Mercury Studies
among the Cree of Eeyou Istchee

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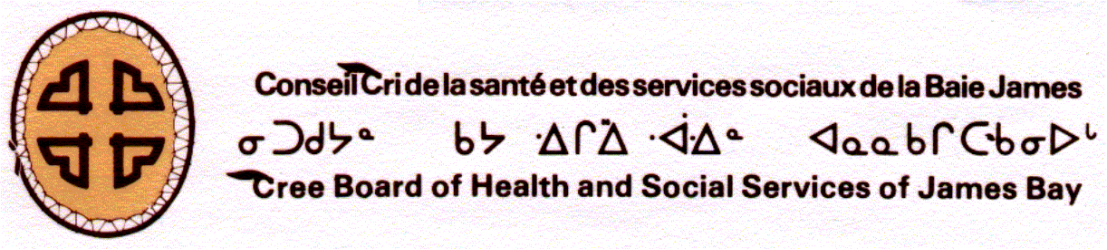

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1.0 Overview of health studies related to mercury exposure of the Cree of Eeyou Istchee

This report provides a summary of studies measuring the levels of mercury exposure[1] among Cree of Eeyou Istchee and the investigations into possible health effects. A brief overview, intended to illustrate the scope of this literature, is presented below, followed by more detailed summaries of the individual studies. While some historical information is included in this review, a more complete treatment of the historical context of the mercury issue and the Cree of Eeyou Istchee can be found elsewhere[2]. Moreover, further notes on scientific issues associated with the health studies cited in this report have been provided by Alan Penn, and are included in Appendix A[3]. This report does not include studies on the health effects of mercury carried out in other populations outside Eeyou Istchee.

In the late 1960s, high levels of mercury in fish were first documented in some rivers and lakes in Canada affected by local sources of mercury-containing industrial effluent, and in the early 1970s, severely contaminated fish were found in two regions affected by mercury released from chlor-alkali plants.[4] The levels of mercury in fish in the English-Wabigoon river system in northern Ontario, downstream from a chlor-alkali plant in Dryden, were found to be as high as 24 ppm (Department of National Health and Welfare 1979), whereas the mercury limit for commercial fish is 0.5 ppm. In the Bell and Nottaway region in northern Quebec, levels of mercury in pike and walleye were reported to be as high as 4 ppm (Barbeau, Nantel et al. 1976). One clear source of the mercury in this region was the Domtar chlor-alkali plant, located at Lebel-sur-Quévillon upstream from the Bell river. Mining operations in the Chibougamau region and the Noranda smelter at Rouyn-Noranda were also cited as potential sources of mercury emissions and the subsequent contamination of rivers and lakes in the region (Barbeau, Nantel et al. 1976).

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[1] The form of mercury of concern in the context of fish consumption is primarily the organic form, methylmercury. In this review, mercury exposure refers to exposure to methylmercury through fish consumption.

[2] See for example Penn A (1996) and Appendix 1 of McGill University Methylmercury Study Group (1979).

[3] Methylmercury exposure and human health: some reflections on the studies of the Cree population, Alan Penn, Cree Regional Authority, March 2005.

[4] Chlor-alkali plants produce chlorine for use in paper manufacture. One type of chlor-alkali production process requires the use of a mercury cell and produces a mercury-containing effluent, which in the 1960s and 1970s was discharged to nearby rivers and lakes. Inorganic mercury in water is microbially transformed to methylmercury and subsequently incorporated into the food web of the lake or river ecosystem. Methylmercury levels in fish may reach between one and ten million times the level of methylmercury in the water.

Recognizing the potential for high mercury exposure in certain populations in Canada, the Medical Services Branch of Health Canada (then the Department of National Health and Welfare) first began monitoring mercury levels among the Grassy Narrows and Whitedog Ojibway in Ontario, then among the Cree in Quebec, and subsequently extended the program to native peoples across Canada. Exposure was evaluated by measuring mercury levels first in blood and, later in the program, in hair samples. Clinical examinations were conducted for individuals judged to be "at risk". In the 1970s, the majority of individuals in Canada (402 of 546) with "at risk" blood mercury levels (>100 ppb) were from northern Quebec (Department of National Health and Welfare 1979; Health Canada 1999).

In 1975, the Quebec government intervened to establish the *Comité d'étude et d'intervention sur le mercure au Québec*. This committee examined 33 members of the Waswanipi and Mistissini Bands, as well as 16 Algonquin from Lac Simon and Amos, with regard to their neurological health (Barbeau, Nantel et al. 1976). The study included individuals (Lac Simon and Amos Algonquin) who fished near the confluence of the Quévillon and Bell rivers. This area had been directly affected by the industrial effluent from the Domtar chlor-alkali plant at Lebel-sur-Quévillon, which had discharged mercury-containing effluent to Lac Quévillon during its operation in the 1960s.

The Comité d'étude et d'intervention sur le mercure au Québec reported finding neurological disabilities among the Cree and Algonquin consistent with signs of methylmercury intoxication. On the basis of these findings, a lawsuit was brought by Cree Bands against industries in the region, which responded by mandating health investigations The first study, commissioned by Domtar, was led by W. O. Spitzer and colleagues (Spitzer, Baxter et al. 1988); the second study, commissioned by a coalition of mining companies, was led by Oscar Kofman (Kofman, Simard et al. 1979). The Kofman data were recently reanalyzed (Auger, Kofman et al. 2002) but the reanalysis has not yet been published. The results of the Spitzer investigation were presented in a 1979 report to the Montreal General Hospital, and published in the scientific literature in 1988.

An epidemiological investigation, conducted in 1978 by the McGill University Methylmercury Study Group, examined the effects of mercury exposure in both adults and in children exposed prenatally. The findings of this investigation were released in 1980 and published, in part, in the scientific literature in 1983 (McGill University Methylmercury Study Group 1979; McKeown-Eyssen and Ruedy 1983; McKeown-Eyssen and Ruedy 1983; McKeown-Eyssen, Ruedy et al. 1983).

In 1982, annual screening of mercury exposure in the Cree of Eeyou Istchee began through a program funded by the Ministère des Affaires Sociales and administered by the Montreal General Hospital's Community Health Department. In the fall of 1983, the department learned of a sharp increase in fish mercury levels in the Robert Bourassa (LG-2) reservoir of the La Grande hydroelectric complex, which had been impounded in 1979 and subject to monitoring starting in 1981 (Hayeur 2001). This led to the subsequent

negotiation and signing of the Mercury Agreement between the Grand Council of the Cree, Hydro-Quebec, and the Quebec government in 1986.

The annual mercury screening program was thereafter conducted within the framework of the Mercury Agreement. The data from these annual campaigns were reported in annual reports and numerous scientific publications. The screening program included a component for measuring prenatal exposure, through measurements of mercury in the mother's hair during pregnancy and in umbilical cord blood in the case of babies delivered at three hospitals in the region.

In the early 1990s, members of the James Bay Mercury Committee considered the possibility of conducting an epidemiological investigation among the Cree. In contrast to the previous screening program, which focused on measuring exposures, an epidemiological study would have investigated the neurological health of individuals in relation to their mercury exposure. Five preliminary studies were carried out to develop testing procedures and facilitate the exposure assessment. However, the full epidemiological investigation was never undertaken.

In 1995, the mercury screening program in the Cree communities of Eeyou Istchee came to a close and the James Bay Mercury Committee completed its mandate in 1997, including the publication of a final report (Dumont, Noel et al. 1998a).

Since the close of the Mercury Agreement (1986-96) mercury exposure levels were measured in 2002 within the Oujé-Bougoumou health study, participants having been drawn from both Oujé-Bougoumou and Nemaska (Dewailly and Nieboer 2003). This investigation focused on a range of environmental contaminants, including mercury, and included dietary and health questionnaires.

Two sociological studies relevant to the issue of mercury exposure through fish consumption were conducted in the early 1990s. An extensive socio-economic study was carried out by the firm Castonguay, Dandenault and Associés, inc. concerning the cultural and economic importance of fishing and fish consumption (Clément 1992). An anthropological study carried out in 1993 documented the knowledge and attitudes among the Cree regarding mercury in fish and its health effects (Scott 1993). These two reports are available, but are not included in the present summary as they do not deal directly with the investigation of exposure and health effects.

2.0 Screening in the 1970s by the Department of National Health and Welfare

In 1971, the Department of National Health and Welfare investigated mercury exposure among Cree in northwestern Quebec and identified 22 out of 401 people with blood

mercury levels greater than 100 ppb[5], with a maximum level of 341 ppb detected (Bernstein 1975, as reported in Department of National Health and Welfare 1979). Some neurological examinations were carried out but the neurologists were unable to directly link certain observed disorders to mercury exposure (Department of National Health and Welfare 1979).

The 1975 data for blood mercury levels in aboriginal populations in northwestern Quebec show that approximately 37% of the individuals sampled had a blood mercury level above 25 ppb (equivalent to 6 ppm in hair), as measured in the peak fish consumption period of July to September. Approximately 5.8% of the individuals had a blood mercury level above 100 ppb (as reported in Barbeau et al 1976**).** More comprehensive results (cumulative to 1978) for certain Cree communities are available in the Department of National Health and Welfare report. However, the information is presented in terms of test results, rather than results for individuals, such that the results of repeated tests for one individual cannot be distinguished from single results for different individuals (Department of National Health and Welfare 1979).

By 1979, the responsibility for investigating mercury exposures among the Cree of northwestern Quebec was transferred to the province of Quebec (and eventually to the CBHSSJB – see section 7.0). A compilation of the federal data for the period 1971 to 1979 is available[6].

3.0 Comité d'étude et d'intervention sur le mercure au Québec (Barbeau, Nantel et al. 1976)

The 1975/76 study conducted by this committee consisted of clinical examinations of 33 members of the Waswanipi and Mistissini Cree Nations and of 16 Algonquin from Lac Simon and Amos. The authors state that previous fish consumption data from nutritional studies, considered in conjunction with the data on mercury levels in fish, suggested that an individual's exposure to mercury during one summer might be sufficient to bring about the symptoms of mercury poisoning (Barbeau, Nantel et al. 1976; Department of National Health and Welfare 1979). Note, however, that the authors considered 10 ppb to be the "normal upper limit" for mercury levels in blood. This corresponds to a hair mercury level of 3 ppm,[7] and would be lower than exposures in populations practicing subsistence fishing, even in regions not subject to local mercury pollution.

[5] A level of 100 ppb corresponds to a hair mercury level of approximately 25 to 30 ppm, depending on the conversion factor used. The Canadian Department of Health and Welfare considered that an individual with a blood mercury level above 100 ppb was "at risk" for adverse health effects. They therefore selected this concentration as the intervention threshold.

[6] This data is found in the document "Prélèvements de sang dans les années 70 – données préliminaries." However, the data is reported as preliminary and should be verified with the author (Manon Girard).

[7] Currently Health Canada considers that levels of Hg in hair below 6 ppm represent the normal acceptable range.

Individuals consuming large amounts of fish were targeted in this study; one mission in particular focused on Algonquin individuals fishing near the confluence of the Quevillon and Bell rivers, an area directly affected by mercury-containing industrial effluent from the Domtar chlor-alkali plant at Lebel-sur-Quevillon. The levels of mercury in pike and walleye in the Bell River downstream from the plant had been measured at 4.8 and 3.65 ppm, respectively. In contrast, mean mercury levels in northern pike and walleye taken from the Bell River near Lac Matagami (over 100 km downstream from Lac Quevillon), were 1.85 and 1.14 ppm respectively. In regions to the east and north of Lac Matagami, the mean concentration of mercury in pike was found to be considerably lower, at 0.6 to 0.7 ppm (Penn 1996). The individuals tested included 49 Cree and Algonquin (20 women, 29 men) aged 21 to 80 years. No further details on the selection of subjects were provided. The researchers participating in the study also measured mercury exposure in non-Natives from the Matagami region, and carried out clinical exams for these individuals as well as a group of six men and six women from Montreal (non-consumers of fish).

Barbeau and colleagues measured mercury levels in the hair and blood of subjects. The authors do not provide information on the segment of hair sampled, and so it is unclear what exposure period is represented. The blood mercury levels of the Cree and Algonquin measured in July and August 1975 (Matagami test centre) varied from 25 to 649 ppb. Among the Cree and Algonquin who were tested from October to December 1975, blood mercury levels varied between 15 and 235 ppb (Mistassini test centre). These lower values for the later sampling period may be the result of decreased fish consumption, rather than an indication of different levels of exposure for different communities.

The clinical exam consisted of a general medical exam and detailed neurological exam, followed by a second detailed neurological exam with emphasis on signs of mercury intoxication. The symptoms were weighted according to severity and a brief family history taken. The authors observed what they term the classic tetrad of signs of mercury poisoning (sensory disturbances, constriction of visual fields, tremors, and coordination problems) in 14 (30%) of the Cree, None of the non-Natives were diagnosed with this set of conditions. Based on the overall neurological exam score and the severity of the symptoms observed, the authors concluded that at least six and possibly 25 of the 49 Cree and Algonquin individuals examined showed signs of mercury poisoning (Barbeau, Nantel et al. 1976).

The investigation carried out by Barbeau and colleagues did not conform, in all respects, to a well-designed epidemiological study. For example, the importance of confounding factors (age, alcohol intake, and nutritional status) was noted but these factors were not explicitly included in any statistical analysis. There was no control group made up of Cree adults with low mercury exposures and the total number of subjects was small. The neurologists were not blind with regard to the subjects' exposures.

While Barbeau and colleagues originally reported that mercury intoxication was occurring among the Cree, later evaluations presented a more nuanced conclusion. For example, in 1979 Wheatley and Barbeau wrote that signs compatible with mercury poisoning had been observed in certain Cree individuals with elevated mercury exposure but that a definitive causal relationship between the exposure and the symptoms could not be made because of confounding with other factors. Specifically, the neurological signs observed in the Barbeau study could also be attributed to other conditions, including nutritional status, alcohol consumption, and age (Wheatley, Barbeau et al. 1979; Health Canada 1999)**.**

4.0 Health investigation commissioned by an industrial consortium (Kofman, Simard et al. 1979; Auger, Kofman et al. 2002)

An epidemiological investigation of 306 Cree, all of whom were plaintiffs in a lawsuit brought against 15 mining and industrial companies in northwestern Quebec, was commissioned by the industrial consortium and led by Oscar Kofman in 1977-78. A combined group of 18 neurologists and ophthalmologists from six university centers conducted the clinical examinations. Multiple factors, including mercury analysis of blood and hair, age, nutrition, fish, drug, and alcohol ingestion were assessed. Special problems were assessed using such tools as EMG, EEG C.T. Scan, nerve conduction tests, CSF examination, myelography. The principal conclusion of this study, as stated in a published abstract, was that "*no individual revealed a constellation of symptoms and signs that conformed to the suggested concept of chronic Minamata Disease*" (Kofman, Simard et al. 1979).

The results of this investigation were presented at several scientific conferences, but not published (aside from the abstract) in the peer-reviewed literature. However, a re-analysis of the original data was conducted by N. Auger in 2002, in collaboration with O. Kofman, T. Kosatsky, and B. Armstrong. The information included in Table 2 is taken from this re-analysis.

In the original 1979 study, ordinal data on a number of neurologic outcomes was converted to an overall neurologic abnormality score. A covariance analysis between hair mercury levels and the overall neurologic score was conducted, leading to the conclusion that manifestation of disease related to mercury was not present. In the re-analysis, Auger, Kofman, et al (2002) used a more refined statistical technique (ordinal regression), which allowed them to make use of the original ordinal data without converting it to an overall score. Moreover, they analysed the exposure data for ten separate neurological outcomes, rather than for one overall neurologic score.

Auger et al. (2002) found a statistically significant association between tremor in young adults and mercury exposure. A 6 ppm increase in scalp hair mercury (corresponding to exposure over the previous month)[8] was associated with an increased risk of 2.22 of

[8] Scalp hair was highly correlated with both peak hair Hg concentration and mean hair Hg concentration.

having tremor (95% CI of 1.15 to 4.06). There was little or no evidence for effects of chronic mercury exposure less than 50 ppm, on sensory disturbance, incoordination, auditory defects, motor abnormalities, reflexes, cranial nerves, systemic symptoms, or cognitive impairment.

This association between mercury exposure and tremor did not hold for adults over 40 years, nor did the researchers find associations between increasing mercury exposure and other neurological abnormalities, such as sensory disturbances, incoordination, auditory defects, motor abnormalities, reflexes, cranial nerve effects, systemic symptoms, or cognitive impairment.

Although the re-analysis differed in its statistical treatment of the original Kofman study data, the limitations of the data set are the same. As noted by Auger, Kofman et al (2002), these are:

- Potential selection bias. All of the subjects were plaintiffs in a lawsuit, which may have skewed the composition of subjects towards individuals with both high long-term mercury exposures symptoms of neurological abnormalities;

- Potential misclassification of co-variates: The authors suspect that alcohol use was under-reported, which is important as the effects of alcohol include increased tremor;

- Hair mercury levels were only assessed for the previous year. Educational campaigns aimed at reducing the intake of contaminated fish, and the closure of the domestic subsistence fishery reduced fish consumption by individuals with previously high exposures (personal communication, Alan Penn). It may be that some neurological effects would be related to past long-term exposure, rather than exposure during the previous year;

- Although the researchers carrying out the clinical exams did not know the results of the hair mercury measurements, they were aware of the litigation, and that they were assessing subjects who might have had elevated mercury exposure in the past. Moreover, the subjects themselves may have communicated information on their past fish-consumption patterns during the exam.

In addition to these limitations, Auger et al (2002) note that the investigation of multiple outcomes (20 endpoints: 10 outcomes for two age groups) increases the chance of spurious associations. The p-value for the association between tremor in younger adults and mercury exposure was, however, very low (0.001).

5.0 Health investigation commissioned by Domtar (Spitzer, Baxter et al. 1988)

This investigation was commissioned by Domtar in response to litigation regarding mercury emissions from its chlor-alkali plant in Lebel-sur-Quévillon. As such, the study was designed to distinguish health effects related to the presence of the chlor-alkali plant

(and higher mercury concentrations in the fish in downstream waters), as well as investigating the effects related to high mercury exposure, regardless of the source.

Mercury was measured in the hair and blood of four groups:

- Self-designated disease group (n=81): Cree living in the Nottaway drainage system affected by mercury pollution who alleged mercury intoxication and who were plaintiffs in the litigation;
- Neighborhood controls (n=69): Cree from same villages as group (1), but not alleging mercury intoxication (to detect bias from self-selection of first group);
- Ancestral controls (n=62): members of the Algonquin nation living in the Outaouais drainage system (free of local industrial mercury pollution). Individuals for whom fish provided major source of dietary protein;
- General comparison group (n=98): White and Algonquin individuals living in the Nottaway Drainage system, at varying distances from the chlor-alkali plant responsible for local mercury pollution.

Ten target variables, based on assessments on diverse neurological functions (somatosensory, motor, visual fields, hearing) were established prior to the analysis. These included:

1-any neurologic or ophthalmologic abnormality;
2-abnormalities recorded by field neurologist (11 conditions assessed);
3-physical functional disability;
4-bilateral neurosensory hearing loss;
5-motor nerve conduction velocities;
6-coexistent upper and lower extremity tremor;
7-abnormalities recorded by nurse practitioner (neuro-physiological status);
8-stated sickness;
9-definite EEG abnormalities;
10-sensory nerve conduction velocities.

Minamata Disease, as based on the criteria of constriction of visual fields, ataxia, paraesthesia, and hearing deficit was not found. In their regression analysis, the authors found a definite relationship between mercury in hair and four target variables (Nos. 1, 6,7,10 above) suggesting verifiable biological threshold levels for clinical effects. In a review of this study, Kosatsky and Foran note that the findings suggest effects at levels of exposure in the 60 to 100 ppb blood mercury range (Kosatsky and Foran 1996).

Diabetes and alcohol-related health problems, which were recognized as significant potential confounders, were common. The authors found that the relationship between the neurological signs studied and these two conditions was far stronger than the relationship observed in relation to mercury levels. They state, “this fact helps keep in perspective the low total effect of mercury levels in comparison with other common diseases associated with the same target variables which are assessed in this study.”

6.0 McGill University Methylmercury Study (1978)

This epidemiological study was initiated subsequent to the discovery in the early 1970s of elevated mercury exposures among the Cree of Eeyou Istchee. It differed from the Kofman and Spitzer investigations in that it did not draw subjects from among plaintiffs in law suits related to mercury contamination, and that it included both an investigation into the effects of mercury exposure among adults, and the effects of prenatal exposure in children.

This study intended to cover the entire population of adults aged 30 yr or more and children aged between 1 and 2.5 yr in the communities of Whapmagoostui, Chisasibi, Waswanipi, and Mistissini. These communities had been found to have the highest levels of mercury in a surveillance campaign conducted in 1975. The findings for adults and children, presented in Table 2, are discussed separately below.

6.1 Study of neurological abnormalities in adults exposed to mercury (McGill University Methylmercury Study Group 1979; McKeown-Eyssen and Ruedy 1983):

A case-control study was conducted for a total of 281 men and 311 women aged 30 and over from Mistissini, Whapmagoostui, and Waswanipi, with the more complete neurological examinations carried out in Mistissini and Whapmagoostui. Mercury exposure was assessed by measuring both hair and blood levels, including one exposure index corresponding to the months of April to July of 1978. The authors note that past exposure was probably higher than the exposure reflected in their assessment. The neurological examination assessed nystagmus, coordination and gait, tremor, movements and reflexes, sensation, stereognosis, and two-point discrimination. Visual fields and hearing were also measured.

The definition of a case was established a priori as subjects with bilateral visual impairments or signs on neurologic examination with no definitive alternative diagnosis. The selection of cases was blind to the mercury measurements. However, observer variability among the neurologists was considerable, and the matching of cases and controls according to age was not possible.

Using discriminant analysis, the authors identified age as the confounding variable best distinguishing cases from controls; use of alcohol provided additional discrimination among women in Mistissini. After adjustment for age and alcohol use, the discriminant analysis showed a positive association between neurologic abnormality and mercury exposure, which was significant for Mistissini but not Whapmagoostui. With each increment of 20 ppm in hair, the probability of having symptoms defining a “case” increased by a factor of approximately 5 in men and 3 in women. Odds ratios (OR) were estimated for pooled data: for subjects with exposures of 10 to 19.9 ppm in the hair (summer 1978 index), the OR was 2.12 (95% CI 0.98 to 4.60). For subjects with exposures greater than 20 ppm in hair, the OR was 3.72 (95% CI 1.18 to 11.76).

The authors comment that although age and alcohol adjustments were carried out, the residual effects may still not be entirely attributable to mercury exposure. However, no alternative explanatory factors were identified. The authors note, as well, that the data do not allow for the estimation of a threshold level, above which an excess of neurologic abnormality might occur.

6.2 Study of neurological abnormalities in children exposed prenatally to methylmercury (McGill University Methylmercury Study Group 1979; McKeown-Eyssen, Ruedy et al. 1983):

In this study 247 children (12 to 30 months old) from Mistissini, Waswanipi, Whapmagoostui, and Chisasibi were examined. Exposure was assessed by the maximum concentration in maternal hair for the period one month before conception to one month after delivery. Mean exposure was 6 ppm in maternal hair, with 6% of mothers having an exposure >20 ppm. The maximum exposure was 24 ppm.

The neurologic examination of children assessed such variables as tendon reflexes, muscle tone, the Babinski reflex, coordination, cranial nerves, as well as any other sensory abnormalities. Development was assessed using the Denver developmental scale.

The investigation into the effects of prenatal exposure was also carried out as a case-control study. However, there was an important methodological difference in the children's study as compared to that of the adults. The definition of a case for the children was not defined a priori, but rather a regression analysis was used to see which of the eight measures of neurologic function were associated with mercury exposure. Children were then identified as cases depending on the presence of abnormality with respect to that function.

The researchers found that abnormality of muscle tone or reflexes in boys was positively associated with the index of prenatal mercury exposure. No other measure of neurologic function or development was significantly associated with exposure, in a direction indicating an adverse effect, either before or after adjustment for confounding variables. However, incoordination in girls was negatively associated with prenatal mercury exposure, although this relationship was not found to be statistically significant.

The authors concluded that the abnormality of muscle tone was mild in severity and of doubtful clinical importance. They recommended continued medical surveillance of the cohort to evaluate the significance of these findings. (The children were subsequently re-evaluated clinically, but there was no published follow-up study.) The authors also commented that the muscle tone abnormality was not entirely consistent with previous knowledge of the effects of prenatal exposure to mercury. In the Japanese and Iraqi poisoning incidents, affected children exhibited generalized neurologic disease and not isolated abnormalities. In the McGill study, no consistent dose-response relationship was observed and there was no consistency between the sexes.

6.3 Discussion of the McGill University Methylmercury Study at the 1988 Val d'Or Conference on Mercury and Health[9]

The results of the McGill adult and child investigations were presented by John Ruedy at the Val d'Or conference. Transcripts of the discussion following the two presentations are included in the symposium proceedings. These discussions included the following paraphrased remarks:

(1) Dr. Tom Clarkson of the University of Rochester noted that the abnormalities observed in adults correspond to exposure levels lower than the threshold levels identified in the acute poisoning epidemic in Iraq. He suggests that there must have been a higher consumption of fish in the past (1950s and 1960s) to explain these abnormalities. Dr. Ruedy responded that the abnormalities observed were much milder [as compared to the symptoms found in Iraqi cases] and of a more long standing nature. His guess is that the researchers were observing residual damage secondary to fish intake in the past.

(2) Dr. Leonard Kurland found that the lack of consistency between the sexes observed in the children's study was difficult to explain. Dr. Ruedy agreed, but added that there is suggestive evidence for a sex difference in mice. He added that he is less convinced of the data in [the children's] study than of the data of the adults study.

(3) Dr. Ruedy mentioned that the 234 children examined were a unique cohort, and that he still has the hair samples that gives their prenatal exposure. Further testing of these individuals would thus be possible.

[9] Le Mercure et la Santé/ Mercury and Health. Val d'Or, Quebec 1988/08/22-24. Sponsored by the Cree Board of Health and Social Services of James Bay.

7.0 Mercury Agreement (1986): health surveillance data and findings (Dumont, Noel et al. 1998a)

The mercury surveillance program was transferred to the CBHSSJB in the early 1980`s, and in 1986, after high levels of mercury were observed in fish in the new hydro-electric reservoirs, a Mercury Agreement was signed between the CBHSSJB, Hydro-Quebec, and the government of Quebec. Surveillance was then intensified, with the objectives of (1) identifying individuals with levels of mercury potentially dangerous to their health in order to provide advice on limiting mercury exposure, and (2) characterizing mercury exposure throughout the nine communities with respect to variations over time and according to age, gender, and community affiliation (Kosatsky and Dumont 1990).

The following summary and discussion is drawn primarily from the report: Dumont, Noel et al., 1998. James Bay Mercury Agreement (1986) Health Component. 1987-97 Activity Report. References to journal articles, published by members of the James Bay Mercury Committee, are included where appropriate.

7.1 Summary of data: See tables 3 to 8 for summary of mercury levels, in men and women in all communities (1982 to 1995), and in Chisasibi and Wemindji in particular. Maternal mercury concentration data (1983 to 1991) are shown in Table 10. Note that the CBHSSJB did not collect data on the species and amounts of fish consumed, and the bodies of water from which they were taken.

7.2 Evolution of mercury exposure over time: The entire database cannot be used to characterize time trends, as the target groups varied from year to year. One study (Perrault 1992, as reported in Dumont, Noel et al. 1998a), using comparable portions of the database, found that mercury exposures increased from 1977 to 1984, but declined in 1988.

The Mercury Agreement surveillance did assess mercury levels in the population as a whole in the 1993/94 campaign. On the basis of these results, the authors conclude that exposures were lower in 1993/94, as compared to 1988, both for groups as a whole and for individuals examined. For example, the proportion of the Cree population with hair mercury levels in excess of 15.0 ppm declined from 14.2 % in 1988 to 2.7 % in 1993/94 (Dumont, Girard et al. 1998b). The decrease in mercury concentrations was found in all age groups, and in all communities, in trappers as well as non-trappers.

7.3 Influence of community affiliation: There have always been differences in exposure between communities. In 1994, for example, the greatest exposures were found in Whapmagoostui (90^{th} percentile = 13.3 ppm, men and women). The least exposed community was Waskaganish (90^{th} percentile = 3.2 ppm, men and women). The reason for the high levels in Whapmagoostui are unclear. There is no road link with the hydroelectric reservoirs. However, Band Council members have suggested that a greater proportion of predatory fish species is eaten in this community as compared to others,

because of a greater proportion of such species in nearby waters. Consumption of marine mammals is another possibility. Studies done in the 1970`s showed that more fish were harvested in Whapmagoostui than in the other Cree communities (James Bay and Northern Quebec Native Harvesting Research Committee 1982).

7.4 Gender and age: No major difference between mercury concentrations were found between men and women. In all the years studied, youth have the lowest levels. Exposure increases with age and the levels off after age 70. This trend, however, may no longer hold. The younger cohorts, as they age, may retain the low fish consumption patterns typical of the 1990s.

7.5 Influence of family affiliation: In 1993/94 an effort was made to correlate the mercury exposure of the head of household, with the mercury exposure of family members. The correlation between spouses was statistically significant, but still not very strong; the correlation was much weaker for other members of the household.

7.6 Influence of lifestyle: In general, trappers have higher exposures than non-trappers, for all age groups except the 10 to 14 bracket. However, certain high concentrations are found in non-trappers – possibly because of the redistribution of fish within communities or because, as a result of new roads, salaried employees can now go on weekend fishing trips to lakes and reservoirs with high contamination that were inaccessible to them previously.

7.7 Seasonal influence: In 1987/88, hair samples representing exposure in November, February, and July were analyzed to examine seasonal variation. For all the communities, the median exposure is higher in July, but it is far from negligible in other seasons. Maximum concentrations are most often found in July, but there is wide variation between communities (Kosatsky 1989).

7.8 Effects of short-term changes in fish consumption: In the summer of 1992, the consumption of fish in Eastmain increased considerably, as a result of organized fishing expeditions to inland lakes targeting lake trout. The population's mercury exposure increased sharply as well (median concentration of 9.9 ppm in 1992 compared to 4.1 ppm in 1988). Individuals with hair long enough to test for exposure in spring and winter showed a sharp increase in mercury in their hair during the period corresponding to the arrival of the fish in the village. For example in 1992, 10 % of women had more than 9ppm of mercury in hair, and 3% had more than 15 ppm; the maximum level was 19 ppm.

The study does suggest that individual hair mercury levels may increase rapidly when there are changes in fish consumption. The authors question the wisdom of encouraging fishing expeditions aimed at species of fish known to have high mercury concentrations.

7.9 Potential effect of hydroelectric development: Chisasibi and Wemindji have the greatest access to the La Grande hydroelectric reservoirs and downstream water.

Members of these two communities could have been exposed to high levels of mercury from fish caught from these reservoirs (up to 3.34 ppm in pike, and 0.53 ppm in whitefish), particularly prior to 1983 when the problem of high mercury levels resulting from reservoir development was not yet recognized. Few data for Chisasibi were collected prior to 1984. However, as indicated in Tables 5 to 8, high exposures were observed in 1984-85 in the two communities (as well as in one man in Wemindji in 1987 and one woman in Chisasibi in 1995).

In Table 9, mercury exposures in all the communities for the time period 1983 to 1985 are presented. The median and 90th percentile exposures of individuals from Chisasibi and Wemindji are slightly higher than two other coastal communities (Waskaganish and Eastmain). However, two other communities – Waswanipi (inland) and Whapmagoostui (coastal) – recorded relatively high median and maximum exposures, as well. The relatively high exposure levels among individuals in Chisasibi in 1984 have since greatly decreased.

Consumption of reservoir fish, particularly in the decade following impoundment, could have theoretically led to high exposures in individuals. However, as no information on the consumption of fish from reservoirs is available, and because high exposures can result from eating fish not affected by hydroelectric development, it is not possible to evaluate the extent to which hydroelectric development increased mercury exposure among the Cree.

7.10 Monitoring fetal exposure (Girard and Dumont 1995): The Mercury Agreement resulted in increased maternal and fetal monitoring for mercury, such that after the signing of the agreement (1986) at least 80% of mothers had at least one hair sample taken during their pregnancy, as compared to 41% previous to the agreement. Following the agreement, in 26% of cases, samples of the mother's hair were taken early in pregnancy and shortly after delivery. A sample of umbilical cord blood was taken at delivery. Prior to the agreement these data were available in only 12% of cases.

The principal findings of the prenatal screening program were:

- Maternal hair mercury concentrations were relatively high in 1984. From 1985 to 1991, a gradual reduction in these concentrations was observed (see Table 10). For example, in 1984, 10% of maternal hair tested showed >15 ppm, at the time of conception. In 1994/95 these levels were mostly at the detection limit of 2.5 ppm;

- From 1983 to 1991, the maternal hair mercury concentrations for mothers considered as full-time trappers were slightly higher than those for mothers considered non-trappers. Concentrations are slightly higher in coastal communities than in inland communities;

- For the data from 1983-91 mercury concentrations in hair at the time of conception are generally slightly higher than those at the time of delivery. There is a significant relationship between mercury concentration in the newborn's umbilical cord and the mercury concentration in the maternal hair at delivery.

  Mercury[newborn] = 8.532 + 2.925 * Mercury[maternal hair-delivery].

  No such relationship exists for mercury in the umbilical cord blood and maternal hair concentration at conception;

- Mercury concentrations in umbilical cord blood are significantly higher for mothers who are trappers as compared to mothers who are not trappers;

- Mercury concentrations in umbilical cord blood in boys differ little from those concentrations in girls. For both boys and girls, there is a decline in mercury concentration during the period 1987 to 1991;

- The data collected do not indicate any relationship between birth weight and mercury concentration in the maternal hair at delivery;

- Sampling of umbilical cord blood stopped in 1995, and of hair in 1996, as a result of consistent observations of mercury concentrations at the detection level.

7.11 Discussion of findings: What is the explanation for the observed gradual decline in exposure to mercury in all age groups? One hypothesis, proposed by Dumont and colleagues, was that the mercury concentration in fish could be declining. However, they concluded that this does not appear to be the case. There has been some decline in the levels of mercury in reservoir fish, but these drops occurred after the onset of the decline in the concentrations in human hair. Moreover, the concentrations of mercury in fish from natural lakes have not decreased.

A second potential factor contributing to the decline could be the public information campaigns aimed at convincing the Cree to consume mostly non-predatory fish such as whitefish and cisco.

A third factor is changes in Cree lifestyle, including less time spent in the bush and the consumption of more store-bought food, which may have led to a general decline in fish consumption.

Dumont (1998) concludes that the decrease in mercury exposure can likely be attributed to the second and third factors; he also recognized that the decline in fish consumption might quickly be reversed, as the result, for example, of an economic crisis or the absence of game. Such a change would quickly be manifested in hair-mercury concentrations of the population (see study regarding Eastmain fishing expeditions).

The general conclusion is that very few people have mercury exposures that could possibly represent a danger to their health, based on current knowledge regarding mercury toxicity.

8.0 Other research carried out under the Mercury Agreement

A series of research projects regarding the measurement of exposure to mercury and its health effects were carried out in preparation for an eventual epidemiological study among the James Bay Cree (personal communication with C.Dumont). The results of these projects are summarized below. However, the full epidemiological study was never undertaken.

8.1 Study of the relationship between the mercury exposure of the head of a household and the other members of the family. Report presented to the Cree Board of Health and Social Services of James Bay (CBHSSJB), February 17, 1998 (Bellavance 1998).

This analysis makes use of hair-mercury data from the 1993/94 general survey of the level of mercury exposure in the nine Cree communities (August 1993 sampling for inland communities, August 1994 for coastal communities). A random sample of households was chosen within each community, consisting of 25 % of households in communities of >2000 individuals, 50% of households in communities with a population between 1000 and 2000, and 100% of households in communities of less than 1000 persons.

A total of 317 households (fromWaswanipi, Mistissini, Waskaganish, and Chisasibi) were identified in which both the head of the household and at least one other family member were tested. Among these, 98 households included the head of household and the spouse (Waswanipi and Mistissini).

The statistical analysis carried out for these data showed a relatively high correlation between the mercury exposure of the head of a household and the spouse. This relationship does not hold for other family members living in the same household.

The purpose of this study was to see if the exposure of an individual could be estimated by the exposure of his or her spouse. This was done in preparation for an eventual epidemiological study. A strong correlation between spouses would allow researchers to estimate missing values of mercury exposure on the basis of data for a husband or wife.

8.2 Evaluation de la neurotoxicité du mercure chez les indiens cris. Standardisation de l'évaluation neurologique. Report submitted to the CBHSSJM, March 1998. (see Table 11) (Panisset and Gauthier 1998).

The main objective of this study was to develop and validate a standard clinical neurological exam and neuropsychological tests that could be used to evaluate

neurological deficits in individuals chronically exposed to mercury. The exam had three components:

- Questionnaire: OECD long-term disability questionnaire to detect the impact of health problems on daily activities; United Parkinson's Disease Rating Scale; a review of medical history to reveal past health conditions that could confound the results. Also included questions concerning drug, tobacco, and alcohol usage.

- Neuropsychological tests: based on a battery of tests used by the WHO for detecting neuropsychological effects of AIDS in Africa. The intention was to select tests that were relatively insensitive to the effects of culture and education: verbal fluidity, block-tapping, trail-making test, digit symbol test.

- Clinical neurological exam: seven sub-components based on the classical model for this type of exam.

The three components were administered to individuals of three different groups: 21 patients with Parkinson's Disease, 29 control subjects, and 36 Cree. Certain exclusion criteria were used to reduce confounding factors (e.g. medical conditions resulting in neurological deficits, amputation, visual acuity greater than 20/30 (corrected)).

Among the 36 Cree subjects, aged 34 to 70 years, exposure to mercury was assessed as the mean of annual maximum measurements across 25 years. Average mercury exposure for the 36 subjects was 8.2 ± 6.8 ppm of mercury in hair. Among the 36 subjects, two exposure groups of six individuals each were constructed, matching for age. The lower-exposure group had an average mercury exposure of 8.49 ± 6.8 ppm in hair. The high-exposure group had a mercury exposure of 27.52 ± 2.81 ppm in hair.

The authors of this study found that:

- the neurological exam was quantifiable, and appeared to be sensitive to effects that can be attributed to mercury exposure, or to the beginning stages of Parkinson's disease;

- the clinical protocol could be used in future studies evaluating Cree populations, with some modifications. For example, only the Corsi block-tapping test was found to be appropriate by the authors;

- Authors recognize that the fact that the examiners knew what subgroup each individual fell into could introduce bias in the interpretation of the results. However, they were blind to the mercury exposure among Cree. Authors observed a dose-effect response (no statistical significance given).

The authors also concluded that the study showed the existence of a neurological syndrome in Cree subjects similar to the syndrome described in Minamata. They point, in particular, to the Corsi test results, used by the WHO and that are supposed to be

insensitive to the effects of culture and education. Other neurological tests also support the hypothesis of deficits in Cree individuals due to mercury exposure, notably one of the vision tests[10]. Anomalies in fine movements of hands and legs, problems with the axial musculature, problems with coordination of lower limbs, with walking, with getting up from a chair, a curved posture, bradykinesia (extreme slowness of movement) and lower sensitivity in fingertips were also observed.

This study was commissioned with the intent of developing a protocol that could be used within an eventual epidemiological study. It was not designed to investigate whether Cree with elevated mercury exposure have a greater incidence of neurological abnormalities. The authors state their conclusion of finding neurological anomalies among the Cree, similar to those reported for mercury poisoning. However, this finding is, at most, suggestive of neurological effects that are possibly related to methylmercury exposure. In particular, it should be emphasized that the number of subjects is very small, little information is given regarding the selection of Cree subjects and controls, and that hair mercury levels in the controls (presumably very low) were not measured.

8.3 Evaluation of Visual Changes as a Consequence of Long-term Ingestion of Methylmercury among the James Bay Cree. Report submitted to the CBHSSJB (Faubert 1997).

The objective of this study was to develop a vision test that would detect effects from chronic mercury exposure in an eventual epidemiological study (see Table 11). The study was carried out with the same subjects as the study by Panisset and Gauthier 1998 (see 8.2).

A test was developed to measure temporal modulation visual fields (TMF) in order to evaluate the contrast sensitivity throughout the individual's visual field for different spatio-temporal combinations. It had been previously demonstrated that the assessment of TMFs will detect early peripheral loss in glaucoma, multiple sclerosis, and central loss in optic neuritis and other visual pathologies. Other reasons for favoring this measure are given as well.

No statistical significance between the Cree subjects and the control group was found. However, TMF results did significantly vary with age, indicating that these measurements are sensitive to neurotoxic effects that produce premature aging.

The author of the study concluded that:

- the test protocol met goals of being portable, reliable, repeatable, relatively short duration, and well accepted;

- the tests are suited for assessing visual dysfunction produced by neurotoxicity effects; sensitive to subtle visual changes, have good test-retest reliability, are

[10] This test was referred to in the study as the "decomposition de la poursuite oculaire en saccades."

easy to perform by subjects from a variety of populations, including the Cree population.

8.4 Validation of measures evaluating the neuromotor system following chronic exposure to methylmercury. Report submitted to the CBHSSJB. (see Table 11) (Beuter 1997).

As with the two studies noted above, this study was carried out to validate measures that could be used in an eventual epidemiological investigation evaluating the neurological effects of mercury exposure in James Bay Cree. The tests used examined eye movements, tremor in the upper extremities, rapid alternating movements, and pointing movements with speed and precision. The study was carried out with the same subjects as the study by Panisset and Gauthier 1998 (see 8.2).

The authors conclude:

- In EKM (eurythmokinesimeter) tests, which measure speed and precision in pointing, irregularity was the most discriminating characteristic between more exposed and less exposed Cree subjects. Precision was not found to discriminate well between the two groups;

- Likewise the authors found that certain submeasures in the other tests discriminated better between high and low exposure groups than did others. A total of 30 submeasures were scored;

- Differences observed between the control group and the Cree subjects suggest that mercury may be having some effect on neuromotor control. A study with more subjects and better control of extraneous variables would be required.

Several reports based on these data were subsequently published in the peer-reviewed literature: Beuter and Edwards 1998 report findings concerning tremor in Cree subjects; Beuter, De Geoffroy, et al 1999 discusses the analysis of rapid pointing movements (EKM); and Beuter, De Geoffroy and Edwards 1999 reports on the analysis of rapid alternating movements (RAM) in Cree subjects. These reports focus on the logistics of the tests and the capacity of the tests to discriminate between different groups. The reports suggest that the techniques would be useful in exploring the neurological effects of mercury exposure among the Cree.

8.5 Development of biological markers for monitoring neurotoxicity due to methylmercury exposure (Chakrabarti, Durham et al. 1997).

The objective of this study was to develop and validate the most sensitive and/or specific and reliable biomarkers using peripheral blood cells, which can serve as reliable early bioindicators of damage to the central nervous system by mercury. – e.g. certain

biochemical parameters in blood cells that could be used as early biomarkers of neurotoxicity of mercury.

The study was carried out in adult male Sprague-Dawley rats and male New Zealand rabbits. Various in vitro and in vivo studies were conducted in an effort to relate changes in blood cells to central nervous system damage. Human blood samples were also obtained from adult human volunteers (5 men, 4 women, 24-43 years) and these were exposed in vitro to various concentrations of mercury over one hour.

The authors conclude that microtubules in platelets (immunocytochemical visualization) may be a useful biomarker in humans; Further laboratory animal studies should be conducted for determining the dose-effect relationship for depolymerization of platelet microtubules under conditions of repeated or chronic exposure to mercury.

9.0 Oujé-Bougoumou/Nemaska Health Study

In September and October 2002, an environmental health survey was carried out within the communities of Oujé-Bougoumou and Nemaska in response to concerns regarding the contamination from mine tailing operations near the community of Oujé-Bougoumou. Exposures to various toxic elements, including mercury, were measured, and health and dietary questionnaires administered. At the time of writing, the final report of this health study was not yet available, and so the overall conclusions are not presented here. However, the results with respect to hair mercury levels are presented in Table 12 and compared with previous levels measured in 1993. In both communities, and in all age groups, mercury exposures have on average declined (Dewailly and Nieboer 2003).

10.0 Summary of studies

The studies described in this report can be grouped into four categories, according to their overall objectives.

(1) Screening and surveillance programs: These included the screening program administered in the 1970`s by the federal Department of National Health and Welfare (Medical Services Branch), which sought to identify individuals at risk for neurological disease, and the program carried out by the CBHSSJB under the Mercury Agreement (1986). The latter generally targeted individuals with the highest exposures, but also included a general survey of the communities for two years (1988, 1993/94) over the course of the Agreement.

(2) Reports of clinical examinations of individuals identified with high exposures: These included examinations provided to individuals with high exposures, identified through the federal program as well as the exams provided in the Quebec study carried out by Barbeau and colleagues (Comité d'étude et d'intervention sur le mercure au Québec).

(3) Epidemiological studies investigating the health effects of mercury exposure: The principal epidemiological investigation was that of the McGill University Methylmercury Study Group. Two other studies, led by Kofman and Spitzer, are referred to as epidemiological studies, but their ability to provide evidence for a hypothesis was hampered by the fact that they were carried out within the framework of a litigation process. This influenced the objectives of the study, the selection of participants, and to some extent the knowledge of the examining neurologists as to the degree of mercury exposure among the subjects.

(4) Small pilot studies carried out in preparation for epidemiological studies (Panisset and Gauthier; Beuter; Faubert). Although these studies did examine the relationship between neurological health and mercury exposure, their primary purpose was to evaluate the utility of different tests which could be used as outcome measures of the effect of mercury, in a larger epidemiological study.

The Comité d'étude et d'intervention sur le mercure au Québec reported cases of mercury intoxication, but the investigation was not designed as an epidemiological study, and did not adjust for other conditions (e.g. age, alcohol consumption) that might produce similar clinical effects.

The findings of the epidemiological study carried out by the McGill University Methylmercury Study Group were suggestive of neurological effects in adults and children associated with mercury exposure. However, the study's methodological problems with regard to assessing exposure, assessing effects, and controlling for confounders limit the strength of the evidence.

Finally, the results of two of the pilot studies are suggestive of a relationship between neurological health effects in adults and mercury exposure. However, because of their limited size and study design, the results do not provide evidence for such effects, as might or might not be obtained in a larger, well-designed epidemiological investigation.

In conclusion, most of the studies carried out in the 1980`s and early 1990`s linking mercury exposure and health effects found signs on neurological examination or neuropsychological or neurophysiological testing of older Cree adults, that could be compatible with mercury toxicity. The neurological findings were mild and unlikely to lead to consulting a physician. The association of neurological findings with mercury exposure was not strong; this may be due to difficulties in assessing exposure in the various studies of neurological effects on adults. Most studies use hair mercury levels taken at the time of the study, which reflect average intake over the previous few months. But it may be that mercury level several years previously has a greater impact on neurological examination findings. Or perhaps several short-term, high blood levels have a greater impact on health than the average levels measured in hair samples.

Screening and surveillance investigations, carried out since the early 1970s, show a steady decline within the nine communities with respect to mercury exposure. This trend was most recently confirmed in 2002 in the communities of Oujé-Bougoumou and Nemaska. Nonetheless, fish consumption, and with it exposure to mercury, may increase sharply in response to particular events, such as a fish distribution program carried out in Eastmain in 1992.

Table 1 Clinical studies, northwestern Quebec

Reference/type of study/ year	Study populations/ Exposure measure	Effects measured	Findings	Conclusions
(Barbeau, Nantel et al. 1976): Clinical examinations during three missions: Nov 1975, Feb and March 1976.	1) Waswanipi Cree fishing from Lac Matagami and from lakes in the region of Lacs Goeland and Waswanipi, in the Bell-Nottaway catchment basin; 2)Mistissini Cree 3)Algonquin who fish near the confluence of the Quevillon and Bell rivers. Area directly affected by industrial effluent (Domtar chlor-alkali plant). 4) 4 Domtar employees, 7 non-native fishermen, 62 non-native persons from Matagami 5) Control group from Montreal, 6 men and 6 women, non-consumers of fish with no known neurological disease. Exposure: blood and hair mercury levels measured.	General medical exam and detailed neurological exam (Mayo Clinic exam protocol) 2nd detailed neurological exam by Dr. Barbeau, with emphasis on signs and symptoms associated with mercury poisoning. Weighting of symptoms according to severity. Brief family history also taken.	A constellation of four signs of mercury poisoning – problems in touch sensitivity, constriction of visual fields, tremors, and coordination problems - were found in 30% of Cree and Algonquin and none of the non-natives. Conclusion: at least 6 Cree or Algonquin and possibly 25 of the 49 examined, showed signs of mercury poisoning. Among Native subjects no dose-response relationship is readily apparent. However, the mercury blood and hair concentrations in the Cree were substantially higher than the levels measured in the non-native subjects.	Authors' conclusions: The neurological conditions, when taken together, were not typical of any neurological condition encountered by the senior neurologist, other than mercury poisoning. The general nutritional state was judged to be highly influential with regard to the manifestation of mercury intoxication, but authors do not specifically account for this or alcoholism in their analysis. Comments: Medical study rather than epidemiological investigation: small number of subjects, neurologists not blinded to subject's exposure; no adjustment for potential confounders.

Table 2 Results of epidemiological investigations in northern Quebec in the 1970s

Reference/type of study/ year	Study population/ Exposure measure	Effects measured	Findings	Conclusions
(1) (Kofman, Simard et al. 1979): original analysis and report (Auger, Kofman et al. 2002): re-analysis. Cross-sectional, 1977-78	306 Cree, all plaintiffs in a lawsuit brought against mining and industrial companies in the region. Mercury measured in hair samples corresponding to exposure over the past year (scalp, peak, and mean values obtained); blood mercury measured at time of exam. Range: 0.5 to 46 ppm in scalp hair mercury. Max hair mercury concentration of 48.5; maximum blood mercury of 150 ppb.	Neurological abnormalities including sensory disturbance, incoordination, auditory defects, motor abnormalities, reflex abnormalities; also effects on cranial nerves, systemic symptoms, and cognitive impairment.	In the original report, authors concluded that no individual manifested a set of symptoms conforming to what would be expected from chronic mercury intoxication. In the reanalysis, authors found an association between tremor in young adults and mercury exposure. Odds ratio of 2.22 (95% CI 1.15 to 4.06) corresponding with a 6 ppm increase in scalp hair mercury.	Limitations of data set (see text for details): i) possible selection bias, ii) potential misclassification of co-variates, iii) inadequate exposure assessment, and iv) clinicians not completely blind to mercury exposure levels.

Table 2 continued. Results of epidemiological investigations in northern Quebec in the 1970s				
Reference/ type of study/ year	**Study population/ Exposure measure**	**Effects measured**	**Findings**	**Conclusions**
(Spitzer, Baxter et al. 1988) Cross-sectional study, July/ August 1977.	Hair and blood mercury in 4 groups of volunteers: **1)** Self-designated disease group (n=81): Cree living in the Nottaway drainage system (affected by mercury pollution) who alleged mercury intoxication; **2)** Neighborhood controls (n=69): Cree from same villages as group (1), but not alleging mercury intoxication; **3)** Ancestral controls (n=62): members of the Algonquin nation living in the Outaouais drainage system (free of local industrial mercury pollution). Fish provided major source of dietary protein; **4)** General comparison group (n=98): White and Algonquin individuals living in the Nottaway Drainage system, at varying distances from the chlor-alkali plant responsible for local mercury pollution.	10 target variables: 1-any neurologic or ophthalmologic abnormality; 2-abnormalities recorded by field neurologist (11 conditions assessed); 3-physical functional disability; 4-bilateral neurosensory hearing loss; 5-motor nerve conduction velocities; 6-coexistent upper and lower extremity tremor; 7-abnormalities recorded by nurse practitioner (neuro-physiological status); 8-stated sickness; 9-definite EEG abnormalities; 10-sensory nerve conduction velocities.	Mercury intoxication not found (as based on the criteria of constriction of visual fields, ataxia, paraesthesia, hearing deficit); diabetes and alcohol-related health problems (possible confounders) were common. However, definite relationship between mercury in hair and four target variables (Nos. 1, 6,7,10) suggesting verifiable biological threshold levels for clinical effects. This study suggests effects at levels of exposure in the 60 to 100 ppb blood mercury range (Kosatsky and Foran 1996).	Study designed to distinguish effects related to the presence of the chlor-alkali plant, as well as investigating the effects related to high mercury exposure, regardless of the source. The group comparisons of the findings showed gradients for 2 of the 10 target variables. The authors could not "rule in or rule out" a causal relationship for mercury emitted by the chlor-alkali plant and either clinical exam results or measurement of mercury in body tissues.

Table 2 continued. Results of epidemiological investigations in northern Quebec in the 1970s

Reference/type of study/ year	Study population/ exposure measure	Effects measured	Findings	Conclusions
(McGill University Methylmercury Study Group 1979; McKeown-Eyssen and Ruedy 1983) Case-control study: Jan 1975 to Dec 1977; most samples taken from July to Dec 1975 in Mistassini and July to Dec 1976 in Great Whale. Also 1978 index: 4 cm in length corresponding to April to July 1978.	Mistassini: 176 men, 185 women (86% of adults over age 30) Great Whale: 47 men, 52 women (92.5% of adults over age 30). Mercury in blood and hair to measure exposure; statistical analyses in terms of hair concentration.	Neurologic examination assessed nystagmus, coordination and gait, tremor, movements and reflexes, sensation, stereognosis, and two point discrimination. Cases considered to be those subjects with certain visual impairments or neurologic disease, with no definitive alternative diagnosis (e.g. Parkinson's Disease). Selection of cases blind to mercury measurements.	After adjustment for age and alcohol use, discriminant analysis revealed a positive association between neurologic abnormality and mercury, significant for Mistassini but not Great Whale. With each increment of 20 ppm in hair, probability of being a case increased by a factor of approx. 5 (in men) and 3 (in women). Estimation of odds ratio (pooled data across age categories): Subjects with exposures of 10 to 19.9 ppm: OR=2.12, 95%CI 0.98-4.60) Subjects with exposures > 20 ppm: OR=3.72, 95%CI 1.18 to 11.76.	Factors other than mercury possibly related to neurologic findings were discussed (e.g. age and alcohol, diabetes, nutritional differences, variability in neurologists' assessments). No alternative explanatory factors identified (although age and alcohol adjustments were carried out); authors conclude that the residual effects may still not be entirely attributable to mercury. Moreover, the data do not allow for the estimation of a threshold level, above which an excess of neurologic abnormality might occur. Past exposure was probably higher than recent exposure.

Table 2 continued. Results of epidemiological investigations in northern Quebec in the 1970s				
Reference/type of study/ year	**Study population/ exposure measure**	**Effects measured**	**Findings**	**Reference/ authors' conclusions**
(McGill University Methylmercury Study Group 1979; McKeown-Eyssen, Ruedy et al. 1983). Case/control study: Examination of children in 1978; 48% of hair samples collected at this time (sufficiently long to estimate exposure during pregnancy); 52% of samples collected during pregnancy or in Dec 1977.	247 children (12 mo to 30 mo) in Mistassini, Waswanipi, Great Whale, Fort George Mercury measured in maternal hair samples taken during pregnancy, or by measuring hair segments estimated to correspond to pregnancy. Max concentration in hair for period one month before conception to one month after delivery. Average exposure index for boys and girls was 6 ppm; 6% of children had prenatal exposures of over 20 ppm.	Neurologic examination of children assessed special senses, cranial nerves, sensory function, muscle tone, stretch reflexes, coordination, persistence of the Babinski response, and overall summary of neurologic abnormalities. Development assessed using the Denver developmental scale. Cases identified as follows: 1) neurologic examination carried out; 2) regression analysis used to see which of the 8 measures of neurologic function were associated with mercury exposure; 3) children identified as cases depending on the presence of abnormality with respect to function.	In boys, abnormality of muscle tone or reflexes was positively associated with the index of prenatal mercury exposure. No other measure of neurologic function or development was significantly associated with exposure, in a direction indicating an adverse effect, either before or after adjustment for confounding variables.	Abnormality of muscle tone was mild in severity and of doubtful clinical importance. The importance can only be determined through continued medical surveillance. Authors concluded that positive finding was not entirely consistent with previous knowledge of the effects of prenatal exposure to methyl mercury. In Japanese and Iraqi poisoning incidents, affected children exhibited severe generalized neurologic disease and not isolated abnormalities. No consistent dose-response relationship; no consistency between sexes.

Table 3: Mercury exposure in <u>men</u> in all communities (data from Dumont, Noel et al. 1998a); hair monitoring results in parts per million (ppm).

Year	No. individuals tested (N)	Mercury in hair (ppm)			Comments
		50th percentile	90th percentile	Max	
Testing carried out prior to the Mercury Agreement					
1982	149	9.5	19.5	88.1	Mercury concentration in 1st cm of hair, if sample taken in July, August, or Sept. Otherwise, concentration in the cm corresponding to one month of this period. Previous campaigns had showed peak exposure during these months. Exception: 1982/83 where value is maximum during the 6 months preceding the hair sampling. Data provided in Dumont Noel et al 1998 available according to age group and community. Target groups varied from one year to the next and to a certain extent, from one community to the next. In general the campaigns targeted probable high-exposure cases (e.g. trappers, individuals with previous high exposure) as well as women of child-bearing age and pregnant women, in order to maximize the detection of high-exposure cases using limited resources. The data is therefore illustrative, but does not allow for the statistical analysis of time-trends. See section 7.2 for yearly comparisons.
1983	329	11.3	27.4	128.0	
1984	496	14.3	39.6	143.0	
1985	451	10.7	27.9	143.0	
1986	1033	5.2	17.7	49.5	
Testing carried out under Mercury Agreement					
1987	569	9.5	26.2	124.2	
1988	696	8.3	21.9	85.6	
1989	447	7.3	20.4	63.0	
1990	448	7.4	22.4	57.8	
1991	537	6.0	17.1	95.1	
1992	296	7.4	20.0	51.2	
1993	540	2.9	14.5	70.0	
1994	848	2.5	10.7	55.7	
1995	17	16.3	27.1	54.6	

For men and non-reproductive age women: CBHSS intervention threshold set at 30 ppm, based on a NOEL (No observed effects level) of 100 ppm, with a safety factor of 3 due to the uncertainty of the effects of a lifetime of seasonal exposure. Intervention threshold for pregnant women set at 15 ppm. Detection threshold is 2.5 ppm.

Table 4: Mercury exposure in <u>women</u> in all communities (data from Dumont, Noel, et al 1998); hair monitoring results in parts per million (ppm).

Year	No. individuals tested (N)	Mercury in hair (ppm)			Comments
		50th percentile	90th percentile	Max	
Testing carried out prior to the Mercury Agreement					1982/83 concentrations – maximum during the 6 months preceding the hair sampling. In other years, concentration in July, August, or September.
1982	144	9.2	20.5	72.8	
1983	461	6.7	22.6	79.4	
1984	594	11.6	35.3	168.0	
1985	593	8.2	22.8	91.6	
1986	1171	4.4	16.3	44.2	
Testing carried out under the Mercury Agreement					
1987	1657	3.3	15.1	68.0	
1988	1979	2.9	13.7	91.7	
1989	930	2.9	13.7	44.7	
1990	944	2.5	15.0	45.1	
1991	1385	2.5	10.5	42.3	
1992	633	2.6	14.7	47.2	
1993	746	2.5	13.5	42.5	
1994	1129	2.5	7.9	40.7	
1995	128	2.5	14.2	106.2	

For men and non-reproductive age women: CBHSS intervention threshold set at 30 ppm, based on a NOEL (No observed effects level) of 100 ppm, with a safety factor of 3 due to the uncertainty of the effects of a lifetime of seasonal exposure. Intervention threshold for pregnant women set at 15 ppm. Detection threshold is 2.5 ppm.

Table 5: Mercury exposure in men from Chisasibi (data from Dumont, Noel, et al 1998); hair monitoring results in parts per million (ppm).

Year	No. individuals tested (N)	Mercury in hair (ppm)			Comments
		50th percentile	90th percentile	Max	
Testing carried out prior to the Mercury Agreement					
1982	-	-	-	-	1983 concentrations – maximum during the 6 months preceding the hair sampling.
1983	3	11.3	17.0	18.4	
1984	141	21.1	95.4	143.0	
1985	80	14.1	46.5	143.0	
1986	253	7.0	20.8	49.5	
Testing carried out under Mercury Agreement					
1987	177	7.3	22.9	72.0	
1988	175	10.1	30.3	85.6	
1989	126	9.9	26.0	63.0	
1990	113	7.1	24.4	43.5	
1991	167	6.9	19.0	39.4	
1992	159	5.8	15.6	47.9	
1993	20	14.2	31.9	56.1	
1994	258	2.8	12.5	55.7	
1995	4	21.5	46.1	54.6	

For men and non-reproductive age women: CBHSS intervention threshold set at 30 ppm, based on a NOEL (No Observed Effects Level) of 100 ppm, with a safety factor of 3 due to the uncertainty of the effects of a lifetime of seasonal exposure. Intervention threshold for pregnant women set at 15 ppm. Detection threshold is 2.5 ppm.

Table 6: Mercury exposure in <u>women</u> from Chisasibi (data from Dumont, Noel, et al 1998); hair monitoring results in parts per million (ppm).

Year	No. individuals tested (N)	Mercury in hair (ppm)			Comments
		50th percentile	90th percentile	Max	
Testing carried out prior to the Mercury Agreement					
1982	-	-	-	-	1983 concentrations – maximum during the 6 months preceding the hair sampling.
1983	81	3.2	8.5	26.0	
1984	193	17.8	58.2	168.0	
1985	144	7.8	28.3	91.6	
1986	287	5.0	18.9	44.2	
Testing carried out under Mercury Agreement					
1987	543	3.0	11.7	58.1	
1988	464	3.4	15.7	91.7	
1989	280	2.5	14.8	41.7	
1990	211	2.5	18.1	42.7	
1991	332	2.5	12.1	42.3	
1992	249	2.5	10.8	29.7	
1993	46	3.1	19.9	27.1	
1994	347	2.5	8.3	27.9	
1995	36	2.5	9.4	106.2	

For men and non-reproductive age women: CBHSS intervention threshold set at 30 ppm, based on a NOEL (No Observed Effects Level) of 100 ppm, with a safety factor of 3 due to the uncertainty of the effects of a lifetime of seasonal exposure. Intervention threshold for pregnant women set at 15 ppm. Detection threshold is 2.5 ppm.

Table 7: Mercury exposure in men from Wemindji (data from Dumont, Noel, et al 1998); hair monitoring results in parts per million (ppm).

Year	No. individuals tested (N)	Mercury in hair (ppm)			Comments
		50th percentile	90th percentile	Max	
Testing carried out prior to the Mercury Agreement					
1982	74	10.3	20.4	26.2	1982/83 concentrations – maximum during the 6 months preceding the hair sampling.
1983	75	15.5	29.0	46.1	
1984	87	9.0	19.3	40.2	
1985	75	9.0	23.1	100.0	
1986	150	5.0	14.5	38.8	
Testing carried out under Mercury Agreement					
1987	85	6.7	18.6	124.2	
1988	83	9.3	18.7	41.3	
1989	46	6.7	15.0	33.5	
1990	54	6.2	18.1	42.1	
1991	56	4.3	12.8	95.1	
1992	53	8.3	20.3	51.1	
1993	14	7.4	20.2	37.5	
1994	219	2.5	8.4	23.5	
1995	5	13.9	25.7	26.2	

For men and non-reproductive age women: CBHSS intervention threshold set at 30 ppm, based on a NOEL (No Observed Effects Level) of 100 ppm, with a safety factor of 3 due to the uncertainty of the effects of a lifetime of seasonal exposure. Intervention threshold for pregnant women set at 15 ppm. Detection threshold is 2.5 ppm.

Table 8: Mercury exposure in women from Wemindji (data from Dumont, Noel, et al 1998); hair monitoring results in parts per million (ppm).

Year	No. individuals tested (N)	Mercury in hair (ppm)			Comments
		50th percentile	90th percentile	Max	
Testing carried out prior to the Mercury Agreement					
1982	64	9.8	17.1	25.9	1982/83 concentrations – maximum during the 6 months preceding the hair sampling.
1983	79	10.2	30.0	53.8	
1984	83	7.8	15.7	21.1	
1985	82	8.9	21.5	37.2	
1986	129	5.0	15.5	44.2	
Testing carried out under Mercury Agreement					
1987	211	2.5	11.1	68.0	
1988	217	3.2	10.5	21.8	
1989	95	3.2	9.3	44.7	
1990	112	2.5	8.0	42.5	
1991	108	2.5	9.3	31.0	
1992	72	5.4	16.3	45.0	
1993	33	2.5	7.2	16.8	
1994	250	2.5	6.6	18.8	
1995	7	2.5	6.6	12.7	

For men and non-reproductive age women: CBHSS intervention threshold set at 30 ppm, based on a NOEL of 100 ppm, with a safety factor of 3 due to the uncertainty of the effects of a lifetime of seasonal exposure. Intervention threshold for pregnant women set at 15 ppm. Detection threshold is 2.5 ppm.

Table 9: Exposure of men and women in different Cree communities from 1983 to 1985 (data from Dumont, Noel, et al 1998); hair monitoring results in parts per million (ppm)

Community	No. individuals tested (N)			1983 Mercury in hair (ppm)			1984 Mercury in hair (ppm)			1985 Mercury in hair (ppm)		
	'83	'84	'85	50th pct.	90th pct.	Max	50th pct.	90th pct.	Max	50th pct.	90th pct.	Max
Oujebougoumou	9	7	8	9.8	29.4	77.0	17.4	20.1	20.2	7.4	10.5	12.6
Waswanipi	77	76	60	11.2	30.1	128.0	13.5	32.6	58.5	10.5	23.9	42.8
Mistissini	297	251	295	10.4	25.0	44.0	15.5	30.2	68.8	10.2	22.9	42.9
Eastmain	64	87	76	4.8	11.6	25.1	4.9	12.3	18.8	6.2	18.1	35.7
Wemindji	154	170	157	12.3	29.2	53.8	8.4	18.3	40.2	8.9	22.7	100
Waskaganish	80	55	73	7.4	19.4	38.8	5.3	13.6	24.2	5.3	13.1	38.1
Chisasibi	84	334	224	3.2	9.6	26.0	20.0	75.2	168	9.7	38.5	143
Nemaska	5	59	69	15.2	18.3	19.1	16.3	30.2	49.9	11.5	20.2	44.3
Whapmagoostui	20	51	82	12.3	73.6	107.0	14.3	42.0	127	9.7	24.6	42.0

For men and non-reproductive age women: CBHSS intervention threshold set at 30 ppm, based on a NOEL(No Observed Effects Level) of 100 ppm, with a safety factor of 3 due to the uncertainty of the effects of a lifetime of seasonal exposure. Intervention threshold for pregnant women set at 15 ppm. Detection threshold is 2.5 ppm.

Table 10: Mercury exposure among pregnant women (Girard and Dumont 1995); hair monitoring results in parts per million (ppm) for women at conception, at delivery, and maximum value during pregnancy.

Year	No. individuals tested (N)	Conception, mercury in hair (ppm)			Delivery, mercury in hair (ppm)			Pregnancy maximum, mercury in hair (ppm)		
		50th percentile	95th percentile	Max	50th percentile	95th percentile	Max	50th percentile	95th percentile	Max
1983	266	3.0	11.8	25.6	3.4	12.4	26.0	4.0	19.5	41.9
1984	250	3.0	19.2	31.0	2.3	9.8	30.0	3.8	19.0	33.0
1985	257	2.0	8.9	24.0	1.5	9.3	10.4	2.5	12.5	27.1
1986	241	1.5	6.1	15.2	1.5	5.5	14.0	2.0	8.1	15.5
1987	252	1.5	4.3	8.0	2.3	4.5	11.6	2.0	6.9	19.3
1988	267	2.5	6.3	15.2	2.5	4.9	9.3	3.0	7.3	15.2
1989	265	2.5	5.5	9.2	2.5	3.8	7.7	3.0	7.7	10.3
1990	287	2.5	4.2	10.8	2.5	4.1	9.8	3.0	6.7	13.3
1991	275	2.5	5.0	10.4	2.5	3.2	10.2	2.5	5.9	12.8

Intervention threshold of 15 ppm for women of childbearing age. Detection limit is 2.5 ppm.

Table 11: Development of test protocols, results of studies.

Type and year of study	No. subjects tested	Avg. Age (range)	Mercury in hair (ppm)*	Study conclusions	Reference and comments
Questionnaire, neuropsychological testing, selective clinical neurological exam. 1997.	Control: n=29 12 men, 17 women.	55.6 ± 8.1 (34-70)	-	Authors conclude that: -the neurological exam was quantifiable and sensitive to effects that could be attributed to mercury exposure, or to the beginning stages of Parkinson's disease. -the clinical protocol could be used in future studies evaluating Cree populations, with some modifications (see text); -the neurological protocol is adequately sensitive to detect neurological differences in a population chronically exposed to mercury. - study shows the existence of a neurological syndrome in Cree subjects that is similar to the syndrome described for Minamata.	(Panisset and Gauthier 1998) Although the authors state their conclusion of finding neurological anomalies among the Cree, similar to those reported for mercury poisoning, this finding is, at most, suggestive of neurological effects that are possibly related to mercury exposure. It should be emphasized that 1) the number of subjects is a very small, 2) little information is given regarding the selection of Cree subjects and controls, 3) none of the exposures, as indicated by the average over the years, are particularly high, even in the "high exposure" group, and 4) hair mercury levels in the controls (presumably very low) were not measured.
	Subjects with Parkinson's disease: n=21, 15 men, 6 women.	55.1± 9.4 (36-70)	-		
	Cree subjects n=36, 10 men, 26 women	56.6± 11.5 (38-82)	8.2 ± 6.8 (for n=35) **		

***** Mean of annual maximum measurements across 25 years.

** Low exposure group (n=6): 8.49 ± 2.02 High exposure group (n=6): 27.52 ± 2.81. See text for explanation.

Table 11 continued: Development of test protocols, results of studies.

Type and year of study	No. subjects tested	Age (avg)	Mercury in hair (ppm) Mean of annual maximum measurements across 25 years.	Study conclusions	Reference and comments
Tests of eye movements, upper extremity tremor, rapid alternating movements, and pointing speed and precision. 1997	Control: n=30	55.9 ± 8.2	-	Tests simple to administer and the testing equipment is portable. For all tests, agreement between clinical data and experimental data consistently low: possible reasons for this include a) test is continuous while clinical exam is dichotomous (normal, abnormal) and/or b) tests are detecting pre-clinical abnormalities.	(Beuter 1997; Beuter and Edwards 1998; Beuter, de Geoffroy et al. 1999; Beuter, Geoffroy et al. 1999)
	Subjects with Parkinson's disease: n=21	55.1± 9.4 (36-70)	-		
	Cree subjects n=36	56.6± 11.5 (38-82)	8.2 ± 6.8 (for n=35) Low exposure group (n=6): 8.49 ± 2.02 High exposure group (n=6): 27.52 ± 2.81		
	Subjects with cerebellar deficits n=6	49.8 ± 13.6			
	Subjects with essential tremor n=3	57.7± 11.9			

Table 11 continued: Development of test protocols, results of studies.

Type and year of study	No. subjects tested	Age (avg)	Mercury in hair (ppm) Mean of annual maximum measurements across 25 years.	Study conclusions	Reference and comments
1997 Temporal modulation visual fields	Control group, Parkinson's disease group, and Cree group the same as in Panisset and Gauthier 1998 study.			Test protocol met goals of being portable, reliable, repeatable, relatively short duration, and well accepted. Tests are suited for assessing visual dysfunction produced by neurotoxicity effects; sensitive to subtle visual changes, have good test-retest reliability, are easy to perform by subjects from a variety of populations, including the Cree population.	(Faubert 1997)
	Subjects with essential tremor, n=3, 2 men, 1 woman.	57.7 ± 11.8 (44-65)	-		
	Subjects, ex-alcoholic, n=2, 1 man, 1 woman.	59.0± 5.7 (55-63)	-		

Table 12 Hair mercury levels in the communities of Oujé-Bougoumou and Nemaska, 2002

	Hair Mercury (ppm) Percentiles				
Group	10th	50th	90th	Max	Reference
Women 15 to 39 yr Oujé-Bougoumou, 2002 (n=78)	<DL	0.70	2.80	7.40	(Dewailly and Nieboer 2003)
Women 15 to 39 yr Oujé-Bougoumou, 1993 (n=60)	-	2.5	4.0	8.8	(Dumont, Noel et al. 1998)
Men and women > 40 yr Oujé-Bougoumou, 2002 (n=51)	0.90	3.90	10.8	13.9	(Dewailly and Nieboer 2003)
Men and women > 40 yr Oujé-Bougoumou, 1993 (n=56)	-	8.2	21.4	28.1	(Dumont, Noel et al. 1998)
Women 15 to 39 yr Nemaska, 2002 (n=42)	<DL	0.20	1.10	2.70	(Dewailly and Nieboer 2003)
Women 15 to 39 yr Nemaska, 1993 (n=69)	-	2.5	4.3	11.9	(Dumont, Noel et al. 1998)

Table 12 continued.

Group	10th	50th	90th	Max	Comments/ Reference
Men and women > 40 yr, Nemaska 2002 (n=13)	0.70	2.80	6.50	8.80	(Dewailly and Nieboer 2003)
Men and women > 40 yr, Nemaska 1993 (n=69)	-	8.2	17.3	23.4	General survey (n=69) (Dumont, Noel et al. 1998)

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APPENDIX A

Methylmercury exposure and human health

Some reflections on the studies of the Cree population

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These notes are intended as a supplement to the review of existing studies on the Cree population in Québec prepared for the Cree Health Board by Deborah Schoen. I was involved in, or a party to, many of the discussions about the planning of investigations of mercury exposure in the Cree population and its implications. The studies that have been published, as Deborah Schoen's report makes clear, took place in a complex social and cultural setting which directly influenced the nature and scope of the studies themselves. The literature referred to in the report, and in particular the peer-reviewed journal articles, typically do not make reference to the context in which the studies were carried out.

The purpose of this note, therefore, is to provide some of the contextual information which may be helpful to, and hopefully relevant in, the interpretation of the studies presented by Deborah Schoen and the data sets on which they are based. I hope that these observations will contribute to the analysis and evaluation of existing data, and be of some assistance in the planning of future studies.

By way of introduction, it is important to keep in mind that the Cree are, with respect to mercury exposure, among the most intensively studied populations on any continent. All of the investigations carried out so far, to my knowledge, have identified neurological signs or symptoms which the investigators found were consistent with evidence of methyl mercury toxicity. The problem of interpretation has been, in part, that these signs or symptoms could have alternative explanations. It has also, as explained below, proved very difficult to link these signs and symptoms to reliable and toxicologically relevant indices of human exposure to mercury. Finding results which appear statistically significant from an epidemiological perspective may not necessarily mean that the same findings can be reliably or consistently observed in a clinical setting.

1. *Mercury exposure and the regional geographical setting*

When cases of elevated exposure to mercury were first identified in the Cree population (in 1971), environmental mercury contamination was primarily seen as a problem associated with the pulp and paper industry – first because of the use of organomercurials as slimicides, and later when it was realized that mercury cells used in chlor-alkali plants provided a source of inorganic mercury for the biological-mediated methylation of mercury. Mines, especially gold

mines, and metal smelting operations were also seen as potentially important regional sources of mercury contamination.

These assumptions influenced the first collections of blood and hair samples in the Cree population. The emphasis shifted from an initial focus on occupational exposure (in commercial fisheries) to a broader search for patterns of exposure at the community level – but still in the context of local industrial sources of exposure. The realization that local factors did not account for community-wide patterns of exposure was followed by the discovery that patterns of exposure were similar wherever communities had access to inland fisheries and maintained fish production systems (harvesting and distribution) through the year. In this way, exposure came to be associated with life style.

At the same time, and contrary to expectations at the time, it was found that mercury concentrations in a given species of fish were remarkably similar, from north to south and from east to west. There are some regional differences which can be traced to physiographic and geological factors, but the main drivers of human exposure were found to be the species consumed and their body burdens of mercury – especially the mercury body burdens in the predatory species – pike, lake trout and walleye in particular.

These factors, taken together, illustrated the importance of understanding the structure and function of local fisheries and their relation to other food resources (wildlife resources as well as store bought foods) and in relation to local food distribution systems.

2. ***Mercury exposure, history and demography.***

The tracking of mercury exposure in Cree society, in Canadian aboriginal communities in general, and the Canadian population as a whole, dates back approximately 35 years. The last 35 years, in the case of the Crees in Québec and in other aboriginal societies, has been a period of rapid institutional and cultural change.

One of the consequences, already apparent in the 1970's, was a marked difference in patterns of wildlife consumption, and especially of fish, in different segments of the Cree population. There is now, and always has been since 1970, a strong association between age and the role of fish in the diet. The communities have grown rapidly – they have doubled in size during this time period. They are young, and this directly affects the distribution of exposure as well as apparent trends over time based on the indices for the population at a whole.

What is important to keep in mind is that the first reasonable cross sections of exposure (based first on blood and later on hair analyses) demonstrated consistently very high levels of exposure in adults over, roughly, the age of 35. If we concentrate on the older segments of the population, both women and men, we find that in the mid-1970's, most adults probably exceeded the WHO/NHW (World Health Organization/Department of National Health and Welfare Canada – now called Health Canada) standards for acceptable exposure (20 ppb in blood, 6 ppm in hair) by a factor varying from 3 to 5. Some individuals exceeded the WHO/NHW criterion by an order of magnitude – 200 ppb in hair or 50-60 ppm in hair. Levels in the 20-30 ppm range (now associated with the neurological signs documented in Deborah Schoen's report) were quite common, and quite possibly involved between one-fifth and one third of the population over the age of 40. The older the age group, the more frequent the elevated exposure levels.

There was much debate at the time about the interpretation of the exposure levels – a problem that would later become a major pre-occupation when epidemiological studies were planned.

The Federal government was obviously concerned. It moved in the early fall of 1975 to try and close the subsistence fishery altogether until the sources of exposure was better understood. The very large number of individuals found with blood levels over 20 ppb (or the hair equivalent) were subject to repeat measurements until their exposure levels had dropped below the intervention level. Field workers were hired to distribute information about Minamata disease and reinforce the messages supplied by the NHW nurses. And, as Deborah Schoen points out in her report, some of the more highly exposed individuals were sent to Montréal for clinical neurological assessments.

The extent to which the subsistence fisheries changed (collapsed might be a more accurate description) is clearly reflected in the data accumulated on Cree fisheries during the 1970's for the Native Harvesting Research Project, and presented in the document 'The Wealth of the Land'. In some communities, reported harvests of fish dropped by as much as 90%.

With the partial exception of the Barbeau study described in the report, all of the epidemiological studies were planned and implemented after these major policy interventions to limit human exposure. This comment applies both the studies of adults and children. Also, the reports based on the studies relied for the most part on exposure indices concurrent with the neurological assessments. This was widely debated at the time, but the studies conducted for litigation purposes did not have access to the recent historical data bases.

The underlying question, therefore, was whether the neurological signs which were present reflected exposure at the time of the assessment, exposure over the previous few years, or exposure over the life-times of the individuals involved. There was, and still is, no clear way to answer these questions.

However, the Cree communities had known periods of real hardship in the 1930's, 1940's and even the 1950's. Fur-bearing animals were scarce and limited (especially beaver, which is now a major source of bush meat). There were very few caribou in the region, and the range of moose was limited to the southern portion of the territory. There were few signs then that the Cree hunting economy would evolve into the big-game hunting economy that is evident today. Small game (ptarmigan, grouse, hares) fluctuate in availability widely from one year to the next in a cyclical fashion. The success of waterfowl hunts varied both with the status of the population of individual species and with weather – access was generally more limited than it was in the 1970's and 1980's.

The combination of these factors meant that the Cree families (some of which experienced famine, starvation and death during this period) were particularly dependent on fish at times. It is difficult not to reach the conclusion that these periods of hardship were not also periods of particularly high levels of exposure to mercury. We do not have any evidence that mercury levels in fish populations have changed enough during the 20th century to result in differences in levels of exposure which would be considered significant from an epidemiological or toxicological perspective.

These sources of uncertainty both about historical exposure and about the levels of exposure associated with the neurological evidence gathered in the 1970's have an important bearing on the communication of risks associated with methyl mercury exposure, and have made it

appreciably more difficult to provide clear messages about the level of risk associated with a given level of exposure to methyl mercury.

The final introductory remark here concerns the influence of litigation. The study by Barbeau et al. prompted the initiating of lawsuits against Domtar, the owner of the chlor-alkali cell at the Quévillon pulp mill, Noranda Mines and a number of smaller mining companies. As Deborah Schoen's report explains, some of the neurological data available for the Crees was derived from studies on an epidemiological scale, but conducted for defensive purposes by companies alleged to have caused neurological harm.

The circumstances of litigation, however, also influenced the design of the McGill Methyl Mercury study – both the selection of communities and the choice of neurological signs to investigate – and finally but not least in importance, the strategy adopted for data analysis. The context of litigation does not emerge readily from the published literature, but inevitably plays an important role in understanding what epidemiological and toxicological questions were asked, and why.

The following notes deal more specifically with selected aspects of the studies reported by Deborah Schoen in her report.

3. ***Interpreting the Barbeau et al. study***

a. Barbeau's assessment procedures relied on a battery of neurophysiological tests which are similar in some respects to those used by Donna Mergler and her collaborators in later studies of Amazonian populations. Some of these tests involved manual dexterity and rapidity of movement. There was debate at the time about the extent to which performance was culturally determined; and whether life style (i.e. activities associated with hunting) pre-determined the outcome of tests which relied on such measures of performance. Although an epidemiological approach was used for the design of the study, the lack of culturally determined controls was a constraint (in this and in other studies available at the time).

b. It is unfortunate, in retrospect, that no further efforts were made to address the problem of devising appropriate controls in order to assess such cultural or life-style factors. Problems of cross-cultural differences in test response have arisen in other studies, including notably the Iraqi pediatric investigation.

c. Barbeau himself saw the Cree as impoverished and his investigation as a stimulus to moving the Cree away from a subsistence harvesting economy. He was unsympathetic to the notion that it might be culturally important for the Cree to maintain their hunting economy (an issue which, with the signing of the JBNQA, was being given some prominence). Issues of dose:response relationship and providing advice to permit the survival of subsistence fisheries was not on the policy agenda at the time.

d. The possibility of cultural influences on neurological performance was a major pre-occupation for subsequent investigators. Spitzer, in particular, stressed the use of neurophysiological tests (such as nerve conduction velocities) as a way of getting around this problem. Ruedy, also, sought to avoid or minimize reliance on self-reported signs such as paraesthesia. This meant eliminating

from consideration some of the signs which had previously been thought to be most sensitive as early indicators of methyl mercury toxicity.

e. The litigation initiated by the Grand Council of the Crees (of Québec) in late 1976 on the basis of the Barbeau study reinforced the reluctance to rely on self-reported signs – a factor which also influenced the design of the Ruedy study. Since the definition of plaintiff was generally based on a record of having exceeded the 20 ppb NHW standard for exposure, most of the older members of the populations qualified as plantiffs. It is doubtful whether the individuals had any awareness at the time of the symptoms associated with the lower limits of detectable neurological effects; what they had seen was the photographic evidence from Minimata – a very different profile.

4. ***What is 'normal' neurological behaviour in the Cree population?***

a. This was discussed at length by the neurologists in Ruedy's team. What I gleaned from the exchanges was a perception that individual neurologists make their own intuitive judgments about the effects of age on various indicators of neurological performance, based on their own clinical experience and the populations with which they are most familiar. The evaluation process is inherently subjective, and did not lend itself readily to quantification. When working across cultural boundaries, the problem of deciding what is 'normal' in a given age group becomes difficult to resolve, and a major source of inter-observer variance.

b. As a result of these differences in experience, and approaches to assessing cross-cultural differences, there were considerable differences in the assessments by different neurologists. At the time of the McGill study, this was recognized as an important challenge in the context of further epidemiological work (for example, if a decision had been taken to use the 'cases' and 'controls' as the basis for a longitudinal study).

c. This issue of defining a reference standard also emerged, as I recall, in the context of interpreting the visual field data, but it was also a problem in audiology, and in the interpretation of abnormal gait (particularly in women). In the case of audiology, exposure to chain saws, outboard motors and skidoos over the years becomes an important issue, and eventually tests of hearing were not retained for further analysis.

d. The problem of diverging views about the interpretation of neurological signs was particularly acute at Whapmagoostui, where all the 'cases' identified with signs of methyl mercury toxicity were associated with one of the two neurologists involved. This discrepancy led to a separate study, conducted at a prestigious hotel in Montréal, to document the extent of inter-observer variability in studies of this kind. The results are discussed in the final report by Dr. Ruedy and his colleagues to McGill University. Inter-observer variability is obviously an important consideration in developing a protocol for future assessments.

5. ***Identifying and accounting for confounding variables***

a. There was much discussion, in the case of the McGill study about confounders and how they might be addressed. The major sources of concern were: histories of alcohol use, smoking, caffeine and medication for the treatment of tuberculosis. Early child rearing practice was also a consideration in the interpretation of gait abnormalities. The interview schedules included questions on some of these topics, but there was also some skepticism with respect to how well these variables had been handled. Cold-related injury, including damage to the eyes, was also a source of concern.

b. Similarly, there was concern about the nutritional status of the participants and the possible role of vitamin deficiencies in the neurological assessments. Domtar's consultants, in particular, advanced the thesis of thiamine and possibly magnesium deficiency as a source of peripheral neuropathy (an argument was made at the time that fish contained a thiamine-destructive factor, further complicating the interpretation of neurological signs).

c. The discussions I heard at the time reinforced the impression that the extent to which confounders had been identified and adequately addressed was a critical factor in evaluating the findings from other investigations (including, I suggest, the later reports on possible mercury-related disease in Amazonian populations). Dealing with confounders is more difficult when working across cultural and linguistic boundaries.

d. At the time (the early 1980's), there was much interest in the reports from the first phase of the Kjellstrom study in New Zealand. This was a case in which the results might have been interpreted along ethnic lines (European vs. Maori vs. Pacific Islanders). I recall discussion about sources of cultural bias in the study of Cree infants and indeed the decision to study an 18-30 month cohort was at least in part dictated by concerns about confounders of cultural origin. In retrospect, of course, we can now see that it would quite possibly have made more sense to conduct a longitudinal study the Cree children at later stages in their development (as was done in the case of the Seychelles and Faroese studies).

e. There were some exploratory discussions along these lines with specialists at the Montréal Children's Hospital. A number of factors came into play (including the lack of interest on the part of both Canadian and Québec authorities to pursue the matter further). However, to be fair, I think it also has to be said that there was real concern about the possibility of conducting a useful study (in an epidemiological sense) in a context of rapid cultural, linguistic and institutional change.

6. ***Exposure indices in studies of adults***

a. I was struck by the considerable (and often under-appreciated) difficulties involved in establishing relevant indices of human exposure, despite the apparent ease and convenience of measurements of mercury concentrations

in blood and hair. There was much informal discussion about this problem, but it does not surface in the published literature.

b. The first and most obvious source of uncertainty is the potential for cumulative neurological effects of life-time exposure. Because we do not know how to define life-time exposure, we have no way of knowing whether cumulative effects over time are 'significant' (in either an epidemiological or clinical sense). The problem is compounded (at least in the Cree case) by the usually strong association between age and current exposure to mercury (i.e. fish tends to be quantitatively more important in the diet of older individuals).

c. There are a number of lines of ethnohistorical evidence which suggest that fish were more important in the diet in the past (e.g. from the 1930's to the 1950's). As noted above, these were years of considerable hardship (including famine and death) for some families, and fish were probably much more important in the nutrition of children and adolescents. It is quite possible that fish were a major source of calories at times. Periodic pulses of methyl mercury intake at rates much higher than are observed today seem plausible. This scenario obviously also applies to the issue of *in utero* exposure, and indeed the problem of cumulative, life-time, exposure is directly relevant to the assessment of the significance of pre-natal exposure.

d. More recently, at the time of the planning of the Ruedy study, the debate revolved around the relevance of cumulative exposure over the one or two or three year period preceding the study. Should an 'area under the curve' approach be used? Or some kind of index which reflected peak exposure during that three year period? Or should the emphasis be on exposure (blood or hair) at the time of the examination? In the case of the Cree studies, and notwithstanding the large data base for the preceding years, the tendency was to emphasise exposure at the time of examination. With the partial exception of the Barbeau study, this has meant that exposure was measured after the introduction of severe restrictions on local fish consumption (extending to a complete ban in some cases).

e. It is, as a result, difficult to know quite how to interpret the data on exposure for the Cree which was used in the epidemiological studies. An additional confounding factor in the critical period from 1975 to 1976 was the negotiation and ratification of the JBNQA itself, which resulted in abandoning the fall and winter hunting seasons by many active hunting families. This was an anomalous year, when the restrictions imposed by the federal government were superimposed on a year when the negotiation, conclusion and ratification of the James Bay and Northern Québec Agreement were also taking place.

f. Quite apart from these considerations, there is the problem of using 1-cm segments of hair, or of blood, to measure exposure at the time of assessment. There is a sizeable literature on this subject on the relationship between blood and hair concentrations, and a growing reluctance to use blood because of the influence of the diet in the previous day or so. In other words, even a decision has been taken to rely on measurements of exposure at the time of neurological assessment, there remains significant uncertainty about the

interpretation of the analytical data. The nature of the problems can be illustrated using the results of the Seychelles and Faroese longitudinal studies.

g. However, methyl mercury tends to be distributed rapidly between body compartments (including the brain), and it looks as though the exposure of the brain and central nervous system may take place in the kind of pulses which have been picked up in some studies of blood mercury levels. It is quite possible, then, that hair determinations – even the 1-cm segments, which represent roughly a month of hair growth – are not particularly good predictors of pulsed exposure on time scales of a day or a few days.

h. The latter problem is potentially of increasing significance for the Crees if it turns out that there has been a shift towards the consumption of the larger predatory species of fish as a result of the replacement of gill-netting by rod-and-line fishing. Short periods of high rates of exposure at weekend camps will not necessarily be reflected in hair measurements unless higher resolutions than the standard 1-cm segment are used. This is a potentially important factor in the planning of both adult studies and studies of pre-natal exposure.

7. ***Exposure indices in studies of children***

a. Similar debates took place over the selection of exposure indices in studies of pre-natal exposure. The studies in the Seychelles and the Faroese Islands used different approaches and this has made it considerably more difficult to compare findings from the two studies.

b. It has been argued that the first trimester of pregnancy may be particularly important (an argument based on histopathology of Iraqi victims), but this assumption apparently also is increasingly open to question. In any case, exposure based on measurements of blood or hair at the time of birth may not adequately reflect this early period.

c. As in the case of adult exposure, it is also possible that 'bolus' exposure, on time scales of a few hours or days, is critical – in which case the kind of exposure indices used in both the Seychelles and Faroese studies (not to mention the Cree population) may ultimately prove unsatisfactory. The point made here is that the selection of appropriate indices in studies of prenatal exposure is a continuing source of debate in the assessment of the effects of pre-natal exposure to methyl mercury.

8. ***Dose-response relationships and the Ruedy study***

a. When the Ruedy study was in the planning stage, the original intention was to use a multiple correlation and regression model for relating different indices of exposure to neurological effects, and to take into account various potentially confounding variables.. There was much debate about this, but one of the constraints was the time required for data entry and analysis. The strategy was eventually dropped under pressure from McKeown-Eyssen.

b. There were important time and financial constraints. The senior investigators (i.e. Drs. Ruedy and McKeown-Eyssen) left Québec after the completion of the field studies (i.e. in 1979). There was pressure to complete the statistical analysis if not before then at least shortly after their departure. None of the investigators (including the neurologists), in other words, were effectively available to work with the Cree directly or with Provincial (or Federal) authorities to pursue actively further strategies for the assessment of the data and to assist in the planning of the longitudinal studies which they recommended. Dr. Kreeft, responsible for the original study design, having been excluded from the later phases of the study, was in effect, also unavailable to pursue further statistical analysis.

c. McKeown-Eyssen made the case for the discriminant analysis which was eventually used in the final report – way of asking the simplest possible question – is there an apparent effect or not? We were warned at the time not to use the results of this analysis for the derivation of a dose:response relationship, and advised that further work would have to be done on dose:response relationships. In practice, all that the Cree advisors had to work with for subsequent policy development were the results, ironically, of this discriminant analysis.

d. After extended discussion, an agreement was reached whereby the primary data for the McGill study were transferred to the Cree Health Board. This was justified at the time by the argument that the data would be needed for further longitudinal study and for clinical assessments – but these did not take place. The raw data, though, remains with the Cree Health Board.

e. The problem of assessing acceptable dietary intakes of methyl mercury for the adult Cree population is compounded by the limited guidance available in the international literature. This is one reason why close attention should be paid to the results from the studies in the Amazon, and perhaps to the Samoan and Peruvian surveys conducted by the team at the University of Rochester (and more generally, studies on fishing communities elsewhere in the world).

9. ***The effects of pre-natal exposure in the Cree population***

a. The choice of the cohort retained for the Ruedy study was constrained by the timing and circumstances of the study. There was a limited window of opportunity both for initiating and for completing the study. It was apparent at the time that the selection of the cohort was less than ideal, and that it would make more sense to look at child development over a longer period. This would also have made it possible to include the more highly exposed children for whom data had been obtained in 1975 (most of the cohort was recruited from mothers who were pregnant after the restrictions on fish consumption had been introduced).

b. The pediatricians and pediatric neurologists were well aware of this, and patiently exhorted the Cree representatives to explore with Québec (or Canada) the possibilities of a longitudinal study.

c. These recommendations (for pre-natal, but also for adult exposure) were later reflected in the language of the original mercury agreement with Hydro-Québec, although in retrospect one can argue that the language should have been more explicit. By that time, however, five years had already lapsed – perhaps too long a delay for the resumption of the study.

d. As a result, the Cree Health Board and the Cree Health Board have necessarily relied on other sources of information on the risks of pre-natal exposure. The Iraq, New Zealand, Seychelles and Faroese studies have all played an important role in this process. Each of these sources of information, however, have significant limitations when applied to the Cree population in Québec.

e. It has therefore become important to understand what these limitations are and how they affect the application of risk assessment and the development of risk management strategies. Among these limitations are the cultural practices of fishing at family camps and the distribution of fish within households. The availability of large predatory fish, weighing several kilograms and with tissue mercury concentrations, in some cases, of 2-3 mg/kg, poses a significant problem in this regard. There remains a real possibility of 'bolus' dose exposure – an aspect of mercury exposure (for the foetus as well as for adults) which remains particularly difficult to address.

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