# Arsenic, cadmium, lead and mercury levels in blood of Finnish adults and their relation to diet, lifestyle habits and sociodemographic variables

Khaled Abass[1,2,3]*, Markku Koiranen[4], Darja Mazej[5], Janja Snoj Tratnik[5], Milena Horvat[5], Jukka Hakkola[1], Marjo-Riitta Järvelin[4,6,7] and Arja Rautio[2]

[1] Research Unit of Biomedicine, and Medical Research Centre Oulu, Oulu University Hospital and University of Oulu, Finland.

[2] Centre for Arctic Medicine, Thule Institute, University of Oulu, Finland

[3] Department of Pesticides, Menoufia University, Egypt.

[4] Institute of Health Sciences, University of Oulu, Finland

[5] Department of Environmental Sciences, Jožef Stefan Institute, Ljubljana, Slovenia

[6] Biocentre Oulu, University of Oulu, Finland

[7] Department of Epidemiology and Biostatistics, MRC PHE Centre for Environment and Health, School of Public Health, Imperial College London, UK

*Corresponding author

Address: Research Unit of Biomedicine, P.O. Box 5000, FI-90014 University of Oulu, Oulu, Finland

Tel.: +358 45 1106720

E-mail addresses: khaled.m.abass@gmail.com, khaled.megahed@oulu.fi

**Abstract**

The Northern Finland Birth Cohort program (NFBC) is the epidemiological and longitudinal prospective general population research program, which was established to promote health and wellbeing of the population in northern Finland. The aim of present study, as a part of the NFBC program, was to analyze the blood levels of arsenic (B-As), cadmium (B-Cd), lead (B-Pb), total mercury (B-Hg), and selenium (B-Se); to compare these levels with threshold limits; to study sociodemographic factors; and to correlate these levels with calcium and hemoglobin. The study was comprised of 249 NFBC subjects, of which 123 were female and 126 were male (ages 31.1±0.3 and 31.1±0.4, respectively). All participants were asked to complete a questionnaire regarding diet and living habits. The geometric means (± SD) of B-As were 0.49 ± 2.80 µg/l and 0.44 ± 2.72 µg/l; B-Cd were 0.18 ± 4.02 µg/l and 0.12 ± 3.21 µg/l; B-Pb were 17.0 ± 1.8 µg/l and 9.06 ± 2.20 µg/l; B-Hg were 2.18 ± 2.02 µg/l and 1.85 ± 1.78 µg/l; and B-Se were 106.0 ± 1.3 and 94.3 ± 1.3 µg/l in males and females, respectively. Among the subjects in the present analysis, 23% of males and 17.1% of females had B-As levels above the ATSDR normal human levels of B-As in unexposed individuals (1.0 µg/l). The B-Pb geometric mean (12.44 µg/l) was approximately one-eighth the CDC toxicological cut-off point of 100 µg/l. Twenty-one individuals (8.4%) exceeded a B-Hg level of 5.8 µg/l. Fifty-eight females (47%) had a B-Hg higher than 2.0 µg/l, the German Federal Environmental Agency cut-off point for women (18-69 years) who consume fish at least three times/month; therefore, their babies could be at risk of of adverse effects during development.

**Keywords:** Toxic metals; Metalloids; Northern Finland Birth Cohort 1966

## 1. Introduction

There is an acknowledged growing awareness of the impact of environmental pollutants on human health. Humans are exposed to environmental pollutants such as toxic metals and other chemical elements, organochlorines and pesticides either voluntarily or involuntarily due to the increase of industrial activities and pollution. Risk assessment of chemicals is widely recognized as a scientific tool to evaluate the probability of adverse human health effects resulting from environmental pollutants. Human internal levels of environmental pollutants depend on several factors such as toxicokinetics, exposure routes and frequencies of exposure (Calafat et al. 2006; Son et al. 2009). Therefore, human biomonitoring is a vital tool for internal levels evaluation of environmental exposure (Angerer et al. 2007; Schulz et al. 2007).

Arsenic (As) has been considered to cause cancer in humans in multiple tissues such as skin, lung, liver, kidney and urinary bladder (Hutchinson 1988; IARC 2002; NTP 2000). Both organic and inorganic arsenic are readily absorbed (70–90%) by the gastrointestinal tract. Arsenic is eliminated fairly rapidly from the human body with a half-life of 40–60 hours (Fowler et al. 2007). Cadmium (Cd) and its compounds are classified by the International Agency for Research on Cancer (IARC) as group 1, carcinogenic to humans (Satarug et al. 2010). Exposure to cadmium is associated with cancer incidence (Akesson et al. 2008; Menke et al. 2009), kidney damage, lung diseases, osteoporosis (Satarug et al. 2010), and toxicity on fetal growth through accumulation and transmission through the placenta (Menai et al. 2012). Cd accumulates in the kidneys, the lungs and the liver. Cd has an exceptionally long half-life in the human body and the biological half-life is estimated to range from 6 to 38 years in the kidney and 4 to19 years in the liver (Hays et al. 2008). Lead (Pb) is classified in its inorganic form as a possible human carcinogen (group 2A) by IARC (Wilhelm et al. 2010). It is well established that leaded gasoline is a major source of population lead exposure and contaminated dust, food and water are also sources of lead exposure (Bernard and McGeehin 2003; Rastogi et al. 2007; Thomas et al. 1999). Relatively low levels of B-Pb (e.g. <200 μg/L) are associated with adverse effects (ATSDR 2007b). Pb is well known as a neurotoxicant. Exposure to lead is associated with intelligence and behavioural deficits (Canfield et al. 2003; Lanphear et al. 2005). Lead could potentially affect any system or organ in the body (Bleecker et al. 2007; Wilhelm et al. 2010). Mercury (Hg) is naturally found in the water, soils and sediments. In the aquatic environment Hg is transformed to the organic form, methyl mercury (MeHg), which is accumulated and biomagnified in fish and marine mammals (Clarkson et al. 2003). Humans are exposed to mercury mostly through fish consumption and amalgam fillings and to a lesser extent from medical and cosmetic compounds (Clifton II 2007; NFA 2012). MeHg represents 80-90 % of the total mercury in blood in the US population (Mahaffey 2005; Tsuchiya et al. 2008) and is found in high levels among populations with higher seafood consumption (Bjornberg et al. 2003; Clarkson and Magos 2006). Exposure to elemental/metallic mercury vapor is common among people with amalgam fillings (Goldman and Shannon 2001; Palkovicova et al. 2008; US EPA 2002). People living in Hg contaminated sites are commonly exposed to inorganic mercury through consumption of contaminated water and food and inhalation of elemental Hg from polluted air (US EPA 2002). Mercury and its compounds are very toxic. Toxicity is largely dependent on the chemical species of mercury. Elemental mercury is neurotoxic and nephrotoxic, while MeHg mercury compounds are primarily neurotoxic with irreversible damage particularly during exposure in early life (Grandjean et al. 1998; Karagas et al. 2012).

Selenium is an element that can be toxic at higher levels, but it is also well known for its essential role in the normal function of many of the systems of the body (Raymond and Ralston 2004). Selenium deficiency can have adverse consequences on these systems. The recognition of selenium's role in health has prompted worldwide response. Selenium status in China and northern Europe is sufficiently low that nationwide trials of selenium supplementation are under way (Blot 1997; Hercberg et al. 1998). Finland has instituted selenium supplementation in its fertilizers (Varo et al. 1994), and Sweden has experimented with adding selenium to its lakes (Paulsson and Lundbergh 1989). Numerous studies indicate that selenium, present in many foods (including fish), protects against mercury exposure. Owing to the extremely high affinity between mercury and selenium, selenium sequesters mercury and reduces its biological availability (Raymond and Ralston 2004).

This paper aims to evaluate the levels of arsenic, cadmium, lead, selenium and mercury in human blood in northern Finland; to compare the geometric means vs. threshold limits; and to study sociodemographic factors in addition to correlation studies with selenium, calcium, and hemoglobin

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## 2. Materials and methods

### 2.1 Selection of study population and data collection

Finland is a subarctic country located between 60 and 70° N latitude and 20 and 31° E longitude. The population density in 1997 was 17 inhabitants per square kilometer, and the total land area is 338,145 $km^2$, of which only 30% is inhabited. The study area comprised Northern Finland. We selected blood samples of 249 subjects (126 male and 123 female) from the Northern Finland 1966 Birth Cohort (NFBC 1966), which consists of all individuals in the two northernmost provinces of Finland (Oulu and Lapland) whose mothers' expected date of delivery was in 1966. The cohort has been followed up since birth; the present analysis is based on a survey conducted in 1997, when the subjects were 31 years of age. The subjects were selected based on being born and living the last 5 years in the Lapland province. The study was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. Aliquots of venous blood (15 ml) were collected after signing of the informed consent. Information on potential cofounders such as personal characteristics, occupation, lifestyle factors, the environment near the residence and dietary factors were collected from questionnaires.

### 2.2 Determination of blood metal/metalloid concentration (As, Cd, Pb and Se)

An aliquot of blood sample (0.3 mL) was diluted ten times with an alkaline solution containing Triton X-100 and ethylenediaminetetraacetic acid disodium salt dehydrate (EDTA) (Barany et al. 1997). Internal standard solution containing Sc, Ge, Rh and Bi was added. For calibration the standard addition procedure was performed. Measurements of prepared solutions were made by an Octapole Reaction System (ORS) Inductively Coupled Plasma Mass Spectrometer (7500ce, Agilent) equipped with an ASX-510 Autosampler (Cetac). Instrumental conditions: Babington nebulizer, Scott-type spray chamber, spray chamber temperature 5 °C, plasma gas flow rate 15 L/min, carrier gas flow rate 0.8 L/min, make-up gas flow rate 0.1 L/min, RF power 1500 W, reaction cell gas helium 4.3 mL/min, isotopes monitored $^{75}As$, $^{78}Se$, $^{111}Cd$, $^{206}Pb$, $^{207}Pb$ and $^{208}Pb$. Tuning of the instrument was

made daily using a solution containing Li, Mg, Y, Ce, Tl and Co. Quantification of all isotopes was performed using one central point of the spectral peaks and five repetitions.

### 2.3 Total Hg determination

Concentration of total Hg in blood was determined by the Direct Mercury Analyser DMA-80 (Milestone Srl, Italy). The system integrates thermal decomposition sample preparation, amalgamation and atomic absorption detection.

In principle, 100-200 mg of blood sample was weighed in a quartz boat and placed in an autosampler. Controlled heating in an oxygenated decomposition furnace was used to liberate mercury from the sample in the instrument. The sample was dried and then thermally and chemically decomposed within the decomposition furnace at 650 °C. An oxygen stream passing through the tube carried the remaining decomposition products through an amalgamator that selectively trapped Hg vapour, which was subsequently desorbed for quantisation. Flowing oxygen carried the Hg vapour through absorbance cells positioned in the light path of a single wavelength atomic absorption spectrophotometer. Absorbance was measured at 254 nm as a function of Hg concentration.

### 2.4 Determination of MeHg in blood

About 200 mg of blood sample was weighed directly in a 30 ml screw-capped Teflon vial to which 6 ml of a mixture of 5% $H_2SO_4$ (Merck, Germany, suprapur), 18% KBr (Merck, Germany, p.a.) and 1.0 ml of a 1 M solutions of $CuSO_4$ (Merck, Germany, p.a.) was added. After shaking the vials vigorously for 15 minutes, 10 ml of $CH_2Cl_2$ (Merck, Germany, supra solv) was added to each vial and the vials were again shaken for 15 minutes and centrifuged for 5 minutes at 3200 rpm. The organic phase was separated from the aqueous phase in a Teflon separating funnel and collected in a 60 ml Teflon vial. A further 5 ml of $CH_2Cl_2$ (Merck, Germany, supra solv) was added to the vials and the same extraction was then repeated. Aqueous phase ethylation was performed by addition of approximately 30 ml of Milli-Q water, evaporation of the samples in a water bath at about 90°C, removal of the remaining $CH_2Cl_2$ (Merck, Germany, supra solv) with nitrogen gas, adjustment of the pH to 4.6 with acetate buffer in a Teflon reaction vial and the addition of 50 µl of 1 % $NaBEt_4$ (Stream Chemicals, USA). The mixture was left at room temperature for 15 minutes and then the ethylated MeHg as ethylmercury was purged onto a Tenax trap for 15 minutes with nitrogen gas. The Tenax trap was then connected to a flow of argon and MeHg was thermally desorbed (180 °C) onto an isothermal GC column. Hg species were converted to $Hg^0$ by pyrolysis at 600 °C and measured by a cold vapour atomic fluorescence detector (CV AFS). The procedure has been described in detail elsewhere (Horvat et al. 1993a; Horvat et al. 1993b; Liang et al. 1994).

### 2.5 Determination of calcium intake and haemoglobin

Calcium intake (g/day) was calculated as a sum of portions (2 dl) of milk products (milk, sour milk, and other milk products, e.g. Bulgarian milk and ice cream) multiplied by 240 mg and the number of cheese slices multiplied by 86.5 g (Laitinen et al. 2005). Haemoglobin was analysed by the Coulter STKR haematological analyser.

### 2.6 Statistical analysis

We used means (arithmetic and geometric), standard deviations and proportions to describe the data. Chi square test for the analyses of categorical variables and analyses of variance (ANOVA) for continuous data were used to test for statistical differences between the groups. The distributions of the variables were explored and logarithmically transformed as necessary to achieve normality. Pearson correlations and p-values between metals, calcium intake and haemoglobin were calculated. P-values lower than 0.05 were regarded as statistically significant. We conducted the analyses separately for males and females. Assessment of socioeconomic position has been described in detail in the study of Kantomaa *et al*. (Kantomaa et al. 2010). 1/2 LOD was applied in cases where measured values were less than LOD when calculating the descriptive statistics. The statistical analysis of the data was performed using SAS 9.3 version software.

## 3. Results and Discussion

### 3.1 Quality control of used methods

Inductively coupled plasma mass spectrometry (ICP-MS) was employed in our study to detect As, Se, Cd and Pb. The ICP-MS is the most widely used method for the determination of total arsenic in blood samples (Hung et al. 2004) and it is a sensitive analytical tool to detect cadmium and lead at low concentrations (Nordberg et al. 2007; Skerfving and Bergdahl 2007). Other technologies used for the determination of As in different biological matrixes, i.e. blood, hair, nails and urine, has been extensively reviewed by Taylor *et al.* (Taylor et al. 2004). In addition to ICP-MS, atomic absorption spectrophotometry and atomic fluorescence are employed to detect cadmium in prepared and treated samples (Nordberg et al. 2007). Furthermore, several other instrumentations are employed for determination of Pb levels, i.e. hand-held X-ray fluorescence and anodic stripping voltammetry, in environmental and biological samples and other matrices (Skerfving and Bergdahl 2007). Mercury concentration was detected by thermal decomposition coupled with amalgamation and atomic absorption spectrophotometry. This detection method is one of the analytical methods typically used for determination of total Hg in blood and hair samples (Berlin et al. 2007).

Analytical precision for As was 15 %, Se, Cd 12 % and for Pb 7%. Limits of detection for As, Se, Cd and Pb calculated as three times the standard deviations of the blank sample, were 0.15, 25, 0.1, 1.5 ng/mL blood sample, respectively. LOD for total Hg was 0.1 ng/mL blood, and precision was 5%. Table 1 shows results obtained for reference material Seronorm Trace Elements Whole Blood L-1 used for quality control for As, Cd, Pb, total and methyl Hg and Se.

The accuracy of the Me-Hg results was verified by analysing Seronorm Trace Elements Whole Blood L-1 as the reference material. The measured values were in good agreement with the certified values or reference values. The precision of MeHg determined in blood samples was 12 % at levels higher or equal to 1 ng/g and 14 % at lower levels (less than 1 ng/g). The LOD of the method for MeHg determination in cord and venous blood calculated on the basis of three standard deviations was 0.02 ng/g.

### 3.2 General characteristics of the study subjects

Table 2 shows the characteristics of the participants. Mean age was 31.1 ± 0.34 years, 50.6 % were males and 49.4% were females. Of the participants, 73% had secondary education, 15% basic and 12% tertiary. 57.3% of the subjects had never smoked, while 27.8% were regular smokers (7 days/week). Mean alcohol consumption was higher among males than females.

**3.3 Blood concentration of Arsenic (B-As)**

Table 3 shows the descriptive statistics for toxic elements and selenium. Geometric mean ± SD B-As was 0.49 ± 2.83 µg/l with a range of 0.08 – 18.02 µg/l in males, while it was 0.44 ± 2.72 µg/l with a range of 0.08 – 5.92 µg/l in females. Table 4 represents geometric means of the examined metals by sociodemographic factors, eating habits and health behaviour. Average levels of B-As in males were higher than B-As in females, but non-significantly (p = 0.415). Arsenic levels were elevated, non-significantly, among those with higher fish consumption and, statistically significantly (p = 0.018), among those with lower reindeer, moose and wild fowl consumption (Table 4) compared to the reference group category.

Arsenic inorganic form is considered a potent developmental neurotoxicant (Calderon et al. 2001; Rocha-Amador et al. 2007). Prenatal exposure to As is correlated with learning and behavioural deficits in exposed rats (Rodríguez et al. 2002). A cross-sectional study in Mexico suggests that exposure to As could have a negative influence on verbal abilities, long-term memory and linguistic abstraction (Calderón et al. 2001). In another cross-sectional pilot study conducted in Miami, USA, children's general neuropsychological function, particularly verbal IQ scores, were significantly impacted by hair As levels (Wright et al. 2006). Thirty individuals, 9 males (7.1%) and 21 females (17.7%), had B-As levels less than the method detection limit (<0.15 µg/l). We also compared our results with values reported in Germany and Canada (Table 5). Males had B-As geometric mean (0.49 µg/l) lower than the Canadian and German values (0.85 and 0.71 µg/l, respectively). Similarly, females had B-As geometric mean (0.44 µg/l) lower than the Canadian and German values (0.88 and 0.71 µg/l, respectively). Among the subjects in the present analysis, twenty-nine males (23%) and twenty-one females (17.1%) had B-As levels above those recommended by the Agency for Toxic Substances and Disease Registry (ATSDR) in unexposed individuals, i.e. above 1.0 µg/l (ATSDR 2007a).

The major part of the arsenic is eliminated in humans faster than in experimental animals. Since arsenic clearance from human blood is very rapid (half-times of 40–60 hours), B-As levels and As urine levels are related to the current exposure. As concentration in urine may be used as an index of exposure to study over-exposed populations, other factors such as diet and timing should be considered (Fowler et al. 2007). Moreover, seafood intake may greatly influence the B-As levels in our study because B-As levels were elevated among those with higher fish consumption. After absorption into the body by the lungs or the gastrointestinal tract, As is transported by the blood to other parts of the body and most of it is cleared from the blood at a very high rate. In a case of human fetal ingestion of 8 g of arsenic trioxide (approximately 3g of As), a much higher concentration of As was observed in the liver (147 µg/g) than in the kidneys (27 µg /g) or muscle, heart, spleen, pancreas, lungs or cerebellum (11–12 µg/g) (Benramdane et al. 1999), while small amounts were also found in other parts of the brain (8 µg /g), skin (3 µg /g), and hemolysed blood (0.4 µg/g). Therefore, B-As is considered a useful indicator of current exposure (Fowler et al. 2007). On the other hand, the concentration of As in hair has been found to be

influenced by the degree of As in the surrounding environment (Hinwood et al. 2003). Characterising As adsorbed onto hair from external sources from arsenic incorporated into hair from the internal body burden might be a challenging task (Fowler et al. 2007). No correlation was found between food, drinking water, dust intake or exposure and hair As in The U.S. National Human Exposure Assessment Survey (NHEXAS) (Pellizzari and Clayton 2006).

It has been proposed that selenium can reduce the cytotoxic and teratogenic effects of As via either the formation of a Se-As complex that is eliminated more rapidly than each compound alone or via selenium rapid methylation of As (Biswas et al. 1999; Styblo and Thomas 2001; Walton et al. 2003). In our studies the geometric means of selenium in male and female blood (106.0 and 94.34 µg/l, respectively) were similar to reference values reported in Germany (79-130 and 60-120 µg/l, respectively). A non-significant correlation was seen between As and Se ($r = 0.103$ and 0.108) for males and females, respectively. (Table 6).

**3.4 Blood concentration of cadmium (B-Cd)**

53.1 % and 43.1% of males and females had B-Cd levels above the method detection limit (0.10 µg/l). The geometric mean of B-Cd in males was 0.18 ± 4.02 µg/l, with a range of 0.05 – 4.03 µg/l, and 0.12 ± 3.21 µg/l, with a range of 0.05 – 3.37 µg/l in females. The geometric means of cadmium were stratified by the characteristics of the participants. Average male B-Cd levels were significantly higher than the average female B-Cd ($p = 0.012$). Cd levels were elevated among smokers ($p < 0.000$) and those with lower educational level ($p = 0.001$) (Table 4).

Geometric B-Cd mean in males (0.18 µg/l) in this study was lower than those reported for 20-39 years old group from Canada during 2007-2009 (0.33 µg/l) and during 2009-2011 (0.26 µg/l). Similarly, the level was lower for females in this study (0.12 µg/l) than that of 20-39 years old female group from Canada during 2007-2009 (0.36 µg/l) and during 2009-2011 (0.33 µg/l). Overall, the geometric B-Cd mean value (0.15 µg/l) for all participants ($n = 249$) in this study was lower than those reported in Germany (0.38), Sweden (0.22), , USA (0.38) and Korea (0.967 µg/l), while it was higher than the pooled geometric B-Cd mean value reported in Brazil (0.082 µg/l).

We also compared our results with the geometric mean of B-Cd concentrations for the U.S. population from the National Health and Nutrition Examination Survey Between 1999 and 2012. The calculated geometric mean blood cadmium levels among total NHANES participants age 1 year and older was 0.412 µg/L during 1999-2000, which decreases to 0.302 µg/L during 2011-2012 (CDC, 2015). Nineteen males (15.1%) and nine females (7.3%) had B-Cd higher than 1.0 µg/l, while forty-two males (33.3%) and twenty-nine (23.5%) females exceeded a B-Cd level of 0.41 µg/l. In an environmentally exposed population, exposure to a low level of Cd was found to be associated with reproductive outcomes, kidney dysfunction, osteoporosis and carcinogenic risk (Satarug et al. 2010; WHO. 1992). Humans are exposed to Cd mainly through food and tobacco smoke (Järup and Åkesson 2009).

**3.5 Blood concentration of lead (B-Pb)**

B-Pb geometric mean ± SD in males was 17.06 ± 1.84, with a range of 3.9 – 145.5 µg/l, and was significantly higher than females, 9.06 ± 2.20 µg/l, with a range of 0.80 – 91.9 µg/l. The B-Pb values were also stratified by the

characteristics of the participants. B-Pb levels were significantly higher among those with a higher consumption of sugar-sweetened soft drinks ($p = 0.004$), smoking ($p = 0.002$), higher use of alcohol ($p < 0.001$) and lower educational level ($p = 0.026$) (Table 4).

The geometric mean of B-Pb in males (17.06 µg/l) in this study was lower than those reported in Brazil (26.46 µg/l), while it was higher than those reported in Canada (14, and 11 µg/l). Similar to males, the geometric mean of B-Pb in females in this study (9.06) was lower than those found in Brazil (17.61 µg/l), while the level in this study was higher than that reported in Canada (8.9 and 8.5 µg/l). Overall, the geometric mean of B-Pb in this study (12.44 µg/l) was lower than reported in the USA (14.3), Sweden (13.4), Germany (19), and Korea (22.9 µg/l). We also compare our results with international guideline values. The United States Centre for Disease Control (CDC) level of concern for B-Pb is 100 µg/l for adults (CDC. 2013). In our study, the pooled geometric mean of B-Pb (12.44 µg/l) was approximately about one-eighth the CDC toxicological cut-off point. Only in two study subjects B-Pb concentrations (145.5 µg/l and 125.9 µg/l) were higher than the CDC level of concern for B-Pb.

B-Pb is the most commonly used marker of Pb exposure in biological monitoring. B-Pb has limitations because there is saturation at high exposure. Pb accumulates in teeth and in the skeleton, where it may be determined by *in vivo* methods that reflect long-term uptake. Therefore, B-Pb concentration serves as an indicator of recent exposure, whereas bone Pb is an indicator of long-term exposure. During pregnancy, Pb is released from bones into the blood. Therefore, B-Pb levels during pregnancy are an intermediate biological marker of Pb levels between bone and soft tissues. Consequently, calcium is a key player in Pb level in females. Insufficient calcium supplementation during pregnancy would increase the demineralisation rate and the release of Pb from the bones, while higher calcium intake would lower B-Bb levels in females during pregnancy (Al-Saleh et al. 2011). A diet rich in calcium acts as a prevention strategy to reduce lead circulation in mothers. In our study, there was a correlation between lead and calcium levels in females $r = 0.239$, $p = 0.010$ (Table 6).

**3.6 Blood concentrations of mercury (B-Hg) and selenium (B-Se)**

All of the studied individuals had blood mercury levels above the method detection limit (0.1 µg/l). The geometric mean ± SD of B-Hg was 2.18 ± 2.02 µg/l, with a range of 0.32 – 14.54 µg/l, and 1.85 ± 1.78 µg/l, with a range of 0.33 – 11.0 µg/l in males and females, respectively. Average male B-Hg levels were significantly higher than the average B-Hg in females ($p=0.043$). B-Hg levels were elevated among those with higher fish, reindeer and alcohol consumption (Table 4). The geometric mean of B-Hg in males (2.18 µg/l) in this study was higher than those reported in Canada for ages 20-39 years (0.61 and 0.62 µg/l) and Brazil for ages 18-39 years (0.94 µg/l). Similar to males, the geometric mean of B-Hg in females in this study (1.85 µg/l) was higher than values found in Canada for ages 20-39 years (0.69 and 0.66 µg/l) and Brazil for ages 18-39 years (0.94 µg/l). The pooled geometric mean of mercury in this study (2.02 µg/l) was lower than reported in Korea for 18 years older adults (4.94 and 3.27 µg/l), while it was higher than B-Hg found in Sweden for 18-74 years old (1.08 µg/l).

We also compare our results with international guideline values. Among the studied individuals only 21 individuals (8.4%) exceeded a B-Hg level of 5.8 µg/l, a value based on the US 1999 re-evaluation, which derived a mercury Benchmark Dose Level (58 µg/l) and advised a ten-fold safety factor (Donaldson et al. 2010). The B-Hg geometric

mean (2.02 µg/l) was about half the level of concern. The highest value (14.54) was approximately 2.5 times the level of concern, but still lower than the normal acceptable range of 20 µg/l (AMAP 1998) and lower than the German Human Biomonitoring Commission reference value of 15 µg/l (at which children and adults will be at increased risk of exposure to mercury) (Ewers et al. 1999). According to the German Federal Environmental Agency, a mercury reference value of 2.0 µg/l should be used as a cutoff point for women (18-69 years) who consume fish at least three times/month (Wilhelm et al. 2004). In our study, 58 women out of 123 (47%) had mercury levels higher than 2.0 µg/l. Consequently, that exposure level of mercury would be risk for adverse effects during any period of development (Bose-O'Reilly et al. 2010). Similarly, the National Health and Nutrition Examination Survey (NHANES, 1999-2000) stated a geometric mean value of 1.02 µg/l for B-Hg in females (16-49 years) which decreases to 0.7 µg/l during 2011-2012 (CDC, 2015). In our study 107 females (86.9%) had B-Hg higher than 1.02 µg/l. The high levels of mercury could be explained by fish consumption and dental amalgam (Al-Saleh et al. 2011; Hsu et al. 2007; Oken et al. 2005; Unuvar et al. 2007). However, in the current study population the age of women was roughly 31 years old and the percentage of amalgam was relatively low. The B-Hg geometric mean increased with fish consumption (Table 4).

The total mercury in blood represents both inorganic and organic forms. Dietary intake of methylmercury is the main source of total blood mercury (Mahaffey et al. 2004). It has been estimated that fish consumption, as the main source of MeHg (Mahaffey et al. 2004; Mozaffarian and Rimm 2006), represents 20% to 85% of the total B-Hg level. In our study, mercury speciation was performed in 70 subjects. The geometric mean level of blood MeHg was 1.66 ng/g. The geometric mean of whole blood concentrations for the Canadian population aged 20-39 years was 0.56 µg/l (Health Canada, 2015). The percentage of methyl mercury relative to total Hg was dependent on the level of the B-Hg. Methyl mercury represented up to 50% of B-Hg, when B-Hg was below 3 µg/l. Above a B-Hg of 3 µg/l, the methylmercury percentage was higher than 50% (up to 96%) of B-Hg. Similar to our findings, the National Institute of Environmental Research (National Institute of Environmental Research 2006) found that, in general, methylmercury contributed to 85% of the total B-Hg. Other sources of B-Hg include dental amalgam fillings, which are the main source of exposure to mercury vapor and inorganic mercury, or foods other than seafoods such as reindeer, moose and wild fowl ($p < 0.001$) (Table 4).

On the other hand, selenium (Se) is an essential nutrient and plays a role in antioxidative enzymes such as glutathione peroxidase (Tapiero et al. 2003). Fish consumption is a source of both mercury and selenium. In addition to seafood, especially fish, other food items such as meat, dietary products and wheat are the main source of Se in the human diet (Lyons et al. 2005; Navarro-Alarcon and Cabrera-Vique 2008; NIH Office of Dietary Supplements. 2015; Smrkolj et al. 2005). In our study, the B-Se geometric mean in males was 106.0 ± 1.27, with a range of 49.5-195.2 µg/l, and was higher than females; 94.34 ± 1.30 µg/l, with a range of 30.0 – 244.8 µg/l. The geometric means of B-Se in males and females in this study were lower than those reported in Canada and Germany (Table 5). Significant correlations were observed between B-Se and B-Hg ($r = 0.275$, $p = 0.002$) in females but not in males (Table 6). Lack of correlation in males could be explained by the lack of other sources of selenium rather than fish or use of reindeer meat. Similarly, Bjornberg *et al*. found a lack of correlation between fish consumption and selenium, but a positive correlation with methyl mercury in cord blood samples (Bjornberg et al. 2003).

While the antagonistic effect of Se-Hg is well known and essential in reducing the harmful impact of Hg on mammals, birds and fish (Beijer and Jernelov 1987; Culvin-Aralar and Furness 1991), little is known about Se-MeHg protective interactions in humans (NRC (National Research Council) 2000). The potential protective effects of Se against MeHg toxic effects could be through binding reactions, but this has not been confirmed in longitudinal epidemiology studies (Chen et al. 2006; Choi et al. 2008; Saint-Amour et al. 2006; Yoneda and Suzuki 1997). On the other hand, Se interacts strongly with As. Se can reduce the teratogenic and cytotoxic effects of As. In humans and mammals, a high level of As compared with Se inactivates the synthesis of selenium-dependent enzymes by binding to either the active center or binding to the other sulfur-group (Das et al. 1995; Harding-Barlow 1983; Samanta et al. 2004).

### 3.7 Correlations between toxic metals in blood

Inter-metal correlation was examined. Table 6 shows the correlations (r) between studied metal/metalloids in males (N = 126) and females (N = 123). Significant correlations were observed between B-As and B-Hg ($r = 0.193$, $p = 0.032$), B-Cd and B-Pb ($r = 0.227$, $p = 0.011$), B-Pb and B-Hg ($r = 0.223$, $p = 0.012$), B-Pb and calcium ($r = 0.239$, $p = 0.010$), B-Cd and selenium ($r = 0.242$, $p = 0.006$) and B-Hg and selenium ($r = 0.275$, $p = 0.002$) in females. Furthermore, significant correlations were observed in males for B-Cd and B-Pb ($r = 0.178$, $p = 0.045$), B-Cd and selenium ($r = 0.210$, $p = 0.018$) and B-Pb and B-Hg ($r = 0.260$, $p = 0.003$). Mercury dental amalgam fillings contain trace amounts of lead and that could explain the correlation between lead and mercury (Minoia et al. 2007).

### 3.8 General discussion

The arsenic, cadmium and lead but not the mercury levels reported in the Northern Finland population were lower than the values reported in other countries. It is well documented that exposure to metals alone affects a number of major organ systems (Díez 2009; Fowler et al. 2007; Nordberg et al. 2007; Skerfving and Bergdahl 2007). Alterations of biomarkers associated with exposure depend on a number of factors such as dose, duration of exposure and genetic factors. Multi-chemical interactions of ecologically relevant mixtures (at relevant concentrations) can have an effect different from the sum of the effects of each component of the mixture. The mixtures of contaminants have either agonistic or antagonistic effects. The internal levels and toxicokinetics of contaminants in the human body may be affected also by the source of contamination, life style and genetic factors (Taylor et al. 2013; Wang and Fowler 2008). The impact of lifetime exposure to mixtures of contaminants has been considered a pressing environmental health problem (Suk et al. 2002). Among a number of other factors, mineral status plays an essential role in metal absorption and accumulation in the human body (Chaney et al. 2001; Reeves 2001; Reeves and Chaney 2001; Reeves and Chaney 2001; Smolders 2001). Zinc, calcium and iron are considered natural competitors of Cd. Moreover, co-exposure to arsenic, cadmium, lead and mercury may produce agonistic or antagonistic interactions, or potential effects that are not observed for single contaminant exposures. Co-exposure to lead and cadmium altered reproductive performance in pregnant rats (Nampoothiri and Gupta 2008). Gestational and lactational co-exposure to lead and cadmium altered hepatic Phase I and Phase II xenobiotic metabolizing enzymes in exposed rats (Pillai and Gupta 2005; Pillai et al. 2009). In humans, co-exposure to a metal mixture, cadmium and lead, has been linked to significant renal dysfunction in people living in the contaminated area (Cui et al. 2005). Exposure to Cd altered not only renal Pb concentrations, but also essential

elements such as Cu and Zn. Exposure to Cd or Pb or both reduced the accumulation of As (Wang and Fowler 2008). Human occupational chronic exposure to lead and cadmium altered a number of oxidative stress markers such as alpha-glutathione-S-transferase, which is a useful biomarker for clinical renal disease (Garçon et al. 2004; Garçon et al. 2007). Combined exposure to lead and cadmium also altered the essential trace elements (Cu, Se, and Zn) in occupationally exposed individuals (Wasowicz et al. 2001; Wasowicz et al. 2003).

## 4. Conclusions

In summary this study provides the blood levels of 4 studied toxic metals in Northern Finland. Arsenic levels were elevated, statistically significantly, among those with lower reindeer, moose and wild fowl consumptions ($p = 0.018$). B-Cd levels were higher among smokers ($p < 0.001$) and those with a lower educational level ($p= 0.001$). B-Pb levels were elevated among those with higher consumption of sugar-sweetened soft drinks ($p = 0.004$), smokers ($p = 0.002$), higher use of alcohol ($p < 0.001$) and lower educational level ($p= 0.026$). Average male B-Hg levels were significantly higher than the average in females. B-Hg levels were elevated among those with higher fish, reindeer, moose and wild fowl consumptions ($p < 0.001$), and alcohol consumption ($p = 0.037$). Future research is needed to investigate environmental and cultural factors contributing to human exposure.

## Conflicts of interest

None of the authors has a conflict of interest related to this study


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