Targeted Biomonitoring in Children and Women of Reproductive Age Living in Rural Mining Communities Located in the Kadamjay district, Batken Province, Kyrgyzstan

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Abstract

The Kyrgyz Republic is a mountainous landlocked country located in Central Asia. The country has rich mineral deposits, including elemental mercury. The mercury producing region of Kyrgyzstan is largely located in the rural community of Aidarken and Chauvai, within the Kadamjay district, in the Batken province of Kyrgyzstan. A targeted cross-sectional biomonitoring study was conducted to assess the level of heavy metal exposure in the most sensitive individuals (children and reproductive aged women) in the most contaminated region of the Kadamjay district. The study design involved recruiting households with children (5-14 years old) and/or women (15-49 years old) in specific areas of the three communities that were identified through a previous assessment as having soil, water, dust, and locally grown food with high levels of heavy metal contamination. These households were all homes within the highest risk areas (HRA) of Aidarken, Eshme and Chauvai towns. The study included 255 participants from 116 different households that were randomly selected from the eligible and recruited homes within the HRA. Standardized questionnaires were used to conduct an exposure assessment and collect demographic information immediately prior to the spot-collection of blood and urine samples for analysis of arsenic, cadmium, antimony, mercury, lead, and uranium in a fully accredited laboratory. The study sample of 255 included 131 women and 124 children that exceeded an established reference value in blood or urine, with almost 20% offered a clinical assessment as a result of having a level above an established action level. These results, representative of the most sensitive individuals living near the most contaminated region of the district, will be used to inform individual and community level interventions to reduce the burden of disease from long-term exposure to harmful levels of heavy metal contamination. Individual results were shared with all participants and interpreted relative to population-based comparison values or clinical action levels established by authoritative studies and peer-reviewed literature.

Introduction

The Kyrgyz Republic is a mountainous landlocked country located in Central Asia. Kyrgyzstan is bordered by Kazakhstan to the north, Uzbekistan to the west, Tajikistan to the south, and China to the east. The nation has rich mineral deposits and there is an active enterprise that is engaged in primary mining and the production of metallic mercury. The mercury producing region of Kyrgyzstan is located in the rural communities of Aidarken and Chauvai, within the Kadamjay district (population of 157,000[1]), Batken province of Kyrgyzstan. The mercury processing facility (Kombinot) in Aidarken is still in production, while the Kombinot in Chauvai is closed and the building has been demolished/salvaged. Both communities have active antimony mining activities nearby. These mines are located in a region that is especially vulnerable to natural disasters such as drought, earthquakes, and floods.

[1] 2009 population census

Available data from the rural area of Aidarken suggests that the prevalence of non-communicable diseases (NCD) among adults, children, and infants is higher than the average prevalence at the district level. For example, childhood anemia is more than twice the average rate at district level (17% vs. 7%). Anemia among women (29%), as well as hypertension among all adults (19% compared to 8% at district level) is also elevated[2]. Since 2016, Médecins Sans Frontières (MSF) and the Ministry of Health of the Kyrgyz Republic (MoH KR) have collaborated on the management of these and other chronic diseases in the region.

As the Kadamjay district is characterized by the presence of mining and metallurgic processing facilities as well as regional vulnerability to migrating contamination from natural disasters such as drought, earthquakes, and floods, the MoH KR, MSF, and Terragraphics International Foundation (TIFO) collaborated to conduct human health risk assessments to identify areas where human exposure to heavy metals may present the greatest human health exposure risks. These assessments considered risks of residential exposures from pathways such as the inhalation of mercury vapors and dust-blown particulates, consumption of contaminated food, or incidental ingestion of soils/dusts, and ingestion of drinking water contaminated by heavy metals.

This "Kadamjay Area Biomonitoring" (KAB) study was designed to evaluate if hypothetical pathways of exposure to contaminants in the highest exposed areas(s) of the community were active (e.g., if hypothetical or predicted exposure to heavy metals estimated by the human health assessment were leading to actual individual exposures). This targeted biomonitoring study was part of a broader collaborative effort to develop regional capacity in public health surveillance and environmental medicine to identify heavy-metal related illnesses. A significant part of this regional capacity building exercise was the engagement of participants, to whom we provided individual participant-level counselling, results reporting, and recommendations on how to reduce heavy metal exposure or participate in clinical screening to evaluate the presentation of any heavy-metal related illnesses.

Methods

Study design

The KAB study included sampling the most susceptible individuals in the region of the Kadamjay most vulnerable to heavy metal contamination. The study was reviewed and approved by the Ethical Review Board Committees from both MSF and the Kyrgyz Republic. The cross-sectional study design involved sampling individuals from residential households in the most heavily contaminated sections of Aidarken, Eshme and Chauvai towns. Each participant was asked to complete a study questionnaire and provide blood and urine specimens for measurement of arsenic, cadmium, antimony, mercury, lead, and uranium. Because the heavy metals evaluated in this study are known carcinogens, as well as reproductive and developmental toxicants that may have significant effects at critical life stages (e.g., reproduction, development, and childhood), sensitive populations include children and reproductive age women. While male members of the community are certainly at-risk of heavy metal exposure, this study focused on identifying those at greatest risk, so that interventions informed by the most susceptible

[2]MSF/Epicentre, 2015. "Health assessment in Kadamjay district, Batken region, Kyrgyz Republic Exploratory mission". Final Report, October 30th, 2015,

population (e.g., children 5-14 years old[3] and women 15-49 years old), can benefit to all members of the community.

We used a cross-sectional study design and simple random sampling to select women and children living in regions of the community where contaminants in food, water, dust, and soil were expected to pose the greatest human health risk. The households in the high-risk areas (HRA) of the three communities were identified from area census maps. Each eligible member of the household (child aged ≥ 5 - ≤ 14 years; female ≥ 15 - ≤ 49 years) was offered an opportunity for potential enrolment in the study. Once the community outreach to recruit individuals from the HRAs was complete, we used simple random sampling of the recruited individuals to select households for enrolment (or specimen collection). Every candidate that was selected through this process was offered an opportunity to participate, with no distinction of physical condition, socio-economic status, religion or sexual orientation.

We targeted a sample size of 264 individuals. This target was based on WHO recommendations for a minimum sample size of 120 randomly selected individuals to allow for the estimation of reference values within a population[4,5]. Thus, a sample size of 240 individuals was used (120 women in childbearing age and 120 children 5-14 years old) as a target to ensure an accurate estimation of the reference values for each chemical in each group. Adding a 10% of non-response to the sample size, we ended up with 264 individuals. According to the last available census, the average household size in Kyrgyzstan rural area was 4.6 with 20% (~ 1 member) in the age group of 5-14 years old and 22% (~1 member) in the group of women in childbearing age. Considering the average household size in the rural area and the age/sex distribution among those households, we planned to contact 132 households to interview and collect samples for 264 people.

High Risk Areas

The HRAs were identified from analysis of environmental samples taken in 2019 and a Human Health Risk Assessment (HHRA) of the Kadamjay Area of Aidarken, Chauvai, and surrounding villages conducted in 2021. This HHRA identified that arsenic, mercury, and antimony were the most significant hazards defining the high-risk areas. The analysis found that arsenic was a primary risk factor, with high levels in certain vegetables and soils located in Chauvai. Though data were not available, high arsenic concentrations were suspected to be present in air near the mining operation haul roads (especially in Chauvai). In general, area roads were found to have both high arsenic and silt content that likely results in suspension of fine particulate arsenic during operations. The form of inorganic arsenic, having high bioavailability, also contributed to the estimated human risk levels. Antimony was also found to be a primary risk driver in residential soils in Chauvai and for combined pathways of exposure (from residential and agricultural sources) in Aidarken and Chauvai, although the chemical form of antimony suggested that the bioavailability in soils would be low. Mercury was also a significant factor in identifying the HRAs as the vegetables and soils in Aidarken had elevated levels of

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[3] While children younger than five years old are very sensitive to heavy metal exposure, they represent a challenging age group for the field-based collection of blood and urine specimens. Due to this limitation, there are few comparison data available for interpreting the analysis of urine in young children (< 5 years old). For this reason, we prioritized children of at least 5 years old.
[4] https://apps.who.int/iris/bitstream/handle/10665/334181/WHO-EURO-2020-1069-40815-55163-eng.pdf
[5] https://www.euro.who.int/__data/assets/pdf_file/0020/276311/Human-biomonitoring-facts-figures-en.pdf

this metal. Mercury (in the form of methylmercury) was of greatest concern in the abandoned Sludge Ponds near Aidarken and posed the greatest risk due to grazing livestock.

The HRAs were used to define the geographical boundaries (polygons) in a map from where the households were recruited for participation in the study. In general, the boundaries of the polygon were defined by community roads and natural landscape features (rivers, mountains) that help shape the natural boundary of a community. Boundaries are not representative of environmental levels alone because the environmental sampling strategy targeted areas identified in previous studies and near to mining operations and did not create a geographical distribution that allows for estimating contamination between sampling locations. The highest risk communities within a polygon were estimated from HHRA results, including specific data on heavy metals in vegetables, soils, and drinking water. The recruitment was done through community information sessions, followed by household-to-household visits within the HRAs identified through the HHRA.

Participant Recruitment, Enrolment and Sampling

The household-to-household recruitment was conducted by local biomonitoring study staff to identify members of the community interested in participating in the study. Once the recruitment phase was complete, we used simple random sampling to select households for enrolment in the study.

Once identified, we contacted the randomly selected individual households and provided a recruitment brochure that explains the rationale and objectives of the study, and well as the rights of study participants. If the head of the household provided consent, we executed a household questionnaire and an appointment for a future participant interview and specimen collection within 7 days. If more than one individual for each of the two categories (children 5-14, and women of childbearing age) were found in the household, all of them were offered an opportunity to participate.

The specimen collection appointment was confirmed one day prior to meeting with participants at a convenient community-based location. Written informed consent or assent was provided by all participants, and each participant or caretaker was asked to complete a detailed WHO standardized questionnaire, to assist with both identifying sources of environmental exposure and the interpreting results. Following the completion of the questionnaire, blood and urine specimens were collected and the participant was provided with modest nourishment (juice and a snack) and an "exit package" that explained the next steps of the study (e.g., when to expect further contact, whom to contact with additional questions), as well as complete contact information for study staff.

Biological samples

Each participant provided approximately 6 mL of whole blood for elemental (metals) analysis, that was collected via venipuncture into EDTA vacutainer tubes that were manufactured for trace metal human biomonitoring studies (BD Vacutainer® trace element tubes). Urine specimen containers were prescreened for background contamination in the laboratory. The Department of Environmental Sciences at the Jožef Stefan Institute (e.g., laboratory performing the analyses) provided pre-collection training and written instructions for collecting and labeling specimens prior to collection of 6 mL of whole blood for elemental (metals) analysis via venipuncture and approximately 40 mL of randomly collected "spot" urine specimens into sterile pre-screened 60 mL containers. After collection, the blood tube and urine collection container were placed upright and kept cool (e.g., refrigerated and/or placed in a cooler with cold/ice packs) until arrival at the laboratory. Cold chain was tracked using cold tag tracking devices.

Laboratory procedures

The blood and urine specimens were analyzed by the Department of Environmental Sciences at the Jožef Stefan Institute (Jamova cesta 39, SI-1000 Ljubljana, Slovenia). The laboratory methods for the various analyses are described briefly here.

Blood specimens were analyzed by Inductively Coupled Plasma Triple Quadrupole Mass Spectrometry (ICP-QQQ) where prior to analyses 0.3 g of blood sample was transferred into pre-cleaned teflon digestion vial. Samples were digested by 0.5 mL of 65% nitric acid (suprapur) in a microwave system (ULTRAWAVE, Single Reaction Chamber Microwave Digestion System, MILESTONE) using the following program: 1) 20 minutes temperature rise to 240°C, 2) kept for 15 minutes at 240°C and 100 bar). Digested solutions were transferred into measuring tubes and diluted to 5 mL. Prepared solutions were measured in an Agilent 8800 ICP-QQQ, with daily tuning of the instrument using a solution containing Li, Mg, Y, Ce, Tl and Co. Isotopes monitored were 75->91As, 114Cd, 123Sb, 202Hg, 208Pb and 238U. External calibration was used for quantification. In each set of samples reference materials and blank samples were analysed under the same conditions. Accuracy of results was checked by the use of reference materials: Seronorm Whole blood Level 1 and 2. Limits of detection for As, Cd, Sb, Hg, Pb and U, calculated as three times the standard deviations of the blank sample, were 0.3, 0.01, 0.07, 0.05, 0.5 and 0.003 µg/L of blood sample, respectively.

Urine specimens were also analyzed by ICP-QQQ, after transfer of 0.5 mL of urine sample was into pre-cleaned teflon digestion vial, and digestion with 0.5 mL of 65% nitric acid (suprapur) in a microwave system (ULTRAWAVE, Single Reaction Chamber Microwave Digestion System, MILESTONE) using the following program: 1) 20 minutes temperature rise to 240°C, 2) kept for 15 minutes at 240°C and 100 bar). Digested solutions were transferred into measuring tubes and diluted to 5 mL. Prepared solutions were measured by Agilent 8800 ICP-QQQ. Tuning of the instrument and external calabration for urine was conducted as described for blood. Accuracy of urine results was checked by the use of reference materials: Seronorm urine Level 1 and 2 and ClinChek Level 1. Limits of detection for As, Cd, Sb, Hg, Pb and U, calculated as three times the standard deviations of the blank sample, were 0.03, 0.008, 0.02, 0.04, 0.1 and 0.002 µg/L of urine sample, respectively.

Speciation of arsenicals in urine was conducted for samples with a total arsenic content > 15 µg/L using High performance liquid chromatography-hydride generation-atomic fluorescence spectrometry. Samples of 50 µL of 1:1 diluted samples were injected on anion exchange HPLC column (Hamilton PRP-X100) and eluted with 15 mmol L-1 KH2PO4, pH 6.15. After separation, eluent was on-line mixed with HCl (40 mL L-1, 2.5 mL min-1) and NaBH4 (0.7 % in 0.1 % NaOH, 3 mL min-1; both reagents were added with peristaltic pump and mixed with sample in a PEEK mixing cross). Arsenic hydrides, which were formed, were on-line separated from liquid waste in an A-type gas-liquid separator, dried in a Perma-Pure dryer and detected in AFS detector (Millenium, PS Analytical, UK). Freshly prepared standard solution contained As(III), As(V), monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA).

Methyl mercury (MeHg) was determined in one blood specimen. The vial containing the blood sample was shaken for homogenization, and approximately 0.2 g of sample was carefully weighted in a precleaned 30 mL glass tube. 10 mL of 4 M HNO3 was added, they were capped loosely and heated in a heating block for 24 hours on 67 °C. After cooling, the samples were dilute with Milli-Q water to 30 mL and left at room temperature overnight. Next day samples were measured by cold-vapor atomic fluorescence spectrometer (CVAFS), following EPA method 1630.

Data collection and analysis

Data collection was conducted by executing the questionnaire on iPads using REDCap, a secure web application for building and managing study questionnaires. Cleaning and analysis was performed using R version 4. Briefly, the measured levels of each analyte was compared to a reference range for the respective matrix (e.g., blood, urine) and stratified by demographic group (e.g., age category, gender, and race/ethnicity). Aggregate data included descriptive statistics on the levels for each environmental chemical in blood and urine. Statistics included were arithmetic means, ranges, and 95^{th} percentiles with confidence intervals. To estimate central tendency, geometric means were used. This procedure provides a better estimate of central tendency for data that are distributed with a long tail at the upper end of the distribution. Geometric means were calculated by taking the log of each concentration and then computing the weighted mean of those log-transformed values. The ninety-five percent confidence intervals around this weighted mean were calculated by adding and subtracting an amount equal to the product of a Student's t-statistic and the standard error of the weighted mean estimate. The weighted geometric mean and its confidence limits were then be then obtained by taking the antilog of this weighted mean and its upper and lower confidence limits. For chemicals measured in urine, separate tables were initially calculated for the chemical concentration expressed per volume of urine (uncorrected table) and the chemical concentration expressed per gram of creatinine (creatinine corrected table). A level per gram of creatinine (i.e., creatinine corrected) adjusted for urine dilution and was preferentially used for aggregate data interpretation.

Participant Report-Back

Individual participant sample results were reviewed by study staff and compared to appropriate biological reference values (e.g., reference range, or clinically relevant action values; see Table 1). Participants were provided with information on how to specifically reduce exposure to the heavy metals evaluated in the study, informed by previous testing and evaluation in the huma health risk assessment.

We distributed results to study participants by sharing individual report-back letters populated with a narrative explanation of the health effects of heavy metal exposure, levels measured in the blood and/or urine specimen relative to comparison levels, and opportunities to reduce exposure informed by previous risk assessments in the region. The outreach was conducted by MoH nurses visiting each household to explain the contents of the letter, comparison or reference levels that are used, and directions for follow-up with any concerns.

Individual consultation (telephone calls or in-person visits) was conducted by the study physician when measured concentrations exceed an actionable level. In all cases where a participant level exceeded an action level, the participant was given a recommendation to have a clinical follow-up and options for referral to a medical toxicology specialist. Once the individual follow-up was made, the participant was no longer followed in the study.

Results

Single blood and/or spot-collected urine specimen were collected from 255 participants (see Table 2 for a description of the study participants) (85% of eligible individuals) from 116 households (89% of the households approached). We were unable to draw blood from 2 participants and one participant was unable to produce a urine specimen. More than half (51%; n = 131) of the participants were women over 15 years old (median age 32 years), and 124 (49%) were female (n = 61) children under the age of 15 (median age 9). The majority of the population self-identified as being ethnically Kyrgz (n = 193; 76%), with the remainder as Tajik (n = 57; 22%) or other (n = 5, 2%). Most of the adult population had completed secondary school (67%; n = 88) and 23% were post-secondary graduates (n = 30). In general the study participants reported having income that provided for basic needs, although 9% (n = 24) reported having some basic needs unmet. Only 1% (n = 3) reported having excess (or disposable) income for purchasing high quality goods (Table 2).

The creatinine corrected urine and blood results for all participants is provided in Table 3. The average (mean) levels of antimony (Sb), arsenic and uranium in urine were all above the reference levels used in this study. In general, 82% of study participants (n = 209) had a level of urine Sb above the reference level (mean = 1.704 µg/g, versus a reference level of 0.6 µg/L for adults and 0.3 µg/L for children). The average level of antimony in participant blood (3.977 µg/L) was also above the action level. When evaluating total arsenic exposure, 72% of participants (n = 184) had levels sufficiently high in urine to warrant speciation (e.g., 15 µg/L or total arsenic). Once total arsenic was speciated, the majority (72%) was in the form of inorganic arsenical species (sum of monomethylarsonic acid [MMA], dimethylarsinic acid [DMA] and arsenous [III] acid). The mean level of inorganic As (iAs) in urine was 23.903 µg/L, a level that is significantly higher than the iAs reference level (10 µg/L), with individual participant levels ranging between 9.0 – 141.7 µg/L.

Individually, 235 study participants (92%) had levels of at least one chemical in either blood or urine that exceeded a reference value: 209 (82%) for antimony, 176 (69%) for arsenic, 143 (56%) for uranium, 51 (20%) for cadmium, 11 (4%) for lead and 3 (1%) for mercury. Of these individuals, 48 (19%) had values above the action level and were offered individual follow-up by the study physician: 45 (18%) for antimony, 4 (2%) for arsenic and 2 (1%) for mercury (Table 4).

Despite the presence of a large primary mercury mine, average mercury levels were below the established reference levels. In general, levels of urine mercury were highest in Aidarken, the community where the primary mercury mine is located.

The levels of all metals appeared to be highest in the youngest children in the study (5-10 years old). For example, the levels of blood antimony in children under 10 was almost 3 times higher than levels in adults older than 45 (10 µg/L [95% CI 8.6-18] vs. 3.7 µg/L [2.5-3.8]). A comparison of male and female children under 15 years old suggests that there may be gender differences with respect to blood levels of heavy exposure (Table 5). While no difference was evident in urine specimens, the cadmium levels appeared higher in girls than boys, and antimony, mercury, lead, and uranium all appeared higher in boys.

In addition to demographics, we evaluated data on socioeconomic status, lifestyles, occupational history, previous mercury exposure, water and fuel sources and food/dietary information. Most participants described using multiple sources of fuel for cooking and heating (e.g., natural gas, coal, electric, or wood). While fuel sources differed, most participants reported using only water from the public water system. A limited number described using other sources of water for drinking (7% mainly from private wells or springs) and only 6% reported using other sources of water for cooking. There were no consistent and significant differences between analyte levels based on a screening review of results stratified based on the response to these questions. It was notable in this group that no participants that self-reported smoking, and participants rarely consumed any fish (a potential source of total arsenic and mercury). For example, only 10% of participants *ever* consumed any fish (211 out of 236 responses reported never eating fish).

We distributed results to study participants by sharing individual report-back letters that were populated with a narrative explanation of the health effects of heavy metal exposure, levels measured in the blood and/or urine specimen relative to comparison levels, and opportunities to reduce exposure informed by previous risk assessments in the region. The outreach was conducted by having Ministry of Health nurses visit each household to discuss individual results with study participants (e.g., head of household or adult participant). During the visit, the nurses explained the contents of the letter, described the comparison or reference levels, and encouraged to contact the study medical coordinator with any concerns. Participants with levels greater than an established action level were informed that they would be contacted by the study physician within a week. Except for 3 participants, all individuals received an in-person visit and interpreted results. The 3 exceptions were due to participants relocating outside of the area. These individuals were informed of their results and the opportunity to engage with the study physician via a secure internet-based messaging tool (e.g., WhatsApp)

Discussion

This is the first biomonitoring study to measure levels of mercury, lead, antimony, cadmium, uranium, and arsenic in specimens collected from individuals suspected of having the highest levels of exposure. However, several biomonitoring studies have been conducted in the same geographical region (~ 60 km) of this study (e.g., within the Batken province [or oblast] of the Kyrgyz Republic). These studies provide important context and are summarized below.

A study of 1,135 men, women, and children (3.5 to 7 years old) from Aidarken conducted between 1991 and 1996 identified mercury in blood of 330 (29.1%) of participants, with 116 (35%) in men and (25.3%) in women with a mean concentration of 1.9 (±0.54) µg/L. Urine mercury was detectable in 229 (62%) of participants, with an average level of 1.09 µg/L, with individual levels ranging from 0.11 to 24 µg/L. Elevated levels of urine mercury (e.g., above 7.5 µg/L) were found in 2.2% of study participants, of which 0.7% were men and 3.1% of women. Of the children included in the study, 77 (68%) had detectable levels of urine mercury between 0.6 to 19.5 µg/L, with an average level of 2.96 µg/L, or 2.7 times greater than adults. Mercury levels exceeded established critical action level (15.0 µg/L) in 1.8% of all children.

A World Health Organization study conducted between 2016-17 assessed prenatal exposure to mercury in 107 pregnant women recruited from the Aidarken Hospital. Maternal urine and post-partum cord blood samples were collected at the Aidarken Hospital between September 2016 and March 2017. The geometric mean (GM) level of mercury was 0.89 µg/L in cord blood, and 0.59 µg/L in urine (with a corrected maternal urine level of 0.50 µg/g creatinine). Almost all (n= 106) participants had a total concentration of mercury in blood less than 5 µg/L.

A 2017 study by the Scientific and Production Centre for Preventive Medicine of the Ministry of Health evaluated the levels of arsenic, cadmium and mercury in blood and urine samples of women living in the city of Batken. The study involved a convenience sample of women of reproductive age that live in or near the city. A total of 62 women were included (age 22-68) all of whom had no known contact with any heavy metals. Mercury levels in these women averaged 0.59 µg/L, with urine averaging 0.64 µg/L. Cadmium levels in blood averaged 0.52 µg/L, with urine Cd levels averaging 0.74 µg/L. Arsenic levels in blood were 0.44 µg/L, with urine levels averaging 17.76 µg/L. All 62 women from this study had levels that were at or below population-based reference levels (e.g., German HBM I levels).

As described in the study methods, we targeted a sample size of 264, with a minimum requirement of at least 240 individuals from the entire area. This target was based on a minimum sample size to have sufficient statistical power to compare study results to established reference values. Given this type of study design, we did not have sufficient power to opine on differences at the individual community level (e.g., comparison of Aidarken, Chauvai and Eshme results). These communities all have different numbers of participants (124, 91, and 40, respectively) and our study was not designed to look at inter-community differences. While the findings may be a biased representation of these communities, we are exploring the differences in the three communities to identify any opportunities for targeted community-specific interventions. These data are shown in Table 6 and suggest that levels of arsenic and cadmium are highest in participants from Eshme and mercury and lead are highest in participants from Aidarken. This observation is supported by analyses of both blood and urine.

The study was not designed with an a priori consideration of exploring differences in analyte levels among ethnic groups in the area. While not designed with the intent, it was a notable observation that the levels of almost all heavy metals appear to be highest in 23% of participants (n =57) that self-identified as being ethnically Tajik. A comparison of all metals, in both urine and blood, reveals that geometric mean levels of all analytes, except for blood mercury, is higher in Tajiks, as compared to Kyrgyz participants (Table 7).

These results, representative of the most sensitive individuals living in the most vulnerable region of the Kadamjay district have been compared to levels from nationally representative population-based studies. This comparison of antimony suggests that individuals in this region have levels of exposure 14-30 times greater than would be expected in North America or Europe (Table 8).

It was expected that the levels of heavy metal exposure in this study would differ from studies conducted in regions not representative of Kyrgyzstan. For example, individuals targeted for this study are all located in a region of Central Asia, with sources of fuel, food, water, air, consumer products, as well as lifestyle factors and behaviors that would contribute to differences in environmental exposure as compared to populations in North America or Europe. We also know that unlike studies of nationally representative populations (e.g., not targeted to a specific region), our participants represented the most vulnerable (exposed) people in the community, as they were recruited based on empirical evidence that the food, water, and soil in the area where they live had levels of heavy metals that exceeded health-based thresholds.

Based on the proximity of the contaminated sites to these communities, we expect that the elevated results in children may be the result of child age-appropriate behaviors (e.g., crawling and playing) that exposes them to a greater magnitude and range of hazards, such as crawling and playing on floors indoors covered in fugitive dust (sometimes even para-occupational dust that is "taken home" from an adult workplace), or playing outside where they can be exposed to harmful substances in area soils or water. They are also more likely to put objects in their mouths or display pica behavior. The physical size of children also results in a greater burden of total exposure. For example, children breathe more air, drink more water, and eat more food per kilogram of body weight than adults (WHO, 2006).

The initial comparison of the levels of exposure in blood between boys and girls in the study suggests that cadmium is the only analyte that is significantly higher in females. Given that reproductive age women have a significant loss of iron during menstruation, and the absorption and toxicity of cadmium is greater in women when there is a decrease in iron stores, this finding will inform targeted interventions (e.g., outreach and awareness, nutritional supplementation, exposure mitigation, etc.).

In planning post-study interventions in the communities included in the study, we conducted outreach with local doctors and nurses. The outreach was conducted to provide primary care providers the opportunity to share any thoughts or observations on possible pathways for heavy metal exposure (e.g., food consumption or personal behaviors) that may help inform interventions. These semi-structured, yet informal interviews identified some important potential sources of heavy metal exposure that we are currently seeking to better understand. For example, it appeared that Tajik people in the study area may have unique dietary preferences, and may eat more vegetables (greens, usually sourced in their own gardens) and eggs (instead of meats) as compared to the Kyrgyz people. In addition, it was suggested that some Tajik women may use a form of kohl, a traditional eyelid cosmetic that has been previously shown to contain high levels of heavy metals. It was reported that some local women may also be making homemade versions of this type of cosmetic, by specifically grinding antimony stones from area mountains, in addition to sourcing it from outside the country (e.g., Saudi Arabia). As almost all heavy metals, in both urine and blood (with the exception) of blood mercury, appeared to be higher in Tajiks, we are actively exploring this observation.

Conclusion

The overwhelming majority of study participants had levels of at least one chemical in either blood or urine that exceeded a population-based reference value (92%), with a significant number (19%) elevated above health-based action levels. Coupled with a recent human health risk assessment, these results suggest that there is a significant level of community exposure to heavy metals associated with reproductive, developmental, and carcinogenic risks.

The results from this targeted biomonitoring study will be used to inform a multidisciplinary collaborative effort to develop regional capacity in environmental assessment, public health surveillance and environmental medicine. The aggregate results will be used to inform health-protective interventions designed to reduce heavy metal exposure and improve cancer and non-cancer health outcomes in the region.

Acknowledgements

The Kadamjay Area Biomonitoring (KAB) study protocol (Principal Investigators Ainash Sharshenova, Marc A. Nascarella, Manuel Albela) was reviewed and approved by the Ethics Review Board from both Médecins Sans Frontières (ID: MSF ERB 2111, 5 May 2021) and the Kyrgyz Republic (7 June 2021).

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[to be completed after stakeholder feedback has been received]

Tables

Table 1. Comparison values for blood and urine usind in the KAB Study

	Blood (µg/L)		Urine (µg/L)		
Chemical	**Reference Value**	**Action Level**	**Reference Value**	**Action Level**	
Antimony	3.5	10	0.6 (0.3 children)	2	1,2
Arsenic, total	20		15	50	2,3
Inorganic Arsenic	--	--	10	50	2,3
Cadmium	1 (0.3 children)	5	1 (0.5 children)	5	4
Lead*	50 (35 children)	150	80		2,5
Mercury, total	5		7	20	6,7,8
Uranium			0.03	15	9,10

Notes

Urine results were interpreted relative to unadjusted values in micrograms per liter of urine (µg/L) and creatinine adjusted values (µg/g) to account for the dilution status of the urine.

Reference Value: Level used as a comparison on results reported back to study participants.

Action Level: Level used to identify prioritized report-back by medical staff.

A reference level has not been established for uranium in blood.

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Table 2. Characteristics of Study Particpants (n = 255)

Participants	***n***	***%***
Total	255	
Households	116	
Age at Enrollment	***n***	***%***
5-14 years old	124	49%
15-49 years old	131	51%
Sex	***n***	***%***
Females ≥ 15 years old	131	51%
Females < 15 years old	61	24%
Males < 15 years old	63	25%
Ethnicity	***n***	***%***
Kyrgz	193	76%
Tajik	57	22%
Other	5	2%
Kadamjay Area Community	***n***	***%***
Aidarken	124	49%
Chauvai	91	36%
Eshme	40	16%
Education*	***n***	***%***
Less than Primary School	6	5%
Primary School Graduate	6	5%
Secondary School Graduate	88	67%
Post-Secondary Graduate	30	23%
Missing	1	1%
Household Income	***n***	***%***
Difficult, some needs are unmet	24	9%
Limited, income meets needs	94	37%
Comfortable, no disposable income	129	51%
omfortable, excess for high quality goods	3	1%
Missing	5	2%

** Education is described for particpants older than 15 years old.*

Table 3. Urine (a), creatinine corrected urine (b), and blood (c) levels of heavy metals for all participants (n = 255).					
	Reference Value*	Mean (SD)	Geometric mean (95% CI)	95% percentile (95% CI)	Range
(a) Urine (µg/L)					
Antimony	0.3	1.190 (1.880)	0.68 (0.59-0.77)	3.7 (3-4.7)	0.010 - 23.640
Arsenic	15	24.336 (17.131)	20 (18-21)	50 (46-55)	1.500 - 189.800
Arsenic - Inorganic	10	23.903 (13.383)	22 (20-23)	42 (37-50)	9.042 - 141.700
Cadmium	0.5	0.489 (0.504)	0.32 (0.28-0.36)	1.4 (1.2-1.9)	0.010 - 4.130
Lead	80	1.099 (0.793)	0.87 (0.8-0.95)	2.5 (2-3.7)	0.070 - 4.900
Mercury	7	0.762 (0.994)	0.52 (0.47-0.57)	2.3 (1.5-2.9)	0.040 - 7.450
Uranium	0.03	0.058 (0.194)	0.031 (0.027-0.034)	0.11 (0.096-0.16)	0.001 - 2.247
(b) Creatinine Corrected Urine (µg/g creatinine)					
Antimony	0.3	1.704 (2.139)	1.1 (0.93-1.2)	5.4 (4.7-6.7)	0.010 - 22.230
Arsenic	15	35.269 (20.469)	31 (29-33)	67 (64-76)	9.700 - 189.200
Arsenic - Inorganic	10	26.912 (12.222)	24 (23-26)	51 (44-60)	8.969 - 66.508
Cadmium	0.5	0.623 (0.478)	0.5 (0.47-0.55)	1.6 (1.3-1.9)	0.100 - 3.540
Lead	80	1.696 (1.344)	1.3 (1.2-1.5)	4.2 (3.4-5.9)	0.070 - 8.810
Mercury	7	1.246 (1.628)	0.81 (0.73-0.9)	4.2 (3.2-6.8)	0.150 - 11.130
Uranium	0.03	0.090 (0.337)	0.048 (0.043-0.053)	0.13 (0.12-0.19)	0.001 - 4.414
(b) Blood (µg/L)					
Antimony	3.5	3.977 (1.954)	3.7 (3.6-3.9)	7.4 (5.4-9.1)	0.350 - 18.070
Arsenic	20	1.771 (0.788)	1.6 (1.5-1.7)	3.2 (3-3.7)	0.570 - 4.940
Cadmium	0.3	0.323 (0.264)	0.25 (0.23-0.27)	0.96 (0.72-1)	0.050 - 1.630
Lead	35	17.911 (8.996)	16 (15-17)	35 (31-45)	1.600 - 61.900
Mercury	5	0.737 (0.733)	0.59 (0.55-0.64)	1.6 (1.3-2.9)	0.120 - 6.880
Uranium	--	0.008 (0.021)	0.0037 (0.0032-0.0041)	0.034 (0.021-0.074)	0.002 - 0.212

*The most conservative reference value (for children) is shown for relative comparison.
See Table 1 for additional information.

Table 4. Participant results compared to KAB study reference values.				
	All Participants *(n = 255)*		***Children < 15 years old*** *(n = 124)*	
Chemical	**Above Reference Value**	**Above Action Value**	**Above Reference Value**	**Above Action Value**
Antimony	209 (82%)	45 (18%)	113 (91%)	20 (16%)
Arsenic	182 (71%)	4 (2%)	86 (69%)	1 (1%)
Cadmium	51 (20%)	0 (0%)	23 (19%)	0 (0%)
Lead	11 (4%)	0 (0%)	11 (9%)	0 (0%)
Mercury	3 (1%)	2 (1%)	1 (1%)	1 (1%)
Uranium	143 (56%)	0 (0%)	71 (57%)	0 (0%)

Table 5. (a) Urine (µg/g creatinine) and (b) blood (µg/L) levels of heavy metals in female and male partcipants under 15 years old.

	Reference Value	Parameter	Female (N=61)	Male (N=63)	Total (N=124)
(a) Urine Levels					
Antimony	0.3	Mean(SD)	1.950 (1.860)	1.999 (2.166)	1.975 (2.013)
		Geometric mean	1.3 (1-1.7)	1.3 (0.96-1.6)	1.3 (1.1-1.5)
		95% percentile	5.9 (3.4-9.2)	6.7 (4.4-12)	6.1 (5.3-12)
		Range	0.230 - 9.170	0.010 - 12.270	0.010 - 12.270
Arsenic (inorganic)	15	Mean(SD)	30.422 (13.222)	32.809 (14.332)	31.671 (13.785)
		Geometric mean	28 (24-32)	30 (26-34)	29 (26-32)
		95% percentile	51 (9-65)	61 (9.9-67)	59 (51-67)
		Range	8.969 - 64.909	9.885 - 66.508	8.969 - 66.508
Cadmium	10	Mean(SD)	0.446 (0.338)	0.504 (0.463)	0.476 (0.406)
		Geometric mean	0.38 (0.33-0.43)	0.41 (0.36-0.48)	0.4 (0.36-0.44)
		95% percentile	1.1 (0.62-2.2)	0.93 (0.7-3.5)	1.1 (0.85-3.5)
		Range	0.160 - 2.240	0.100 - 3.490	0.100 - 3.490
Lead	0.5	Mean(SD)	1.898 (1.288)	2.195 (1.570)	2.049 (1.440)
		Geometric mean	1.5 (1.3-1.8)	**1.8 (1.6-2.1)**	1.7 (1.5-1.9)
		95% percentile	4.1 (2.9-7.7)	5.7 (3.4-8.3)	4.2 (4.1-8.3)
		Range	0.070 - 7.700	0.450 - 8.330	0.070 - 8.330
Mercury	7	Mean(SD)	1.491 (2.080)	1.387 (1.624)	1.438 (1.855)
		Geometric mean	0.92 (0.73-1.2)	0.96 (0.78-1.2)	0.94 (0.81-1.1)
		95% percentile	4.4 (2.5-11)	6.1 (2-7.7)	5.8 (3.3-11)
		Range	0.180 - 11.130	0.280 - 7.690	0.180 - 11.130
Uranium	0.03	Mean(SD)	0.151 (0.572)	0.066 (0.037)	0.108 (0.402)
		Geometric mean	0.064 (0.052-0.079)	0.058 (0.052-0.066)	0.061 (0.054-0.069)
		95% percentile	0.14 (0.11-4.4)	0.12 (0.098-0.26)	0.13 (0.12-4.4)
		Range	0.012 - 4.414	0.018 - 0.260	0.012 - 4.414
(b) Blood Levels					
Antimony	3.5	Mean(SD)	4.102 (1.711)	4.777 (3.112)	4.445 (2.535)
		Geometric mean	3.9 (3.5-4.2)	**4.2 (3.8-4.7)**	4 (3.8-4.3)
		95% percentile	7.4 (5.4-11)	9.1 (7.4-18)	9 (7.9-18)
		Range	1.650 - 10.580	2.670 - 18.070	1.650 - 18.070
Arsenic	20	Mean(SD)	1.714 (0.652)	1.738 (0.813)	1.726 (0.736)
		Geometric mean	1.6 (1.4-1.8)	1.6 (1.4-1.8)	1.6 (1.5-1.7)
		95% percentile	3 (2.4-3.4)	3.3 (2.8-3.8)	3.1 (2.9-3.8)
		Range	0.740 - 3.380	0.570 - 3.810	0.570 - 3.810
Cadmium	0.3	Mean(SD)	0.193 (0.122)	0.157 (0.070)	0.175 (0.100)
		Geometric mean	**0.17 (0.15-0.19)**	0.14 (0.13-0.16)	0.15 (0.14-0.17)
		95% percentile	0.37 (0.27-0.72)	0.28 (0.24-0.4)	0.34 (0.29-0.72)
		Range	0.060 - 0.720	0.050 - 0.400	0.050 - 0.720
Lead	35	Mean(SD)	18.647 (9.351)	21.718 (10.384)	20.207 (9.968)
		Geometric mean	17 (15-19)	**20 (18-22)**	18 (17-20)
		95% percentile	36 (25-62)	45 (32-56)	37 (36-62)
		Range	5.800 - 61.900	7.100 - 55.500	5.800 - 61.900
Mercury	5	Mean(SD)	0.664 (0.820)	0.692 (0.399)	0.678 (0.639)
		Geometric mean	0.49 (0.42-0.58)	**0.61 (0.54-0.69)**	0.55 (0.49-0.61)
		95% percentile	1.7 (0.83-5.2)	1.3 (1.1-2.2)	1.6 (1.2-5.2)
		Range	0.180 - 5.190	0.210 - 2.250	0.180 - 5.190
Uranium	--	Mean(SD)	0.006 (0.014)	0.008 (0.009)	0.007 (0.012)
		Geometric mean	0.0032 (0.0026-0.0041)	**0.0046 (0.0036-0.0059)**	0.0039 (0.0033-0.0046)
		95% percentile	0.015 (0.007-0.078)	0.032 (0.019-0.042)	0.026 (0.021-0.078)
		Range	0.002 - 0.078	0.002 - 0.042	0.002 - 0.078

Table 6. (a) Urine results (µg/g creatinine) and (b) blood results(µg/L) for participants by community.

(a) Urine analyses (µg/g)		Aidarken (N=124)	Chauvai (N=91)	Eshme (N=40)	Total (N=255)
Antimony	Mean(SD)	1.521 (2.399)	2.226 (1.985)	1.078 (1.149)	1.704 (2.139)
	Geometric mear	0.87 (0.72-1)	1.6 (1.3-1.9)	0.78 (0.61-1)	1.1 (0.93-1.2)
	95% percentile	5.2 (2.4-6.7)	6 (5.2-12)	2.4 (0.23-5.9)	5.4 (4.7-6.7)
	Range	0.010 - 22.230	0.130 - 12.270	0.230 - 5.910	0.010 - 22.230
Arsenic*	Mean(SD)	37.778 (22.388)	28.811 (16.696)	42.195 (18.296)	35.269 (20.469)
	Geometric mear	34 (31-37)	25 (23-28)	39 (34-44)	31 (29-33)
	95% percentile	66 (53-73)	61 (47-114)	76 (21-94)	67 (64-76)
	Range	12.100 - 189.200	9.700 - 113.800	20.700 - 94.200	9.700 - 189.200
Cadmium	Mean(SD)	0.597 (0.382)	0.634 (0.598)	0.682 (0.445)	0.623 (0.478)
	Geometric mear	0.5 (0.45-0.56)	0.48 (0.41-0.56)	0.58 (0.48-0.69)	0.5 (0.47-0.55)
	95% percentile	1.4 (0.98-1.7)	1.7 (1.2-3.5)	1.4 (0.2-2.2)	1.6 (1.3-1.9)
	Range	0.130 - 2.100	0.100 - 3.540	0.200 - 2.240	0.100 - 3.540
Lead	Mean(SD)	1.789 (1.186)	1.548 (1.360)	1.745 (1.734)	1.696 (1.344)
	Geometric mear	1.5 (1.3-1.7)	1.2 (1-1.4)	1.3 (1-1.7)	1.3 (1.2-1.5)
	95% percentile	4.2 (2.9-5.8)	3.5 (2.9-8.3)	4.5 (0.07-8.8)	4.2 (3.4-5.9)
	Range	0.250 - 6.670	0.070 - 8.330	0.070 - 8.810	0.070 - 8.810
Mercury	Mean(SD)	1.506 (1.968)	0.952 (1.206)	1.094 (1.092)	1.246 (1.628)
	Geometric mear	0.97 (0.83-1.1)	0.64 (0.54-0.75)	0.81 (0.64-1)	0.81 (0.73-0.9)
	95% percentile	6.1 (2-9.6)	3.6 (2.5-7.2)	3 (0.23-5.9)	4.2 (3.2-6.8)
	Range	0.150 - 11.130	0.180 - 7.240	0.230 - 5.870	0.150 - 11.130
Uranium	Mean(SD)	0.108 (0.402)	0.044 (0.031)	0.138 (0.470)	0.090 (0.337)
	Geometric mear	0.057 (0.05-0.065)	0.033 (0.028-0.04)	0.063 (0.049-0.081)	0.048 (0.043-0.053)
	95% percentile	0.14 (0.094-0.46)	0.12 (0.098-0.14)	0.12 (0.02-3)	0.13 (0.12-0.19)
	Range	0.012 - 4.414	0.001 - 0.135	0.020 - 2.992	0.001 - 4.414
Inorganic	Missing values	29	33	10	72
Arsenic*	Mean(SD)	27.651 (10.770)	23.656 (13.095)	30.865 (13.610)	26.912 (12.222)
	Geometric mear	26 (24-28)	21 (19-24)	28 (24-33)	24 (23-26)
	95% percentile	49 (41-52)	53 (9-67)	59 (12-61)	51 (44-60)
	Range	9.885 - 54.985	8.969 - 66.508	11.650 - 61.111	8.969 - 66.508

(b) Blood analyses (µg/L)		Aidarken (N=124)	Chauvai (N=91)	Eshme (N=40)	Total (N=255)
Antimony	Mean(SD)	4.440 (2.481)	3.606 (1.203)	3.353 (0.753)	3.977 (1.954)
	Geometric mear	4.1 (3.8-4.3)	3.5 (3.3-3.7)	3.2 (2.8-3.6)	3.7 (3.6-3.9)
	95% percentile	9 (5.6-13)	5.1 (4.8-12)	4.4 (0.35-5.2)	7.4 (5.4-9.1)
	Range	2.380 - 18.070	1.650 - 12.360	0.350 - 5.180	0.350 - 18.070
Arsenic	Mean(SD)	1.896 (0.828)	1.497 (0.624)	2.016 (0.837)	1.771 (0.788)
	Geometric mear	1.7 (1.6-1.9)	1.4 (1.3-1.5)	1.9 (1.7-2.1)	1.6 (1.5-1.7)
	95% percentile	3.4 (3-3.8)	2.5 (2.4-4)	3.2 (0.97-4.9)	3.2 (3-3.7)
	Range	0.570 - 4.320	0.670 - 3.950	0.970 - 4.940	0.570 - 4.940
Cadmium	Mean(SD)	0.321 (0.238)	0.283 (0.240)	0.425 (0.363)	0.323 (0.264)
	Geometric mear	0.26 (0.23-0.29)	0.21 (0.18-0.25)	0.31 (0.24-0.4)	0.25 (0.23-0.27)
	95% percentile	0.84 (0.51-1)	0.69 (0.59-1.3)	1.1 (0.1-1.6)	0.96 (0.72-1)
	Range	0.070 - 1.440	0.050 - 1.330	0.100 - 1.630	0.050 - 1.630
Lead	Mean(SD)	20.565 (9.580)	15.581 (8.454)	14.832 (5.056)	17.911 (8.996)
	Geometric mear	19 (17-20)	14 (12-15)	14 (12-16)	16 (15-17)
	95% percentile	37 (29-52)	33 (25-46)	23 (5.8-28)	35 (31-45)
	Range	8.100 - 61.900	1.600 - 46.000	5.800 - 27.900	1.600 - 61.900
Mercury	Mean(SD)	0.828 (0.950)	0.627 (0.396)	0.705 (0.470)	0.737 (0.733)
	Geometric mear	0.63 (0.56-0.7)	0.53 (0.48-0.6)	0.62 (0.53-0.72)	0.59 (0.55-0.64)
	95% percentile	2 (1.1-4.3)	1.5 (1.2-2.2)	1.4 (0.28-3)	1.6 (1.3-2.9)
	Range	0.180 - 6.880	0.120 - 2.250	0.280 - 2.980	0.120 - 6.880
Uranium	Mean(SD)	0.007 (0.015)	0.009 (0.019)	0.010 (0.036)	0.008 (0.021)
	Geometric mear	0.0038 (0.0032-0.0045)	0.0037 (0.003-0.0046)	0.0031 (0.0022-0.0043)	0.0037 (0.0032-0.0041)
	95% percentile	0.031 (0.012-0.052)	0.038 (0.019-0.11)	0.027 (0.002-0.21)	0.034 (0.021-0.074)
	Range	0.002 - 0.133	0.002 - 0.111	0.002 - 0.212	0.002 - 0.212

Table 7. (a) Urine results (µg/g creatinine) and (b) blood results(µg/L) for partcipants identfying an ethnicity (n = 250).

		Kyrgyz (n=193)	Tajik (n=57)
(a) Creatinine Corrected Urine Levels			
Antimony	Geometric mean	1 (0.88-1.2)	1.2 (0.95-1.5)
	Range	0.010 - 22.230	0.280 - 9.170
Arsenic (inorganic)	Geometric mean	24 (22-26)	27 (23-31)
	Range	8.969 - 66.508	9.885 - 54.985
Cadmium	Geometric mean	0.5 (0.46-0.55)	0.53 (0.46-0.61)
	Range	0.100 - 3.540	0.130 - 2.100
Lead	Geometric mean	1.2 (1.1-1.4)	**1.8 (1.5-2.1)**
	Range	0.070 - 8.810	0.250 - 6.670
Mercury	Geometric mean	0.76 (0.67-0.85)	**1 (0.83-1.3)**
	Range	0.150 - 9.590	0.210 - 11.130
Uranium	Geometric mean	0.046 (0.04-0.052)	**0.055 (0.046-0.065)**
	Range	0.001 - 4.414	0.018 - 0.938
(b) Blood Levels			
Antimony	Geometric mean	3.6 (3.4-3.8)	4 (3.7-4.4)
	Range	0.350 - 17.780	2.780 - 18.070
Arsenic	Geometric mean	1.5 (1.4-1.6)	**2 (1.8-2.2)**
	Range	0.670 - 4.940	0.570 - 3.830
Cadmium	Geometric mean	0.24 (0.22-0.27)	0.27 (0.23-0.33)
	Range	0.050 - 1.630	0.080 - 1.440
Lead	Geometric mean	15 (14-16)	**21 (19-24)**
	Range	1.600 - 47.700	8.700 - 52.000
Mercury	Geometric mean	0.6 (0.55-0.65)	0.56 (0.47-0.66)
	Range	0.120 - 6.880	0.240 - 5.190
Uranium	Geometric mean	0.0036 (0.0031-0.0042)	0.0038 (0.0029-0.0049)
	Range	0.002 - 0.212	0.002 - 0.052

Table 8. Comparison of the 95th percentile of urine antimony exposure in KAB study compared to population-based studies designed to establish "reference values".

Age	Agency	Value (µg/L)
3 to 14	Germany (2003-2006)	0.30*
5 to 14	**Kadamjay (2021)**	**4.3**
3 to 79	Canada (2009-2011)	0.17
3 to 80	United States (2015-2016)	0.201
5 to 49	**Kadamjay (2021)**	**5.4**

*German Human Biomonitoring Value used as the urine antimony "Reference Value" for children in the KAB study.