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Cohort Profile: Health Effects Monitoring Program in Ndilǫ, Dettah, and Yellowknife (YKHEMP)

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Title: Cohort Profile: Health Effects Monitoring Program in Ndilǫ, Dettah, and Yellowknife (YKHEMP)

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Abstract

Purpose: The Yellowknife Health Effects Monitoring Program (YKHEMP) was established to examine the relationship of exposure to arsenic and other chemicals of potential concern (COPCs) such as antimony, cadmium, lead, manganese, and vanadium and health outcomes.

Design: YKHEMP is designed as a prospective cohort study.

Participants: We recruited a total of 2037 individuals, including children (age 3-19) and adults (age 20+), residing in Dettah, Ndilǫ, and Yellowknife, in the Northwest Territories, Canada, in two waves in Fall 2017 and Spring 2018. In Yellowknife, there were 890 (673 adults, 217 children), randomly selected participants with a participation rate of 64%. In addition, we also recruited a total of 876 (685 adults, 191 children) volunteer participants. A total of 225 (138 adults, 87 children) of the Yellowknives Dene First Nation (YKDFN), and 46 (35 adults, 11 children) of the North Slave Métis Alliance (NSMA) participated in the study. Each participant answered a lifestyle questionnaire as well as provided toenail clippings and urine for contaminant testing and saliva samples for testing of genetic polymorphisms associated with arsenic metabolism. Participants also provided consent to have their medical records reviewed by the research team for the past 5 years to allow for the investigation between exposure and health outcomes.

Findings to date: This cohort profile report presents the descriptive statistics of the COPC concentrations in urine and toenail samples. Concentrations in the urine were compared to the population data based on the Canadian Health Measures Survey.

Future plans: The children participants will be re-examined in 2022 and both adult and children participants in 2027. Investigators interested in learning more about how to obtain YKHEMP data can contact ykhemp@uottawa.ca.

Strengths and limitations

- Multiple validations were designed to account for potential inaccuracy in exposure characterization and recalling bias in the questionnaire interview.
- Community meetings were organized with each population to review study protocols and seek public input.
- Does not address the potential long-term effects of legacy arsenic exposure of the populations in Yellowknife when the Giant Mine was still in operation.
- Urine is a good medium to measure arsenic exposure; however, it may not be the optimal one for the other COPCs, e.g., lead.

Introduction

Giant Mine was a gold mine located within the boundary of the City of Yellowknife, where it operated from 1948 to 2004. The site reverted to the Crown when owner Royal Oaks Mine went into receivership in 1999. Gold was extracted from arsenopyrite ores through a roasting process that generated arsenic trioxide as a toxic byproduct. As a result, there are currently 237,000 tonnes of arsenic trioxide dust present at the site, contained in 15 underground chambers, and 4 large tailings ponds. Contaminated mine water is currently treated onsite to ensure it is within approved limits prior to discharge into Baker Creek and eventually to Yellowknife Bay. For its first 10 years of operation from 1948 to 1958, an estimated 20,000 tonnes of arsenic trioxide dust was released into the environment every year without any filtration. Following reports of arsenic poisoning in the 1950s, a baghouse filtration system was installed in 1958 to filter and store the arsenic trioxide in underground chambers.[1]

At present, the mine is considered one of the most contaminated sites in Canada.[2] Although Giant Mine is no longer in operation, there are concerns of chemical contamination originating from the site via surface runoff and groundwater migration or from historical aerial deposition.[3] The list of chemicals of potential concern (COPC) includes arsenic, antimony, cadmium, lead, manganese, and vanadium. Arsenic exposure is of particular concern because of its known toxic effects including increased risk of skin cancer and other health conditions.[4–9] To address concerns about arsenic and other COPCs, the Giant Mine Remediation Project was established and approved by the Mackenzie Valley Environmental Impact Review Board. The Giant Mine Remediation Project's primary goal is to protect human health and safety and the environment. To do so, the Project is focused on the long-term containment and management of the stored underground arsenic trioxide waste, demolition, and removal of on-site buildings, water management and treatment, and the remediation of all surface areas including the tailings ponds at the Giant Mine site. As required by the review board, the Project is subject to 26 measures aimed at preventing significant adverse impacts on the environment and public health and mitigating the public concern.

This research program titled "Health Effects Monitoring Program in Ndilǫ, Dettah, and Yellowknife (YKHEMP)" was developed to make sure the remediation activities that take place at Giant Mine will not have a negative impact on people's health. The project objective will be achieved by investigating the exposure and impact of the COPCs, particularly arsenic, on the Ndilǫ, Dettah, and Yellowknife population. The YKHEMP will be a long-term program that will monitor the level of COPCs within the human population as the remediation at the Giant Mine progresses.

The overall objective of YKHEMP is to implement a broad health effects biomonitoring program for the population of Yellowknife, Ndilǫ, and Dettah, focusing on arsenic and other COPCs such as antimony, cadmium, lead, manganese, and vanadium. It will provide a comprehensive overview of the levels of contaminants currently present in the human population. The specific project objectives are as follows:

a) Investigate any associations between COPC concentrations, particularly arsenic, within the population and observed or reported health outcomes within that same population.
b) Explore results sharing with other related studies to understand sources of contaminant exposure and their relationships with health outcomes.
c) Establish a detailed protocol, including a set of benchmarks for the future ongoing monitoring program.

Cohort description

The YKHEMP is a prospective cohort study, and it comprises four groups of participants; 1) randomly selected Yellowknife participants, 2) Yellowknives Dene First Nation, 3) North Slave Métis Alliance (NMSA) members, and 4) volunteer Yellowknife participants. Yellowknife has a population of roughly 21,183 residents including 1,540 Yellowknives Dene, in 10 districts. Participant recruitment and biomonitoring were conducted from September 2017 to December 2017 (wave 1) and from April 2018 to June 2018 (wave 2) for the baseline survey. The two-wave approach was designed to account for any potential seasonal effect on exposure.

For the Yellowknife general population, a two-stage stratified systematic sampling approach was exploited to yield a representative sample of residents from 3 to 79 years, who have lived in Yellowknife for at least one year, excluding members of the YKDFN and NSMA. Before sampling, a list of the dwellings was prepared. A sample of dwellings was selected from the list. The households in the selected dwellings then formed the sample of households, with the assumption of an 80% response rate . From each selected household, up to one adult (18+) and one child (3-17) was randomly selected based on whose birth date was next. Population aged 6 and above were invited to participate during wave 1, and the population aged 3 and above were included in wave 2.

For YKDFN, a mixed sampling approach was adopted, as suggested by the Yellowknives Dene leadership. All YKDFN members were invited to participate on a voluntary basis. Additional members were contacted and invited to participate if a specific demographic or household characteristic was lacking to better represent the population. For the North Slave Métis Alliance, all members were invited to participate as recommended by the NSMA leadership. In responding to the request of the Yellowknife residents during the consultation period, the study also welcomed any resident who volunteered to participate who formed the fourth group.

A total of 2037 individuals participated in the baseline survey, which included 891 randomly selected general population participants with a participation rate of 64%, 875 volunteer participants from the general population, a total of 225 YKDFN and 46 NSMA members. For the randomly selected participants, survey weights were generated to account for the sampling probability and non-response rate. A set of 500 bootstrap weights was also generated to account for the sampling error. Details of the demographic and socioeconomic characteristics for the four participation groups are shown in Table 1.

Table 1. Demographic and socioeconomic characteristics by participant group in the Yellowknife Health Effects Monitoring Program. The bracketed numbers are the percentage of all participants within the group.

	Random sample	Volunteers	YKDFN	NSMA
Sex				
Male	400 (44.8)	400 (45.7)	97 (43.1)	22 (47.8)
Female	491 (55.2)	474 (54.3)	128 (56.9)	24 (52.2)
Age				
3 to 19	216 (24.3)	206 (23.5)	88 (39.1)	13 (28.3)
20 and above	675 (75.7)	669 (76.5)	137 (60.9)	33 (71.7)
Adult current smoker	121 (13.6)	125 (14.3)	63 (28.0)	13 (28.3)
Working experience				
Giant mine site	47 (6.9)	72 (10.7)	24 (17.4)	5 (14.3)
Hunting	94 (10.6)	127 (14.5)	68 (30.2)	14 (30.4)
Fishing	462 (51.9)	461 (52.7)	113 (50.2)	36 (78.3)
Water recreation activity	595 (66.9)	613 (70.1)	123 (54.7)	33 (71.7)
Local food consumption				
Meat	476 (53.5)	536 (61.3)	216 (96.0)	38 (82.6)
Fish	714 (80.2)	744 (85.0)	194 (86.2)	44 (95.7)
Plant	545 (61.3)	574 (65.6)	71(31.6)	28 (60.9)
Mushrooms	97 (10.9)	459 (18.2)	10 (4.4)	7 (15.2)

YKHEMP is designed as a prospective cohort study that lasts for at least 10 years (Figure 1).

Phase two, 2022 to 2023:

The children who participated in the baseline survey (2017-2018) will be contacted again. A random selection will be conducted to make up for the attrition of participants over the 5-year period, in case that some of these children will not live in Yellowknife at the time of re-sampling.

Phase three, 2027 to 2028:

All participants (children and adults) from the baseline survey (2017-2018) and the children from phase 2 (2022-2023) will be contacted. In addition, another sample of adults and children will be selected in 2027-2028 to make up for the attrition of participants over this 10-year period. This sample will be designed later with the updated values for the population size of Yellowknife and updated requirements for the Project.

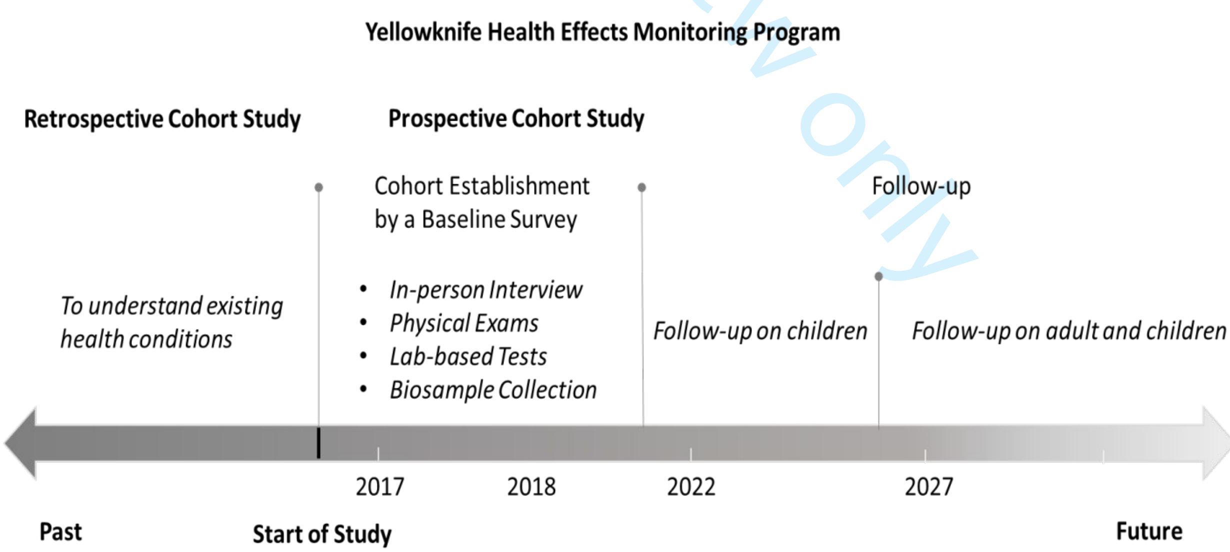

Figure 1. Study Design for the YKHEMP

The retrospective phase of YKHEMP collected the medical history of all participants for the past 5 years. The baseline survey of YKHEMP includes three main components: questionnaire interview, physical examination (YKDFN only), laboratory chemical measurements, and genotyping (Table 2). The medical history included diagnosed diseases, e.g., hypertension, diabetes, cancer and common clinical symptoms associated with contaminant exposure. Diseases were extracted according to International Classification of Diseases, Revision 9 (ICD-9) and clinical symptoms were extracted through keyword searching in the participants' medical records from the Wolf EMR electronic medical record system, Northwest Territories Health Authority.

All participants who provided consent were invited to complete a Lifestyle Questionnaire. The lifestyle questionnaire contained two components: general information and exposure history (e.g. lifestyle, diet, water source, occupational history). Participants were also asked to complete a short Food Frequency Questionnaire (FFQ) on the types and amounts of fish consumed. Information about serving sizes was collected using food models. The FFQ for the YKDFN included additional components including the types and amounts of local traditional foods including wild animals, wild birds, wild berries, wild plants for tea, other edible plants: greens, onions, rhubarb, spruce gum, birch sap and mushrooms consumed, as suggested by the YKDFN leadership. All participants were also asked to complete a medical questionnaire and invited to undergo a brief medical exam that included taking a person's height, weight, and blood pressure.

Urine, toenail, and saliva samples were collected, and COPCs were analyzed for participants. Sample kits were distributed to all participants by trained research assistants to collect urine, toenail clippings, and saliva, at their own time. Participants were instructed to abstain from eating seafood 3 days before urine sampling and to provide the first-morning urine void. Samples were kept at the local research office under appropriate storage conditions: at room temperature for saliva and toenails, and in the refrigerator at 4ºC for urine, and until shipped to the University of Ottawa (urine and toenail) or Génome Quebec (saliva) for analysis within 30 days. All chemical analyses were performed at the Laboratory for the Analysis of Natural and Synthetic Environmental Toxicants (LANSET) at the University of Ottawa. For quality control, certified reference materials, as well as in-house and external quality controls were used (e.g. field blanks and spiked samples). Details of the sample processing and chemical analysis procedures can be found elsewhere (http://www.ykhemp.ca/reports.php). To ensure laboratory analysis quality, 2.5% of the urine samples were randomly selected and sent to Institut National de Santé Publique du Québec (INSPQ). There was a strong correlation between the two sets of results, and there was no statistical difference in both total and inorganic arsenic results.

Genetic polymorphisms may occur as sequences or single nucleotides. The latter is referred to as single nucleotide polymorphism (SNP). Several SNPs have been identified to be associated with arsenic, most notably the metabolism of arsenic.[10–19] Based on previous evidence, 72 SNPs were selected that were hypothesized to underlie inter-individual differences in arsenic metabolism including SNPs in genes of the following pathways and classes: sheath interacting, nucleotide excision repair, organic anion transporter, reduction activity in arsenic metabolism, DNA repair, efflux carrier, transporter (ZIP family metal transporter), one-carbon metabolism, and folate metabolism pathway. In this study, buccal swabs were collected from participants using a DNA Genotek buccal swab kit (OCR-100) and sent to Genome Quebec where DNA was isolated from buccal swab with the QIA symphony instrument along with the DSP Midi kit (cat# 937255, QIAGEN) according to the manufacturer's protocol and genotyped using the Sequenom iPLEX Gold platform.[20]

Table 2. Summary of measurements at baseline in the Yellowknife Health Effects Monitoring Program

Survey component	Measurements
Lifestyle questionnaire	Demographics and socioeconomic information: age, sex, ethnicity, date of birth, education, occupation, marital status, household income, years living in Yellowknife
	Lifestyle: smoking, alcohol drinking, drinking water, hunting, swimming, and fishing
	Occupational exposure: Currently or previously worked in Giant Mine and other occupational exposures
	Environmental exposure: exposure to wood preservatives, chemical fertilizers, pesticides, rat poison, and other chemicals
FFQ for all	Consumption of types and amounts of fish
FFQ for YKDFN	Consumption of different types of locally harvested meat, local lake fish, locally grown vegetables and herbs, and locally collected berries, mushrooms, tea, birch sap and spruce gum
Physical examination	Anthropometric measures: weight, height, and blood pressure (for YKDFN only)
Medical questionnaire for YKDFN	Medication and symptoms: dermatological, respiratory, cardiovascular, hematological, hepatic, neurological, cancer, other
Laboratory chemical measurements	Urinary concentrations of total arsenic, different components of inorganic arsenic, vanadium, manganese, cadmium, antimony, and lead
	Toenail concentrations of arsenic, vanadium, manganese, cadmium, antimony, and lead
Medical records	Diseases certified by ICD-9 codes and medical conditions identified from free text in the medical record
Genotyping	Single nucleotide polymorphism for genes related to arsenic exposure, metabolism, regulation, and DNA repair

Findings to date

We are at the very early stage of analyzing the YKHEMP baseline data. Here, the descriptive statistics of the concentrations of COPCs measured in urine and toenail samples of participants are presented. Currently, the key question addressed was whether the residents of Ndilǫ, Dettah, and Yellowknife had elevated exposure to arsenic and selected COPCs in relation to the general Canadian population. Risk assessment and characterization analysis is part of the reiterative process to identify people at risk and characteristics related to high exposure. The second step is to investigate the disease pattern among YKHEMP participants and compare it to National and regional data. The third step will explore factors associated with COPCexposure and metabolism among YKHEMP participants.

Geometric mean (GM) and the corresponding 95% confidence interval (CI) for urinary and toenail COPC concentrations are reported. Urinary inorganic arsenic concentration was calculated as the total concentration of arsenite As(III), arsenate As(V), monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA). Values below the limit of detection (LOD) were replaced with half the LOD. Sample weights and 500 bootstrap weights were used to adjust for sampling design, generate population-representative statistics, and to produce appropriate variance estimation for both the YKHMEP random sample and the CHMS. Combined data on urine total arsenic, cadmium, and lead collected in CHMS cycles 1 (2007-2009) and 2 (2009-2011) and the combined data for urine inorganic arsenic collected from CHMS cycles 2 (2009-2011), 3 (2012-2013), and 4 (2014-2015) were used as references.[21,22] The data were merged with the appropriate combined weights file for the specific combination of cycles being combined and taking into account differences in age. As CHMS did not measure arsenic in the toenail, there is no comparable data for reference levels as in the case for metals in urine samples.

All analyses were performed using Stata SE® (version 14). A two-sample t-test was performed to compare the urinary COPC concentrations between YKHEMP populations and the Canadian general population concentrations, as reported by the CHMS. Sampling weights were used for comparisons between YKHEMP random sample and the CHMS.

Among the 2037 YKEHMP participants, 1966 participants have urinary COPC measurements, and 1872 have toenail COPC measurements. In general, the urinary total arsenic concentration was lower in the YKHEMP participants (especially in YKDFN and NSMA children), compared with the CHMS (Table 3).

However, for urinary inorganic arsenic, children participants from the Yellowknife randomized sample group, the volunteer group, and the YKDFN had higher urinary concentrations than the adults within the group, as well as CHMS results for the same age group (especially age 6-11, Table 4). The YKHEMP participants (both children and adults) had lower urinary cadmium concentrations, compared to the CHMS participants. Within YKHEMP participants, children had lower urinary cadmium concentrations compared to adults. The urinary lead concentration of YKHEMP participants was comparable to CHMS participants. In general, YKHEMP children participants had lower urinary concentrations of total arsenic, cadmium, and lead, compared to adults; however, children were found to have higher toenail concentrations of such COPC (Table 5).

Table 3. Urinary total arsenic, inorganic arsenic, cadmium, and lead concentrations (µg/L) – geometric means for Yellowknife population by participation group from YKHEMP and Canadian population from CHMS. Values presented in the parentheses are the 95% confidence interval. *Significantly different from CHMS.

	Random sample	Volunteers	YKDFN	NSMA	Canadian
3 to 19 years old					
Sample size	211	198	75	13	4709*
Total arsenic	7.5 (6.6,8.6)	8.2 (7.1,9.5)	6.7* (5.7,7.8)	4.1* (2.8,6.0)	8.2 (7.5,9.1)
Inorganic arsenic	6.6* (6.0,7.3)	7.2* (6.4,8.1)	6.4* (5.7,7.3)	4.7 (3.3,6.7)	5.4 (5.1,5.7)
Cadmium	0.06* (0.05,0.07)	0.06* (0.05,0.07)	0.08* (0.06,0.09)	0.05* (0.02,0.09)	0.26 (0.23,0.28)
Lead	0.44 (0.38,0.50)	0.44 (0.40,0.48)	0.52 (0.44,0.62)	0.37 (0.25,0.55)	0.42 (0.41,0.44)
20 to 79 years old					
Sample size	659	658	119	33	7094*
Total arsenic	8.1* (7.4,8.8)	8.1* (7.5,8.7)	5.4* (4.6,6.4)	5.9* (4.5,7.7)	10.7 (9.5,12.1)
Inorganic arsenic	5.3 (5.0,5.6)	5.7 (5.4,6.0)	4.5* (4.1,5.0)	4.2* (3.3,5.3)	5.4 (5.1,5.7)
Cadmium	0.22* (0.20,0.23)	0.22* (0.20,0.24)	0.24* (0.21,0.28)	0.24* (0.16,0.35)	0.41 (0.39,0.44)
Lead	0.57 (0.53,0.61)	0.58 (0.54,0.61)	0.66* (0.58,0.75)	0.52 (0.40,0.67)	0.54 (0.52,0.57)

The differences between adults and children for the four participation groups in YKHEMP were also tested.
*The sample size for CHMS varied for total and inorganic arsenic, cadmium and lead. The presented numbers are the total participants in the four cycles.

Table 4. Urinary total arsenic and inorganic arsenic concentrations (µg/L) – geometric means for randomly selected samples from YKHEMP and Canadian population aged 3-79 from CHMS cycle 1 and 2. Values presented in the parentheses are the 95% confidence interval. *Significantly different from CHMS.

	YHKEMP random sample				**CHMS**			
			Total arsenic	Inorganic arsenic			Total arsenic	Inorganic arsenic
Age group	n	weighted N	GM (95% CI)	GM (95% CI)	N*	weighted N	GM (95% CI)	GM (95% CI)
3 - 5	39	686	7.3 (5.6,9.5)	6.5 (5.1,8.2)	584	1081167	6.6 (5.3,8.2)	5.1 (4.8,5.4)
6 - 11	91	1579	9.0 (7.0,11.6)	7.3 (6.2,8.8)*	2104	2122370	8.1 (7.5,8.9)	5.5 (5.1,5.8)
12 - 19	81	1529	6.4 (5.2,7.8)*	6.0 (5.3,6.9)	2021	3287580	9.1 (8.0,10.4)	5.5 (5.0,5.9)
20-39	260	6777	8.4 (7.4,9.6)*	5.9 (5.3,6.5)	2478	8978147	10.7 (9.5,12.1)	5.7 (5.2,6.2)
40-59	292	5538	7.9 (7.0,9.0)*	4.9 (4.5,5.4)	2455	9827356	10.7 (9.2,12.3)	5.1 (4.7,5.6)
60-79	107	1841	7.4 (5.9,9.2)*	4.4 (3.8,5.1)	2161	5116239	11.2 (9.4,13.4)	5.3 (4.9,5.8)

* Sample sizes shown are for total arsenic. The sample sizes for inorganic arsenic for the different age groups are 1528, 1531, 1526, 1072, 980, and 1002 respectively.

Table 5. Toenail total arsenic, cadmium, and lead concentrations (μg/g) – geometric means for the Yellowknife population by participation group from YKHEMP. Values presented in the parentheses are the 95% confidence interval.

	Random sample	Volunteers	YKDFN	NSMA
3 to 19 years old				
Total arsenic	0.40 (0.33,0.47)	0.51 (0.43,0.62)	0.29 (0.24,0.37)	0.53 (0.25,1.14)
Cadmium	0.03 (0.02,0.03)	0.04 (0.03,0.04)	0.02 (0.01,0.02)	0.03 (0.01,0.09)
Lead	0.65 (0.55,0.75)	0.70 (0.59,0.84)	0.39 (0.30,0.49)	0.72 (0.44,1.17)
20 to 79 years old				
Total arsenic	0.11 (0.10,0.11)	0.13 (0.12,0.14)	0.09 (0.08,0.10)	0.13 (0.09,0.17)
Cadmium	0.01 (0.01,0.01)	0.01 (0.01,0.01)	0.01 (0.01,0.01)	0.01 (0.01,0.02)
Lead	0.25 (0.23,0.27)	0.25 (0.23,0.27)	0.17 (0.14,0.20)	0.19 (0.14,0.24)

There was a total of 225 participants whose urine sample had at least one of the COPCs exceeding the reference values, which is set at the 95th percentile of the CHMS participants.[23] The YKHEMP team followed up with those participants to re-test the urine samples to confirm the higher exposure and to investigate the possible sources as well as provide advice on ways to lower their exposure. Participants with persistently elevated levels would be followed up every 6 months. The Health Effects Monitoring Program Advisory Committee (HEMPAC) decided to use the 80th percentile for children (1.35 mg/Kg) and 95th percentile (0.54 mg/Kg) for adults as screening levels for arsenic in toenails to identify participants with an elevated level of exposure for follow up.

It is important to note that, in addition to contamination from historical gold mining activity, arsenic also occurs naturally in the Yellowknife area because of the local geological formations. The YKHEMP study currently cannot distinguish arsenic exposures from natural sources, the Giant mine, or dietary sources. Several ongoing analyses are being conducted to gain a better understanding of the sources of arsenic exposure in Yellowknife and its potential health impacts. Arsenic species will be measured in different layers of the toenail. This will help to understand the proportion of arsenic exposure from dietary sources and toenail contamination from external contact (surface metal/contaminant adsorption). The relationships between the diet and lifestyle variables, the genetic information, and the concentrations of metals in urine and the arsenic concentrations in the toenail will also be conducted. A comparison of the prevalence of major health outcomes between YKHEMP and CHMS will be conducted to examine the differences in COPC exposure-related health burdens experienced by these populations.

YKHEMP provides a unique opportunity to understand the potential long-term health impacts as the Giant Mine Remediation Project progresses, which may also apply to remediation processes at other mining sites worldwide. Metal concentrations in urine and toenail provide an estimate of arsenic and other COPC exposure in different time periods and forms.[24–27] Indigenous people (YKDFN and NSMA) who were more vulnerable to environmental contamination were also included in the YKHEMP. YKDFN lived closer to the Giant Mine area compared to other YKHEMP participants. The higher rates of consumption of locally harvested food also make YKDFN and NSMA more likely to have a higher exposure to arsenic and other COPCs from dietary sources. The comparison of their arsenic exposure and health conditions to other YKHEMP participants, as well as to the Canadian population, may provide additional information on arsenic's health effect. A separate medical history questionnaire was designed for YKDFN as well. The information collected by this questionnaire will be compared with the medical file. YKHEMP welcomed volunteers to join the study. The number of volunteers was similar to the random sample. By comparing the arsenic exposure levels in the randomly selected sample and the volunteers, we will be able to see if any individual or group with high exposure might be ignored by systematic sampling. In this study, buccal swabs were collected from participants. Analysis of polymorphisms will provide indications on how the genetic makeup of the study participants may affect the metabolism and kinetics of arsenic. The baseline measurement of urine and toenail only reflect arsenic exposure of the participants in recent days or months before the sample collection period, and the medical files only trace back up to 5 years. Therefore, while the YKHEMP baseline and subsequent data will provide essential information regarding the potential health impact during and after the Giant Mine remediation process in the future, it will be limited in examining the association between legacy arsenic exposure and its long-term health impact. Urine is a good medium to measure arsenic exposure; however, it may not be the optimal one for the other COPCs, e.g., lead. Therefore, in cases when participants had elevated levels of urinary lead, they were asked to have their blood lead concentrations measured to confirm the lead exposure. Finally, this study only aims to address health risks associated with chemical exposures and does not capture other indirect health risks such as those related to changes in their traditional diet and lifestyle. It also reports current body burden only and has not accounted for behavioral changes that people may have taken to protect themselves from arsenic in the environment e.g. not picking berries near the mine site, by travelling further from their community to fish and hunt, and reduce their local fish and meat consumption.

Public Involvement

Our study is committed to engaging a variety of affected stakeholders. A Health Effects Monitoring Program Advisory Committee (HEMPAC) was created as a mechanism for member stakeholders to contribute to the development and implementation of the study. HEMPAC meets once a month and consists of the following representatives: Crown-Indigenous Relations and Northern Affairs Canada, the Government of the Northwest Territories Department of Environment and Natural Resources, the Government of the Northwest Territories Department of Health and Social Services, Health Canada, City of Yellowknife, Yellowknives Dene First Nation, North Slave Métis Alliance, Giant Mine Oversight Board, and the University of Ottawa.

The HEMPAC will continue the collaboration, consultation and coordination on matters arising from the YKHEMP, including ongoing data analyses, management of data files and requests from researchers and students for access to data, the approval process for publications and conference presentations, reports, funding opportunities, knowledge translation, and intervention strategies. A detailed communication plan has been developed to facilitate public engagement. Progress of the study and results are communicated through public meetings, news channels, social media and web site www.ykhemp.ca.

Collaboration

The HEMPAC has full governance of and access to the data; however, the University of Ottawa maintains the database. Investigators interested in learning more about the Project and how to obtain YKHEMP data can contact ykhemp@uottawa.ca.

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References

1 Sandlos J, Keeling A. Giant Mine: Historical Summary. 2012. http://reviewboard.ca/upload/project_document/EA0809-001_Giant_Mine__History_Summary.PDF (accessed 19 Aug 2019).

2 Officer of the Auditor General Canada. Chapter 3—Federal Contaminated Sites and Their Impacts. In: *2012 Spring Report of the Commissioner of the Environment and Sustainable Development*. 2012. http://www.oag-bvg.gc.ca/internet/English/parl_cesd_201205_03_e_36775.html

3 Stantec Consulting Company. Analysis of Contaminants in Tissues of Fish Captured in the Yellowknife Bay Area, Northwest Territories final report. Retrieved from Public Works and Government Services Canada. 2014.

4 Acute and chronic arsenic toxicity R N Ratnaike. *Postgr Med J* 2003;**79**:391–6. doi:10.1136/pmj.79.933.391

5 Hong Y-S, Song K-H, Chung J-Y. Health Effects of Chronic Arsenic Exposure. *J Prev Med Public Heal* 2014;**47**:245–52. doi:10.3961/jpmph.14.035

6 Atsdr. PUBLIC HEALTH STATEMENT Arsenic. 2007. www.atsdr.cdc.gov/ (accessed 19 Aug 2019).

7 Abernathy CO, Thomas DJ, Calderon RL. Toxicity and Risk Assessment of Trace Elements Health Effects and Risk Assessment of Arsenic 1,2. https://academic.oup.com/jn/article-abstract/133/5/1536S/4558544 (accessed 19 Aug 2019).

8 Kapaj S, Peterson H, Liber K, *et al.* Human Health Effects From Chronic Arsenic Poisoning-A Review. *J Environ Sci Heal Part A* 2006;**41**:2399–428. doi:10.1080/10934520600873571

9 Abernathy C 0, Liu Y-P, Longfellow D, *et al.* Arsenic: Health Effects, Mechanisms of Actions, and Research Issues. https://ehp.niehs.nih.gov/doi/pdf/10.1289/ehp.99107593 (accessed 19 Aug 2019).

10 Agusa T, Fujihara J, Takeshita H, *et al. Individual variations in inorganic arsenic metabolism associated with AS3MT genetic polymorphisms*. 2011. doi:10.3390/ijms12042351

11 Agusa T, Iwata H, Fujihara J, *et al.* Genetic polymorphisms in glutathione S-transferase (GST) superfamily and arsenic metabolism in residents of the Red River Delta, Vietnam. *Toxicol Appl Pharmacol* 2010;**242**:352–62. doi:10.1016/j.taap.2009.11.007

12 Applebaum KM, Karagas MR, Hunter DJ, *et al.* Polymorphisms in Nucleotide Excision Repair Genes , Arsenic Exposure , and Non-Melanoma Skin Cancer in New Hampshire. 2007;**115**:1231–6. doi:10.1289/ehp.10096

13 Banerjee M, Marensi V, Conseil G, *et al.* Polymorphic variants of MRP4/ABCC4 differentially modulate the transport of methylated arsenic metabolites and physiological organic anions. *Biochem Pharmacol* 2016;**120**:72–82. doi:10.1016/J.BCP.2016.09.016

14 De Chaudhuri S, Ghosh P, Sarma N, *et al.* Genetic Variants Associated with Arsenic

Susceptibility: Study of Purine Nucleoside Phosphorylase, Arsenic (+3) Methyltransferase, and Glutathione *S* -Transferase Omega Genes. *Environ Health Perspect* 2008;**116**:501–5. doi:10.1289/ehp.10581

15 Engström KS, Broberg K, Concha G, *et al.* Genetic Polymorphisms Influencing Arsenic Metabolism: Evidence from Argentina. *Environ Health Perspect* 2007;**115**:599–605. doi:10.1289/ehp.9734

16 Fujihara J, Soejima M, Yasuda T, *et al.* Global analysis of genetic variation in human arsenic (+ 3 oxidation state) methyltransferase (AS3MT). *Toxicol Appl Pharmacol* 2010;**243**:292–9. doi:10.1016/j.taap.2009.11.020

17 Gomez-Rubio P, Meza-Montenegro MM, Cantu-Soto E, *et al.* Genetic association between intronic variants in AS3MT and arsenic methylation efficiency is focused on a large linkage disequilibrium cluster in chromosome 10. *J Appl Toxicol* 2010;**30**:260–70. doi:10.1002/jat.1492

18 Hsu LI, Wu MM, Wang YH, *et al.* Association of environmental arsenic exposure, genetic polymorphisms of susceptible genes, and skin cancers in Taiwan. *Biomed Res Int* 2015;**2015**. doi:10.1155/2015/892579

19 Lesseur C, Gilbert-diamond D, Andrew AS, *et al.* A case-control study of polymorphisms in xenobiotic and arsenic metabolism genes and arsenic-related bladder cancer in New Hampshire. *Toxicol Lett* 2012;**210**:100–6. doi:10.1016/j.toxlet.2012.01.015

20 Gabriel S, Ziaugra L, Tabbaa D. SNP Genotyping Using the Sequenom MassARRAY iPLEX Platform. In: *Current Protocols in Human Genetics*. Hoboken, NJ, USA: : John Wiley & Sons, Inc. 2009. 2.12.1-2.12.18. doi:10.1002/0471142905.hg0212s60

21 Health Canada. Second report on Human Biomonitoring of Environmental Chemicals in Canada --Results of the Canadian Health Measures Survey Cycle 2 (2009-2011). Ottawa, Ontario: 2013. https://www.healthcanada.gc.ca

22 Health Canada. Forth Report on Human Biomonitoring of Environmenta Chemicals in Canada - Results of the Canadian Health Mesures Survey. Ottawa, Ontario: 2017.

23 Saravanabhavan G, Werry K, Walker M, *et al.* 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* 2017;**220**:189–200. doi:10.1016/j.ijheh.2016.10.006

24 Button M, Jenkin GRT, Harrington CF, *et al.* Human toenails as a biomarker of exposure to elevated environmental arsenic. *J Environ Monit* 2009;**11**:610. doi:10.1039/b817097e

25 Mandal BK, Ogra Y, Suzuki KT. Speciation of arsenic in human nail and hair from arsenic-affected area by HPLC-inductively coupled argon plasma mass spectrometry. *Toxicol Appl Pharmacol* 2003;**189**:73–83. doi:10.1016/S0041-008X(03)00088-7

26 Normandin L, Ayotte P, Levallois P, *et al.* Biomarkers of arsenic exposure and effects in a Canadian rural population exposed through groundwater consumption. *J Expo Sci Environ Epidemiol* 2014;**24**:127–34. doi:10.1038/jes.2013.80

27 Pearce DC, Dowling K, Gerson AR, *et al.* Arsenic microdistribution and speciation in toenail clippings of children living in a historic gold mining area. *Sci Total Environ* 2010;**408**:2590–9. doi:10.1016/j.scitotenv.2009.12.039