COMMENTARY

Methylmercury Blood Guidance Values for Canada

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ABSTRACT

Exposure to methylmercury (MeHg) from fish and marine mammal consumption continues to present a public health concern. To date, developmental neurotoxicity is the most sensitive health outcome, forming the basis for health-risk assessments and the derivation of biomonitoring guidance values. This article summarizes existing Health Canada MeHg blood guidance values for general population and expands them to include a harmonized provisional interim blood guidance value of 8 µg/L based on the existing provisional Tolerable Daily Intake for children, pregnant women and women of childbearing age. Associated public health actions, according to age, sex, and level of exposure are recommended.

Key words: Methylmercury; biomonitoring; guidance

La traduction du résumé se trouve à la fin de l'article.

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Exposure to methylmercury (MeHg) from fish and marine mammal consumption continues to present a public health concern in Canada and elsewhere.[1,2] Extensive toxicological and epidemiological evidence have indicated that neurotoxicity resulting from *in utero* exposure is the most sensitive health outcome.[2-6] This evidence has formed the basis of health-risk assessments and biomonitoring guidance values that allow researchers and clinicians to evaluate individual and population risk and guide public health actions when necessary. This article summarizes Health Canada MeHg blood guidance values and their associated public health recommendations, according to age, sex, and level of exposure. Included are existing guidance values for the general adult population and provisional interim guidance values for children, pregnant women and women of childbearing age for the protection of the developing nervous system.

Health Canada methylmercury biomonitoring guidance values

In the 1970s, the Medical Services Branch (currently First Nations and Inuit Health Branch of Health Canada, hereafter FNIHB) was involved in the initial investigations of blood and hair mercury levels among First Nations residents in Ontario and Quebec.[3] In 1973, a Task Force on Organic Mercury in the Environment was established by the Minister of National Health and Welfare (currently Health Canada) "in order to respond to the problem of high and unusual mercury levels in relation to the health and well-being of residents of Grassy Narrows and Whitedog, Ontario".[3]

On the recommendation of the Task Force, FNIHB implemented a systematic mercury biomonitoring program among First Nations and Inuit in the early 1970s. Between 1970 and December 1992, 71,842 hair and blood tests for MeHg on 38,571 individuals were carried out in 514 indigenous communities across Canada.[7]

To identify "at risk" individuals and provide appropriate preventive action, FNIHB established a set of biomonitoring guidance values applicable to the general population of high fish consumers (e.g., First Nations and Inuit).[3] The guidance values were based on the recommendations of the 1971 Swedish Expert Group report,[8] which concluded that the lowest blood concentration associated with adverse clinical effects was approximately 200 µg/L. This analysis was based on the findings from investigations of large outbreaks of organic mercury poisoning – in Japan in the 1950s-60s and in Iraq in the 1970s. The Expert group recommended applying a safety factor of 10 to derive "safe" levels in human populations.[8] This analysis became the basis for the World Health Organization (WHO)'s Joint Expert Committee on Food Additives (JECFA) 1972 derivation of the Tolerable Weekly Intake (TWI) for MeHg of 3.3 µg/kg bw (body weight)/week.[9] This TWI was adopted by Health Canada's Food Directorate, and expressed as the Provisional Tolerable Daily Intake (pTDI) of 0.47 µg MeHg/kg bw/day.[10]

In 1976, a WHO Expert Group also concluded, based on the Japan and Iraq data, that the earliest effects (paraesthesia) in the most sensitive 5% of exposed adults could be expected at blood levels of 200-500 µg/L with corresponding hair concentration of 50-125 mg/kg and that the lower values could be reached by a daily mercury intake of 3-7 µg/kg bw/day.[11]

Based on the reports by WHO[11] and the Swedish Expert Group,[8] taking into account existing evidence of possible effects at blood levels below 200 µg/L,[12] a decision was made by FNIHB in the 1970s to refer to blood levels below 20 µg/L (or 6 mg/kg in hair) as being "acceptable" and levels greater than 100 µg/L in blood (or 30 mg/kg in hair) as "at risk".[3,7] Clinical neurological examinations were offered to all individuals considered to be in the "at risk" group.[3,7] For the sake of consistency, FNIHB employed a hair to blood ratio of 300, derived from Canadian data with First Nations[13,14] and volunteer data.[15] See below for further discussion on hair to blood conversions.

Although the developing fetus was considered as a sensitive subgroup, no specific threshold values were proposed. In its 1990 review, WHO[5] suggested neurological effects in infants might be

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Table 1. The Range of Benchmark Dose Lower Limits (BMDL)* (mg/kg in maternal hair) Reported from Three Major Epidemiological Studies That Examined the Association between Prenatal MeHg Exposure from Fish Consumption and Child Neurodevelopmental Outcomes

Study Population (reference)	BMDL Excess risk = 5%	BMDL Excess risk = 10%
Faroe Islands[16] Assessment at age 7 years	9.4-14	16-24
Seychelles[4,17] Assessment at age 5.5 years	17-25	24.7-27.8
Seychelles[18] Assessment at age 9 yrs	15.5-21.9	17.9-23.0
New Zealand†[4,19] Assessment at age 6-7 years	Excluding outlier: 4-6 Including outlier: NA‡	Excluding outlier: 7.4-10 Including outlier: 17-24

* BMDLs are defined as the lower 95% of the confidence interval of the Benchmark Dose (BMD). The BMDs are calculated from the k-power model under the assumption that 5% of the responses will be abnormal in unexposed subjects (P_0=0.05), assuming a 5% or 10% excess risk.
† The NRC (2000) and JECFA (2004)[2,4] reported some reservations in regard to the use of the New Zealand study. One child out of the 237 subjects had a maternal hair mercury concentration of 86 mg/kg which was more than four times the level measured in the next highest subject and had a significant effect on the derivation of the BMDLs. Further, as compared to the Faroe Islands and Seychelles studies, the New Zealand study included a much smaller sample size (only 237 children compared to over 700 in the Faroe and Seychelles) and had not been comprehensively evaluated to the same level of scrutiny and re-analysis.[2,4]
‡ NA = not available

Table 2. Overview of Health Canada Existing and Harmonized Blood Methylmercury Guidance Values

Age-Sex Category	Blood Guidance Levels*	Recommended Follow-up‡
Pregnant women Females birth-49 years Males ≤18 years	Blood level <8 µg/L (40 nmol/L)	• No follow-up required
Pregnant women Females birth-49 years Males ≤18 years	Blood level 8 µg/L-40 µg/L† (40-200 nmol/L)	• Repeat hair/blood test in 6 months • Provide dietary advice
Pregnant women Females birth-49 years Males ≤18 years	Blood level >40 µg/L† (200 nmol/L)	• Repeat blood/hair test immediately • Schedule an appointment with a public health professional to review exposure history to identify sources of mercury exposure and provide dietary advice
Females ≥50 years Males >18 years	Blood level <20 µg/L (100 nmol/L)	• No follow-up required
Females ≥50 years Males >18 years	Blood level 20 µg/L-100 µg/L (100-500 nmol/L)	• Repeat hair/blood test in 6 months • Provide dietary advice
Females any age Males any age	Blood level >100 µg/L (500 nmol/L)	• Repeat blood/hair test immediately • Schedule an appointment with a public health professional to review exposure history to identify sources of mercury exposure and provide dietary advice • Refer study participant to a physician or medical toxicologist for assessment and follow-up in terms of checking basic neurological signs and symptoms and making a decision concerning appropriateness of any therapeutic intervention

* In order to derive corresponding hair values, a hair/blood ratio of 250/1 is currently recommended for all population groups. The equation is as follows: hair value (in mg/kg) = (blood value (in µg/L) X 250) / 1000.
† The proposed action level of 40 µg/L in blood is the blood equivalent of the toxicological reference value of 10 mg/kg in hair (using a hair to blood ratio of 250) used to derive Health Canada's pTDI. Although clinical adverse health outcomes at the individual level may not be perceptible at this level, public health professionals may wish to provide additional guidance to prevent subjects from reaching body burden levels at which individual poisoning has been observed.
‡ The recommendations are intended as general guidance on intervention levels. There is flexibility in the formulation of dietary advice depending on individual circumstances.

occurring from prenatal exposures equivalent to maternal hair mercury levels of 10-20 mg/kg. At the time, it was recommended that additional epidemiologic studies be conducted in children exposed *in utero* in order to more fully assess the potential risk. In the 1990s, two large prospective epidemiological studies, in the Seychelles and the Faroes Islands, were initiated to investigate subtle neurodevelopmental effects in children from chronic low level prenatal MeHg exposure.[16-18] In these populations, exposure to MeHg was primarily attributable to frequent consumption of fish and/or marine mammals, but was not linked to local sources of mercury pollution.

Following the release of preliminary results from both the Seychelles and Faroe Island infant cohort studies, and considering the findings from a smaller New Zealand fish-eating cohort,[19] the Food Directorate of Health Canada proposed that the increased susceptibility of the developing fetus to MeHg toxicity should be recognized. In 1998, 10 mg/kg mercury in maternal hair was proposed as a toxicological reference on which to set a tolerable intake for sensitive subgroups. Using an international standard of hair to blood ratio of 250, a steady-state single compartment toxicokinetic model[2] (see equation 1) and a 5-fold uncertainty factor to account for inter-individual variability, Health Canada developed the pTDI for pregnant women, women of reproductive age and infants, set at 0.2 µg/kg bw/day.[10]

Table 1 outlines toxicological reference values reported as Benchmark Dose Lower Limits (BMDLs) for various neurobehavioural endpoints reported from the above-mentioned epidemiological studies.

In its 2003 assessment, JECFA concluded that neurotoxicity resulting from *in utero* exposure should be considered to be the most sensitive health outcome. Using a composite maternal hair mercury value of 14 mg/kg but a larger uncertainty factor, JECFA suggested that a pTWI of 1.6 µg/kg bw (approximately 0.23 µg/kg bw/day) was sufficient to protect the most vulnerable population subgroup.[2]

Equation 1:

$$d = \frac{C \times b \times V}{A \times f \times bw}$$

Table 3. Blood (µg/L) Total Mercury* across Selected Recent Published Canadian Studies

Target Group (sample size)	Arithmetic Mean (AM), Geometric Mean (GM), or Median (MD)	Variation
Canadian population[25] (n=2678)	GM:	95% CI
Children 6-19 years of age	0.31	0.23-0.43
Adults men and women, 20-79 years	0.91	0.63-1.32
Labrador,[23] Innu community – adults, men and women (n=118)†	AM:	Standard deviation:
	1.6	1.44
New Brunswick[26] communities – adults, men and women†	AM:	Standard deviation:
Grand Manan community (n=91)	2.8	2.2
St. Andrews/St. Stephen communities (n=52)	1.68	0.6
Quebec,[27] St. Lawrence river lakes (St. François and St. Louis Lakes) – pregnant women	GM:	5%-95% CI
First trimester (n=39)	0.85	0.40-2.20
Second trimester (n=147)	0.56	ND‡-2.00
At delivery (n=101)	0.48	ND-1.2
Cord blood (n=92)	0.52	ND-1.6
Quebec[23] – adults, men and women†	AM:	Standard deviation:
Lake St. Pierre (n=130)	3.32	3.88
Abitibi (n=146)	4.8	5.6
Quebec,[28] greater Quebec City area – adults, men and women (n=470)	GM:	2.5%-97.5% CI
	0.74	0.2-3.21
Ontario,[29] Lake Ontario licensed anglers – adults, men and women:	GM:	Range:
Sport-fish noneaters (n=56)	1.5	<1.1-5.4
Sport-fish eaters (n=176)	2.2	<1.1-16.3
Ontario,[29] Ontario Great Lakes Area sport-fishers – adults, men and women:	GM:	Range:
Euro-Canadian sport-fish eaters (n=45)	2.0	0.4-7.5
Asian-Canadian sport-fish eaters (n=41)	7.9	1.0-26.0
British Columbia,[30] Vancouver area – children, 1.5-5 years	MD:	Range:
All children (n=201)	0.9	ND-13.7
Caucasians (n=56)	0.2	ND-3.6
Chinese (n=68)	2.2	0.1-13.7
Other (n=72)	0.7	ND-2.6
Northern Canada[24] – pregnant women:	GM:	Range:
Caucasian (n=134)	0.9	ND-4.2
Metis/Dene (n=92)	1.4	ND-6.0
Other (n=13)	1.3	0.2-3.4
Inuit – Baffin (n=31)	6.7	ND-34
Inuit – Inuvik (n=31)	2.1	0.60-24
Inuit – Kitikmeot (n=63)	3.4	ND-13
Inuit – Kivalliq (n=17)	3.7	0.60-12
Inuit – Nunavik (n=162)	10.4	2.6-44

* Total mercury rather than MeHg is often measured in blood or hair. This is due to prohibitive laboratory costs of measuring MeHg and to the observation that in non-occupationally exposed fish-consuming populations, measurements of total mercury consist primarily of MeHg.[14,18]
† Blood total mercury values were converted from hair using a hair/blood ratio of 250/1.
‡ ND = non-detect

Where:

d = dose (µg/kg bw per day)

C = mercury concentration in blood (µg/l)

b = elimination rate constant (0.014 per day)

V = blood volume (9% of body weight for a pregnant female)

A = fraction of the dose absorbed (0.95)

f = the absorbed fraction distributed to the blood (0.05)

bw = body weight (65 kg for a pregnant female)

The current Health Canada pTDI can also be expressed (using the same equation 1) as a blood value of 8 µg/L and used as a provisional interim blood guidance value applicable to women of childbearing age and pregnant women for the protection of the fetus. Currently there is insufficient data to fully characterize the vulnerability of infants and children to the neurotoxic effects of postnatal MeHg exposure.[6] Although this subgroup is viewed as being less vulnerable than the fetus, it remains unclear whether it is more or less vulnerable than adults.[4,6] In this context, it is proposed that the interim blood guidance value for the protection of the fetus be likewise applicable to infants and children, including adolescents.

Table 2 outlines both existing and harmonized Health Canada blood guidance values as well as associated recommendations for public health actions with respect to advising individuals. Table 3 provides an overview of recent (mid 1990s-2008) published blood and hair mercury levels in Canada. Guidance values are provisional in nature and subject to periodic review. Emerging evidence, although less conclusive than data on neurotoxic effects, suggests that low level MeHg exposure may be associated with other health outcomes in humans, such as cardiovascular effects. As more robust evidence becomes available, those effects should be considered when revising the proposed provisional guidance values.[4,6]

Hair to blood ratio

Scalp hair has been widely used for biomonitoring of MeHg exposure. Incorporation of mercury into the hair follicles is proportionate to its bioavailable concentration in blood.[20,21] In its 2003 evaluation, JECFA reported that most of the published hair to blood mean ratios fall within a range of 140-370. Variability in hair growth rates has been proposed as one explanatory factor.[4] Average growth rate of 1.1cm per month for scalp hair is commonly used.[4,15,22] However, inter-study hair growth rates ranging from 0.6 to 1.5, and up to 3.4 cm per month have been described.[4,20] Further, the hair segment with the maximum mercury concentration has been reported to appear 20 days following the appearance of

the maximum concentration in the blood.[4,21] Thus the time period represented by concurrent measurements of blood and hair may be different.[13,22] These and other factors such as age, gender, metabolic predispositions, hair characteristics (molecular structure, colour, weight) and use of artificial waving solutions[4,20,22,23] may further influence the observed inter-study variability and require further investigation. A hair to blood ratio of 250 was determined as an acceptable average of existing values.[2]

Managing methylmercury biomonitoring results

Management of MeHg biomonitoring levels typically focuses on identifying and reducing the source of exposure, except in very rare situations where levels are sufficiently elevated warranting clinical management by medical specialists. In non-occupationally exposed individuals, the main source of MeHg exposure, fish, also carries significant nutritional (omega-3 fatty acids, vitamin D, protein, selenium), social and cultural benefits, especially for Aboriginal groups or populations who subsist on fish.[2,24] Health Canada recognizes these benefits and generally encourages fish consumption by recommending fish species that are high in omega-3 fatty acids and that tend to be low in mercury.[1] Complete Health Canada fish advisories can be accessed at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2007/2007_31-eng.php. Researchers and clinicians should strive to develop appropriate, audience-specific communication messages that encourage individuals and communities to continue enjoying fish while reducing MeHg exposure.

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RÉSUMÉ

L'exposition au méthylmercure (MeHg) par la consommation de poisson et de mammifères marins constitue toujours une préoccupation de santé publique. À ce jour, l'effet sanitaire le plus préoccupant de l'exposition à cette substance est la neurotoxicité développementale, laquelle sert de base aux évaluations du risque pour la santé et à la détermination des valeurs guides pour la biosurveillance. Le présent article offre une synthèse des valeurs guides actuelles de Santé Canada en ce qui concerne les taux de MeHg dans le sang pour la population générale et propose l'ajout d'une valeur guide harmonisée provisoire de 8 µg/L, fondée sur la dose journalière admissible provisoire s'appliquant aux enfants, aux femmes enceintes et aux femmes en âge de procréer. Des mesures de santé publique, adaptées selon l'âge, le sexe et le degré d'exposition, sont recommandées.

Mots clés : méthylmercure; biosurveillance; valeur guide