International Journal of Hygiene and Environmental Health 230 (2020) 113623

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Health risk assessment of arsenic exposure among the residents in Ndilǫ, Dettah, and Yellowknife, Northwest Territories, Canada

Janet Sze-Jing Cheung [a], Xue Feng Hu [a], Rajendra Prasad Parajuli [a], Renata Rosol [a], Allan Torng [b], Asish Mohapatra [c], Ellen Lye [d], Hing Man Chan [a,*]

[a] Department of Biology, University of Ottawa, Ottawa, ON, Canada, K1N 6N5
[b] Department of Health and Social Services, Government of the Northwest Territories, Yellowknife, NT, X1A 2L9, Canada
[c] Environmental Health Program, Regulatory Operations and Enforcement Branch, Health Canada, Calgary, AB, Canada, T2G 4X3
[d] Population Studies Division, Environmental Health Science & Research Bureau, Health Canada, Ottawa, Ontario, K1A 0K9, Canada

ARTICLE INFO

Keywords:
Biomonitoring
Biomonitoring equivalents
Reference values
Risk assessment
Arsenic
Biomarker

ABSTRACT

There are concerns in Yellowknife, Northwest Territories, Canada, about arsenic exposure due to past mining operations, particularly the former Giant Mine. The objective of this study was to characterize the risk of arsenic exposure and associated risk factors among the local residents. Arsenic (As) and its species were quantified in urine (n = 1966) using inductively coupled mass spectrometry. Children in the study were found to have significantly higher ($p < 0.05$) urinary inorganic-related As (uiAs) concentrations than children in the general Canadian population, as well as adults in the study. Additionally, uiAs concentrations in children, particularly those above the 95th percentile, are above the Biomonitoring Equivalents (BE) levels that are associated with dermal effects, vascular problems and cancer risks. Multiple linear regression results showed that market seafood (fish and shellfish) and rice consumption frequency were significantly positively associated with uiAs. Specific to children, drinking lake water was positively associated with uiAs. Specific to adults, consumption of local mushrooms and berries were significantly positively associated with uiAs while there was a significant negative association with age, smoking and recreational water activities. The risk factors identified in this research can be used for public health education to lower arsenic intake. Overall, these results support the need for an ongoing monitoring program.

1. Introduction

Arsenic (As) is a naturally occurring metalloid in the Earth's crust that can be released into the environment through natural processes (e.g. volcanic eruption and weathering) and anthropogenic activities such as mining and smelting (Oremland and Stolz, 2003). Arsenic exists in the environment as both inorganic and organic forms. Inorganic arsenic (e.g. $As^{3+}$and As^{5+}) is the more abundant form found in mineral, rock, water, air and food (Gomez-Caminero et al., 2001). While organic forms of arsenic (e.g. arsenobetaine, arsenocholine, arsenosugars, and arsenolipids) are predominantly present in fish, shellfish, and algae. Human exposure to arsenic, through sources such as contaminated drinking water and food, is a global public health concern (Ng et al., 2003). Arsenic, specifically inorganic arsenic and related forms (e.g. methylated arsenic species), is known to be toxic. Chronic exposure to inorganic arsenic has been associated with adverse health outcomes, including dermal effects, cardiovascular disease, and impaired lung function (Chen et al., 2013; Parvez et al., 2013; Rahman et al., 2006). Furthermore, inorganic arsenic is a human carcinogen as classified by the International Agency of Research on Cancer (IARC). Moderate to elevated chronic exposures have been observed to lead to increases in cancers of the lung, skin, bladder and kidney in arsenic-endemic areas (Chiang et al., 1993; Ferreccio et al., 2000; Smith et al., 1998; Tseng et al., 1968; Yuan et al., 2010a).

Given its established toxicity and ubiquitous presence in the environment, arsenic has been measured in national biomonitoring programs in countries including France, Germany, South Korea, the United States and Canada (Aylward et al., 2014; Health Canada, 2010; Lee et al., 2012; Saoudi et al., 2012; Schulz et al., 2007). Human biomonitoring is broadly defined as the measurement of a given chemical or product in a biological medium (e.g. arsenic in urine) as a proxy for body burden. The use of biomonitoring data for human health risk assessment

* Corresponding author. 180, Gendron Hall, 30 Marie Curie, Ottawa, ON, K1N 6N5, Canada.
E-mail address: laurie.chan@uottawa.ca (H.M. Chan).

https://doi.org/10.1016/j.ijheh.2020.113623
Received 9 June 2020; Received in revised form 28 August 2020; Accepted 1 September 2020
Available online 12 September 2020

can be limited because of the lack of guideline values for concentrations of contaminants in biological matrices (Hays et al., 2008). The biomonitoring equivalents (BE), which relates the concentration of a chemical in a biological matrix (e.g. urine) to existing exposure guideline values (e.g. tolerable daily intake, reference dose) , has become a useful screening tool for biomonitoring data (Hays et al., 2007). BEs have been developed for inorganic-related arsenic species (As^{3+} and As^{5+}) as well as its metabolites (monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA)) in urine (Hays et al., 2010). It should be noted, consumption of certain seafoods can contribute to urine DMA concentrations (Taylor et al., 2017). Thus, seafood consumption needs to be taken into consideration as a potential confounder for risk assessments. Nevertheless, the sum of urinary inorganic-related arsenic (As^{3+} +As^{5+}+MMA + DMA) is commonly used as biomarkers for arsenic exposure in biomonitoring studies and risk assessment. Additionally, urine is considered as the most consistent and reliable biomarker of recent arsenic exposure, reflecting exposure of 4–5 days (Hughes, 2006). However, urinary arsenic values represent exposure for a single point in time and are not necessarily reflective of chronic, long-term exposure.

In Canada, arsenic is generally present in the environment at low levels except for some regions (Wang and Mulligan, 2006). Nonetheless, arsenic is one of the chemicals included in the Canada Health Measures Survey (CHMS), a nationally representative government-run longitudinal study aiming to characterize the environmental health of Canadians (Haines et al., 2017). Based on the results of CHMS, a reference value derived from the 95th percentile (RV95) of 27 μg/L has been calculated for total arsenic in urine, which includes both organic and inorganic forms (Saravanabhavan et al., 2017). The reference value can be used as a screening value indicating the upper margin of background exposure of a chemical for the Canadian population.

Arsenic exposure is of more significant concern in areas of Canada with the higher geological presence of arsenic or anthropogenic sources. Yellowknife, Northwest Territories, has been shown as a hotspot of arsenic due to geological presence of arsenopyrite and proximity to past mining operations, particularly Giant Mine (Jamieson, 2014). Giant Mine was a gold mine in operation from 1948 to 2004, located 4 km north of city limits (Keeling and Sandlos, 2012). Gold extraction from arsenopyrite ores consisted of a roasting process that resulted in arsenic trioxide (As_2O_3) as a by-product, which was emitted freely for the first three years until 1951 when attempts to control emissions were made. Such emissions have been linked to contributing to local environmental arsenic levels. In addition, mining operations have left a legacy of 237, 000 tonnes of arsenic trioxide in underground chambers (Jamieson, 2014). While local geology is rich in arsenic, a spatial gradient in soil, lake water and lake sediment concentrations corresponding to historical mining emissions from Giant Mine has been reported (Galloway et al., 2012; Houben et al., 2016; Jamieson et al., 2017; Palmer et al., 2015). For example, arsenic concentrations in local lake waters have been reported to be as high as 60 times the drinking water guideline of 10 μg/L, with the highest concentration measured in a small lake near the mine (Palmer et al., 2015). Meanwhile, soil concentrations as high as 4700 mg/kg have been linked to historic roaster emissions (Jamieson et al., 2017). As a result, there are public health concerns about environmental contamination of arsenic and other metals due to the initial uncontrolled roaster emissions as well as potential surface runoff and groundwater migration. However, the degree to which the population living in the Yellowknife area is exposed to arsenic is currently unknown.

The first objective of this study was to characterize the risk of arsenic exposure by comparing inorganic related arsenic (uiAs) concentrations to the established reference values from the CHMS and the BE values. The second objective was to identify risk factors associated with elevated inorganic arsenic exposure among the residents of the City of Yellowknife, the North Slave Métis Alliance (NSMA) and the Yellowknives Dene First Nation (YKDFN) communities of Dettah and Ndilǫ.

2. Materials and methods

2.1. Ethics

The presented research was conducted following the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and in particular Chapter 9, research involving the First Nations, Inuit and Métis Peoples of Canada (Canadian Institutes of Health Research; Natural Sciences and Engineering Research Council of Canada; Social Sciences and Humanities Research Council, 2018), and the document entitled: Indigenous Peoples & Participatory Health Research: Planning & Management, Preparing Research Agreements published by the World Health Organization (Fediuk and Kuhnlein, 2003). The study also follows the First Nations principles of Ownership, Control, Access and Possession (OCAP®) of data (Schnarch, 2004).

The study is approved by the Health Sciences and Sciences Research Ethics Board of the University of Ottawa (http://research.uottawa.ca/ethics/reb) and the Aurora College Research Ethics Committee. In addition, the study has been granted a Scientific Research License from the Aurora Research Institute in Northwest Territories. Individual participation in the project was voluntary and based on informed written consent following an oral and written explanation of each project component.

2.2. Study population and data collection

The Health Effects Monitoring Program is a prospective cohort study. A more detailed description of the study and its design can be found in Chan et al. (2020, *under review*). A total of 2037 individuals from ages 3 to 86 participated in the baseline study. Recruitment and data collection of the baseline cohort was conducted in two waves; the first wave occurred from September to December 2017, and the second wave occurred from April to June 2018.

The study consisted of residents living in Yellowknife as well as the First Nation communities of Dettah and Ndilǫ. Under the recommendation of the local stakeholders, different recruitment strategies were developed for data collection from population groups in the area: (1) Yellowknives Dene First Nation (YKDFN), (2) the North Slave Métis Alliance (NSMA), and the general population of Yellowknife, which was further grouped into (3) Random Selection and (4) Volunteer.

For the Yellowknife general population, households were randomly selected from a list of residential addresses provided by the City of Yellowknife to obtain a representative sample. The inclusion criteria were residents of Yellowknife between the ages of 3 to 79 that have lived in Yellowknife for at least one year on the day of the interview. In the first wave of recruitment, the age range was 6 to 79 years, and it was expanded to ages 3 to 79 in the second wave, which was done to include more child participants. One adult and one child, if applicable, were selected from each consenting household based on the upcoming birth date. In response to the request of the Yellowknife residents during the consultation period, the study also included individuals not selected for random sampling above the age of 3, as a separate sample group labelled as volunteers. All members of the local indigenous communities, the Yellowknives Dene First Nation and North Slave Métis Alliance, above the ages of 3, were also invited to participate on a voluntary basis.

All participants were asked to provide a biological sample of urine and to complete a questionnaire. The questionnaire was conducted by a trained research assistant consisting of lifestyle and potential exposure information (e.g. age, gender, smoking status, water sources, hunting, fishing, etc.), as well as a food frequency questionnaire regarding consumption of local fish. All participants were asked to refrain from seafood consumption three days prior to urine sampling to control for the potential contribution of organic arsenic and DMA that may come from certain seafood. First-morning urine samples were collected by the participants at their earliest convenience. Once collected, urine samples were kept at 4 °C and shipped to the laboratory at the University of

Ottawa within five days.

A total of 2037 individuals, ages 3 to 86, participated in the baseline study of the Health Effects Monitoring Program, as detailed in Fig. 1. Of the 2037 participants, a total of 1966 (497 children, 1469 adults) participants in the study provided urine samples for chemical analysis: 870 randomly selected participants (211 children, 659 adults), 856 volunteers (198 children, 658 adults), 194 YKDFN members (75 children, 119 adults) as well as 46 NSMA (13 children, 33 adults).

2.3. Laboratory analysis

Urine samples (n = 1966) were shipped on ice from Yellowknife to the University of Ottawa. Within 24 h of arrival, the urine samples were divided into aliquots. The aliquots for arsenic quantification were then stored at −20 °C until analysis for total arsenic and arsenic speciation.

All chemical analyses were performed at the Laboratory for the Analysis of Natural and Synthetic Environmental Toxicants (LANSET) at the University of Ottawa.

On the day of analysis, urine samples were thawed then kept on ice. Total arsenic (TAs) was analyzed in urine using inductively coupled plasma mass spectrometry (ICP-MS) (7700x ICP-MS, Agilent Technologies, Mississauga, ON). Urine was diluted 1:10 in 1% nitric acid (Sigma Aldrich (cat. # 84385-2.5l) prior to total metal analysis. For arsenic speciation, samples were diluted in 10 mM ammonium phosphate dibasic, which was prepared by dissolving ammonium phosphate dibasic (Sigma, cat#379980-100G) in Milli-Q water (Millipore) and pH adjusted to 8.25 with 28% Ammonium hydroxide solution (Sigma, Cat#: 338818-100 ML). Measurement of As species (As^{3+}, As^{5+}, MMA, DMA and arsenobetaine) was performed with an Agilent 1200 Infinity Liquid Chromatography (LC) system coupled to an Agilent 7700x ICP-MS (Agilent Technologies, Mississauga, ON). The limit of detection (LOD) of TAs in urine was 0.012 μg/L, and the LOD of arsenic species was 0.005 μg/L. Concentrations below the LOD were replaced with half the LOD.

For quality assurance/quality control (QA/QC), certified reference materials from the National Institute of Standards and Technology, field blanks, and spiked samples were used. The As standards included 1000 mg/L of arsenite (Spex Certiprep, Cat#SPEC AS3M), arsenate (Spex Certiprep, Cat#SPEC-AS5M), 10 mg/L of dimethylarsonic acid (Spex-Certiprep, cat# SPEC-AS-DMA) and methylarsonate (SpexCertiprep, cat# SPEC-AS-MMA). Arsenobetaine stock solution of 1000 mg/L was prepared by precisely weighing and dissolving arsenobetaine salt. The recovery rates of all NIST reference materials and spiked samples tested were not significantly different from 100%. The precision expressed as the relative standard deviations of 20 measurements of the spiked standard was 5% for As^{3+}, 11% for As^{5+}, 3% for MMA, 3% for DMA and 6% for arsenobetaine. Arsenic in the blank samples was not detectable.

An interlaboratory comparison was also conducted to assess laboratory performance. A total of 50 randomly selected urine samples (~2.5% of all urine samples collected) were sent to the Institut Nationale de Santé Public du Québec (INSPQ) for duplicate analysis. There was no statistical difference ($p > 0.05$) between the results obtained from the University of Ottawa and INSPQ laboratories.

2.4. Statistical analysis

Statistical analyses were performed using Stata v14.1 (StataCor LP, College Station, TX, USA) and R v.3.5.3 (R Core Development Team, 2017). For the purpose of analysis, data were organized into three categories based on the recruitment strategy, including random selection, volunteer, and YKDFN. Due to the small sample size (n = 46), NSMA participants group were excluded from group comparisons (Table 1, Figs. 2–4). Within each population group, results were sub-divided by age into children (ages 3–19) and adults (20–86). Data for the random selection group of our study were weighted to represent the population of Yellowknife and compared to the CHMS data for the Canadian population.

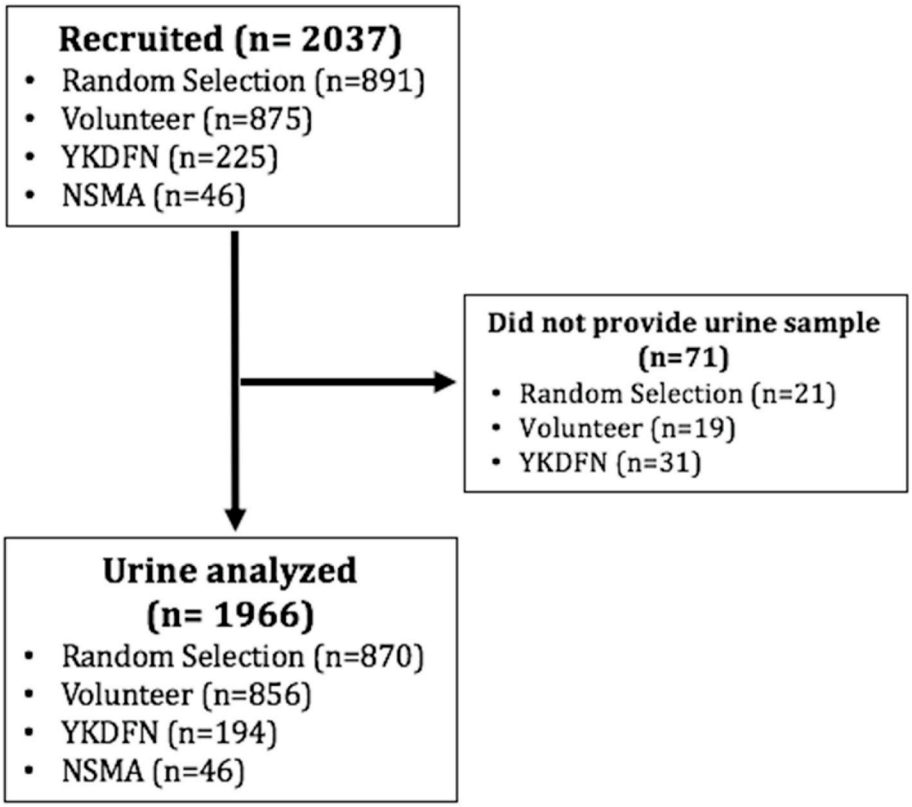

Fig. 1. Summary of recruitment and urine sample collection.

Table 1
Descriptive statistics of inorganic-related arsenic (As^{3+} + As^{5+} + MMA + DMA) in urine (ug/L) among study participants by population (random selection, volunteer, YKDFN and total participants) and age group (Child: 3–19 years old; Adult: 20–86 years old). Starred (*) geometric means indicate a significant difference ($p < 0.05$) in the geometric mean of study participants and CHMS participants of the same age group.

Population	Age	N	Weighted n	GM (95% CI)	P95
Random Selection	Child	211	3794	6.6 (6.0, 7.3) *	22.9
	Adult	659	14290	5.3 (5.0, 5.6)	19.7
	Total	870	18084	5.6 (5.3, 5.9)	20.8
Volunteer	Child	198		7.3 (6.5, 8.1) *	31.2
	Adult	658		5.7 (5.4, 6.0)	18.2
	Total	856		6.0 (5.7, 6.3)	21.7
YKDFN	Child	75		6.5 (5.7, 7.3) *	15.2
	Adult	119		4.5 (4.1, 5.0) *	11.0
	Total	194		5.2 (4.8, 5.7)	14.2
Total Participants[a]	Child	497		6.746 (6.3, 7.2)	23.8
	Adult	1469		5.3 (5.10 5.5)	18.0
	Total	1966		5.6 (5.5, 5.8)	19.3
CHMS	**Child**	4593	7111445	5.4 (5.1,5.7)	19.3
	Adult	3047	21996414	5.4 (5.1,5.7)	22.3
	Total	7640	29809443	5.4 (5.1,5.7)	21.0

P95: 95th Percentile.
[a] Total population includes NSMA population group (n = 46), which were excluded from group comparisons due to the small sample size.

2.5. Summary of urinary arsenic concentrations

Descriptive statistics were generated for concentrations of urinary inorganic-related arsenic, including geometric mean (GM), minimum, maximum, percentiles (P5, P25, P50, P75, P95). Urinary inorganic-related arsenic (uiAs) concentrations were calculated as the sum of inorganic arsenicals and its metabolites: As^{3+} + As^{5+} + MMA + DMA. The sum of urinary inorganic-related arsenic, rather than total arsenic was used as a focus for this risk assessment as the latter may not accurately reflect potential toxicity as non-toxic forms (i.e. arsenobetaine) can be a major contributor to total arsenic concentrations. However, considerations must be made concerning the contribution of certain organic arsenic species in seafood to DMA (Taylor et al., 2017). To control for this potential confounder, participants were asked to refrain from eating seafood for 3 days prior to urine collection.

2.6. Comparison with the Canadian health measures survey (CHMS)

Biomonitoring data from the CHMS was accessed and performed at the Carleton, Ottawa, Outaouais Research Data Center (COOL RDC) at the University of Ottawa, a facility part of the Canadian Research Data Centre Network (CRDCN). Statistics for uiAs (As^{3+} + As^{5+} + MMA + DMA) were calculated from combined data from CHMS cycles 2 (2009–2011), 3 (2012–2013), and 4 (2014–2015). The total sample size was a total of 7640, consisting of 4593 children, 3047 adults. An RV95 of 27 μg/L for total arsenic has been previously reported by Saravanabhavan et al. (2017). For this risk assessment, a reference value (RV95) of 21 μg/L for uiAs was calculated based on the 95th percentile of CHMS data using a similar methodology. Welch's two-sample *t*-tests were used to assess the difference in As concentrations between the population groups and the CHMS data. These tests were corrected for multiple comparisons using the Bonferroni correction and statistical significance using an $\alpha = 0.05$.

2.7. Biomonitoring equivalents

Biomonitoring Equivalents (BE) for uiAs (As^{3+} + As^{5+} + MMA + DMA) have been derived from exposure guideline values associated with both non-cancer and cancer endpoints. For non-cancer endpoints, there is the BE_{POD} and the BE. The BE_{POD} is the urine concentration consistent with the point of departure (POD) associated with vascular problems, hyperpigmentation, and dermal effects, while BE is the value after an intraspecies uncertainty factor (UF) of 3 was applied to the BE_{POD} (Hays

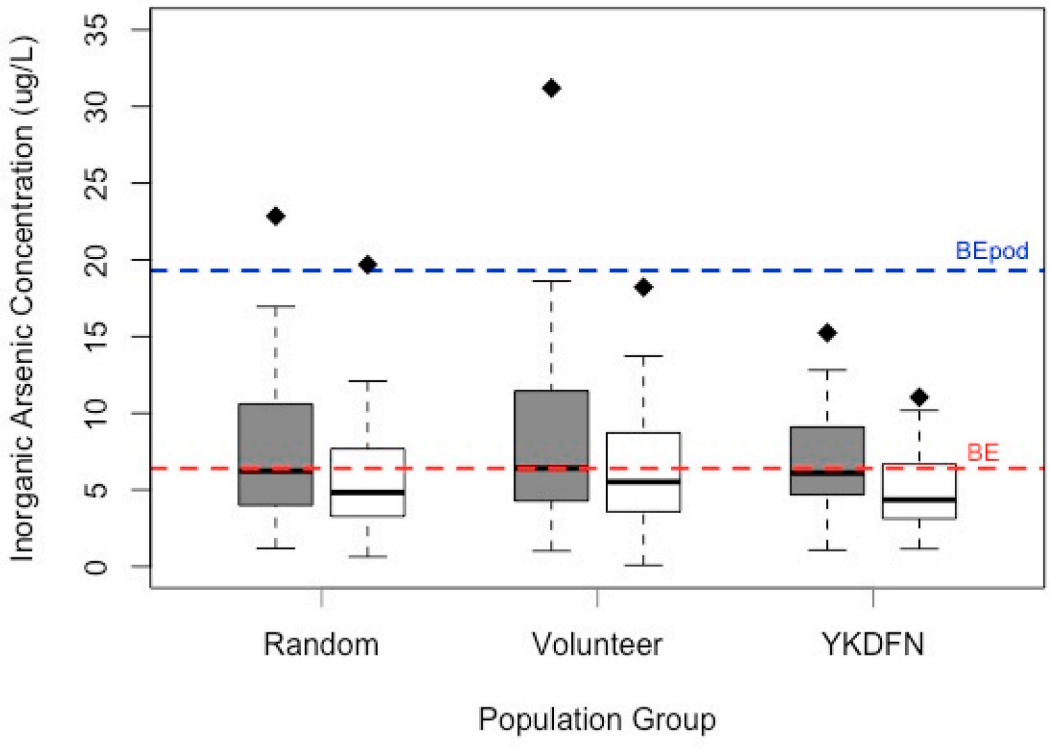

Fig. 2. Boxplot of inorganic arsenic concentrations by population (Random Selection, Volunteer and YKDFN) and age group (Child, 3–19 years old: dark grey; Adult, 20–86 years old: white. The line corresponds to the median, and box corresponds to the interquartile range (IQR), and the whiskers represent 1.5xIQR. For each group, the 95th percentile is depicted as ◆. The blue and red dotted lines represent the BE (6.4 μg/L) and the BE for points of departure (19.3 μg/L), respectively.

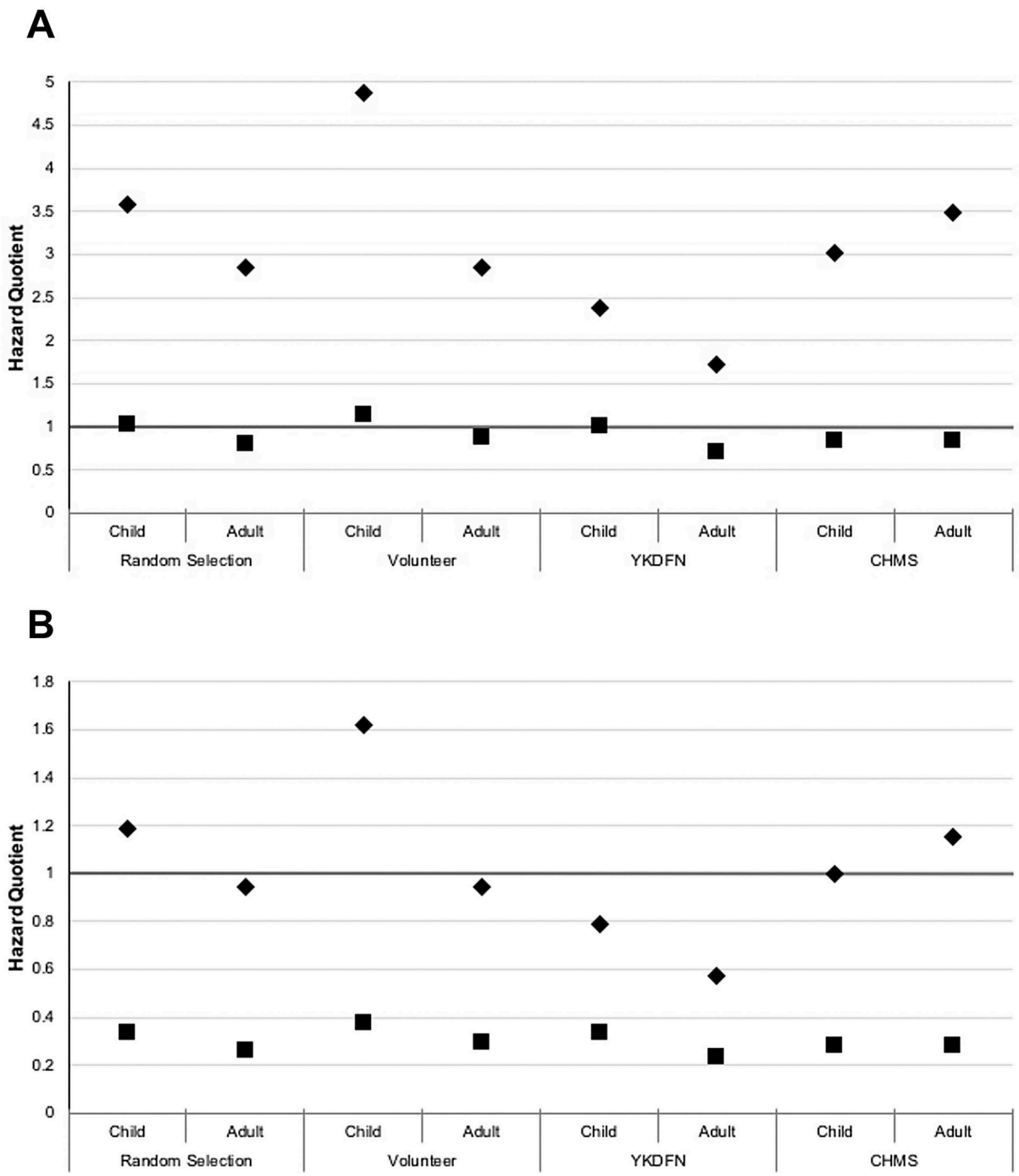

Fig. 3. Hazard quotients (HQ) for inorganic arsenic by population and age group. Participants ages 3–19 are classified as children; participants ages 20–86 are grouped as adults. Squares (■) represent HQ at the geometric mean (GM), diamonds (◆) represent HQ at the 95th percentile (P95). (A) depicts HQs calculated from the BE (6.4 μg/L), and (B) depicts HQs calculation from the BE_{POD} (19.3 μg/L). The line represents a HQ of 1, in which the [biomarker] is equal to the corresponding BE (St-Amand et al., 2014).

et al., 2010). For uiAs, the BE_{POD} is 19.3 μg/L, and the BE is 6.4 μg/L. For cancer endpoint, there is the BE_{RSD}, which is based on a risk-specific dose (RSD) derived from Health Canada's cancer slope factor. BE_{RSD} is the estimated steady-state concentration of urine associated with a given risk level (Ex: 1 in 10, 000) as a result of lifetime chronic exposure at risk specific doses (Faure et al., 2020). The BE_{RSD} can be used to calculate cancer risk. For this study, a risk level range of 1 in 10,000 (i.e. 10^{-4}) to 1 in 1, 000, 000 (i.e. 10^{-6}) was used, where BE_{RSD} is 1.4 μg/L, 0.14 μg/L and 0.014 μg/L for risk levels 10^{-4}, 10^{-5} and 10^{-6}, respectively. Health Canada considers cancer risk at the risk levels of 10^{-5} to 10^{-6} to be essentially negligible.

2.8. Calculation of hazard quotients and cancer risk

Hazard quotients (HQ) were calculated for the non-cancerous endpoint as a ratio of biomarker concentration to the BE (Eq. (1)). Here, [Biomarker] is the concentration of uiAs (e.g. GM and P95), while the Biomonitoring Equivalent is one of the BEs of interest (BE: 6.4 μg/L; BE_{POD}: 19.3 μg/L). HQ values were calculated at both the GM and P95 levels for both BEs. HQs with values exceeding 1 suggest that the

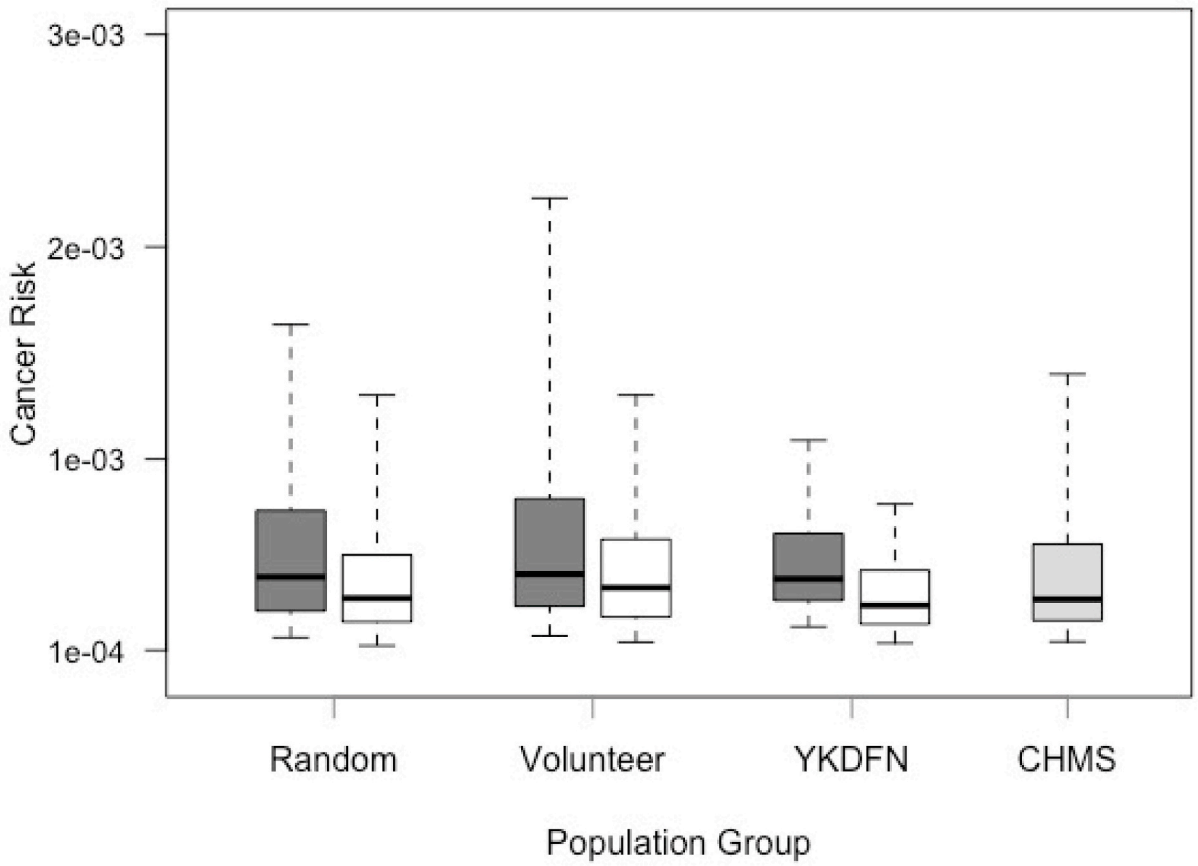

Fig. 4. Cancer risk for inorganic arsenic by population and age based on cancer exposure guideline values (BE_{RSD}) from Health Canada and US EPA. Age is divided into children (ages 3–19) in dark grey and adult (age 20–86) in white. The CHMS data was adopted from Faure et al. (2020) and represented in light grey. The medians are represented by the horizontal line in the box plot. The 25th and 75th percentiles are represented by the ends of the box. The 5th and 95th percentile are represented by the ends of the whiskers.

population in question may be exceeding guidance values from which the BE was derived.

$$HQ = \frac{[\text{Biomarker}]}{Biomonitoring\ \ Equivalent} \quad (1)$$

Cancer risk was calculated using BE_{RSD} derived from risk-specific doses corresponding to the risk level range of 10^{-4} to 10^{-6} (BE_{RSD} for 10^{-4}: 1.4 μg/L; BE_{RSD} for 10^{-5}: 0.14 μg/L; BE_{RSD} for 10^{-6}: 0.014 μg/L) and biomarker concentrations at the 5th, 25th, 50th, 75th and 95th percentiles (Eq. (2)).

$$Cancer\ \ Risk = \frac{[Biomarker]}{BE_{RSD}} \quad (2)$$

2.9. Analysis of risk factors

Factors associated with uiAs concentrations were identified using bivariate analyses and multiple linear regression. For bivariate analyses, Welch's t-tests and ANOVA were used to test for statistical differences in GMs for various potential risk factors associated with arsenic exposure. For all statistical tests, significance was set at $\alpha = 0.05$ and Bonferroni corrections were made. For multiple linear regression analysis, a forward stepwise selection was used, starting with age and sex as the base model. Age and sex were included in the final model, regardless of significance. Variables were included in the final model if the newly entered variable was significant, or if the addition of the variable contributed to an increase in variance explained by the model (i.e. R^2). Age and BMI were continuous variables, while all other variables were categorical. Separate regressions models were created for children (ages 3to19) and adults (ages 20 and over) due to the difference in potential risk factors.

3. Results

3.1. Urinary arsenic concentrations

There was no significant difference in uiAs concentrations of adult and children participants between the two waves of data collection. All results of both waves were combined. A summary of uiAs concentrations by population groups and age group are reported in Table 1. UiAs concentrations ranged from 0.1 μg/L to 152 μg/L. The P95 overall was 19.4 μg/L, which was lower than the CHMS RV95 of 21 μg/L. However, P95 for children (23.9 μg/L) exceeded the RV95, particularly for volunteer children (31.2 μg/L). Overall, 7.9% of child participants exceeded the RV95 of 21 μg/L. Exceedance was highest in volunteer children (11.1%). The GM of uiAs for all study participants was 5.6 μg/L. The GM for CHMS was 5.4 μg/L for both age groups and overall. Overall, no statistical difference ($p < 0.05$) was observed between the GM representative of the Yellowknife population and that of the CHMS data representative of the Canadian population (5.6 μg/L and 5.4 μg/L for Yellowknife and CHMS, respectively). However, uiAs concentrations in children from Yellowknife (GM: 6.6 μg/L) had significantly higher ($p < 0.05$) concentrations than the general Canadian population of the same age group (GM: 5.4 μg/L). For the other population groups, uiAs concentrations were also significantly higher ($p < 0.05$) in children of the Volunteer (GM: 7.3 μg/L) and YKDFN groups (GM: 6.4 μg/L) than the CHMS children (GM: 5.4 μg/L). Among adults, uiAs concentrations in

YKDFN (GM: 4.5 μg/L) were significantly lower ($p < 0.05$) than the CHMS participants (5.4 μg/L). Within the study groups, uiAs concentrations were significantly higher in children than adults for the random selection, volunteer and YKDFN groups. When comparing results of adults across the study groups, uiAs concentrations were significantly higher ($p < 0.05$) in the volunteer group. Among children, no significant difference was observed between the Random Selection, Volunteer and YKDFN study groups.

3.2. Biomonitoring equivalents

Fig. 2 summarizes the distribution of iAs concentrations for each population group by age for the selected BEs (BE: 6.4 μg/L; BE_{POD}: 19.3 μg/L). The GMs for child participants in all population groups (6.6, 7.3, 6.5 μg/L for Random Selection, Volunteer, and YKDFN, respectively) are above the BE but below the BE_{POD}. Meanwhile, the GMs for adults in all groups were below both BEs. Comparatively, the GM from CHMS data (5.4 μg/L) was below both the BE and BE_{POD}. The P95 for both child and adult participants of the Random Selection group (22.9 and 19.7 μg/L), as well as child Volunteers (31.2 μg/L), are above the BE_{POD} while the other groups are above the BE but below the BE_{POD}. Comparatively, the P95 for CHMS participants (21.0 μg/L) is also above the BE_{POD}.

3.3. Calculation of hazard quotients and cancer risk

The HQs values calculated for the GM and P95 are shown in Fig. 3. For the BE, all HQ values were similar using the GM concentrations, while all calculated HQ values were above 1 for the P95 concentrations, ranging from 2.8 to 4.9. (Fig. 3A). Comparatively, results for HQ values based on the BE_{POD} were below 1 for the GM concentrations, and HQ values approached 1 or exceeded 1 at P95 concentrations, with the exception of the YKDFN population group (Fig. 3B).

The cancer risk levels for all three groups of participants (both child and adult) ranged from the 10^{-3} to 10^{-4}, with the highest risk observed for Volunteer children at the 95th percentile (Fig. 4). These values are above the 10^{-5} to 10^{-6} range defined by Health Canada as essentially negligible.

3.4. Analysis of risk factors

The results for uiAs concentrations of participants separated into groups with different potential risk factors are summarized in Table 2. UiAs concentrations were significantly higher in younger participants, those with lower BMI and non-smokers. Additionally, uiAs concentrations were higher in those who consumed market seafood (fish and shellfish) or rice at least once a week or more.

Multiple regression models for children and adult participants are summarized in Table (3). Market seafood (fish and shellfish) intake frequency and rice intake frequency were positively associated with both children and adults after adjusting for age and sex. Drinking lake water was positively associated with uiAs in children only. Meanwhile, in adults, age, smoking status and recreational water activities were negatively associated with uiAs exposure, and consumption of local mushrooms and berries were positively associated with uiAs exposure.

4. Discussion

4.1. Urinary arsenic concentrations

Results from our biomonitoring program showed that the urinary arsenic concentrations of the participants were within a comparable range reported in other national biomonitoring programs (Table 4), with the exception of South Korea, which has much higher concentrations. This has been attributed to diet, particularly seaweed (Lee et al., 2012). However, when compared to a Canadian cohort in rural Québec, our results are comparable to reported uiAs concentrations in children (GM

Table 2
Summary of urinary inorganic-related arsenic (μg/L) by different risk factors.

Variable		n (%)	GM	p-value
Gender	F	1073 (54.6)	5.6	1.0
	M	892 (45.4)	5.6	
	Other	1 (0.1)	17.6	
Age	3–5	81 (4.1)	7.4	**<0.001**
	6–11	226 (11.5)	7.0	
	12–19	190 (9.7)	6.2	
	20–39	576 (29.3)	6.0	
	40–59	617 (31.4)	5.0	
	60+	276 (14.0)	4.6	
BMI	**<18.5**	260 (13.4)	7.5	**<0.001**
	18.5–25	667 (34.5)	6.0	
	25–30	555 (28.7)	5.4	
	>30	454 (23.5)	4.6	
Smoking status (18+ only)	Non-Smoker	739 (50.0)	5.8	**0.02**
	Smoker	304 (20.6)	4.7	
	Former Smoker	435 (29.4)	5.0	
Drink from lake	No	1377 (70.4)	5.6	1.0
	Yes	580 (29.6)	5.7	
Water activities	No	631 (32.3)	5.7	1.0
	Yes	1325 (67.7)	5.5	
Market seafood (Fish and Seafood) intake frequency	None	298 (15.3)	5.4	**<0.001**
	Less than once per month	485 (24.8)	5.5	
	At least once per month	737 (37.7)	5.3	
	At least once per week	424 (21.7)	6.6	
	At least once per day	10 (0.5)	6.7	
Rice Frequency Intake	None	43 (2.2)	5.0	**<0.001**
	Less than once per month	83 (4.2)	4.7	
	At least once per month	394 (20.2)	4.7	
	At least once per week	1218 (62.3)	5.5	
	At least once per day	216 (11.1)	9.4	
Eat local berries	No	890 (45.5)	5.8	0.2
	Yes	1064 (54.5)	5.4	
Eat local mushrooms	No	1687 (86.3)	6.5	0.4
	Yes	267 (13.7)	5.5	
Wave of sampling	Fall/Winter 2017	877 (44.6)	5.7	1.0
	Spring/Summer 2018	1089 (55.4)	5.5	

[a] After Bonferroni correction (Significance: $p < 0.05$).

Table 3
Multiple linear regression model of factors associated with uiAs (μg/L) for children and adults.

Variable	Child		Adult	
	β coefficients	*p* value	β coefficients	*p* value
Intercept	6.79	0.09	11.57	**<0.001**
Sex				
Male	Reference		Reference	
Female	0.01	0.99	0.63	0.11
Age (years)	−0.18	0.10	−0.05	**<0.001**
Market Seafood (Fish & shellfish) intake frequency				
None	Reference		Reference	
Less than once per month	−0.45	0.74	0.75	0.27
At least once per month	0.41	0.75	0.03	0.97
At least once per week	4.64	**0.003**	1.83	**0.01**
At least once per day	N/A		3.04	0.21
Rice intake frequency				
None	Reference		Reference	
Less than once per month	−0.90	0.85	−0.53	0.73
At least once per month	2.83	0.50	−1.46	0.27
At least once per week	2.00	0.62	−0.39	0.76
At least once per day	8.80	**0.03**	3.61	**0.01**
Drink lake water				
No	Reference			
Yes	2.87	**0.02**		
Cigarette smoking status				
Non-Smoker			Reference	
Smoker			−1.03	**0.05**
Former Smoker			−0.65	0.16
Local berry consumption				
No			Reference	
Yes			1.14	**0.008**
Local mushroom consumption				
No			Reference	
Yes			1.33	**0.01**
Recreational water activities				
No			Reference	
Yes			−1.61	**<0.001**
BMI			−0.08	**<0.001**
Adjusted R-Squared	0.075		0.081	

= 7.5 μg/L; n = 43) but lower than concentrations in adults (GM = 8.1 μg/L; n = 261) (Gagnon et al., 2016). Additionally, results from our study were lower than studies in areas of known As contamination such as in Nevada, USA where the uiAs GM in adults (n = 904) was 31 μg/L (Calderon et al., 2013) or in the HEALS study in Bangladesh where the means for total arsenic were 140 μg/L and 136 μg/L in adult males and females (n = 11746), respectively (Ahsan et al., 2006).

Children participants in our study had higher uiAs than adults, and their levels were also higher than children from the general Canadian population (CHMS). For example, uiAs concentrations in children at the P95, particularly volunteer children, were higher than the inorganic As RV95 value of 21 μg/L for CHMS, indicating a higher proportion of child participants were at the upper margin of exposure of the Canadian population level (Table 1 and Fig. 2). Our findings were similar to other cohorts with children and adults where reported urinary concentrations were higher in children compared to adults in studies conducted in Argentina, Bangladesh and Denmark (Gagnon et al., 2016). This could be due to two possible reasons. Children have lower body weight than adults and, as a result, have higher intakes per body weight (Tsuji et al., 2004). Also, children may be exposed to higher intake via hand-to-mouth contact as they play and touch various objects (Cohen Hubal et al., 2000). For example, Canadian children are estimated to have much higher intakes of soil and indoor dust compared to teenagers and adults (Wilson et al., 2013). To assess this possible pathway, we are in the process of gathering additional information on possible soil and dust exposures of child participants with elevated arsenic.

4.2. Biomonitoring equivalents, hazard quotients and cancer risk

Our screening results using BEs were similar to the findings reported for the CHMS (Faure et al., 2020). For both studies, urinary arsenic levels were close to or exceeded the BE for non-cancer endpoints, which are associated with increased risk of hyperpigmentation, dermal effects and vascular complications (Hays et al., 2010). It is important to note that biomonitoring equivalents are not diagnostic but may be used to interpret potential population risk and prioritize follow-up assessments, which is appropriate for a longitudinal study. Concentrations are considered a low priority for any intervention efforts if they are below BE, a medium priority if they fall in between the BE and BE_{POD}, and a high priority if they are above the BE_{POD} value. For the present study, child participants are of medium priority, while the adults are of low priority with regards to the risk of non-cancer endpoints (i.e. hyperpigmentation, dermal effects and vascular complications).

Inorganic arsenic is classified by the International Agency for Research on Cancer (IARC) as a Class-I human carcinogen (Straif et al., 2009). Cancer risk levels calculated based on BE_{RSD} ranged from 10^{-4} and increased to 10^{-3} at the P95 level (Fig. 4). These results are similar to those reported by the CHMS, where the cancer risk estimated for uiAs

Table 4
Arsenic concentrations (GM: Geometric Mean, P95: 95th percentile) in urine reported in national biomonitoring programs in Canada, France, Germany, South Korea and the United States.

Country	Arsenic Species	Study	Year	Age	n	GM (μg/L)	P95 (μg/L)
Canada	As^{3+} + As^{5+} + MMA + DMA	Health Effects Monitoring Program	2017–2018	3–79	1966	5.6	19.4
Canada	As^{3+} + As^{5+} + MMA + DMA	Canadian Health Measures Survey (CHMS)	2009–2011, 2012–2013, 2014–2015	3–79	7640	5.4	21
France	As^{3+} + As^{5+} + MMA + DMA	French National Nutrition and Health Study (ENNS) (Saoudi et al., 2012)	2006–2007	18–74	1500	3.8	10.7
Germany	Total	German Environmental Survey (GerES) (Schulz et al., 2009, 2007)	1990–1992	25–69	4001	6.3	30.2
			1998	25–69	4052	3.9	19.3
			2003–2006	3–14	1734	4.4	14
South Korea	As^{3+} + As^{5+} + MMA + DMA	Korea National Survey for Environmental Pollutants in the Human Body (KorSEP) (Lee et al., 2012)	2008	≥20	4702	43.5	119.7
United States	As^{3+} + As^{5+} + MMA + DMA	National Health and Nutrition Examination Survey (NHANES) (Centers for Disease Control and Prevention, 2019)	2003–2004	≥6	2572	6.52	19.1
			2005–2006	≥6	2588	6.84	18.5
			2007–2008	≥6	2576	6.47	16.8
			2009–2010	≥6	2852	6.56	20.8
			2011–2012	≥6	2517	5.59	17.2
			2013–2014	≥6	2654	4.8	14.7
			2015–2016	≥6	3094	4.41	14.5

was also higher than the BE_{RSD}; the median risk was in the 10^{-4} range, and the P95 was in the 10^{-3} range. Risk levels from both CHMS and our study were higher than the 10^{-5} to 10^{-6} range that Health Canada defines as negligible (St-Amand et al., 2014). The elevated cancer risk from arsenic exposure observed both in our study and the CHMS may be a result of over-estimation due to the contribution of the metabolite DMA to the concentration of uiAs as DMA derives from both sources of organic and inorganic arsenic (Faure et al., 2020). Arsenic-induced cancers may have delayed occurrence, manifesting years after, even after exposure has ceased. Latencies may range from 10 to 50 years, depending on the type of cancer (Martinez et al., 2011; Yuan et al., 2010b). Therefore, continuous efforts to study the long-term relationship between arsenic exposure and cancer rate among the residents of Yellowknife are needed.

4.3. Analysis of risk factors

Our results showed that the frequency of market seafood (fish and shellfish) and rice intake was significantly associated with increased uiAs for both adults and children (Table 3). Fish, seafood, and rice are known to be major dietary sources of both inorganic and organic forms of arsenic (Cubadda et al., 2017). Organic species (e.g. arsenocholine and arsenobetaine), most commonly found in fish and shellfish, are generally not associated with adverse health outcomes (Taylor et al., 2017). The concentration of iAs in rice varies widely, depending on the region in which it is grown in as anaerobic growing environmental conditions favour root uptake (Mitra et al., 2017). There is no rice production locally. Yellowknife residents may be consuming rice imported from areas with higher arsenic in the soil and will warrant further investigations.

We found that uiAs exposure decreased with age, and overall, children had higher exposure than adults. This may be due to the difference in lifestyle and possible exposure scenarios. For example, drinking lake water was observed to be a significant predictor of uiAs in children only. Drinking water is the primary source of arsenic exposure globally. Several studies have observed associations between arsenic concentrations in drinking water and urinary arsenic. Drinking water arsenic concentrations are generally less than 5 μg/L in Canada and, therefore, not the primary source for the majority of Canadians (Health Canada, 2006). However, drinking water may be a major contributor to arsenic exposure for populations living near a source of arsenic (e.g. naturally elevate geological source or contaminated site). We did not measure arsenic in lake waters in our study. However, previous studies have observed spatial gradients linked to mine emissions for water arsenic concentrations in lakes and sediments in Yellowknife (Houben et al., 2016; Palmer et al., 2015). Lake and drinking water concentrations in Yellowknife are regularly tested by the local government. Municipal drinking water in Yellowknife is below Canadian drinking water guidelines of 10 μg/L (GNWT Health and Social Services, 2019). Public health advisories have been issued for certain lakes that are not safe for swimming and fishing. Additionally, the Government of Northwest Territories (GNWT) also does not recommend drinking untreated water from anywhere in the Northwest Territories.

For adults in our study, smokers and the use of recreational water activities were significantly associated with decreased uiAs. The finding that non-smoking adults were associated with higher urinary concentrations was surprising as cigarette smoke has been associated with increased arsenic (Chen et al., 2004; Ferreccio et al., 2000; Hays et al., 2006). The observed negative association between uiAs and water recreational activities was also surprising as it was expected that water activities such as swimming might increase the accidental ingestion of water. We cannot explain these results, but they may be attributed to other confounding factors that were not assessed in our study. Adult uiAs concentrations were also significantly associated with the consumption of local berries and mushrooms. Mushrooms and berries were not considered to be substantial contributors to arsenic in the diet. Mushrooms generally have low arsenic content ranging from 0.27 to 0.51 mg/kg DW (Melgar et al., 2014; Rashid et al., 2018), though one study assessing mushrooms in Hungary reported concentrations >10 mg/kg DW but for certain species (Vetter, 2004). One study assessed arsenic in both mushrooms and berries near a smelter complex, but arsenic levels in both foods were not correlated to smelter emissions (Barcan et al., 1998). Another study analyzed country foods in Canada, including different mushrooms and berries, for arsenic species and found that $As^{3+}+As^{5+}$ ranged from 0.06 to 1.7 mg/kg wet weight for mushrooms and 0.02–5.0 mg/kg for berries (Koch et al., 2013). Recently, a risk assessment study conducted in Yellowknife showed that arsenic concentrations for both mushrooms and berries foraged closer to the Giant Mine were higher, but the estimated risk at the current consumption rate was considered low (Canada North Environmental Services, 2018). Public health advisories in Yellowknife have been issued for mushroom picking and berry foraging. Local berry consumption poses a low health risk though berry picking near historical and current industrial sites is not recommended. Mushrooms within 10 km Giant Mine should not be harvested. Meanwhile, consumption of mushrooms within 10–25 km poses a low health risk, with the exception of the Tricholomataceae family, which should not be consumed within 25 km of the Giant mine (GNWT Health and Social Services, 2019). Our results suggest that the contribution from the consumption of local mushrooms and berries may need to be further characterized.

In conclusion, our study showed that children had higher uiAs compared to adults as well as children in the general Canadian population. Our current results may be used to inform stakeholders on the susceptible groups and risk factors of arsenic exposure. Public engagement through public health messages, education and media should be implemented to inform local communities of how to mitigate exposure to arsenic. Given that children are the vulnerable group to arsenic, children in Yellowknife should be prioritized in follow-up assessments, including a potential further investigation into the association with drinking lake water and characterization of frequency or quantity. Furthermore, as urine is an indicator of recent arsenic exposure, future follow-up could include measurements at multiple time points. The Health Effects Monitoring Program aims to follow-up with child participants every five years, with additional recruitment every cycle.

Funding sources

The Health Effects Monitoring Program is funded through Crown-Indigenous Relations and Northern Affairs Canada. HMC is funded by the Canada Research Chair Program.

Declaration of competing interest

There are none to declare.

Acknowledgements

The implementation of this study was made possible thanks to the Health Effects Monitoring Program Advisory Committee (HEMPAC): Crown-Indigenous Relations and Northern Affairs Canada (CIRNAC), the government of the Northwest Territories Department of Environment and Natural Resources (GNWT ENR), the government of the Northwest Territories Department of Health and Social Services (GNWT HSS), Health Canada (HC), City of Yellowknife, Yellowknives Dene First Nation (YKDFN), North Slave Métis Alliance (NSMA), and Giant Mine Oversight Board (GMOB). We would also like to thank and acknowledge: research assistants and nurses for data collection, Emmanuel Yumvihoze of the University of Ottawa and Alain LeBlanc of the Institut National de Santé for laboratory analysis, Peter Berti for questionnaire platform development, Subramanian Karthikeyan from Health Canada for providing CHMS cancer risk data, and Rossana Manriquez and Jack Singleton from Statistics Canada for sampling methodology.

The analysis presented in this paper was conducted at the Carleton, Ottawa, Outaouais Research Data Center (COOL RDC), which is part of the Canadian Research Data Centre Network (CRDCN). The services and activities provided by the COOL RDC are made possible by the financial or in-kind support of the Social Sciences and Humanities Research Council (SSHRC), the Canadian Institutes of Health Research (CIHR) , the Canada Foundation for Innovation (CFI), Statistics Canada, Carleton University, University of Ottawa, and the Université du Québec en Outaouais. The views expressed in this paper do not necessarily represent the CRDCN's or that of its partners'.

References

Ahsan, H., Chen, Y., Parvez, F., Argos, M., Hussain, A.I., Momotaj, H., Levy, D., Van Geen, A., Howe, G., Graziano, J., 2006. Health effects of arsenic longitudinal study (HEALS): description of a multidisciplinary epidemiologic investigation. J. Expo. Sci. Environ. Epidemiol. 16, 191–205. https://doi.org/10.1038/sj.jea.7500449.

Aylward, L.L., Ramasamy, S., Hays, S.M., Schoeny, R., Kirman, C.R., 2014. Evaluation of urinary speciated arsenic in NHANES: issues in interpretation in the context of potential inorganic arsenic exposure. Regul. Toxicol. Pharmacol. 69, 49–54. https://doi.org/10.1016/j.yrtph.2014.02.011.

Barcan, V.S., Kovnatsky, E.F., Smetannikova, M.S., 1998. Absorption of heavy metals in wild berries and edible mushrooms in an area affected by smelter emissions. Water Air Soil Pollut. 103, 173–195. https://doi.org/10.1023/A:1004972632578.

Calderon, R.L., Hudgens, E.E., Carty, C., He, B., Le, X.C., Rogers, J., Thomas, D.J., 2013. Biological and behavioral factors modify biomarkers of arsenic exposure in a U.S. population. Environ. Res. 126, 134–144. https://doi.org/10.1016/j.envres.2013.04.004.

Canada North Environmental Services, 2018. Giant Mine Human Health and Ecological Risk Assessment.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council, 2018. Chapter 9: Research Involving the First Nations, Inuit and Métis Peoples of Canada. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Government of Canada.

Centers for Disease Control and Prevention, 2019. Fourth Report on Human Exposure to Environmental Chemicals, vol. 1. Updated Tables, (January 2019). Atlanta, GA.

Chen, C.L., Hsu, L.I., Chiou, H.Y., Hsueh, Y.M., Chen, S.Y., Wu, M.M., Chen, C.J., 2004. Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. J. Am. Med. Assoc. 292, 2984–2990. https://doi.org/10.1001/jama.292.24.2984.

Chen, Y., Wu, F., Graziano, J.H., Parvez, F., Liu, M., Paul, R.R., Shaheen, I., Sarwar, G., Ahmed, A., Islam, T., Slavkovich, V., Rundek, T., Demmer, R.T., Desvarieux, M., Ahsan, H., 2013. Arsenic exposure from drinking water, arsenic methylation capacity, and carotid intima-media thickness in Bangladesh. Am. J. Epidemiol. 178, 372–381. https://doi.org/10.1093/aje/kwt001.

Chiang, H.S., Guo, H.R., Hong, C.L., Lin, S.M., Lee, E.F., 1993. The incidence of bladder cancer in the black foot disease endemic area in Taiwan. Br. J. Urol. 71, 274–278.

Cohen Hubal, E.A., Sheldon, L.S., Burke, J.M., McCurdy, T.R., Berry, M.R., Rigas, M.L., Zartarian, V.G., Freeman, N.C., 2000. Children's exposure assessment: a review of factors influencing Children's exposure, and the data available to characterize and assess that exposure. Environ. Health Perspect. 108, 475–486. https://doi.org/10.1289/ehp.108-1638158.

Cubadda, F., Jackson, B.P., Cottingham, K.L., Van Horne, Y.O., Kurzius-Spencer, M., 2017. Human exposure to dietary inorganic arsenic and other arsenic species: state of knowledge, gaps and uncertainties. Sci. Total Environ. 579, 1228–1239. https://doi.org/10.1016/j.scitotenv.2016.11.108.

Faure, S., Noisel, N., Werry, K., Karthikeyan, S., Aylward, L.L., St-Amand, A., 2020. Evaluation of human biomonitoring data in a health risk based context: an updated analysis of population level data from the Canadian Health Measures Survey. Int. J. Hyg Environ. Health 223, 267–280. https://doi.org/10.1016/j.ijheh.2019.07.009.

Fediuk, K., Kuhnheim, H., 2003. Indigenous Peoples & Participatory Health Research: Planning & Management: Preparing Research Assignments.

Ferreccio, C., González, C., Milosavjlevic, V., Marshall, G., Sancha, A.M., Smith, A.H., 2000. Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology 11, 673–679. https://doi.org/10.1097/00001648-200011000-00010.

Gagnon, F., Lampron-Goulet, E., Normandin, L., Langlois, M.F., 2016. Measurements of arsenic in the urine and nails of individuals exposed to low concentrations of arsenic in drinking water from private wells in a rural region of Québec, Canada. J. Environ. Health 78, 76–83.

Galloway, J.M., Sanei, H., Patterson, R.T., Mosstajiri, T., Hadlari, T., Falck, H., 2012. Total Arsenic Concentrations of Lake Sediments Near the City of Yellowknife, Northwest Territories. https://doi.org/10.4095/289911.

GNWT Health and Social Services, 2019. Arsenic in lake water around Yellowknife [WWW Document]. URL. https://www.hss.gov.nt.ca/en/newsroom/arsenic-lake-water-around-yellowknife. accessed 12.9.19.

Gomez-Caminero, A., Howe, P., Hughes, M., Kenyon, E., Lewis, D.R., Moore, M., Ng, J., Aitio, A., Becking, G., 2001. Environmental Health Criteria 224: Arsenic and Arsenic Compounds.

Haines, D.A., Saravanabhavan, G., Werry, K., Khoury, C., 2017. An overview of human biomonitoring of environmental chemicals in the Canadian Health Measures Survey: 2007–2019. Int. J. Hyg Environ. Health. https://doi.org/10.1016/j.ijheh.2016.08.002.

Hays, A.M., Srinivasan, D., Witten, M.L., Carter, D.E., Lantz, R.C., 2006. Arsenic and cigarette smoke synergistically increase DNA oxidation in the lung. Toxicol. Pathol. 34, 396–404. https://doi.org/10.1080/01926230600824926.

Hays, S.M., Aylward, L.L., Gagné, M., Nong, A., Krishnan, K., 2010. Biomonitoring Equivalents for inorganic arsenic. Regul. Toxicol. Pharmacol. 58, 1–9. https://doi.org/10.1016/j.yrtph.2010.06.002.

Hays, S.M., Aylward, L.L., LaKind, J.S., Bartels, M.J., Barton, H.A., Boogaard, P.J., Brunk, C., DiZio, S., Dourson, M., Goldstein, D.A., Lipscomb, J., Kilpatrick, M.E., Krewski, D., Krishnan, K., Nordberg, M., Okino, M., Tan, Y.M., Viau, C., Yager, J.W., 2008. Guidelines for the derivation of biomonitoring equivalents: report from the biomonitoring equivalents expert workshop. Regul. Toxicol. Pharmacol. 51, 4–15. https://doi.org/10.1016/j.yrtph.2008.05.004.

Hays, S.M., Becker, R.A., Leung, H.W., Aylward, L.L., Pyatt, D.W., 2007. Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. Regul. Toxicol. Pharmacol. 47, 96–109. https://doi.org/10.1016/j.yrtph.2006.08.004.

Health Canada, 2010. Report on Human Biomonitoring of Environmental Chemicals in Canada, vol. 1, p. 292.

Health Canada, 2006. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document-Arsenic.

Houben, A.J., D'Onofrio, R., Kokelj, S.V., Blais, J.M., 2016. Factors affecting elevated arsenic and methyl mercury concentrations in small shield lakes surrounding gold mines near the Yellowknife, NT, (Canada) region. PLoS One 11, 1–16. https://doi.org/10.1371/journal.pone.0150960.

Hughes, M.F., 2006. Biomarkers of exposure: a case study with inorganic arsenic. Environ. Health Perspect. 114, 1790–1796. https://doi.org/10.1289/ehp.9058.

Jamieson, H.E., 2014. The legacy of arsenic contamination from mining and processing refractory gold ore at Giant Mine, Yellowknife, Northwest Territories, Canada. Rev. Mineral. Geochem. 79, 533–551. https://doi.org/10.2138/rmg.2014.79.12.

Jamieson, H.E., Maitland, K., Oliver, J.T., Palmer, M.J., 2017. Regional Distribution of Arsenic in Near-Surface Soils in the Yellowknife Area.

Keeling, A., Sandlos, J., 2012. Giant Mine: Historical Summary 21.

Koch, I., Dee, J., House, K., Sui, J., Zhang, J., McKnight-Whitford, A., Reimer, K.J., 2013. Bioaccessibility and speciation of arsenic in country foods from contaminated sites in Canada. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2013.01.047.

Lee, J.W., Lee, C.K., Moon, C.S., Choi, I.J., Lee, K.J., Yi, S.M., Jang, B.K., Yoon, B. jun, Kim, D.S., Peak, D., Sul, D., Oh, E., Im, H., Kang, H.S., Kim, J.H., Lee, J.T., Kim, K., Park, K.L., Ahn, R., Park, S.H., Kim, S.C., Park, C.H., Lee, J.H., 2012. Korea national survey for environmental pollutants in the human body 2008: heavy metals in the blood or urine of the Korean population. Int. J. Hyg Environ. Health 215, 449–457. https://doi.org/10.1016/j.ijheh.2012.01.002.

Martinez, V.D., Vucic, E.A., Becker-Santos, D.D., Gil, L., Lam, W.L., 2011. Arsenic exposure and the induction of human cancers. J. Toxicol. https://doi.org/10.1155/2011/431287.

Melgar, M.J., Alonso, J., García, M.A., 2014. Total contents of arsenic and associated health risks in edible mushrooms, mushroom supplements and growth substrates from Galicia (NW Spain). Food Chem. Toxicol. 73, 44–50. https://doi.org/10.1016/j.fct.2014.08.003.

Mitra, A., Chatterjee, S., Moogouei, R., Gupta, D.K., 2017. Arsenic Accumulation in Rice and Probable Mitigation Approaches: A Review. Agronomy. https://doi.org/10.3390/agronomy7040067.

Ng, J.C., Wang, J., Shraim, A., 2003. A global health problem caused by arsenic from natural sources. Chemosphere. https://doi.org/10.1016/S0045-6535(03)00470-3.

Oremland, R.S., Stolz, J.F., 2003. The ecology of arsenic. Science 300, 939–944. https://doi.org/10.1126/science.1081903.

Palmer, M.J., Galloway, J.M., Jamieson, H.E., Patterson, R.T., Falck, H., Kokelj, S.V., 2015. The Concentration of Arsenic in Lake Waters of the Yellowknife Area. NWT Open File 2015-06 29.

Parvez, F., Chen, Y., Yunus, M., Olopade, C., Segers, S., Slavkovich, V., Argos, M., Hasan, R., Ahmed, A., Islam, T., Akter, M.M., Graziano, J.H., Ahsan, H., 2013. Arsenic exposure and impaired lung function findings from a large population-based prospective cohort study. Am. J. Respir. Crit. Care Med. 188, 813–819. https://doi.org/10.1164/rccm.201212-2282OC.

R Core Development Team, 2017. R: A Language and Environment for Statistical Computing.

Rahman, M., Vahter, M., Wahed, M.A., Sohel, N., Yunus, M., Streatfield, P.K., Arifeen, S. El, Bhuiya, A., Zaman, K., Chowdhury, A.M.R., Ekström, E.C., Persson, L.Å., 2006. Prevalence of arsenic exposure and skin lesions. A population based survey in Matlab, Bangladesh. J. Epidemiol. Community Health. https://doi.org/10.1136/jech.2005.040212.

Rashid, M.H., Rahman, M.M., Correll, R., Naidu, R., 2018. Arsenic and other elemental concentrations in mushrooms from Bangladesh: health risks. Int. J. Environ. Res. Publ. Health 15. https://doi.org/10.3390/ijerph15050919.

Saoudi, A., Zeghnoun, A., Bidondo, M.L., Garnier, R., Cirimele, V., Persoons, R., Fréry, N., 2012. Urinary arsenic levels in the French adult population: the French national nutrition and health study, 2006-2007. Sci. Total Environ. 433, 206–215. https://doi.org/10.1016/j.scitotenv.2012.06.053.

Saravanabhavan, G., Werry, K., Walker, M., Haines, D., Malowany, M., Khoury, C., 2017. Human biomonitoring reference values for metals and trace elements in blood and urine derived from the Canadian Health Measures Survey 2007–2013. Int. J. Hyg Environ. Health 220, 189–200. https://doi.org/10.1016/j.ijheh.2016.10.006.

Schnarch, B.S., 2004. The First Nations Information Governance Centre. Ownership, Control, Access and Possession (OCAP™): the Path to First Nations Information Governance. Ottawa, Canada.

Schulz, C., Angerer, J., Ewers, U., Heudorf, U., Wilhelm, M., 2009. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006 (GerES IV). Int. J. Hyg Environ. Health 212, 637–647. https://doi.org/10.1016/j.ijheh.2009.05.003.

Schulz, C., Conrad, A., Becker, K., Kolossa-Gehring, M., Seiwert, M., Seifert, B., 2007. Twenty years of the German environmental survey (GerES): human biomonitoring - temporal and spatial (west Germany/east Germany) differences in population exposure. Int. J. Hyg Environ. Health 210, 271–297. https://doi.org/10.1016/j.ijheh.2007.01.034.

Smith, A.H., Goycolea, M., Haque, R., Biggs, M. Lou, 1998. Marked increase in bladder and lung cancer mortality in a region of northern Chile due to Arsenic in drinking water. Am. J. Epidemiol. 147, 660–669.

St-Amand, A., Werry, K., Aylward, L.L., Hays, S.M., Nong, A., 2014. Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context. Toxicol. Lett. 231, 126–134. https://doi.org/10.1016/J.TOXLET.2014.10.019.

Straif, K., Benbrahim-Tallaa, L., Baan, R., Grosse, Y., Secretan, B., El Ghissassi, F., Bouvard, V., Guha, N., Freeman, C., Galichet, L., Cogliano, V., WHO International Agency for Research on Cancer Monograph Working Group, 2009. A review of human carcinogens–Part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 10, 453–454. https://doi.org/10.1016/S1470-2045(09)70134-2.

Taylor, V., Goodale, B., Raab, A., Schwerdtle, T., Reimer, K., Conklin, S., Karagas, M.R., Francesconi, K.A., 2017. Human exposure to organic arsenic species from seafood. Sci. Total Environ. 580, 266–282. https://doi.org/10.1016/j.scitotenv.2016.12.113.

Tseng, W.P., Chu, H.M., How, S.W., Fong, J.M., Lin, C.S., Yeh, S., 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in taiwan. J. Natl. Cancer Inst. 40, 453–463. https://doi.org/10.1093/jnci/40.3.453.

Tsuji, J.S., Benson, R., Schoof, R.A., Hook, G.C., 2004. Health effect levels for risk assessment of childhood exposure to arsenic. Regul. Toxicol. Pharmacol. 39, 99–110. https://doi.org/10.1016/j.yrtph.2003.12.002.

Vetter, J., 2004. Arsenic content of some edible mushroom species. Eur. Food Res. Technol. 219, 71–74. https://doi.org/10.1007/s00217-004-0905-6.

Wang, S., Mulligan, C.N., 2006. Occurrence of arsenic contamination in Canada: sources, behavior and distribution. Sci. Total Environ. 366, 701–721. https://doi.org/10.1016/j.scitotenv.2005.09.005.

Wilson, R., Jones-Otazo, H., Petrovic, S., Mitchell, I., Bonvalot, Y., Williams, D., Richardson, G.M., 2013. Revisiting dust and soil ingestion rates based on hand-to-mouth transfer. Hum. Ecol. Risk Assess. 19, 158–188. https://doi.org/10.1080/10807039.2012.685807.

Yuan, Y., Marshall, G., Ferreccio, C., Steinmaus, C., Liaw, J., Bates, M., Smith, A.H., 2010a. Kidney cancer mortality. Epidemiology 21, 103–108. https://doi.org/10.1097/EDE.0b013e3181c21e46.

Yuan, Y., Marshall, G., Ferreccio, C., Steinmaus, C., Liaw, J., Bates, M., Smith, A.H., 2010b. Kidney cancer mortality: fifty-year latency patterns related to arsenic exposure. Epidemiology 21, 103–108. https://doi.org/10.1097/EDE.0b013e3181c21e46.