Review of Keeyask Partnership Human Health Risk Assessment Associated with Mercury in Fish

G&P RESOURCE SERVICES INC.

EXECUTIVE SUMMARY

Summary of Issues

Methyl mercury in fish was identified as a human health concern by Manitoba Hydro, the Keeyask Cree Nations, and federal and Manitoba regulators based on past experience with known environmental impacts of hydroelectric development.

CAC Manitoba is assessing all aspects of the project with a view to the risks of significant adverse effects and the likelihood of a net positive benefit to sustainability. CAC Manitoba is concerned because the operation of the project is anticipated to cause large increases in mercury levels in predatory fish in the Keeyask reservoir and a moderate increase in Stephens Lake.

In response to the concerns voiced by stakeholders, a human health risk assessment (HHRA) was conducted for the Keeyask Partnership. According to the Final HHRA, under present (*i.e.* un-impacted by Keeyask project) conditions, elevated Hazard Quotient values as high as 4.7-fold to 15.1-fold above the Health Canada tolerable daily intake (TDI) were predicted, with the conclusion that "potential unacceptable risks could affect persons of any age if unrestricted consumption of the larger fish occurred on a frequent basis."

Further, under post-impoundment conditions, there is a "potential for unacceptable health risks for persons who decide to frequently consume fish from Gull and Stephens lakes." Predicted risk estimates are up to 14.2-fold above the Health Canada TDI, for average size fish, and would be greater for larger fish under post-impoundment conditions.

The following points were also made in the HHRA:

- As a result of the use of conservative assumptions, actual risks may be substantially lower than those predicted in the HHRA.

- Numerous fish in Gull and Stephens lakes currently have low (<0.2) and very low (<0.01) μg/g total Hg concentrations.

- Pike and walleye have average mean Hg concentrations >0.2 μg/g but less than 0.5 μg/g, which is the Health Canada limit for mercury concentrations in fish for commercial use.

- For wild fish for subsistence purposes, there is no official recommendation from Health Canada or WHO, because of tremendous nutritional benefits of fish consumption.

- The final HHRA did not provide advice for making consumption recommendations.

- Manitoba Health and Health Canada have committed to working with the KCN and Manitoba Hydro on consumption advisories in a separate process.

- Young children and pregnant women are the most sensitive receptors, followed by other age classes of both sexes.

It was noted by the Keeyask Partnership that many KCN members have indicated they had stopped or decreased the eating of fish and traditional foods due to concerns about mercury. In addition it was stated that there has been a reduction in domestic fishing and consumption of country foods as people are afraid to eat fish, resulting in an increase in store bought food. This concern was voiced by all KCN communities.

In response to the concerns regarding mercury in fish consumed by humans, G & P Resource Services Inc., on behalf of CAC Manitoba, conducted the following analyses:

- We compared Health Canada and the Manitoba Government guidelines for fish consumption to the measured and predicted concentrations in Gull and Stephens lakes and the Keeyask reservoir.

- We compared existing MeHg concentrations in affected lakes to concentrations in other Canadian lakes and in retail supermarket fish.

- We compared predicted future MeHg concentrations in affected lakes to concentrations in other Canadian lakes and in retail supermarket fish.

- A comprehensive literature review was conducted of recent epidemiological studies related to moderate MeHg exposures.

- A comprehensive literature review was conducted of recent epidemiological studies related to low MeHg exposures.

- We conducted comprehensive computer modelling to predict mercury concentrations in hair (known to be an accurate bio-indicator of mercury toxicity) under what we believe are realistic exposure assumptions.

- We conducted a detailed review of the health benefits of fish consumption, which are becoming an increasingly important consideration in fish consumption guidelines.

- We present our opinion of possible risk management options that may be considered in deliberations about future fish consumption advisories and communications.

Summary of Results

(i) **We compared Health Canada and the Manitoba Government guidelines for fish consumption to the measured and predicted concentrations in Gull and Stephens lakes and the Keeyask reservoir.**

The Health Canada guideline values are 0.5 ppm total mercury in general commercial fish, and 1.0 ppm total mercury in commercial predatory fish. Health Canada also provides fish consumption

advice to help maximize the nutritional benefits of eating fish while minimizing the risk of exposure to mercury. Health Canada fish consumption recommendations are:

- General Population — 150 g per week

- Women of Childbearing Age — 150 g per month

- Children 5 to 11 years old — 125 g per month

- Children 1 to 4 years old — 75 g per month

Both existing and predicted concentrations at Stephens Lake are below the 0.5 ppm retail guideline. At Gull Lake, existing Hg concentrations for all four species are below the 0.5 ppm Health Canada guideline. Predicted Hg concentrations in whitefish and lake sturgeon are below 0.5 ppm for post-impoundment conditions, but predicted Hg concentrations in northern pike and walleye for post-impoundment conditions exceed both the 0.5 ppm and 1.0 ppm guidelines.

The Manitoba government guidelines assume an average adult meal size of 227 grams (8 ounces) and of 114 grams (4 ounces) for children under 12 years of age.

According to the Manitoba guidelines and based on existing measured concentrations of Hg:

- whitefish (<0.2 µg/g) in Gull Lake and Stephens Lake can be consumed at a rate of 19 meals per month for the general population and 8 meals per month for women of childbearing age and children under 12 years old.

- walleye, northern pike and sturgeon (>0.2 and <0.5 µg/g) can be consumed at a rate of 8 meals per month in the general population and 3 meals per month for women of childbearing age and children under 12 years.

In their fish consumption guidelines, the Manitoba government note that large walleye and northern pike, which feed on other species of fish, are older and will have higher levels of mercury than smaller fish which are younger in age. So for walleye and northern pike, it is recommended that smaller fish be consumed.

Based on predicted concentrations of Hg for post-impoundment conditions, Manitoba guidelines would recommend:

- whitefish in Gull Lake and Stephens Lake can be consumed at a rate of 19 meals per month for the general population and 8 meals per month for sensitive populations (predicted concentration < 0.2 ppm).

- Lake sturgeon could be consumed at a rate of 8 meals per month in the general population and 3 meals per month for sensitive populations (predicted concentrations between 0.2 and 0.5 ppm).

- Walleye and northern pike should only be consumed 3 times per month for the general population and not at all by sensitive populations, based on predicted Hg concentrations in these species.

(ii) **We compared existing MeHg concentrations in affected lakes to concentrations in other Canadian lakes and in retail supermarket fish.**

Existing measured concentrations of Hg in whitefish from Gull Lake (0.07 ppm) and Stephens Lake (0.09 ppm) are slightly lower than the mean concentration reported in commercial whitefish sold in Canada or the United States and considerably less than that measured in whitefish from retail markets in Toronto, Ontario. They are slightly higher than the average concentration measured in whitefish sampled from 9 remote First Nations reserves in Manitoba (Chan et al. 2012), as well as the AEA offsetting lakes, but well within the range reported in freshwater lakes in Alberta, northern Canada and Canada as a whole.

Similarly for walleye, existing Hg concentrations in Gull Lake and Stephens Lake (0.23 to 0.29) are lower than the mean concentration reported in commercial walleye sold in Canada, but higher than the average Hg concentration measured in walleye from nine remote First Nations reserves in Manitoba. Mercury concentrations in walleye from Gull and Stephens Lake are within the range of concentrations reported for other freshwater lakes in Alberta, northern Canada and Canada as a whole and they are also within the range of concentrations measured in AEA offsetting lakes north and south of the Nelson River.

Existing concentrations of mercury in northern pike from Gull Lake (0.22 ppm) and Stephens Lake (0.26 ppm) are lower or within the range of Hg concentrations measured in commercial retail fish in Canada, the U.S. or Toronto, Ontario. They are slightly higher than the average concentration measured in fish sampled from nine remote First Nation reserves in Manitoba and in AEA offsetting lakes, but within the range of concentrations measured in other freshwater lakes in Alberta, northern Canada and Canada as a whole.

Existing concentrations of mercury in Sturgeon from Gull Lake (0.20) are higher than average concentration reported in Canadian retail fish (0.10) but similar to the average concentration reported in fish sampled from First Nation reserves in Manitoba. They are higher than the mean concentration reported in sturgeon from northern Canadian lakes but within the range of reported concentrations in sturgeon from Canadian freshwater lakes as a whole.

Comparisons to mercury concentrations reported in other commonly consumed fish indicate that existing concentrations of mercury in northern pike, walleye and sturgeon from Gull Lake and Stephens Lake are similar or lower to concentrations reported in lake trout, halibut or albacore canned tuna sold commercially in Canada or the U.S. However, they are higher than mercury concentrations in salmon or light/skipjack canned tuna sold commercially. Existing concentrations of mercury in whitefish fall are lower than concentrations reported in lake trout, halibut or canned tuna but higher than that reported in commercial salmon.

(iii) **We compared predicted future MeHg concentrations in affected lakes to concentrations in other Canadian lakes and in retail supermarket fish.**

Predicted post-impoundment concentrations of Hg in whitefish from Gull Lake (0.19 ppm) and Stephens Lake (0.15 ppm) are higher than the mean concentration reported in commercial

whitefish sold in Canada or the United States, but less than that measured in whitefish from eight retail markets in Toronto, Ontario. They are higher than the average concentration measured in whitefish sampled from nine remote First Nations reserves in Manitoba and slightly higher than concentrations measured in Alberta lakes or northern Canadian Lakes. They also were higher than Hg concentrations reported in the AEA offsetting lakes. However, the predicted whitefish concentrations were lower than the mean whitefish concentration reported in Canadian freshwater lakes as a whole.

Predicted lake sturgeon Hg concentrations in Gull Lake and Stephens Lake (0.25 to 0.30) are higher than the mean concentration reported in commercial sturgeon sold in Canada and slightly higher than the average Hg concentration measured in sturgeon from nine remote First Nations reserves in Manitoba (0.20). They are higher than Hg concentrations measured in northern Canadian freshwater lakes but similar to the average concentration reported in sturgeon for freshwater lakes in Canada as a whole.

Mercury concentrations in walleye from Gull and Stephens Lake are within the range of concentrations reported for other freshwater lakes in Alberta, northern Canada and Canada as a whole and they are also within the range of concentrations measured in AEA offsetting lakes north and south of the Nelson River.

Predicted concentrations of mercury in northern pike and walleye from Stephens Lake (0.5 ppm) are higher than the average Hg concentrations measured in commercial retail pike or walleye in Canada and higher than the average concentration measured in fish sampled from nine remote First Nation reserves in Manitoba and in AEA offsetting lakes. However, predicted concentrations at Stephens Lake are within the range of Hg concentrations measured in walleye and northern pike in Alberta Lakes and only slightly higher than Hg concentrations measured in these species in northern Canadian lakes or in Canada as a whole.

At Gull Lake, predicted concentrations of mercury in northern pike and walleye are in the range of 1.0 to 1.4 ppm. These concentrations exceed the commercial guidelines and are higher than average Hg concentrations measured in commercial retail pike and walleye and higher than that measured in lakes from Manitoba First Nation communities, Alberta, northern Canadian lakes, AEA offsetting lakes or Canadian freshwater lakes as a whole.

Comparisons to mercury concentrations reported in other commonly consumed fish indicate that predicted concentrations of Hg in whitefish for Gull Lake and Stephens Lake are lower than concentrations reported in lake trout, halibut or canned tuna but higher than that reported in commercial salmon. Predicted concentrations in lake sturgeon in Gull Lake and Stephens Lake are similar to Hg concentrations reported in halibut, but higher than Hg concentrations reported in salmon, trout or tuna. Predicted concentrations of Hg in northern pike or walleye for Gull Lake and Stephens Lake are higher than concentrations reported in salmon, lake trout, halibut or tuna sold commercially.

> **(iv)** **A summary was prepared of current regulatory agency exposure limits.**

Current government agency guidelines for exposure to MeHg are summarized below.

Summary of Health-Based Government Exposure Limits for Methyl Mercury (MeHg)

	Health Canada		WHO/JECFA		US EPA	ATSDR
	General population[1]	*Sensitive Subgroup[2]*	*General population[1]*	*Sensitive subgroup[2]*	*General population (including sensitive subgroups)*	
Exposure Limits						
µg/kg bw/day	0.47	0.2	0.47[3]	0.23	0.1	0.3
blood (µg/L)	20	8	20	11	5	15
hair (mg/kg)	6	2	5-6	2.2	1	3
Derivation						
Benchmark Dose or NOEL	50 mg/kg (hair) 200 µg/L (blood)	10 mg/kg (hair)	50 mg/kg (hair) 200 µg/L (blood)	14 mg/kg (hair)	12 mg/kg (hair) 58 µg/L (blood)	15 mg/kg (hair)
Uncertainty factor applied	10-fold	5-fold	10-fold	6.4-fold	10-fold	4.5-fold
Primary supporting references	JECFA 1972	Feeley and Lo 1998 ; Grandjean et al. 1997; Davidson et al. 1998; Crump et al. 1998	JECFA 1972	JECFA 2004; Davidson et al. 1998; Grandjean et al. 1997, 1998	US EPA 2001; NRC 2000	ATSDR 1999; Davidson et al. 1998
Population Considered	Iraq	Faroe Islands, Seychelles, New Zealand	Iraq	Faroe Islands, Seychelles,	Faroe Islands, Seychelles, New Zealand	Seychelles

Notes:
(1) Adult males, women past childbearing years
(2) Pregnant women, women of childbearing years and children
(3)   WHO/JECFA exposure limits are expressed as provisional tolerable weekly intakes but in this table were converted to equivalent daily intakes

(v) A comprehensive literature review was conducted of recent epidemiological studies related to moderate MeHg exposures.

Note: References to the studies mentioned below are provided in the main report.

Government agency exposure limits recommended for sensitive populations considered the findings of two large prospective studies in the Seychelles Islands in the Indian Ocean and the Faroe Islands in the North Atlantic Ocean. These studies were initiated in the 1990s to examine low to moderate mercury exposure through fish consumption and associated neurodevelopmental effects in children.

Following the publication of preliminary results from the Seychelles and Faroe Island cohort studies and considering the findings from a smaller New Zealand fish-eating cohort, the Food Directorate of Health Canada proposed a toxicological reference of 10 mg/kg Hg in maternal hair as the approximate threshold for neuropsychological effects in sensitive subgroups. They used an

international standard for hair to blood ratio of 250, a steady-state single compartment toxicokinetic model and a 5-fold uncertainty factor to account for inter-individual variability to derive a pTDI of 0.2 µg/kg body weight/day for pregnant women, women of reproductive age and children. The Manitoba government employs this pTDI to determine fish consumption guidelines.

The Seychelles cohort studies have followed over 700 infant-mother pairs enrolled in 1989 to 1990 from birth until the age of 19 years. The median total mercury in 350 fish sampled from 25 species consumed by the Seychellois was <1 ppm, comparable to mercury concentrations in commercially available fish in North America. The World Health Organization identified 15 mg/kg in maternal hair as a No-Observed-Effects-Level (NOEL) from this study.

The Faroe Island cohort study of almost 900 mother-child pairs did suggest adverse neuropsychological effects of prenatal mercury exposure. However, it has been pointed out by several researchers that the diet in the Faroe Islands is considerably different than the diet in the Seychellois and in the U.S. in that the majority of mercury exposure comes from episodic ingestion of whale meat with mercury concentrations of approximately 2 to 3 ppm.

The ATSDR minimum risk level (MRL) recommended in 1999 of 0.3 µg/kg bw/day based on the Seychelles cohort study, was not changed based on their review of the Faroe Island cohort study.

Several follow-up studies of the Seychelles and Faroe Island cohorts have been published and they continue to report different findings.

- Studies of the Seychelles main cohort enrolled in 1989 to 1990 have not provided evidence of adverse effects of prenatal MeHg exposure on development in a cohort that consumes fish daily, with the most recent assessment of neurodevelopment conducted at 19 years of age and including measures of scholastic achievement, problematic behaviors and IQ.

- By contrast, new data from the Faroe Islands cohort at children's age 14 years indicated that an association observed at age seven years between cord blood MeHg and neurological auditory function was still present at 14 years.

- A reassessment of the data from the Faroese cohort at age seven years indicated that beneficial effects of fish consumption, together with imprecision in the measurements of fish intake and determination of mercury exposure might underestimate the effects of MeHg in this cohort.

- The study of a fish eating population in New Zealand suggested adverse effects of prenatal MeHg exposure on the mental development of children at the ages of 4 and 7 years. This study was incorporated into benchmark dose analyses conducted by the NRC (2000) that were used by US EPA (2001) in the development of their Reference Dose (RfD) for MeHg. However, reservations regarding this study have been noted because one child out of the 237 subjects had a maternal hair Hg concentration of 86 mg/kg which likely had a significant effect on the derivation of the BMDLs in this study.

Overall, maternal hair levels of 10 to 14 ppm have been associated with a measurable or clinically meaningful change in neurocognitive outcomes in some populations.

(vi)   A comprehensive literature review was conducted of recent epidemiological studies related to low MeHg exposures.

Note: References to the studies mentioned below are provided in the main report.

In their recent review (2012) of studies on MeHg and neurodevelopment, the European Food Safety Authority concluded that the overall picture at low-level exposure does not provide adequate information to allow conclusions.

Several recent large studies have not observed significant associations between mercury exposure and neurodevelopment. Studies which did not report associations between prenatal MeHg exposure and cognitive outcomes in preschool children did not adjust for the beneficial effects of fish consumption and this may explain the negative findings. However, since that time two prospective studies in Italy and Spain failed to find associations between prenatal MeHg and neurodevelopmental scores, even after adjustment for fish intake.

Some but not all earlier studies reported neurodevelopmental effects of MeHg after the beneficial effects of fish intake were considered. Several studies reported positive associations between fish consumption and neurodevelopment, even without controlling for mercury exposure. An FDA review in 2009 concluded that the independent negative associations observed between mercury and neurodevelopment in some studies were smaller than independent positive associations observed with maternal fish intake. For example, a study in Massachusetts indicated that higher fish consumption in pregnancy was associated with improved cognitive test performance in offspring, but adverse effects on visual-spatial and total visual motor development at age 3 years were correlated with maternal blood levels of mercury.

In the Seychelles, a nutrition cohort was established specifically to evaluate whether nutrients influence the association between prenatal MeHg and developmental outcomes. It was reported that the beneficial effects of DHA from fish consumption were absent or reduced at maternal hair levels greater than 11 mg/kg (EFSA concluded this level to be a NOEL). However, a follow-up study at age 5 years, demonstrated no associations with prenatal MeHg exposure at any level, even after adjustment for the benefits of fish consumption.

The evidence for adverse neurodevelopmental effects of maternal mercury exposure below 10 to 12 ppm in hair is at present inconclusive, with the possible exception of populations consuming marine mammals such as pilot whale. The preponderance of evidence indicates that hair mercury levels at Health Canada's safe level of exposure for sensitive subgroups (2 mg/kg) or less are not associated with adverse effects on sensitive populations.

(vii)   We conducted comprehensive computer modelling to predict mercury concentrations in hair (known to be an accurate bio-indicator of mercury toxicity) under what we believe are realistic exposure assumptions.

The predicted present health risks in the HHRA were acknowledged as being overly conservative due the uncertainty in predicted exposures. This makes it very difficult to convince the local communities that it is safe and important to eat wild fish. Considering the importance of fish as a protein and nutritional source for local communities, further assessment is needed to properly inform subsistence consumers about the health benefits and costs related to fish consumption. Since blood and hair samples have not yet been conducted by the Keeyask Partnership, we felt that

additional information may be gained through credible computer modelling to predict mercury concentrations in hair, under what we believe are more realistic exposure assumptions.

Since predicted present condition hair concentrations were based on conservative exposure assumptions, the following assumed input parameters were re-visited:

- Fish consumption rates; and

- Ratio of methyl mercury to total mercury in fish tissue.

The table below compares the fish portion size for the adult used in the HHRA to the results presented in the FNFNES Study (Chan et al. 2012) and shows that portion sizes are much smaller in the latter. Additionally, Health Canada (2007) recommends a subsistence fish consumption rate of 20 and 40 grams/day for the toddler and adult, respectively.

Fish	Portion Size for Toddler (grams)	Portion Size for Adult (grams)	Frequency of Consumption (times per week)	Estimated long-term consumption rate for Toddler (grams/day)[1]	Estimated long-term consumption rate for Adult (grams/day)[1]
Whitefish	100	400	3	43	171
Pike	100	400	3	43	171
Walleye	100	400	3	43	171
Sturgeon	100	400	3	43	171
Chan et al. (2012)	NA	Female 50 to 170 and male 141 to 197[2]	NA	NA	Average: Female 2.1 to 10 and male 13 to 17[3] 95th Percentile: Female 11 to 66 and male 36 to 87[3]
Health Canada (2007)				20	40

Notes:
NA: Not available.
(1)   Estimated based on (portion size) x (frequency of consumption) / (7 days per week).
(2)   Range in mean portion size of fish reported for the ages of 19 to 71+.
(3)   Based on consumption of the following fish species: walleye, lake whitefish, pike and sturgeon.

The modified exposure model assumptions include:

- the 95th percentile consumption rate (25 grams/day) derived from a sample of 347 women aged 20 to 50) from the FNFNES Study (Chan et al. 2012),

- the subsistence consumption rate recommended by Health Canada (2007) of 40 grams/day by adults who are at the high end of fish intakes, and

- assumed 85% proportion of organic versus total mercury (Canuel et al. 2006).

Based on the modifications in consumption rates and methyl mercury content in fish, predicted adult female hair mercury concentrations under present conditions were similar to the measured value of 0.25 ppm mercury in hair by the FNFNES Study (Chan et al. 2012). More than 95% and 80% of predicted hair concentrations were below the Health Canada benchmark value of 2 ppm,

respectively, indicating that adverse effects are unlikely under current conditions for Split Lake, Gull Lake and Stephens Lake.

For the predicted future scenario, the same exposure modifications were assumed. Adult female hair mercury concentrations were then predicted to exceed the measured value of 0.25 ppm mercury in hair by the FNFNES Study. More than 45% of predicted hair concentrations were below the Health Canada benchmark value of 2 ppm. In addition, more than 95% of predicted hair concentrations were below the 10 ppm benchmark value. However, the prevalence of predicted hair concentrations above the benchmark value of 2 ppm suggests that adverse effects are possible from future exposures to fish in the aquatic environment study area (i.e., Gull Lake and Stephens Lake).

Exposure and risks reported above were based on assumed consumption of walleye, whitefish, pike and sturgeon of 51, 22, 16 and 11% respectively. The consumption pattern is based on the annual distribution of fish observed in Ecozone 3 native households (Chan et al. 2012).

It was then assumed that only whitefish was consumed from Gull Lake under future conditions. This species of fish was selected as it represents a popular eating fish and it has the lowest mercury concentrations in the future post-impoundment scenario.

The model results predicted that more than 90% of predicted hair concentrations were below the Health Canada benchmark value of 2 ppm, and all of the predicted hair concentrations were below 10 ppm. This indicates that adverse effects are not expected from future consumption of whitefish harvested from Gull Lake.

(Note: Based on the higher consumption rates used in the HHRA, our model, based on Gull Lake whitefish consumption only, predicted that approximately 90% of future post-impoundment hair concentrations exceeded the Health Canada benchmark value of 2 ppm, and 5% were greater than the benchmark value of 10 ppm).

> **(viii)** **We conducted a detailed review of the health benefits of fish consumption, which are becoming an increasingly important consideration in fish consumption guidelines.**

Fish are a rich source of protein, essential fatty acids, vitamins and minerals and an important food resource globally. They are a nutritionally and culturally important food for many Canadians, especially Aboriginal groups or populations that consume wild fish. Fish and seafood are unique in their nutritional benefits due to the low levels of saturated fats and the high levels of the beneficial omega 3 polyunsaturated fatty acids (PUFAs), which are absent in other foods .

When health risks are perceived, traditional foods consumed by First Nations people are frequently replaced by energy dense and nutrient poor market food alternatives. A U.S. study with postnatal methyl mercury exposure (i.e., at background levels) had no detectable adverse effect on neuropsychological and behavioral development among children. Children with higher blood methyl mercury concentration had significantly higher IQ and learning scores. The observed benefits of fish consumption were attributed to the increase in consumption of polyunsaturated fatty acids in the fish.

Studies have consistently shown that mothers who consume fish during pregnancy have children with improved neurobehavioral development. Other studies have reported a reduced risk of hyperactivity and a higher verbal IQ in children whose mothers had eaten fish in late pregnancy. Fish consumption has also been shown to contribute to a reduced risk of cardiovascular disease in adults, and to a lower risk of type 2 diabetes.

Overall, it has been concluded that the benefits of modest fish consumption (1 to 2 servings per week) outweigh the risks among adults and excepting a few select fish species, among women of childbearing age.   This illustrates the importance of targeted fish consumption advice to ensure that non-target consumers (i.e., males or older women) do not reduce their fish consumption unnecessarily.

(ix)   We present our opinion of possible risk management options that may be considered in deliberations about future fish consumption advisories and communications.

Health Canada and Manitoba government advise that choosing fish that are higher in Omega 3 fatty acids and lower in mercury is a means of balancing risks and benefits of fish consumption. Many other countries have used this approach by analyzing omega 3 polyunsaturated fatty acids (n-3 PUFAs) and MeHg levels in local fish to help public health professionals make appropriate recommendations.

Literature values of n-3 PUFA content in the most commonly consumed fish in the Keeyask area (whitefish, walleye, northern pike and sturgeon) were considered together with existing and predicted future Hg concentration data for these species in Gull Lake and Stephens Lake.   Since moderate fish consumption can meet the requirements of n-3 PUFAs that benefit fetal development and cardiovascular risk, as little as two meals per week may suffice, depending on the fish species consumed.

The PUFA content of fish commonly consumed in the lakes impacted by the Keeyask Hydroelectric project are shown below. It is evident that whitefish are a very good source of n-3 PUFAs, with estimated concentrations of docosaheaenoic acid (DHA) and eicosapentaenoic acid (EPA) combined approaching that of Atlantic farmed salmon. (DHA and EPA are not found in other foods). Walleye, northern pike and sturgeon are much poorer sources of these nutrients, while trout contribute a moderate amount of DHA and EPA. Thus, a shift in consumption towards more whitefish and less walleye and pike would maximize health benefits associated with fish consumption. Based on the concentrations of DHA in whitefish, the recommended intake of 200 to 250 mg/day to optimize fetal development in pregnancy and lower cardiovascular risk can easily be met through moderate consumption of whitefish. Even one meal per week of 150 grams of whitefish would meet this requirement for DHA.

	Whitefish	Walleye	Northern Pike	Sturgeon	Atlantic Salmon (farmed)	Trout
DHA	1,206	288	95	119	1,457	936
EPA + DHA	1,200 to 1,612	300 to 398	100 to 137	200 to 368	1,700 to 2,147	677 to 750

Note: based on 100 gram serving size.

Conclusions and Recommendations

It was intended by the authors of this report that the detailed information contained within will be valuable to the Keeyask Partnership, Manitoba Health, Health Canada and the Manitoba Clean Environment Commission in ongoing deliberations about fish consumption advisories and communications to KCNs regarding the risks and importance of wild fish consumption. It was noted by the partnership that "many KCN members have indicated they had (already) either stopped, or decreased the eating of fish and traditional foods (due to concerns about mercury). It was also stated that "TCN (Tataskweyak Cree FN) formally expressed concern over high concentrations of Hg in Split and Clark lakes. Therefore has been a reduction in domestic fishing and consumption of country foods as people are afraid to eat fish …, resulting in an increase in store bought food. This concern was voiced by all KCN communities".

Our study has affirmed statements made in the Keeyask HHRA that highly conservative exposure assumptions may have substantially overestimated risks of fish consumption. In particular, assumed fish consumption rates, based on consumer information provided by local communities, are the major contributor to predicted health risks. Health risks predicted in the HHRA for existing conditions also exists in the "offsetting" lakes (e.g., Moose Nose and Recluse), indicating that risks may exist regardless of where the community harvests fish.

The data included in this report have shown that present average mercury concentrations in study area lakes are below the commercial guideline of 0.5 – 1.0 ppm, are similar to or lower to mercury concentrations measured in other (un-impacted) Canadian lakes, and are similar or lower to mercury concentrations measured store-bought fish.

While consumption recommendations were removed from the final HHRA, our review concludes that fish in Gull Lake and Stephens Lake can safely be consumed based on guidance provided by Health Canada (2007, 2010) and Manitoba government (2013).

Overall, it has been concluded that the benefits of modest fish consumption (1 to 2 servings per week) outweigh the risks among adults and excepting a few select fish species, among women of childbearing age. This illustrates the importance of targeted fish consumption advice to ensure that non-target consumers (i.e., males or older women) do not reduce their fish consumption unnecessarily.

Prior to making recommendations on how post-impoundment risks will be managed among community members, the existing risks to the community should be more fully characterized to help ensure that the management of risk does impact the nutritional benefits of wild fish consumption. In this regard, collection of data on distributions of actual fish consumption rates, and measured mercury in blood/hair of consumers of fish from impacted and offset lakes will be needed.

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Abbreviations

ADHD	attention deficit hyperactivity disorder
BMDL05	benchmark dose level (5th percentile)
CFIA	Canadian Food Inspection Agency
CI	confidence interval
Hg	mercury
HQ	hazard quotient
MeHg	methyl mercury
mg/kg	milligram per kilogram (equivalent to 1 part per million)
MOS	margin of safety
MRL	minimum risk level
PCB	polychlorinated biphenyls
ppm	parts per million
pTDI	provisional tolerable daily intake
RfC	reference concentration
RfD	reference dose
TDI	tolerable daily intake
TWI	tolerable weekly intake
UCLM	upper confidence limit mean

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1.0   INTRODUCTION AND BACKGROUND

1.1   Preamble and Problem Definition

Methyl mercury and Health were identified as a VEC, in part due to past experience of the KCNs and Manitoba Hydro with mercury effects of hydroelectric development. The Canadian Environmental Assessment Agency Final Environmental Impact Statement Guidelines call for examination of health issues and of mercury in fish and wildlife. The collection of relevant evidence would assist the Commission in providing accurate recommendations for the Minister's consideration.

CAC Manitoba is assessing all aspects of the project with a view to the risks of significant adverse effects and the likelihood of a net positive benefit to sustainability. Human beings are exposed to mercury through a number of pathways the most significant of which may be the consumption of local wild fish. CAC Manitoba is concerned because the operation of the project is anticipated to cause "large increases in mercury levels in predatory fish in the Keeyask reservoir and moderate increase in Stephens Lake". Unsafe mercury levels in fish are a major concern among public participants and have been identified by KCNs as a key concern in relation to the Project.

In June 2012, the Human Health Risk Assessment was undertaken by the Keeyask Partnership.

The Partnership engaged Dr. Laurie Chan, an international expert in the field of mercury and health, to provide an external review of the HHRA. According to TAC Public RD 1 HC-0002, Dr. Chan "endorsed the methodology and recommendations and also stressed the nutritional benefits of fish. He was concerned that caution should be taken not to discourage use of fish, or impose unnecessary restriction, due to the conservative nature of the risk assessment paradigm."

In 2010, Dr. Chan conducted a study called the *First Nations Food, Nutrition and Environment Study* (Chan et al. 2012). This report was conducted in nine randomly selected on-reserve First Nations communities in Manitoba and analyzed mercury-related health components. This Study concluded that mercury levels of First Nations living on Manitoba reserves are below the established Health Canada mercury guideline. This Study also concluded that there are "greater nutritional quality" and important nutritional benefits to eating wild fish (see p 5).

The assessment of methyl mercury levels in fish and associated potential health risks presents a challenge to risk assessors due to uncertainty regarding health effects at lower levels of exposure and the considerable health benefits associated with fish consumption. Health risks also are very much dependent on consumption rates and the types of fish species typically harvested. Methyl mercury (MeHg) is known to be a neurotoxin, particularly in children and the developing fetus, but due to both natural and anthropogenic sources it is found in virtually all fish to varying degrees (Davidson et al. 1998). However, fish are the primary dietary source of n-3 polyunsaturated acids, which are essential for fetal neurodevelopment and contribute other health benefits (Oken et al. 2013). Disentangling the risks and benefits of fish consumption at various mercury exposure levels has proven challenging and is an evolving process.

1.2   Report Objectives

This report endeavours to put the human health risks predicted for MeHg in fish associated with the proposed Keeyask project into perspective through a variety of means. In this section Health Canada and the Manitoba Government guidelines for fish consumption relating to mercury are summarized below in relation to the measured and predicted concentrations in Gull and Stephens lakes and the Keeyask reservoir. Comparisons between existing MeHg concentrations in impacted lakes are compared to concentrations in other Canadian lakes and in retail supermarket fish.

Section 2.0 is a toxicity assessment of MeHg from the current scientific literature. Due to the incredible amount of published literature on this subject, it focuses on recent studies that examined moderate and low dose exposure to MeHg through fish consumption.

Section 3.0 presents results of hair modelling analyses that evaluate the influence of varying assumptions such as consumption rates or the amount of mercury present in fish that is methyl mercury.

Section 4.0 summarizes the health benefits of fish consumption, which are becoming an increasingly important consideration in fish consumption guidelines.

Section 5.0 presents risk management suggestions that are specific to the proposed Keeyask hydroelectric project.

Section 6.0 contains conclusions and recommendations.

1.3   Summary of Final HHRA (Wilson Scientific 2013)

According to the Final HHRA, under present (*i.e.* un-impacted by Keeyask project) conditions, elevated Hazard Quotient (HQ) values (above 1.0) are listed in HHRA Tables 5-1 and 5-2, where predicted HQ values as high as 4.7-fold to 15.1-fold above the Health Canada tolerable daily intake (TDI) are reported for large fish. At page 5C-48 of the HHRA, under present conditions, it is stated "it is apparent that persons could have elevated Hazard Quotient values for certain fish... potential unacceptable risks could affect persons of any age if unrestricted consumption of the larger fish occurred on a frequent basis."

Further, under post-impoundment conditions, there is a "potential for unacceptable health risks for persons who decide to frequently consume fish from Gull and Stephens lakes." Tables 5-3 and 5-4 in the HHRA show that predicted risk estimates are up to 14.2-fold above the Health Canada TDI, for average size fish. This implies that risk estimates would be greater for larger fish under post-impoundment conditions.

Additional pertinent statements from the final HHRA are summarized below:

- The HHRA did not measure Hg concentrations in people.
- Fish mercury data used in HHRA compiled from Aquatics section of EIS.

- Future assumed fish Hg concentration was 1.0 ppm in the HHRA (Comment: the aquatics section reported maximum values of 1.3 ppm to 1.4 ppm – meaning that predicted maximum risks could be 30 % to 40 % higher than what were reported in the HHRA. We interpret the 1.0 ppm as an average future concentration, reasonable for risk assessment, but not overly conservative).
- Hazard Quotients (HQ's) >1 do not automatically mean consumption of fish needs to be restricted, since the following conservative assumptions were made due to uncertainties in the HHRA:
  - It was assumed that total mercury in fish was all organic methyl mercury, according to Health Canada (2007) recommendation. The actual range of methyl mercury in fish is 30% to 95%.
  - It was assumed that human receptors will be exposed 100 % of time for 80 years (although 3 months is considered chronic exposure).
  - The HHRA did not consider likely lower exposures during the winter.
  - Assumed fish consumption rates were based on KCN statements of 100 g three times a week for young children and 400 g three times a week for adults.
  - It was stated in the HHRA that these assumed serving sizes were quite large compared to typical (150 g for adults) serving sizes.
  - Health Canada exposure limits contain safety factors.
- As a result of the use of the above conservative assumptions, actual risks may be substantially lower than estimated in the HHRA.
- Issuance of consumption advisory is a complex issue that requires evaluation of the benefits and risks.
- Manitoba Health and Health Canada have committed to working with the KCN and Manitoba Hydro on consumption advisories in a separate process.
- Young children and pregnant women are the most sensitive receptors, (followed by other age classes of both sexes).
- According to Health Canada (2007) acceptable Hg concentrations in fish for commercial retail is 0.5 µg/g.
- The assumed Health Canada exposure limits (TDI) used in risk calculations in the HHRA for sensitive receptors was 0.2 µg/kg/day, and for adults was 0.47 µg/kg/day.
- For wild fish for subsistence purposes, there is no official recommendation from Health Canada or WHO, because of tremendous nutritional benefits of fish consumption.
- The final HHRA did not provide advice for making consumption recommendations.
- It was noted in the HHRA that numerous fish in Gull and Stephens lakes currently have low (<0.2) and very low (<0.01) µg/g total Hg concentrations.
- Pike and walleye had mean Hg concentrations >0.2 µg/g but less than 0.5 µg/g.
- It was beyond the scope of the HHRA to attempt to predict blood and hair levels that may currently be present
- Health effects of not eating fish (and substituting less healthy food) have not been quantified in the HHRA.
- It is important that persons be encouraged to use, to the maximum extent possible, programs that enable use of lakes unaffected by the project.

1.4 Regulatory Agency Review of HHRA (through Information Requests)

Many of the regulatory review comments associated with the draft HHRA were addressed in the final HHRA, in particular fish consumption advice that was withdrawn from the final document. Additional pertinent information related to the regulatory health review is summarized below:

- Health Canada (HC) recommends following "Guidelines for Consumption of Recreationally Angled Fish in Manitoba (2007) that states "children under 12 and women of child-bearing age (should) limit consumption to 8 meals per month" (HC 0002).
- HC is willing to review proposed risk management approaches and communication products. Note: The Partnership responded that according to the Keeyask Adverse Effects Agreement Local First Nation communities that it will replace domestic supply or provide an alternative resource program. Each of the KCNs is responsible for implementing relevant programs with their community (HC0006).
- HC conducted biomonitoring (hair and blood) for mercury from 1976-1990 and found most samples were in the acceptable range, but approximately 25 % tested "in greater risk". HC suggests hair mercury sampling of current communities at this time and would provide their opinion on the results (HC0008). In response the Partnership stated that Manitoba Hydro and the KCNs considered the merits of blood and hair Hg sampling and arrived at the conclusion that it was not be appropriate for the following reasons:
  - Mitigation measures will be in place including food replacement and consumption advisories,
  - Monitoring of fish will be done to guide action re: consumption advisories,
  - Concerns about anxiety created through testing, and
  - KCNs may pursue this with Health Canada but haven't yet.
- Cree Nation partners are preparing the "Fish Harvest Suitability Plan" for the "Healthy Food Fish Program", to replace fish that may no longer be suitable (HC0009).
- Manitoba regulators are concerned that walleye and pike mercury concentrations in Keeyask and Stephens lakes may increase beyond what is considered safe (0.5 ppm) for unrestricted human consumption (MCWS-WQ-0002).

1.5 Health Canada and Manitoba Fish Consumption Guidelines

1.5.1 Health Canada

Health Canada has established guidelines for levels of mercury in fish to ensure that Canadians are not exposed to excessive quantities of mercury through fish consumption. The guideline values are 0.5 ppm total mercury in general commercial fish, and 1.0 ppm total mercury in commercial predatory fish (Health Canada 2010). Health Canada also provides fish consumption advice to help maximize the nutritional benefits of eating fish while minimizing the risk of exposure to mercury. For example, it is recommended that Canadians — particularly vulnerable groups such as pregnant

women and children — consume only limited quantities of certain types of fish in which methyl mercury tends to accumulate (Health Canada 2010). These include fresh/frozen tuna, shark, swordfish, marlin, orange roughy and escolar. They note that Canadians who like to consume these types of fish should limit their consumption to the amounts shown below. Other types of fish should be chosen to make up the rest of their recommended weekly fish consumption.

- General Population — 150 g per week
- Women of Childbearing Age — 150 g per month
- Children 5 to 11 years old — 125 g per month
- Children 1 to 4 years old — 75 g per month

The consumption amount of 150 grams represents two Food Guide servings of 75 grams each and is equivalent to approximately one cup (Health Canada 2008). They also have advice for consumption of canned albacore (i.e., white) tuna, but this does not apply to canned light tuna, which has considerably lower Hg levels.

In 2007, Health Canada conducted a risk assessment of potential health effects associated with consumption of retail fish (Health Canada 2007). For the exposure assessment, they used mercury concentration data reported by the Canadian Food Inspection Agency(CFIA) for various fish species together with consumption rates determined in a Canadian market survey in 1991. The average consumption of fish per day for adults (a function both of meal size and meal frequency) was 22 grams/day. For children aged 1 to 5 years the consumption rate was 10 grams per day, while for children aged 6 to 12 years, it was 14 grams per day (Health Canada 2007). For the toxicity assessment, they assumed the provisional tolerable daily intakes (pTDIs) derived by the Bureau of Chemical Safety at Health Canada for the general population and for sensitive sub-populations. Risk characterization assumed chronic consumption of various fish species and compared predicted exposures to "safe" exposures. The following findings were reported:

- For members of the general adult population, based on the available data, swordfish is the only fish for which regular weekly consumption would result in exposure that exceeds tolerable intakes
- Regular consumption, by women of child-bearing age, of barracuda (from the U.S.), escolar, marlin, sea bass, shark, swordfish, bigeye tuna, and "fresh" tuna could result in the MeHg pTDI being exceeded. These fish contained an average of 0.54 ppm or more total mercury, assumed to be 100% MeHg. The intake of MeHg from the regular consumption of grouper, orange roughy and walleye, although somewhat high (80% of the pTDI), would not cause the pTDI to be exceeded.
- For young children (12 years of age and younger), regular consumption of fish that contain on average 0.3 ppm or more total mercury (assumed to be 100% MeHg) could result in the pTDI being exceeded. In consideration of the relative popularity of different types of fish in general, it is not considered likely that a child would regularly consume the fish types with higher mercury levels, except in the case of canned albacore tuna.
- Halibut, sea bass, grouper, and walleye were found to contain average mercury at levels somewhat similar to those found in canned albacore tuna. In the case of canned albacore

tuna, the available information led to the conclusion that consumption of canned albacore tuna may be higher than other seafood, which could lead to an unacceptably high exposure to mercury.

The Canadian Food Inspection Agency (CFIA) regularly monitors domestically produced and imported fish to ensure that mercury levels in fish consumed by Canadians meet Health Canada standards (Health Canada 2010). Test results obtained by the CFIA are provided to Health Canada to assist in its review of guidelines. According to CFIA survey data for fish (mainly from 2002 to 2004), none of the species of non-predatory fish sampled had mean mercury levels above the guideline value of 0.5 ppm, but two species of predatory fish had mean mercury levels above the guideline value of 1.0 ppm (Health Canada 2010). In some of the fish species for which mean mercury levels were below guideline values, levels in some individual fish samples exceeded guidelines (Health Canada 2010).

Measured and predicted concentrations of mercury in commonly consumed fish species from Stephens Lake and Gull Lake are shown in Table 1-1 in relation to the Health Canada guideline for mercury in retail fish of 0.5 ppm. It is evident from this table that both existing and predicted concentrations at Stephens Lake are not above the 0.5 ppm retail guideline. At Gull Lake, existing Hg concentrations for all four species are below the 0.5 ppm Health Canada guideline. Predicted Hg concentrations in whitefish and lake sturgeon are below 0.5 ppm for post-impoundment conditions, but predicted Hg concentrations in northern pike and walleye are above this level for post-impoundment conditions.

1.5.2   Manitoba Government

The Manitoba government has issued fish consumption guidelines based on the range of mercury concentrations measured in fish and assuming the Health Canada TDI for the general population and pTDI for pregnant women, women of childbearing age and children under 12 years old (Manitoba Government 2013). They assumed that women of childbearing age were an average size of 60 kg (132 pounds) and that each person would consume an average meal size of 227 grams (8 ounces). Children under 12 years old were assumed to be 30 kg (66 pounds) in weight and would consume an average meal size of 114 grams (4 ounces).

According to these guidelines and assumptions and based on existing measured concentrations of Hg, whitefish in Gull Lake and Stephens Lake can be consumed at a rate of 19 meals per month for the general population and 8 meals per month for women of childbearing age and children under 12 years old, because the average reported concentration is less than 0.2 µg/g. Walleye, northern pike and sturgeon can be consumed at a rate of 8 meals per month in the general population and 3 meals per month for women of childbearing age and children under 12 years old, because the average reported concentrations fall between 0.2 and 0.5 µg/g (Table 1-1; Manitoba Government 2013). In their fish consumption guidelines, the Manitoba government note that large walleye and northern pike, which feed on other species of fish, are older and will have higher levels of mercury than smaller fish which are younger in age. So for walleye and northern pike, it is recommended that smaller fish be consumed.

Based on predicted concentrations of Hg for post-impoundment conditions, Manitoba guidelines would recommend that whitefish in Gull Lake and Stephens Lake can be consumed at a rate of 19 meals per month for the general population and 8 meals per month for sensitive populations (predicted concentration < 0.2 ppm). Lake sturgeon could be consumed at a rate of 8 meals per month in the general population and 3 meals per month for sensitive populations (predicted concentrations between 0.2 and 0.5 ppm). Walleye and northern pike should only be consumed 3 times per month for the general population and not at all by sensitive populations, based on predicted Hg concentrations in these species.

Table 1-1   Mean Concentrations of Total Mercury in Gull Lake and Stephens Lake compared to Health Canada Retail Guideline of 0.5 ppm

Source	Whitefish	Northern Pike	Walleye	Lake Sturgeon
Commercial Retail Guideline	**0.5**			
Gull Lake[1]				
Present conditions	0.07	0.22	0.23	0.20
Post-impoundment conditions	0.19	1.0 to 1.3	1.0 to 1.4	0.30
Stephens Lake[1]				
Present conditions	0.09	0.26	0.29	n/a
Post-impoundment conditions	0.12 to 0.15	0.40 to 0.50	0.43 to 0.50	0.25

Notes:
(1) Data reported in Appendix 5C of Keeyask Socio-economic Supplemental Filing: Human Health Risk Assessment (Revised) (Keeyask 2013a) (length standardized mean concentrations) and in the fish section of the Aquatic Environment supplement filing (Keeyask 2013b); in some instances there was a discrepancy between the two reports so a range is shown.

1.6   Comparison to Supermarket Data and Other Freshwater Lakes Hg Data

The concentrations of mercury measured in Gull Lake and Stephens Lake in recent years, as well as the predicted concentrations as a result of post-impoundment conditions from the proposed Keeyask project are shown in Table 1-2. Also shown are mean concentrations of total Hg in commercial retail fish and Canadian freshwater lakes. Mean concentrations of Hg in other commonly consumed retail fish are shown in (e.g., salmon, trout, halibut and canned tuna). These are summarized for present conditions and then predicted future conditions.

1.6.1   Present Conditions

Existing measured concentrations of Hg in whitefish from Gull Lake (0.07 ppm) and Stephens Lake (0.09 ppm) are slightly lower than the mean concentration reported in commercial whitefish sold in Canada or the United States and considerably less than that measured in whitefish from eight retail markets in Toronto, Ontario (Table 1-2). They are slightly higher than the average concentration measured in whitefish sampled from 9 remote First Nations reserves in Manitoba (Chan et al. 2012), as well as the AEA offsetting lakes, but well within the range reported in freshwater lakes in Alberta, northern Canada and Canada as a whole.

Similarly for walleye, existing Hg concentrations in Gull Lake and Stephens Lake (0.23 to 0.29) are lower than the mean concentration reported in commercial walleye sold in Canada, but higher than the average Hg concentration measured in walleye from nine remote First Nations reserves in Manitoba (Table 1-2). Mercury concentrations in Walleye from Gull and Stephens Lake are within the range of concentrations reported for other freshwater lakes in Alberta, northern Canada and Canada as a whole and they are also within the range of concentrations measured in AEA offsetting lakes north and south of the Nelson River.

Existing concentrations of mercury in northern pike from Gull Lake (0.22 ppm) and Stephens Lake (0.26 ppm) are lower or within the range of Hg concentrations measured in commercial retail fish in Canada, the U.S. or Toronto, Ontario (Table 1-2). They are slightly higher than the average concentration measured in fish sampled from nine remote First Nation reserves in Manitoba and in AEA offsetting lakes, but within the range of concentrations measured in other freshwater lakes in Alberta, Northern Canada and Canada as a whole.

Existing concentrations of mercury in Sturgeon from Gull Lake (0.20) are higher than the mean concentration reported in Canadian retail fish (0.10) but the same as the average concentration reported in fish sampled from First Nation reserves in Manitoba. They are higher than the mean concentration reported in sturgeon from Northern Canadian lakes but within the range of reported concentrations in sturgeon from Canadian freshwater lakes as a whole (Table 1-2).

Comparisons to mercury concentrations reported in other commonly consumed fish indicate that existing concentrations of mercury in northern pike, walleye and sturgeon from Gull Lake and/or Stephens Lake are similar or lower to concentrations reported in lake trout, halibut or albacore canned tuna sold commercially in Canada or the U.S. (Table 1-3). However, they are higher than mercury concentrations in salmon or light/skipjack canned tuna sold commercially. Existing concentrations of mercury in whitefish fall are lower than concentrations reported in lake trout, halibut or canned tuna but higher than that reported in commercial salmon (Table 1-3).

1.6.2 Predicted Future Conditions

Predicted post-impoundment concentrations of Hg in whitefish from Gull Lake (0.19 ppm) and Stephens Lake (0.15 ppm) are higher than the mean concentration reported in commercial whitefish sold in Canada or the United States, but less than that measured in whitefish from eight retail markets in Toronto, Ontario (Table 1-2). They are higher than the average concentration measured in whitefish sampled from nine remote First Nations reserves in Manitoba and slightly higher than concentrations measured in Alberta Lakes or Northern Canadian Lakes. They also were higher than Hg concentrations reported in the AEA offsetting lakes. However, the predicted white fish concentrations were lower than the mean whitefish concentration reported in Canadian freshwater lakes as a whole (Table 1-2).

For Lake sturgeon, predicted Hg concentrations in Gull Lake and Stephens Lake (0.25 to 0.30) are higher than the mean concentration reported in commercial sturgeon sold in Canada and slightly higher than the average Hg concentration measured in sturgeon from nine remote First Nations

reserves in Manitoba (0.20; Table 1-2). They are higher than Hg concentrations measured in Northern Canadian freshwater lakes but similar to the average concentration reported in sturgeon for freshwater lakes in Canada as a whole.

Predicted future mercury concentrations in walleye from Gull and Stephens Lake are within the range of concentrations reported for other freshwater lakes in Alberta, Northern Canada and Canada as a whole and they are also within the range of concentrations measured in AEA offsetting lakes north and south of the Nelson River.

Predicted future mercury concentrations in northern pike and walleye from Stephens Lake (0.5 ppm; Table 1-2) are higher than the average Hg concentrations measured in commercial retail pike or walleye in Canada and higher than the average concentration measured in fish sampled from nine remote First Nation reserves in Manitoba and in AEA offsetting lakes. However, predicted concentrations at Stephens Lake are within the range of Hg concentrations measured in walleye and pike in Alberta Lakes and only slightly higher than Hg concentrations measured in these species in northern Canadian lakes or in Canada as a whole.

At Gull Lake, predicted concentrations of mercury in northern pike and walleye are in the range of 1.0 to 1.4 ppm (Table 1-2). These concentrations are higher than average Hg concentrations measured in commercial retail pike and walleye and higher than that measured in lakes from Manitoba First Nation communities, Alberta, Northern Canadian Lakes, AEA offsetting lakes or Canadian freshwater lakes as a whole.

Comparisons to mercury concentrations reported in other commonly consumed fish indicate that predicted concentrations of Hg in whitefish for Gull Lake and Stephens Lake are lower than concentrations reported in lake trout, halibut or canned tuna but higher than that reported in commercial salmon (Table 1-3). Predicted concentrations in lake sturgeon in Gull Lake and Stephens Lake are similar to Hg concentrations reported in Halibut, but higher than Hg concentrations reported in salmon, trout or tuna. Predicted concentrations of Hg in northern pike or walleye for Gull Lake and Stephens Lake are higher than concentrations reported in salmon, lake trout, halibut or tuna sold commercially (Table 1-3).

Table 1-2   **Mean Concentrations of Total Mercury in Commercial Retail Fish and Canadian Freshwater Lakes compared to Gull Lake and Stephens Lake and study area lakes (µg/g wet weight)**

Source	Whitefish	Northern Pike	Walleye	Lake Sturgeon
Commercial Retail				
Canada[1]	0.10 (0.02 to 0.28)	0.25 (0.08 to 1.22)[2]	0.37 (0.08 to 1.24)	0.1 (0.02 to 0.2)
United States[3]	0.11 (0.02 to 0.35)	0.40 (0.247 to 1.34)[2]		
Ontario[4]	0.29	0.24[2]		
Freshwater Lakes				
Manitoba[5] (First Nation Reserves)	0.06	0.20	0.16	0.20
Alberta[6]	0.02 to 0.14	0.13 to 0.59	0.13 to 0.79	
Canada[7]	0.17 (<d.l. to 2.4)	0.56 (0.04 to 3.40)	0.41 (0.03 to 1.88)	0.31 (0.07 to 0.57)
Northern Canada[8]	0.11 (0.11 to 0.13)	0.38 (0.2 to 0.43)	0.47 (0.41)	0.11

Source	Whitefish	Northern Pike	Walleye	Lake Sturgeon
Keeyask Study Area				
Gull Lake[9]				
Present conditions	0.07	0.22	0.23	0.20
Post-impoundment conditions	0.19	1.0 to 1.3	1.0 to 1.4	0.30
Stephens Lake[9]				
Present conditions	0.09	0.26	0.29	n/a
Post-impoundment conditions	0.12 to 0.15	0.40 to 0.50	0.43 to 0.50	0.25
Other Split Lake area lakes[10]	0.03 to 0.11	0.19 to 0.34	0.12 to 0.31	n/a
AEA offsetting lakes North and South of Nelson River[11]	0.036 to 0.056	0.11 to 0.22	0.11 to 0.38	n/a
Health Canada Guideline		**0.5**		

Notes:
(1) Health Canada (2007); sample sizes were 64, 282, 51 and 14 for whitefish, pike, walleye and sturgeon, respectively. Fish were analyzed by the Canadian Food Inspection Agency in 2002 to 2004
(2) Concentrations reported for pike (did not specify northern pike)
(3) Data obtained from Seafood Mercury Database in U.S. (Karimi et al. 2013); database represents aggregation of available data from government monitoring programs and the scientific literature. A grand mean was calculated for individual seafood items, based on reported means from individual studies, weighted by sample size.
(4) Fish were selected from eight retail markets in the Toronto area in 2007 (Del Gobbo et al. 2010). Sample size was 84 and 52 for whitefish and pike, respectively.
(5) Fish were sampled from 9 remote First Nations Reserves in 2010; 3 sample sites per reserve were selected based on where fish were typically harvested. Data reported in First Nations Food, Nutrition and Environment Study (FNFNES) (Chan et al. 2012). Sample size was 9 to 10 per fish species, with the exception of lake sturgeon (n=2)
(6) Mean fish concentrations reported in Alberta water bodies (Alberta Health 2009) (sample sizes not reported)
(7) Data from the Canadian Fish Mercury Database; summarizes data collected from over 5000 locations across Canada between 1967 to 2010, with the exclusion of records from reservoirs or contaminated sites (Depew et al. 2013). No clear temporal trends were noted. Sample sizes were 1573, 584, 165 and 16 for whitefish, northern pike, walleye and sturgeon, respectively (skin on fillets)
(8) Summary of data reported in individual studies of remote lakes in Northern Canada, from the Yukon to Labrador (Lockhart et al. 2005). Total sample sizes were 95, 1169 and 868 for whitefish, northern pike and walleye, respectively. No consistent regional trends of increasing or decreasing concentrations over time were observed. Bracketed values represent mean concentrations adjusted for length in each territory (Yukon, Northwest Territory, Nunavut)
(9) Data reported in Appendix 5C of Keeyask Socio-economic Supplemental Filing: Human Health Risk Assessment (Revised) (Keeyask 2013a) (length standardized mean concentrations) and in the fish section of the Aquatic Environment supplemental filing (Keeyask 2013b); in some instances there was a discrepancy between the two reports so a range is shown.
(10) Mean standardized mercury concentrations from Split, Assean, Clark and Aiken Lake in 1998 to 2005 (Keeyask 2013b)
(11) 2004 to 2006; lakes include Caldwell, Christie, Kiask, Limestone, Thomas, Waskaiowaka, Cyril, Rhomas, Atkinson, Moose Nose, War, Pelletier, Recluse and Thomas lake (Keeyask 2013b). (standardized concentrations)

Table 1-3　　**Mean Concentrations of Total Mercury in Other Commonly Consumed Commercial Retail Fish (µg/g wet weight)**

Source	Salmon	Lake Trout	Halibut	Canned Tuna	
				Light/skipjack	Albacore
Commercial Retail Fish					
Canada[1]	0.03 (0 to 0.12)	0.23 (0.10 to 0.65)	0.31 (0.04 to 1.03)	0.06 to 0.14	–
United States[2]	0.048	0.349	0.254	0.118	0.328

Notes:
(1)　Health Canada (2007)　Fish were analyzed by the Canadian Food Inspection Agency in 2004 to 2006 for halibut (n=19) and in 2002 to 2004 for salmon (n=116), lake trout (n=70) and canned skipjack (n=114) or light (n=6) tuna.　Highest tuna value (0.148) was obtained in Whitehorse by Dabeka et al. (2003)
(2)　Data obtained from Seafood Mercury Database in U.S. (Karimi et al. 2013); database represents aggregation of available data from government monitoring programs and the scientific literature. A grand mean was calculated for individual seafood items, based on reported means from individual studies, weighted by sample size.

2.0　　TOXICITY ASSESSMENT

The body of evidence on the toxicity of MeHg indicates that the developing fetus is the most sensitive sub-population, with fetal exposure affecting the developing nervous system at substantially lower doses than in adults (Health Canada 2007). Epidemiological studies of fish-eating populations in the Seychelles Islands in the Indian Ocean and the Faroe Islands in the North Atlantic Ocean have employed very sensitive neurobehavioral tests to observe subtle neurodevelopmental effects in children and some, but not all have shown that nervous system domains involving fine motor function, attention, verbal learning and memory can be affected (Grandjean et al. 1997; Debes et al. 2006; Health Canada 2007).

Government agency exposure limits for MeHg are presented below and recent studies of moderate or low dose MeHg exposure in relation to neurodevelopment are summarized.　Finally, the results of recent studies on other endpoints such as cardiovascular disease are highlighted.

2.1　　Government Exposure Limits

Available government agency guidelines for exposure to MeHg are shown in Table 2-1.　Each government exposure limit can be variably expressed as a hair limit, blood guidance values or acceptable daily intakes in µg/kg/day, so all are shown in the table.　The toxicity reference values employed, uncertainty factors and study references are provided for comparison.　Exposure limits are referred to differently depending on the agency (e.g., tolerable daily or weekly intake (TDI or TWI), reference dose (RfD) or minimum risk level (MRL)).　In general they represent the amount of exposure on a body weight basis that is considered to be safe, or without appreciable risk of adverse health effects, even for sensitive populations such as children and pregnant women.　In some cases, separate exposure limits were recommended for sensitive populations versus the general population.

The World Health Organization (WHO) and Health Canada have separate exposure limits for the general population and for women of childbearing age and children (Table 2-1). Exposure limits for the general population were based on neurotoxicity endpoints in adults while all other limits were developed to protect the most sensitive sub-population, notably pregnant women and children. All of the exposure limits were derived from measured hair or blood concentrations (primarily hair) of Hg that have been related to the presence or absence of effects on neurocognitive outcomes. These hair concentrations were converted through pharmacokinetic models to an equivalent daily dose on a body burden basis and then uncertainty factors were applied to derive a final exposure limit that should not be associated with adverse effects.

The derivation of the Health Canada exposure limit is discussed in more detail below (section 2.2).

Table 2-1   Summary of Health-Based Government Exposure Limits for Methyl Mercury (MeHg)

	Health Canada		WHO/JECFA		US EPA	ATSDR
	General population[1]	Sensitive Subgroup[2]	General population[1]	Sensitive subgroup[2]	General population (including sensitive subgroups)	
Exposure Limits						
µg/kg bw/day	0.47	0.2	0.47[3]	0.23	0.1	0.3
blood (µg/L)	20	8	20	11	5	15
hair (mg/kg)	6	2	5-6	2.2	1	3
Derivation						
Benchmark Dose or NOEL	50 mg/kg (hair) 200 µg/L (blood)	10 mg/kg (hair)	50 mg/kg (hair) 200 µg/L (blood)	14 mg/kg (hair)	12 mg/kg (hair) 58 µg/L (blood)	15 mg/kg (hair)
Uncertainty factor applied	10-fold	5-fold	10-fold	6.4-fold	10-fold	4.5-fold
Primary supporting references	JECFA 1972	Feeley and Lo 1998 ; Grandjean et al. 1997; Davidson et al. 1998; Crump et al. 1998	JECFA 1972	JECFA 2004; Davidson et al. 1998; Grandjean et al. 1997	US EPA 2001; NRC 2000	ATSDR 1999; Davidson et al. 1998
Population Considered	Iraq	Faroe Islands, Seychelles, New Zealand	Iraq	Faroe Islands, Seychelles,	Faroe Islands, Seychelles, New Zealand	Seychelles

Notes:
(1)   Adult males, women past childbearing years
(2)   Pregnant women, women of childbearing years and children
(3)   WHO/JECFA exposure limits are expressed as provisional tolerable *weekly* intakes but in this table were converted to equivalent daily intakes

2.2	Studies of Moderate MeHg Exposure

All of the exposure limits recommended for sensitive populations considered the findings of two large prospective studies in the Seychelles Islands in the Indian Ocean and the Faroe Islands in the North Atlantic Ocean. These studies were initiated in the 1990s to examine low to moderate mercury exposure through fish consumption and associated neurodevelopmental effects in children (Health Canada 2007; Legrand et al. 2010). In the Faroe Island cohort but not the Seychelles cohort, significant associations were observed on some neuropsychological tests indicating some adverse cognitive outcomes (e.g., outcomes related to verbal memory, motor or attention performance) (Grandjean et al. 1997; Davidson et al. 1998). Both the Faroe Island and Seychelles populations consume a lot of seafood, but where the Seychellois consume ocean fish daily and little to no marine mammals, the Faroese consume fish 1 to 2 times per week but also consume considerable amounts of marine mammals, particularly pilot whale meat (ATSDR 1999).

Following the publication of preliminary results from the Seychelles and Faroe Island cohort studies and considering the findings from a smaller New Zealand fish-eating cohort (Crump et al. 1998), the Food Directorate of Health Canada proposed a toxicological reference of 10 mg/kg Hg in maternal hair as the approximate threshold for neuropsychological effects in sensitive subgroups (Feeley and Lo 1998; Legrand et al. 2010). They used an international standard for hair to blood ratio of 250, a steady-state single compartment toxicokinetic model and a 5-fold uncertainty factor to account for inter-individual variability to derive a pTDI of 0.2 µg/kg body weight/day for pregnant women, women of reproductive age and children (Feeley and Lo 1998). The Manitoba government employs this pTDI to determine fish consumption guidelines each year (described further below). The Bureau of Chemical Safety at Health Canada continues to periodically assess the pTDI, taking into consideration any new research findings on the toxicity of methyl mercury (Health Canada 2007).

The Seychelles cohort studies have followed over 700 infant-mother pairs enrolled in 1989 to 1990 from birth until the age of 19 years (van Wijngaarden et al. 2013) and the results are particularly relevant because a) the Seychellois regularly consume a high quantity and variety of ocean fish (~8 to 12 meals per week), b) the median total mercury in 350 fish sampled from 25 species consumed by the Seychellois was < 1 ppm, comparable to mercury concentrations in commercially available fish in North America, c) the Seychelles represent a relatively pristine environment, with no local industrial pollution sources and situated more than 1000 miles from any continent or large population centres, d) the large sample size and e) the use of standardized neurobehavioral tests (ATSDR 1999). The World Health Organization identified 15 mg/kg in maternal hair as a No-Observed-Effects-Level (NOEL) from this study.

The Faroe Island cohort study of almost 900 mother-child pairs was also a well-conducted study and it did suggest adverse neuropsychological effects of prenatal mercury exposure (Grandjean et al. 1997). However, it has been pointed out by several researchers that the diet in the Faroe Islands is considerably different than the diet in the Seychellois and in the U.S. in that the majority of mercury exposure comes from episodic ingestion of whale meat with mercury concentrations of approximately 2 to 3 ppm (ATSDR 1999; US EPA 2001; Boucher et al. 2013). In addition to

mercury, whale meat contains high levels of several persistent organic compounds, such as PCBs and DDE (Weihe and Joensen 2012). In a recent addendum to its toxicological profile for mercury, ATSDR reviewed the more recent studies from the Seychelles and the Faroe Islands and they concluded that the MeHg neurotoxicity observed in the Faroe Island cohort appears to have been affected by concomitant PCB exposure (ATSDR 2013). The minimum risk level they recommended in 1999 of 0.3 μg/kg bw/day based on the Seychelles cohort study was not changed based on their review.

Several follow-up studies of the Seychelles and Faroe Island cohorts have been published and they continue to report very different findings. Studies of the Seychelles main cohort enrolled in 1989 to 1990 have not provided evidence of adverse effects of prenatal MeHg exposure on development in a cohort that consumes fish daily, with the most recent assessment of neurodevelopment conducted at 19 years of age and including measures of scholastic achievement, problematic behaviors and IQ (van Wijngaarden et al. 2013).

By contrast, new data from the Faroe Islands cohort at children's age 14 years indicated that an association observed at age seven years between cord blood MeHg and neurological auditory function was still present at 14 years (Murata et al. 2004; EFSA 2012). Associations with decreased finger tapping speed, reaction time and cued naming tests were still present but weaker at age 14 years (Debes et al. 2006; EFSA 2012). A reassessment of the data from the Faroese cohort at age seven years indicated that beneficial effects of fish consumption, together with imprecision in the measurements of fish intake and determination of mercury exposure might underestimate the effects of MeHg in this cohort (Budtz-Jorgensen et al. 2007, 2010; EFSA 2012).

The study of a fish eating population in New Zealand suggested adverse effects of prenatal MeHg exposure on the mental development of children at the ages of 4 and 7 years (Crump et al. 1998). This study was incorporated into benchmark dose analyses conducted by the NRC (2000) that were used by US EPA (2001) in the development of their Reference Dose (RfD) for MeHg. However, reservations regarding this study have been noted because one child out of the 237 subjects had a maternal hair Hg concentration of 86 mg/kg which likely had a significant effect on the derivation of the BMDLs in this study (JECFA 2004; Legrand et al. 2010).

It is evident from Table 2-1, that there is some disagreement about what constitutes an "acceptable" level of exposure to MeHg. Different government agencies chose different dose-response models, different uncertainty factors and emphasized different data sets in some cases (Hansen and Gilman 2005). Among studies that did report adverse effects, the threshold above which a measurable increase in adverse neuropsychological response was observed seems to be in the range of 10 to 14 ppm hair MeHg. Benchmark dose analyses that incorporated data from all three populations (Faroes, Seychelles and New Zealand) have supported the view that findings across studies are not meaningfully different, with a 5% increase in abnormal responses at an approximate hair mercury level of 12 mg/kg (NRC 2000; van Wijngaarden et al. 2013).

The key difference between the US EPA and the WHO (JECFA)/Health Canada evaluations is that the US EPA took a more conservative view in deciding that a factor for toxicodynamic variability should be incorporated into the uncertainty factor (US EPA 2001; EFSA 2012). WHO/JECFA considered

that that this factor was not needed because the data were derived from sensitive subgroups representing diverse populations (JECFA 2004). Health Canada employed an uncertainty factor similar to WHO/JECFA (5-fold; Table 2-1).

It is important to note that the US EPA (2001) do not consider the benchmark dose of 10 to 12 ppm in maternal hair as a threshold below which no adverse effects of MeHg would be expected (US EPA 2001). WHO (JECFA 2004) determined their point of departure in maternal hair by averaging the NOEL from the Seychelles cohort (15 ppm) with the Benchmark Dose Limit (BMDL$_{05}$) of 12 ppm in hair derived from the Faroe Island cohort (used by the US EPA 2001). In so doing they gave equal weight to both studies. ATSDR, by contrast, based their minimum risk level (MRL) solely on the Seychelles data and employed 15 ppm in maternal hair as the NOEL.

What can be concluded is that maternal hair levels of 10 to 14 ppm have been associated with a measurable or clinically meaningful change in neurocognitive outcomes in some populations. A quantitative analysis of the three major prospective studies (Faroes, Seychelles and New Zealand) indicated that prenatal exposure sufficient to increase hair MeHg by 1 μg/g was associated with an IQ loss of 0.18 points (Axelrad et al. 2007). Another analysis using different assumptions estimated that a 1 μg/g increase in hair MeHg is associated with an IQ loss of 0. 47 points (Pichery et al. 2012).

Some studies in Arctic Canada have also evaluated relatively high prenatal MeHg exposure in relation to neurodevelopment endpoints (Despres et al. 2005; Saint Amour et al. 2006; Boucher et al. 2010, 2013; Plusquellec et al. 2010). These studies are of particular interest since mean cord blood levels of mercury in the Inuit cohorts studied were very similar to the mean cord blood levels reported in the Faro Islands (22 to 24 μg/L, Despres et al. 2005; Plusquellec et al. 2010). An important strength of these studies was an ability to control for confounding by other contaminants present in seafood, specifically lead and PCBs.

In one cohort, an association between cord blood mercury and a measure of tremor in pointing movements at age 5 years was observed, but no associations were found with behavioral outcomes or measures of attention or level of activity (Despres et al. 2005; Plusquellec et al. 2010). In a separate cohort of Inuit children, auditory electrophysiological testing in 116 Inuit children at the age of 11 years revealed a few associations with cord blood mercury (Boucher et al. 2010) but the exact cognitive implications of slightly delayed electrical signals in the brain are unclear at this point in time (Grandjean et al. 2010). In a further study of this cohort, a model adjusting for the effects of other contaminants indicated no associations with mercury, but prenatal mercury exposure was found to interact with prenatal lead exposure on certain electrophysiological tests (Boucher et al. 2013).

A larger cohort of Inuit children including the 116 children studied earlier by Boucher et al. (2010) indicated that compared with children in the lowest tertile of cord blood Hg concentrations, children in the second and third tertiles were significantly more likely to be classified as having attention deficit hyperactivity disorder (ADHD) – Inattentive type (Boucher et al. 2013). Children with higher cord Hg concentrations were approximately 4 times more likely to be identified as exhibiting behaviors that characterize the inattentive type of ADHD. Associations with ADHD-type

behaviors were observed at cord blood Hg concentrations greater than 11.4 μg/L (equivalent hair concentration approximately 2.8 ppm).

The authors note that their results are consistent with findings from neuropsychological assessments of children in the Faroe Islands (Debes et al. 2006) and earlier findings from electrophysiological testing of a subsample of the Inuit cohort (Boucher et al. 2010). Importantly, they suggest that the consistency of their findings with the Faroese but not the Seychelles studies points to different exposure sources — namely marine mammal meat in the Inuit and Faroese (e.g., whale), which is not eaten in the Seychelles. The Seychellois eat primarily ocean fish in which the benefits of the seafood nutrients likely counteract adverse effects from MeHg (Boucher et al. 2013). They also note that marine mammals contain an extensive array of contaminants, which may contribute to MeHg effects. Current blood lead levels were associated with ADHD symptoms in Inuit children (Boucher et al. 2013).

The results of recent epidemiological studies of prenatal exposure to moderate levels of MeHg and neurocognitive outcomes are shown in Table 2-2.

2.3   Studies of Low Dose MeHg Exposure

In their review of recent studies on MeHg and neurodevelopment, the European Food Safety Authority (EFSA 2012) reported that a few, but not all, studies from the U.S. or Europe found associations between prenatal mercury exposure and cognitive outcomes at lower mercury levels than those reported in the Faroe Islands and Seychelles cohorts (Daniels et al. 2004, Jedrychowski et al. 2006, 2007; Oken et al. 2005, 2008; Stewart et al. 2008; Lederman et al. 2008; Sagiv et al. 2012). They concluded that the overall picture at low-level exposure does not provide information to allow conclusions.

The results of recent epidemiological studies of prenatal exposure to lower levels of MeHg and neurocognitive outcomes are shown in Table 2-3. It is of note that several recent large studies have not observed significant associations between mercury exposure and neurodevelopment (see Appendix A). In a review of the evidence for health effects of MeHg at low exposures, Karagas et al. (2012) indicated that studies which did not report associations between prenatal MeHg exposure and cognitive outcomes in preschool children did not adjust for the beneficial effects of fish consumption and this may explain the negative findings. However, since that time two prospective studies in Italy and Spain failed to find associations between prenatal MeHg and neurodevelopmental scores, even after adjustment for fish intake (Llop et al. 2012; Valent et al. 2013).

Table 2-2   **Summary of Methyl Mercury Neurodevelopmental Studies – Moderate Exposure**

Study Location	Number of Children	Age of Children Tested	Prenatal Exposure Level[1]	Outcome[2]	References
Faroe Islands – cohort 1	859 to 917	7, 14 years	22.6 µg/L in cord blood (highly correlated to maternal hair – 4.22 mg/kg)	Adverse effect on verbal learning and memory at age 7 years; adverse effects in motor speed, attention and language at age 14 years; increased auditory potential latencies at age 14 years.	Grandjean et al. 1997; Murata et al. 2004; Debes et al. 2006; Budtz-Jorgensen et al. 2007; Julvez et al. 2010
Faroe Islands – cohort 1 and 2	860 (cohort 1) 182 (cohort 2)	7	22.6 µg/L cord blood (cohort 1) 20.4 µg/L cord blood (cohort 2) 4.27 mg/kg hair (cohort 1) 4.08 mg/kg hair (cohort 2)	Joint analysis of two cohorts showed significant association with verbal function variable and near significant association with motor function variable. Close agreement between 2 cohorts seen only for the Boston Naming test (verbal memory)	Budtz-Jorgensen et al. 2010
Seychelles Islands – main cohort	779	5.5, 9, 10.5, 17 and 19 years	6.8 mg/kg maternal hair	No significant associations with tests of cognitive ability, language development, visual motor coordination, letter-word recognition, reading, scholastic achievement, memory, IQ or child behavior. Improved scores on some tests were associated with fish consumption	Davidson et al. 1998, 2004, 2010, 2011; Huang et al. 2005; van Wijngaarden et al. 2013
Seychelles Islands – nutrition cohort	229	5,9,25 and 30 months; 5 years	5.7 mg/kg in maternal hair	Association between prenatal MeHg and psychomotor development scores at age 9 and 30 months, only after adjusting for the beneficial effects of fish intake. Maternal n-3 LCPUFA (from fish) was positively associated with test scores, but benefits were absent or reduced at maternal Hg levels > 11 mg/kg. No associations observed with prenatal Hg at age 5 years (even adjusting for fish intake benefits)	Davidson et al. 2008; Strain et al. 2008, 2012; Lynch et al. 2011; Stokes-Riner et al. 2011.
Canadian Arctic – Nunavik	109	5.4 years	22.2 µg/L in cord blood	Association with tremor in pointing movements but not reaction time or measures relating to sway or alternating movements. No effects on behavioral outcomes (BSID II) or , attention and emotional expression (observational data); Increased latency of P100 of visual evoked potential at 30%	Despres et al. 2005; Saint Amour et al. 2006; Plusquellec et al. 2010

Study Location	Number of Children	Age of Children Tested	Prenatal Exposure Level[1]	Outcome[2]	References
Canadian Arctic – Nunavik	116-193	11 years	21.2 µg/L in cord blood	Prenatal Hg associated with slower reaction times and greater amplitude and delayed latency of the N1 wave; In an adjusted model, an independent effect of Hg was not observed but an interaction effect with other contaminants was suggested.	Boucher et al. 2010, 2013
Canadian Arctic – Nunavik	279	11.3 years	21.6 µg/L in cord blood	Associations with ADHD-type behaviors were observed at cord blood Hg concentrations greater than 11.4 µg/L (approximately 3 ppm in hair)	Boucher et al. 2013
South America	395	7-12 years (mean=9.5)	10.3 mg/kg maternal hair; 9.8 mg/kg in children's hair	A score reduction of 1.2 in visiospatial ability was observed in children with hair Hg > 10 mg/kg vs. those with hair < 1 mg/kg mercury. Influence of prenatal vs. postnatal exposure could not be distinguished.	Chevrier et al. 2009

Notes:
(1)   Mean concentrations, unless otherwise specified
(2)   Associations are statistically significant unless otherwise noted

Table 2-3   **Summary of Methyl Mercury Neurodevelopmental Studies – Low Dose Exposure**

Study Location	Number of Children	Age of Children Tested	Prenatal Exposure Level[1]	Outcome[2]	References
Italy	606	18 months	1.06 mg/kg maternal hair	No associations between Hg and neurodevelopmental scores (assessed via Bayley Scales), but positive association observed with child intake of fresh fish.	Valent et al. 2013
	242	7-9 years	1.38 mg/kg maternal hair	Children born from mothers with hair mercury levels greater than or equal to 2 mg/kg had IQs which were 4-5 points lower than children born from women with lower hair mercury (not statistically significant)	Deroma et al. 2013
Spain	1,683	14 months	8.4 µg/L cord blood	Doubling in total mercury levels did not show an association with mental or psychomotor developmental delay.	Llop et al. 2012
	72	4 years	0.96 mg/kg (children' hair)	Hair Hg > 1.0 mg/kg associated with decreased scores in general cognitive, memory and verbal subsets of the McCarthy Scales of Children's Abilities (after adjustment for fish intake)	Freire et al. 2010
	302	4 years	1.4 mg/kg (children's hair)	No associations with any subtests of the McCarthy Scales of Children's Abilities (fish intake included in the model). Low fish consuming children scored lower on neurodevelopmental tests than moderate or high fish consumers.	Gari et al. 2013
Poland	198	12, 24 months	0.2 mg/kg (maternal hair)	No association with psychomotor development (assessed via Bayley Scales of Infant Development)	Polanska et al. 2013
	374	12 months, 2 and 3 years	0.9 µg/L cord blood	Increased risk for delayed performance (assessed via Bayley Scales) associated with cord blood Hg at age 12 months but not at age 2 or 3 years	Jedrychowski et al. 2006, 2007
Hong Kong	608	8.2 years	81% had cord blood > 5.8 µg/L; mean=10 µg/L (median hair=1.7 mg/kg)	Cord blood mercury associated with 3 out of 23 subtests of neurodevelopment (a visual sequencing task and retention ability of verbal memory (short and long delay recall)	Lam et al. 2012, 2013
United Kingdom	7,421	15 and 18 months	0.01 mg/kg in cord blood tissue	No effects on social or language skills were observed.	
Canada (Ontario)	212	Birth, 6 and 12 months	0.5 mg/kg (maternal hair)	No effects on behavioral performance.	Stewart et al. 2000; Darvill et al. 2000
United States	212	3 and 4.5 years	0.5 mg/kg (maternal	No direct association with cognitive performance at age 3 or	Stewart et al. 2003

Study Location	Number of Children	Age of Children Tested	Prenatal Exposure Level[1]	Outcome[2]	References
			hair)	4.5 years. An interaction between cord blood PCBs and maternal hair Hg was found at 3 years but not at 4.5 years (i.e., negative effects of prenatal Hg found only in subjects with higher PCB exposure)	
	135	6 months	0.55 mg/kg (maternal hair)	Decreased visual recognition memory	Oken et al. 2005
	341	3 years	2.8 ng/g in maternal erythrocytes	Adverse effects on visual-spatial and total visual motor development	Oken et al. 2008
	151	1,2,3, and 4 years	5.58 µg/L in cord blood	No associations at 1 or 2 years of age; at 3 years of age an association with psychomotor development was observed and at 4 years with performance, verbal and full IQ scores	Lederman et al. 2008
	421	8 years	0.45 mg/kg (maternal hair)	Association with ADHD-related behaviors observed. Apparent threshold at 1 µg/kg maternal hair.	Sagiv et al. 2012
	780	2, 5 and 7 year	0.5 µg/L MeHg in children's blood	A 1 µg/L increase in MeHg was associated with a 2.1 point increase in Full-Scale IQ at age 7 years (i.e., beneficial effect likely associated with fish intake)	Cao et al.2010; Wang et al. 2013

Some but not all earlier studies reported neurodevelopmental effects of MeHg after the beneficial effects of fish intake were considered. Several studies reported *positive* associations between fish consumption and neurodevelopment, even without controlling for mercury exposure. An FDA review in 2009 concluded that the independent negative associations observed between mercury and neurodevelopment in some studies were smaller than independent positive associations observed with maternal fish intake (FDA 2009). For example, a study in Massachusetts indicated that higher fish consumption in pregnancy was associated with improved cognitive test performance in offspring, but adverse effects on visual-spatial and total visual motor development at age 3 years were correlated with maternal blood levels of mercury (Oken et al. 2005, 2008).

In the Seychelles, a nutrition cohort was established specifically to evaluate whether nutrients influence the association between prenatal MeHg and developmental outcomes (Strain et al. 2008, 2012; Lynch et al. 2011). In this cohort it was reported that the beneficial effects of DHA from fish consumption were absent or reduced at maternal hair levels greater than 11 mg/kg (EFSA concluded this level to be a NOEL) (Lynch et al. 2011). However, a follow-up study at age 5 years, demonstrated no associations with prenatal MeHg exposure at any level, even after adjustment for the benefits of fish consumption. (Strain et al. 2012).

Other possibilities to explain discrepancies among studies include genetic variability, biomarkers of exposure, presence of concomitant exposures potentially affecting neurodevelopment, cognitive endpoints measured and statistical analysis methods employed (van Wijngaarden et al. 2013). It is also possible that other sources of mercury contribute to mercury exposure levels besides seafood. A recent large study in the U.K. (n=4484) reported that seafood explained a relatively small proportion of the variation in total blood mercury (Golding et al. 2013). The estimated intakes of the three seafood items evaluated in the study (white fish, oily fish, and shellfish) accounted for only 8.75% of the estimated variation in log-transformed blood mercury concentrations. The authors concluded that limiting seafood intake during pregnancy may have a limited impact on prenatal blood mercury levels (Golding et al. 2013).

In summary, the evidence for adverse neurodevelopmental effects of maternal mercury exposure below 10 to 12 ppm in hair is at present inconclusive, with the possible exception of populations consuming marine mammals such as pilot whale. The preponderance of evidence indicates that hair mercury levels at Health Canada's safe level of exposure (2 ppm) or less are not associated with adverse effects on sensitive populations. In their recent review, EFSA (2012) concluded that the Faroe Island and Seychelles cohort data remain the best data from which to derive health-based guidance values.

2.4   Cardiovascular and Other Endpoints

Another area of Hg toxicity that has received considerable focus is an association with cardiovascular disease. Two early studies indicated a significant association between mercury concentrations in adults and an increased risk of an acute coronary event or myocardial infarction (Guallar et al. 2002; Virtanen et al. 2005). Another early study found a decreased risk of MI

associated with elevated Hg levels (Hallgren et al. 2001) and two others found no associations (Ahlqwist et al. 1999; Yoshizawa et al. 2002).

More recently, mercury exposure was not associated with risk of cardiovascular disease in two large U.S. cohorts (Mozaffarian et al. 2011), nor was it associated with adverse cardiovascular effects in a study in Sweden (Wennberg et al. 2011). In Finnish men, an association between mercury in hair and risk of sudden death was reported (Virtanen et al. 2012), but a prospective study of women in Sweden observed that women with higher Hg concentrations in their blood had a reduced risk of fatal acute MI at 32 years follow-up (Bergdahl et al. 2013).

A recent pooled analysis of Finnish and Swedish data indicated that methyl mercury was associated with an increased risk of MI, while higher S-PUFA concentrations were associated with a decreased risk of MI (Wennberg et al. 2012). The authors reported that a significant net harm of hair-Hg was not seen before amounts reached > 2 ppm and with simultaneously low S-PUFA, which they note is an unusual combination. The majority of subjects in the interval that implied harmful effects were from Finland and it was suggested that a higher consumption of lean predatory fish (e.g., pike, perch) in Finland versus Sweden may explain the difference (Wennberg et al. 2012). This study highlighted the importance of studies considering both MeHg and benefits of PUFA in fish in their analyses.

It is important to note that in the two studies observing higher CVD risk with higher mercury levels, the net effect of fish consumption was still beneficial — i.e., higher mercury exposure lessened the benefit associated with consumption of fish or n-3 PUFAs but did not increase overall risk (Mozaffarian and Rimm 2006; Guallar et al. 2002; Yoshizawa et al. 2002; Virtanen et al. 2005).

Recent findings from two large prospective cohorts in the U.S. do not support adverse effects of MeHg on the development of diabetes (Mozaffarian et al. 2013). Similarly in Finland, hair Hg was not associated with the Type 2 Diabetes in men, while fish intake was associated with long-term lower risk of diabetes (Virtanen et al. 2013). Studies on blood pressure and Hg exposure give an inconsistent picture; at present there is no firm basis for a dose-response relationship (EFSA 2012).

In summary, the evidence for adverse health effects of Hg exposure on cardiovascular outcomes is inconclusive, but the net benefits of fish consumption on cardiovascular risk are likely to be positive. Studies do not support an association between Hg exposure and diabetes or strokes.

3.0 HAIR MERCURY MODELLING

3.1 Introduction

The predicted present health risks in the HHRA were acknowledged as being overly conservative due the uncertainty in predicted exposures. This makes it very difficult to convince the local communities that it is safe and important to eat wild fish.   Considering the importance of fish as a protein and nutritional source for local communities, further assessment is needed to properly

inform subsistence consumers about the health benefits and costs related to fish consumption. Since blood and hair samples are not being conducted at this time by the Keeyask Partnership, we felt that additional information may be gained through credible computer modelling to predict mercury concentrations in hair, under what we believe are more realistic exposure assumptions.

Although blood and hair sampling were not conducted for the HHRA and it appears that it is not planned at this time, the following information was stated in the final Keeyask HHRA:

- Blood and hair measurements are a well known and accurate method for estimating both exposure and risks from methyl mercury in fish. To evaluate potential health risks, the Health Canada approach has been employed whereby mercury hair concentrations less than 5 ppm (or 20 μg/L in blood) are considered to be in the "normal range" while concentrations between 5 and 25 ppm (25 to 100 μg/L in blood) are in the "increasing risk" range and concentrations above 25 ppm (or 100 μg/L in blood) are considered to be "at risk" levels (INAC 2009).
- In addition to these broad classifications, the following tissue concentrations would be close to known effects levels from the literature: Health Canada (1998) and US EPA (2011) have indicated that maternal mercury concentrations of 10 ppm in hair and/or 58 μg/L in blood are generally equal to the threshold for a 5% increased risk of developmentally delayed children. Although there have been no clear-cut clinical abnormalities in children born to mothers with mercury concentrations above 10 ppm in hair or 58 μg/L in blood, there have been effects on language, attention and memory that have been reported to be mercury-related.
- US EPA (2011) has developed a Benchmark Dose Level (BMDL05) (the lower 95% confidence limit of the BMD05) of 59 μg/L in maternal blood for neurological effects in children. This blood concentration would result in a doubling of the number of children with a neurological response at the fifth percentile of the population.

The above guidelines will be helpful in combination with historical measured blood mercury and hair concentrations observed across Canada in Table 3-1 (Legrand et al. 2010). Recently the geometric mean blood levels of total mercury in the Canadian population was measured to be 0.69 μg/L (95% CI 0.56 to 0.86 μg/L) and the majority (98%) of women aged 16 to 49 years of age, including pregnant women, had blood mercury levels below the Health Canada guidance value of 8 μg/L (Lye et al. 2013). There was no difference in blood mercury concentrations between Aboriginal-Canadians versus Caucasians (0.56 vs. 0.62 μg/L, p=0.29).

Table 3-1 **Historical Blood (µg/L) and Hair (ppm) Total Mercury Concentrations In Canadian Studies**

Location	Target Group	Stat[1]/ Variation[2]	Blood Measured From Literature (Legrand et al 2010)		Calculated[3]	
			Stat Value (µg/L)	Variation (µg/L)	Hair Value (ppm)	Hair Variation (ppm)
Canadian Population	Children age 6-19	GM/CI	0.31	0.23-0.91	0.08	0.06-0.23
	Adults	GM/SD	0.91	0.63-1.32	0.23	0.16-0.33
Labrador (Adults)	Innu community	AM/SD	1.6	1.44	0.4	0.36
New Brunswick (Adults)	Grand Manan	AM/SD	2.8	2.2	0.7	0.55
	St. Andrews/ St. Stephen	AM/SD	1.68	0.6	0.42	0.15
Quebec	1st trimester	GM/CI	0.85	0.4-2.2	0.21	0.1-.55
	2nd trimester	GM/CI	0.56	ND-2.0	0.14	ND-0.5
	At delivery	GM/CI	0.48	ND-1.2	0.12	ND-0.3
	Cord blood	GM/CI	0.52	ND-1.6	0.13	ND-0.4
Quebec (Adults)	Lake St. Pierre	AM/SD	3.32	3.88	0.83	0.97
	Abitibi	AM/SD	4.8	5.6	1.2	1.4
Quebec (Adults)	Greater Quebec city area	GM/CI	0.74	0.2-3.21	0.19	0.05-0.8
Ontario (Adults)	Sport Fish Non eaters	GM/R	1.5	0.4-7.5	0.38	<0.28-1.35
	Sport Fish Eaters	GM/R	2.2	1.0-26.0	0.55	<0.28-4.08
Ontario (Adults)	Euro-Canadian Sport fish eaters	GM/R	2	0.4-7.5	0.5	0.1-1.875
	Asian Canadian sport fish eaters	GM/R	7.9	1.0-26.0	1.98	0.25-6.5
British Columbia (Children age 1.5 -5)	All Children	MD/R	0.9	ND-13.7	0.23	ND-3.425
	Caucasians	MD/R	0.2	ND-3.6	0.05	ND-0.9
	Chinese	MD/R	2.2	0.1-13.7	0.55	0.025-3.4
	Other	MD/R	0.7	ND-2.6	0.18	ND-0.65
Northern Canada (Pregnant Women)	Caucasians	GM/R	0.9	ND-4.2	0.23	ND-1.05
	Other	GM/R	1.4	ND-6.0	0.35	ND-1.5
	Metis/Dene	GM/R	1.3	0.2-3.4	0.33	0.05-0.85
	Inuit/Baffin	GM/R	6.7	ND-34	1.68	ND-8.5
	Inuit/Inuvik	GM/R	2.1	0.6-12	0.53	0.15-6
	Inuit/Kitikmeot	GM/R	3.4	ND-13.7	0.85	ND-3.25
	Inuit/Kivalliq	GM/R	3.7	0.6-12	0.93	0.15-3
	Nunavik	GM/R	10.4	2.6-44	2.6	0.65-11
Average			2.4		0.59	
Min - Max			0.2 - 10		0.05 - 2.6	

(1) GM = Geometric Mean, AM = Arithmetic Mean, MD = Median.
(2) SD = Standard Deviation, CI = Confidence Interval, R = Range.
(3) Hair data was calculated by multiplying the given data from literature by a conversion factor of 0.25 ppm-hair / µg/L-blood (Legrand et al 2010). This conversion factor may not be appropriate for children.
ND = Non-detect

3.2   Hair mercury model

A "hair mercury model" was used by us to predict maternal hair concentrations of mercury for comparison to effect benchmarks, epidemiological studies and bio-monitoring results. Model description details are provided in Appendix B. Following a description of existing and predicted mercury concentrations in fish used in our model, the model results for following scenarios is presented:
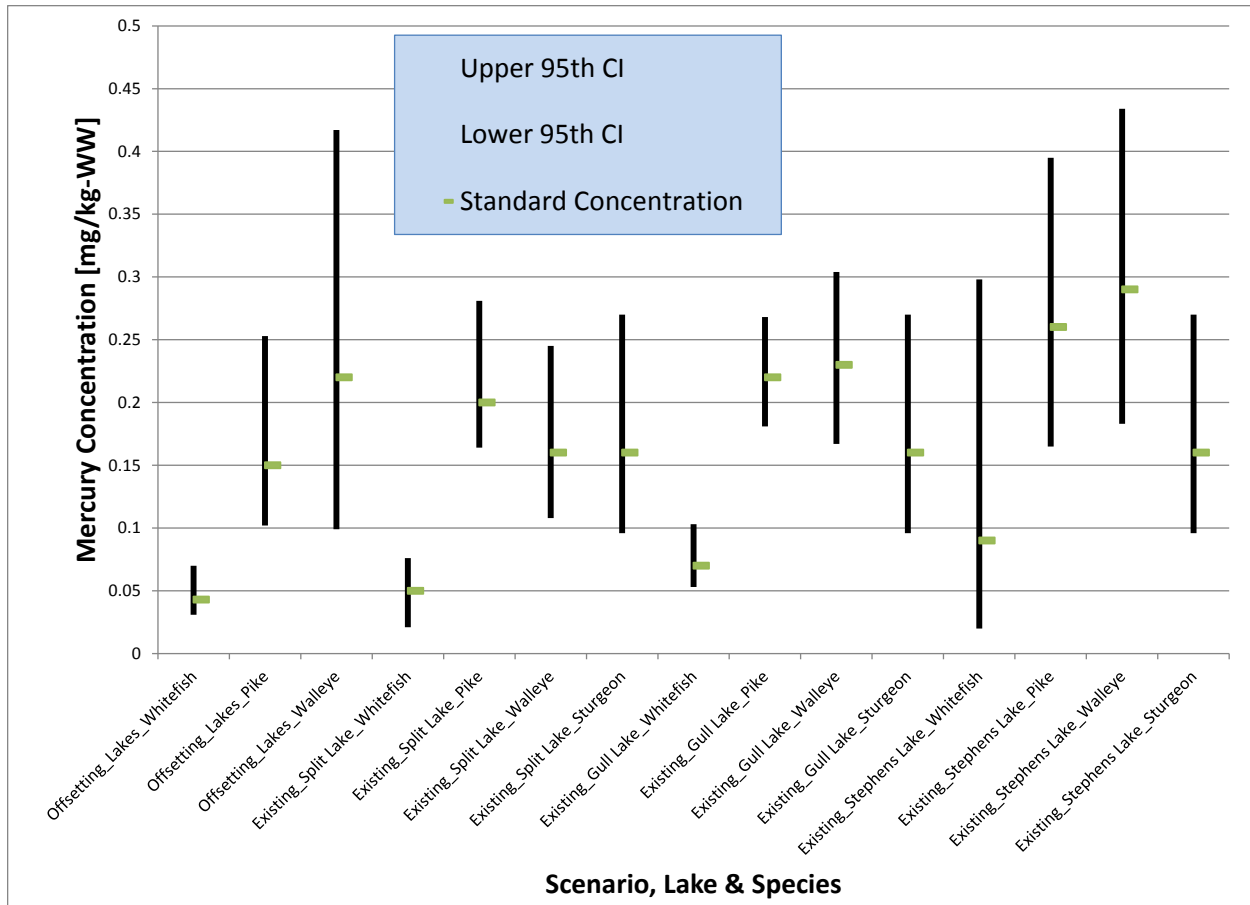
- Existing mercury concentrations in fish using conservative exposure assumptions from the Keeyask HHRA.
- Existing mercury concentrations in fish using modified exposure assumptions that we believe are more realistic than those in HHRA.
- Predicted post-impoundment mercury concentrations in fish using conservative exposure assumptions from the Keeyask HHRA
- Predicted post-impoundment mercury concentrations in fish using modified exposure assumptions that we believe are more realistic than those in HHRA.
- Predicted future hair mercury concentrations assuming consumption of only whitefish, the species with the lowest predicted mercury concentrations..

3.3   Existing Mercury Concentrations in Fish

Figure 3-1 and Table 3-2 present the standardized fish mercury concentrations and the upper and lower 95th percent confidence interval (CI) for large bodied fish sampled from 1999 to 2006.[1] The data are presented for Whitefish, Pike and walleye from the lakes assessed in the HHRA (i.e., Split Lake, Gull Lake and Stephens Lake) and includes the 2004 to 2006 fish mercury concentrations from the AEA offsetting lakes. Offsetting lakes consist of the following: Caldwell, Christie, Kiask, Limestone, Thomas, Waskaiowaka, Cyril, Atkinson, Moose Nose, War, Pelletier, and Recluse. The standardized mean concentrations presented in Figure 3-1 are identical to the values used in the HHRA and the upper and lower 95th CI are based on the maximum and minimum annual CI for sampling periods used in the HHRA.

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[1] Concentration data duplicated from Aquatic Environment Section 7: Fish Quality Table 7H-1.

Figure 3-1   Existing Standardized (±95% Confidence Interval) Mean Mercury Concentrations in Fish from Aquatic Environment Study Area

Table 3-2   Summary of Present Mercury Concentrations in Fish Used in the HHRA and Exposure Model [mg/kg-WW]

Lake	Fish	HHRA Value[1]	Exposure Model Value[2]	Comment[3]:Source and Year(s) of Sample Data
AEA Offsetting Lakes	Whitefish	NA	N(0.031, 0.07)	Table 7-1; 2005 & 2006
	Pike	NA	N(0.102, 0.253)	Table 7-1; 2004 to 2006
	Walleye	NA	N(0.099, 0.417)	Table 7-1; 2005 & 2006
Split Lake	Whitefish	0.05	N(0.021, 0.076)	Table 7H-1; 2001, 2002 & 2005
	Pike	0.2	N(0.164, 0.281)	Table 7H-1; 2001, 2002 & 2005
	Walleye	0.16	N(0.108, 0.245)	Table 7H-1; 2001, 2002 & 2005
	Sturgeon	0.16	N(0.096, 0.27)	Table 7A-2; 2004
Gull Lake	Whitefish	0.07	N(0.053, 0.103)	Table 7H-1; 1999 to 2002
	Pike	0.22	N(0.181, 0.268)	Table 7H-1; 2001, 2002 & 2006
	Walleye	0.23	N(0.167, 0.304)	Table 7H-1; 2001, 2002 & 2006
	Sturgeon	0.16	N(0.096, 0.27)	Table 7A-2; 2004
Stephens Lake	Whitefish	0.09	N(0.02, 0.298)	Table 7H-1; 2001 to 2003 & 2005
	Pike	0.26	N(0.165, 0.395)	Table 7H-1; 2001 to 2003 & 2005
	Walleye	0.29	N(0.183, 0.434)	Table 7H-1; 2001 to 2003 & 2005
	Sturgeon	0.16	N(0.096, 0.27)	Table 7A-2; 2004

Notes:
(1)   Fish concentrations based on weighted standard concentration for years of sample data.
(2)   Standardized lower and upper 95% confidence interval of large bodied fish concentrations defined by normal distribution –
      N(Lower CI, Upper CI).
(3)   Keeyask (2012)

3.4   Future Mercury Concentrations in Fish

Figure 3-2 and Table 3-3 summarize predicted future fish mercury concentrations and the upper
and lower 95th percent confidence interval (CI) for large bodied fish in Gull Lake and Stephens Lake.
The standardized mean concentrations presented in Figure 3-2 are based on the predicted increase
in fish concentrations used in the HHRA. A similar factor increase was applied to the upper and
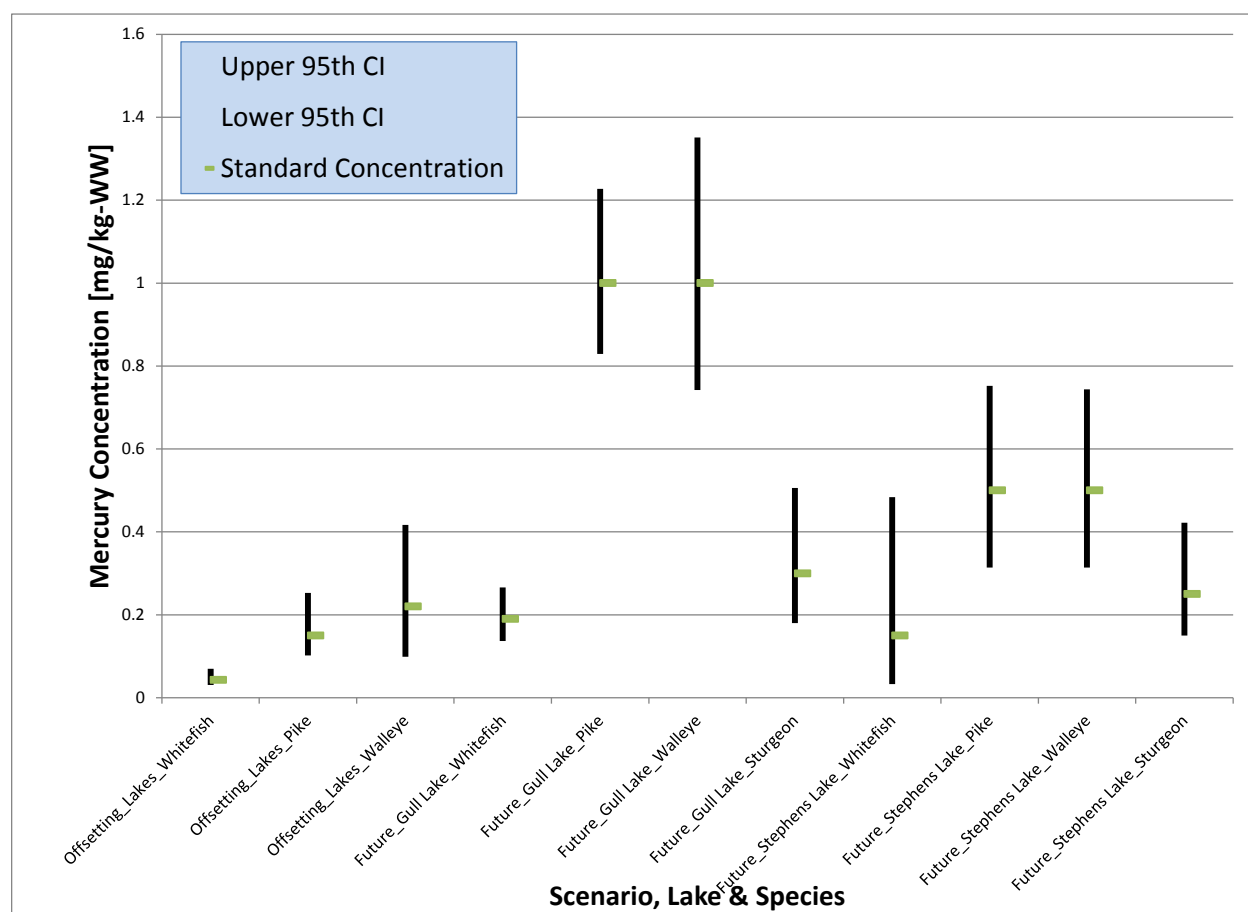lower 95th CI.

**Figure 3-2   Future Standardized (±95% Confidence Interval) Mean Mercury Concentrations in Fish
from Aquatic Environment Study Area**

Table 3-3 **Summary of Future Mercury Concentrations in Fish Used in the HHRA and Exposure Model [mg/kg-WW]**

Lake	Fish	Present HHRA Value[1]	Future HHRA Value[2,4]	Factor Increase	Exposure Model Value[3]
Gull Lake	Whitefish	0.07	0.19	2.6	N(0.14, 0.27)
	Pike	0.22	1.0	4.6	N(0.83, 1.2)
	Walleye	0.23	1.0	4.4	N(0.74, 1.4)
	Sturgeon	0.16	0.30	1.9	N(0.18, 0.51)
Stephens Lake	Whitefish	0.09	0.15	1.6	N(0.03, 0.48)
	Pike	0.26	0.50	1.9	N(0.31, 0.75)
	Walleye	0.29	0.50	1.7	N(0.31, 0.74)
	Sturgeon	0.16	0.25	1.6	N(0.15, 0.42)

Notes:
(1) Fish concentrations based on weighted standard concentration for years of sample data.
(2) Future or post-impoundment fish concentrations.
(3) Predicted standardized upper and lower 95% confidence interval of large bodied fish concentrations defined by normal distribution – N(Lower CI, Upper CI).
(4) Keeyask (2013b)

3.5   Predicted Existing Hair Concentrations

3.5.1   Using HHRA Exposure Assumptions

Using the HHRA assumptions, present female adult (Figure 3-3) and toddler (Figure 3-4) exposures were predicted by our model to exceed the Health Canada benchmark of 0.2 µg/kg/day at Split Lake, Gull Lake and Stephens Lake more than 95% of the time. Predicted hair concentrations of mercury were expected to range from 1.5 to 14 ppm 95% of the time (Figure 3-5). In all circumstances, the predicted maternal hair mercury concentrations were greater than the 95UCLM of 0.25 ppm measured in the FNFNES Study (Chan et al. 2012) among females aged >19 to 50 years of age living on First Nations reserves in Manitoba. Predicted hair concentrations based on consumption of fish from Split Lake, Gull Lake or Stephens Lake are up to 124 times higher than measured values. In addition (see Table 3-4) over 80% of the predicted exposures exceed the Health Canada benchmark value of 2 ppm for sensitive members of the population (see Table 3-).
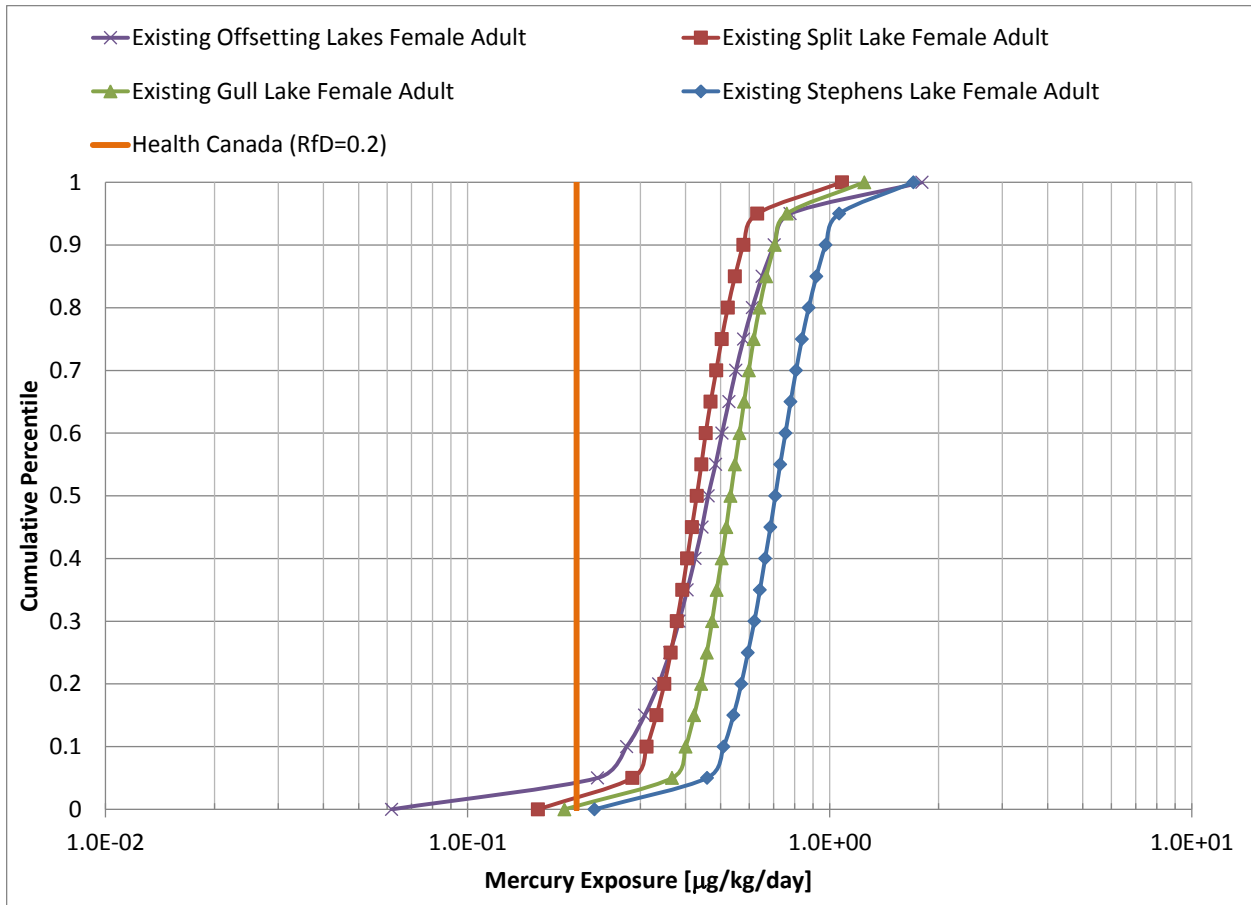
Figure 3-3   Predicted Present Adult Female Exposure to Mercury Based on HHRA Assumptions
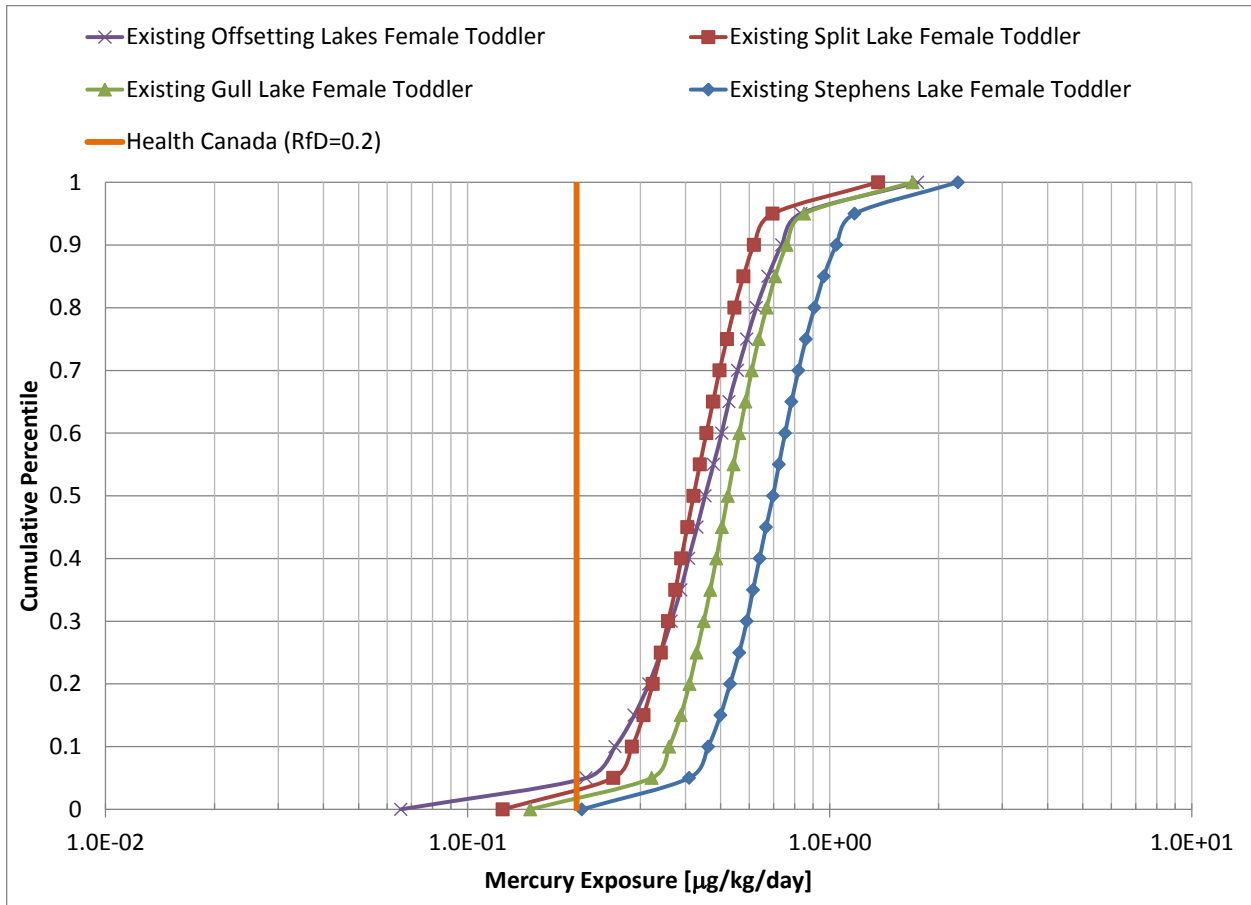
Figure 3-4   Predicted Present Female Toddler Exposure to Mercury Based on HHRA Assumptions
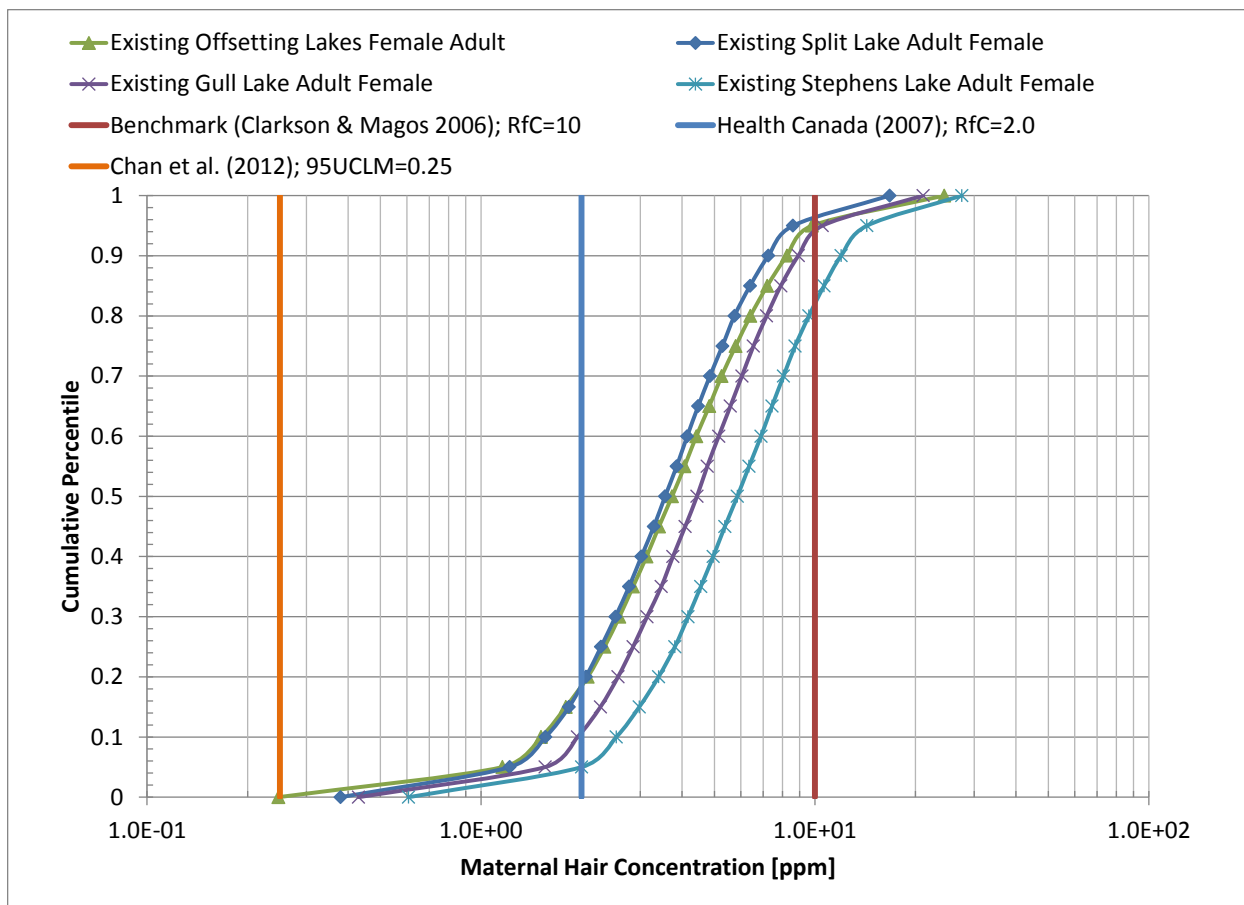
Figure 3-5   Predicted Existing Maternal Hair Concentrations of Mercury Based on HHRA Assumptions

Table 3-4   Percentage of Predicted Maternal Hair Levels Above Benchmark Values

Area	Percentage of Predicted Existing Maternal Mercury Exposures Associated with Hair Concentrations Greater than Benchmarks [%]		
	Chan et al. (2012) Background Value 0.25 ppm	Health Canada (2007) Guidance Value 2 ppm	Clarkson and Magos (2006) Benchmark Value 10 ppm
AEA Offsetting Lakes	100%	85%	<10%
Split Lake	100%	85%	<5%
Gull Lake	100%	90%	<10%
Stephens Lake	100%	95%	<20%

3.5.2   Using Modified Exposure Assumptions

Given that predicted existing exposures and associated maternal hair concentrations were greater than measured hair concentrations among females aged >19 to 50 years of age living on First Nations reserves in Manitoba, the following exposure assumptions were re-visited:

- Consumption rates; and
- Ratio of methyl mercury to total mercury in fish tissue.

Table 3-5 compares adult fish portion size and consumption rates assumed in the HHRA to the results from the FNFNES Study (Chan et al. 2012). Portion sizes are 2 to 8 times smaller in the FNFNES Study, and upper consumption rates are about half of what was assumed in the HHRA. Health Canada (2007) recommends a subsistence fish consumption rate of 20 and 40 grams/day for the toddler and adult, respectively.

Table 3-5   Assumed Portion Size and Estimated Fish Consumption Rates by First Nation Communities in the HHRA

Fish	Portion Size for Toddler (grams)	Portion Size for Adult (grams)	Frequency of Consumption (times per week)	Estimated long-term consumption rate for Toddler (grams/day)[1]	Estimated long-term consumption rate for Adult (grams/day)[1]
Whitefish	100	400	3	43	171
Pike	100	400	3	43	171
Walleye	100	400	3	43	171
Sturgeon	100	400	3	43	171
Chan et al. (2012)	NA	Female 50 to 170 and male 141 to 197[2]	NA	NA	Average: Female 2.1 to 10 and male 13 to 17[3] 95th Percentile: Female 11 to 66 and male 36 to 87[3]
Health Canada (2007)				20	40

Notes:
NA: Not available.
(1) Estimated based on (portion size) x (frequency of consumption) / (7 days per week).
(2) Range in mean portion size of fish reported for the ages of 19 to 71+.
(3) Based on consumption of the following fish species: walleye, lake whitefish, pike and sturgeon.

To be consistent with the upper consumption rates assumed in the HHRA, our exposure model used the 25 grams/day upper consumption rate (95th percentile) for females aged >19 to 50 from the FNFNES Study (Chan et al. 2012). Our model also used the Health Canada adult subsistence consumption rate of 40 grams/day as another consumption scenario.

For the HHRA it was assumed that 100% of the mercury in fish consisted of methyl mercury, consistent with Health Canada (2007) but is considered conservative. Therefore, our exposure model assumed 85% total mercury was the organic form. The study by Canuel et al. (2006), conducted for three regions in Northern Quebec (Lake St. Pierre, Abitibi and Labrador) should be representative of large bodied fish in Manitoba. In addition, the FNFNES Study (Chan et al. 2012) measured methyl mercury and total mercury in pike and walleye, and the ratio of methyl mercury

to total mercury ranged from 62 to 80%. Therefore, the assumption of 85% is determined to be a reasonable and conservative estimate of methyl mercury content in fish.

Table 3- presents the two modification scenarios (i.e., #1 and #2), assumptions and parameter values that were used in our exposure model.

Table 3-6   Modified Assumptions and Parameter Values Used in the Exposure Model

Parameter	Value	Comment / Reference
Modification #1		
Consumption rate for female aged >19 to 50 [grams/day]	25	Fixed value based on upper consumption rate (i.e., 95th percentile); Chan et al. (2012)
Ratio of methyl mercury to total mercury in fish tissue	85%	Fixed value; Canuel et al. (2006)
Modification #2		
Consumption rate for female [grams/day]	40	Fixed value for subsistence consumers; Health Canada (2007)
Ratio of methyl mercury to total mercury in fish tissue	85%	Fixed value; Canuel et al. (2006)

Based on the modifications in consumption rates and methyl mercury content in fish, adult female hair mercury concentrations were predicted to be lower and closer to the measured value of 0.25 ppm mercury in hair by the FNFNES Study, and 80% to 95 % of predicted hair concentrations were lower than the Health Canada benchmark value of 2 ppm. The prevalence of predicted hair concentrations below the benchmark value of 2 ppm suggests that adverse effects are unlikely from existing exposures to fish in the Keeyask study area (Split Lake, Gull Lake and Stephens Lake).
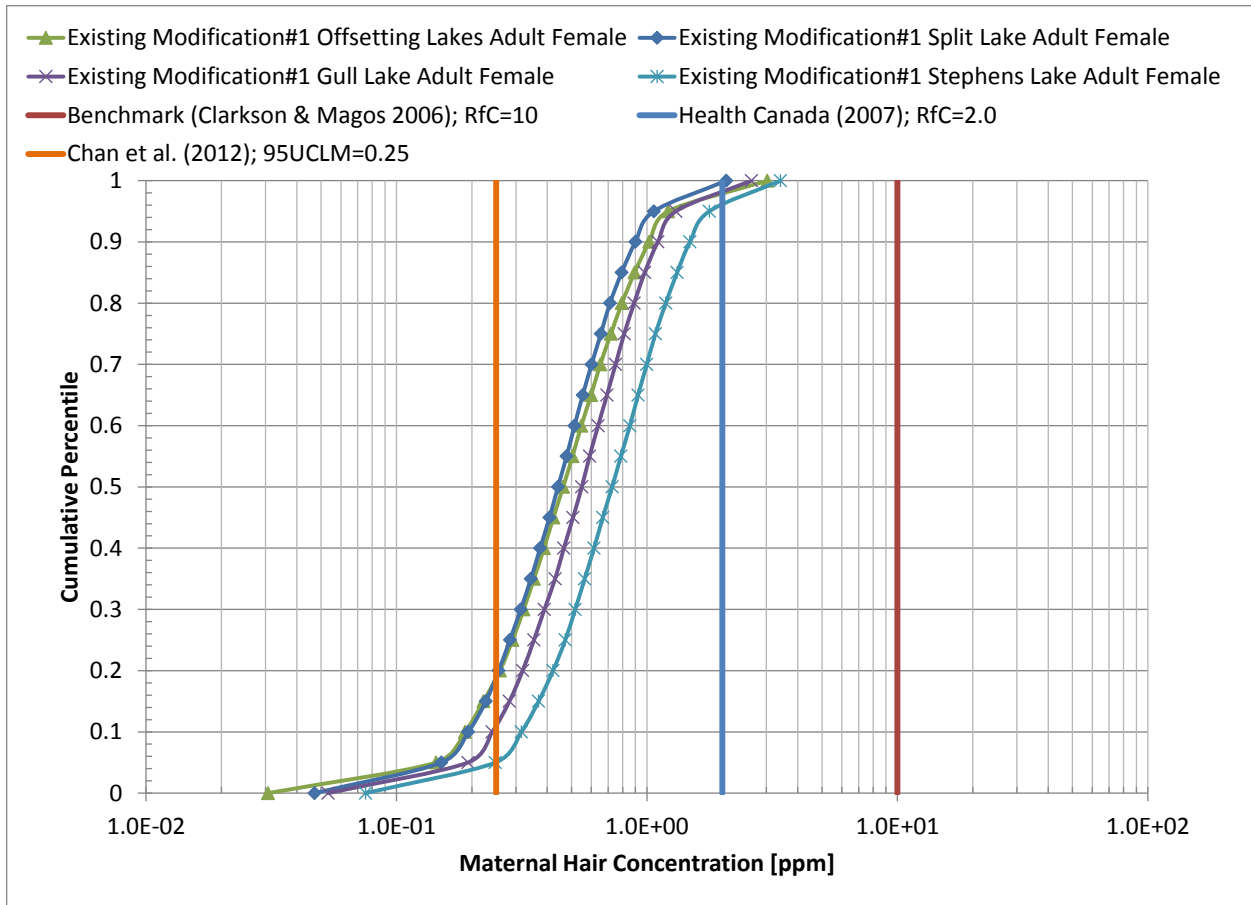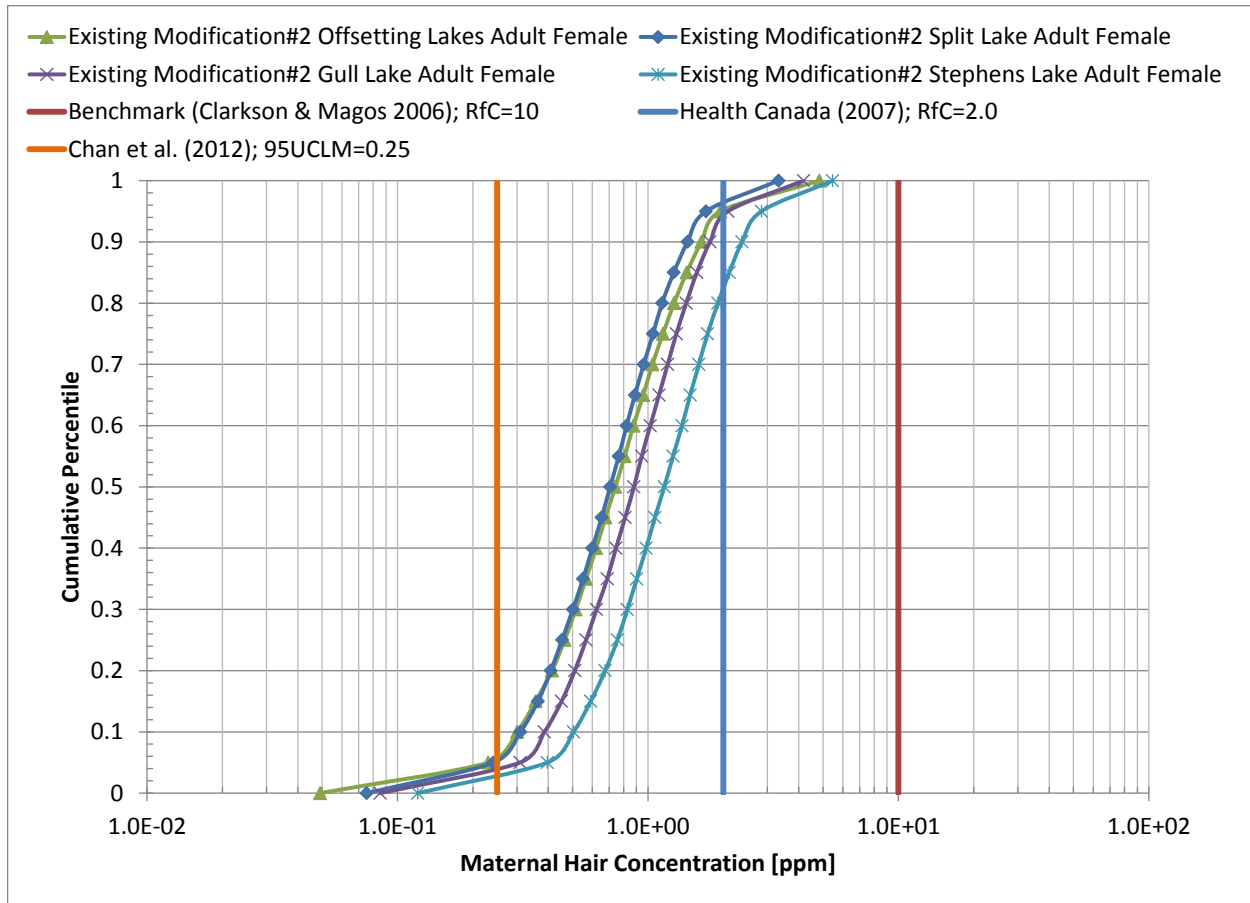
Figure 3-6   Predicted Existing Maternal Hair Concentrations of Mercury Based on Modification #1 Assumptions (FNFNES Consumption Rates)

Figure 3-7   Predicted Existing Maternal Hair Concentrations of Mercury Based on Modification #2 Assumptions (Health Canada Consumption Rates)

3.6   Future Predicted Exposure and Hair Concentrations

3.6.1   Using HHRA Assumptions

Based on our model using the HHRA exposure assumptions, future female adult (Figure 3-8) and toddler (Figure 3-9) exposures are predicted to always exceed the Health Canada benchmark of 0.2 µg/kg/day at Gull Lake and Stephens Lake. Predicted hair mercury concentrations ranged from 3.5 to 43 ppm 95% of the time (Figure 3-10). Predicted maternal hair mercury concentrations substantially exceeded the 95UCLM of 0.25 ppm measured in the FNFNES Study among females aged >19 to 50 years. In addition the predicted hair concentrations are substantially higher than benchmark hair concentrations levels, with over 95% of exposures exceeding the Health Canada benchmark value of 2 ppm (Table 3-7).
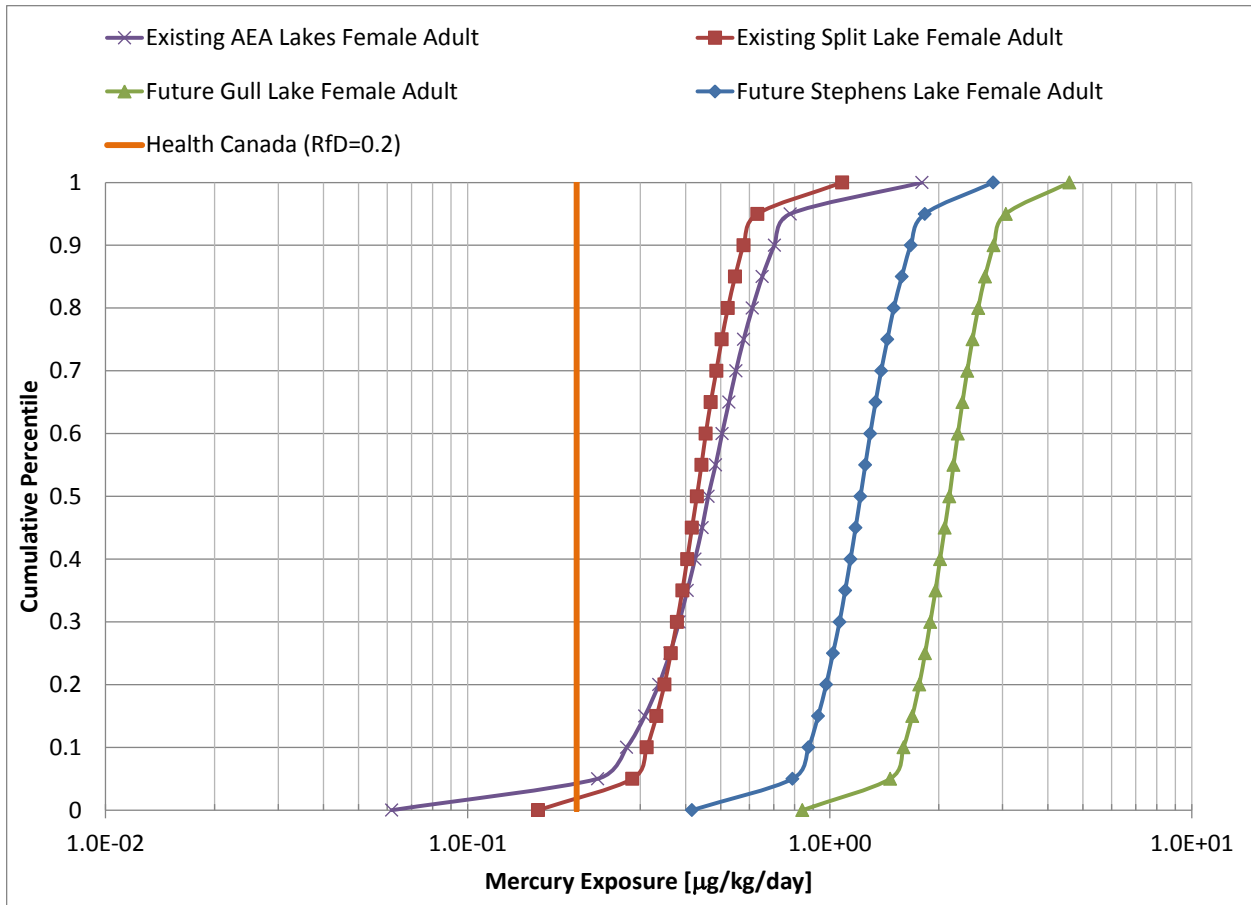
Figure 3-8   Predicted Existing Offsetting and Split Lake, and Future Gull and Stephens Lake Adult Female Exposure to Mercury Based on HHRA Assumptions
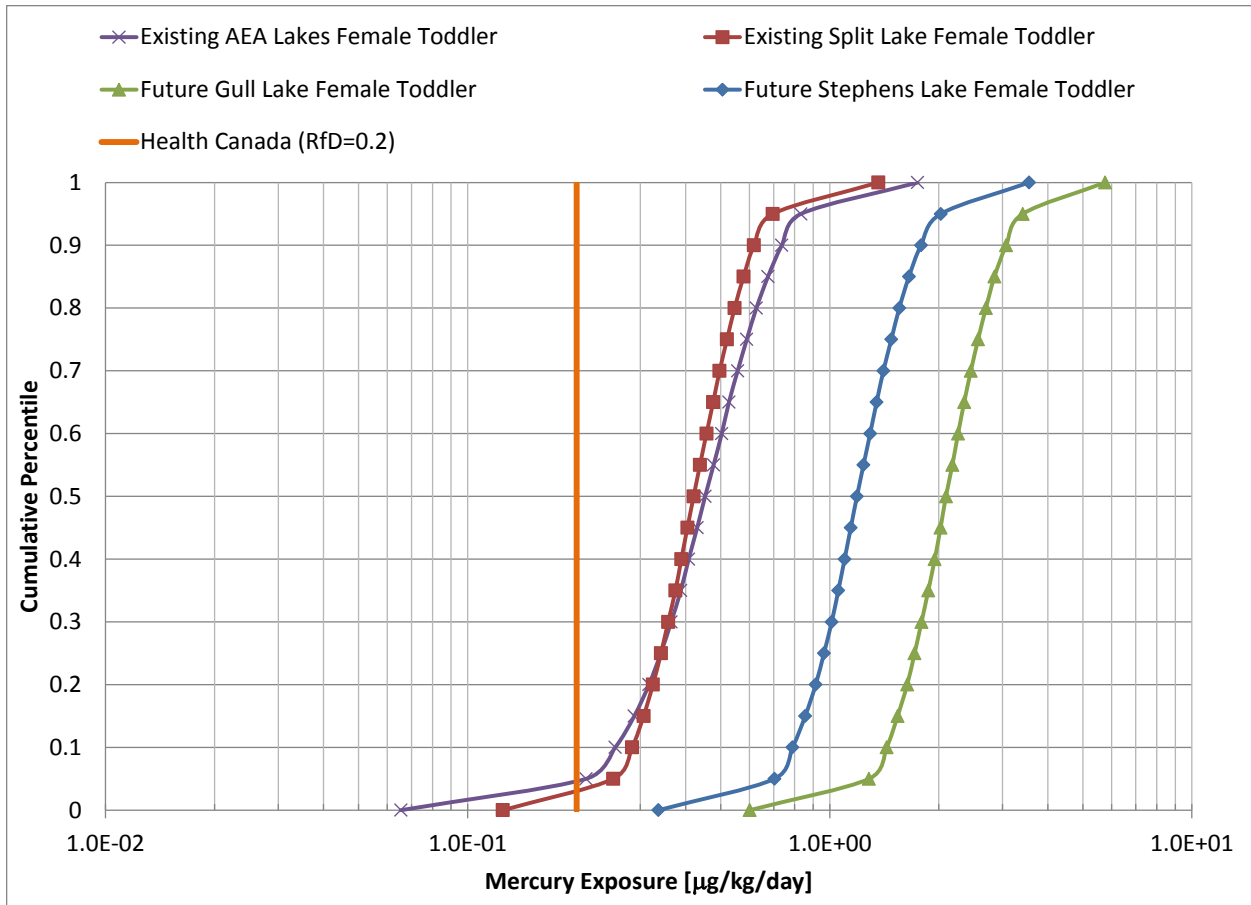
Figure 3-9   **Predicted Existing Offsetting and Split Lake, and Future Gull and Stephens Toddler Female Exposure to Mercury Based on HHRA Assumptions**
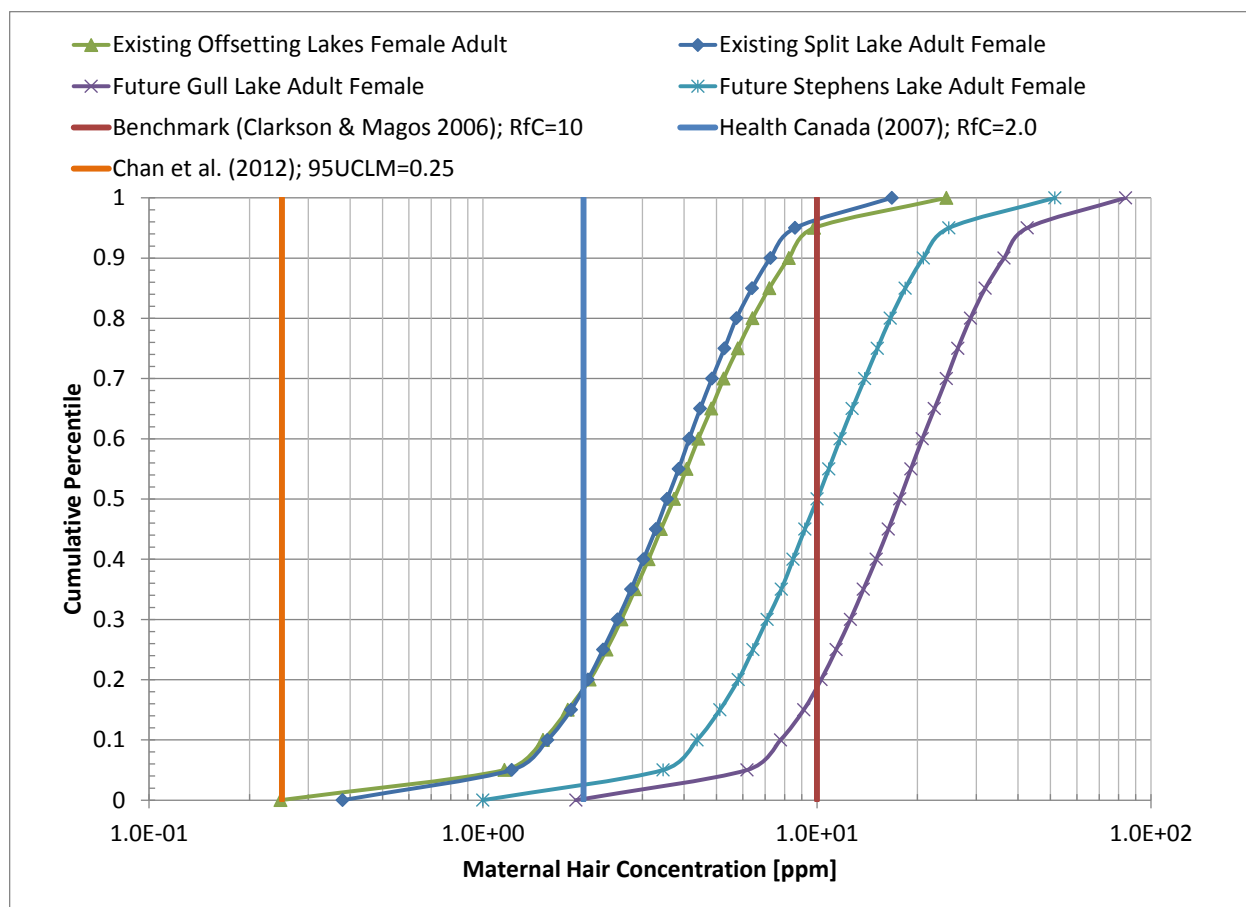
Figure 3-10   **Predicted Existing Offsetting and Split Lakes, and Future Gull and Stephens Lake Maternal Hair Concentrations of Mercury Based on HHRA Assumptions**

Table 3-7   **Percentage of Predicted Maternal Hair Levels Above Benchmark Values**

Area	Percentage of Predicted Existing and Future Maternal Mercury Exposures Associated with Hair Concentrations Greater than Benchmarks [%]		
	Chan et al. (2012) Background Value 0.25 ppm	Health Canada (2007) Guidance Value 2 ppm	Clarkson and Magos (2006) Benchmark Value 10 ppm
AEA Offsetting Lakes	100%	90%	<10%
Split Lake	100%	80%	<5%
Gull Lake	100%	100%	>80%
Stephens Lake	100%	<95%	>50%

3.6.2   Using Modified Assumptions

The future scenario was modelled with the modified exposure assumptions described above. Using these assumptions, adult female hair mercury concentrations were predicted to be closer to the measured value of 0.25 ppm mercury in hair by the FNFNES Study. A minimum of 20 % to more than 45% of predicted hair concentrations were below the Health Canada benchmark value of 2 ppm. In addition, more than 95% of predicted hair concentrations were below the 10 ppm

benchmark. However, the prevalence of predicted hair concentrations above the benchmark value of 2 ppm suggests that adverse effects are possible from future exposures to fish in the aquatic environment study area (i.e., Gull Lake and Stephens Lake).

Figure 3-11   Predicted Existing Offsetting and Split Lakes, and Future Gull and Stephens Lake Maternal Hair Concentrations of Mercury Based on Modification #1 Assumptions (FNFNES Consumption Rates)
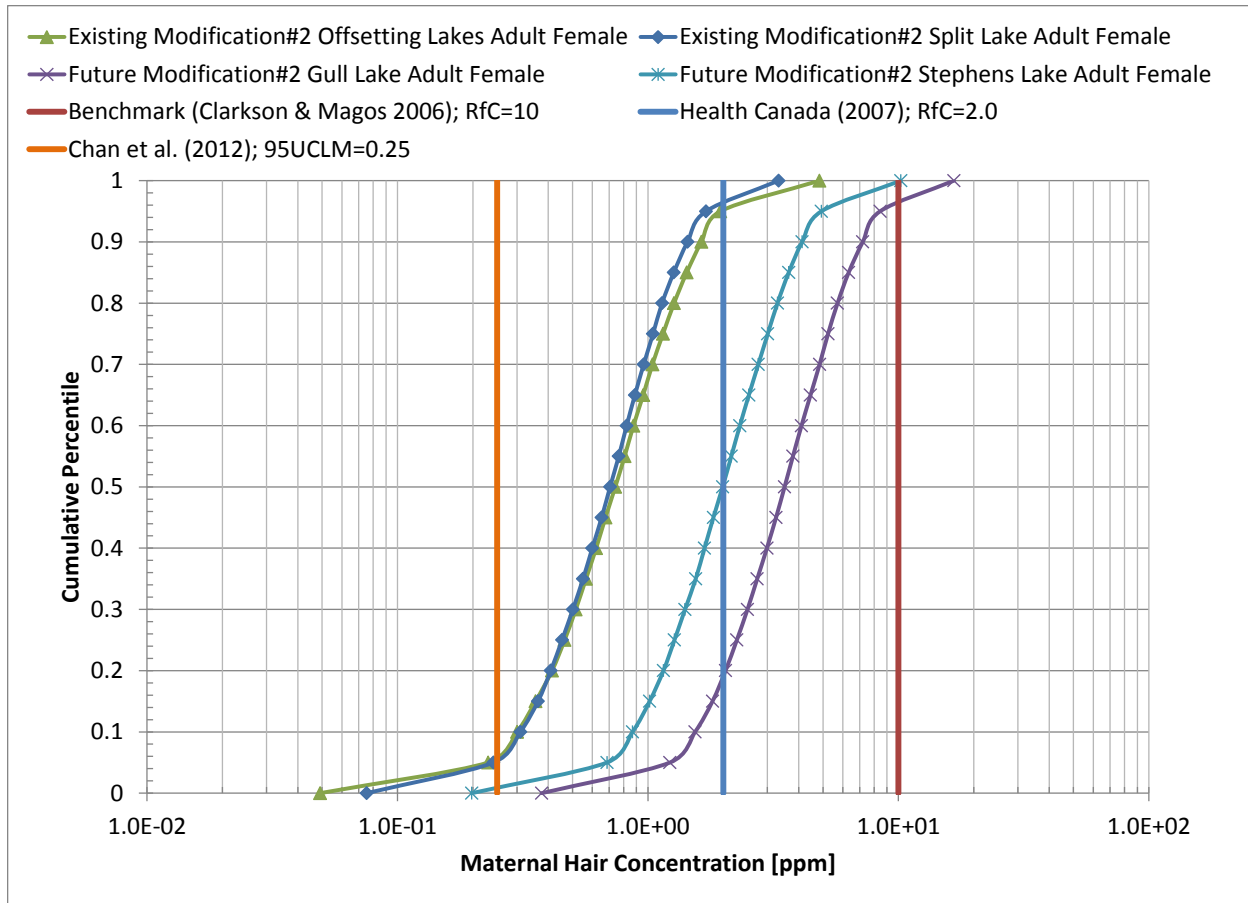
Figure 3-12   Predicted Existing Offsetting and Split Lakes, and Future Gull and Stephens Lake Maternal Hair Concentrations of Mercury Based on HHRA Modification #2 Assumptions (Health Canada Consumption Rates)
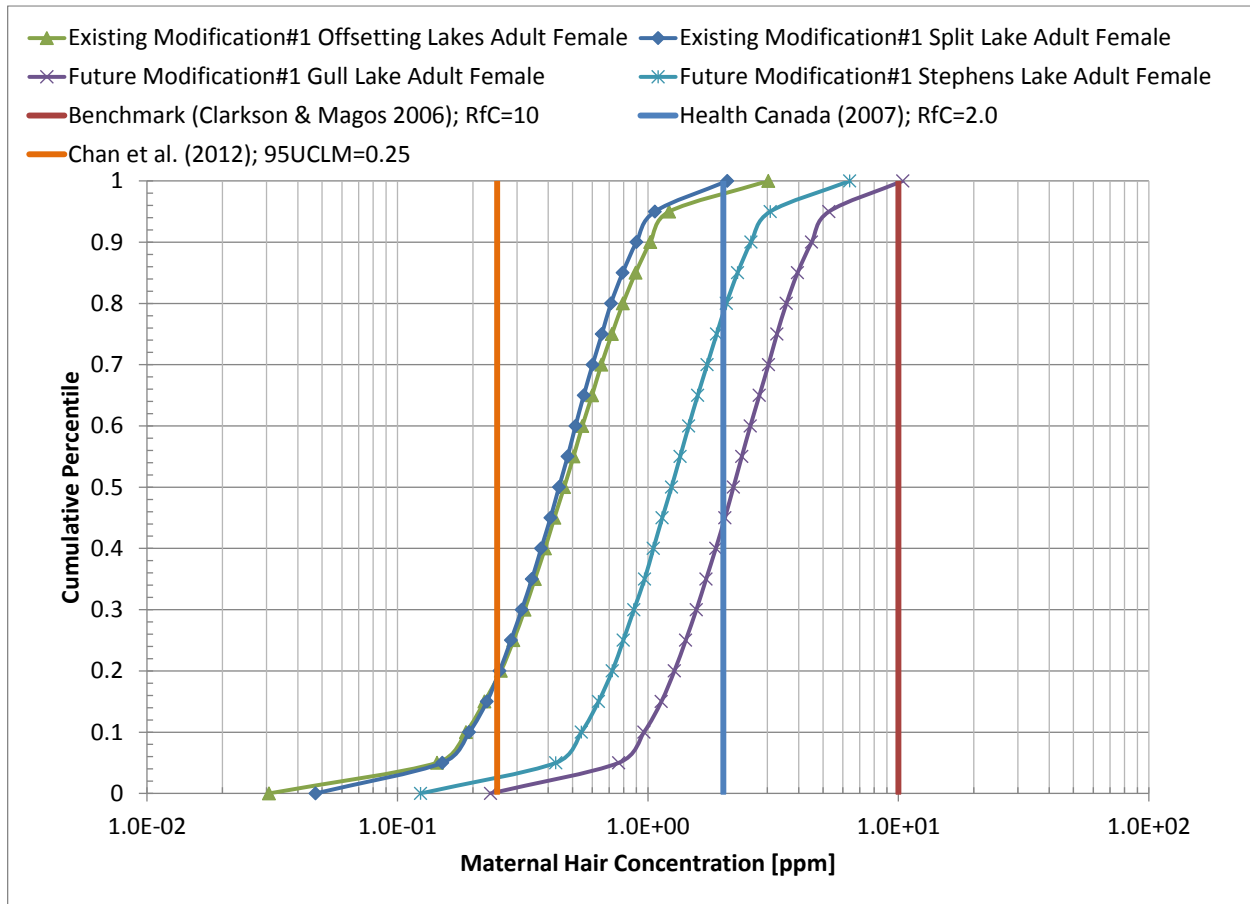
3.7   Modification of Type of Fish Consumed

Exposure and risks were predicted above based on assumed consumption rates of walleye, whitefish, pike and sturgeon of 51, 22, 16 and 11% of total fish diet, respectively, reflecting the consumption pattern of fish observed in FNFNES ecozone 3 native households (Chan et al. 2012). Alternatively, it was assumed that the entire fish diet consisted of only whitefish from Gull Lake. This species of fish was selected as it represents one of the most common fish species consumed that has the lowest mercury concentrations in the future or post-impoundment scenario. The Gull Lake post-impoundment scenario was selected as it represents the worst case mercury concentrations in fish. As shown in Figure 4-13, more than 90% of predicted hair concentrations were below the Health Canada benchmark value of 2 ppm, and all were below the 10 ppm benchmark. The prevalence of predicted hair concentrations below the benchmark value of 2 ppm suggests that adverse effects are not expected from future exposures to whitefish harvested from Gull Lake.

(Note: Based on the HHRA consumption rates, for whitefish only from Gull lake, approximately 90% of hair concentrations were predicted be above the Health Canada benchmark value of 2 ppm, and 5% were greater than the benchmark value of 10 ppm).

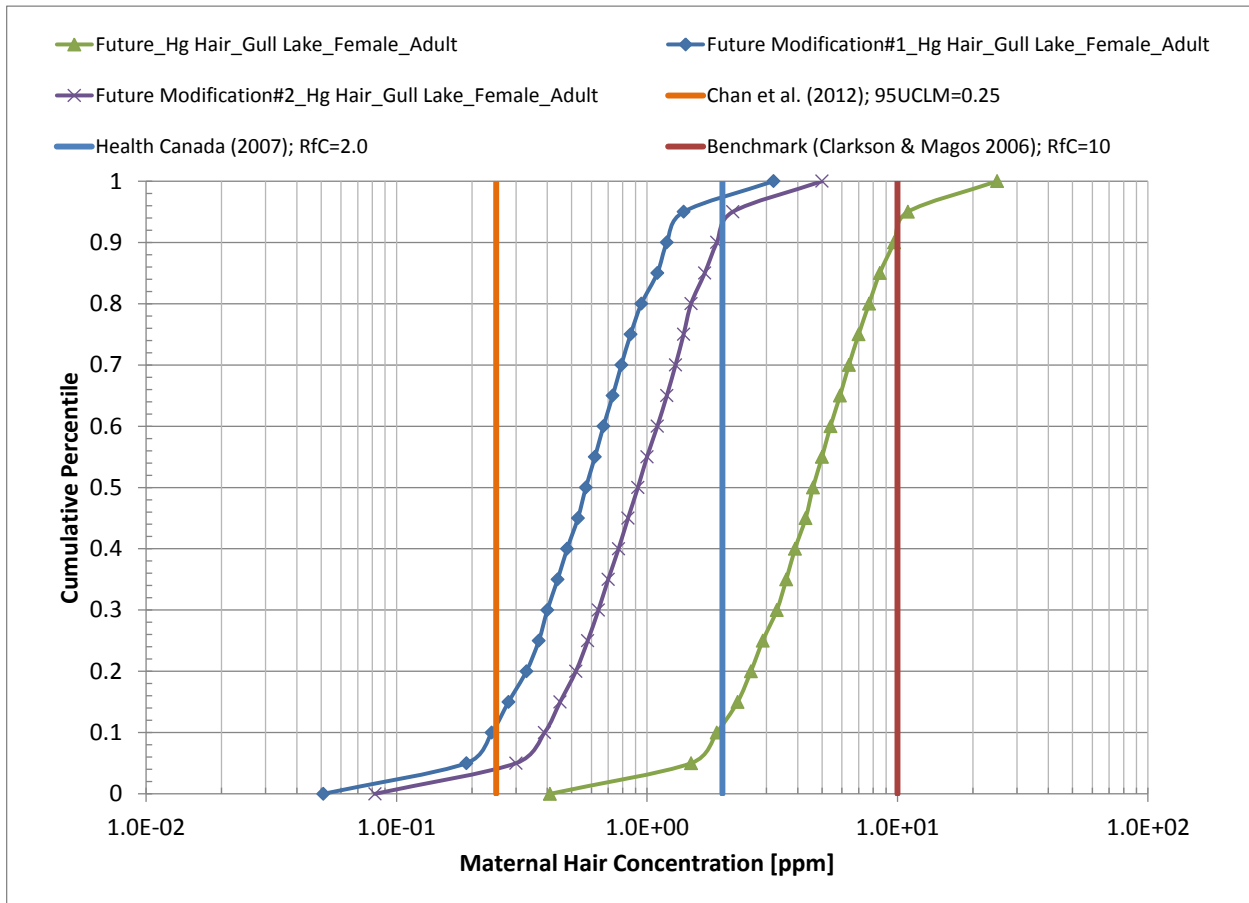**Figure 4-13   Predicted Future Gull Lake Maternal Hair Concentrations of Mercury Based on HHRA Assumption, Modification #1 Assumptions (FNFNES Consumption Rates) and Modification #2 Assumptions (Health Canada Consumption Rates)**

4.0   BENEFITS OF FISH CONSUMPTION

Fish are a rich source of protein, essential fatty acids, vitamins and minerals and an important food resource globally. They are a nutritionally and culturally important food to many Canadians, especially for Aboriginal groups or populations that subsist on fish (Legrand et al. 2010; Del Gobbo et al. 2010). Fish and seafood are unique in their nutritional benefits due to the low levels of saturated fats and the high levels of the beneficial omega 3 polyunsaturated fatty acids (PUFAs), namely eicosapentaenoic acid (EPA) and docosaheaenoic acid (DHA), which are absent in other foods (Wine et al. 2012).

The risk perception of a health problem inherent in eating a traditional diet must be considered in parallel with predicted risks to the population (Tian et al. 2011). Traditional foods consumed by First Nations people are rich sources of protein, essential fatty acids, vitamins and minerals are frequently replaced by energy dense and nutrient poor market food alternatives when health risks are perceived. Successful interventions to reduce dietary Hg exposures must be based on a comprehensive understanding of benefits and risks. A U.S. study with postnatal methyl mercury exposure (i.e., at background levels) had no detectable adverse effect on neuropsychological and behavioral development among children, and children with higher blood methyl mercury concentration had significantly higher IQ and learning scores (Wang et al. 2013). The observed benefits of fish consumption were attributed to the increase in consumption of polyunsaturated fatty acids in the fish. Mozaffarian and Rimm (2006) concluded that major health outcomes among adults, based on the strength of the evidence and the potential magnitudes of effect, the benefits of fish intake exceed the potential risks. For women of childbearing age, benefits of modest fish intake, excepting a few selected species, also outweigh risks.

Observational studies have consistently shown that mothers who consume more n-3 PUFAs during pregnancy have children with improved neurobehavioral development (Mahaffey et al. 2011; Strain et al. 2012). In a cohort of over 25,000 mothers and children in Denmark, the highest versus the lowest quintile of fish intake was associated with higher child developmental scores at 18 Months (Oken et al. 2008; Mahaffey et al. 2011). The Avon Longitudinal Study of Parents and Children (ALSPAC) examined fish consumption and neurocognitive outcomes in 11,875 mother-child pairs in the U.K. (Hibbeln et al. 2007). Children born to non-fish consumer mothers had a higher risk for low verbal and full scale IQ when compared with children born to mothers with a fish intake of more than 340 grams per week (Hibbeln et al. 2007; Deroma et al. 2013). Children of mothers who ate more than 340 grams (12 ounces) of low-mercury seafood per week had a lower risk of suboptimal scores on measures of verbal IQ, prosocial behavior, fine motor skills, and social development compared with women who ate less seafood (Hibbeln et al. 2007; Mahaffey et al. 2011).

Another U.K. study reported a reduced risk of hyperactivity and a higher verbal IQ in children whose mothers had eaten oily fish in late pregnancy compared with those whose mothers did not eat fish (Gale et al. 2008). Significant benefits of maternal fish consumption were demonstrated in cohorts of children in Boston and New York city with respect to neurocognitive outcomes (Oken et

al. 2005, 2008; Lederman et al. 2008) and this has also been found in European studies (Daniels et al. 2004; Deroma et al. 2013).

The recommended optimal amount of DHA from fish during pregnancy to benefit fetal development is 200 mg (Koletzko et al. 2008). Del Gobbo et al. (2010) note that DHA intake among women of childbearing years has decreased in Canada and is among the lowest worldwide, with some pregnant Canadian women shown to be DHA-deficient (Brenna et al. 2007; Innis et al. 2008). Less than half of pregnant women in the U.S. eat the 200 mg/day of DHA recommended for optimal maternal and child health (Oken et al. 2013). A recent randomized study to promote healthy fish consumption during pregnancy demonstrated that targeted fish consumption advice can increase the intake of DHA without increasing mercury (Oken et al. 2013). Depending on the fish selected, as little as two fish meals per week can meet DHA requirements (US EPA 2001). This is discussed further under risk management considerations below.

Importantly, fish consumption has also been shown to contribute to a reduced risk of cardiovascular disease in adults (FDA 2009; FAO/WHO 2011). A meta-analysis that included 5 randomized controlled trials and 15 prospective cohort studies of fish or fish oil intake and CHD death among > 300,00 subjects indicated a significant 17% decrease in total CHD mortality (Mozaffarian and Rimm 2006). Intakes of 250 mg per day of EPA/DHA were associated with a 36% reduction in risk. A recent prospective study in Finland observed that serum long-chain Omega-3 PUFA concentrations, an objective biomarker for fish intake, was associated with long term lower risk of type 2 diabetes (Virtanen et al. 2013).

Mozaffarian and Rimm (2006) attempted an evidence based comprehensive assessment of the risks and benefits of fish consumption. Based on strength of evidence and potential magnitudes of effect, they concluded that the benefits of modest fish consumption (1 to 2 servings/week) outweigh the risks among adults and excepting a few select fish species, among women of childbearing age. They further concluded that avoidance of modest fish consumption due to confusion regarding risks and benefits could result in thousands of excess CHD deaths annually and suboptimal neurodevelopment in children (Mozaffarian and Rimm 2006). Approximately 250 mg/day of EPA and DHA is a reasonable target intake to reduce cardiovascular mortality and since n-3 PUFAs persist for weeks in tissue membranes this can be converted to a weekly intake of 1,500 to 2,000 mg.

An interesting recent study attempted to quantify the risk trade-offs in fish consumption from a public health perspective (Rheinberger and Hammit 2012). They used NHANES consumption data to simulate exposure to contaminants and nutrients in fish, employed dose-response relationships to convert exposure to health endpoints, and monetize them using benefit transfer. Results suggested that newborns would gain an average of 0.033 IQ points from their mother's compliance with the FDA/EPA advisory to keep exposure below the RfD, with an estimated welfare gain at $386 million. They found, however, that this gain could be fully offset by increments in cardiovascular risk if 0.6% of consumers aged 40 and older reduced fish intake by one monthly meal until they reached the age of 60 or if 0.1% of them permanently reduced fish intake (Rheinberger and Hammit 2012). This illustrates the importance of targeted fish consumption

advice to ensure that non-target consumers (i.e., males or older women) do not reduce their fish consumption unnecessarily.

The FAO and WHO convened a Joint Expert Consultation on the Risks and Benefits of Fish Consumption in 2010. The consultation concluded that among women of childbearing age, pregnant women and nursing mothers, considering the benefits of docosahexaenoic acid (DHA) versus the risks of methyl mercury, fish consumption lowers the risk of suboptimal neurodevelopment in their offspring compared with not eating fish in most circumstances evaluated (FAO/WHO 2011).

Finally, it is important to consider that traditional foods such as fish, which are rich sources of protein, essential fatty acids, vitamins and minerals are frequently replaced by energy dense and nutrient poor market food alternatives as evidenced by reduced nutrient intakes on days without traditional foods in First Nations communities (Tian et al. 2011).

5.0   RISK MANAGEMENT CONSIDERATIONS FOR KEEYASK

The above review has presented evidence that: a) there is still uncertainty regarding what level of mercury contamination in fish presents health risks, b) Health Canada guidance values for daily intake of MeHg and acceptable Hg hair levels can be considered to be protective of adverse health effects, and c) including fish in the diet offers considerable health benefits, both for children and adults.

Government advice at present for balancing the risks and benefits of fish consumption is to choose fish that are higher in Omega 3 fatty acids and lower in mercury (Health Canada 2007; FDA 2004; Manitoba Government 2013). Mahaffey et al. (2011) note that many countries have used this approach by analyzing n-3 PUFA and MeHg levels in local fish to help public health professionals make appropriate recommendations. This section attempts to do that for the proposed Keeyask project by presenting literature values of n-3 PUFA content in the most commonly consumed fish (i.e., whitefish, walleye, northern pike and sturgeon). This information is considered together with existing and predicted future Hg concentration data for these species in Gull Lake and Stephens Lake to get a better picture of the local situation. Existing and predicted Hg concentrations are also compared to mean concentrations of Hg measured in commercial retail fish in Canada and in other Canadian freshwater lakes.

The other important factor in determining health risks is consideration of consumption rates. As described earlier, moderate fish consumption can meet the requirements of n-3 PUFAs that benefit fetal development and cardiovascular risk, as little as two meals per week depending on the fish species consumed. Since fish consumption rates may be relatively high in the KCN communities, as stated in the HHRA (see Table 3-5 in this document), measurement of baseline human hair mercury concentrations would be of benefit in establishing baseline health risks and predicting health risks into the future.

It is of note that a First Nations Food, Nutrition and Environment Study (FNFNES) is being implemented region by region across Canada over a 10-year period. As part of this effort, data collection was conducted in nine randomly selected on-reserve First Nations communities in Manitoba in the fall of 2010 (Chan et al. 2012). However, consumption rates of local fish were considerably lower in these communities relative to what was determined in the Keeyask area survey. Similar to the Keeyask survey, walleye were the most commonly consumed fish, with whitefish as the second most commonly consumed (Chan et al. 2012). Hair mercury levels were measured in the First Nations communities studied, with 0.33 µg/g reported as the overall arithmetic mean and 0.18 µg/g as the mean hair level among women of childbearing age (n=236). Health Canada's guideline for mercury in hair is 2 µg/g.

The PUFA content of fish commonly consumed in the lakes impacted by the Keeyask Hydroelectric project are shown in Table 5-1, below. It is evident that whitefish are an very good source of n-3 PUFAs, with estimated concentrations of DHA and EPA and DHA combined approaching that of Atlantic farmed salmon (Health Canada 2001; USDA 2005). Walleye, northern pike and sturgeon are much poorer sources of these nutrients, while trout contribute a moderate amount of DHA and EPA. Thus, a shift in consumption towards greater consumption of whitefish and lower consumption of walleye and pike would maximize health benefits associated with fish consumption. Based on the concentrations of DHA in whitefish, the recommended intake of 200 to 250 mg/day to optimize fetal development in pregnancy and lower cardiovascular risk can easily be met through moderate consumption of whitefish. Even one meal per week of 150 grams of whitefish would meet this requirement for DHA.

Table 5-1 **Estimated concentrations of DHA or EPA+DHA in fish species commonly consumed in the Keeyask area (mg/100 gram fish tissue) as well as salmon and trout for comparison[1]**

	Whitefish	Walleye	Northern Pike	Sturgeon	Atlantic Salmon (farmed)	Trout
DHA	1,206	288	95	119	1,457	936
EPA + DHA	1,200 to 1,612	300 to 398	100 to 137	200 to 368	1,700 to 2,147	677 to 750

Sources:
(1)   Canadian File of Nutrients (Health Canada 2001; Philibert et al. 2006) and U.S. Department of Agriculture (USDA 2005)

An interesting study examined the relationship between fish intake and serum fatty acid profiles in 243 moderate consumers of freshwater fish (Philibert et al. 2006). No relationship overall was observed between the quantity of locally caught fish consumed (grams/day) and serum n-3 PUFA concentrations in the blood, but fatty fish intake (including whitefish and trout as well as salmon) was significantly associated with serum EPA and DHA. The subjects with the highest fish intake and the highest estimated intake of n-3 fatty acids had the lowest serum fatty acid concentrations in their blood if they predominantly ate lean fish such as northern pike or walleye (Philibert et al. 2006).

In summary, based on existing concentrations of mercury measured in Gull Lake and Stephens Lake, and considering estimated n-3 PUFA content in various species, the benefits of fish

consumption can be enjoyed in the local Keeyask area while minimizing Hg exposure by favoring whitefish over other species and limiting walleye, pike and sturgeon consumption. As noted previously, smaller sized predatory fish are associated with lower risks than larger fish (walleye and northern pike).

Based on predicted future concentrations of mercury in Gull and Stephens Lake, whitefish and sturgeon should be preferred over northern pike and walleye, with the latter only being consumed occasionally by the general population and should be avoided by women of childbearing age and children.

6.0 CONCLUSIONS AND RECOMMENDATIONS

It was intended by the authors of this report that the detailed information contained within will be valuable to the Keeyask Partnership, Manitoba Health, Health Canada and the Manitoba Clean Environment Commission in ongoing deliberations about fish consumption advisories and communications to KCNs regarding the risks and importance of wild fish consumption. It was noted by the partnership that "many KCN members have indicated they had (already) either stopped, or decreased the eating of fish and traditional foods (due to concerns about mercury). It was also stated that "TCN (Tataskweyak Cree FN) formally expressed concern over high concentrations of Hg in Split and Clark lakes. Therefore has been a reduction in domestic fishing and consumption of country foods as people are afraid to eat fish …, resulting in an increase in store bought food. This concern was voiced by all KCN communities".

Our study has affirmed statements made in the Keeyask HHRA that highly conservative exposure assumptions may have substantially overestimated risks of fish consumption. In particular, assumed fish consumption rates, based on consumer information provided by local communities, are the major contributor to predicted health risks. Health risks predicted in the HHRA for existing conditions also exists in the "offsetting" lakes (e.g., Moose Nose and Recluse), indicating that risks may exist regardless of where the community harvests fish.

The data included in this report have shown that present average mercury concentrations in study area lakes are below the commercial guideline of 0.5 – 1.0 ppm, are similar to or lower to mercury concentrations measured in other (un-impacted) Canadian lakes, and are similar or lower to mercury concentrations measured store-bought fish.

While consumption recommendations were removed from the final HHRA, our review concludes that fish in Gull Lake and Stephens Lake can safely be consumed based on guidance provided by Health Canada (2007, 2010) and Manitoba government (2013).

Overall, it has been concluded that the benefits of modest fish consumption (1 to 2 servings per week) outweigh the risks among adults and excepting a few select fish species, among women of childbearing age.   This illustrates the importance of targeted fish consumption advice to ensure that non-target consumers (i.e., males or older women) do not reduce their fish consumption unnecessarily.

Prior to making recommendations on how post-impoundment risks will be managed among community members, the existing risks to the community should be more fully characterized to help ensure that the management of risk does impact the nutritional benefits of wild fish consumption.   In this regard, collection of data on distributions of actual fish consumption rates, and measured mercury in blood/hair of consumers of fish from impacted and offset lakes will be needed.

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Appendix A

Methyl Mercury Toxicity and Associated Uncertainties

This review of the toxicity of methyl mercury endeavours to more fully summarize and explain the government health-based exposure limits for MeHg, namely their basis and uncertainty factors. In addition, the results of recent epidemiological studies on MeHg in fish and neurodevelopmental or cardiovascular outcomes are discussed in greater detail. Finally, some ongoing uncertainties and potential modifying factors in the relationship between low-level mercury exposure and adverse health effects are presented.

Summary of MeHg exposure limits

Available government agency guidelines for exposure to MeHg are shown in Table 1. The toxicity reference values employed, uncertainty factors and study references are provided for comparison. In some cases, separate exposure limits were recommended for sensitive populations versus the general population.

The neurotoxicity of high dose MeHg was first widely documented as a result of exposure to contaminated fish in Minimata, Japan (1953-1960) and contaminated seed grain in Iraq (1971) (Harada, 1995; WHO, 1990). In Minimata, the prevalence of neurological/mental disorders was 59% among the exposed population and hair concentrations ranged from 50 to 700 µg/g (Harada, 1995; Hansen and Gilman, 2005). . In Iraq, toxicity was observed in exposed adults and children, but severe neurological effects (e.g. cerebral palsy) occurred in the offspring of exposed women at doses that did not affect the mother or caused only minor toxicity (WHO, 1990).

Based on a review of these studies, a Swedish Expert Group report in 1971 concluded that the lowest blood concentration associated with adverse clinical effects was approximately 200 µg/L (50 µg/g in hair) and they recommended a safety factor of 10 to derive "safe" levels in human populations (Legrand et al., 2010). This recommendation was the basis for the World Health Organization (WHO)'s Joint Expert Committee on Food Additives (JECFA) derivation of a

Tolerable Weekly Intake (TWI) for MeHg of 3.3 µg/kg bw/week (JECFA, 1972). Health Canada adopted this TWI and expressed it as a Provisional Tolerable Daily Intake (pTDI) of 0.47 µg MeHg/kg bw/day (Feeley and Lo, 1998).

In 1990, WHO recommended additional epidemiologic studies be conducted in children exposed *in utero* to more fully assess potential health risks associated with mercury exposure (WHO, 1990). Of particular note, two large prospective studies in the Seychelles Islands in the Indian Ocean and the Faroe Islands in the North Atlantic Ocean were initiated in the 1990s to examine low to moderate mercury exposure through fish consumption and associated neurodevelopmental effects in children (Health Canada, 2007; Legrand et al., 2010). These studies compared biomarkers of methylmercury exposure of the mother and fetus with neuropsychological and other endpoints of the children using very sensitive tests. In the Faroe Island cohort but not the Seychelles cohort, significant associations were observed on some neuropsychological tests indicating some adverse cognitive outcomes (e.g., outcomes related to verbal memory, motor or attention performance) (Grandjean et al., 1997; Davidson et al., 1998).

Both the Faroe Island and Seychelles populations consume a lot of seafood, but where the Seychellois consume ocean fish daily and little to no marine mammals, the Faroese consume fish

one to two times per week but also consume considerable amounts of marine mammals, particularly pilot whale meat (ATSDR, 1999). In the Faroe Island main cohort, the geometric mean umbilical cord blood level was 22.6 µg/L (IQR=13.2-40.8 µg/L) and the geometric mean maternal hair level was 4.22 mg/kg (IQR=2.55-7.68). In the Seychelles main cohort, cord blood levels were not measured but the mean maternal hair concentration was 6.8 mg/kg (range of 0.5-26.7). The first detailed examination of the Faroe Island cohort occurred at age 7 years (Grandjean et al., 1997), while children in the Seychelles cohort were first tested at the age of for developmental outcomes at 6, 19, and 29 months (Davidson et al. 1998) (subsequently at 5.5, 9, 10.5 and 17 and 19 years of age)

Following the publication of preliminary results from the Seychelles and Faroe Island cohort studies and considering the findings from a smaller New Zealand fish-eating cohort (Crump et al., 1998), the Food Directorate of Health Canada proposed a toxicological reference of 10 mg/kg mercury in maternal hair as the approximate threshold for neuropsychological effects in sensitive subgroups (i.e., offspring) (Feeley and Lo, 1998; Legrand et al., 2010). They used an international standard for hair to blood ratio of 250, a steady-state single compartment toxicokinetic model and a 5-fold uncertainty factor to account for inter-individual variability to derive a pTDI of 0.2 µg/kg/day for pregnant women, women of reproductive age and infants Feeley and Lo, 1998). This pTDI can also be expressed as a blood value of 8 µg/L and is used as a provisional interim blood guidance value for pregnant women or women of childbearing age (Legrand et al. 2010).   The Manitoba government employs this pTDI to determine fish consumption guidelines each year (Manitoba Government, 2013).

In 2003, JECFA also concluded that neurotoxicity effects associated with in utero exposure should be considered the most sensitive health outcome for MeHg exposure. They used a composite maternal hair mercury value of 14 mg/kg as the toxicological reference. The reference value of 14 mg/kg represents an average of the Benchmark Dose Limit (BMDL$_{05}$) of 12 mg/kg in hair derived from the Faroe Island cohort and a No-Observed-Effect-Level (NOEL) of 15 mg/kg in hair derived from the Seychelles cohort (JECFA, 2004).   A BMDL$_{05}$ represents the 95% lower confidence limit of maternal hair concentrations corresponding to a 5% increase in risk of abnormal response on neuropsychological tests. JECFA used a pharmacokinetic model to convert the hair level of 14 mg/kg to an ingested dose and applied an uncertainty factor of 6.4 to derive a pTWI of 1.6 µg/kg bw/week (equivalent to 0.23 µg/kg bw/ day) (JECFA, 2004). The uncertainty factor of 6.4 incorporated a data-derived factor of 2 for variation in hair to blood ratio, and a default factor of 3.2 for toxicokinetic variability in the relationship between blood mercury and steady state dietary intake (JECFA, 2004).

In 1995, the USEPA derived an oral Reference Dose (RfD) of 0.1 µg/kg bw/day for methyl mercury based on the poisoning episode in Iraq and the developmental toxicity that was observed (USEPA IRIS, 2001). The assessment was updated in 2001 based on an integrative quantitative analyses of data from the fish-eating island cohort studies, performed by the National Research Council (NRC, 2000). An RfD was derived based on the BMDL maternal cord blood concentrations corresponding to a 5% increase in risk of abnormal response on various neuropsychological endpoints (e.g. finger tapping test, Boston naming test, delayed recall test) in 7 year old offspring of fish-eating mothers

(USEPA IRIS, 2001).   The BMDL$_{05}$ was 58 µg/kg in cord blood, corresponding to 12 mg/kg in maternal hair.   The blood level was converted to an equivalent ingested dose using a pharmacokinetic model and a 10-fold uncertainty factor was applied to take into consideration pharmacokinetic and pharmacodynamics variability. The resulting RfD was 0.1 µg/kg bw/day (USEPA IRIS, 2001).

The Agency for Toxic Substances and Disease Registry (ATSDR) developed a minimum risk level (MRL) of 0.3 µg/kg-bw/day for methyl mercury based on the Seychelles Child Development Study (Davidson et al., 1998; ATSDR, 1999). A maternal hair NOEL (no-observed-effect-level) of 15 mg/kg was selected as the toxicological reference and a 4.5-fold uncertainty factor was applied to the equivalent daily dose (determined via a pharmacokinetic model).

The Seychelles Child Development Study (SCDS) followed over 700 infant-mother pairs, with testing from parturition through 66 months at the time (Davidson et al. 1998; follow-ups have since been reported). ATSDR (1999) selected this study as the basis for its MRL because: a) the Seychellois regularly consume a high quantity and variety of ocean fish, with 12 meals per week representing a typical methyl mercury exposure; b) the median total mercury in 350 fish sampled from 25 species consumed by the Seychellois was < 1 ppm, comparable to mercury concentrations in commercially available fish in the U.S., c) the Seychelles represent a relatively pristine environment, with no local industrial pollution sources and situated more than 1000 miles from any continent or large population centres, d) the large sample size and e) the use of standardized neurobehavioral tests. Children were exposed to MeHg *in utero*, via breastfeeding and subsequently through their diet, but none of the tests administered at 66 months indicated an adverse effect of MeHg exposure and in fact scores were better for four of the six tests in the highest MeHg-exposed groups (Davidson et al., 1998). This was attributed to the beneficial effects of omega-3 fatty acids in fish.

The Faroe Island cohort study of almost 900 mother-child pairs was also a well-conducted study and as detailed above, it did suggest adverse neuropsychological effects of prenatal mercury exposure (Grandjean et al. 1997). This study was not selected by ATSDR, primarily because the diet in the Faroe Islands is considerably different than the diet in the Seychellois and in the U.S. (ATSDR, 1999). The majority of mercury exposure in the Faroe Island cohort comes from episodic ingestion of whale meat with mercury concentrations of approximately 2-3 ppm (USEPA IRIS, 2001). The possibility of peak intake levels during critical developmental phases in the Faroese had not been evaluated (ATSDR, 1999).

Several follow-up studies of the Seychelles and Faroe Island cohorts have since been published and they continue to report very different findings. Studies of the Seychelles Child Development Study (SCDS) main cohort enrolled in 1989-1990 have not provided evidence of adverse effects of prenatal MeHg exposure on development in a cohort that consumes fish daily, with the most recent assessment of neurodevelopment conducted at 19 years of age (van Wijngaarden et al., 2013). Strengths of this study include levels of prenatal MeHg exposure at least ten times higher than those found in developed countries such as the U.S. and Canada, large sample size, longitudinal design with repeated testing at multiple ages, and the use of developmental tests that increase in

specificity as the children have aged and that have both clinical and environmental validity (Davidson et al., 2006; van Wijngaarden et al. 2013).

By contrast, new data from the Faroe Islands cohort at children's age 14 years indicated that an association observed at age seven years between cord blood MeHg and neurological auditory function was still present at 14 years (Murata et al., 2004; EFSA, 2012). Associations with decreased finger tapping speed, reaction time and cued naming tests were still present but weaker at age 14 years (Debes et al. 2006; EFSA, 2012). A reassessment of the data from the Faroese cohort at age seven years indicated that beneficial effects of fish consumption, together with imprecision in the measurements of fish intake and determination of mercury exposure might underestimate the effects of MeHg in this cohort (Budtz-Jorgensen et al., 2007, 2010; EFSA, 2012).

The study of a fish eating population in New Zealand suggested adverse effects of prenatal MeHg exposure on the mental development of children at the ages of 4 and 7 years (Crump et al., 1998). This study was incorporated into benchmark dose analyses conducted by the NRC (2000) that were used by USEPA IRIS (2001). However, reservations regarding this study have been noted because one child out of the 237 subjects had a maternal hair mercury concentration of 86 mg/kg which likely had a significant effect on the derivation of the BMDLs in this study (JECFA,2004; Legrand et al., 2010).

It is evident from Table 1, that there is some disagreement about what constitutes an "acceptable" level of exposure to MeHg. Different government agencies chose different dose-response models, different uncertainty factors and emphasized different data sets in some cases (Hansen and Gilman, 2005). Among studies that did report adverse effects, the threshold above which a measurable increase in adverse neuropsychological response was observed seems to be in the range of 10 to 14 ppm hair MeHg. Benchmark dose analyses that incorporated data from all three populations (Faroes, Seychelles and New Zealand) have supported the view that findings across studies are not meaningfully different, with a 5% increase in abnormal responses at an approximate hair mercury level of 12 mg/kg (NRC, 2000; van Wijngaarden et al. 2013).

The key difference between the USEPA and the JECFA evaluations is that the USEPA took a more conservative view in deciding that a factor for toxicodynamic variability should be incorporated into the uncertainty factor (USEPA IRIS, 2001; EFSA, 2012). By contrast, WHO/JECFA considered that a factor for toxicodynamic variability was not needed because the data were derived from sensitive subgroups representing diverse populations (JECFA, 2004). They employed an uncertainty factor of 6.4-fold to derive the MeHg exposure limit versus the USEPA uncertainty factor of 10-fold (Table 1). Health Canada employed an uncertainty factor similar to WHO/JECFA (5-fold; Table 1).

It is important to note that the health endpoints on which MeHg exposure limits were based were not symptomatic neurodevelopmental toxicity, but subclinical effects detectable only with specialized testing and in some studies prenatal mercury exposure was associated with improved scores on neurocognitive tests (Mozaffarian and Rimm, 2006; Davidson et al., 1998).

The U.S. EPA indicated in their assessment that a threshold for MeHg-related neurotoxicity was not evident within the range of exposures in the Faroe Islands study" (interquartile range of cord blood levels was 13.2-40.8 μg/L and the interquartile range of maternal hair levels was 2.55-7.68 mg/kg) (U.S. EPA IRIS, 2001). However, the RfD they derived focuses on a single exposure level and does not identify the risk associated with that level (Axelrad et al. 2007). Axelrad (2007) concluded that a dose–response model was needed to estimate the potential risk of neurodevelopmental effects in the population and the benefits of any efforts to reduce mercury exposure. They conducted a quantitative analysis of the three major prospective studies (Faroes, Seychelles and New Zealand), which suggested that prenatal exposure sufficient to increase hair MeHg by 1 μg/g was associated with an IQ loss of 0.18 points (Axelrad et al. 2007). Another analysis using different assumptions estimated that a 1 μg/g increase in hair MeHg is associated with an IQ loss of 0. 47 points (Pichery et al. 2012). Axelrad et al. (2007) noted that IQ is a useful end point for estimating neurodevelopmental effects, but may not fully represent cognitive deficits associated with mercury exposure; for example, it does not represent deficits related to attention and motor skills.

Recent Epidemiological Studies of MeHg

Neurodevelopmental Endpoints – moderate/high exposure

Faroe Islands/Seychelles

The European Food Safety Authority (EFSA, 2012) recently summarized the updates to the Faroe Island and Seychelles studies and concluded the following:

- 14 years of follow-up and reanalysis of data from the Faroe Islands continue to indicate a detrimental effect of prenatal MeHg exposure in this population, but the associations were weaker at 14 years of age *vs.* those documented at 7 years of age (i.e., smaller impact) (Murata et al. 2004; Debes et al. 2006; Budtz-Jorgensen et al. 2010). Results from a smaller Faroe Island cohort (n=182 children) tested for neurodevelopmental effects at age 7 years did not confirm most of the associations between mercury and neurodevelopment observed in the main cohort, with the exception of effect estimates for the Boston Naming test (an indication of cognitive effects on verbal memory) (Budtz-Jorgensen et al. 2010)
- Adjustment for the beneficial effects related to maternal fish consumption in the statistical analyses of the Faroese Cohort 1 indicated that the effects of prenatal methylmercury exposure may have previously been underestimated (Budtz-Jorgensen et al. 2007; EFSA, 2012). Assessment of the Faroese Cohorts 1 and 2 together did not identify major confounding from PCB exposure (Budtz-Jorgensen et al. 2010).
- In the Seychelles, reassessments of the early results at age 10.5 and 17 years have not revealed any significant association between prenatal mercury exposure and neurodevelopmental endpoints (Davidson et al. 2010, 2011). Several neuropsychological tests were administered in addition to measures of scholastic achievement, problematic behaviors and IQ.
- The results of a new nutrition cohort in the Seychelles suggested an effect of methylmercury at age 9 and 30 months on psychomotor development scores, only after adjustment for the beneficial effects related to n-3 LCPUFA from fish (Strain et al. 2008, 2012). The beneficial

effects of DHA from fish consumption were absent or reduced at maternal hair levels greater than 11 mg/kg (EFSA concluded this level to be a NOEL) (Lynch et al. 2011). A follow-up study at age 5 years, showed no associations with prenatal MeHg, even after adjustment for the benefits of fish consumption. (Strain et al. 2012).

Since the EFSA (2012) review, a further follow-up study of the Seychelles main cohort at 19 years of age was published (van Wijngaarden et al., 2013). This latest follow-up provided no evidence of an adverse association between prenatal MeHg exposure from fish consumption and neurobehavioral development.

Canadian Arctic Studies

Some studies in Arctic Canada have also evaluated relatively high prenatal MeHg exposure in relation to neurodevelopment endpoints (Despres et al. 2005; Saint Amour et al. 2006; Boucher et al. 2010, 2013; Plusquellec et al. 2010). These studies are of particular interest since mean cord blood levels of mercury in the Inuit cohorts studied were very similar to the mean cord blood levels reported in the Faro Islands (22-24 µg/L (Despres et al. 2005; Plusquellec et al. 2010). An important strength of these studies was an ability to control for confounding by other contaminants present in seafood, specifically lead and PCBs.

Despres et al. (2005) studied Inuit children born in Nunavik (n=109) and observed a statistically significant association between cord blood mercury and a measure of tremor in pointing movements at age 5 years, but no associations were found with other functions or reaction time. A follow-up study of these children found no associations between cord blood mercury and behavioral outcomes from the BSID-II or observational data related to attention or level of activity after adjustment for confounders (Plusquellec et al. 2010). Mean total mercury in cord blood for these children was 22-24 µg/L (range of 1.8-104). Visual-evoked potentials were studied in a subset of 78 children from this cohort and increased latency of the P100 component at 30% contrast was statistically significantly associated with cord blood mercury, but other measures were not (Saint Amour et al. 2006). Unexpectedly, decreased latencies were associated with current child mercury for N75 and P100.

In a separate cohort of 116 Inuit children, auditory electrophysiological testing in 116 Inuit children at the age of 11 years revealed associations between cord blood mercury and slower reaction times and greater amplitude and delayed latency of the N1 wave in linear regression analyses (Boucher et al., 2010). The authors suggested this indicates that relatively high prenatal exposure to mercury has effects on early processing of sensory information (Boucher et al. 2010), but the exact cognitive implications of slightly delayed electrical signals in the brain are unclear at this point in time (Grandjean, 2010). In a further study of this cohort, a model adjusting for the effects of other contaminants indicated no associations with mercury, but prenatal mercury exposure was found to interact with prenatal lead exposure on certain electrophysiological tests (Boucher et al. 2012).

A larger cohort of Inuit children including the 116 children studied by Boucher et al. (2010) were recently studied in relation to prenatal contaminant exposure and ADHD (n=279) (Boucher et al. 2013). Compared with children in the lowest tertile of cord blood Hg concentrations, children in

the second and third tertiles were significantly more likely to be classified as having ADHD – Inattentive type and these children had a substantially increased risk of teacher-reported symptoms consistent with ADHD. Specifically, children with higher cord Hg concentrations were approximately 4 times more likely to be identified as exhibiting behaviors that characterize the inattentive type of ADHD (Boucher et al. 2013). Associations with ADHD-type behaviors were observed at cord blood Hg concentrations greater than 11.4 µg/L (equivalent hair concentration approximately 2.8 ppm).

The authors note that their results are consistent with findings from neuropsychological assessments of children in the Faroe Islands (Debes et al. 2006) and earlier findings from electrophysiological testing of a subsample of the Inuit cohort (Boucher et al., 2010). This suggests that earlier reported subtle effects from neuropsychological or electrophysiological tests may be clinically significant and interfere with learning and performance in the classroom. Of note is that a recent reanalysis of the Faroe Island data suggested a specific effect on sustained attention (Julvez et al. 2010), a neuropsychological domain particularly affected in ADHD-Inattentive type (Boucher et al. 2013).

Boucher et al. (2013) suggested that the consistency of their findings with the Faroese but not the Seychelles studies points to different exposure sources - namely marine mammal meat in the Inuit and Faroese (e.g. whale), which is not eaten in the Seychelles. The Seychellois eat primarily ocean fish in which the benefits of the seafood nutrients likely counteract adverse effects from MeHg (Boucher et al. 2013).   They also note that marine mammals contain an extensive array of contaminants, which may contribute to or accentuate MeHg effects. Current blood lead levels were associated with ADHD symptoms in Inuit children (Boucher et al. 2013).

South America

Chevrier et al. (2009) reported a reduction in scores on a task of visiospatial ability was observed in children aged 7-12 years with a hair mercury concentration above 10 mg/kg compared to those with a hair level below 1 mg/kg and the associations appeared to be stronger in the younger children (n=395). The impacts of prenatal versus postnatal exposure could not be distinguished in this study (Chevrier et al., 2009; EFSA, 2012).

Neurodevelopmental Endpoints – Low Exposure

In their review of recent studies on MeHg and neurodevelopment, EFSA (2012) reported that a few, but not all, studies from the U.S. or Europe found associations between prenatal mercury exposure and cognitive outcomes at lower mercury levels than those reported in the Faroe Islands and Seychelles cohorts (Daniels et al. 2004, Jedychowski al. 2006, 2007; Oken et al. 2005, 2008; Stewart et al. 2006; Lederman et al. 2008; Sagiv et al. 2012).   They concluded that the overall picture at low-level exposure does not provide information to allow conclusions.

It is of note that several studies published since the EFSA (2012) review have largely reported negative results for an association between prenatal MeHg and neurodevelopment. A prospective cohort study in Italy measured maternal hair and blood during pregnancy and in umbilical cord blood and breast milk in 606 women (Valent et al. 2013). No associations between prenatal Hg

exposure and neurodevelopment were observed in their children at 18 months (assessed via Bayley Scales) but neurodevelopment was positively associated with child intake of fresh fish and maternal IQ. The mean Hg level in maternal hair was 1.06 mg/kg.

Similarly, a large study from four areas in Spain (n=1683) (geometric mean cord blood mercury of 8.4 µg/L) did not indicate significant associations between prenatal mercury exposure and delayed mental and psychomotor development during the second year of life (Llop et al., 2012, 2013). This was true even when controlling for the protective effect of fish intake. In multivariate analysis, a doubling in total mercury levels did not show any associations with neurodevelopment, but stratified findings by sex suggested a negative association with female infants only (not statistically significant) (Llop et al., 2012). The authors concluded that at present, there is insufficient evidence of the possible neurotoxic effects of prenatal mercury exposure, especially at early ages and more research is needed (Llop et al. 2012).

An earlier study in Spain reported an association between children's hair mercury levels and scores on the McCarthy Scales of Children's Abilities (MSCA) at age 4 years, after adjustment for fish intake (Freire et al. 2010) (n=72; mean concentration in hair was 0.96 mg/kg). By contrast, a larger study in Spain found no associations between child hair mercury and the MSCA in 4-year old children in Menorca, Spain with arithmetic mean hair concentrations of 1.4 mg/kg, including fish consumption in the model (n=302; Gari et al. 2013).

A recent study in Poland found no associations between prenatal exposure to Hg and psychomotor development (assessed via Bayley scales) at age 12 months (406 subjects) or 24 months (198 subjects) (mean hair Hg=0.21 mg/kg)(Polanska et al. 2013). Another Polish study reported an increased risk for delayed performance at age 12 months for cord blood mercury > 0.9 µg/L, but no associations were observed at 2 or 3 years of age (n=374)(Jedrychowski et al. 2006). A cord blood level of 0.9 µg/L is roughly equivalent to a hair concentration of 0.2 mg/kg in hair.

In another study in Italy, neuropsychological assessments at school age (age 7-9 years) did not indicate differences in maternal Hg levels in hair or breast milk when comparing children with low or extremely low or high or extremely high scores vs. others, considering separately full-scale, verbal and performance IQs (n=242; Deroma et al. 2013). Children born from mothers with hair mercury levels greater than or equal to 2 mg/kg had IQs which were 4-5 points lower than children born from women with lower mercury levels, but this result was not statistically significant. Fresh fish intake of mothers in pregnancy was positively correlated with full scale and performance IQs but not with verbal IQs (Deroma et al. 2013).

In the U.K., no effects on social or language skills were observed at age 15 and 18 months in a very large cohort of children prenatally exposed to low levels of MeHg (n=7421; mean cord tissue concentration= 0.01 µg/g) (Daniels et al, 2004). Maternal and infant fish intake was associated with improved neurodevelopmental scores in this study.

A recent study in Hong Kong examined neurocognitive outcomes in a cohort of children (mean age = 8.2 years) prenatally exposed to MeHg (Lam et al. 2012; 2013). Of 608 children, 81% had umbilical cord mercury concentrations of > 5.8 µg/L (equivalent to USEPA RfD). Mean maternal

cord blood levels were 10 µg/L and the median hair level was 1.7 mg/kg (Lam et al. 2013; Fok et al. 2007). Cord blood Hg concentrations were associated with three out of 23 neurocognitive subtest (a visual sequencing task and retention ability of verbal memory) in children born to mothers with cord blood levels greater than 5.8 µg/L versus those born to mothers with lower concentrations.

The authors initially concluded that their results were more consistent with the Seychelles data versus the Faroese data, due to the limited number of statistically significant associations observed (Lam et al. 2012). In a later publication, they concluded that their results were qualitatively consistent with the Faroese data and suggested that mild adverse neurocognitive outcomes are possible at lower levels than demonstrated in the Faroe Islands (cord blood concentrations in the range of 5.7 to 40 µg/L, equivalent to approximately 1.4 to 10 mg/kg in maternal hair) (Lam et al. 2013). The cutoff level for the more highly exposed group (5.7 µg/L in cord blood) cannot be considered a threshold because it is unknown how much the findings were weighted by those at the higher end of exposure.

In Hong Kong, mercury exposure occurs as a result of steady fish consumption, similar to the Seychelles cohort. Women assessed in the study consumed on average 2440 grams of seafood/month (including marine and freshwater fish and other seafood), equivalent to approximately 81 grams/day (Lam et al. 2013). Other important contributors to mercury in Hong Kong include the application of Hg-containing cosmetic creams and the intake of contaminated herbs used in traditional Chinese medicine (Fan et al. 2011). An earlier study of this population showed that the group with cord blood levels of Hg above 5. 7 µg/L were significantly different than those with lower Hg levels with respect to the number of dental amalgams and the use of traditional Chinese medicine. (Fok et al. 2007).

Finally, Hong Kong is a city known for it's poor air quality, unlike the Seychelles or Faroe Islands and potential confounding by concomitant exposure to other contaminants was not evaluated. Unlike most other studies, a beneficial neurocognitive benefit of maternal fish consumption was not observed by Lam et al. (2013), which raises the question of what types of fish were most commonly consumed. Fok et al. (2007) showed that freshwater fish consumption influenced cord blood less than marine fish consumption in this population).

The results of studies of low-level mercury exposure in North America have been largely mixed. In Ontario, Canada, no effects on behavioral performance were observed at birth, 6 months or 12 months in relation to maternal Hg hair levels in a population consuming Lake Ontario fish (Stewart et al. 2000; Darvill et al. 2000). , No direct effects on cognitive performance at age 38 or 54 months (assessed via the McCarthy Scales of Children's Abilities) were observed in a fish-eating cohort in Oswego, New York in relation to maternal hair mercury (median 0.5 mg/kg), but an interaction effect was found with cord blood PCB levels at age 38 months but not at 54 months (i.e., association with maternal Hg found only in children with higher cord blood PCB levels) (Stewart et al. 2003).

Studies by Oken et al. (2005, 2008) in Boston, Massachusetts showed that higher fish intake during pregnancy was associated with better child cognitive test performance, but mercury was associated with decreases in visual recognition memory at age 6 months (n=135; mean maternal hair Hg=0.55mg/kg; Oken et al., 2005) and adverse effects on visual-spatial and total visual motor

development at age 3 years (n=341; mean Hg in maternal erythrocytes of 2.8 ng/g) Oken et al. 2008). These associations strengthened with inclusion of both fish intake and mercury exposure in the model.

In New York, Lederman et al. (2008) found no associations between cord blood mercury and mental and psychomotor development at age 12 and 24 months, but they did find inverse associations at 36 month and 48 months with performance, verbal and full IQ scores (n=151; mean cord blood=5.58 µg/L). A Massachusetts cohort study indicated a protective association for fish consumption (>2 servings/week) with ADHD-related behaviors, but prenatal mercury exposure was associated with a greater risk of ADHD-related behaviors (Sagiv et al. 2012). The median maternal hair Hg level in this study was 0.45 mg/kg and there was an apparent threshold at 1 mg/kg or greater hair Hg.

An important limitation of this study is that breastfeeding was not examined as a confounding factor since a recent study found a clear link between rates of breastfeeding and likelihood of developing ADHD (Mimoumi Bloch et al. 2013). Children who were not breastfed were observed to have a 3-fold higher risk of ADHD (Mimoumi Bloch et al. 2013). Sagiv et al. (2012) reported that mothers who consumed fish more than twice a week had children with 40% risk of ADHD relative to children of mothers who consumed fish two or less times per week, while maternal hair Hg levels of 1 mg/kg or greater were associated with a 1.4 times increase in risk of ADHD compared to those with lower maternal hair Hg levels (Sagiv et al. 2012). Adjusting for mercury exposure enhanced the protective association of fish consumption with neuropsychological testing. Given the recent study findings on breastfeeding and ADHD, it may be significant that Sagiv et al. (2012) did not control for mode of infant feeding as a confounding factor. It is possible that those with less knowledge to choose fish species higher in mercury but lower in omega 3 fatty acids are also less likely to breastfeed. Maternal IQ is strongly associated with the choice to breastfeed (Der et al. 2006).

No significant associations between child blood levels of MeHg and IQ or neurobehavioral performance were observed in a cohort of children from several U.S. states tested at age 2,5 and 7 years (Cao et al. 2009). The most recent assessment of these children reported that a 1 µg/L increase in MeHg in blood was associated with a 2.1 point increase in Full-Scale IQ, which the authors concluded reflects the beneficial polyunsaturated fatty acids from seafood (Wang et al. 2013).

A summary of the findings from recent epidemiological studies of prenatal exposure to moderate or low levels of MeHg and neurocognitive outcomes are shown in Tables 2-2 and 2.-3 of the main report.

<u>Uncertainties and Modifying Factors in Neurodevelopmental Studies</u>

In moderately exposed populations that consume a considerable amount of seafood, adverse effects on neurodevelopment at hair levels below 10-12 mg/kg (or equivalent concentrations in blood) have been observed in the Faroe Islands or the Arctic, where much of the mercury exposure comes from marine mammals such as pilot whale. Of particular note is the association with ADHD-type

behaviors that was recently observed in Inuit children at cord blood Hg concentrations greater than 11.4 µg/L (equivalent hair concentration approximately 3 ppm). By contrast, a high fish eating population in the Seychelles has not observed any adverse effects on neurodevelopment in several studies at various ages. Median hair concentrations in the Seychelles were 6.5 mg/kg (Davidson et al. 1998).

Various reasons have been proposed for why results might differ in a predominantly fish-eating population versus those that consume marine mammals such as pilot whale. As mentioned earlier, exposure to episodic spikes in mercury might be more harmful than chronic exposure to lower concentrations (Boucher et al. 2013). Another explanation offered is that ocean and freshwater fish are rich in selenium, which offers protective effects against methylmercury toxicity (Ralston and Raymond, 2010). By contrast, marine mammals such as whales are low in selenium. A study of a high seafood consuming population in Norway demonstrated a significant relationship between iodine, selenium, arsenic and mercury in blood and urine, demonstrating the significance of both essential nutrients and toxic elements resulting from seafood consumption (Birisdottir et al. 2013).

The recent study in Hong Kong is interesting because it appears to indicate the potential for mild adverse effects on neurodevelopment in a high fish eating population at lower doses than that observed in the Faroe Islands (Lam et al. 2013). However, this population may have had other important contributors to mercury exposure and they did not evaluate other contaminant exposures as confounding variables (e.g., lead, PCBs). It also failed to demonstrate neurocognitive benefits of fish consumption raising the question of whether the types of fish commonly consumed may have influenced the findings.

The results of low dose mercury exposure studies on the whole are mixed, but it of note that several recent large studies have not observed significant associations between mercury exposure and neurodevelopment. In a review of the evidence for health effects of MeHg at low exposures, Karagas et al (2012) indicated that studies which did not report associations between prenatal MeHg exposure and cognitive outcomes in preschool children did not adjust for the beneficial effects of fish consumption and this may explain the negative findings. However, since that time two prospective studies in Italy and Spain failed to find associations between prenatal MeHg and neurodevelopmental scores, even after adjustment for fish intake (Llop et al. 2012; Valent et al. 2013).

Some but not all earlier studies reported neurodevelopmental effects of MeHg after the beneficial effects of fish intake were considered. Several studies reported *positive* associations between fish consumption and neurodevelopment, even without controlling for mercury exposure. An FDA review in 2009 concluded that the independent negative associations observed between mercury and neurodevelopment in some studies were smaller than independent positive associations observed with maternal fish intake (FDA, 2009).

In the Seychelles, a nutrition cohort was established specifically to evaluate whether nutrients influence the association between prenatal MeHg and developmental outcomes (Strain et al. 2008, 2012; Lynch et al. 2011). In this cohort it was reported that the beneficial effects of DHA from fish consumption were absent or reduced at maternal hair levels greater than 11 mg/kg (EFSA

concluded this level to be a NOEL) (Lynch et al. 2011). However, a follow-up study at age 5 years, demonstrated no associations with prenatal MeHg exposure at any level, even after adjustment for the benefits of fish consumption. (Strain et al. 2012). The benefits of fish consumption are discussed in greater detail below.

Other possibilities to explain discrepancies among studies include genetic variability, biomarkers of exposure, presence of concomitant exposures potentially affecting neurodevelopment, cognitive endpoints measured and statistical analysis methods employed (van Wijngaarden et al. 2013). It is also possible that other sources of mercury contribute to mercury exposure levels besides seafood. A recent large study in the U.K. (n=4484) reported that seafood explained a relatively small proportion of the variation in total blood mercury (Golding et al. 2013). The estimated intakes of the three seafood items evaluated in the study (white fish, oily fish, and shellfish) accounted for only 8.75% of the estimated variation in log-transformed blood mercury concentrations. Other dietary components positively associated with blood mercury included wine and herbal teas. The authors concluded that limiting seafood intake during pregnancy may have a limited impact on prenatal blood mercury levels (Golding et al. 2013). In a recent Canadian study, fish and shellfish consumption significantly influenced blood Hg levels, but so did alcohol consumption and the presence of dental amalgams (Lye et al. 2013).

Breastfeeding is also a source of mercury exposure in children and some but not all studies included mode of feeding or duration of feeding as a potential confounding variable. This may be of particular importance since breastfeeding can influence both exposure variables and outcome variables (Marques et al. 2013). A recent large study found a causal relationship between breastfeeding duration and receptive language and verbal and nonverbal intelligence at ages 3 and 7 years (Belfort et al. 2013). Another study reported that both maternal fish intake during pregnancy and duration of breastfeeding were independently associated with better early child development (Oken et al. 2008).

Finally, there is some evidence that differences in populations such as ethnic variability and genetic variation can influence MeHg toxicokinetics and toxicity (Canuel et al. 2006; Schlawicke et al. 2008; Barcelos et al. 2013; Ng et al. 2013) and this subject should be considered in future studies (van Wijngaarden et al. 2013).

In summary, the evidence for adverse neurodevelopmental effects of maternal mercury exposure below 10-12 ppm in hair is at present inconclusive, with the possible exception of populations consuming marine mammals such as pilot whale. The preponderance of evidence indicates that hair mercury levels at Health Canada's safe level of exposure (2 ppm) or less are not associated with adverse effects on sensitive populations.

In their recent review, EFSA (2012) concluded that the Faroe Island and Seychelles cohort data remain the best data from which to derive health-based guidance values. They recommended a point of departure that was an average between the $BMDL_{05}$ of 14 mg/kg maternal hair from the Faroese data and a new apparent NOEL in the Seychelles cohort of 11 mg/kg maternal hair (based on findings at age 9 and 30 months after the results were adjusted for beneficial fatty acids from

fish intake) (Strain et al. 2008; EFSA, 2012). Previously a NOEL of 15 mg/kg maternal hair from the Seychelles studies was assumed (JECFA, 2004).

Other Health Endpoints

Fetal and Infant Growth

In their review of the evidence for health effects of low-level MeHg exposure, Karagas et al (2012) concluded that the evidence for MeHg effects on fetal growth is mixed - a couple of studies did report a significant association between birth weight and infant hair Hg (Sikorski et al. 1986) or cord blood Hg (Ramon et al. 2009), but most studies did not find significant associations between measures of prenatal Hg exposure and birth weight (Drouillet-Pinard et al. 2010; Lederman et al. 2008; Gundacker et al. 2010; Lucas et al. 2004 and Daniels et al. 2004). An interesting study recently found evidence that a genetic GST polymorphism may modify the relationship between prenatal exposure to Hg and birth weight (Lee et al. 2010). They reported that total Hg level in maternal blood during late pregnancy or in cord blood was associated more significantly with a decreased birth weight in women with the GSTM1 and GSTT1 null genotype than in those with an intact genotype or only one of the null genotypes. This genotype is believed to be associated with an impaired ability for detoxification (Lee et al. 2010).

A South Korean study recently reported an association between late-pregnancy maternal blood Hg and impaired infant growth within the first 2 years of life (Kim et al. 2011). However, the study population was unusual in that 30% of the mothers received amalgam restorations during pregnancy. The restorations were not found to correlate with maternal or cord blood Hg concentrations, but the study did not determine the influence of total amalgam surfaces on blood mercury concentrations (Kim et al. 2011). A recent Canadian study indicated that amalgams do contribute significantly to blood Hg concentrations (Lye et al. 2013). A surprising finding from a recent study in the U.K. was that maternal diet accounted for only 19.8% of the variation in total blood mercury in a large population of pregnant women (n=4484) (Golding et al. 2013).

Cardiovascular Outcomes

Another area of Hg toxicity that has received considerable focus are potential associations with cardiovascular disease. When JECFA evaluated methylmercury in 2006, they considered cardiovascular outcomes in adults in addition to neurodevelopmental endpoints in children (FAO/WHO, 2007). Five epidemiological studies of mercury concentrations in adults in relation to cardiovascular disease were considered and they noted that two of these (Guallar et al., 2002; Virtanen et al., 2005) found an increased risk of acute coronary event or myocardial infarction with higher mercury concentrations. One study (Hallgren et al., 2001) found a decreased risk of myocardial infarction with higher concentrations of mercury (considered by the authors as a biomarker for fish consumption); and the other two studies (Ahlqwist et al., 1999; Yoshizawa et al., 2002) did not show a statistically significant association between myocardial infarction and mercury concentrations.

In its' review of more recent epidemiological studies on low level MeHg exposure and cardiovascular disease, EFSA (2012) concluded the following:

Some studies indicate an association between MeHg and increased risk for acute myocardial infarction and acute cardiac death, while other studies do not show increased cardiac disease risk. The studies that showed association had used biochemical measurements as basis for adjustment for n-3 LCPUFA, while the ones that found no association had based adjustments on dietary questionnaire data. Some additional studies have dealt with lower exposure levels and provided no associations. Studies on stroke in relation to mercury exposure do not suggest an association. The importance of taking the beneficial effects of fish consumption into account when studying cardiovascular outcomes of MeHg has become evident.

Mercury exposure was not associated with risk of cardiovascular disease in two large U.S. cohorts (Mozaffarian et al. 2011), nor was it associated with adverse cardiovascular effects in a study in Sweden (Wennberg et al. 2011).

In Finnish men, an association between mercury in hair and risk of myocardial infarction (MI) (Virtanen et al. 2005) or sudden death (Virtanen et al. 2012) has been reported. In another study in Finland, mercury exposure was not associated with serum C-reactive protein (an inflammatory marker associated with risk of CVD), but serum n-3 PUFAS, a marker of fish consumption were inversely associated with serum CRP (Reinders et al., 2012).

A recent pooled analysis of the Finnish and Swedish data indicated that methylmercury was associated with an increased risk of MI, while higher S-PUFA concentrations were associated with a decreased risk of MI (Wennberg et al. 2012). The authors reported that a significant net harm of hair-Hg was not seen before amounts reached > 2 ppm and with simultaneously low S-PUFA, which they note is an unusual combination. The majority of subjects in the interval that implied harmful effects were from Finland and it was suggested that a higher consumption of lean predatory fish (e.g., pike, perch) in Finland versus Sweden may explain the difference (Wennberg et al. 2012). This study highlighted the importance of studies considering both MeHg and benefits of PUFA in fish in their analyses.

A prospective population study of serum mercury concentrations and disease outcomes in women in Sweden recently reported a strong inverse association between CVD and baseline serum mercury, after controlling for several confounding factors (Bergdahl et al. 2013). Women with higher mercury concentrations in their blood had a reduced risk of fatal acute myocardial infarction at follow-up 32 years later. The authors suggested this finding was due to confounding either by fish consumption or good dental health (correlated with number of amalgam fillings in this population) (Bergdahl et al. 2013.

It is important to note that in the two studies observing higher CVD risk with higher mercury levels, the net effect of fish consumption was still beneficial – i.e., higher mercury exposure lessened the benefit associated with consumption of fish or n-3 PUFAS but did not increase overall risk (Mozaffarian and Rimm 2006; Guallar et al. 2002; Yoshizawa et al. 2002; Virtannen et al. 2005). Accordingly, the primary question may not be whether consumption of mercury in fish increases cardiovascular risk but whether fish consumption would decrease CVD risk even further if mercury were not present (Mozaffariana and Rimm 2006).

Recent findings from two large prospective cohorts in the U.S. do not support adverse effects of MeHg on the development of diabetes (Mozaffarian et al. 2013). Similarly in Finland, hair mercury was not associated with the risk of Type 2 Diabetes in men, while fish intake was associated with long-term lower risk of diabetes (Virtanen et al. 2013). Studies on blood pressure in relation to mercury exposure give an inconsistent picture and at present there is no firm basis for a dose-response relationship (EFSA, 2012).

In summary, the evidence for adverse health effects of MeHg exposure on cardiovascular outcomes is inconclusive, but the net benefits of fish consumption on cardiovascular risk are likely to be positive. Studies do not support an association between Hg exposure and diabetes or strokes.

Based on the evidence available at the time, Roman et al. (2010) recommended the development of a dose-response function relating Hg exposure with myocardial infarctions (MI) for use in regulatory benefits analyses. However, since that time three large prospective cohorts have not indicated a relationship between Hg and MI (Mozaffarian et al. 2011; Wennberg et al. 2011). It might also be relevant that that recent literature has suggested an association between persistent organic pollutants present in fish and cardiovascular risks (Goncharov et al., 2011; Lee et al., 2012) and none of the studies on cardiovascular outcomes and mercury exposure controlled for these pollutants (EFSA 2012).

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Appendix B

Exposure Modelling

A literature based pharmacokinetic model was used to convert the predicted mercury exposures from the HHRA into body burdens (i.e., hair levels) for comparison to measured values and aid in the interpretation of health risks. A pharmacokinetic model is a quantitative model that describes the process of chemical disposition (i.e., absorption, distribution, biotransformation and excretion) in the body. Therefore, the pharmacokinetic model (i.e., single compartment model by Stern (2005)) uses several physiologic and metabolic parameters to predict the relationship between blood concentration and dose to predict hair concentrations in females during pregnancy. Neurotoxicity resulting from *in utero* exposure to mercury should be considered to be the most sensitive health outcome (JECFA 2004). The values of these parameters vary among individuals within a population or race and the variability was modelled to predict the distribution of hair concentrations that are expected within the adult female portion of the First Nation community. Figure 1 presents a flowchart that describes how the pharmacokinetic model fits in the overall exposure model.

| Fish concentration | × | Total daily fish consumption weighted by frequency of use |

Estimated intake and exposure

Single compartment model

Predict hair concentrations

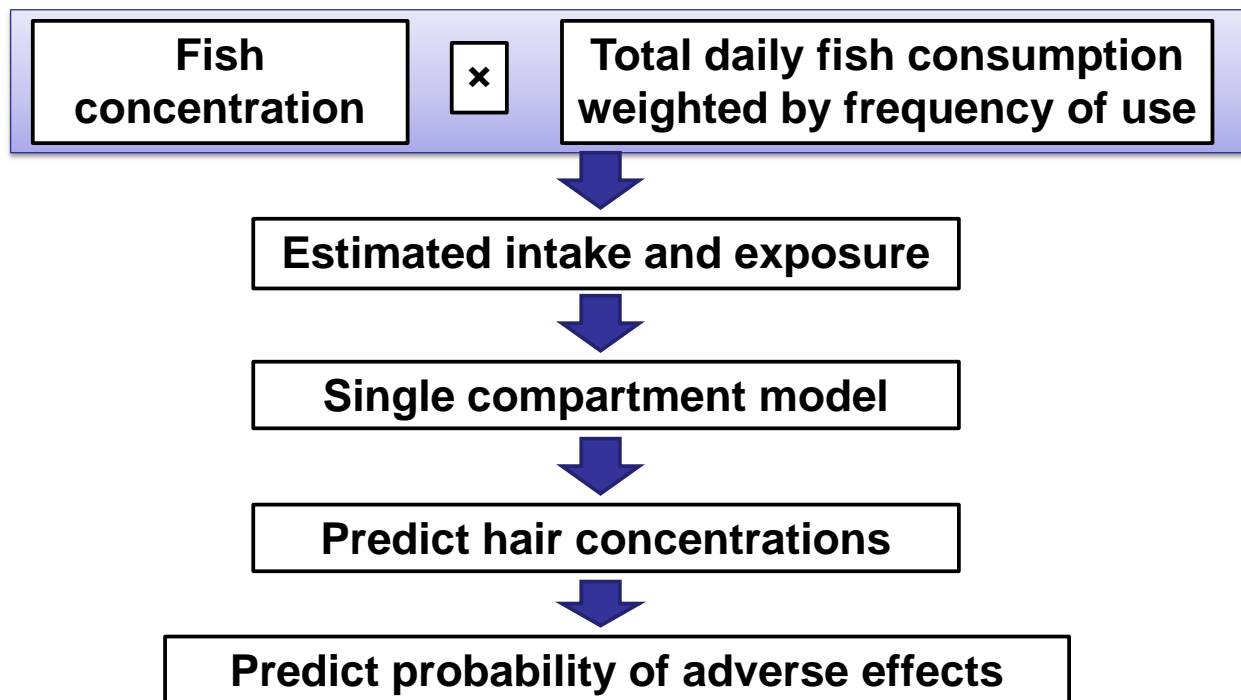Predict probability of adverse effects

Figure 1   Model Description

The assessment revised the method in which fish concentrations were used in the exposure model. Rather than calculate a hazard quotient for each species of fish (i.e., whitefish, walleye, pike and sturgeon), the assessment combined the fish concentrations into an overall fish concentration that was weighted by dietary preference or distribution. The annual distribution of fish consumption for Native households in Ecozone3 (i.e., Sagkeeng First Nation, Hollow Water First Nation, Cross Lake Band of Indians) was reported for 232 individuals and presented in Table (Chan et al. 2012).

Overall, walleye is the most abundant species of fish consumed, followed by whitefish and pike. Sturgeon was the least frequently consumed fish species. The percent distribution presented in Table 1 was used in the exposure model to calculate an overall weighted fish concentration that consists of all species of fish combined with the following equation:

$$C_f = \sum_{i=1}^{n} C_i \times PD_i$$

Where

C_f = Overall concentration in fish consumed (mg/kg-WW);

C_i = Concentration in fish species "i" (mg/kg-WW); and

PD_i = Percent distribution of fish species "i" in diet (%).

This method of estimating fish intake is more representative of actual practices as it permits a combination of fish species to be consumed which is more reflective of long-term feeding practices.

Table 1   Annual Distribution of Fish Dietary Preferences for Households in Ecozone Three[3]

Fish	Percent of Individuals[1]	Number of Individuals[2]	Percent Distribution[3]
Whitefish	32%	74	22%
Pike	23%	53	16%
Walleye	76%	176	51%
Sturgeon	17%	39	11%
Total	N=232 individuals in survey	343	100%

Notes:
(1) Percent of individuals who consumed species of fish in survey (Chan et al. 2012).
(2) Calculated number of individuals who consumed fish species. Based on [Percent of Individuals] x [232].
(3) Calculated percent distribution of fish species in diet. Based on [Number of Individuals] / [Total=343].

As in the HHRA, exposure was predicted based on the following equation:

$$E = \frac{C_f \times IR}{BW}$$

Where

E = Exposure (µg/kg/day);

Cf = Concentration in fish (mg/kg-WW or µg/g-WW);

IR = Ingestion rate (grams/day); and

BW = Body weight (kg).

The single compartment model can be expressed as follows (Adapted from Stern 2005 and Legrand et al. 2010):

$$D = \frac{C_{cb} \times \left(\frac{1}{R}\right) \times b \times V}{W \times A \times F}$$

Where

D   =   Maternal dose (µg/kg/day);

C_{cb} =   Mercury concentration in cord blood (µg/L);

R   =   ratio of cord blood Hg concentration/maternal blood Hg concentration (unitless);

b   =   Rate constant for elimination of methyl mercury from blood (day^{-1});

V   =   Maternal blood volume (L);

W   =   Maternal body weight (kg);

A   =   Fraction of ingested dose that is absorbed (unitless); and

F   =   fraction of the absorbed dose that is present in the blood at steady state (unitless).

Similar methods are used by the US EPA and Health Canada to estimate the exposure limit based on a cord blood concentration of 58 µg/L except the ratio of cord blood Hg concentration to maternal blood Hg concentration is assumed to be one. The equation can be re-arranged to yield the maternal blood mercury concentration based on the following equation:

$$C_{mb} = C_{cb} \times \left(\frac{1}{R}\right)$$

Where

Cmb   =   Mercury concentration in maternal blood (µg/L);

Ccb   =   Mercury concentration in cord blood (µg/L); and

R   =   Ratio of cord blood Hg concentration/maternal blood Hg concentration (unitless).

Followed by re-arranging the terms to yield the maternal blood mercury concentration by:

$$C_{mb} = \frac{D \times W \times A \times F}{b \times V}$$

Finally, the maternal blood mercury concentration is converted to maternal hair concentrations based on the following equation (Clarkson and Magos 2006; Diez 2009):

$$H = C_{mb} \times CV \times R_{hb}$$

Where

H   =   Hair concentration (ppm or µg/g or mg/kg);

Cmb   =   Mercury concentration in maternal blood (μg/L);

CV   =   Conversion factor 0.001 (mg/mg); and

R_{hb} =   Ratio hair to corresponding blood concentration [ppm-Hair / mg/L-blood];

Table 2   Input Values used in the Exposure Model

Variable	Value	Reference / Comment
Fish Mercury Concentration (mg/kg-WW)	Varies by species	See Table 3-
Female body weight (kg)[1]	LN(63.1, 11.8)	Richardson and O'Connor 1997
Female ingestion rate (grams/day)	171	Fixed value; See Table 3-
Female blood volume (L)[1]	N&T(5.57, 0.93, 3.7, 7.9)	Stern (2005)
Fraction of ingested dose that is absorbed – A (unitless)	U(0.94, 0.999)	Stern (2005)
Fraction of absorbed dose that is present in blood at steady state – F (unitless)	N(0.052, 0.0095)	Stern (2005)
Rate constant for elimination of MeHg from blood – R (days)	U(15, 75)	Stern (2005)
Ratio for hair to corresponding blood concentration – (ppm-Hair / mg/L-blood)	U(140, 370)	WHO (2003); Clarkson and Magos (2006); Diez (2009); Legrand et al. (2010)
Ratio of cord blood to maternal blood concentration – (ppm-cord / ppm-maternal)	LN(1.7, 0.9)	Stern (2005)
Ratio of methyl mercury to total mercury in fish tissue	100%	Fixed value; Health Canada (2007)

Notes:
(1)   As recommended by Stern (2005), female body weight was correlated with blood volume (r=0.5).
Uniform distribution defined by U(Minimum, Maximum).
Normal distribution defined by N(Mean, Standard Deviation).
Normal and Truncated distribution defined by N&T(Mean, Standard Deviation, Minimum, Maximum)
Lognormal distribution defined by LN(Mean, Standard Deviation).

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