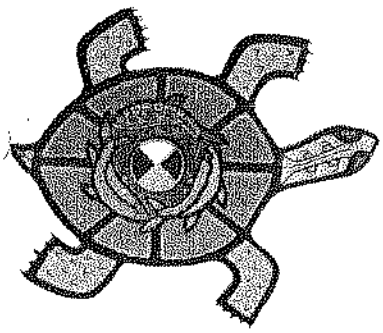

MERCURY
DISABILITY BOARD

Literature Review:

The Impact of Mercury on Human Health

2010

Mercury Disability Board
Literature Review: The Impact of Mercury on Human Health

INTENT

The approach used by the Mercury Disability Board to assess whether or not an applicant has signs or symptoms consistent with mercury poisoning was designed based on the state of science and knowledge of the impact of mercury on human health in the 1980s. In 2009 the Board commissioned a review of the literature to determine if there is new knowledge that might in some way inform the Board's work. Proposals were sought from senior scientists who have published in this field in the scholarly literature. Drs. Laurie Chan and Donna Mergler were engaged in July, 2009 to complete the work, as follows.

The intent of this project was to address the literature since 1985 on mercury contamination in human populations in order for the Board to review its current procedures and tools:

a) The effects of mercury contamination on human health (including the fetus) particularly:
- *the effect of human physiology over the life course including short and long term effects;*
- *disability related to mercury;*
- *mental health or behavioural effects of mercury including psychosis;*
- *any evidence that mercury accelerates the development of chronic diseases related to the thyroid gland, arthritis, diabetes and the nervous system.*

b) Any evidence of an interactive effect of mercury and other contaminants on human health.

c) Methods of measuring past or present mercury exposure in humans.

d) Independent review of literature produced by Dr. Masuzumi Harada.

e) Opinions on environmental contamination reporting in the area.

OUTCOMES

The following reports as provided by Laurie Chan, Ph.D. and Donna Mergler, Ph.D. and bound together in this package are:

A Review of Current Understanding of Mercury Poisoning - September 21, 2009
This provides a review and presentation of literature on mercury exposure and effects in humans building on earlier literature, other reviews and more recent literature (since 1985) highlighting current understanding in the field.

Opinions on Dr. Masazumi Harada's studies in Ontario based on articles provided by the Mercury Disability Board – October 29, 2009 and updated September 15, 2010
This provides a review and opinions on the following articles regarding Dr. Masazumi Harada's studies in Ontario:

1. Harada, M.; Fujino, T.; Akagi, T.; Nighigaki, S. Epidemiological and Clinical Study and Historical Background of Mercury Pollution on Indian Reservations in Northwestern Ontario, Canada. Bull. Inst. Constit. Med. 26 (3-4). 15 pgs. 1975.

2. Harada, S. Harada Report, translated, titled : " Minamata Disease Report – an investigation into Mercury Contamination in the Indian Reserves – A Clinical Study" with advisory note re the translation, 1975 from the Ministry of Health, Ontario.

3. Harada, M.; Fujino, T.; Akagi, T.; Nighigaki, S. Mercury Contaimination in Human Hair at Indian Reserves in Canada. Kumamoto Med. J. Vol. 30, No. 2, 1977, 99: 57-64.

4. Harada, M,; Fujino, T.; Oorui, T.; Nakachi, S.; Nou, T.; Kizaki, T.; Hitomi, Y.; Nakano, N.; Ohno, H.; Followup Study of Mercury Pollution in Indigenous Tribe Reservations in the Province of Ontario, Canada, 1975 - 2002. Bulletin of Environmental Contamination and Toxicology, Vol. 74, No. 4, 2005. 8 pgs.

5. Harada, M,; Fujino, T.; Oorui, T.; Nakati, S.; Ohno, H.; Clinical Follow up Research of Mercury Intoxication in a Reserve (1975 – 2002) (Literal summary translation) Sources Unknown.

6. International Forum on Environmental Pollution and Health Effects. "What are the lessons from 50 years of Minamata disease?" 8-12 Sept. 2006.

- Opening Greetings by Dr. M. Harada
- "Thirty Years of Uncertainty – Mercury Poisoning in Wabaseemoong" by Anthony Henry
- " How to test for Mercury Poisoning Mercury Disability Claims" by Gabriel Fobister

7. "Long-term study on the effects of mercury contamination on two indigenous communities in Canada (1975-2004)" by Masazumi Harada et al. Translation by Tadashi Orui, proofread by Thor Aitkenhead.

PowerPoint Presentation Slides – Donna Mergler, Ph.D., Presentation to Mercury Disability Board – January 27, 2010

This provides all powerpoint slides produced and used by Donna Mergler, Ph.D., in presenting to the Board and Search Committee a summary of text produced for the Literature Review.

Opinions on environmental contaminants studies in Ontario based on reports provided by the Mercury Disability Board – May 16, 2010

This provides a review and opinions on the following articles provided to the Board from Health Canada:

1. Asubpeechoseewagong Netum Anisinaabek and Wabauskang First Nation Contaminants Project, 2004-2005 (Summary) submitted in May 31, 2005
2. Mercury in the sediment and crayfish of lakes supporting Grassy Narrows and Wabauskang First Nations, Ontario submitted in May, 2005
3. Wild Meat Contaminants Study Year 3: Heavy Metals June 2005.
4. Wild Meat Contaminants Study Year 3: Organochlorines December 2005.
5. Report on the Indigenous Knowledge Workshop Asubpeechoseewagong Netum Anishinaabek and Wabauskang First Nation 2005.
6. Final Report of the Anishinabek knowledge Component National First Nations Environmental Contaminants Program (NFNECP) Health Canada 2008-2009

A Review of Current Understanding of Mercury Poisoning

Prepared by Laurie Chan, Ph.D. and Donna Mergler, Ph.D.

September 21, 2009

Introduction

This paper is commissioned by the Mercury Disability Board (MDB) to review literature on the impact of mercury on human health. The paper is not intended to be a comprehensive review and presentation of all the literature on mercury (Hg) exposure and effects in humans, but builds on earlier literature, other reviews, and more recent literature (since 1985) in highlighting current understanding in the field and addresses issues raised by the MDB.

There has been an increasing interest and growing knowledge on Hg toxicity in recent years primarily because of the concern of chronic exposure via fish consumption. A number of critical reviews of the toxicology of Hg and its health effects have been published [i,ii]. Several governments, international agencies, and other organizations have compiled extensive information on the sources, environmental fate and transport, potential health effects, exposure estimates, and potential risks of elemental mercury, inorganic mercury and methylmercury (MeHg). Several useful resources are listed below with their full citations appearing in the reference list at the end of this document.

- Elemental Mercury and Inorganic Mercury Compounds: Human Health Aspects (WHO, 2003)[iii]
- Toxicological Profile for Mercury (Update) (US ATSDR, 1999)[12]
- Toxicological Effects of Methylmercury (NRC, 2000)[119]
- Mercury - Environmental Health Criteria Documents (WHO, 1990)[128]
- Mercury – Guidance for identifying populations at risk from mercury exposure (UNEP/WHO, 2008)[iv]

Humans are exposed to different forms of mercury (Hg), and potential health risks from forms other than MeHg can occur, including mercury vapor from dental amalgams as well as from occupational exposures (e.g. dental offices, chlor-alkali plants, fluorescent lamp factories, mercury mining) and from artesanal and small-scale gold and silver mining operations[v,vi,vii,viii,ix]. The main focus of this paper will be on MeHg as most of the current advance in understanding is on the toxicity of this form of Hg and as it is the form that is found in fish, its toxicity has wider human health implications.

1. The effects of mercury contamination on human health

All humans are exposed to low levels of mercury. Almost all people have at least trace amounts of mercury in their tissues (i.e. MeHg in their hair). Generally, these low exposures are not likely to cause adverse health effects. However, Hg can cause significant effects on human health if exposure levels exceed established safe levels.

The factors that determine the occurrence of adverse health effects and how severe the health effects include:

- chemical form of mercury;
- dose;
- age of the person exposed (developing systems are susceptible);
- duration of exposure;
- route of exposure (inhalation, ingestion or dermal contact); and,
- dietary patterns of fish and seafood consumption.

The primary targets for toxicity of Hg and Hg compounds are the nervous system, the kidneys and the cardiovascular system. It is generally accepted that developing organ systems (such as the fetal nervous system) are the most sensitive to toxic effects of Hg. Fetal brain MeHg levels are higher than in maternal blood [x], and the developing central

nervous system of the fetus is currently regarded as the system of highest concern as it demonstrates the greatest sensitivity[xi]. It should be noted, however, that in humans the nervous system continues to develop through adolescence.

Other systems that may be affected include the respiratory, gastrointestinal, hematologic, immune, and reproductive systems. The health effects caused by elevated exposures to elemental Hg, inorganic Hg compounds, and organic Hg compounds such as MeHg differ [xii].

1.1 Effect on human physiology over the life course including short- and long-term effects

1.1.1 Overview of toxic effects of different forms of mercury

The ingestion of liquid metallic mercury or "quicksilver" does not appear to be toxic in itself. Health hazards from quicksilver are due to its potential to release of mercury vapor. Inhaled mercury vapor can also cause damage to the central nervous system due to its ability to cross the blood–brain barrier[1]. The high mobility of inhaled mercury vapor in the body is assumed to be due to its physical properties as an uncharged, monatomic gas that can readily diffuse through the lipid monolayers of the cell membrane. The mechanisms of transport of mercurous and mercuric cations are not well understood. Neurological and behavioral disorders in humans have been observed following inhalation of Hg vapor. Symptoms include tremors, initially affecting the hands and sometimes spreading to other parts of the body; emotional lability (often referred to as "erethism" and characterized by irritability, excitation, excessive shyness, confidence loss, and nervousness); insomnia; neuromuscular changes (such as weakness, muscle atrophy, or muscle twitching); headaches; polyneuropathy (such as paresthesia, stocking-glove sensory loss, hyperactive tendon reflexes, slowed sensory and motor nerve conduction velocities); and memory loss and performance deficits in tests of cognitive function. At higher concentrations, adverse kidney and thyroid effects, pulmonary dysfunction, changes in vision and deafness may also be observed [xiii,xiv,xv]. Short-term exposure to high concentrations of Hg vapor damages the lining of the mouth, irritates

lungs, cause tightness of chest, coughing, nausea, vomiting, diarrhea, and increased blood pressure[11]. Dental amalgam releases mercury vapor that can be inhaled and presumably behaves toxicologically like mercury vapor inhaled from external sources such as in occupational exposures. However, other than rare cases of contact allergy, no convincing evidence is yet forthcoming that dental amalgam can cause adverse health effects[1].

Mercurous mercury, in the form of mercurous chloride or calomel, has a long history of medicinal uses, especially as a laxative and in infant teething powders. Both mercurous and mercuric compounds are believed to be the causal agents in the childhood disease of acrodynia or "pink disease." Symptoms include profuse sweating, and swollen red feet and hands, which were cold, clammy, desquamating, and painfully sensitive to touch. Sometimes there was a rash on body, legs, and arms. There was progressive weight loss, marked weakness, and apathy. Insomnia and photophobia were also distressing attributes of the disease [xvi].

The mercuric cation, Hg2+, is believed to be the proximate toxic agent for all these inorganic forms of mercury. All species of inorganic mercury have the capacity to elicit idiosyncratic reactions. Such reactions require exposure to mercury, but the prevalence and severity do not appear to be dose related. The nephrotic syndrome and acrodynia are examples[1]. Mercuric mercury is known to exit liver cells into bile as a complex with reduced glutathione. Mercuric mercury has a limited capacity to cross the blood–brain and placental barriers but is accumulated by the kidneys. The most sensitive adverse effect observed following exposure to Hg2+ is the formation of autoimmune glomerulonephritis (inflammation of kidney). Accidental ingestion of mercuric chloride by children resulted in cardiac effects (increased heart rate and blood pressure)[11,12]. Accidental drinking or ingestion of inorganic Hg can cause damage to the digestive tract and kidney. In addition, dermal exposures to ionic mercury can lead to adverse effects to the skin [11].

1.1.2 Toxic Effects of organic mercury on infants and adults

The methyl- and ethylmercury compounds have similar chemical properties and are often referred to as the "short-chain alkyl mercurials." The primary target is the central nervous system. The ethyl compounds differ from their methyl relatives in that they are converted more rapidly to inorganic mercury in the body and produce kidney damage, whereas methylmercury appears to exclusively damage the central nervous system, at least in primates. The intact organomercurial cation is believed to be the proximate toxic agent responsible for damage to the central nervous system, and the mercuric cation released from ethylmercury plays this role in kidney damage. The high mobility of methylmercury in the body is due to the formation of a complex with the amino acid cysteine. The structure of this complex resembles that of a large neutral amino acid, methionine, and thereby gains entry into cells on the large neutral amino acid carrier. Methylmercury exits from cells as a complex with reduced glutathione on the membrane carrier for this peptide. Much more toxicological information is available for methylmercury than for ethylmercury. However, there has been concern about ethylmercury toxicity among children from Thimerosal. Thimerosal is used as a preservative in vaccines (such as DTP, hepatitis B, and Hib), to protect against bacterial contamination; this preservative contains nearly 50 % ethylmercury. Once in the body, thimerosal is transformed into organic (ethyl) mercury. Canada has decreased or eliminated the use of thimerosal from many vaccines[xvii]. However, thimerosal still exists in some vaccines used. Therefore, when assessing exposures to mercury for a population or subpopulation, this possible source of exposure should be considered. The Global Advisory Committee on Vaccine Safety of WHO concluded that there is currently no evidence of mercury toxicity in infants, children, or adults exposed to thimerosal in vaccines and advised continued use of thiomersal-containing vaccines was recommended[xviii].

Other organomercurials include phenylmercury and methoxyethylmercury compounds. This group of mercurials is rapidly converted to inorganic mercury so that their toxic effects are similar to those of mercuric mercury compounds. In general, however, they are more efficiently absorbed into the body than inorganic mercury. Toxic effects of on the nervous system are due to damage to discrete anatomical regions in the brain with sensory and motor coordination functions[xix]. The outcome is usually irreversible as

neuronal cells are destroyed. There is also evidence of peripheral neuropathy that may account for the signs of sensory loss in the extremities[xx]. The appearance of signs and symptoms of poisoning can be preceded by a latent period after exposure has ceased. This latent period can amount to weeks or even months or years. Weiss et al presented three examples of delay (latency) in the appearance of signs and symptoms of poisoning after exposure to methylmercury[xxi]. First, a case was presented of a 150-day delay period before the clinical manifestations of brain damage after a single brief (<1 day) exposure to dimethylmercury. The second example was taken from the Iraq outbreak of methylmercury poisoning in which the victims consumed contaminated bread for several weeks without any ill effects. Indeed, signs of poisoning did not appear until weeks or months after exposure stopped. The last example was drawn from observations on nonhuman primates and from the sequelae of the Minamata, Japan, outbreak in which low chronic doses of methylmercury may not have produced observable behavioral effects for periods of time measured in years.

The toxic effects of methylmercury differ between adult and prenatal exposures. They differ both in terms of the type of damage to the brain and in terms of the lowest toxic doses. They are therefore treated separately here. Distinction between acute and chronic toxicity of methylmercury is not really meaningful. A single dose can elicit the same syndrome of clinical methylmercury poisoning as chronic exposure.

Clinical manifestations of exposure to methylmercury

In 1958, McAlpine and Araki[xxii] linked the unusual neurological disease that had been associated with fish consumption from Minamata Bay to MeHg exposure. This historic recognition of the brain and nervous system as the primary target organ for MeHg poisoning, resulting in marked distal sensory disturbances, constriction of visual fields, ataxia, dysarthria, auditory disturbances and tremor, remains unchanged[xxiii,xxiv]. Based on analysis of the studies of human poisoning, the WHO estimated that 5% of MeHg-exposed adults would experience neurologic effects with a blood Hg level of 200 μg/L

(corresponding to a hair level of approximately 50 μg/g). This estimate has, however, been called into question by a re-analysis of the these studies by Kosastsky and Foran[xxv] and the recent studies conducted among Minamata residents (see Section 1.2 below for detailed discussion) who suggested that the lowest-observed-effect level for clinical effects is likely to be considerably lower. Indeed, anecdotal and case reports of diffuse and subjective neurologic symptoms in adults and older children with moderately elevated MeHg exposures continue to appear[xxvi]. In many cases, cessation or significant curtailing of fish consumption results in improvement of symptoms in conjunction with reduction in biomarker concentrations. These suggest the possibility of clinical effects, perhaps in a sensitive sub-set of the general population, at levels of exposure considerably below those previously associated with clinical effects in poisoning episodes. Currently, there is no formal case description or diagnostic criteria for such effects.

While exposures throughout the world are lower than those producing the historical epidemics of MeHg poisoning, there is growing evidence that for many populations, exposures are sufficient to alter normal functioning of several systems and constitutes an important public health problem.

Effects in neonates, infants and children

Central Nervous System development encompasses a tightly regulated temporal and spatial sequence of events (proliferation, migration, synaptogenesis, selective programmed cell death, myelination). Even a short-term impairment in this cascade may cause irreversible neurotoxicity if the tissue cannot compensate for the damage. The routes of exposure to toxicants during development are rather unique (e.g., transplacental in fetus, *via* breast milk in nursing infants, hand-to-mouth in early childhood) and have no parallel among adults. Moreover, on a body-weight basis children eat and drink more than average adults, and thus they are potentially more heavily exposed to food contaminants than grown-up individuals[xxvii].

The poisoning in Minamata brought attention to the risk from fetal exposure. Exposed to MeHg through the placenta of the exposed mother, infants showed severe cerebral palsy-like symptoms, even when their mothers had mild or no manifestation of the poisoning[xxviii]. Mental retardation, cerebellar ataxia, primitive reflexes, disarthria and hyperkinesias were observed. These symptoms described over 25 years ago[xxix], continue as the clinical hallmark of congenital methylmercury poisoning. Reconstruction of maternal or fetal doses resulting in these symptoms is difficult due to lack of concurrent sampling. An estimate of the mean maternal hair concentration resulting in such symptoms of 41μg/g ppm was proposed[xxx], however, large uncertainty surrounds this estimate. Health effects observed with poisonings should not be confused with the more subtle population effects observed at lower levels of exposure.

At the sub-clinical and population level, several studies in different parts of the world, have reported poorer neurologic status and slower development in newborns, infants and/or children exposed *in utero* MeHg and/or during early childhood[xxxi,xxxii,xxxiii,xxxiv,xxxv,xxxvi,xxxvii,xxxviii,xxxix,xl,xli,xlii], although some studies did not observe effects[xliii,xliv,xlv]. In children, MeHg exposure has been associated with lower performance on tests of language, attention, memory, and/or visuo-spatial and/or motor functions. Detailed review of the recent cohort studies showing evidence of Hg effects on neurodevelopment will be presented in Section 1.3.1.

Effects in adults

Much of the effects of MeHg have been learned from the poisoning cases in Minamata, Japan which is now know as Minamata Disease (MD). MD was first discovered in 1956 around Minamata Bay, Kumamoto Prefecture (KP), Japan. A second epidemic in Japan occurred in 1965 along the Agano River, Niigata Prefecture (NP). The severe contamination by methylmercury continued until 1968, when the plant finally stopped discharging its wastewater into Minamata Bay. According to Japanese government

figures, 2,955 people contracted Minamata disease, and 1,784 people have since died[xlvi]. MD patients showed neurologic signs including sensory loss, ataxia, constriction of visual field, dysarthria, and hearing difficulties. It was recently reported that large amounts of methylmercury were generated by the chemical processes of the Chisso acetaldehyde plant and later dumped directly into Minamata Bay[xlvii]. This has significant implications that MD was likely caused by consumption of MeHg directly released in the environment and accumulated in fish instead of from inorganic Hg methylated and bioaccumulated in the environment[l]. Eto[xlviii] reported that in the cases found in KP, at autopsy, the most conspicuous destructive lesion in the cerebrum was found in the anterior portions of the calcarine cortex. Less severe but similar lesions were found in the post-central, pre-central and temporal transverse cortices. Secondary degeneration from primary lesions was seen in cases with long survival. In the cerebellum, pathological changes occurred deep in the hemisphere. The granule cell population was more affected, compared with Purkinje cells. Among peripheral nerves, sensory nerves were more affected than motor nerves. More recently, Eto et al[xlix] reevaluated 30 autopsy cases related to MD in Niigata Prefecture (NP) and found that the pathological findings leading to the diagnosis of MD in the NP cases were essentially the same as those in KP, including the peripheral nerve lesions. In the most severely affected case of MD in NP, formation of multiple vacuoles of various sizes was observed in the cerebellar cortex, which was never encountered in the KP cases.

The current WHO threshold for adult exposure (hair level: 50 μg/g) was based on evidence from NP, which included only acute and severe cases. Many residents in the area and researchers have questioned the possibility of more subtle effects at lower exposure levels. A recent case control study published in 2009 identified 120 residents from exposed areas who had mercury in hair data measured in 1960 and neurological outcomes measured in 1971, compared to a control of 730 residents from an unexposed area[l]. They found that hair mercury levels were associated with perioral sensory loss in a dose-response relationship. The adjusted prevalence odds ratios and 95% confidence intervals for perioral sensory loss, compared with the lowest exposure category (0–10 μg/g), were 4.5 (0.5–44), 9.1 (1.0–83), and 10 (0.9–110), for the dose categories >10 to

20, >20 to 50, and >50 μg/g, respectively. The prevalence of all neurologic signs was higher in the exposure area than in the control area. This result suggests that neurologic signs, especially perioral sensory loss, was found among residents with hair mercury content below 50 μg/g after exposure was ceased for 11 years. Ninomiya et al reported that sensory loss remained even 30 years after the cessation of methylmercury exposure[lii,liii]. The study also reported a weak trend for other neurological symptoms such as bilateral sensory disturbance, ataxia, and dysarthria suggesting that some neurologic functions may have improved due to central nervous system plasticity[liii].

Other than the major accidents and industrial release, few studies have addressed the neurotoxic effects of Hg exposure in adults. Mercury related deficits in motor, psychomotor, visual and/or cognitive functions have been reported for different populations within the Brazilian Amazon[liv,lv,lvi,lvii] and for tuna consumers from the Mediterranean[lviii]. A recent study of older adults (50-70 years old) in the United States, with low blood Hg levels, (mean = 2.1 μg/L), however, showed inconsistent evidence of effect across neurobehavioral tests[lix]. A Canadian study of fish eaters with levels of blood Hg <20μg/L, showed a negative association between Hg and monoamine oxidase activities in platelets[lx]. Experimental studies have shown that Hg exposure disrupts the function and transmission of the monoaminergic nervous system, inhibiting the enzyme activities of monoamine oxidase (MAO, EC 1.4.3.4)[lxi]. Biochemical changes may constitute a sensitive, although non-specific, early indication of Hg-induced alterations to the nervous system, but more work is needed in this area.

Studies of associations between nervous system outcomes and MeHg exposure in adult populations in which frequent and lifetime fish consumption is a cultural norm, generally cannot distinguish between effects due to adult exposure and permanent developmental effects due to gestational and early childhood exposures.

1.2 Disability related to Hg

Classical mercury poisoning is characterized by a triad of signs, namely tremors, erethism and gingivitis. Mercurial erethism, which is characterized by behavioral and personality changes such as extreme shyness, excitability, loss of memory, and insomnia are also observed[lxii]. Recently, the effects of mercury exposure at levels around 0.05 mg/m3 or lower have been of concern and may include minor renal tubular damage, increased complaints of tiredness, memory disturbance and other symptoms, subclinical finger tremor, abnormal EEG by computerized analysis and impaired performance in neurobehavioral or neuropsychological tests. Abnormal gait, dysarthria, ataxia, deafness and constriction of the visual field are typical of the symptoms of methylmercury poisoning observed in Minamata and Iraqi outbreaks, as well as in occupational methylmercury poisoning cases. Disability caused by Hg exposure can be demonstrated from reports for observed effects among patients suffering from occupational exposure. For example, Powell[lxiii] reported neurobehavioural symptoms of mercury poisoning, in a group of Zulu chemical workers (n = 16), employed by a mercury processing plant, exposed to neurotoxic levels of mercury, 5 years after exposure. A group-control design was adopted, where the exposed group was matched for age, sex, race, occupational and educational background. Both groups were administered a specially selected battery of psychometric tests to measure neuropsychological functioning. The exposed group had significantly impaired short term verbal and spatial memory, impaired sustained and divided attention, and impaired motor speed. They also suffered from elevated clinical levels of psychiatric symptomatology, including anxiety, depression and phobic avoidance, and neurological symptoms of tremor, weakness in the limbs, and excessive sweating. This results suggest that exposure to Hg can cause varying degrees of permanent neuropsychological disability.

Paresthesias

Paresthesias are the first symptom that people report following toxic doses of methylmercury. Takaoka et al[lxiv] conducted a psychophysical study of tactile sensation to evaluate the somatosensory abilities of subjects living in a methylmercury-polluted area

around Minamata City, Japan. Acuity of fine-surface-texture discrimination was disturbed not only in subjects with clinical complaints of hand numbness, but also in subjects without hand numbness who lived in the district where methylmercury exposure occurred. In a more recent study, Takaoka et al[76] studied 197 residents from the Minamata area who had a history of fish consumption. They divided the exposed subjects into non-complicated (E) and complicated (E+N) groups based on the absence or presence of other neurological or neurologically related disorders and compared them to residents in control area (C) after matching for age and sex. They quantitatively measured four somatosensory modalities (minimal tactile sense by Semmes-Weinstein monofilaments, vibration sense, position sense, and two-point discrimination) and did psychophysical tests of fine-surface-texture discrimination. Subjective complaints were higher in groups E and E+N than C. Over 90% of E+N and E subjects displayed a sensory disturbance on conventional neurological examination. The prevalence of these neurological findings was significantly higher in exposed subjects than controls. All sensory modalities were impaired in the E and E+N groups. All four quantitatively measured sensory modalities were correlated. The prevalence of complaints, neurological findings, and sensory impairment was similar or a little worse in group E+N than in group E. These findings suggest that sensory symptoms resulting from Hg exposure could be determined even in the presence of neurological or neurologically related diseases.

Ataxia

Takaoka et al studied 197 residents from the Minamata area who had a history of fish consumption during the polluted period and found that about 50% had upper and lower extremity ataxia and about 70% had truncal ataxia[lxv].

Vision

Impairment of visual functions has been studied in patients exposed to mercury. These studies have been shown partial loss of color vision in workers exposed to several

solvents and to metallic mercury[lxvi,lxvii,lxviii]. Amazon gold miners exposed to mercury vapor were found to show visual dysfunction[lxix]. Color vision and contrast sensitivity (CS) impairment were also found in fish-eating Amazonian populations where Hg exposure is today among the highest in the world due to deforestation and gold-mining activities[lxx]. The loss of color vision and CS has been demonstrated in these populations, at methyl mercury levels of contamination below 50 μg/g of total hair Hg, which was traditionally considered the threshold for clinical effect[65,66,78] . In the Minamata study, 28% of the study group reported visual constriction[74]. The measurement of CS in 7-yr old children with prenatal exposure to methylmercury did not show impairment in their CS[lxxi].

Activities of Daily Living

Reports of ill health increased sharply following the 2004 Supreme Court ruling instructing the Japanese government to pay damages to MD patients. Over 13,000 residents came forward to be examined for MD[74]. Ushijima et al examined the distribution of disability in activities of daily living (ADL), and the association between MD status in terms of compensation system and ADL disability among the general population of previously methylmercury-polluted areas[lxxii]. They collected data by two-stage stratified sampling of residents 40–79 years old in 172 postal-code on the endemic area of MD. Questionnaires were distributed to eligible subjects (n = 2100) and collected at a later visit or by mail. Information on demographic factors, basic ADL (BADL), and instrumental ADL (IADL) was obtained using questionnaires. Logistic regression analysis were used to assess the relationship between MD status in terms of compensation system and ADL disability. They classified the 1422 residents who completed the questionnaire in accordance with their MD status in terms of compensation system: *Early* (those who received MD compensation before the Supreme Court decision), *Recent* (those who applied for compensation after the Supreme Court decision), *Not Yet* (those who have not yet applied for compensation, but have health-related anxieties about MD effects), and *Normal* (those who have not applied for compensation, and do not have health-related anxieties about MD effects). Adjusting for

confounding factors, MD status was significantly associated with the disability grades of BADL and IADL with an increasing trend in the order of *Normal*, *Not Yet*, *Recent*, and *Early*. The odds ratios (95% CI) based on *Normal* were 2.08 (1.08–4.01), 3.87 (2.14–7.01), and 4.50 (2.66–7.61) for BADL and 2.41 (1.62–3.61), 3.20 (2.12–4.85) and 3.68 (2.52–5.38) in *Not Yet*, *Recent*, and *Early* for IADL, respectively. The authors concluded that *Early*, *Recent*, and *Not Yet* had lower ADL grades than *Normal*. Moreover, the population with a low ADL grade and health-related anxieties had increased throughout the previously methylmercury-polluted areas.

Learning and Development

Human neurodevelopmental consequences of exposure to methyl-mercury (MeHg) from eating fish remain a question of public health concern. The current knowledge is based on the findings of a number of on-going cohort studies. A cohort of 1022 consecutive singleton births was generated during 1987–1988 in the Faroe Islands, where increased methylmercury exposure occurs from traditional seafood diets that include pilot whale meat[lxxiii]. The prenatal exposure level was determined from mercury analyses of cord blood, cord tissue, and maternal hair. At age 14 years, 878 of 1010 living cohort members underwent detailed neurobehavioral examination. Indicators of prenatal methylmercury exposure were significantly associated with deficits in finger tapping speed, reaction time on a continued performance task, and cued naming. These findings are similar to those obtained at age 7 years. An analysis of the test score difference between results at 7 and 14 years suggested that mercury-associated deficits had not changed between the two examinations. In structural equation model analyses, the neuropsychological tests were separated into five groups; methylmercury exposure was significantly associated with deficits in motor, attention, and verbal tests. These findings are supported by independent assessment of neurophysiological outcomes[lxxiv]. The effects on brain function associated with prenatal methylmercury exposure therefore appear to be multi-focal and permanent.

Axelrad et al[lxxv] estimated a dose-response relationship between maternal mercury body burden and subsequent childhood decrements in intelligence quotient (IQ), using a

Bayesian hierarchical model to integrate data from three epidemiologic studies conducted in the Faroe Islands, New Zealand, and the Seychelles Islands. They found a central estimate of -0.18 IQ points (95% confidence interval, -0.378 to -0.009) for each part per million increase of maternal hair mercury. IQ is a useful end point for estimating neurodevelopmental effects, but may not fully represent cognitive deficits associated with mercury exposure, and does not represent deficits related to attention and motor skills. Nevertheless, the integrated IQ coefficient provides a more robust description of the dose-response relationship for prenatal mercury exposure and cognitive functioning than results of any single study.

1.3 Mental health or behavioural effects of mercury including psychosis

1.3.1. Effects of mercury on children's neurodevelopment

As discussed in Section 1.1.2, infants are at the most susceptible life stage for mercury toxicity. Much effort has been devoted to identify the subtle effects on neurodevelopment due to fetal and childhood low dose chronic exposure. The evidence for mercury developmental neurotoxicity continues to accumulate. Most published information comes from the two major child cohort studies carried out in the Faroe Islands, where mercury exposure is from the consumption of marine fish and pilot whale, and in the Seychelles, where marine fish is the source of exposure.

Several hundred children have now been followed from birth to 14 years of age in the Faroes and 9 years of age in the Seychelles. For many years the results coming from these two studies were contradictory. The study in the Faroes has showed effects of mercury on children's neurobehavioral performance and electrophysiological measures, while up until recently, the study in the Seychelles has not shown associations between mercury exposure and neurobehavioral outcomes.

In the Faroe Islands, where there were relatively high levels of mercury exposure, evidenced by median umbilical cord blood levels of 24μg/L, a cohort of over 1000 newborns were initially enrolled in a study in 1987-88 and most or selected groups have

been periodically tested from birth to 14 years of age. Although in the initial cohort, no effects were observed on developmental milestones in the first year[lxxvi], a later study of 182 Faroese newborns, born in 1994-95, showed lowered neurologic optimality scores associated with increased cord blood mercury[lxxvii] and mercury-related decreased height and weight at 18 months and a lesser relation at 42 months[lxxviii]. When examined at the age of 7 years, the 1987-88 cohort presented neuropsychological dysfunctions which increased with prenatal mercury exposure; the most pronounced were in the domains of language, attention, and memory, and to a lesser extent in visuo-spatial and motor functions. These associations remained after adjustment for covariates and after exclusion of children with maternal hair mercury concentrations above 10 micrograms[33]. Electrophysiological studies of a subgroup of these children showed mercury-related delayed latencies for Auditory Brain Stem Evoked Potentials[lxxix]; similar results had previously been reported for 7 year olds from Madeira, Portugal[lxxx]. At 14 years old, over 80% of the Faroes children were again tested. Indicators of prenatal methylmercury exposure were significantly associated with deficits in finger tapping speed, reaction time on a continued performance task, and cued naming. Mercury-associated deficits did not change between the two examinations; methylmercury exposure was significantly associated with deficits in motor, attention, and verbal tests. The results for electrophysiological measures showed similar delays to those observed at 7 years[lxxxi].

On the other hand, until recently, the birth cohort studies carried out in the Seychelles, consistently have shown no association between prenatal mercury exposure and neuro-outcomes (for review see: Davidson et al, 2006[lxxxii]). A total of 779 newborns, exposed to mercury through maternal fish consumption, were enrolled in this study in 1989-90. Prenatal exposure was measured in maternal hair and recent postnatal exposure in the child's hair. The cohort was examined six times over 11 years using extensive developmental test batteries and only one adverse association was observed at 9 years on a test of fine dexterity, speed and coordination[lxxxiii], while at 66 months, prenatal mercury was associated with improved performance on a language scale, but this was not observed at older ages. Further analyses of the data from the fine dexterity test suggest that the relation between prenatal exposure and this motor performance may be non-

linear, with no effect until exposures were relatively high (maternal hair mercury above 10-12 μg/g)[lxxxiv]. The authors suggest that there may be delayed toxicity and continue to follow-up these children. Further analyses of the 9-year old data[lxxxv] showed that motor proficiency and activity level improved significantly with increasing mercury for 53% of the children who had an average home environment. However, motor proficiency significantly decreased with increasing prenatal exposure in 7% of the children whose home environment was below average. This analysis suggests that effects may be non-homogeneous. This may be similar to what has been shown for lead exposure, where children with lower socio-economic status present deficits in intellectual functioning at lower exposures than children from families with medium or high economic status. These findings suggest that factors often associated with a poorer home environment, such as poorer nutrition and less parental stimulation, may increase vulnerability to toxics[lxxxvi, lxxxvii].

Because of the importance of the nutritional input from fish consumption, in 2001, the researchers in the Seychelles study initiated another birth cohort study, where they examined the maternal nutritional status by measuring a series of indicators including the omega-3 fatty acid, docosahexaenoic acid (DHA)[lxxxviii,lxxxix]. Mothers were enrolled at 14-24 weeks of pregnancy and evaluations took place at 5, 9, 25 and 30 months of age. A total of 229 children completed the 30-month examination. Results from this study showed that when examined separately from nutritional intake, there was, as in previous studies, no relation between mercury exposure and children's performance on the Bayley Scales of Infant Development. However, when both mercury and nutritional intake were taken into account in the analyses, mercury was significantly and negatively related to the Psychomotor Development Index.

More recent cohort studies have similar findings. The risks from mercury exposure and the benefits from fish consumption on infant development were likewise examined in the United States[xc] for 135 mother-infant pairs. The investigators assessed maternal fish intake during pregnancy and maternal hair mercury at delivery with respect to a visual recognition memory test given at 6 months of age. Higher fish intake was associated with

higher infant cognition, but an increase in mercury was associated with lower cognition. In another study[xci], this research group examined 3 year olds who had been enrolled in a birth cohort study of 341 mother-child pairs in Massachusetts. Children's performance was assessed on a picture vocabulary test and a test of a wide range of visual motor abilities. For both these tests, higher fish intake during pregnancy was associated with better child cognitive test performance, and higher mercury levels with poorer test scores. It should be noted that mercury exposure in these groups was particularly low.

While most of the studies on children have examined fetal exposure, the Seychelles study recently published their results with respect to post-natal exposure[xcii]. Although there were some relations between mercury exposure and neurobehavioral performance, the authors conclude that the results were not consistent. In the Amazon region, where freshwater fish are a dietary mainstay, there have been two studies of children. In French Guiana, 156 indigenous children living downstream of gold mines were examined[xciii]. The authors report a dose-dependent association between maternal hair mercury level and increased deep tendon reflexes, poorer coordination of the legs, and decreased performance on a test of visuo-spatial organization. In a region of the Brazilian Amazon, where mercury contamination of the aquatic food chain is from deforestation and subsequent soil erosion, Grandjean and his coworkers[xciv] reported poorer performances on tests of motor function, attention, and visuo-spatial associated with mother's hair-mercury concentrations at the time of testing.

Electrophysiological measures made on 102 Inuit children, with exposure to both Hg and PCBs showed changes in visual evoked potentials; the association with blood mercury levels at the time of testing was much stronger than with fetal exposure measured in cord blood[xcv].

In summary, our knowledge on the developmental effects of mercury following fetal exposure has increased substantially since the tragedy of Minamata where mothers with high mercury exposure gave birth to children with a debilitating, progressive neurological disorder, Fetal Minamata Syndrome, although they themselves were asymptomatic.

Today there is a wide consensus that at even at low levels of mercury, mercury can affect children's intellectual and motor development, which is not immediately obvious in children examined individually, but can be observed in population studies. This is important for society because the reduction of an average of 5 points of the IQ scale means that there are twice as many children with learning difficulties and half as many children "high performers"[xcvi]. Recent studies also reveal that there are nutritional elements in some fish that can offset the effects of mercury, notably omega-3 fatty acids and possibly other nutrients. Current studies are focusing on these factors.

1.3.2 Effects of mercury exposure on the adult nervous system

Neurological effects caused by high dose of Hg occupational exposure were discussed in Section 1.2. There are very few reports on chronic effects of exposure to Hg vapor. Heyer et al[xcvii] reported low dose exposure to elemental mercury among 230 female dental assistants associated with increased self-reported neurological symptoms and mood. The brain-derived neurotrophic factor (BDNF) polymorphism was also associated with increased symptom and mood scores. Moreover, the combined effects of Hg exposure and BDNF polymorphism were additive. No association was found among the 193 male dentists in the same study. More recently[xcviii], the same group reported no association between Hg exposure and symptoms among 183 male dentists and 213 female dental assistants in a follow up study.

Similarly, relatively few studies have been carried out on the neurotoxic effects of low level exposure to methylmercury in adults. As indicated above, the adult victims of mercury poisoning in Minamata and Iraq suffered from a severe neurological disorder with marked distal sensory disturbances, constriction of visual fields, ataxia (loss of coordination), dysarthria (motor speech disturbance), auditory disturbances, and tremor [xcix]. More recently, studies were carried out of persons over 40 who had lived in the mercury-polluted areas surrounding the city of Minamata[c]. Annual medical examinations, performed on about 1,500 persons, showed no difference in the prevalence of disease between those from the polluted area and those from other areas, although those from the

polluted area had more complaints of poor health. Persons with a history of compensated Minamata Disease scored significantly lower on a scale of activities of daily life[ci]. Other studies of persons from a nearby polluted area, who had been exposed to lower doses of mercury over a twenty year period, still suffered from distal paresthesia of the extremities and lips 30 years after cessation of exposure[cii].

The effects of mercury on nervous system function have been examined in fish-eaters in different parts of the world. In the Brazilian Amazon, studies have shown motor, visual and cognitive deficits associated with increasing mercury exposure in communities who consume fresh-water fish almost daily[52,54,55]. A follow-up study was undertaken in the Brazilian Amazon subsequent to a campaign to encourage persons to eat more fish that didn't eat other fish. The findings showed that over a 5-year period, persons continued to eat the same amount of fish, but preferentially consumed non-predators. Their hair mercury concentrations diminished by almost 40% and re-testing of motor and visual functions showed that the former significantly improved while the latter continued to deteriorate in relation to previous exposures (article in preparation). In this same region of the Brazilian Amazon, we recently completed a major study of 450 persons in the Brazilian Amazon that confirms a negative effect of mercury exposure on motor and visual functions (articles in preparation), but selenium (which is high in this region primarily due to the consumption of Brazil nuts[ciii] seems to offset some of the meurbehavioral effects of mercury, notably for motor functions (Lemire et al. article in preparation). In Italy, Carta et al.[120] examined 22 fishers who habitually eat tuna and noted loss of cognitive and motor functions associated with increasing blood organic mercury.

In an urban adult population, a cross-sectional study found no effects between mercury levels in blood on neurobehavioural tests in 474 randomly selected participants in the Baltimore Memory Study, a longitudinal study of cognitive decline involving 1140 Baltimore residents aged 50 to 70 years[civ]. The median blood mercury level was very low at 2.1 microg/L (range, 0-16 microg/L).

1.3.4. Fish consumption, mercury and mental health

To date there is no evidence that Hg exposure from fish consumption directly affects children's mood and behavior. In a recent Korean study of ADHD in relation to blood lead and mercury, Ha and coworkers[cv] reported a positive association between attention deficit and hyperactivity disorders ADHD and blood lead, despite the fact that lead levels were very low, but no relation with blood mercury concentrations. Although there does not seem to be a direct effect of Hg on mood and behavior, the loss of cognitive and motor skills affects children's coping and learning skills for adulthood.

It has been suggested that omega-3 fatty acids and fish consumption may be protective for depression in adults and children[cvi,cvii], however results are inconsistent and few studies consider Hg exposure that may come from fish consumption. In a study of neuropsychiatric symptoms in Quebec fresh-water fish eaters, Philibert et al[cviii] reported a positive association between hair Hg concentrations and symptoms. In men, there was a positive association between omega-3 fatty acids and neuropsychiatric symptoms, particularly on the scales of depression and interpersonal sensitivity; further analyses showed that this relation was strongest among those with higher alcohol intake, suggesting that there may be an interaction between omega-3 and alcohol. On the other hand, in women, there was no association between omega-3 fatty acids and neuropsychiatric symptoms, but there was a positive between hair mercury and scores on the scales for obsessive compulsiveness, interpersonal sensitivity, depression, anxiety, and psychotism, as well as the General Stress Index. Gender differences with respect to omega-3 fatty acids have also been reported by others; one population-based study reports a protective effect of omega-3 fatty acids on depression was observed for men, but not for women[106].

1.4 Evidence that mercury accelerates the development of chronic diseases

1.4.1 Cardiovascular disease

There is growing evidence that fish consumption is protective for cardiovascular disease[cix]. However, mercury exposure may offset some of the benefits. The evidence for causal association of mercury with cardiovascular events has been reviewed by Chan and Egeland[cx] and by Stern[cxi]. The strongest evidence is for acute myocardial infarction (AMI) in adult men. A cohort of men from eastern Finland [cxii,cxiii,cxiv] and a case-control study of men with a first diagnosed myocardial infarction from a European and Israeli multicenter study[cxv] found significant associations between biomarkers of MeHg exposure and acute myocardial infarction (AMI). The relative risk and odds ratios for AMI from these studies showed a doubling in the upper range of exposures and suggest that dietary mercury exposure at levels found relatively commonly in western populations can result in a significantly elevated risk of AMI. In the study by Guallar et al [102], both the positive effects of DHA and the negative effects of mercury were evident.

Other studies have not observed a relation between bioindicators of mercury and coronary heart disease. In a prospective Swedish study of 1462 women, who were 38 to 60 years of age at baseline examination (1968–1969), baseline total serum Hg concentrations were not related to an increased risk of MI, stroke, and many other outcomes within a 20-year follow-up period[cxvi]. In another Swedish study[cxvii], where a new cases of myocardial infarction among persons participating in a very large cohort study, both fatty acids and mercury (measured in erythrocytes) were associated with a lower incidence of myocardial infarction. In this study, men and women were not studied separately and there were many more men (n = 60), compared to women (n = 16). The authors suggest that both of these are indicators of fish consumption; the average mercury concentrations in this cohort were very low. In a cohort of U.S. professionals, no association was observed between mercury exposure and coronary heart disease[cxviii]. It should be noted that in that study, dentists accounted for 63% of controls and had Hg exposure more than twice that of the other groups in the cohort. Presumably, the dentists' exposures were influenced by occupational exposure to elemental mercury from amalgams. A mortality study of Finnish fishermen and their wives showed that they had a reduced rate for many causes, including ischaemic heart diseases[cxix].

The conflicting findings may indicate that high mercury intake may have an effect on cardiovascular health but that the consequences of exposure may vary among populations owing to various modifying factors.[97]

Other cardiovascular endpoints have likewise been examined with respect to mercury exposure, these include hypertension and R-R variability (a measure of function of the autonomic nervous system that innervates the heart). Sorensen et al.[cxx] found an association between gestational exposure to mercury and increased systolic and diastolic blood pressure in the Faroese children at 7 years old and. This association was strongest for those children with decreased birth weight. However, the association did not persist when the cohort was re-examined at 14 years old[cxxi]. Studies of mercury exposure in adults have reported inconsistent associations between blood or hair Hg and blood pressure[cxxii,cxxiii], while a recent study in non-indigenous communities in the Brazilian Amazon indicates a positive relation between hair Hg and blood pressure[cxxiv]. In a recent study of 42 Faroese whaling men, mercury exposure was associated with blood pressure and carotid intima-media thickness[cxxv].

Decreased heart rate variability was observed in the Faroes children's cohort, and appears to result from gestational exposure to MeHg [107]. This effect persisted through 14 years of age. The health significance of this finding, however, is unclear. Decreased heart rate variability is observed in adults following myocardial infarction and is predictive of sudden cardiac death, but there does not appear to be evidence suggesting that decreased heart rate variability, in isolation, in children is either *per se* adverse, or predicative of an adverse outcome.

1.4.2 Other conditions and/or illnesses

There is no evidence of elevated diabetes associated with Hg exposure, although there is a growing literature on increased risk for diabetes in relation to organochlorine pollutants such as PCBs and DDT[cxxvi]. In a recent study that we carried out in collaboration with a Candian First Nation community and Health Canada, we observed an increased risk for

diabetes with certain PCB congeners and DDE (a metabolite of DDT). Consumption of trout and white, but not walleye and pike, were protective for diabetes (submitted for publication).

Animal studies have shown that mercury exposure can affect thyroid function[cxxvii]. In humans, few studies have examined this relation. In a study that we carried out with fresh-water fish-eaters from Quebec, we observed an increase in serum thyroid stimulating hormone (TSH) with hair and blood Hg concentrations in men, but not in women[cxxviii]. The long-term consequences of these changes are not known.

In a recent study of fish-eaters in the Brazilian Amazon, we observed a cataractogenic effect of mercury exposure (Lemire et al, submitted). The prevalence of age-related cataracts increased with increasing mercury exposure. This relation was not present for those with elevated plasma selenium, suggesting that selenium can offset this effect of mercury.

Like for diabetes, no evidence has been found for an association between mercury exposure and arthritis.

There is a clear need for more studies on the effects of mercury with age. In non-human primate studies, visual deficits, that had not been present in the monkeys when they were young, developed with age, in relation to prenatal exposure to Hg[cxxix,cxxx].

2. Any evidence of an interactive effect of mercury and other contaminants on human health

Fish tend to accumulate halogenated organics including PCBs, dioxins and related compounds. The neurodevelopmental effects of PCBs and, to a lesser extent, dioxins, share some similarities to those observed for MeHg[cxxxi]. This can potentially present difficulties in determining causality and in constructing MeHg-specific dose-response relationships. Because MeHg tends to associate more with proteins than fats, fish species

with elevated levels of MeHg are not necessarily those with elevated levels of the lipophilic halogenated organics. Thus, for fish consumption where both exposures occur, the influence of the individual contaminants can potentially be separated by statistical techniques if a variety of fish species is consumed and sufficiently precise exposure metrics are collected. In the Faroe Islands studies, both MeHg and PCBs appear to jointly affect some developmental endpoints. However, while MeHg appeared to enhance the PCB-attributable effects, the PCBs appeared to make a relatively minor contribution to the MeHg-specific effects[cxxxii,cxxxiii]. Contradictory findings were observed in a study of cognitive development associated with exposures to MeHg and PCBs in the Lake Oswego area of New York State.[cxxxiv]. In that study, elevated PCB exposure appeared to potentiate MeHg effects. However, both MeHg and PCB levels were considerably lower than in the Faroes study, and no PCB-MeHg association was observed on follow-up testing of the cohort. As yet, the limited epidemiological and experimental data do not support that developmental PCB co-exposure markedly exacerbates MeHg toxicity. In some cases, a competitive rather than synergistic action of PCBs was demonstrated on endpoints related to MeHg neurotoxicity[cxxxv]. The latter finding cannot be considered a neuroprotective action of PCBs. The final outcome may be masked by neuronal compensation or plasticity in young individuals, but may be uncovered with age[cxxxvi]. Humans are exposed to complex mixtures of contaminants through food. This implies that pollutants other than the PCBs may concur to toxicity. PCBs themselves do not behave as a single chemical entity. Distinct congeners possess different intrinsic toxicity and neurotoxic potential. This should be kept in mind when analyzing the biomarkers data of PCB exposure. Indeed, the scant knowledge in this field calls for additional human and animal studies that address these unresolved issues, as well as other metal contaminants that may also be present in fish[cxxxvii].

Elemental Hg continues to be used in dental amalgam for the treatment of dental carries. In populations with significant amalgam use, elemental Hg may account for a proportion of total Hg exposure comparable to or greater than MeHg [cxxxviii]. It is known that elemental Hg vapor can cross the placenta and accumulate in fetal tissue[cxxxix,cxl,cxli] and animal data suggests that elemental Hg has the potential to cause adverse neurologic

developmental effects[cxliii]. Both elemental Hg and MeHg are metabolized in the brain to the inorganic mercuric form[92]. It is not known whether the ultimate neurodevelopmental toxicant of MeHg is MeHg itself, the inorganic mercuric ion, free radicals generated in the conversion to the inorganic species, or some combination of these. If the inorganic form is the ultimate toxicant of MeHg in the developing brain, or if MeHg and inorganic Hg share common neurodevelopmental toxic mechanisms, then current estimates of risk based on MeHg exposure alone could underestimate the population risk. Additional research is clearly needed to address these questions.

3. Methods of measuring past or present mercury exposure in humans.

Hair and blood Hg concentrations are both accepted as valid biomarkers of MeHg exposure, although each provides a somewhat different reflection of exposure[cxliii]. Blood gives an estimate of exposure over the most recent one to two half-lives with the half-life of MeHg in blood being 50-70 days, while hair reflects the average exposure over the growth period of the segment[cxliv]. Hair Hg is predominantly MeHg with MeHg constituting from 80% to 90-98% of hair total Hg [cxlv]. For populations with regular and frequent fish consumption, hair total Hg and blood MeHg are consistently correlated[cxlvi]. Generally, hair is 250 to 300 times more concentrated in mercury than is blood[cxlvii]. However, in populations and individuals with infrequent fish consumption, or where bolus doses of MeHg occur, there can be considerable inter- and intraindividual variability in the relationship between hair and blood Hg levels resulting from temporal differences in the retention of Hg by each biomarker[128,cxlviii]. Segmental analyses of hair Hg can provide a chronology of exposure over time[101,102]. However, information on short term peaks in exposure is not well represented by such analyses[97]. Another consideration is that the growth rate of hair, generally estimated at 1 cm per month, can have both inter- and intra-individual variability[119]. Recent advances in a single hair strand analysis[cxlix], including measurement of Hg at micron resolution using laser ablation[cl] should yield more information on the relationship between Hg uptake and Hg deposition in hair.

Hg levels in toe and fingernails have also been used as biomarkers of Hg exposure, mostly in major studies of the cardiovascular effect of MeHg[cli,cliii], but to what extent these reflect organic or inorganic Hg exposures remains to be clarified[cliii]. A recent study of women, with no history of occupational exposure to Hg, showed similar correlations between Hg intake through fish consumption and both toenail and hair Hg concentrations, however only total Hg was assessed[cliv]. In this study, hair, toenail and urinary total Hg were highly correlated. Urinary Hg levels largely reflect exposure to inorganic Hg[100] and are not considered useful bioindicators of MeHg exposure. There are, however, several recent reports of positive correlations between fish consumption and urinary Hg[clv,clvi,clvii] authors of these studies propose that demethylation may account, at least partially, for this observation. The relation of fish consumption and inorganic Hg in different biological tissues, and its consequence for human health still need to be elucidated.

Health effects from low to moderate levels of MeHg exposure have been reported in a variety of systems and domains. Each of these effects may depend on different aspects of exposure (e.g. fish-eating patterns, time of exposure (first, second or third trimester, childhood, adulthood)). Therefore, the different reflections of exposure provided by hair and blood Hg concentrations may provide different information about dose-response for different exposure populations and different exposure scenarios. Few studies have investigated side-by-side dose-response relationships for both biomarkers. In the study in the Faroe Islands, maternal hair and fetal cord blood predicted similar, but not identical patterns of effect across various measures of neurologic performance.[119]

5. Concluding Remarks

Many of the high dose exposure occurred decades ago. It is increasingly difficult to re-establish the dose-response relationship among the exposed population. Moreover, many of the health complains from the affected population have not been properly diagnosed and documented. It is important to have data from comprehensive health surveys in

affected areas to have a better understanding of the health effects. Meanwhile, the issue of mercury poisoning is a global concern. Burning of fossil fuel is the main source of Hg pollution in the atmosphere[clviii] and recent modeling study showed that Hg deposition in the Pacific Ocean would double relative to circa 1995 by 2050[clix]. Fish is an invaluable resources in many countries and about 20% of the world's population derives one-fifth of its animal protein from fish[clx] and it is an important component of traditional food among Aboriginal Peoples in Canada[clxi]. It is our hope that the recent increase of scientific research can generate results that can be used effectively in promoting healthy diet and good health.

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Opinions on Dr. Masazumi Harada's studies in Ontario based on articles provided by the Mercury Disability Board.

Prepared by Donna Mergler, Ph.D. and Laurie Chan, Ph.D.
October 29, 2009 (Updated September 15, 2010)

We have received the following articles from the Mercury Disability Board for review.

1. Harada, M.; Fujino, T.; Akagi, T.; Nighigaki, S. Epidemiological and Clinical Study and Historical Background of Mercury Pollution on Indian Reservations in Northwestern Ontario, Canada. Bull. Inst. Constit. Med. 26 (3-4). 15 pgs. 1975.

2. Harada, S. Harada Report, translated, titled : " Minamata Disease Report – an investigation into Mercury Contamination in the Indian Reserves – A Clinical Study" with advisory note re the translation, 1975 from the Ministry of Health, Ontario.

3. Harada, M.; Fujino, T.; Akagi, T.; Nighigaki, S. Mercury Contaimination in Human Hair at Indian Reserves in Canada. Kumamoto Med. J. Vol. 30, No. 2, 1977, 99: 57-64.

4. Harada, M,; Fujino, T.; Oorui, T.; Nakachi, S.; Nou, T.; Kizaki, T.; Hitomi, Y.; Nakano, N.; Ohno, H.; Followup Study of Mercury Pollution in Indigenous Tribe Reservations in the Province of Ontario, Canada, 1975 - 2002. Bulletin of Environmental Contamination and Toxicology, Vol. 74, No. 4, 2005. 8 pgs.

5. Harada, M,; Fujino, T.; Oorui, T.; Nakati, S.; Ohno, H.; Clincial Follow up Research of Mercury Intoxication in a Reserve (1975 – 2002) (Literal summary translation) Sources Unknown.

6. International Forum on Environmental Pollution and Health Effects. "What are the lessons from 50 years of Minimata disease?" 8-12 Sept. 2006.
   - Opening Greetings by Dr. M. Harada
   - "Thirty Years of Uncertainty – Mercury Poisoning in Wabaseeemoong" by Anthony Henry
   - " How to test for Mercruy Poisoning Mercury Disability Claims" by Gabriel Fobister

7. "Long-term study on the effects of mercury contamination on two indigenous communities in Canada (1975-2004)" by Masazumi Harada et al. Translation by Tadashi Orui, proofread by Thor Aitkenhead.

The seven documents contain information on 3 studies conducted by a team of Japanese researchers led by Dr. M. Harada:

1. Results of neurological examinations conducted on 89 inhabitants of Grassy Narrows and White Dog in March and August of 1975 and 71 hair samples were collected for mercury analysis.
2. Results of neurological examinations conducted on 57 inhabitants of Grassy Narrows in August/September 2002 and 47 hair samples were collected for mercury analysis.
3. Results of clinical examinations including tests on sensation, fingertip movement and sociological research conducted on 87 residents from Grassy Narrows and 69 residents from White Dog.

Dr. M. Harada has 29 publications on mercury poisoning as cited in PubMed with the first one published in 1964. His team of researchers are affiliated with departments of Neuropsychiatry, Psychology and Environmental Medicine at various institutions in Japan. Most of them are from Kumamoto, the Prefecture where Minamata disease occurred. The authors have clinical experience on diagnosing neurological symptoms associated with mercury exposure and recently published (2008-2010) 5 papers on observations from follow up studies on Minamata residences in the journal Epidemiology, Environmental Research and Science of the Total Environment. However, only 1 of the 7 documents supplied reporting results from the studies in Canada was published in an international journal, Bulletin of Environmental Contamination and Toxicology which has a very low impact factor of 0.609 (2008).

Harada et al, 1977. Mercury contamination in human hair at Indian reserves in Canada; Kuamoto Med. J. 30:57-64

This article reports some of the aspects of the study that was performed in 1975. A total of 89 persons from the Grassy Narrows and White Dog Reserves were examined for signs and symptoms of Minamata Disease and 71 hair samples were analysed for mercury.

The presentation of the results for hair sampling would not be accepted by today's standards, but the information presented was important. They show that hair mercury concentrations were high and related to fish consumption patterns based on answers from an interview question of the participants "do eat fish during summer" versus "not eating fish since 1970". Sequential hair mercury analyses revealed that in summer when fish consumption increased, there was a parallel increase in hair mercury.

Among the group that continued to eat fish following 1970: 23/71 (32.4%) had levels above 30 ppm, 20/71 (28.1%) had concentrations above 20 ppm (one assumes between 20 and 29 ppm), and one person had a maximum hair mercury level of 80.3 ppm. For those who had not continued to eat fish since 1970, levels were considerably lower and from Figure 2, one can see that most were below 10 ppm, although at times, this level was exceeded.

The authors indicate that no one presented all of the classical signs and symptoms of Minamata Disease, determined through examination of the Minamata victims, although many persons presented one or more classical signs of the disease. Since this was a clinical study and not an epidemiologic study, the authors based their diagnosis on the combination of clinical signs such as visual field constriction and 'glove an stocking' type sensory disturbance and high mercury levels. In addition, the authors describe what they refer to as a 'correlation' between characteristic signs of Minamata Disease and exposure; indeed there were more persons with

more and more severe signs and symptoms with higher levels of mercury, better confirming a possible causal relation. Results presented in Figure 3 of this paper is the only evidence available showing there is a relationship between body burden of mercury and neurological symptoms among inhabitants in the two First Nation communities. Although there is no true statistical analysis, the results are compelling.

Harada et al, 1976. Epidemiological and clinical study and historical background of mercury pollution on Indian Reservations in Northwestern Ontario, Canada. Bul. Inst. Constitut. Med. 26: 169-184.

In this article, the authors indicate that the situation is more serious than they previously believed. One learns in this article that of the 89 persons reported on above, 33 reported that they had reduced or stopped eating fish, while 14 replied that they continue to eat "just as much as before". They also indicated in this article that bread was being baked with fish roe and concentrations of 0.41 ppm were measured in bread, which was consumed more regularly than fish.

They report on the mercury concentrations in fish, indicating that they were very high and many largely surpassed government agency recommended levels. They also briefly describe the study that was preformed by Takeuchi on a cat from White Dog, where damage, characteristic of methylmercury poisoning, was observed primarily in the brain and to a lesser extent in the peripheral nerves. These results were consistent with studies that had been previously carried out by Health Canada with cats that had eaten fish from Clay Lake. They present a table that show similar concentrations of mercury in the various organs of the cat from White Dog to the cats from Minamata.

With respect to human exposure, they indicate that the Environmental Services Branch (of Health Canada?) had reported in 1970 maximum exposure concentrations of 198 ppm from White Dog and 95.7 ppm from Grassy Narrows. It is not clear how all of the numbers from the 1970 measurements fit together, except to say that exposure was very high. They indicate that in 1975, they measured hair samples (see above) and reproduce a table from the Environmental Health Services Branch that show declining concentrations. We do not know from this table whether it was the same people that were sampled over time and at what time of year the sampling was done since the Harada et al study had shown important seasonal variations, with the highest levels in the summer.

In this article they provide more detailed information on the 89 persons that were examined using the "same methods that were applied in our mass examination for Minamata Disease in Japan". Here we learn that that the age of those examined ranged from 6 – 84 years. It should be noted that sick persons, who were unable to work, were excluded from this study which only included persons who were healthy enough to work. Many worked as guides, but some had sought other work.

They present the results of the neurological signs and symptoms that are characteristic of Minamata Disease, indicating that these were immediately recognized. They describe the details of the results of the neurologic examination, with emphasis on constricted visual fields, eye movement disturbances, sensory disturbances (including 'glove and stocking' paresthesia),

tremor, changes in reflexes and other motor dysfunctions. They conclude that although they observed a fair number of signs of Minamata poisoning, these are mild cases and many may have been caused by other factors. For sensory deficits, they did however report a dose-effect relation (see above).

This was not an epidemiologic study, but a clinical study and no causal relation was established. No data are presented with respect to age, and we have no information in this article whether the persons who presented neurological signs of dysfunction were young or old. Nor do we have any information on other factors, such as diabetes that may affect certain neurological functions. There is also no mentioning of how the participants of the study was chosen and it is not possible to deduce the level of representativeness of the observations to other inhabitants in the 2 First Nation communities.

Harada, S. Harada Report, translated, titled : " Minamata Disease Report – an investigation into Mercury Contamination in the Indian Reserves – A Cliuical Study" with advisory note re the translation, 1975 from the Ministry of Health, Ontario.

This translated article appears to be an earlier draft manuscript for the publications discussed above. Many of the tables and figures are the same. However, it provided some raw data such as observations on constriction of visual field of an individual participant and the clinical history of two participants who had 44 ppm and 33 ppm mercury in hair. Both of them worked as fishing guide. One participant showed symptoms of abnormal movement of the eyeball, adiadochokinesis, sensory disturbances in upper lip and the end of limbs, and weakening of muscular strength and the other showed symptoms of audio disturbances, subtle trembling, adiadochokinesis, sensory disturbances in the end of limbs.

Harada et al, 2005. Follow-up study of mercury pollution in indigenous tribe reservations in the province of Ontario, Canada 1975 – 2002. Bull. Environmental Contamination and Toxicology 74. 689-697.

In 2002, Dr. Harada's group went back to Grassy Narrows and examined 57 people, using the same neurological protocol as previously and as was used for Minamata patients in Japan. They also measured visual fields using Förester's perimetry.

Statistical analyses were minimal; they did not report any paired statistics, comparing those who had been examined twice or any multiple regressions that would take into account age or other factors.

No information is provided on the bases for recruitment.

They provide tables of symptoms and signs, and on the basis of clinical criteria for Minamata Disease, they classified the persons examined into 4 categories: those with Minamata Disease (11 persons); those with Minamata Disease with complications (12 persons); those with Light Minamata Disease (22 persons) and others (12 persons). Those with Minamata Disease were the older than those with milder forms, and the group 'others' included 8 children. They seem to indicate there were statistically more men than women in the more severe categories.

They indicate that the rate for Minamata Disease was 78.9%, but we have no idea what is the denominator. It may be 78.9% of this group of persons, most of whom had multiple subjective symptoms. Because there is no mention whether the samples were randomly selected, the results provide no information on whether the same percentage can be applied to other inhabitants in Grassy Narrows. In the discussion, the authors mention compensation and indicate that 21 of he persons examined here had received compensation, 20 were denied and a decision is pending for 3, while 13 did not file claims. Was this the basis for inclusion in the study? The compensation decisions appear to be related to age. The question of foetal mercury poisoning is not discussed.

The authors note that 43.2% of the 44 persons from Grassy Narrows that had been evaluated in 1975, had died, but do not provide any information on those that had been retested.

Harada, M,; Fujino, T.; Ooruí, T.; Nakati, S.; Ohuo, H.; Clincial Follow up Research of Mercury Intoxication iu a Reserve (1975 – 2002) (Literal summary translation) Sources Unknown.

This unpublished report provided many of the critical information missing in the previous article. The same two doctors conducted the examination in both the 1975 and 2002 studies. Nine persons participated in both studies. Hair mercury concentration results presented in Chart 1 show that their mercury body burden has significantly decreased. All nine of them had hair mercury concentration higher than 6 ppm and the maximum concentration was 44.2 ppm in 1975. In 2002, 8 of them were below 6 ppm and only one individual had higher mercury concentration at 18.1 ppm (the same person had 13.1-36.3 ppm in 1975). However, the authors concluded that the nine people only showed mild symptoms in 1975 but seven of the nine people had progressed from mild symptoms to typical or typical with complications in 2002 even though their hair mercury body burden had decreased.

The average of all 47 hair samples collected was quite low at 2.11 ppm (minimum: 0.11 ppm and maximum 18.1 ppm). Based on the results of the repeated participants, the authors predicted that the other examinees in the mild Minamata Disease group will likely progress to Minamata Disease in the future. Without information on the age of the participants, it is not possible to comment on whether this prediction is valid.

"Long-term study on the effects of mercury contamination on two indigenous communities in Canada (1975-2004)" Masazumi Harada, Masanori Hanada, Takashi Miyakita, Tadashi Fujino, Kazuhito Tsuruta, Akira Fukuhara, Tadashi Orui, Shigeharu Nakachi, Chihito Araki, Masami Tajiri, Itsuka Nagano. Translation by Tadashi Orui, proofread by Thor Aitkenhead.

This is a translation of a review paper (source is unknown). It summarized the findings of Dr. Harada's research on the two communities since 1975 including results of the study conducted in 2004 which has not been reported before.

The authors classified participants as having Minamata Disease if they showed more than one symptom, such as sensory disturbances (specifically the loss of sensation in the extremities), ataxia, disturbed ocular movement, imbalance, concentric construction of the visual field (tunnel

vision) and speech impairment. However, in cases when the participants were showing only sensory disturbances, they also classified them as Minamata Disease as long as there was no other disease causing the symptom. If the participants had another disease and also showed symptoms of Minamata Disease (but were not explained by that other disease), they classified the case as Minamata Disease with complications. If Minamata Disease symptoms were observed in case when the participants also reported other complications or were suffering from unstable mental state, or symptoms were inconsistent, they classified them as possible Minamata Disease. If symptoms, caused by another disease, were observed or no symptoms stated above were observed, they either classified them as another disease or normal.

Using the criteria above, they reported 60 cases of Minamata Disease (34.2% of total participants, excluding people 10 years old and younger), 54 cases (30.8%) of Minamata disease with complications and 25 cases (14.2%) of possible Minamata Disease for a total of 139 cases (79.4%). The rest were other diseases or normal.

They also reported 7 cases of cerebral palsy, 7 cases of intellectual developmental delay among toddlers and children. The authors did not specify how they defined the age of children but they reported 12 participants between 1 to 10 years old and 12 participants between 11 to 20 years old. However, they did not relate the cases to mercury poisoning.

The authors also compared their diagnoses with the decisions made by the Mercury Disability Board (MDB). Among the 60 participants diagnosed with Minamata Disease, 21were acknowledged and 39 were not acknowledged by the MDB. Among the 54 participants diagnosed as Minamata disease with complications, 27 were acknowledged and 27 were not by the MDB. In total, the MDB acknowledged 38.1% of the people we diagnosed with Minamata Disease, Minamata Disease with complications and possible Minamata Disease. Among the 75 participants not acknowledged by the MDB, 28 were diagnosed to have Minamata disease, 21 were diagnosed to have Minamata disease with complications and 11 were diagnosed to have possible Minamata disease by the authors, with a total of 60 (80.0%). Most of them had mild Minamata disease with sensory disturbances or sensory disturbances and impaired hearing, or mental symptoms. It is clear that the criteria used by the MDB were relatively more stringent.

The most valuable information reported was the observations of the 27 individuals who participated in both studies in 1975 and the follow up study in 2004. Most of them had moderate elevated level of mercury exposure with hair concentrations ranging between 10 to 20 ppm and the highest at 44.2 ppm in 1975. However, the authors did not report the hair concentrations of these individuals in 2004 but we presumed they were lower as the mean of all the participants were 2.3 ppm with the maximum at 25 ppm. Comparing the symptoms of the 27 residents between 1975 and 2002-04, 2 cases of sensory disturbances (the loss of sensation in extremities and around the mouth) and 6 cases of only sensory disturbances (the loss of sensation in extremities) in 1975 increased to 6 cases and 13 cases respectively in 2002-04. Seven of them also indicated the loss of sensation in whole body (2 cases duplicated with the loss of sensation in extremities). Three of them did not have sensory disturbances. Those with ataxia increased from 2 to 16 cases, concentric constriction of the visual field increased from 3 to 4 cases, speech impairment increased from 3 to 8 cases, imbalance increased from 2 to 7 cases, tremor increased from 5 to 10 cases, walking difficulties increased from 0 to 6 cases and stroke (cerebral

infraction) increased from 0 to 4 cases. According to their diagnosis, 13 of them had Minamata Disease, 11 had Minamata Disease with complications for a total 24 (88.8%). For comparison, the MDB acknowledged 21 applicants (77.7%) out of 27 participants and is providing them a pension. The authors acknowledged the possible effects of aging and complications but the progression of Minamata Disease-like symptoms were evident.

Conclusions:

There is no doubt that there was high mercury exposure in these two communities in the late sixties and early seventies. Although not as high as those that had been observed in Minamata, the concentrations are certainly considerably higher than those reported in the many studies that have conducted since that time, and in which neurological and/or cardiovascular effects have been reported in adults and children.

There is no doubt that at these levels of exposure many persons were suffering from mercury-related neurologic disorders. Following the results of exposure and effects in 1975, as well as earlier mercury in blood monitoring study conducted by Health Canada since 1970, there should have been extensive examinations and follow-up of these communities from that time forward, and assistance with respect to health and nutrition.

Dr. Harada's follow-up study indicates that there is probably still a problem due to previous mercury exposure. This is consistent with findings from animal studies, where effects, which were absent when the animals were young, became evident as they aged[i,ii]. Similar latency period between exposure and neurological symptoms was also observed in humans (see Weiss et al. 2002) for review[iii]. Their study focussed only on neurological clinical outcomes when the scientific literature shows that neurobehavioral performance and cardiovascular functions can be affected through *in utero* and post-natal exposure.

The discrepancies between Dr. Harada's assessment and the MDB are due to different criteria used for evaluations. Similar discrepancies between Dr. Harada's team and the Japanese government are reported in Japan. However, the Japanese government is revising their definition of Minamata Disease victims to be more inclusive and a new round of compensation is expected to release in 2011 (Dr. Hikaru Kobayashi, Vice-Minister of the Environment Ministry of the Environment in Japan, personal communication, April 2010).

Even though the general populations in the two communities have almost background levels of mercury exposure as indicated by the hair mercury concentration. Some individuals may still have high exposure as shown by Dr. Harada's latest report that the maximum was 25 ppm. One of us (Chan) conducted a study with the two communities in 2003 and found similar low level of mercury in hair samples as reported by Dr. Harada in Grassy Narrows. However, higher levels (maximum at 60.3 ppm) were found in some individuals in White Dog suggesting that the problem of mercury exposure still persists in White Dog. Unfortunately, as stated in the latest report from Dr. Harada: "there is hardly a report with data of both hair mercury levels and clinical examinations, together, on each examinee, even in Canada".

We acknowledge Dr. Harada and his team for their effort that spans three decades of research. They have made significant contributions to the understanding of long-term effects of

mercury contamination and the health of the residents in the two communities. However, Dr. Harada's follow-up clinical evaluation should be seen as a preliminary study showing the need for a comprehensive epidemiologic study that would include all of the known outcomes of mercury exposure (including cardiovascular disease) and could take into account co-morbidity from other diseases, such as diabetes and /or alcohol and test for possible interactions. Such a study should also take into account the presence of other contaminants. For this study it would be most useful to have all of the results of hair and blood sampling by Health Canada, Dr. Chan and Dr. Harada, as well as the results of the neurological examinations that were done by Dr. Harada.

We also want to highlight the urgent need to improve the general health of the two communities as the health status of the participants was clearly poor. The rate of residents reporting neurological symptoms was very high for such as small population. There were many other reported diseases including 49 cases (28.0%) of high blood pressure, 42 cases (24.0%) of diabetes, 19 cases (10.8%) of heart disease, 13 cases (7.4%) of stroke, 7 cases (4%) of thyroid problems, 5 cases (2.8%) of Kennedy-Alter-Sung Syndrome (genetic diagnosis). In addition to those, dystrophy, an impaired spinal column in the cervical vertebrae, wounds such as broken bones, cancer, tuberculosis, sniffing, liver disease, kidney disease, Buerger's disease and sarcoidosis were seen. It is paramount that members of the two communities are receiving the necessary medical care and support. In contrast, residents in Minamata, Japan enjoy superb health care from neurologists and therapists even they had not officially been classified as victims of Minamata Disease.

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[i] Rice DC, Hayward S. Comparison of visual function at adulthood and during aging in monkeys exposed to lead or methylmercury. Neurotoxicology. 1999;20:767-84.

[ii] Burbacher TM, Grant KS, Mayfield DB, Gilbert SG, Rice DC. Prenatal methylmercury exposure affects spatial vision in adult monkeys. Toxicol Appl Pharmacol. 2005 Oct 1;208:21-8.

[iii] Weiss B, Clarkson TW, Simon W. 2002. Silent latency periods in methylmercury poisoning and in neurodegenrative disease. Environ Health Perspect 110(S5): 851-4.

Literature Review regarding the Impact of Mercury on Human Health

Summary of a text produced by Drs. Laurie Chan and Donna Mergler for the Mercury Disability Board

presented by
Donna Mergler PhD
Professor Emerita
University of Quebec at Montreal

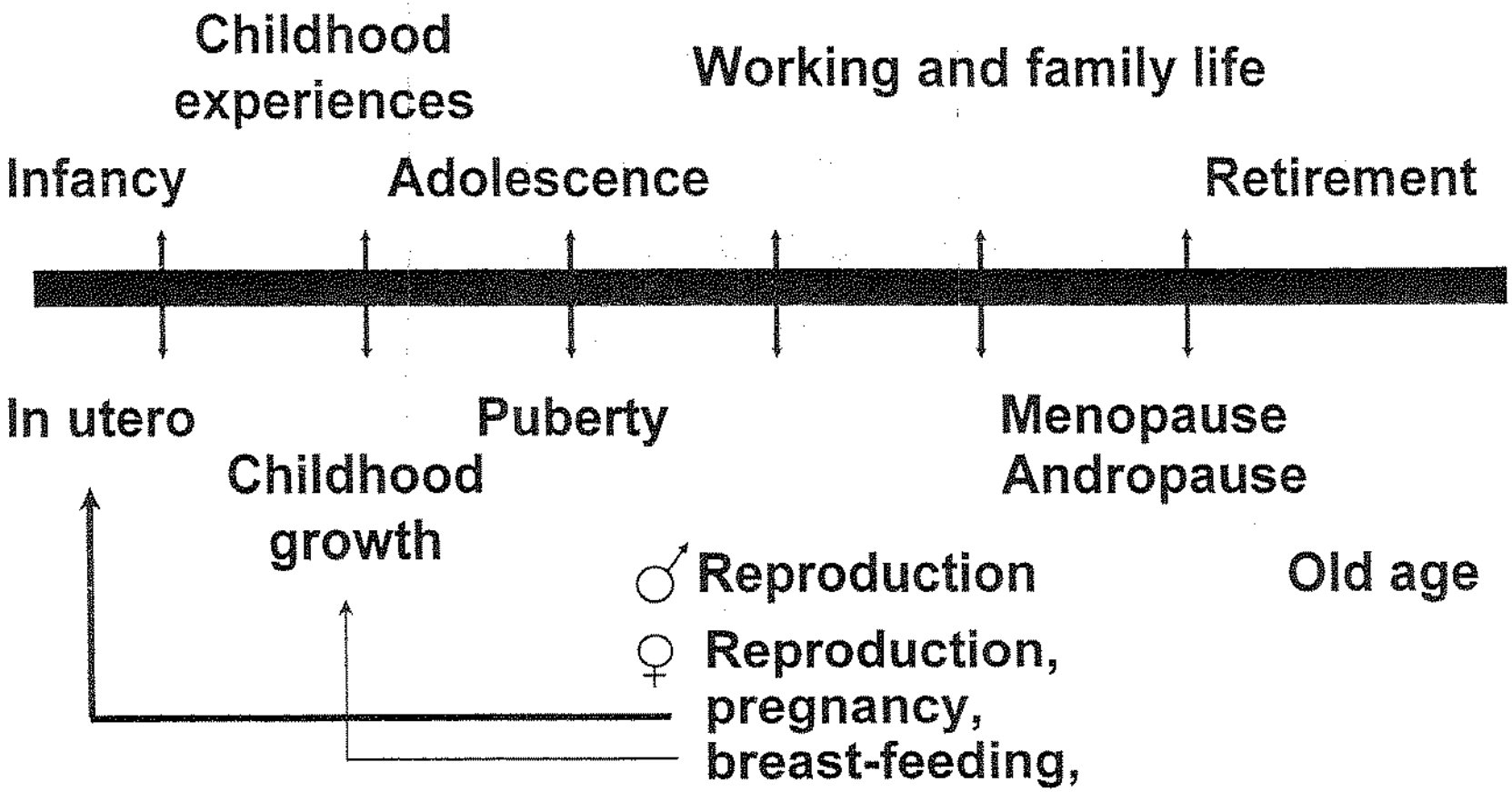
Cinbiose – PAHO-WHO Collaborating Center for the Prevention of Work and Environment related Illness – PAHO/WHO

Mandate

1. The effects of mercury contamination on human health, including the fetus particularly:
    - 1.1 Effect on human physiology over the life course including short- and long-term effects;
    - 1.2 Disability related to mercury;
    - 1.3 Mental health or behavioural effects of mercury including psychosis;
    - 1.4 Any evidence that mercury accelerates the development of chronic diseases related to the thyroid gland, arthritis, diabetes and the nervous system.
2. Any evidence of an interactive effect of mercury and other contaminants on human health.
3. Methods of measuring past or present mercury exposure in humans.
4. A review of Dr. Harada's work

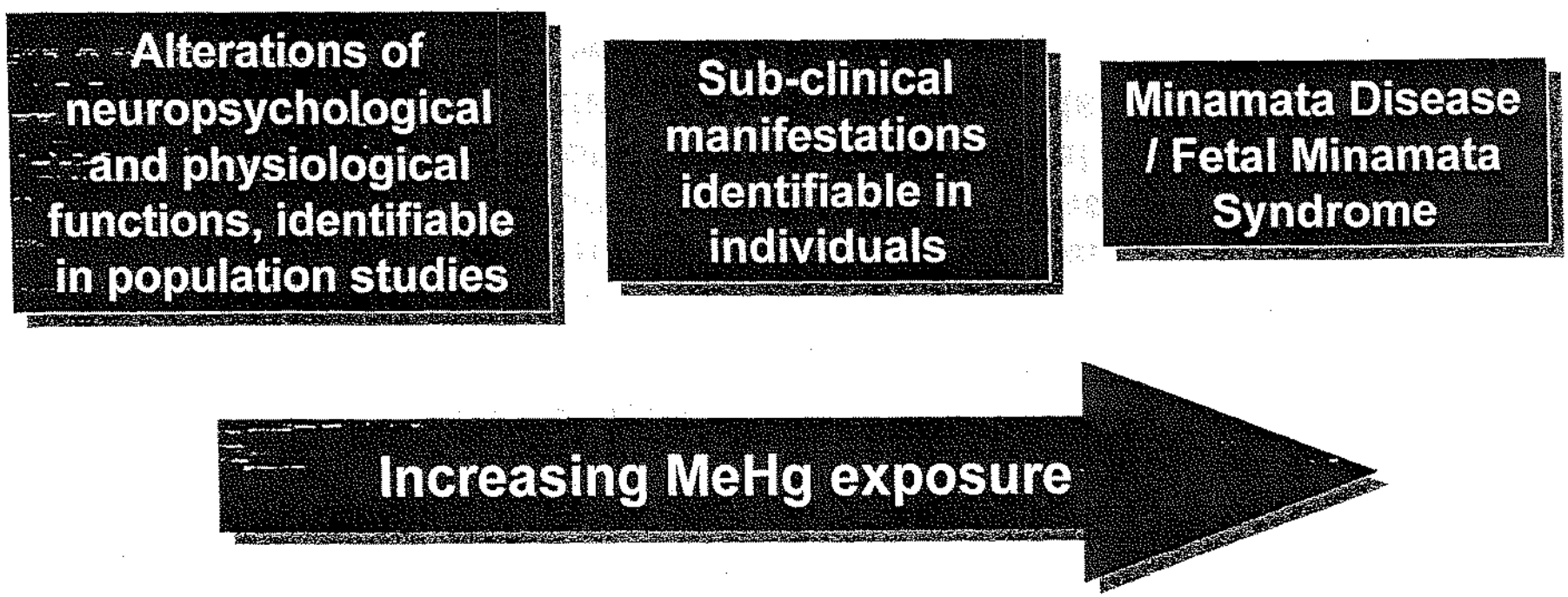
The Board intends to use the literature review to inform a process regarding the value of the current tools used in assessing eligibility for funding

Social and biological life span



Sinbiose

A continuum of severity of effects with increasing exposure



Effects on human physiology throughout the lifespan

- *In utero* exposure:
  - **In Minamata, infants exposed to mercury through the mothers' placenta showed severe cerebral palsy-like symptoms, even when their mothers had mild or no manifestation of the poisoning: mental retardation, cerebellar ataxia, primitive reflexes, disarthria and hyperkinesias were observed.**
  - **At the sub-clinical and population level, several studies in different parts of the world, have reported poorer neurologic status and slower development in newborns, infants and/or children exposed *in utero* MeHg and/or during early childhood.**
  - **Some studies have shown both positive effects of fish consumption and negative effects of mercury**

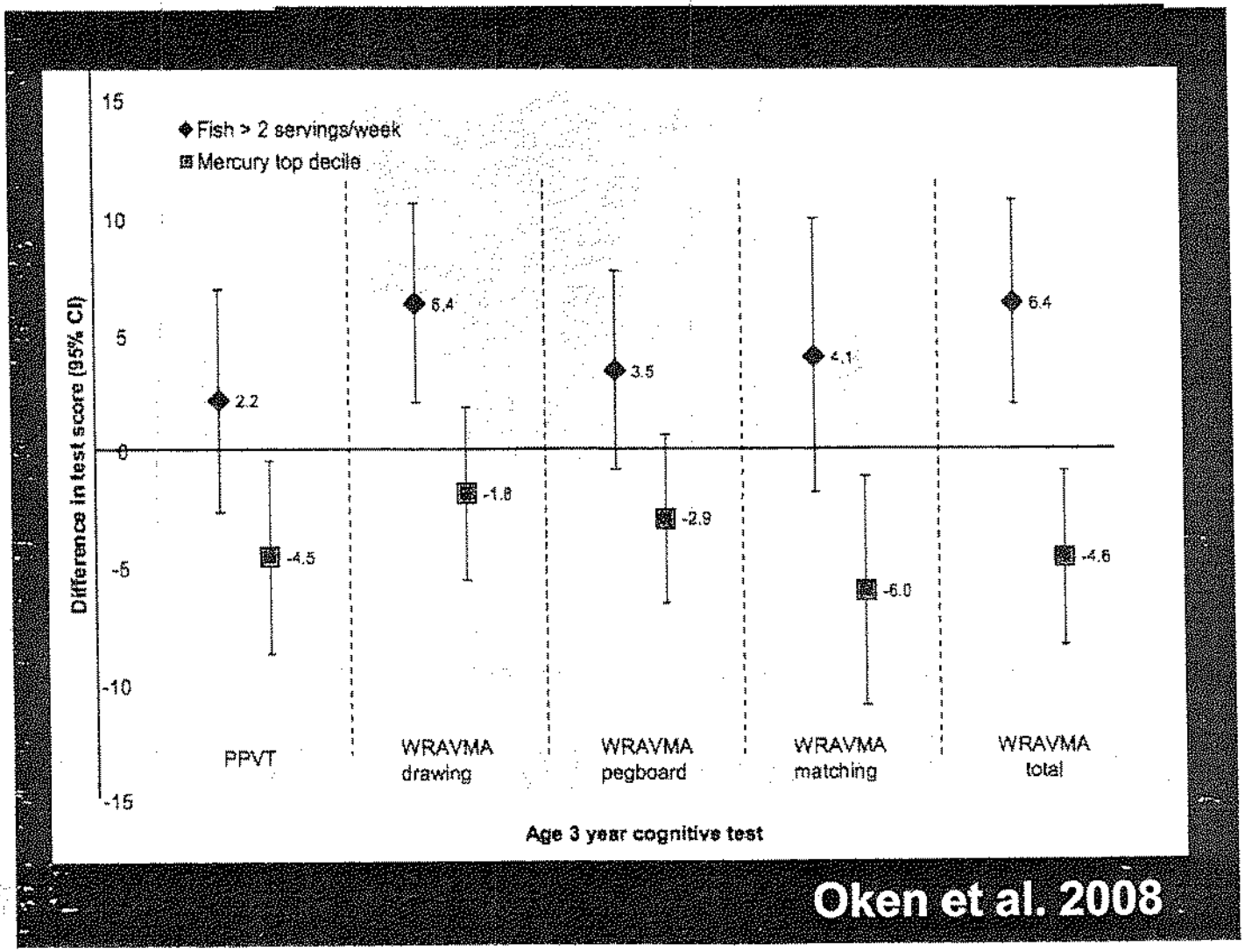
Opposing effects of Hg and fish consumption on neurobehavioral performance in 3 year olds

N = 341 mother/child pairs (Massachusetts)

Mean maternal total fish intake :1.5 ± 1.4 servings/week

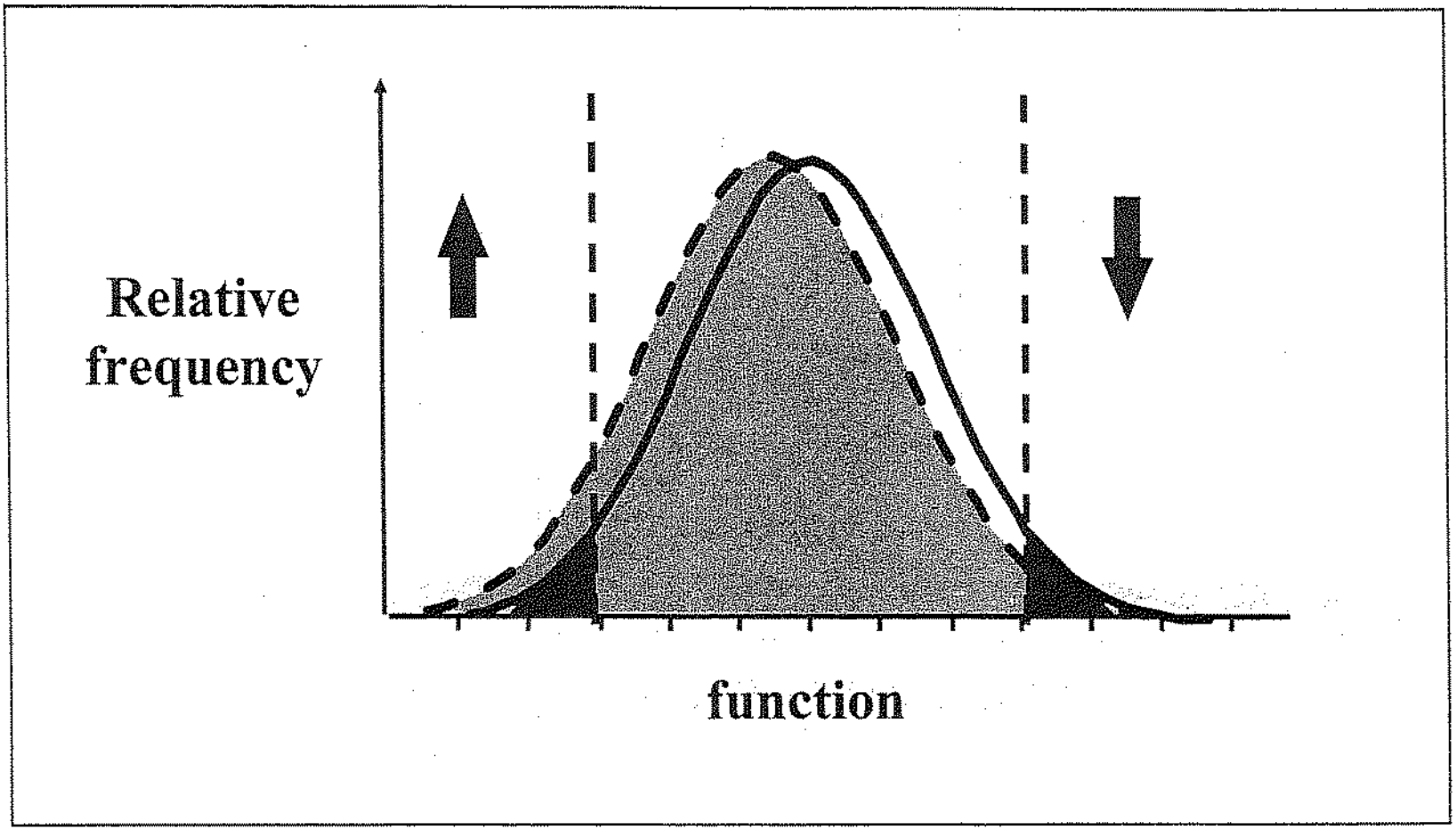
40 (12%) mothers consumed >2 servings/week

Mean maternal hair mercury level: 3.8 ng/g. Top decile >1.2µg/g



Oken et al. 2008

Why subtle alterations are important



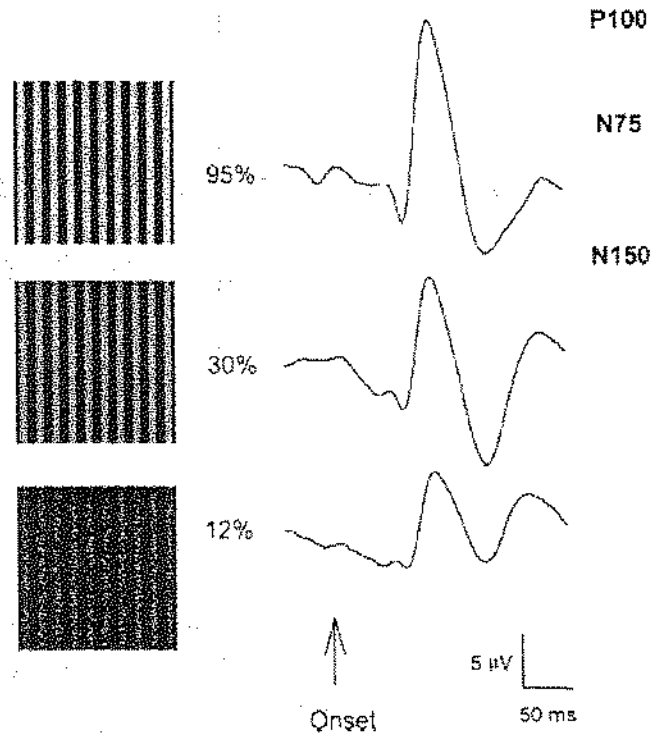
(adapted from Rice, 1998)

Effects on human physiology throughout the lifespan

- **Childhood exposure**
  - **Studies of children exposed to mercury through fish-consumption have shown cognitive and motor deficits.**
  - **Electrophysiological studies of children exposed in relation to mercury have shown changes in evoked potentials**

A study with Inuit children reported Hg-induced electrophysiological changes

- In Canadian Inuit children, prenatal and current Hg exposure were associated with changes in latencies for Visual Evoked Potentials



(St-Amour et al, 2006)

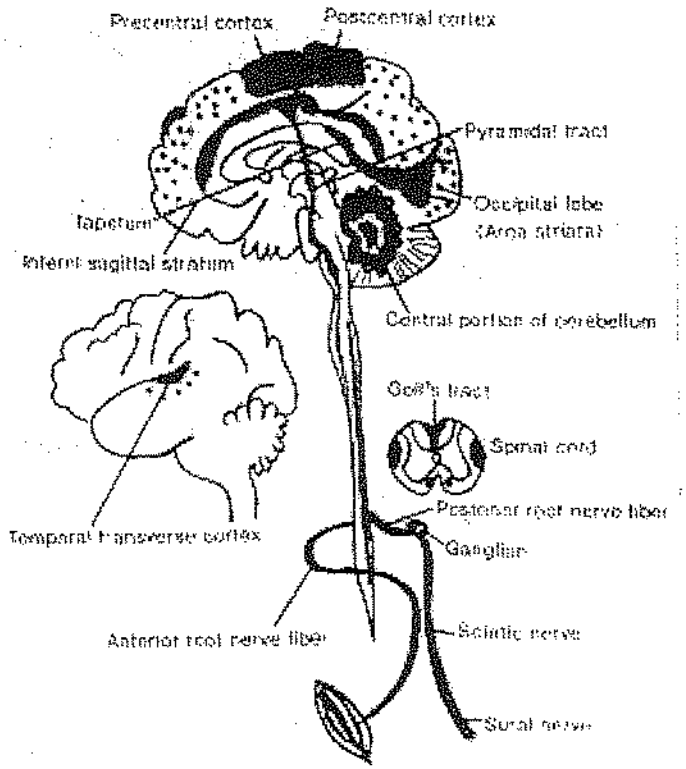
Sinbiose

Effects on human physiology throughout the lifespan

- **Reversibility**
  - **In our studies with fish-eaters in the Brazilian Amazon:**
    - Following reduction of exposure, motor functions improved but visual functions continued to decline in relation to past mercury exposure;
    - Age-related cataracts increased with mercury exposure

Effects on human physiology throughout the lifespan

- Adult exposure
  - MD at very high exposures
  - Lower exposures have been associated with motor, cognitive and visual deficits
  - Inconsistent results at very low exposures



Red: primary lesions
Blue : secondary lesions
(from the Minamata Institute)

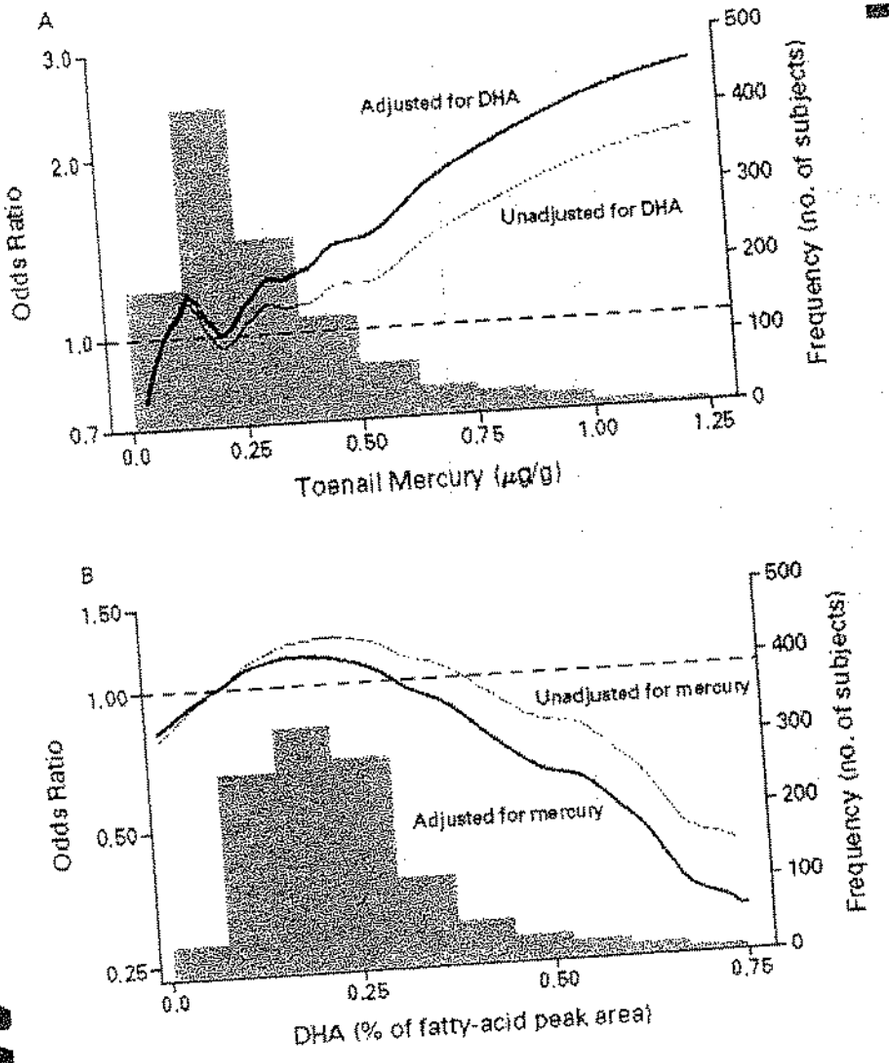
Effects on human physiology throughout the lifespan

- Aging and past mercury exposure
  - Studies carried out of persons over 40 who had lived in the mercury-polluted areas surrounding the city of Minamata. Annual medical examinations, performed on about 1,500 persons, showed no difference in the prevalence of disease between those from the polluted area and those from other areas, although those from the polluted area had more complaints of poor health.
  - Persons with a history of compensated Minamata Disease scored significantly lower on a scale of activities of daily life.
  - Other studies of persons from a nearby polluted area, who had been exposed to lower doses of mercury over a twenty year period, still suffered from distal paresthesia of the extremities and lips 30 years after cessation of exposure.

Cardiovascular system in adults

The Panel on Health Risks and Toxicological Effects of Methylmercury:
Donna Mergler, Henry A. Anderson, Laurie Hing Man Chan, Kathryn R. Mahaffey, Michael Murray, Mineshi Sakamoto and Alan H. Stern

Methylmercury Exposure and Health Effects in Humans: A Worldwide Concern



Case control study of 684 men with a first diagnosis of myocardial infarction and 724 controls

(Guallar et al, 2002)

Cardiovascular function

- Blood Hg was associated with changes in heart rate variability (HRV) and increased systolic pressure in Canadian Inuit men and women (Valera et al, 2008)
- In Faroese whalers, Hg exposure was associated with increased blood pressure and common carotid intima-media thickness, but HRV was equivocal (Choi et al, 2009)

Sinbiose

Systolic Blood Pressure in a Canadian Inuit Population (n =731)

	Beta estimate	p
Blood Hg (log)	+1.27	0.05
Serum %EPA	- 1.75	0.05
Blood Se	- 2.80	0.03
Blood Hg (log)	+2.14	0.0004

- EPA and Hg did NOT modify the relation between blood Hg and blood pressure (interaction term not significant)
- Not adjusting for these elements could underestimate effect size

Valera et al . 2009

Study of Dr. Harada's team

- Returned to the population-based study of 1971.
- Compared hypertension in exposed group from Minamata (n= 833) with control group (n=755) for the exposed group in relation to hair mercury from 1960
- Prevalence Odd's ratios for the Minamata population compared to controls :
  - Past history of hypertension: 1.6 [95%CI:1.2–2.1]
  - Measured hypertension: 1.4 [95% CI: 1.1–1.9],
- The authors conclude a causal relation

Sinbiose

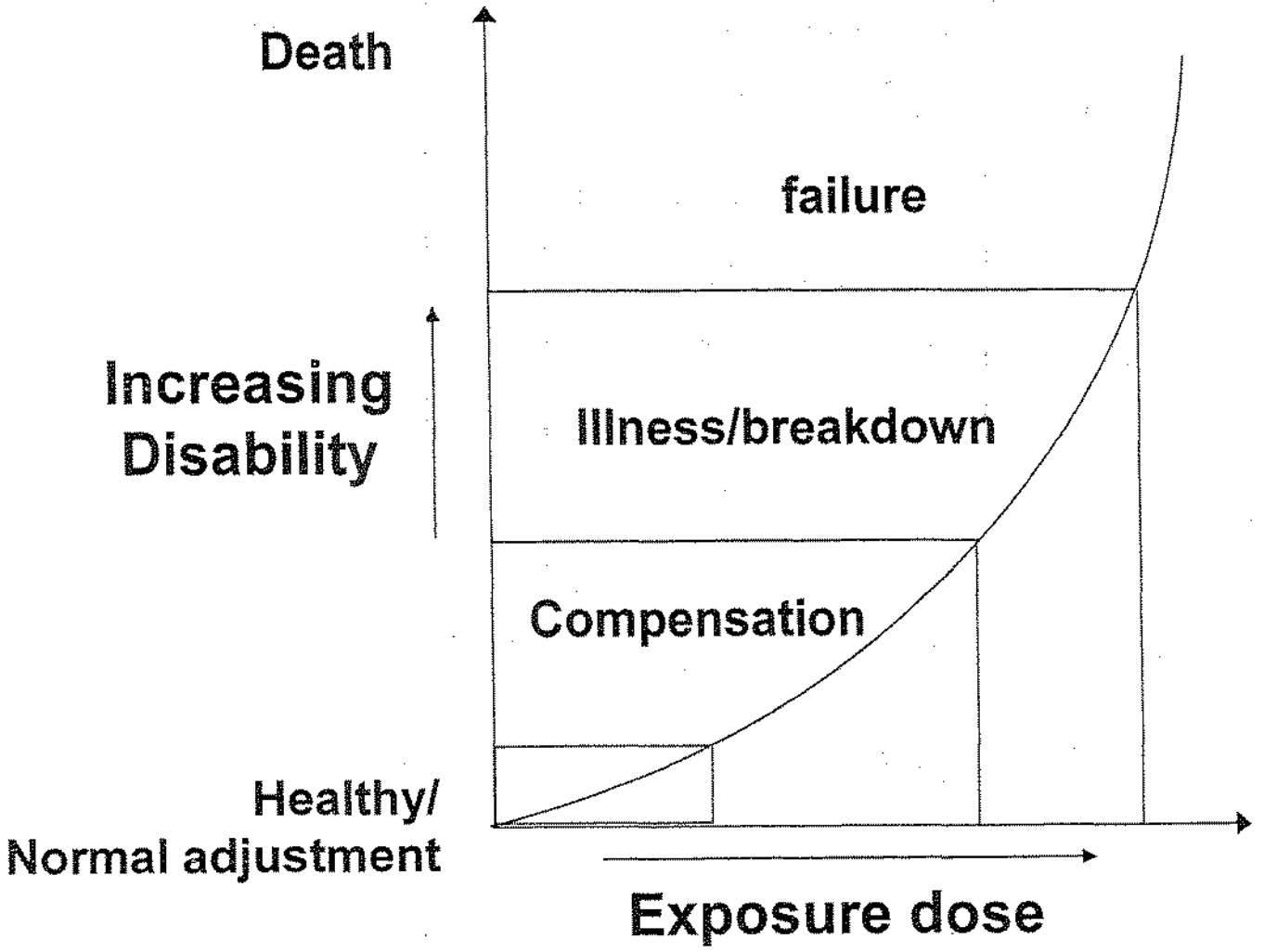
(Yorifuji et al, 2010)

Other physiological effects

- There is some evidence for effects of mercury on thyroid hormones, but more research needs to be done before this is confirmed
- There is some evidence for effects of mercury on mood states, but more research needs to be done before this is confirmed
- Although some studies suggest that mercury and other pollutants (such as PCBs) may act through different pathways, PCBs have also been shown to be neurotoxic and there is growing evidence linking PCBs with a higher prevalence of Type 2 Diabetes

Sinbiose

Exposure & Disability



(Hatch, 1962)

Minamata Disease (MD)

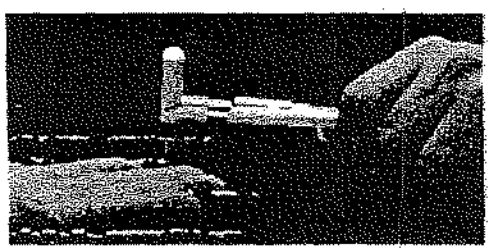
- Sentinal neurologic signs of MD
  - distal sensory disturbances (glove & stocking)
  - constriction of visual fields
  - ataxia (loss of coordination)
  - dysarthria (motor speech disturbance)
  - auditory disturbances
  - tremor

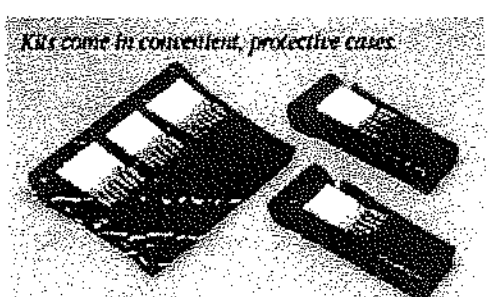
Sensory Testing

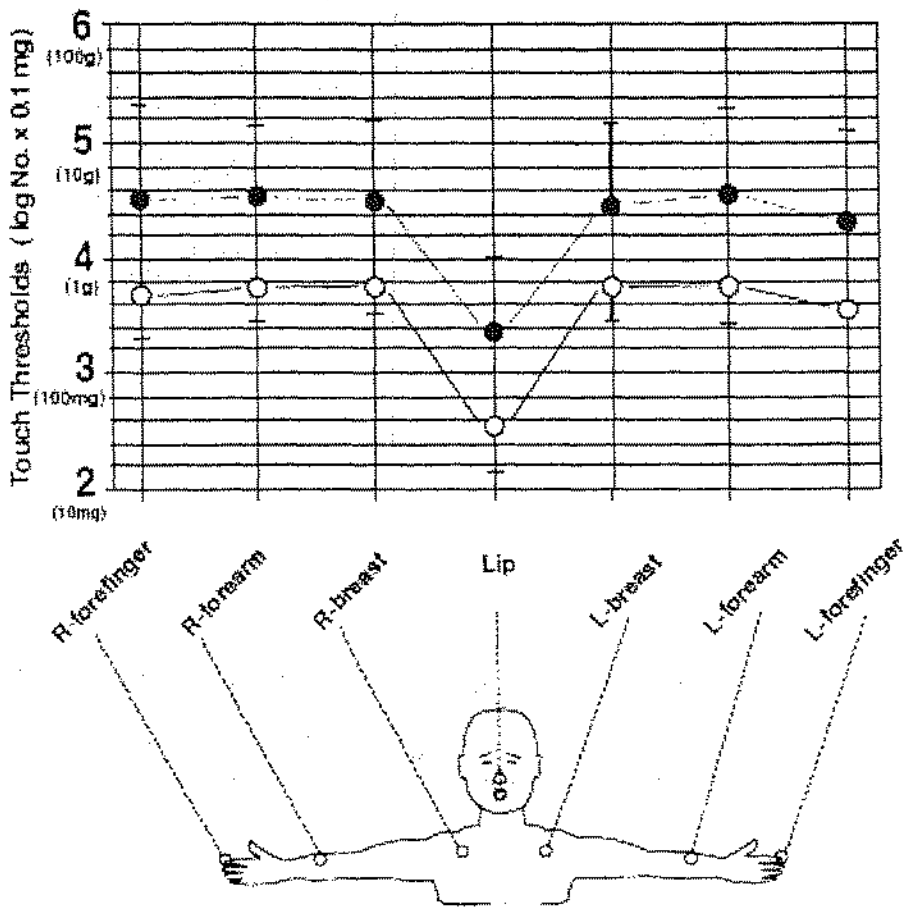
- **The Minamata Disease diagnosis includes glove and stocking sensory loss, which reflects damage to the peripheral sensory nerves**
- **In 2001, Uchino et al, wrote about the 2 different theories on MD sensory loss:**
  - ***"..it is derived from lesions in the peripheral nerves based on clinical observation that most patients present so-called "glove and stocking" like sensory disturbances based on clinical observations"***
  - ***"..sensory disturbances are caused by lesions in the sensory cortex based on pathological and electrophysiological findings"***

Sensory testing

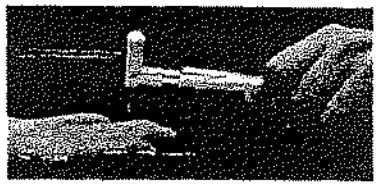
Touch threshold



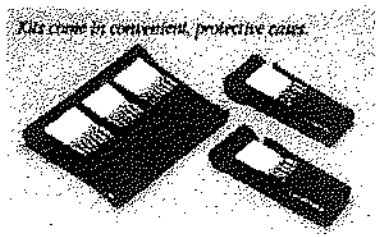




(Ninomiya et al, 2005)

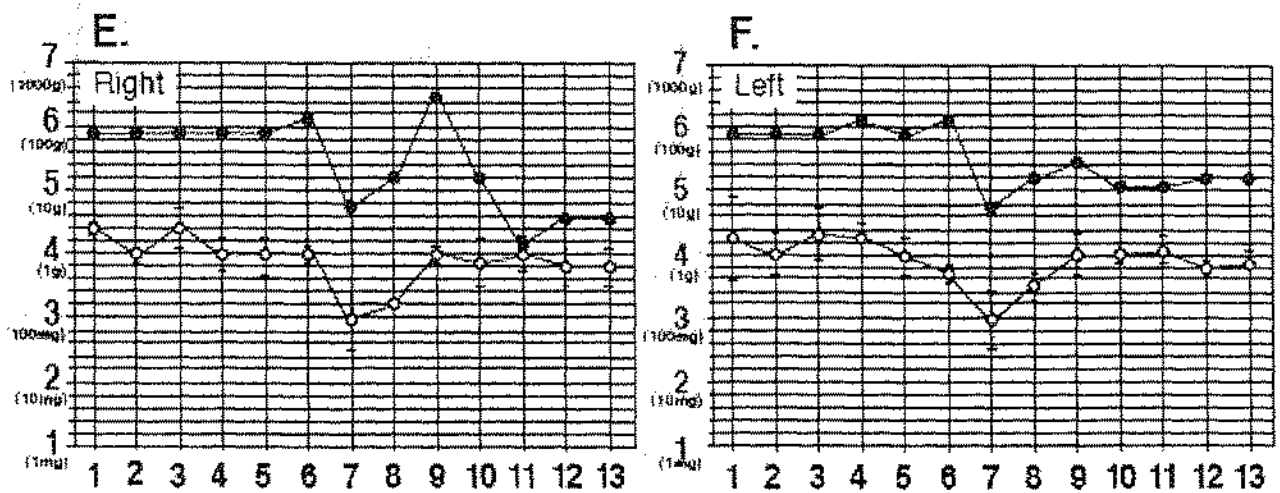


Sensory testing

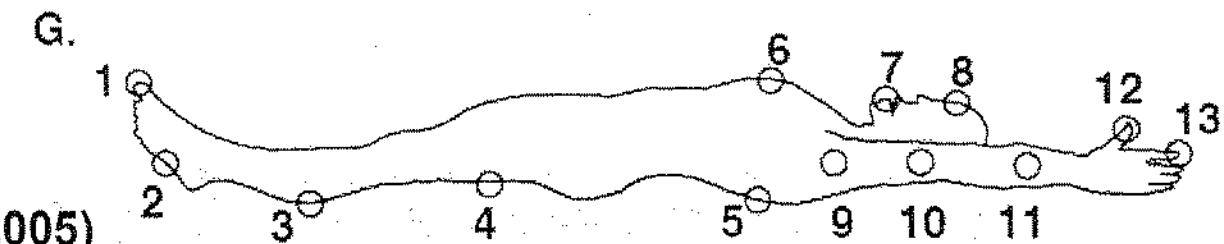


Touch threshold : Minamata patient

Case 3

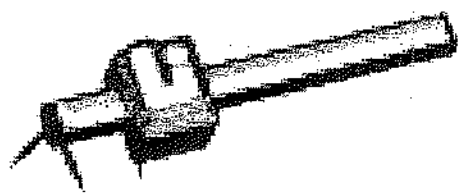


Control group
(n= 53)

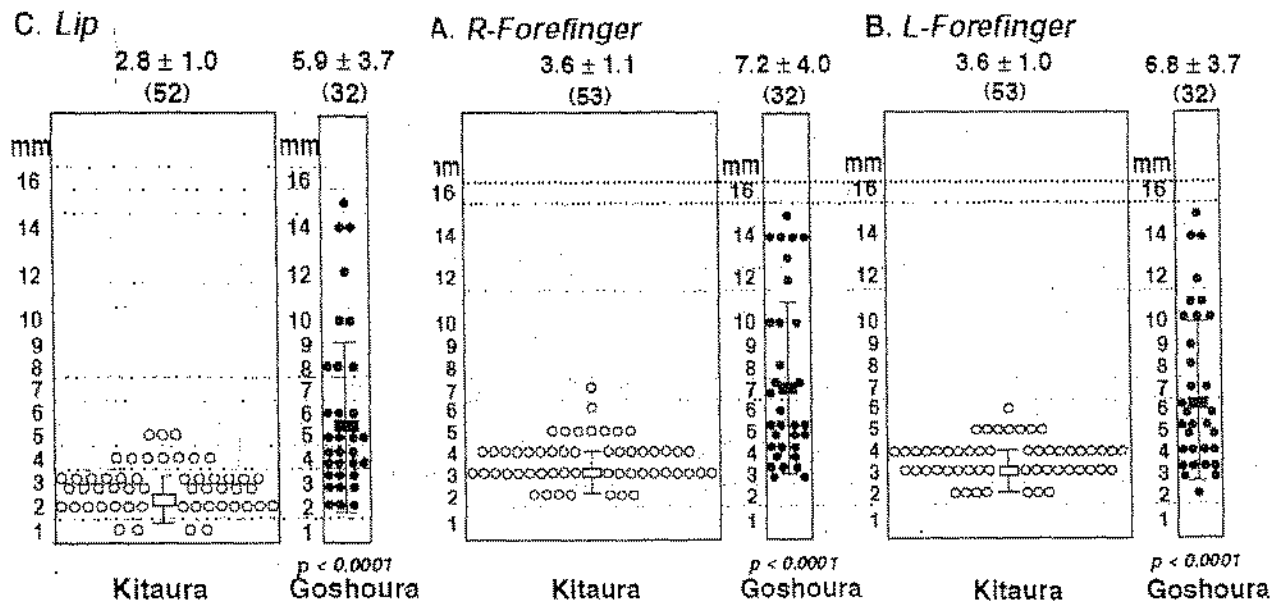


(Ninomiya et al, 2005)

Sensory testing



Two-point discrimination



(Ninomiya et al, 2005)

A recent study on sensory loss

- 197 residents from Minamata with a history of fish consumption during the period of high pollution, compared to 214 controls from non-polluted area.
- Persons from Minamata:
  - Most had never applied for certification for MD
  - Divided into 2 groups:
    - E+N : exposed with complications: diabetes mellitus; cervical spondylosis; lumbar radiculopathy; carpal tunnel disturbance; cerebrovascular disease; and other
    - E: exposed with no complications

(Takaoka et al, 2008)

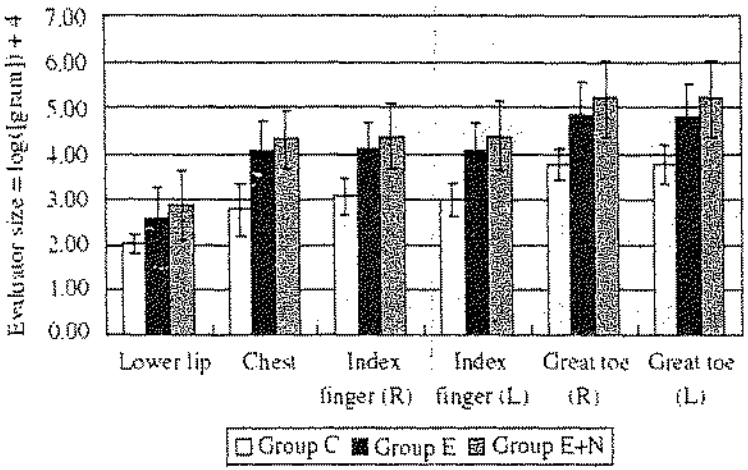
A recent study on sensory loss

- Neurologic examination, questionnaire and 4 quantitative tests of sensory function:
  - Touch (minimal tactile sense)
  - Two-point discrimination
  - Vibration sense (tuning fork)
  - Position sense

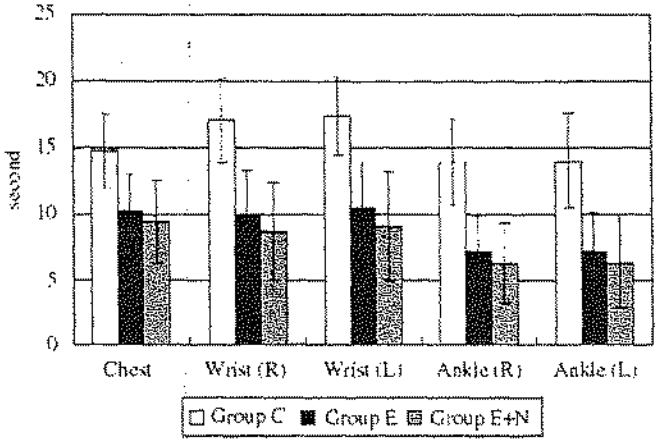
(Takaoka et al, 2008)

Results of sensory loss

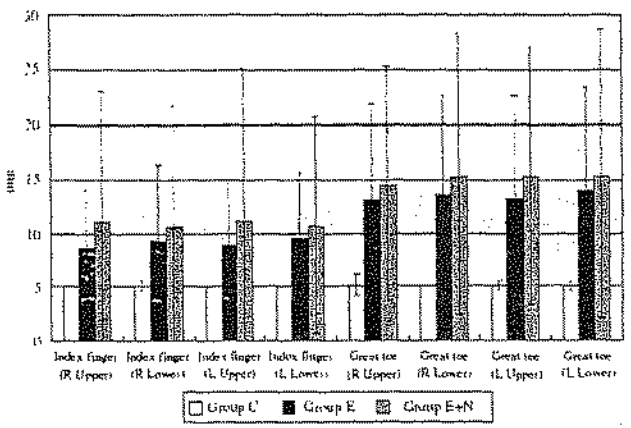
Touch



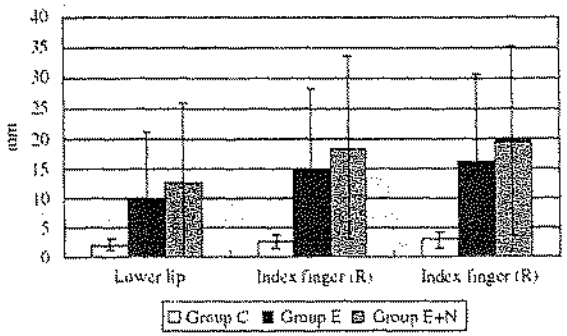
Vibration



Position sense



2-point discrimination



(Takaoka et al, 2008)

A recent study on sensory loss

- Findings:
  - Differences between Controls and Exposed without (E) and with complications (E+N) on all tests
  - No differences between E and E+N on all tests
  - No differences between E and E+N on the large majority of reported MD symptoms
  - Sensory and motor nerve conduction velocities of the right median nerve were similar in group E and controls
  - Sensory nerve conduction velocity was correlated with discrimination of fine-surface-texture, but not with other sensory modalities

(Takaoka et al, 2008)

A recent study on sensory loss

- **Conclusions** :

"Residents of Goshoura and MD patients have not been aware of the sensory disturbances in their whole body. Thus, it is speculated that paresthesia at the distal parts of the extremities is a subjective complaint of MeHg poisoning patients. The crude clinical tests using a painting brush and pinprick are effective in evaluating gross sensory response. However, they are not quantifiable and their reproducibility is poor. On the other hand, the examinations of threshold of touch and two-point discrimination are semiquantitative, and more reproducible and reliable than the crude clinical tests. Consequently, it could be stated that the quantifiable sensory examinations are more suited to detect the somatosensory disorders caused by damage to the cerebral cortex."

(Takaoka et al, 2008)

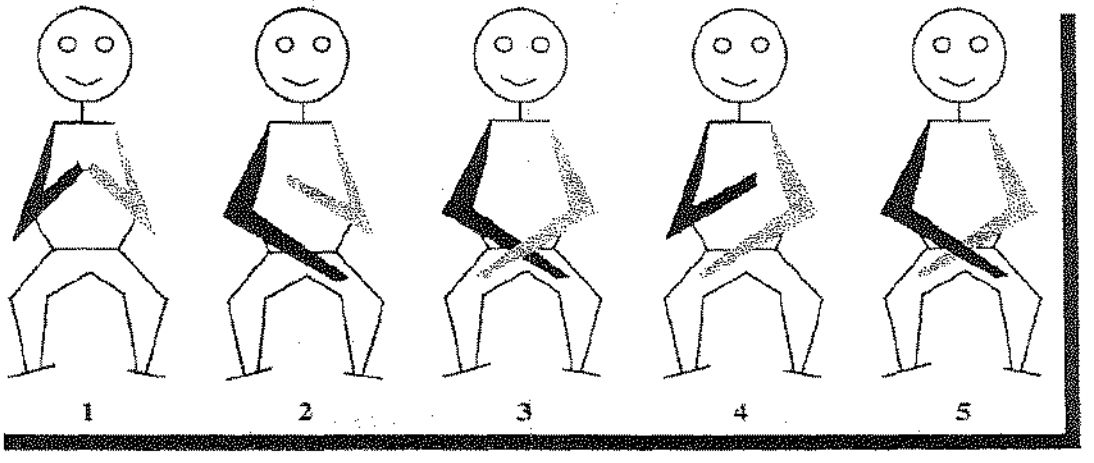
Visual functions

- Different types of visual deficits have been shown with mercury exposure :
  - restricted visual fields,
  - near visual contrast sensitivity loss,
  - color vision loss
  - changes in visual evoked potentials.
- In a recent study in the Amazon, we showed that the prevalence of age-related cataracts increased with mercury exposure

Motor testing

- In the early nineties, Dr. Fernando Branches, the Brazilian physician who first identified neurologic abnormalities in persons exposed to mercury vapours from gold mining activities and in fish-eaters exposed to methylmercury, was invited to Minamata where he learned to apply the neurologic examination for MD.
- His examinations of Brazilian fish-eaters with high mercury exposure showed some abnormalities, but not classical or chronic MD.
- He devised a new motor test that has proven to be very sensitive to methylmercuy exposure.

Branches Alternate Movement Task



- For Amazonian fish-eaters with hair mercury greater than 10µg/g the Odds Ratio for disorganized movements is: 1.88 [CI : 1.22-2.92]
- For those who can do the movement, the number of movements in 30 seconds decreases significantly with increasing hair mercury

Neurobehavioral Testing

- Neurobehaviorat tests which provide quantitative measures of cognitive, sensory and motor functions and emotional state have been used since the 1980's to describe acute and chronic effects of exposure to toxic substances on the nervous system.
- Clinically, they provide a complement to the neurologic examination.
- For mercury exposure, they have been extensively used to show deficits in children subsequent *in utero* exposure; in adults they likewise show mercury-related deficits, but there are fewer studies.

Dr. Harada's studies

- Dr. Harada did pioneering work in Japan, demonstrating neurologic damage of Minamata Disease
- In a recent report, he stated: *"During the early stages of the MD crisis in Minamata, patients, who were diagnosed with MD, seemed to be typical and severe cases of the Hunter-Russell syndrome, including sensory disturbance, concentric constriction of the visual field, ataxia, speech impairment and impaired hearing. However, through more study, it became clear that such severe cases were rather exceptional and many more mild cases were progressing to chronic Minamata Disease. I observed that the symptoms of Minamata Disease became more chronic and atypical in the 1970s. Also I have been proving that sensory disturbances, specifically stronger loss of sensation in the extremities, were seen among patients of methylmercury poisoning at a very high rate, through clinical examinations on family members of patients with sever and typical symptoms or mothers of congenital Minamata Disease patients"*

Dr. Harada's studies

- In the '70s, he showed that persons in Grassy Narrows and White Dog manifested similar signs and symptoms to MD and there appeared to be a dose-relation with mercury exposure
- In 2002 and 2004, he and his team went back. In total they examined 156 people from Grassy Narrows and White Dog.
  - Age ranged from 1-90 years
  - No information was provided on how persons were recruited

Dr. Harada's studies

- Diagnostic criteria:
  - MD: more than one symptom of: sensory disturbances,ataxia, disturbed ocular movement, imbalance, concentric construction of the visual field and speech impairment.
  - In cases where examinees were showing only sensory disturbances, we acknowledged MD as long as there was no other disease causing the symptom.
  - If an examinee had another disease and still showed symptoms of MD that were not explained by that other disease, we defined the case as MD with complications.

Dr. Harada's studies

- **Findings:**
  - 60 cases of MD (34.2% of total examinees, excluding people 10 years old and younger);
  - 54 cases (30.8%) of MD with complications;
  - 25 cases (14.2%) of possible MD for a total of 139 cases (79.4%).
- **They conclude :**
  - It is very high rate of neurological symptoms for a sample of a population, even though examinees came because of other health issues. It is as high as contaminated areas in Minamata. We cannot help but recognize the effects of methylmercury from the symptoms we have seen.

Our conclusions

- Dr Harada and his group did not evaluate the prevalence of MD in this population, but reported on the percentage of MD signs and symptoms within the group that they examined.
- We consider that Dr. Harada's follow-up clinical evaluation should be seen as a preliminary study showing the need for a comprehensive epidemiologic study that would include all of the known outcomes of mercury exposure and could take into account co-morbidity from other diseases, such as diabetes and /or alcohol and test for possible interactions. Such a study should also take into account the presence of other contaminants. For this study it would be most useful to have all of the results of hair and blood sampling by Health Canada, Dr. Chan and Dr. Harada, as well as the results of the neurological examinations that were done by Dr. Harada.

Opinions on environmental contaminants studies in Ontario based on reports provided by the Mercury Disability Board.

Prepared by Laurie Chan, Ph.D.
May 16, 2010

We have received the following 6 reports from the Mercury Disability Board for review.

1. Asubpeechoseewagong Netum Anisinaabek and Wabauskang First Nation Contaminants Project, 2004-2005 (Summary) submitted in May 31, 2005

2. Mercury in the sediment and crayfish of lakes supporting Grassy Narrows and Wabauskang First Nations, Ontario submitted in May, 2005

3. Wild Meat Contaminants Study Year 3: Heavy Metals June 2005.

4. Wild Meat Contaminants Study Year 3: Organochlorines December 2005.

5. Report on the Indigenous Knowledge Workshop Asubpeechoseewagong Nwtum Anishinaabek and Wabauskang First Nation 2005.

6. Final Report of the Anishinabek knowledge Component National First Nations Envrionmental Contaminants Program (NFNECP) Health Canada 2008-2009

1. Asubpeechoseewagong Netum Anisinaabek and Wabauskang First Nation Contaminants Project, 2004-2005 (Summary) submitted in May 31, 2005

2. Mercury in the sediment and crayfish of lakes supporting Grassy Narrows and Wabauskang First Nations, Ontario submitted in May, 2005

These two reports documented results from the same study. Sediment and crayfish samples were collected from 16 sites around the territory of the Asubpeechoseewagong Netum Anisinaabek and Wabauskang First Nations in 2005 and measured for Hg. The results provide insights on whether the chemical pollution in Dryden in the 1960s and 1970s is still having an impact on the English-Wabigoon River system.

The key findings are:

a) Sediment in water bodies that are closed to Dryden like Clay Lake and Ball Lake were still highly contaminated with Hg even though the levels had decreased compared to the 1970s.
b) The decreasing trend will continue as evidenced by the sediment core data.
c) The Hg in the sediment is bioavailable as evidenced by the elevated levels of Hg in crayfish collected in Ball Lake.
d) Sediments and crayfish collected from Grassy Narrow Lakes showed higher levels of Hg but the evidence is less convincing and no statistical tests were performed.
e) Sediment in Wabauskang Lake had background level of Hg.

Significance:

People should be advised not to consume fish collected from Clay Lake and Ball Lake as there are still residual effects of Hg pollution. Lakes around Grassy Narrows may still be affected and monitoring of Hg in fish should be continued.

3. Wild Meat Contaminants Study Year 3: Heavy Metals June 2005.

4. Wild Meat Contaminants Study Year 3: Organochlorines December 2005.

These two reports documented results of heavy metals including arsenic, cadmium, lead and mercury, and organochlorines including dioxins and furans, PCBs, chlorobenzens, hexachlorohexanes, chlordanes and DDTs in 159 wild meat (fish, mammals, and birds) collected by local hunters in 2005. Results help to identify potential chemical hazard as a result of consuming these food items.

The key findings are:

a) All metal and organochlorine concentrations in the wild meat samples were low or comparable to the concentrations found in like samples in Canada.
b) Concentrations of mercury and organochlorines were found in animals a higher trophic level such as otter, walleye, pike etc. as these contaminants are known to bioaccumulate and biomagnify along the food chain.
c) Migratory waterfowls had higher levels of organochlorines as they might have exposed to organochlorines in more polluted areas elsewhere.
d) One otter sample had higher level of mercury from unknown reason. One possible reason is age as mercury is known to accumulate in older animals but age was not determined.

Significance:

Results of this study show that there is no evidence of local pollution. The presence of the contaminants is likely due to either long-range transport or natural sources. There is no particular health concern from the consumption of these food items.

From the public health point of view, there is little value reporting whether Hg is detectable in certain food or comparing the Hg level to the guideline level used for regulation of commercial fisheries (i.e. 0.2 ug/g). The results can even evoke fear of the presence of contaminants in the local food supply. It will be more useful to combine the contaminant concentration data with food use data (in terms of gram per day intake) to estimate daily dose of contaminants. Such food frequency data are available at least for the fish species from an earlier study. See
Chan et al. (2005) "Our waters, our fish, our people" Mercury contamination in fish resources of two Treaty #3 communities.

5. Report on the Indigenous Knowledge Workshop Asubpeechoseewagong Nwtum Anishinaabek and Wabauskang First Nation 2005.

6. Final Report of the Anishinabek knowledge Component National First Nations Envrionmental Contaminants Program (NFNECP) Healtb Canada 2008-2009

These two reports presented results of two Elders meetings conducted in 2004-5 and 2008-9 on Anishinabek knowledge and perspectives on environmental contaminants. It is important the elders who are the local knowledge holders identify and report what are the main health issues in the communities. The information is also very useful in evaluating the effectiveness of the research activities and public health program as well as using the lessons learned to plan for future programs.

The key findings are:

a) The perceived risk of mercury pollution is still high. Scientists and health professionals have not been able to communicate the level of certainty in different findings and recommendations. People are confused with the scientific findings and public health messages and think that scientific information is not reliable.

b) There is a high level of mistrust for the scientific communities and the government. The risk communications including dietary advice have not been effective. The advices were either issued by the government or by scientists in different reports. The scientific studies and public health advice have been perceived to be out of context and did not take into account of the Indigenous perspectives. There is no long–term knowledge base available locally for such information.

c) The overall impact of mercury pollution has been more than just the health effects of mercury poisoning. Many other determinants of health including disruptions of culture, rapid change of diet, decline in jobs and income etc. have not been properly addressed and are clearly still having an impact on the overall health status of the people.

Significance:

Future studies should ensure local participation/leadership and capacity building. Risk communications need to be done on an ongoing basis with trained local personnel taking the lead. Proper dietary advice should be provided by individuals who have the authority and are trusted by the communities.