assessment of heart rate variability." Tohoku J Exp Med **198**(4): 215-21.

Oskarsson, A., I. Palminger Hallen, et al. (1998). "Risk assessment in relation to neonatal metal exposure." The analyst **123**: 19-23.

Palumbo, D. R., C. Cox, et al. (2000). "Association between prenatal exposure to methylmercury and cognitive functioning in Seychellois children: a reanalysis of the McCarthy Scales of Children's Ability from the main cohort study." Environ Res **84**(2): 81-8.

Panisset, M. and S. Gauthier (1998). Evaluation de la neurotoxicité du mercure chez les indien cris; standardisation de l'évaluation neurologique. Montreal, Centre McGill d'études sur le vieillissement, Hôpital Douglas, Verdun, Quebec.

Passos, C. J., D. Mergler, et al. (2003). "Eating tropical fruit reduces mercury exposure from fish consumption in the Barzilian Amazon." Environmental Research **93**: 123-130.

Pauletto, P., M. Puato, et al. (1996). "Blood pressure and atherogenic lipoprotein profiles of fish-diet and vegetarian villagers in Tanzania: the Lugalawa study." The Lancet **348**: 784-88.

Penn, A. (1978). The Distribution of Mercury, Selenium, and Certain Heavy Metals in Major Fish Species from Northern Quebec. A report on the Screening Programme for Mercury in Fish: Mistassini and Waswanipi Regions, Northwestern Quebec, Summer 1976. Montreal, Canada, The Grand Council of the Crees of Quebec**:** 395 pp.

Penn, A. (1996). An introductory essay on methyl mercury contamination in the James Bay territory, with special reference to the ecological setting, and related public health matters. Montreal, Canada, Cree Regional Authority.

Peterson, D. E., M. S. Kanarek, et al. (1994). "Fish consumption patterns and blood mercury levels in Wisconsin Chippewa Indians." Archives of Environmental Health. **49**(1): 53-8.

Health Effects of Methylmercury, Appendix A

Philbert, M. A., M. L. Billingsley, et al. (2000). "Mechanisms of injury in the central nervous system." Toxicol Pathol **28**(1): 43-53.

Pilgrim, W., W. Schroeder, et al. (2000). "Developing consensus: mercury science and policy in the NAFTA countries (Canada, the United States and Mexico)." Sci Total Environ **261**(1-3): 185-93.

Plante, M. and S. Babo (2003). "Mercury and the risk of myocardial infarction.[comment]." New England Journal of Medicine. **348**(21): 2151-4; author reply 2151-4.

Ponce, R. A., S. M. Bartell, et al. (2000). "Use of quality-adjusted life year weights with dose-response models for public health decisions: a case study of the risks and benefits of fish consumption." Risk Anal **20**(4): 529-42.

Porvari, P., M. Verta, et al. (2003). "Forestry practices increase mercury and methyl mercury output from boreal forest catchments." Environmental Science & Technology **37**(11): 2389-2393.
Québec, (1998). A Dietary Profile of the Cree, Santé Québec Health Survey of the James Bay Cree 1991: Food and Nutrition Intake. Montreal, Ministère de la
Santé et des Services Sociaux, Gouvernement du Québec**:** 91 pp.
Rasanen, L. and M. Mutanen (1995). "Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men." Circulation **92**(8): 2355.

Reuhl, K. R. (1997). "Mechanisms of Mehg Neurotoxicity During Development." Crisp Data Base National Institutes Of Health.

Reuhl, K. R. (2002). "Historical methylmercury exposure and developmental toxicity." Neurotoxicol Teratol **24**: 419-434.

Rhainds, M. (2003). Avis sur les valeurs seuils proposées à déclaration obligatoire par les laboratoires pour le mercure sanguin et urinaire. Québec, Institution national de santé publique du Québec**:** 9 pp.

Rice, D. and S. Barone (2000). "Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models." Environmental Health Perspectives **108**(Suppl 3): 511-533.

Rice, D. C. (2000). "Effects of methylmercury and PCBs: the Faroe Islands and related studies." Neurotoxicology **21**(1-2): 244.

Rice, D. C. (2000). "Identification of functional domains affected by developmental exposure to methylmercury: Faroe islands and related studies." Neurotoxicology **21**(6): 1039-44.

Rice, D. C. (2002). "EPA hazard assessment for methylmercury relies on recent epidemiological studies." Neurotoxicol Teratol **24**(3): 423-4.

Rice, D. C., R. Schoeny, et al. (2003). "Methods and rationale for derivation of a reference dose for methylmercury by the US EPA." Risk Analysis **23**(1): 107-115.

Rice, G., J. Swartout, et al. (2000). "Derivation of U.S. EPA's oral Reference Dose (RfD) for methylmercury." Drug Chem Toxicol **23**(1): 41-54.

Rohlman, D. S., W. K. Anger, et al. (2001). "Development of a neurobehavioral battery for children exposed to neurotoxic chemicals." Neurotoxicology **22**(5): 657-65.

Ruedy, J. (2001). "Methylmercury poisoning." Cmaj **165**(9): 1193-4.

Sakamoto, M., M. Kubota, et al. (2002). "Declining risk of methylmercury exposure to infants during lactation." Environ Res **90**(3): 185-9.

Sakamoto, M., A. Nakano, et al. (2001). "Declining Minamata male birth ratio associated with increased male fetal death due to heavy methylmercury pollution." Environ Res **87**(2): 92-8.

Salonen, J. T., K. Seppanen, et al. (1995). "Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men - response." Circulation **92**(8): 2355-2356.

Sanga, R. N., S. M. Bartell, et al. (2001). "Effects of uncertainties on exposure estimates to methylmercury: a Monte Carlo analysis of exposure biomarkers versus dietary recall estimation." Risk Anal **21**(5): 859-68.

Schetagne, R. and R. Verdon (1999). Post-impoundment evolution of fish mercury levels at the La Grande Complex, Québec, Canada (from 1978-1996). Mercury in the Biogeochemical Cycle. Natural Environments and Hydroelectric Reservoirs of Northern Québec. M. Lucotte, R. Schetagne, N. Thérien, C. Langlois and A. Tremblay. Berlin, Springer-Verlag**:** 235-258.

Schmidt, C. W. (1999). "Poisoning young minds." Environ Health Perspect **107**(6): A302-7.

Schober, S. E., T. H. Sinks, et al. (2003). "Blood mercury levels in US children and women of childbearing age, 1999-2000." Jama **289**(13): 1667-74.

Schoeny, R. (1996). "Use of genetic toxicology data in U.S. EPA risk assessment: the mercury study report as an example." Environ Health Perspect **104 Suppl 3**: 663-73.

Scott, R. T. (1993). Bringing Home Methylmercury: The construction of an authoritative object of knowledge for a Cree community in northern Quebec. Department of Anthropology. Montreal, Canada, McGill University**:** 102 + app.

Shipp, A., M., P. R. Gentry, et al. (2000). "Determination of a site-specific reference dose for methylmercury for fish-eating populations." Toxicology and Industrial Health **16**: 335-438.

Slikker, W., Jr., K. S. Crump, et al. (1996). "Biologically based, quantitative risk assessment of neurotoxicants." Fundam Appl Toxicol **29**(1): 18-30.

Smith, A. E. (2002). "Management and communication of risk: the Maine experience." Neurotoxicol Teratol **24**(3): 424.

Sorensen, N., K. Murata, et al. (1999). "Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age." Epidemiology **10**(4): 370-5.
Spitzer, W. O., D. W. Baxter, et al. (1988). "Methylmercury and the health of autochthons in northwest Quebec." Clinical & Investigative Medicine **11**(2): 71-97.

St-Amour G, M. D., Lafond J, Smargiassi A, Baldwin M, de Grosbois S (2002). Abstract # 19 - Fish Consumption And Contaminants During Pregnancy: Preliminary Data, Health Canada – Canadian Children's Environment Health Research Workshop – Ottawa, Mar. 17-19, 2002 – Report on Key Findings, ANNEX III - Poster Session Abstracts. **2003**.

Stern, A. H. (1997). "Estimation of the interindividual variability in the one-compartment pharmacokinetic model for methylmercury: implications for the derivation of a reference dose." Regul Toxicol Pharmacol **25**: 277-288.

Stern, A. H. and L. R. Korn (2001). "How useful is linear regression analysis in detecting the existence of dose-response relationships in large-scale epidemiologic studies when only a fraction of the population is sensitive? The case of methylmercury." Regul Toxicol Pharmacol **33**(1): 29-36.

Stern, A. H. and A. E. Smith (2003). "An assessment of the cord blood:maternal; blood Methylmercury ratio:Implication for risk assessment." Environ Health Perspect **111**(12): 1465-1470.

Steuerwald, U., P. Weihe, et al. (2000). "Maternal seafood diet, methylmercury exposure, and neonatal neurologic function." J Pediatr **136**(5): 599-605.

Swartout, J. and G. Rice (2000). "Uncertainty analysis of the estimated ingestion rates used to derive the methylmercury reference dose." Drug Chem Toxicol **23**(1): 293-306.

TERA (1999). Comparative Dietary Risks: Balancing the Risks and Benefits of Fish Consumption, Toxicology Excellence for Risk Assessment (TERA).
Thomas, K. W., L. S. Sheldon, et al. (1997). "Testing duplicate diet sample collection methods for measuring personal dietary exposures to chemical contaminants." Journal of Exposure Analysis and Environmental Epidemiology **7**(1): 17-36.

Trip, L. and J. Weiss (1999). "Mercury: a regional problem requires collaborative efforts." Public Health Rep **114**(5): 414-5.

Tsubaki, T. and K. Irukayama (1977). History and Background. Minamata Disease, Methylmercury poisoning in Minamata and Niigata, Japan. T. Tsubaki and K. Irukayama. Amsterdam, Elsevier Scientific Publishing Co.**:** 317pp.

Vahter, M., A. Akesson, et al. (2000). "Longitudinal study of methylmercury and inorganic mercury in blood and urine of pregnant and lactating women, as well as in umbilical cord blood." Environ Res **84**(2): 186-94.

Vena, J. E., G. M. Buck, et al. (1996). "The New York Angler Cohort Study: exposure characterization and reproductive and developmental health." Toxicol Ind Health **12**(3-4): 327-34.

Weihe, P. and P. Grandjean (1998). "Methylmercury risks." Science **279**(5351): 639; author reply 641.

Weihe, P., P. Grandjean, et al. (1996). "Health implications for Faroe islanders of heavy metals and PCBs from pilot whales." Sci Total Environ **186**(1-2): 141-8.

Weiss, B., T. W. Clarkson, et al. (2002). "Silent latency periods in methylmercury poisoning and in neurodegenerative disease." Environ Health Perspect **110 Suppl 5**: 851-4.

Weiss, J., L. Trip, et al. (1999). "Human exposures to inorganic mercury." Public Health Rep **114**(5): 400-1.

Wheatley, B., A. Barbeau, et al. (1979). "Methylmercury poisoning in Canadian Indians -- the elusive diagnosis." Le Journal canadien des sciences neurologiques **6**(4): 417-422.

Wheatley, B. and S. Paradis (1995). "Exposure of Canadian Aboriginal Peoples to Methylmercury." Water, Air, and Soil Pollution **80**(104): 3-11.

Wheatley, B. and S. Paradis (1996). "Balancing human exposure, risk and reality: questions raised by the Canadian aboriginal methylmercury program." Neurotoxicology **17**(1): 241-9.

Wheatley, B., S. Paradis, et al. (1997). "Exposure patterns and long term sequelae on adults and children in two Canadian indigenous communities exposed to methylmercury." Water, Air and Soil Pollution **97**: 63-73.

Wheatley, B. and M. A. Wheatley (2000). "Methylmercury and the health of indigenous peoples: a risk management challenge for physical and social sciences and for public health policy." Sci Total Environ **259**(1-3): 23-9.

Wheatley, M. A. (1996). "The importance of social and cultural effects of mercury on aboriginal peoples." Neurotoxicology **17**(1): 251-256.

White, R. F., F. Gerr, et al. (1994). "Criteria for progressive modification of neurobehavioral batteries." Neurotoxicology & Teratology. **16**(5): 511-24.
Wooltorton, E. (2002). "Facts on mercury and fish consumption." Cmaj **167**(8): 897.

Yagev, Y. and G. Koren (2002). "Eating fish during pregnancy. Risk of exposure to toxic levels of methylmercury." Can Fam Physician **48**: 1619-21.

Yang, R. S. (1999). "Mixture Effect on Cns Development--Integrated Approach." Crisp Data Base National Institutes of Health.

Yasutake, A., M. Matsumoto, et al. (2003). "Current hair mercury levels in Japanese: survey in five districts." Tohoku J Exp Med **199**(3): 161-9.

Yokoo, E. M., G. Valente, et al. (2003). "Low level methylmercury exposure affects neuropsychological function in adults." Environmental Health: A Global Access Science Source **2**(8): 11pp.

Yoshizawa, K., E. B. Rimm, et al. (2002). "Mercury and the risk of coronary heart disease in men." N Engl J Med **347**(22): 1755-60.

Young, J. F., W. D. Wosilait, et al. (2001). "Analysis of methylmercury disposition in humans utilizing a PBPK model and animal pharmacokinetic data." J Toxicol Environ Health A **63**(1): 19-52.

Methodology for Methylmercury Literature Searches

1.0 Search for articles: Go to the website (see step 2.0), enter the search string shown below, and select the articles to download.

General search
methylmercury OR "methyl mercury" *Selection of articles made on the basis of abstracts; time limits can be placed on the search.*

Adult Epidemiology
(methylmercury OR "methyl mercury") AND human AND adult AND (epidemiology OR epidemiologic OR epidemiological OR "case control" OR cohort)

Adult Neurological Epidemiology
(methylmercury OR "methyl mercury") AND human AND adult AND (neurological OR neurotoxic) AND (epidemiology OR epidemiologic OR epidemiological OR "case control" OR cohort)

Children Epidemiology
(methylmercury OR "methyl mercury") AND human AND (child OR prenatal) AND (epidemiology OR epidemiologic OR epidemiological OR "case control" OR cohort)

Animal Models
(methylmercury OR "methyl mercury") AND (animal OR rat OR mice)

Clinical and Pathological Effects
(methylmercury OR "methyl mercury") AND human AND (pathology OR toxicity)

Exposure
(methylmercury OR "methyl mercury") AND human AND (dosage OR exposure OR contamination OR diet)

Guidelines and Criteria
(methylmercury OR "methyl mercury") AND human AND (benchmark OR NOAEL OR "reference dose" OR regulation OR guideline)

In vitro Studies
(methylmercury OR "methyl mercury") AND ("in vitro" OR cells OR cultured)

James Bay
(methylmercury OR "methyl mercury") AND (“James Bay” OR Cree)

Risk Assessment
(methylmercury OR "methyl mercury") AND human AND “risk assessment” AND (food OR diet OR nutrition OR fish)

Reviews
(methylmercury OR "methyl mercury") AND human AND health AND review

Protective Effects and Nutrition
(methylmercury OR "methyl mercury") AND (protective OR antidote OR therapeutic OR antagonist)

Synergistic Interactions
(methylmercury OR “methyl mercury”) AND synergistic

2.0 Download records of selected articles.

Toxline

http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE

Use Toxline Special

a) Select records to download

b) Click 'Save checked items'

c) When finished selecting articles on all pages, click 'Display saved items'

d) Click 'Download'

e) Select Tagged format

f) File → Save As

PubMed

http://www.ncbi.nlm.nih.gov/PubMed/

a) Select records to download

b) Click 'Send to: Clipboard'

c) When finished selecting articles on all pages, click on 'Clipboard' at the top (right under the search line)

d) Display: Medline; Show: 500; Send to: Text

e) File → Save As

Note: After you have saved a file, if you would like to start a different search and add more onto the clipboard, select 'Send to: Clip Remove'

1.1.1

1.1.2

1.1.3

1.1.4 Ovid Online

With password:

http://gateway.ovid.com

a) Select a database (most helpful: MEDLINE or Current Contents)

b) Enter individual words in search string line

c) Click combine and choose words to combine

d) Check the box of articles you want

e) Go down to the bottom of the page and select

Health Canada Website

http://www.hc-sc.gc.ca/english/search.html

ATSDR Website

www.atsdr.cdc.gov/cgi-bin/search

US EPA Website

www.epa.gov/epahome/search.htm

Native Health Research Database

http://hscapp.unm.edu/nhd/nhrd_search.cfm

National Library of Medicine Gateway

http://gateway.nlm.nih.gov/gw/Cmd

a) Enter search and enter limits, click on search

b) Look at results from different categories

c) Check box of articles you want & click Expand

d) When selected: Click download or display Results from: selected items

Details: complete

Format: export

Destination: save to file

Download or save as: Text

e) If these are the only articles you want from the database, save this file. If you want others (ex: from page 2 of your search) then go to Edit → Select All, then Edit → Copy and then paste into a Notepad file

f) When completed, import into EndNote with Import Option: Gateway (NLM)

3.0 Import selected articles into EndNote

File → Import

a) Import Data File: Choose file to import;

b) Import Option: Select the database used to search for articles from the list; if the database is not on the list, click 'Other Filters' and select from this list.

c) Duplicates: Discard duplicates ;

Text Translation: No translation

4.0 Entering references into EndNote by hand

a) If possible, find the article on PubMed, Gateway, Toxline or Ovid and add it in the same way as adding in an article from those databases;

b) If the reference is not available in the databases, enter it manually (References → Add Reference) by copying and pasting information for the article;

c) For Reference Type: select Electronic Source if it is a website.

5.0 Making a bibliography of articles in Word

a) Choose a library;

b) Edit → Select All;

c) Edit → Output styles → Put checkmark in front of author-date;

d) Edit → Copy Formatted;

e) Paste into Word.

Test Endpoints: Faroe Islands and Seychelles Prenatal Exposure Studies

	10.2.8.1 Seychelles								**Faroes**	
10.2.9 Tests used	5-109	6 months	19 months	29 months	66 mos (girls)	66 months	108 mos (girls)	108 months	1 year (12 mos)	7 years (84 mos)
10.3 Neurobehavioural Tests										
Bayley Scales of Mental Development				†						
Mental Scale	☐	☐	☒	☒	☐	☐	☐	☐	☐	☐
Psychomotor Scale	☐	☐	☒	☒	☐	☐	☐	☐	☐	☐
Beery-Buktenica Developmental Test of Visual Motor Integration	☐	☐	☐	☐	☐	☐	☒	☒	☐	☐
Bender Visual Motor Gestalt test	☐	☐	☐	☐	☐	☒	☐	☐	☐	
Copy Condition	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Memory Condition	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Boston Naming Test	☐	☐	☐	☐	☐	☐	☒	☒	☐	☒
Bruininks-Oseretsky test of motor proficiency	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
California Verbal Learning Test (Children)	☐	☐	☐	☐	☐	☐	☒	☒	☐	☒
Child Behavior Checklist										
Total T score	☐	☐	☐	☐	☐	☒	☐	☐	☐	☐
Connor's Continuous Performance Test	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
Connor's Teacher Rating Scale	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
Denver Developmental Screening Test-Revised	☒	☒	☐	☐	☐	☐	☐	☐	☐	☐
Fagan Infantest	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐

Grooved Pegboard	☐	☐	☐	☐	☐	☐	☒	☒	☐	☐
Haptic Matching Test	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
Letter and Word Recognition	☐	☐	☐	☐	☐	☒	☐	☐	☐	☐
McCarthy Scales of Children's Abilities					†					
General Cognitive Index	☐	☐	☐	☐	☒	☒	☐	☐	☐	☐
Perceptual Performance	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐
Memory	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐
Motor Ability	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐
Neurobehavioural Evaluation System										
Continuous Performance Test	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Finger Tapping Test	☐	☐	☐	☐	☐	☐	☒	☒	☐	☒
Hand-Eye Coordination Test	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Nonverbal Analogue Profile of Mood States	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Parent-Child Behaviour Checklist	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
Preschool Language Scale					†					
Total Score	☐	☐	☐	☐	☒	☒	☐	☐	☐	☐
Verbal Ability	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐
Auditory Comprehension	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐
Tactual Performance Test	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Trailmaking	☐	☐	☐	☐	☐	☐	☒	☒	☐	☐
	Seychelles								**Faroes**	
10.3.1 Tests used	9 wks (Pilot)	6 months	19 months	29 months	66 mos (pilot)	66 months	108 mos (pilot)	108 months	1 year (12 mos)	7 years (84 mos)
Wide Range Assessment of Memory and Learning										

Learning	☐	☐	☐	☐	☐	☐	☒	☐	☐	☐
Design Memory	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
Visual Memory										
Woodcock-Johnson Tests of Achievement										
Applied Problems	☐	☐	☐	☐	☒	☒	☐	☒	☐	☐
Letter-Word Recognition	☐	☐	☐	☐	☒	☐	☐	☒	☐	☐
10.4 Neurophysiological Tests										
Brain Stem Auditory Evoked Potentials	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Computerized Posturography	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
Deep Tendon Reflexes	☒	☒	☐	☐	☐	☐	☐	☐	☐	☐
Limb Tone	☒	☒	☐	☐	☐	☐	☐	☐	☐	☐
Overall Neurological Examination	☒	☒	☐	☐	☐	☐	☐	☐	☐	☐
Pattern Reversal Evoked Potentials	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
R-R interpeak intervals on the ECG	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
10.5 Physical Tests										
Audiometry	☐	☐	☐	☐	☐	☒	☐	☒	☐	☒

10.6	Functional Acuity Contrast Test	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
10.7	Otoscopy	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
10.8	Snellen's board	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
10.9	Tympanometry	☐	☐	☐	☐	☐	☐	☐	☒	☐	☒
10.10	**Other Tests**										
10.11	Caldwell-Bradley Home Observation for Measurement of the Environment Inventory for Families of Preschool Age Children	☐	☐	☒*	☒*	☐	☒*	☐	☒*	☐	☐
10.12	Family Resource Scale	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
10.13	Henderson Early Learning Process Scale	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
10.14	Kaufman Brief Intelligence Test	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
10.15	Raven Standard Progressive Matrices	☐	☐	☒	☐	☐	☒	☐	☐	☐	☒

† Modified versions of these tests were used.

* HOME test was performed when children were 42 to 56 months old, but results were used in analysis of this study.

Neurobehavioural Tests	
Bayley Scales of Mental Development Mental Scale Psychomotor Scale	Measures infant intelligence.
Beery-Buktenica Developmental Test of Visual Motor Integration	Measures visual motor integration. Copying of geometric figures, ranging from simple to complex.
Bender Visual Motor Gestalt test Copy Condition Memory Condition	Measures visual-spatial ability. An indicator of non-specific brain damage and right cerebral hemisphere function. Sensitive to brain damage due to metal exposure. Children draw figures by copying. Errors are scored by Göttingen system. Children draw figures from memory. Scored by number of recognizable figures.
Boston Naming Test	Measures language. Children are shown line drawings of common to rare objects and are asked to name them. If they cannot answer correctly within 20 seconds, a semantic cue is given. If they still cannot answer, a phonetic cue is given. The score is the total correct without cues and the total correct with cues.
Bruininks-Oseretsky test of motor proficiency	Measures motor function.
California Verbal Learning Test (Children)	Measures short-term memory, assesses strategies and processes in learning and remembering words. Children are shown a list of 12 words that can be categorized over five learning trials. Children have to recall words after a short period of time and after 20 minutes. The score is the total correct in each learning trial and memory condition.
Child Behavior Checklist Total T score	Measures children's social and adaptive behaviour. The checklist is completed by the children's primary caregiver.
Connor's Continuous Performance Test	Measures sustained attention.

Performance Test	
Connor's Teacher Rating Scale	Measures behaviour and hyperactivity.
Denver Developmental Screening Test-Revised	Measures personal-social, fine motor adaptive, language and gross motor development. Determines whether children from birth to six years of age have normal, abnormal or questionable developmental progress.
Fagan Infantest	Measures visual memory and attention using visual novelty preference. The test is 10 trials long. In the first three test trials, children are shown two identical stimuli (pictures) at the same time, and then are shown the same stimulus along with a new stimulus. The next seven trials the children are shown the identical stimulus along with novel stimuli. The score is the amount of time it takes for the children to familiarize with the object (the amount of time it spends looking at the identical and novel stimuli).
Grooved Pegboard	Measures dexterity. Children place pegs into holes on a board.
Haptic Matching Test	Measures visual motor integration.
Letter and Word Recognition	

McCarthy Scales of Children's Abilities General Cognitive Index Perceptual Performance Memory Motor Ability	Measures overall cognitive ability.
Neurobehavioural Evaluation System (NES2) Continuous Performance Test	Measures vigilance and attention. Animals are flashed on a screen for a 4-minute period and children have to press a button every time a cat appears. The score is the total number of missed responses and the reaction time in the last 3 minutes of the test.
Finger Tapping Test	Measures manual motor ability, especially for speed. Children rapidly tap a key with the index finger for 15 seconds, twice each for preferred hand, non-preferred hand and both hands. The score is the maximum number of taps for each condition.
Hand-Eye Coordination Test	Measures manual motor coordination. Children follow sine waves on a computer screen with a joystick. The score is the average deviation from the curves in the two best trials.
Nonverbal Analogue Profile of Mood States	Measures mood. This test is an experimental test. Children are presented with a scale that has cartoon pictures on each end. At one end is a neutral face, and at the other end is a face with a mood state. Children must mark their mood on the scale. The score is the distance from the neutral face. One score is obtained for positive moods (happy, energetic) and one score is obtained for the negative moods (tired, afraid, angry, sad, confused, tense).

Parent-Child Behaviour Checklist	Measures behaviour.
Preschool Language Scale Total Score Verbal Ability Auditory Comprehension	 Measures language ability for both speaking and understanding.
Tactual Performance Test	Measures tactual processing. Children are blindfolded and have to place forms on a board in the appropriate cutout areas with preferred hand, non-preferred hand and both hands. The score is the amount of time each task takes.
Trailmaking	Measures visual search, attention, mental flexibility and motor function. Children are asked to draw a route through two forms.

Wechsler Intelligence Test for Children-III/Revised	
Block Design	Measures visuospatial organization and reasoning. Children use red and white blocks to replicate designs that are drawn on cards.
Coding	Measures the reproduction of visual symbol sequences.
Digit Span	Measures attention, tracking and short-term memory. Children are presented with digit spans of increasing length until they fail both trials with a series of the same length. The score is the total number of correct trials.
Full-scale IQ	Measures intelligence.
Information	Measures knowledge of common events
Similarities	Measures reasoning and cognitive flexibility. Children have to identify a category linking two objects or ideas. The score is the number of correct trials.
Vocabulary	Measures word knowledge.
Wide Range Assessment of Memory and Learning	

Design Memory	Children draw four geometric figures from memory.
Visual Memory	Measures memory.
Woodcock-Johnson Tests of Achievement	
Applied Problems	Measures arithmetic ability.
Letter-Word Recognition	Measures reading ability.
10.16 Neurophysiological Tests	
Brain Stem Auditory Evoked Potentials	Measures the latency of EEG peaks. Children put on earphones. In the right earphone, click signals of 65 dB are given at a rate of 20 and 40 per second. In the left ear, white noise is given at 45 dB.
Computerized Posturography	Measures postural sway. Children stand on a platform, either with or without foam underneath them, and with eyes opened or closed. The location of the child's body is measured in both the X and Y directions to determine whether the centre of gravity is moved in each of the four conditions.
Deep Tendon Reflexes	
Limb Tone	

Overall Neurological Examination	Measures child's attention and interaction with the environment, mother and examiner, social interaction, vocalizations, behaviour, coordination, dexterity, postures, movement, evaluation of cranial nerves, strength, muscle tone, deep tendon reflexes, and age-appropriate functional abilities (rolling, sitting, standing). The test is scored either normal, abnormal or questionable for pathological changes in muscle tone or deep tendon reflexes, or if the child's functional abilities are not similar to other children of the same age.
Pattern Reversal Evoked Potentials	Measures the latency of one positive and two negative EEG peaks. Children sit 127 cm in front of a 17-inch monitor in a darkened room, and stare at the screen as black and white squares are reversed two times per second.
R-R interpeak intervals on the ECG	Measures autonomic nervous system function. Children lay quiet for 5 minutes, then 300 R-R intervals are measured. The 100 consecutive R-R intervals that have the lowest standard deviation are used for calculation of the coefficient of variation.
10.17 Physical Tests	
Audiometry	Measures pure tone hearing thresholds.

10.18 Functional Acuity Contrast Test	Measures visual contrast sensitivity.
10.19 Otoscopy	
10.20 Snellen's board	Measures visual acuity.
10.21 Tympanometry	
10.22 Other Tests	
10.23 Caldwell-Bradley Home Observation for Measurement of the Environment Inventory for Families of Preschool Age Children	Measures the home environment. A visit is made to the house of the child's primary caregiver.
10.24 Family Resource Scale	Measures the quality of stimulation in the home environment. Test is given to the child's primary caregiver.
10.25 Henderson Early Learning Process Scale	Measures the quality of stimulation in the home environment. Test is given to the child's primary caregiver.
10.26 Kaufman Brief Intelligence Test	Measures caregiver intelligence.
10.27 Raven Standard Progressive Matrices	A standard intelligence test used for determining caregiver IQ. It is a non-verbal test and is designed to minimize the effects of culture on IQ.