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Quantitative estimation of mercury intake by toxicokinetic modelling based on total mercury levels in humans

Abass K.[a,*,1], Huusko A.[a], Knutsen H.K.[b], Nieminen P.[c], Myllynen P.[d], Meltzer H.M.[b], Vahakangas K.[e], Rautio A.[a]

[a] Arctic Health, Faculty of Medicine; and Thule Institute, University of Oulu, Finland
[b] Division for Infection Control and Environmental Health, Norwegian Institute of Public Health, Norway
[c] Medical Informatics and Statistics Research Group, University of Oulu, Finland
[d] Northern Laboratory Centre NordLab, Oulu FI-90220, Finland
[e] Faculty of Health Sciences, School of Pharmacy/Toxicology, University of Eastern Finland, Finland

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ABSTRACT

Mercury is a toxic metal that can be disseminated into the environment from both natural and anthropogenic sources. Human exposure to the metal stems mainly from food, and more particularly from the consumption of fish and other seafoods. Examining dietary exposure and measuring mercury levels in body tissues are two ways of estimating exposure to mercury. In this study, we utilized a modelling system consisting of three linear toxicokinetic models for describing the fate of methyl mercury, inorganic mercury, and metallic mercury in the body, in order to estimate daily intake of mercury as measured through total mercury concentrations in the blood. We then compared the results stemming from our modelling system to those of the detailed semi-quantitative food frequency questionnaire (FFQ) of the Norwegian Fish and Game (NFG) Study, a project that focused on dietary mercury exposure.

The results indicate that toxicokinetic modelling based on blood levels gave higher daily intake values of mercury compared to those of the FFQ. Furthermore, the former had a wider range of estimates than the latter. The properties of the toxicokinetic model or limitations in the dietary exposure assessment could be posited as reasons for the differences between the respective methods. Moreover, the results may have been influenced by sources of mercury exposure that cannot be described as dietary, such as amalgam fillings.

1. Introduction

Mercury (Hg) is a toxic metal that can be passed into the environment via both natural and anthropogenic sources (ATSDR, 1999), Hg undergoes – in nature – a variety of intricate transformations and cycles between the interrelated systems of atmosphere, oceans and land. While elemental (metallic, Hg^0) Hg is aqueous, it swiftly dissipates into a hazardous vapor form (Bernhoft, 2012; Crespo-López et al., 2009; Gupta, 2012; Selin, 2011). Hg has the ability to bind to other elements (e.g. chlorine, sulfur, or oxygen), thereby forming inorganic mercurous (Hg^{1+}) and mercuric mercury (Hg^{2+}) salts; and inorganic Hg can be altered to organic Hg by microbial activity. Toxicologically, the most important organic form is methyl mercury (MeHg) (ATSDR, 1999).

Humans are primarily exposed to Hg through food, with consumption of fish and seafood being the major source (Sheehan et al., 2014). Another source of elemental Hg in humans is dental amalgam (Richardson et al., 2011). Conversely, the atmosphere and drinking water generally have such low levels of Hg that they cannot be seen as significant sources of exposure to the wider public (Amos et al., 2014; Jaffe et al., 2014; Quétel et al., 2014).

The degree to which Hg is toxic varies from case to case, depending on the form of the metal and its route of exposure (Bridges and Zalups, 2017; Ynalvez et al., 2016). Continual exposure to high levels of MeHg mainly affects the nervous system (Rice et al., 2014). Consequences of such exposure include disturbances in neurological function such as vision, hearing and muscle weakness, with children and unborn babies the groups most at risk (Sheehan et al., 2014; Solan and Lindow, 2014). Furthermore, a number of complex nervous system effects have been observed in populations that consume a good deal of seafood as part of their regular diet. Within such social groups, exposure to MeHg in the womb and/or soon after birth has been associated with issues such as altered memory, attention and language development in children

* Corresponding author at: Faculty of Medicine, Arctic Health, University of Oulu, FI-90014 Oulu, Finland.
E-mail addresses: khaled.megahed@oulu.fi, khaled.m.abass@gmail.com (K. Abass).
[1] Permanent address: Department of Pesticides, Menoufia University, P.O. Box 32511, Egypt.

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(reviewed by Grandjean and Landrigan (2014)). However, it should be stressed that this connection has not been made in other studies (Myers et al., 2003; Nieminen et al., 2015; Orlando et al., 2014).

MeHg is freely absorbed from the gastrointestinal tract. In the human body, 1 to 10% of MeHg is absorbed from the GI tract and distributed to the blood. About 5% of MeHg is distributed to tissues within a few days and approx. 1% of the body's MeHg is found in one liter of adult human blood (70 kg) (WHO, 2000). Fish and other types of seafood are the main source of human MeHg exposure (Mergler et al., 2007). In fish, approximately 95% of MeHg is absorbed and distributed to tissues within thirty hours, with around 7% of the ingested dose accounted for by the blood level (Gupta, 2012). MeHg is visible in the body as soluble complexes mainly attached to the sulfur atom of thiol ligands. It passes the blood-brain barrier as a MeHg-L-cysteine complex, transported by the L-system (leucine preferring) amino acid carrier (Gupta, 2012). The MeHg is demethylated over an extended period to mercuric Hg in tissue macrophages, intestines, and the liver, including fetal liver. Bile and feces are significant as the major routes of excretion of MeHg, with 90% of MeHg being excreted as the ionic form in the latter after demethylation. While breast milk is another notable excretion route (Greenwood et al., 1978), the substance is yet to be detected in urine (CDC, 2016; Schindler et al., 2014; Smith et al., 1994). The results of different studies present an enormous variety in the elimination half-life of MeHg in humans, varying from 32 to 164 days (Miettinen et al., 1971; Smith et al., 1994) after an intravenous dose. In people who come into contact with MeHg on a regular basis, it takes approximately five elimination half-lives to reach a steady-state body burden (WHO, 2000).

In the case of inorganic Hg, toxicokinetics is different. There is an estimate of 7–15% for absorption of inorganic Hg from the gastrointestinal tract after an oral dose. The ingested ionic Hg quickly spreads to the blood and organs, while the vast majority of it is excreted in urine and smaller amounts through saliva, bile, sweat, and breast milk. Some is even exhaled.

There is a great deal of variety in the excretory half-lives of metallic and mercuric Hg, and this can be attributed to the organ of deposition and redox state. Values can range from a few days to anything up to several months. Mercuric Hg is primarily excreted via urine and stool (Berlin et al., 2007; Björnberg et al., 2005). Half-lives of metallic and mercuric Hg give the appearance of being multiphasic. When it comes to the former, human studies suggest an effective half-life of 42 days for 80% of an oral tracer dose, while the final 20% seems not to have a rate of excretion that can be measured (Rahola et al., 1971). This could point towards a mechanism yet to be defined or perhaps simply trapping in other organs.

Measuring Hg levels in body tissues, such as blood, urine, human milk, and hair, can help to estimate Hg exposure (Berglund et al., 2005; Björkman et al., 2007; Needham et al., 2011; Sheehan et al., 2014) as they provide an indication of the internal dose. This can be then be utilized to assess the likelihood of health problems (World Health Organization, 2003), although one must take great care in choosing the correct biomarker in order to accurately anticipate internal exposure (Berglund et al., 2005). In terms of the population of this study, Jenssen et al. (2012) have demonstrated the link between consumption of fish and seafood contained Hg, and total Hg concentrations in blood. According to the literature, currently the best proxy for long term MeHg exposure in individuals is the concentration of Hg in hair (Sheehan et al., 2014). Moreover, it is considered that an excellent biomarker for inorganic Hg is Hg level in urine (Berglund et al., 2005).

The key influences on the amount of urinary Hg excretion without occupational exposure are amalgam fillings and fish consumption (Apostoli et al., 2002; Dutton et al., 2013; Johnsson et al., 2005). Amalgam fillings tend to liberate Hg and up to 80% of this metallic Hg can be absorbed through lungs (ATSDR, 2009). After this, the body transports Hg quickly to major organs such as the brain, the liver and the kidneys. In blood, Hg either dissolves in serum or attaches to red cell membranes. In erythrocytes, metallic Hg is rapidly oxidized to mercuric Hg by catalase and hydrogen peroxide. This is a phase with a half-life of approximately two days, after which Hg functions in the same manner as mercuric Hg. Dutton et al. (2013) found that individuals with amalgam fillings had higher urinary Hg levels than those without. The average difference between the two groups was 0.55 μg Hg/g creatinine (0.04 μg Hg/g creatinine per amalgam surface).

During the course of this study we used a linear toxicokinetic model based on the total Hg level in blood for describing the fate of MeHg, inorganic Hg, and metallic Hg in the body, in order to estimate daily intake of Hg from food. The Norwegian Fish and Game (NFG) Study (part C) – a cross sectional study carried out by the Norwegian Institute of Public Health (NIPH) in 2003–2004 – provided us with the published biological data now used in this study for comparison and modelling (Jenssen et al., 2012). While the published literature includes several multi-compartment models for Hg (Farris et al., 1993; Smith et al., 1994), the models of Carrier et al. (2001a, 2001b) and Farris et al. (2008) stand out as being well-documented and for having been utilized in different studies (Noisel et al., 2011). Thus, we have applied both of these models in constructing a new combined model. The linear toxicokinetic model by Carrier et al. (2001a, 2001b) is used for modelling the fate of MeHg in the body, and the model of the Farris et al. (2008) for modelling the fate of inorganic Hg in the body. These models are connected through a blood circulation model and organic blood compartment. Due to the fact that models are linear and do not overlap, we consider the concurrent use of all three models to be justifiable.

2. Materials and methods

The population data are from the Norwegian Fish and Game Study (NFG) which was conducted in 2003–2004 (Jenssen et al., 2012). One of the aims of the original study was to measure total Hg in blood and urine and estimate the dietary exposure of Norwegians with a wide range of seafood and game consumption (Knutsen et al., 2008; Kvalem et al., 2009). Participants delivered blood samples and answered an extensive FFQ. Dietary information for the preceding 12 months was obtained by using a detailed semi-quantitative FFQ designed and validated for the Norwegian mother and Child Cohort study and contained 340 questions covering 255 different food items (Brantsæter et al., 2008; Meltzer et al., 2008). The present study included all participants who were ≥18 years with complete dietary intake information and measured total Hg concentration in blood and urine (n = 176). For three participants, the concentration of creatinine was lacking, and for these, the median level was imputed. Analytical methods used in analysis of blood and urine concentrations of Hg are described in Jenssen et al. (2012). In our study we have used total Hg concentrations in blood for modelling total Hg intake. In Table 1 the main characteristics of the study participants are presented as well as the distribution statistics of total Hg concentration in blood.

The dynamic equations in the toxicokinetic modelling system are solved by the Runge-Kutta method as a one linear differential equation system. The model was implemented using a Mathematica – package (Wolfram Research, Inc., Mathematica, Version 10.0, Champaign, IL) and run into the steady state condition.

Statistical visualization of results (box-and-whisker, residual and Bland-Altman plots) was conducted using the Mathematica – package, and the intra class correlation coefficient was calculated using IBM SPSS Statistics package.

2.1. Toxicokinetic modelling system of the study

The block diagrams of the toxicokinetic modelling system are presented in Fig. 1. The modelling system consists of the inorganic model of Farris et al. (2008) (model A) and the organic Hg model of Carrier et al. (2001a, 2001b) (models C and D). These models are connected through a blood circulation (model B) and organic blood compartment

Table 1
Total mercury concentration in blood and main characteristics and demographics of the study participants with main statistical parameters calculated from a sub-sample of Jenssen et al. (2012).

Total Hg concentration in blood µg/l									
	Group	N	%	Mean	Min	Max	Median	p90[a]	p95[b]
All participants		176	100	5.4	0.6	29.9	4.0	10.1	12.7
Selection group	Randomly selected	71	40	4.5	0.6	29.9	3.8	8.0	10.1
	High consumers	105	60	5.9	1.2	28.1	4.5	11.6	14.4
Gender	Male	78	44	6.7	0.7	29.9	5.2	11.6	19.6
	Female	98	56	4.3	0.6	15.6	3.3	8.3	11.5
Age group	< 40	31	18	2.3	0.6	6.5	1.6	4.3	5.4
	40–60	76	43	5.7	1.3	29.9	4.1	11.1	16.3
	> 60	69	39	6.3	1.0	28.1	5.4	10.7	12.7
Municipality	Coastal	81	46	7.3	1.3	29.9	6.4	12.3	15.6
	Inland	95	54	3.7	0.6	25.2	3.1	6.8	7.9
Education	Basic	50	28	6.7	1.2	28.1	3.3	12.3	14.4
	High school	58	33	5.9	0.6	29.9	4.0	11.6	16.3
	University, college	64	36	3.9	1.0	10.3	3.4	7.0	7.7
BMI	< 25	100	57	5.1	0.6	29.9	3.4	9.7	11.5
	25–30	59	33	5.2	0.7	12.7	4.6	9.6	11.9
	> 30	17	10	7.9	1.0	28.1	6.3	19.6	28.1
Smoking	Never	68	39	5.2	0.8	25.1	3.5	10.3	15.6
	Former	61	35	5.6	0.7	28.1	4.4	10.1	12.7
	Now and then	7	4	4.3	0.6	11.9	3.9	11.9	11.9
	Daily	38	22	5.4	1.2	29.9	3.9	9.6	11.6

[a] 90th percentile of the population.
[b] 95th percentile of the population.

($B^o(t)$) in the models C and D. All models are linear and not interfering with each other, and thus the total Hg concentration in blood can be found by adding concentrations in different blood compartments in the modelling system. The input for model (A) and (B) was the inorganic mercury intake $g^i(t)$ (Eqs. (1) and (5)) and the input for model (C) was organic mercury intake, MeHg g0(t).

2.1.1. Modelling of inorganic Hg

The inorganic Hg model of Farris et al. (2008) consists of two compartments. The mobile compartment represents Hg that is relatively rapidly transported throughout the body. This represents primarily inorganic Hg that is bound to low molecular weight molecules, such as those containing non protein sulfhydryl groups. It was assumed that such complexes undergo rapid transport across blood capillaries and move easily within and are excreted from the body. The immobile compartment represents Hg that is tightly fixed within the body, such as that bound to macromolecules like metallothionein (Piotrowski et al., 1974). Immobile Hg may also be excreted by various physical processes such as exfoliation of renal tubular cells and gastrointestinal mucosal cells (Farris et al., 2008). Although previous evidence (Farris et al.,

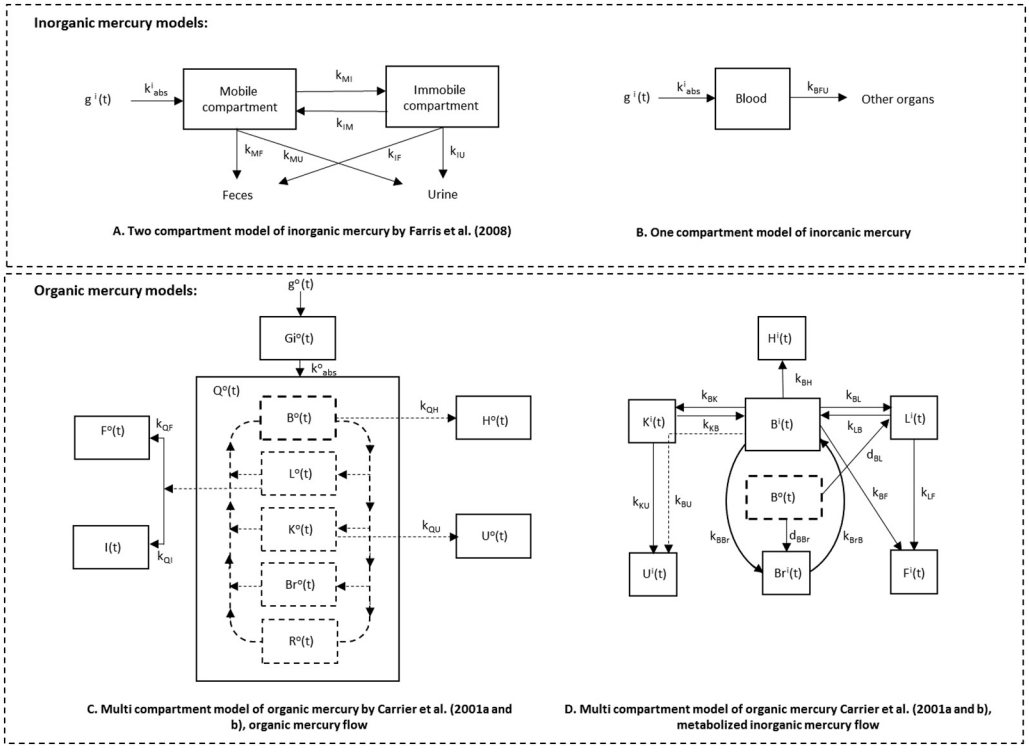

Fig. 1. Modelling system used in the study: The two compartment model of Farris et al. (2008) was employed to simulate the fate of inorganic Hg in the body, while the one compartment model of inorganic Hg in blood was utilized for the purpose of linking the models together. The fate of metabolized organic Hg (along with the change into inorganic Hg in the body) is simulated by the multi-compartment model by Carrier et al. (2001a, 2001b)) for biologically based toxicokinetics. This model is divided into blocks of organic and inorganic Hg (models C and D) that are linked together through the concentration of organic Hg in the blood (see compartment $B^o(t)$ in both blocks).

Table 2
Numerical values of constant parameters taken from the model (A), see Fig. 1A (Farris et al., 2008).

Constant rate parameters	Values
k_{MI}	0.275131
k_{IM}	0.019504
k_{MF}	0.039857
k_{MU}	0.006171
k_{IU}	0.005263
k_{IF}	0.001910

2008) suggests that the majority of Hg in feces might arise from the mobile compartment and that most of the Hg in urine is derived from the immobile compartment, the inorganic Hg model allows for the possibility that both excretion pathways of Hg may arise from either or both compartments.

$$\frac{dMM}{dt} = g^{i}(t) + k_{IM}MI - (k_{MI} + k_{MF} + k_{MU})\,MM \quad (1)$$

Eq. (1) represents the mass balance of the mobile compartment. *MI* (Hg immobile) and *MM* (Hg mobile) are the amounts of inorganic Hg in the immobile compartment and mobile compartment, respectively. The parameters k_{MI} and k_{IM} are the rate constants for transport of inorganic Hg between the mobile and immobile compartments, the direction of the transfer is shown in the subscript, see Fig. 1. The parameters k_{MF} and k_{MU} are the rate constants for transport of inorganic Hg from the mobile compartment to feces and urine, respectively. The rate constants are symbolized as above.

$$\frac{dMI}{dt} = k_{MI}MM - (k_{IM} + k_{IF} + k_{IU})\,M \quad (2)$$

Eq. (2) represents the mass balance of the immobile compartment. The rate constants are symbolized as in the Eq. (1).

$$\frac{dUR}{dt} = k_{IU}MI - k_{MU}MM \quad (3)$$

$$\frac{dFE}{dt} = k_{IF}MI - k_{MF}MM \quad (4)$$

Eqs. (3) and (4) represent cumulative amounts of inorganic Hg in urine and feces compartments, denoted as *UR* and *FE*, respectively. The rate constants are symbolized as in the Eqs. (1) and (2).

There is no individual blood compartment in the inorganic Hg model of Farris et al. (2008). However, inorganic Hg concentration in blood can be approximated with a one compartment model using half-life of 5 days for transfer of inorganic Hg into other organs (Eq. (5)) (Nuttall, 2004).

Table 3
Variables and numerical values of constant parameters used in the models C and D, see Fig. 1 (Carrier et al., 2001a, 2001b).

Organic mercury	
Variables	
$Gi^{o}(t)$	Burden of organic mercury in the gastrointestinal tract as a function of time
$Q^{o}(t)$	Whole body burden of organic mercury excluding hair and excreta as a function of time
$B^{o}(t)$	Burden of organic mercury in blood as a function of time
$L^{o}(t)$	Burden of organic mercury in liver as a function of time
$K^{o}(t)$	Burden of organic mercury in kidney as a function of time
$Br^{o}(t)$	Burden of organic mercury in brain as a function of time
$R^{o}(t)$	Burden of organic mercury in rest of the body as a function of time
$H^{o}(t)$	Cumulative burden of organic mercury in hair as a function of time
$U^{o}(t)$	Cumulative burden of organic mercury in urine as a function of time
$F^{o}(t)$	Cumulative burden of organic mercury in feces as a function of time
I(t)	Whole body and excreta burden of inorganic mercury as function of time
Constant parameters	
K[a]	Constant ratio $Q^{o}(t)/B^{o}(t)$, value = 12.9870
k_{abs}	Oral absorption rate constant, value = 5.5440
k_{QI}	Metabolism rate constant of organic mercury to inorganic mercury, value = 0.01347[b]
k_{QF}	Whole body to feces transfer coefficient of organic mercury, value = 9.0668×10^{-5}
k_{QU}	Whole body to urine transfer coefficient of organic mercury, value ≈ 0
k_{QH}	Whole body to hair transfer coefficient of organic mercury, value = 2.3825×10^{-4}
k_{elim}	Whole body elimination rate constant of organic mercury, value = 0.01380
Inorganic mercury	
Variables	
$B^{i}(t)$	Burden of inorganic mercury in blood as a function of time
$L^{i}(t)$	Burden of inorganic mercury in liver as a function of time
$K^{i}(t)$	Burden of inorganic mercury in kidney as a function of time
$Br^{i}(t)$	Burden of inorganic mercury in brain as a function of time
$H^{i}(t)$	Cumulative burden of inorganic mercury in hair as a function of time
$U^{i}(t)$	Cumulative burden of inorganic mercury in urine as a function of time
$F^{i}(t)$	Cumulative burden of inorganic mercury in feces as a function of time
Constants	
d_{BL}	Blood to liver transfer coefficient combined with liver metabolism rate constant of organic mercury, value = 0.1750
d_{BBr}[c]	Blood to brain transfer coefficient combined with liver metabolism rate constant of organic mercury, value = d_{BL}
k_{LB}	Liver to blood transfer coefficient of inorganic mercury, value = 0.8940
k_{BK}	Blood to kidney transfer coefficient of inorganic mercury, value = 17.1234
k_{KB}	Kidney to blood transfer coefficient of inorganic mercury, value = 0.0010
k_{KU}	Kidney to urine transfer coefficient of inorganic mercury, value = 0.006949
k_{BH}	Blood to hair transfer coefficient of inorganic mercury, value = 0.1400
k_{BU}	Blood to urine transfer coefficient of inorganic mercury, value = 0.06994
k_{BF}	Blood to blood transfer coefficient of inorganic mercury, value = 3.9917
k_{LF}	Liver to feces transfer coefficient of inorganic mercury, value = 1.5479
k_{BBr}	Blood to brain transfer coefficient of inorganic mercury, value = 0.0028
k_{BrB}	Brain to blood transfer coefficient of inorganic mercury, value = 0.0520

[a] Except K which is ratio and not a rate as are the other parameters.
[b] Average value.
[c] The value of d_{BBr} was considered very small compared to that of d_{BL}.

$$\frac{dB}{dt} = k_{abs}^{i}\ g^{i}(t) - k_{BFU}\ B \quad (5)$$

In Eq. (5) B is the concentration of inorganic Hg in the blood, $g^{i}(t)$ is a daily intake of inorganic Hg (daily intake of inorganic Hg mostly from amalgam fillings and food), k_{abs}^{i} is absorption constant of the inorganic Hg into the blood, absorption fraction of 0.8 for elemental Hg vapor from amalgam fillings through lungs and 0.15 for inorganic Hg in food through gastrointestinal tract, and K_{BFU} is blood to other organs transfer coefficient of inorganic mercury (K_{BFU} = 0.34657). The total volume of blood was calculated by the formula of Nadler et al. (1962):

$$\text{Males: } BV = 0.3669 \cdot h^3 + 0.03219 \cdot w + 0.6041 \quad (6)$$

$$\text{Females: } BV = 0.3561 \cdot h^3 + 0.03308 \cdot w + 0.1833 \quad (7)$$

where BV is total Blood Volume in litres, h is person's height in meters, and w is person's weight in kilograms.

2.1.2. Modelling of organic Hg

The organic Hg model is a multi-compartment biological dynamic toxicokinetic model by Carrier et al. (2001a, 2001b). This model estimates body burden of MeHg in the main organs. The model allows quantitatively relating both inorganic and organic Hg in biological matrices, e.g. blood, hair and urine, to the absorbed dose and tissue burdens at any point of time. Compartments of the model represent organic or inorganic Hg burden in an organ or a group of organs or excreta, such as gastrointestinal tract, blood, liver, kidneys, brain, whole body burden of organic Hg. It is represented by a set of coupled differential equations taking into account inter-organ rates of exchange and excretion together with biotransformation of MeHg into inorganic Hg in the body. The structure of the model, variables and constant parameters are presented and validated in Carrier et al. (2001a, 2001b). The structure and parameterization of models are presented in the Fig. 1 (models C and D) and Tables 2 and 3. The first order linear differential equations for the model of organic Hg are presented in the appendix of and coworkers (Carrier et al., 2001a). The absorption fraction of the intake of MeHg through the gastrointestinal track is assumed to be 0.95 and the daily intake of MeHg is considered to be constant (mainly from fish) (Tuomisto et al., 2010).

2.2. Comparison of the estimated Hg intake resulting from the FFQ and the toxicokinetic model

In order to analyze the similarity, we utilized the following methods: correlation analysis, intra class correlation analysis (IIC), residual analysis and Bland–Altman visual comparison (Barregard, 2005).

Residuals (e_i) for subject i were calculated using the following formula:

$$e_i = y_i - f(x_i) \quad (8)$$

where y_i is the result of FFQ, x_i is a biomarker in blood, and $f(xi)$ is the estimated value given by the modelling system.

3. Results and discussion

3.1. Estimated daily intake of Hg using the modelling system

Fig. 2(A) demonstrates the modelled daily intake of Hg (μg Hg/kg bw/day) in respect of the total blood concentration (μg/l), utilizing the modelling system used in this study (Fig. 1). In these simulations the Hg intake arises from both MeHg and inorganic Hg from food consumption. According to calculations based on lower bound (LB) approach (values lower than levels of quantification for both MeHg and inorganic Hg, LOQ, set to zero) (Jenssen et al., 2012), the estimated shares for MeHg and inorganic Hg are 95% and 5% respectively. However, due to the fact that a significant percentage of the concentration of Hg in foods other than fish is lower than the LOQ, there is a good deal of uncertainty pertaining to the contribution from inorganic Hg. It should further be noted that along with Hg ingested during the consumption of food, elemental Hg is also taken in from amalgam fillings, which only adds to the total blood Hg concentration. Fig. 2(B) demonstrates dietary exposure estimates (μg Hg/kg bw/day) for the participants in the NFG Study Part C. The calculated dietary exposure to Hg (LB) among all participants was 0.05 (mean) and 0.043 (median) μg/kg bw/day (Jenssen et al., 2012). Setting aside the insufficient data related to the intake of inorganic and metallic Hg, the modelling system gave quite similar results of MeHg intake for the whole population, with a median of 0.050 μg/kg bw/day compared to FFQ results giving 0.043 μg/kg bw/day. Moreover, there were similarities between the patterns of Hg intake values from both estimates (Fig. 2). The FFQ method seems better than modelling to filter out extreme values. That said, the lack of precise Hg intake information for the study participants makes it challenging to fully resolve the differences in the Hg intake estimate distributions of both methods.

3.2. Estimated exposure to Hg according to FFQ

Jenssen et al. (2012) have documented the results of the FFQ in their paper on the subject. In the present study, the median dietary Hg exposure for the 176 participants was calculated as 0.043 μg/kg bw/day, equal to that of the whole studied population (N = 184) (Jenssen et al., 2012). In terms of our biomarker based exposure modelling, the FFQ results can be used as reference values for two reasons: firstly, the questionnaire is more of an independent method than modelling; secondly, the blood samples were taken from the same people at the end of the study period. Results from the dietary Hg estimation can be seen in Fig. 2B. As can be observed, there are few outliers with FFQ, only 1–3 varying markedly from the Log-normal distribution. The dietary exposure estimates was significantly lower at age of < 40 than at age of > 60 (median 0.028 and 0.057 μg/kg bw/day, respectively, $p < 0.001$). Additionally, there was a significant variation in the dietary exposure estimates between individuals that had participated in basic and higher education (median 0.057 and 0.028 μg/kg bw/day, respectively, $p < 0.001$). The variation in the dietary exposure estimates were related significantly to seafood consumption (median 0.028 vs 0.071 μg/kg bw/day, $p < 0.001$). The variation in the levels of exposure is related primarily to fish consumption, as well as other factors such as gender, residence, age, and the inclusion criteria as elucidated by Jenssen et al. (2012).

3.3. Contribution of inorganic Hg from food and amalgam fillings to intake of Hg

In the model for this study both MeHg and inorganic Hg are summed up as the total Hg level in blood, as their intakes cannot be separated. This then means that the calculated intake of Hg from food can be changed by inorganic Hg stemming from food and amalgam fillings.

The change in the intake of Hg as a function of the intake of MeHg/inorganic Hg ratio in food, as modelled from the total mercury concentration in blood, is shown in Fig. 3. In this particular context, we have not taken into account the intake of inorganic Hg from amalgam fillings. High absorption of MeHg impacts the estimated intake of Hg by changing of MeHg/inorganic Hg ratio from 95/5 to 80/20 the estimated Hg intake changed from 0.050 to 0.057 μg/kg-bw/day.

Hg has been found in other foods, such as meat and milk. This may well be a result of soil intake by animals during grazing. Hg can be absorbed from the soil and the air by plants in the course of their natural growth. The Norwegian estimates by Jenssen et al. (2012) – in which 95% of the daily intake of Hg comes from fish (primarily MeHg) and 5% from other foods – were used in the model simulations. In the French adult population, for example, the mean dietary exposure to inorganic Hg through the consumption of foods other than seafood was

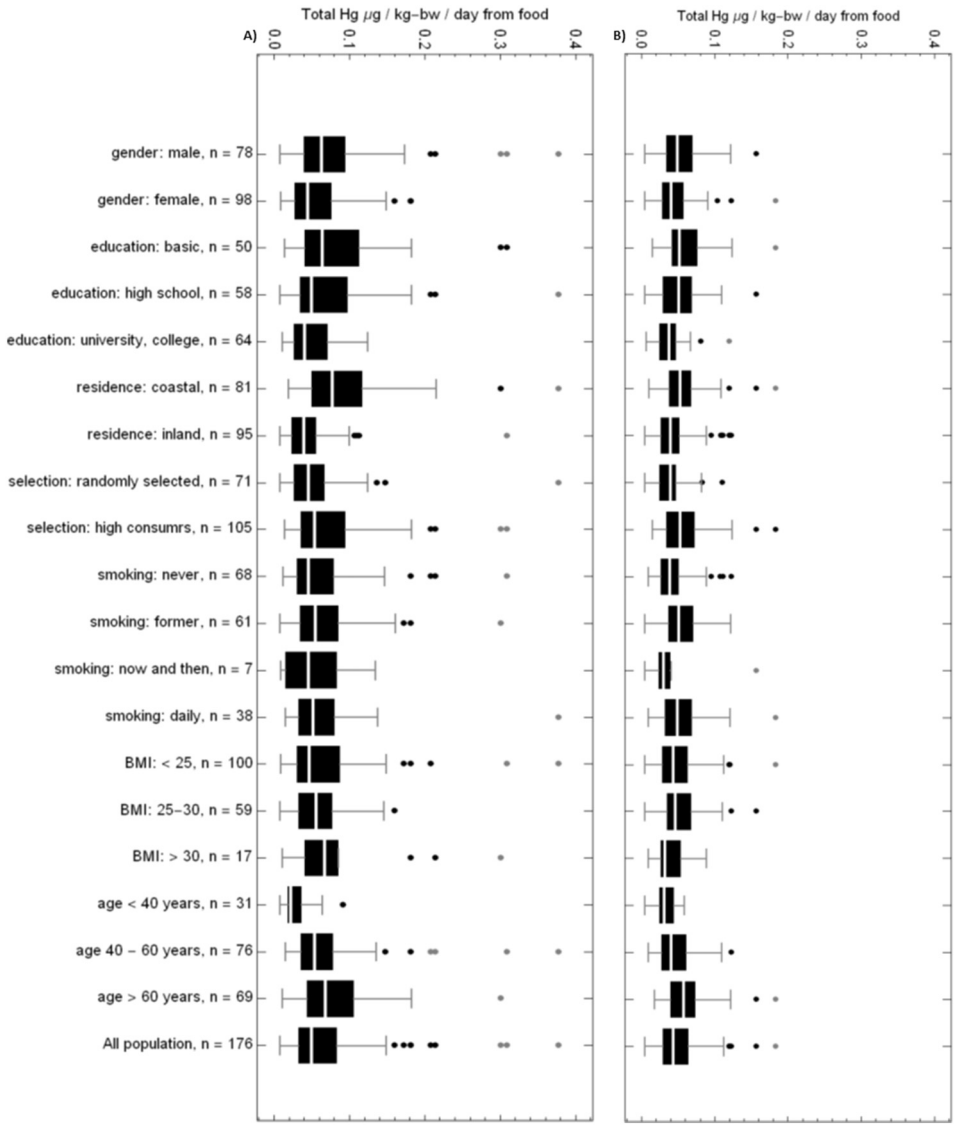

Fig. 2. Daily intake of Hg (µg/kg bw/day): A) intake estimated from total Hg concentration in blood employing the modelling system put forth in this study, and B) intake estimated by the FFQ. Statistical parameters: minimum, 25-percentile, median, 75-percentile, maximum. Outliers are presented as grey and black dots, respectively.

estimated at 0.04 and 1.26 µg/kg bw per week estimated by lower bound approach and upper bound approach, respectively (EFSA, 2012).

The calculated Hg intake as a function of inorganic Hg intake from amalgam fillings is presented in Fig. 4. Here, the food has a Hg ratio of 95% MeHg and 5% inorganic Hg. When the inorganic Hg intake rises from 0 to 0.05 µg/kg-bw/day from amalgam fillings, the estimated median intake of Hg is reduced from 0.050 µg/kg-bw/day to 0.01 µg/kg-bw/day. As previously stated, the model has a great deal of sensitivity to metallic Hg from amalgam. In this instance, the rate of the reduction of Hg was 0.01.

The modelling system gave quite similar results of MeHg intake for the whole population, with a median of 0.050 µg/kg bw/day compared to exposure calculated by the FFQ giving 0.043 µg/kg bw/day. This means that, the lack of precise Hg intake information for of the study participants makes it challenging to fully resolve the differences in the Hg intake estimate distributions of both the methods. One challenging factor is the released Hg from amalgam, since vapor is dependent on the number of all dental amalgam fillings, and their size and free surface area. Residual factors such as change in temperature, bruxism, tooth brushing, and chewing (Isacsson et al., 1997) are also part of the equation. Similarly, estimated total Hg exposures based on blood total Hg modelling were reported to be higher than the estimated exposure by FFQ (Lincoln et al., 2011; Sirot et al., 2008). It should be further noted that the quantity of Hg discharged from dental amalgam decreases as the filling ages. Halbach (1995) estimated that an average daily dose of Hg from amalgam would be 4.8 µg Hg/day (for a 70 kg person 0.07 µg/kg-bw/day), based upon an examination of 21 individuals with amalgam fillings. In a recent study, Golding et al. (2016) demonstrated that over 6% of the total blood Hg level in pregnant women could well be attributed to amalgam fillings. Moreover, the mean inorganic Hg concentration in blood was as high as 30% of total blood Hg in Norway (Jenssen et al., 2012).

3.4. Comparison of the estimated Hg intake resulting from the FFQ and the toxicokinetic model

Fig. 5 sets forth the residuals as a function of age. Within this residual plot, there is a supposed Hg intake ratio from food of 95% MeHg and 5% inorganic Hg. The bias was minimal in terms of the estimates between the median daily intake of Hg, being 0.043 µg/kg bw/day as estimated by the FFQ and 0.050 µg/kg bw/day as estimated by the toxicokinetic model. That said, the values for the intake of MeHg by the FFQ and the toxicokinetic modelling only had a correlation of 0.38. There was also an intra-class correlation coefficient of 0.298 between

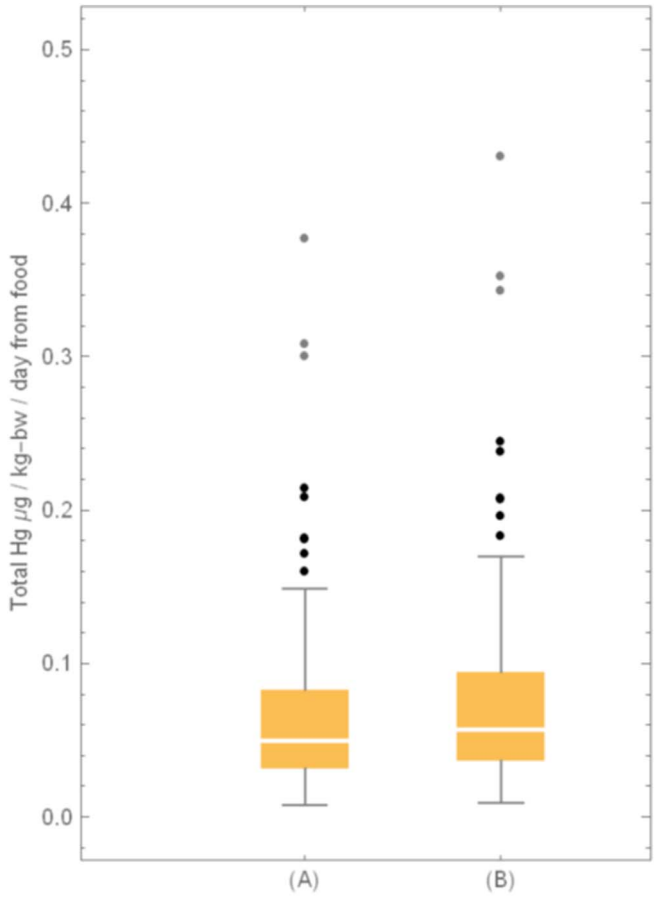

Fig. 3. Increase of the intake of Hg in the whole studied population as a function of the MeHg/inorganic Hg ratio in food. (A) Ratio: 95% MeHg and 5% inorganic Hg. (B) Ratio: 80% MeHg and 20% inorganic Hg. The effect of inorganic mercury from amalgam fillings was not figured into the equation in either case.

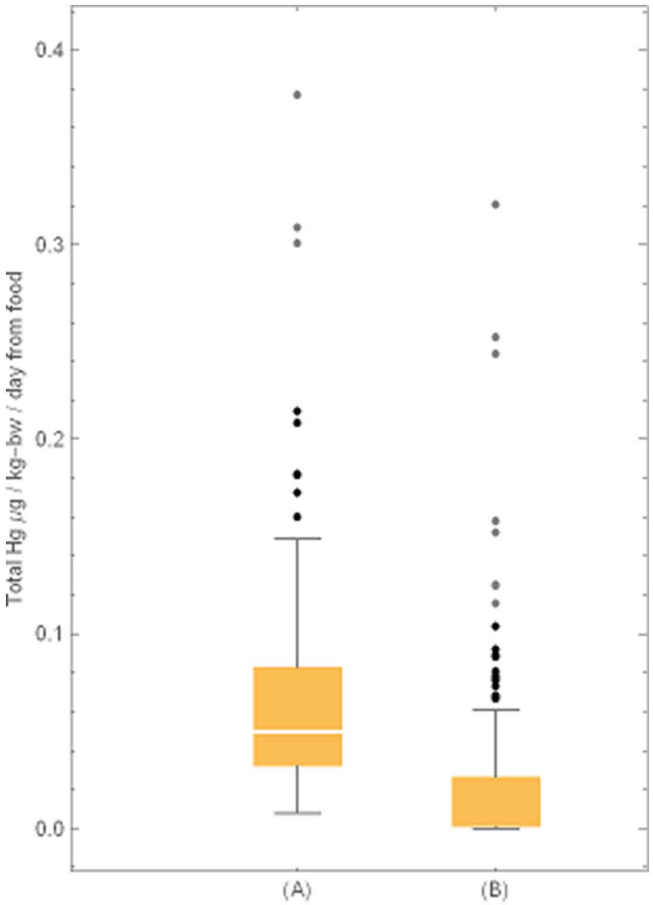

Fig. 4. Calculated intake reduction of MeHg in the whole population as a function of the increased burden of inorganic Hg from amalgam fillings from 0 µg/kg-bw/day (A) to 0.05 µg/kg-bw/day (B). MeHg/inorganic Hg ratio in food was taken as 95% MeHg and 5% inorganic Hg in both cases.

the FFQ and the toxicokinetic model.

Fig. 6 presents the Bland–Altman plot, in which the assumption was a food Hg intake ratio of 95% MeHg and 5% inorganic Hg. The essential deviation in the similarity within individuals over the age of forty is demonstrated in Fig. 5. This deviation can be explained by the amount of inorganic Hg stemming from diet and amalgam fillings (Barregard, 2005; Lindberg et al., 2004; Mergler et al., 2007).

It is difficult to estimate the precise ratio of inorganic Hg on MeHg intake as there is no data on inorganic Hg and dental amalgam fillings in the NFG study. There was a drop of almost 70% in the use of amalgam in Norway between 1995 and 2000, which can be attributed to young people having less amalgam fillings than older people and caries being prevented by use of fluoride. It should be noted that the use of amalgam was becoming even less prevalent when the study was conducted in 2003–2004 (see the Review of Norwegian experiences with the phase-out of dental amalgam use; www.miljodirektoratet.no/old/klif/publikasjoner/2946/ta2946.pdf). Individuals over the age of forty elicited a greater variation in total blood Hg levels than their younger counterparts (Fig. 5). Very few studies include the number of amalgam fillings, a notable exception being Golding et al. (2016), who noted a positive correlation between the number of amalgam fillings in pregnant women and an increase in total blood Hg levels. The Canadian Health Measures Survey (CHMS) 2007–2009 data showed that 17.7 million Canadian aged ≥6 years collectively carry 191.1 million amalgam fillings and 80.4% of them (14.2 million Canadian) had a daily dose of metallic Hg^0 higher than the Canadian chronic reference exposure level (REL) of 0.06 µg Hg^0/m^3. Percentage of Canadians with amalgam that exceed the dose associated with the Canadian REL for Hg^0 was 95% of children (6–11 years), 68% of teenagers (12–19 years), 80% of adults (20–64 years), and 85% of seniors (≥65 years) in the representative population (Richardson, 2014). In addition, significant increases in blood THg, inorganic Hg, and MeHg with dental surface restorations were found in the US population (including 14.703 subjects from The National Health and Nutrition Examination Surveys (NHANES) study (Yin et al., 2016). Moreover, in Germany Hg levels in urine decreased over years because since 1992 amalgam fillings have no longer been recommended for children and women in childbearing age. According to The German Environmental Survey, in 1990/1992 53% of the children had two or more amalgam fillings while the percentage was only 5% in 2003/2006 and 92% at that time had no amalgam fillings (Becker et al., 2013). On the other hand, dental amalgams have been found to increase urinary Hg significantly ($p < 0.01$) in 170 Spanish adults (Castaño et al., 2012).

3.5. General discussion

Humans are exposed to mercury through inhalation of mercury vapor and ingestion of mercury from food, water and dental amalgam. Fish and other seafood consumption is the main source of mercury exposure (Al-Saleh et al., 2011; Clifton II, 2007; NFA, 2012; Sheehan et al., 2014). Several international biomonitoring program (CDC, 2018; GerES, 2018; Kim and Lee, 2012; Statistics Canada, 2018) include a food frequency questionnaire, among other dietary assessment methods, to measure dietary exposures to mercury and other hazardous chemicals. Estimated dietary mercury exposure by using FFQ had some limitations. The elimination half-life of MeHg in humans, varies from

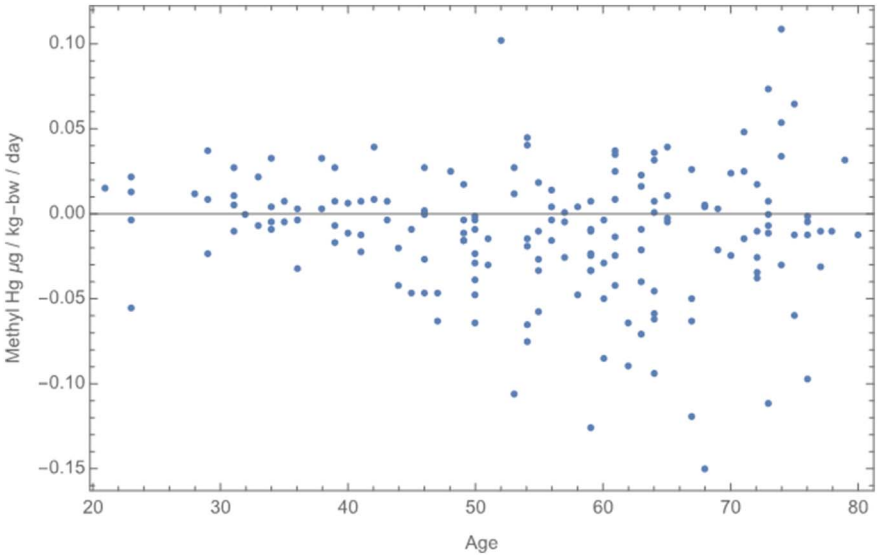

Fig. 5. Residuals between the exposure estimates of Hg intake by the FFQ and toxicokinetic modelling as a function of age.

32 to 164 days after an intravenous dose while it takes at least five biological half-lives in case of regular exposure. The excretory half-lives of metallic and mercuric Hg varies from a few days to anything up to several months. Therefore, present blood Hg concentration indicates mercury exposure several months ago and in the meantime, participants' ability to recall and average their habitual diet correctly is limited. In addition, the dietary exposure is estimated by combining data on consumption and average mercury concentration in specific food items, while, Hg content in food items varies a lot between geographical areas and types of fish, for instance. Furthermore, Hg concentrations could be only available for limited food items. FFQ are rather imprecise instruments for estimating intake (Meltzer et al., 2008). Increased focus or grouped questions can lead to over-reporting or under-reporting of particular food items and inaccurate exposure assessment (Lincoln et al., 2011). On the other hand, the toxicokinetic modelling system presented in this study overcomes FFQ limitations on dietary information. The toxicokinetic modelling depends mainly on the burden of mercury in different body compartments as well as the transfer coefficient between different body compartments.

Mercury concentration in blood provides the sum of exposure from various exposure routes and it depends on the elimination half-life of the mercury in blood and its accumulation in tissues. Few reference values have been established by different organizations as a health-related biological exposure limit value for mercury and other contaminants i.e. PCBs, lead and cadmium (Abass et al., 2016). The German Environmental Surveys derived reference values for mercury in blood or urine. Reference values of 1.5 µg/l and 2.0 µg/l for Hg in Children blood (6–12 years) with fish consumption ≤3 times/month and Adults blood (18–69 years) with fish consumption 3 ≤ times/month, respectively. In addition, values of 0.7 µg/l and 1.0 µg/l in Children urine (6–12 years) without amalgam and Adults urine (18–69 years) without amalgam filling, respectively, were derived (Seifert et al., 2000). Furthermore, two human biomonitoring values (HBM) of 5 µg/l (HBM I) and 15 µg/l (HBM II) mercury in blood were established. HBM I represents the concentration of Hg in humans below which there no risk or adverse health effect are expected and no need for action is recommended. HBM II represents the concentration of Hg in humans above which there is an increased risk for adverse health effects and urgent need to reduce the exposure and to provide individual biomedical care (HBM Commission, 1997; HBM Commission,

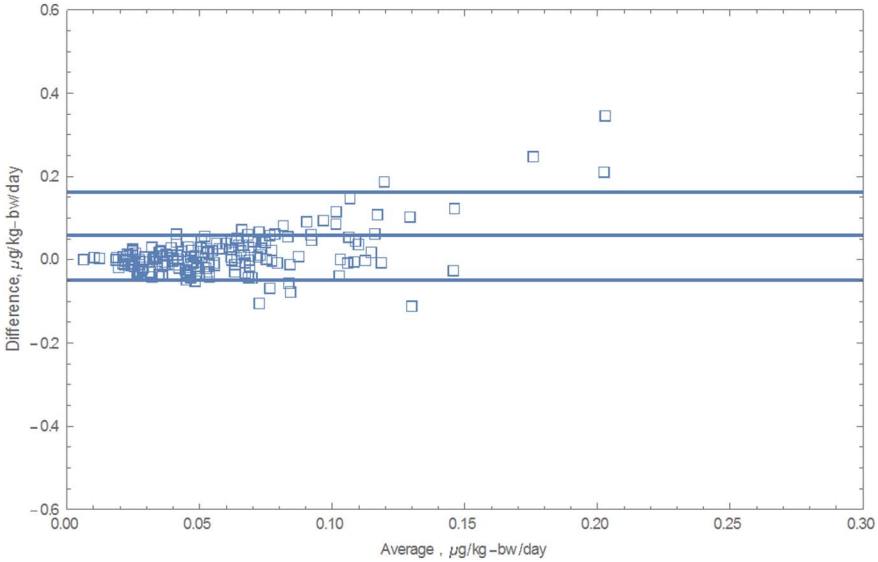

Fig. 6. Bland–Altman plot between the daily intake estimates of Hg in food, calculated by the toxicokinetic model. The FFQ and total Hg concentration in blood were used as biomarkers. On the plot, median and ± 2 ∗ standard deviation lines are presented.

1999). In addition, several guideline values for MeHg in blood were established. US-EPA established a reference dose of 5.8 μg/l MeHg in blood (Rice et al., 2003). In Canada, values of 8.0 μg/l MeHg in blood as an intervention level for children, pregnant women and women of childbearing age were established (Legrand et al., 2010). Values of ≥20 μg/l MeHg in females (≥50 years) and males (> 18 years) indicate increasing risk, while values of ≥100 μg/l MeHg in blood for females (≥50 years) and males (> 18 years) indicate the individual at risk were used as guideline values by Health Canada (1999).

Biological monitoring and modelling are useful complementary tools in estimating human exposure to toxic elements. Despite the wealth of information on the health effects associated with direct measures of Hg and other contaminants in blood, human health risk could be evaluated through other approaches. Blood reference values are employed as toxicological cut-off points for the evaluation of potential health outcomes. On the other hand, the traditional risk assessment process, which incorporates hazard identification, exposure assessment, dose–response assessment and risk characterization, is an analysis used to quantify the probability of harmful and adverse effects to human health. This scientific evidence-based methodology estimates the risks solely based on available dietary information and considers each external source of a contaminant one by one with its own unique characteristics (DeRosa et al., 1998; USEPA-IRIS, 2018). The objective of exposure assessment is to estimate the average daily dose (ADD) and the lifetime average daily dose (LADD), which are used with hazard identification to estimate hazard quotient (HQ) for non-cancer effects and the excess lifetime cancer risk (CR), respectively. Additionally, The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a Provisional Tolerable Weekly Intake (PTWI) of 1.6 μg/kg bw/week. Furthermore, The US-EPA established a reference dose (RfD) of 0.1 μg/kg bw/day (JECFA, 2003; JECFA, 2006; USEPA-IRIS, 2001). Toxicokinetic modelling is a useful complementary tool in quantifying human exposure to elements in the environment by improving the estimation of exposure based on contaminant levels in human blood, which represents sum of exposure routes and scenarios. Toxicokinetic modelling provides a scientific basis for quantitatively estimating exposure and consequently human health risks (Abass et al., 2013; Breivik et al., 2010; Dede et al., 2018; Yu, 1999; Čupr et al., 2011).

Limitations and strengths of the present study should be noted. The main strengths are utilizing a modelling system consisting of a validated two-compartment model to simulate the fate of inorganic Hg, a validated multi-compartment model to simulate the fate of organic Hg, and independent blood compartment for linking the main models together. In addition, data employed in the modelling system were based on detailed information about dietary sources and demographic factors in addition to accurate Hg measurements in blood (Jenssen et al., 2012). In modelling, there are certain limitations that may lead to an under- or overestimation of the actual exposure. Number of participant in this study was limited to 176 participants. In addition, the proportions of different forms of Hg in blood need to be addressed in order to construct a complete model.

In conclusion, while there is a correlation between the Hg data from the toxicokinetic modelling and the FFQ, it cannot be described as particularly strong. Moreover, gaps in the data pertaining to the amount of amalgam in fillings and inorganic Hg in foods need to be addressed in order to construct a complete model. At this point, it can be said with a degree of certainty that the modelling would be more precise if the proportions of different forms of Hg in blood were known. However, it should be emphasized that the levels of total Hg measured from blood provide a firm basis for the future development of toxicokinetic modelling, enabling better estimates of health effects.

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