MIT Open Access Articles

A mass-balance approach to evaluate arsenic intake and excretion in different populations

Massachusetts Institute of Technology

Full length article

A mass-balance approach to evaluate arsenic intake and excretion in different populations

Daniel Beene [a], Philip Collender [b], Andres Cardenas [b], Charles Harvey [c], Linden Huhmann [c], Yan Lin [d], Johnnye Lewis [a], Nancy LoIacono [e], Ana Navas-Acien [e], Anne Nigra [e], Craig Steinmaus [b], Alexander van Geen [f,*]

[a] Community Environmental Health Program, Health Sciences Center, University of New Mexico, Albuquerque, NM, United States
[b] Environmental Health Sciences, University of California, Berkeley. of California, Berkeley, Berkeley, CA, United States
[c] Earth and Environmental Engineering, Massachusetts Institute of Technology, Cambridge MA, United States
[d] Geography and Environmental Studies, University of New Mexico, Albuquerque, NM, United States
[e] Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, United States
[f] Lamont-Doherty Earth Observatory, Columbia University, Palisades, NY, United States

ARTICLE INFO

ABSTRACT

Unless a toxicant builds up in a deep compartment, intake by the human body must on average balance the amount that is lost. We apply this idea to assess arsenic (As) exposure misclassification in three previously studied populations in rural Bangladesh (n = 11,224), Navajo Nation in the Southwestern United States (n = 619), and northern Chile (n = 630), under varying assumptions about As sources. Relationships between As intake and excretion were simulated by taking into account additional sources, as well as variability in urine dilution inferred from urinary creatinine. The simulations bring As intake closer to As excretion but also indicate that some exposure misclassification remains. In rural Bangladesh, accounting for intake from more than one well and rice improved the alignment of intake and excretion, especially at low exposure. In Navajo Nation, comparing intake and excretion revealed home dust as an important source. Finally, in northern Chile, while food-frequency questionnaires and urinary As speciation indicate fish and shellfish sources, persistent imbalance of intake and excretion suggests imprecise measures of drinking water arsenic as a major cause of exposure misclassification. The mass-balance approach could prove to be useful for evaluating sources of exposure to toxicants in other settings.

1. Introduction

Geoscientists calculate the residence time of an element in the ocean by dividing the total mass of the element in the ocean by the input from, for instance, rivers (Broecker and Peng, 1982). The implicit assumption of such a calculation is steady-state and that the input and output of an element in the ocean, or inside any chemical reactor, must balance when averaged over the appropriate time scale. Even if the details of the internal processes that regulate the output of an element are not well understood, an independent estimate of the output that is consistent with the input, as in the case of accumulation of a particular element in marine sediments, can provide an indication that the main fluxes through the system are reasonably well understood.

Mass-balance of new radio-labelled drugs is often tested in early trials using animal models or humans (Roffey et al., 2007). Public-health scientists also rely on mass-balance between compartments within the human body when constructing a pharmacokinetic model to predict concentrations in blood of a toxicant such as lead in house dust, soil, and water (White et al., 1998). Mass-balance is rarely invoked, however, when comparing external sources of toxicants to the human body with losses of these toxicants from the human body. A loss in urine measured as a biomarker, for instance, is usually considered the independent variable in studies linking exposures to a particular disease. Mass-balance is often also obscured in public health studies by log transformations of measures of exposure or normalization to creatinine in urine. Mass-balance cannot be evaluated with log transformed intake and both creatinine concentrations in urine and a creatinine excretion rate are required to determine the loss of a toxicant via urine.

In this paper, we combine the geoscience and biomedical approaches to mass-balance by comparing the intake of a toxicant from multiple sources with the excretion of this toxicant in urine for the purpose of exposure assessment (Fig. 1). In this type of analysis, the biomarker is turned into a dependent variable that is expected to reflect the total intake of the toxicant from various environmental sources. We apply the approach here to arsenic (As) for several reasons. First, our understanding of the negative health impacts resulting from chronic exposure to As of often natural origin continues to grow (Abdul et al., 2015). Second, As is primarily excreted as urine and therefore relatively easy to measure. Applying the mass-balance approach to lead in the human body with a large internal pool and little loss in urine would be more complicated, for instance. Third, water alone is insufficient to explain As exposure in many contexts and several other pathways and sources such as food, air, dust, and smoking need to be considered (Garelick et al. 2008; Mantha et al., 2017). Therefore, As provides a good testing ground for the mass-balance approach even if it has been applied only rarely (Cleland et al., 2009). Finally, due to its impacts on human health, there are a large number of studies on As, such as the three we re-examined here, to which this method could be applied. The data from one of these studies were previously used to constrain a complex pharmacokinetic model of As in the human body by El-Masri et al. (2018). The approach followed here is simpler and may be useful to identify other sources in community studies.

The time-scale of throughput of As in the human body is reasonably well known. Pomroy et al. (1980) conducted a remarkable experiment whereby six volunteers were administered a small dose of the short-lived radioisotope of As ^{74}As (t$_{1/2}$ 17.9 d) orally, after which the inventory of ^{74}As in the whole body, urine, and feces was monitored for up to three months. Following the first day, the sum of the decay-corrected radiation accounted for in the body, urine, and feces remained constant within ± 3% and was therefore fully accounted for. Retention of ^{74}As followed a similar exponential decline in all six volunteers. After 7 days, 68% of the total ingested had already been excreted, 62% in urine and 6% in feces. A controlled-diet experiment conducted by two volunteers also showed even faster elimination of As consumed in the form of rice (He and Zheng, 2010). One of the implications of these studies for our analysis is that it is reasonable to expect mass-balance for As in the human body over time scales of several days to a week. Another implication, however, is that a single urine sample may not be representative of typical intake if As ingestion varies from one day to the other.

Our study applies the mass balance approach to three populations exposed to very different ranges of As by considering more than a single source. The goal is to determine to what extent these additional sources bring intake and excretion of As in closer agreement and can account for additional variance. To our knowledge, this is one of the few studies of As exposure that link biomarker data to various sources through the lens of mass-balance across multiple populations.

2. Methods

2.1. Populations and available data

We harmonized data and analytical methods across three epidemiological cohorts in Bangladesh, Navajo Nation, and Northern Chile (Table 1). Drinking water accounts for some exposure to As in all three studies, but additional sources differ.

2.1.1. Rural Bangladesh: Health Effects of Arsenic Longitudinal Study (HEALS)

The Health Effects of Arsenic Longitudinal Study (HEALS) is a longitudinal birth cohort study that was launched in rural Bangladesh by Columbia University in 2000 and whose management later shifted to the University of Chicago. In this region, most inhabitants obtain their drinking water at home from a privately installed well (Fig. 2a). We rely for this analysis on household well-water As (WAs) and individual urinary (UAs) and urinary creatinine concentrations in samples collected at baseline in 2000–02 from 11,224 participants (van Geen et al., 2003; Ahsan et al., 2006). Participants at recruitment were aged 18 years or older, had lived in the study area for 5 or more years, and had used their primary well as their main source of water for drinking and cooking for at least 3 years. Toward the end of recruitment at baseline, the residency requirement was relaxed to a minimum of 3 years. Geographic coordinates were collected using hand-held GPS units at recruitment for each of the 6,000 wells in the 25 km^2 study area, including a small proportion of public wells. The average number of users per well was 11 at baseline, indicating that two households on average were sharing a well (van Geen et al., 2002). Participants were asked a series of questions and shown examples of various water containers to estimate how much they were drinking on a typical day. Participants were also asked how much of this water came from their primary household well or other wells away from home. The reported fraction of water from non-

Table 1
Overview of characteristics of the three study populations, including where relevant averages and ± 1 standard deviation.

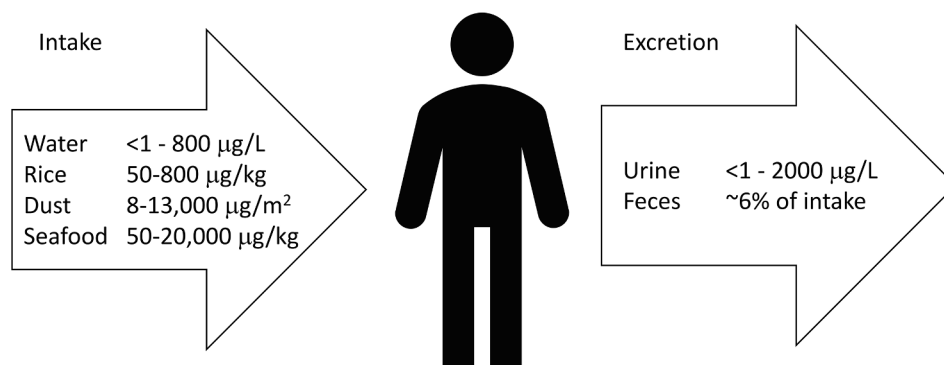|	HEALS	NBCS	Northern Chile
Study type	Longitudinal	Birth cohort	Case-control
n	11,224	619	630
Female	57%	72%	31%
Average age	37 ± 10	28 ± 6	64 ± 11
n	11,224	619	630
Average BMI	20 ± 3	29 ± 6	27 ± 5
n	11,143	379	626
Smoking			
Never	64%	82%	30%
Former	7%	9%	43%
Current	29%	8%	27%
n	11,219	551	630

Fig. 1. Range of As concentrations in various sources and sinks to and from the human body, respectively, for the three populations in this study.
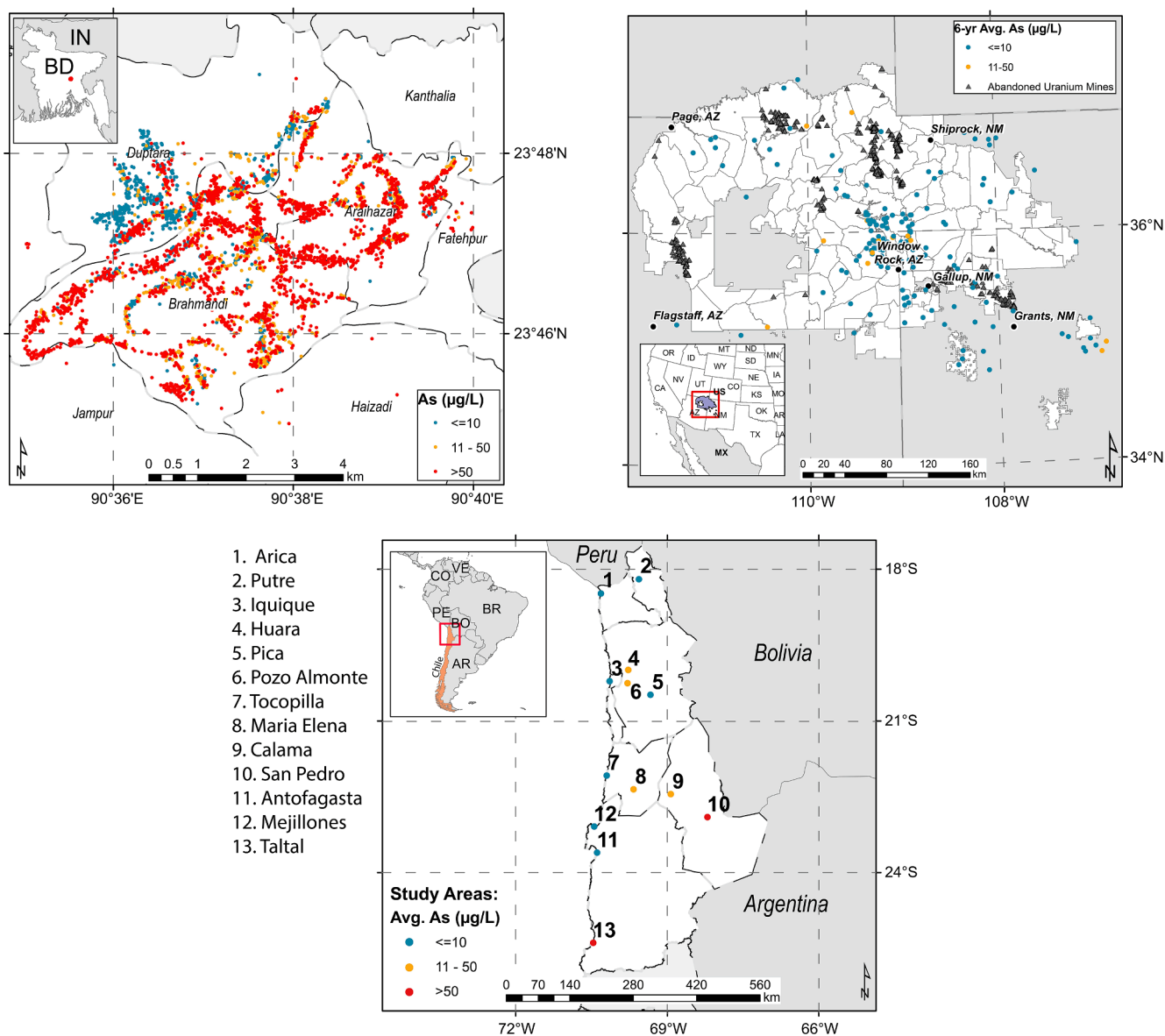
Fig. 2. Map showing the distribution of As sources for the three study populations in (a) rural Bangladesh, (b) Navajo Nation, and (c) Northern Chile. Note that WAs concentrations for the Northern Chile study are assigned to entire municipalities. Precise locations of PWS points in the NBCS map are obscured using a geomasking algorithm.

primary wells ranged from 10 to 30% for women and men, respectively (Huhmann et al., 2021).

We also consider for this analysis a subset of 2331 HEALS participants for whom not only total UAs but also As speciation was determined in urine (Ahsan et al., 2006). Finally, we use in this analysis a data set of total As concentrations measured in rice, both uncooked and cooked, obtained directly from the households for a subset of 410 participants between February and July 2016 (Huhmann et al., 2021). This collection took place a decade and a half after recruitment but there is no reason to expect that the As content of rice consumed at the time was very different. Consumption of high As well water did decline over this period (Huhmann et al., 2019), which means the effect of cooking rice in high As groundwater may have diminished.

2.1.2. Navajo nation: Navajo Birth Cohort Study (NBCS)

Navajo Nation experiences chronic exposures to mixed-metal waste linked to>500 abandoned uranium mines: the legacy of nuclear weapons development during the Cold War. The unlined abandoned mine waste piles frequently contain As and a range of metals geologically co-located with uranium. These piles and more than 600 other mine-related exposure sources, often unmarked or unfenced, have remained in proximity to homes since closure of the last mine in 1986. Led by the UNM Health Sciences Center Community Environmental Health Program, the Navajo Birth Cohort Study (NBCS) was initiated to address community concerns over chronic environmental exposure to uranium mine waste and its impact on birth outcomes and early childhood development (Hunter et al. 2015). In 2013, the NBCS began recruiting women who were between 14 and 45 years old with a confirmed pregnancy, had lived on the Navajo Nation for at least 5 years, were willing to deliver at a participating hospital, and to have their child followed-up for 1 year postnatally. Biomonitoring data, including blood, serum, and urine were collected from each of the participants at the time of enrollment. Home environment (e.g. indoor dust if consented for home assessment, heating source), demographic (e.g. age, gender), socioeconomic, exposure, health, and lifestyle data were also collected during the enrollment period.

>800 pregnant women were enrolled in the first phase of the NBCS. Concentrations of As and metals in urine were measured by the Centers

for Disease Control and Prevention (CDC) Division of Laboratory Sciences. Drinking water total As is based on the EPA six-year review of drinking water standards for the public water system (PWS) reported by participants, or on analysis of participant-identified alternative unregulated drinking water sources. Although 90% of participants relied on PWSs, 13% of participants drank from PWSs delivering water containing > 10 μg/L As and were subjected to additional monitoring by the US EPA. Total As concentrations in drinking water and home dust were measured in the Richmond laboratories of the US EPA or, for PWSs, by Navajo Tribal Utility Authority laboratories. Total As as well as As speciation were measured in urine by the US EPA. A total of 619 participants with complete As data for all sources are included in the mass-balance study.

2.1.3. Northern Chile

Concentrations of total UAs and As species in urine, as well as information on water source and diet, were collected during a series of case-control studies in the Tarapacá and Antofagasta regions of northern Chile (Steinmaus et al., 2013; Melak et al. 2014; Hall et al. 2017). Between October 2007 and December 2010, a single first morning urine sample was collected from each of 283 cancer patients and 347 controls matched on age and gender. Drinking WAs concentrations reported from various sources, including government agencies, scientific research, and commercial water suppliers, were assigned to each subject based on municipality of residence (Steinmaus et al. 2013; Borgoňo et al 1980; Rivara et al. 1997; Zaldívar 1974; Ferreccio et al. 2000; CONAMA 2000; Sancha & O'Ryan 2008). Weekly intakes of various types of foods, as well as typical volumes of water consumed per day, were ascertained for each subject based on a food frequency questionnaire (Hall et al. 2017). A total of 550 subjects with complete data (247 cancer patients and 303 controls) were analyzed for this study.

2.2. Environmental and urinary measures of arsenic exposure

2.2.1. HEALS

2.2.1.1. Water.
HEALS participants identified a subset of 4,153 out of a total 5,971 wells within the 25 km^2 study area as their primary household well. The distribution of As in wells is spatially heterogeneous, with most villages containing a mix of high- and low-As wells and some villages dominated by either high- or low-As wells (van Geen et al., 2002; 2003). At recruitment, about a quarter of HEALS participants were drinking from wells that mt the WHO guideline for As of 10 μg/L (Fig. S1). Slightly less than a quarter of the wells used by these participants did not meet the WHO guideline but met the Bangladesh national standard of 50 μg/L. Therefore, more than half the participants obtained most of their water at recruitment from wells that contained > 50 and up to 860 μg/L As. The overall geometric of primary well As concentrations is 45 μg/L, with successive quartiles averaging 5, 50 120, and 300 μg/L, respectively.

We calculate an average number of 2.7 participants per household well at recruitment. This is no surprise, as married couples with a female of child-bearing age were preferentially recruited and in many cases recruited couples shared a well. The reported quantity of water consumed by HEALS participants averaged 3 ± 1 L/d but ranged very widely from 0.2 to 10 L/d (Fig. S2). There was no detectable difference between the average reported by women (3.1 L/d) and men (2.9 L/d). Based on an average As content of well water of 100 μg/L for the cohort (Table 2), the average As intake from drinking well water at recruitment was therefore on the order of 300 μg/day.

2.2.1.2. Rice.
The As content of rice samples (50–1200 μg/kg) reported in Huhmann et al. (2021) ranges widely, with averages of 244 ± 150 and 235 ± 180 μg/kg (1-sigma) for uncooked and cooked rice, respectively, that are indistinguishable (Fig. S3). A food-frequency survey

Table 2
Concentrations of As in water and urine, along with speciation of As in urine, for three study populations.

	HEALS	NBCS	Northern Chile
Water As (ug/L)			
Average	102 ± 115	2 ± 3	35 ± 15
Range	0.1–860	0.3–13	0.1–60
N	11,751	619	550
Urine As (μg/L)			
Average	138 ± 157	8 ± 13	57 ± 64
Range	1–2300	0.4–190	1.3–670
N	11,226	619	550
Urine speciation			
Average and SD As (III)	6 ± 5%	9 ± 7%	5 ± 4%
Average and SD As (V)	9 ± 8%	16 ± 17%	3 ± 3%
Average and SD MMA	13 ± 5%	6 ± 10%	9 ± 5%
Average and SD DMA	69 ± 9%	57 ± 31%	60 ± 17%
Average and SD AsB	3 ± 4%	4 ± 15%	23 ± 22%
N	2331	619	550

administered to HEALS participants indicates an average of 300 and 520 g of rice consumed per day by women and men, respectively (Chen et al., 2004; El Masri et al., 2018). Combined with the average As content of rice, this corresponds to an overall average intake of 96 μg/d from rice alone, about a third of the average intake of 300 μg/d by drinking well water. Other foods are consumed in lower quantities and are less likely to contain levels of As comparable to rice (Chen et al., 2004).

2.2.1.3. Urine.
The concentration of total As in urine collected from HEALS participants ranged widely from 1 to 2300 μg/L and averaged 140 μg/L (Figure S4). Total UAs concentrations for successive quartiles average 50, 50, 100, and 200 μg/L, respectively, with several dozen concentrations > 1000 μg/L reported. MMA and DMA in urine combined on average account for over 80% of the As in urine in HEALS, whereas AsB levels average only 3% (Table 2). Creatinine concentrations were also measured in the urine samples and range widely from 1.3 to 380 mg/dL.

2.2.2. NBCS

2.2.2.1. Water – Individual.
Approximately 30% of homes on the Navajo Nation lacked access to running water from regulated sources and rely on hauling water from a PWS if accessing PWS. Water As concentrations for 592 NBCS participants using PWSs as their drinking water source is based on EPA's Six Year Review of Contaminant Occurrence database (Nigra et al., 2020). A total of 27 of the participants included in this analysis reported drinking primarily from unregulated water sources, mostly wells. As of 2017, 15% of unregulated wells among the > 500 tested water wells across the reservation exceeded the US Maximum Contaminant Level (MCL) for As (10 μg/L). Arsenic concentrations in these wells generally increase with decreasing distance to abandoned uranium mines (Hoover et al., 2017). Water As data for the 27 participants were either based on sample analysis from USEPA laboratories or obtained from existing water quality data from previous sampling by other agencies. Although about 13% of NBCS participants reported drinking primarily from unregulated water sources, participants might also use unregulated water sources for non-drinking water purposes such as cooking and bathing, which are not captured in the data. It should be noted that because the data used in the present analysis represent participants for whom biomonitoring and home environmental assessments were complete, they represent a smaller proportion of NBCS participants who consume water from unregulated sources (4.6%). The WAs concentrations in NBCS participants are significantly lower than the other two cohorts ranging from 0.3 to 13 μg/L with a geometric mean of 2.6 μg/L. The average As concentration for successive quartiles is 0.28, 1.1, 3.5, and 6.1 μg/L, respectively. Drinking water As exceeds the US MCL for a total of 22 participants.

2.2.2.2. Indoor dust - individual. The desert environment and the prevalence of high winds and dust storms mean that uranium waste piles could contribute respirable particulates containing As to indoor dust of the NCBS cohort (Zychowski et al., 2018). Potential additional contributors to house dust include home-biomass heating and jewelry making (Gonzales et al., 2004). To address such concerns, home dust samples were collected by trained field staff using pre-moistened Ghost Wipes from Environmental Express, Inc. 10 cm by 10 cm in size. Dust was collected over an approximate 100 cm^2 area by wiping vertically on the first swipe, then folding the wipe in half and repeating with horizontal wipes, and finally folding the wipe in half again and wiping the four corners of the sample area. Sample surfaces were prioritized to include high exposure areas, such as near combustible heating sources, high occupancy spaces such as shared living rooms, rooms where dirt accumulates, or in-home work areas. In locations with irregular surfaces such as window ledges or wood-burning stoves with less than a 100 cm^2 area, field staff ensured that a total area of approximately 100 cm^2 was wiped with three passes.

We report here for the first time As levels in home dust analyzed at the USEPA Region IX laboratory by inductively coupled plasma mass spectrometry (ICP-MS) after acid digestion, as described in EPA Laboratory Manual Method 200.8 (USEPA, 1994). Samples below the limit of detection are imputed as the limit of detection for As (6.2 ug/m^2) divided by the square root of 2. Although the number of dust samples vary by home size and floorplans, more than one dust sample (2 samples: 88%; 3 samples: 1.3%; 4 samples: 2.6%) was collected from 90% of the participants and single samples were collected from only 8% of the participants. We used the average As measurements of all dust samples in each participant's home in the analysis. There is a wide distribution of home dust average As measurement ranging from 8.2 to 13,000 μg/m2 with a mean measurement of 230 μg/m^2 and a median of 81 μg/m^2 (Fig. S5).

2.2.2.3. Urine. NBCS urine samples used in this study were collected from mothers (n = 447) and fathers (n = 172) at the time of enrollment. The urinary total As concentration for NBCS population ranges from 0.39 to 190 μg/L with an average of 8.2 μg/L. The average UAs concentration of each quartile is 2.0, 4.4, 7.2, and 19 μg/L respectively. For three participants, UAs was above 100 μg/L. MMA and DMA in urine combined on average account for over 60% of the As in urine in NCBS, whereas AsB levels average only 4% (Table 2).

2.2.3. Chile

2.2.3.1. Water. The procedure of assigning municipal data to study subjects resulted in 16 WAs concentrations ranging from an assigned value of 0.1 μg/L given to two subjects with residences outside of the study area to a maximum of 60 μg/L. A total of 465 subjects were assigned WAs concentrations > 10 μg/L, and 119 subjects were assigned concentrations > 50 μg/L. An average daily water intake of 1.8 ± 1.0 L/d was estimated from recall-based food frequency questionnaires administered during subject interviews (Fig. S2).

2.2.3.2. Food. A recall-based food frequency questionnaire administered during participant interviews provided individual estimates of average daily consumption of various foods for 585 study subjects (96%). Foods assessed included fish and seafood; eggs; nuts; soy; beef, pork, and lamb; processed meats; organ meats; poultry; cheese; citruses, melons and berries; dark green vegetables; deep yellow vegetables; dry beans; milk; non-whole grains; tomatoes; white potatoes; whole grains; yogurt; alcohol; and other fruits and vegetables. These data were originally collected for analysis in relation to health outcomes, such as hypertension, but are used here to track dietary sources of As species in the study population (Hall et al. 2017). The intake of seafood, a likely source of As in this context, averaged 23 ± 23 g/day. The concentration of As in

seafood was estimated to average of 47 ± 17 μg/g based on a combination of proportions of various types of seafood consumed in a survey of residents of Santiago, Chile (Muñoz et al., 2005), and As concentrations from a market basket survey conducted in the USA (Wolle et al, 2019).

Studies conducted in the region have identified raw vegetables and vegetables cooked in contaminated water as dietary sources of As (Díaz et al., 2004, Muñoz et al., 2017). To investigate potential dietary sources of As in the Chile study population, we assessed bivariate relationships between UAs species and self-reported consumption of fish and seafood; beef, pork, and lamb; processed meats; organ meats; poultry; dark green vegetables; deep yellow vegetables; milk; cheese; yogurt; whole grains; and non-whole grains using least squares linear regression. We found total UAs was marginally associated with consumption of fish and seafood (5.14 μg/L per ounce; SE 3.38; R^2 0.0042), beef, pork, and lamb (3.55 μg/L per ounce; SE 1.97; R^2 0.0059), and showed negative marginal associations with dark green vegetables (-3.99 μg/L per serving; SE 2.59; R^2 0.0043), and yogurt (-12.50 μg/L per serving; SE 8.08; R^2 0.0044). Inorganic UAs was significantly negatively associated with dark green vegetables (-3.38 μg/L per serving; SE 1.50; R^2 0.0092) and marginally associated with beef, pork and lamb consumption (1.67 μg/L per ounce; SE 1.14; R^2 0.0039). Dimethyl arsenic was significantly negatively associated with dark green vegetable consumption (-2.51 μg/L per serving; SE 1.13; R^2 0.0088) and marginally negatively associated with milk (-1.08 μg/L per serving; SE 0.72; R^2 0.0041) and yogurt (-5.77 μg/L per serving; SE 3.54; R^2 0.0048).

2.2.3.3. Urine. Urinary As was measured in single first morning urine samples collected from each subject (Melak et al., 2014). Total UAs concentrations ranged from 1.3 to 670 μg/L with a mean value of 59 μg/L. Mean UAs concentrations within each quartile were 13, 30, 52, and 130 μg/L. The 23% average contribution of AsB levels to UAs is considerably higher in Chile than for HEALS and NCBS (Table 2). The mean urinary creatinine concentration was 128 mg/dL, ranging from 13 to 443 mg/dL.

2.3. Calculating as intake and excretion

2.3.1. Common features of three study populations

Water intake by drinking and water loss in urine must be measured or at least estimated to evaluate if mass-balance of As is satisfied based on identified sources of exposure. For HEALS and northern Chile, we can use the average of daily volumes of water consumed reported at the individual level of 3.0 ± 1.0 and 1.8 ± 1.0 L/d, respectively but in the case of NBCS, an average and standard deviation of 2.1 ± 0.7 L/d is assumed based on EPA exposure factors handbook (USEPA, 2017).

Given that water consumption is a significant source of As and urination is the main loss, it would be natural to consider mass-balance of water (Huhmann et al., 2021). This is rarely done because it is difficult to measure all sources of water intake and excretion at the individual level. Even recording all water consumed over a day doesn't take into account ~20% of total water intake as food and ~10% from cellular metabolism (Popkin et al., 2010; Gomella and Haist, 2007). Another complication is that the proportion of water intake lost to urine varies considerably with perspiration and transpiration (Perrier et al., 2013). Nermell et al. (2008) pointed out that urinary creatinine excretion is an imperfect measure of the processes affecting urine dilution and proposed specific gravity of urine as an alternative. Specific gravity was not measured in the overall HEALS, NBCS, and Chile cohorts, however. In light of these limitations, we therefore use Equation D of Ix et al. (2011) to calculate the daily excretion flux of creatinine as a function of weight, age, and sex derived from previous studies. Rather than normalizing UAs concentrations to creatinine, however, we calculate the daily excretion of As from the ratio of the creatinine concentration in the urine relative to that of the daily excretion of creatinine derived from previous studies.

The assumption is that the ratio of As to creatinine concentrations in urine is constant for a given level of As intake, even if absolute concentrations of both As and creatinine may vary over the course of a day. We first use this relation as is and assume no error in the predicted daily creatinine excretion. At a later stage, we propagate the uncertainty in that relationship when examining deviations from mass-balance for As in the three study populations.

Pomroy et al. (1980) showed by tracking low doses of radioactive As ingested by several volunteers that 6% of the total excreted was contained in feces, and this within the first few days. Even if this early excretion may have been exacerbated by the way the capsule of radioactive As was administered compared to a steadier intake of As from water and food, the total flux of As excreted is calculated by increasing the flux of As excreted in urine by 1/0.94 accordingly.

2.3.2. Intake of As specific to HEALS

Intake of As is first calculated by simply multiplying daily water consumption available at the individual level, averaging 3 ± 1 L/d, by the As concentration for the participant's primary well, also available at the individual level. This intake is then modified by considering additional wells that participants are likely to drink from. Relying on a recent analysis of the same HEALS data by Huhmann et al. (2021), female participants are assumed in the present study to obtain 24% of their drinking water from the study area at large and the remaining 76% from their primary well. The same proportions calculated for male participants are 31 and 69%, respectively, which is consistent with men spending more time away from home for work. Intake of As from wells at large is calculated from the average WAs of 95 µg/L As for all wells in the study area (not only primary wells of cohort participants), under the assumption that a secondary source could be located anywhere in the study area (Huhmann et al. 2021). Intake of As from food in the HEALS population is then added by multiplying the average As content of cooked rice of 240 ug/kg and an average daily rice consumption of 300 and 520 g for women and men, respectively. Intake of As from food other than rice is assumed to be small based on a food frequency questionnaire administered to HEALS participants (Chen et al., 2004).

2.3.3. Intake of As specific to NBCS

Intake of WAs is calculated by multiplying daily water consumption, averaging 2.1 ± 0.7 L/day (USEPA, 2017), by the As concentration in the reported drinking water source available at the individual level. The intake of As from home dust is calculated by multiplying the daily home dust ingestion by the As loading (mass per area unit, ug/m^2) in home dust in an individual participant's home. However, daily home dust ingestion rate varies significantly by age, activity pattern, and hand washing frequency especially when home dust is measured as surface loadings (by units of surface area) rather than bulk dust concentrations (Özkaynak et al. 2011; Wilson et al. 2013). Therefore, we adopted a mean indoor dust ingestion rate of 0.0062 ± 0.0050 m^2/day for adults based on previous research with a mechanistic hand-to-mouth model for indoor dust measurements presented as surface loadings (Wilson et al. 2016). The average of multiple measurements of dust As loadings available for most homes was used in the calculation.

Previous work suggests a lower range of bioavailability of As (e.g. 8–61%) in soil/dust based on studies of relative bioavailability of As in soils at 11 hazardous waste sites (USEPA, 2010), which might reduce the estimate of As intake from dust. Given the uncertainties of bioavailability of dust As which tends to be site-specific, and the lack of As bioavailability data for As in home dust among the NBCS cohort, we used the mean bioavailability (34%) from the previous study (USEPA, 2010) when analyzing the daily mass of As excreted as a function daily As intake for NBCS home dust.

2.3.4. Intake of As specific to Chile

The relatively high proportion of AsB to total UAs for Northern Chile population suggests a significant seafood contribution that needs to be estimated based on each subject's reported seafood consumption. We used proportions of total seafood consumption attributable to tuna (32%), hake (21%), mackerel (5%), other fish (23%), clams (6%), mussels (4%), and other shellfish (9%) reported as part of a total diet study of the population of Santiago, Chile (Muñoz et al., 2005), mapping them onto As concentration distributions derived from a market basket survey of commonly consumed seafoods in the USA (Wolle et al., 2019). Since not all species reported in the Santiago survey were collected in the market basket study, we assumed equivalency of As concentrations, mapping hake to cod, mackerel to pollock, "other fish" to salmon and tilapia, mussels to clams, and other shellfish to shrimp and crabs. Inverse-variance weighted mean As concentrations were calculated for each subtype of seafood, deriving standard errors by assuming the 95% confidence intervals reported in Wolle et al. (2019) that correspond to t distributions with 2 degrees of freedom. The overall mean seafood As concentration was calculated as a weighted average across subtypes according to dietary proportions reported in Muñoz et al. (2005). The resulting seafood As concentration of 743 ng/g was then multiplied with self-reported grams of seafood consumed in a typical day derived from the food frequency questionnaire.

2.4. Monte-Carlo simulations

Our calculations of As intake and excretion through urine are subject to uncertainties due to measurement errors and individual variance. In order to assess the potential impacts of these uncertainties on our mass balance calculations, we conducted Monte Carlo simulations to propagate intake and excretion uncertainties through to distributions of parameters pertaining to mass balance. The general process used for each cohort was to randomly draw latent masses of As ingested and excreted for each subject and then fit linear regressions relating excretion to intake, retaining the intercept, slope, and r^2 parameters for each simulation as indicators of proximity to mass balance. Simulations were conducted with 1000 replications for each study population and intake scenario. Arsenic excretion for each cohort was simulated under the assumption that the fraction of daily creatinine excreted in each sample would be equivalent to the fraction of daily arsenic excreted. Total daily creatinine excretion for each subject was simulated randomly based on linear regression parameters and root mean square errors reported in Ix et al. (2011):

$$\widehat{As}_{out} = C_{UAs}/C_{UCr} \times Cr_d(W, A, R, S)/Frac_{UAs}$$

$$Cr_d(W, A, R, S) \sim Normal(879.89 + 12.51 \times W - 6.19 \times A + 34.51 \times R$$
$$- 379.42 \times S, \sigma$$
$$= 357)$$

Where $\widehat{As}_{out}$ denotes the simulated mass of arsenic excreted (mg), C_{UAs} denotes concentration of UAs (mg/L), C_{UCr} denotes concentration of urinary creatinine (mg/L), Cr_d denotes total daily mass of creatinine excreted (mg), W denotes subject's weight, A denotes subject's age, R denotes subject's race (black/non-black), S denotes subject sex, and $Frac_{UAs}$ denotes the fraction of As excreted in urine (set to 0.9393). Simulations of As intake were conducted differently across study populations and intake scenarios, as described below.

2.4.1. HEALS

Simulations were centered around As intake from rice and other wells.

2.4.2. NBCS

For As intake, we first simulated the relationship between WAs and UAs through simulating water intake.

$$\widehat{As}_{in} = C_{WAs} \times SV_{DW}$$

$$SV_{DW} = \mu_{DW} + \sigma_{DW}$$

Where $\widehat{As_{in}}$ denotes the calculated mass of arsenic intake (µg), C_{WAs} denotes the measured concentration of total WAs (µg/L), and SV_{DW} denotes the simulated volume of drinking water intake per day (L), and μ_{DW} and σ_{DW} are the mean and standard error of reported drinking water volume of 2.08 ± 0.74 L/day (USEPA, 2017).

We then simulated the relationship between input As and UAs through adding the home dust As to WAs. We simulated home dust ingestion rate which was considered to have great variations by previous studies (Wilson et al. 2013; Wilson et al. 2016).

$$\widehat{As_{in}} = C_{WAs} \times SV_{DW} + C_{DAs} \times S_{DI} \times RBA$$

$$SV_{DW} = \mu_{DI} \pm \sigma_{DI}$$

Where C_{DAs} denotes the measured concentration of home dust As (ug/m^2), and SV_{DI} denotes the simulated home dust ingestion rate per day (m^2), μ_{DI} and σ_{DI} are the mean and standard error of home dust ingestion rate based on previous research (0.0062 ± 0.0050 m^2/day (Wilson et al. 2016)), and RBA is the bioavailability based on previous work (USEPA, 2010). Additionally, we then simulated a range of bioavailability (8%-61%) (indicated as RBA in the equation) in home dust as discussed above.

2.4.3. Chile

Intake of As was simulated according to two scenarios. In the first, intake from drinking water alone was considered, and no random variables were incorporated:

$$\widehat{As_{in}} = C_{Was} \times V_{DW}$$

Where $\widehat{As_{in}}$ denotes the calculated mass of arsenic intake (mg), C_{Uas} denotes the measured concentration of total UAs (mg/L), and V_{DW} denotes the self-reported volume of drinking water intake per day (L). In the second scenario, seafood was considered as an additional source, with concentrations for each of tuna, hake, mackerel, other fish, clams,

and shellfish simulated from mixture distributions corresponding to reported sample mean concentrations and 95% confidence intervals adapted from Wolle et al. (2019), then combined in a weighted average according to dietary proportions reported in Muñoz et al. (2005):

$$\widehat{As_{in}} = C_{Uas} \times V_{DW} + C_{SF} \times SF_{in}$$

$$C_{SF} = \sum_i \; w_i C_i$$

$$C_i = \mu_{i,j} + \sigma_{i,j} \times \epsilon$$

$$\epsilon \sim t_2$$

Where C_{SF} is the simulated concentration of As in seafood (mg/g), SF_{in} is the self-reported average daily intake of seafood (g), w_i and C_i are dietary proportions and simulated concentrations (mg/g) of As in each seafood subtype, $\mu_{i,j}$ and $\sigma_{i,j}$ are the sample mean and standard error of measured As concentration of the jth (randomly sampled from index length of samples of subtype i) sample of the ith seafood subtype reported in Wolle et al. (2019) and ϵ is a random variate drawn from a student's t distribution with two degrees of freedom.

3. Results

3.1. Relations of urinary to drinking-water arsenic concentrations across populations

The data from rural Bangladesh show a broad increase in UAs concentrations as a function of WAs in the household's primary well, but there is considerable scatter (Fig. 3). Univariate linear regression indicates that WAs concentrations account for about 25% of the variance in UAs levels. There is no reason to expect a slope close to one given that concentration in urine from water loss to perspiration and transpiration alone would raise the slope above one. The considerably lower actual slope of ~0.6 indicates that other processes are probably at play.

When compared to HEALS or Chile cohorts, the NBCS cohort shows a narrower range of lower As concentrations in both water and urine
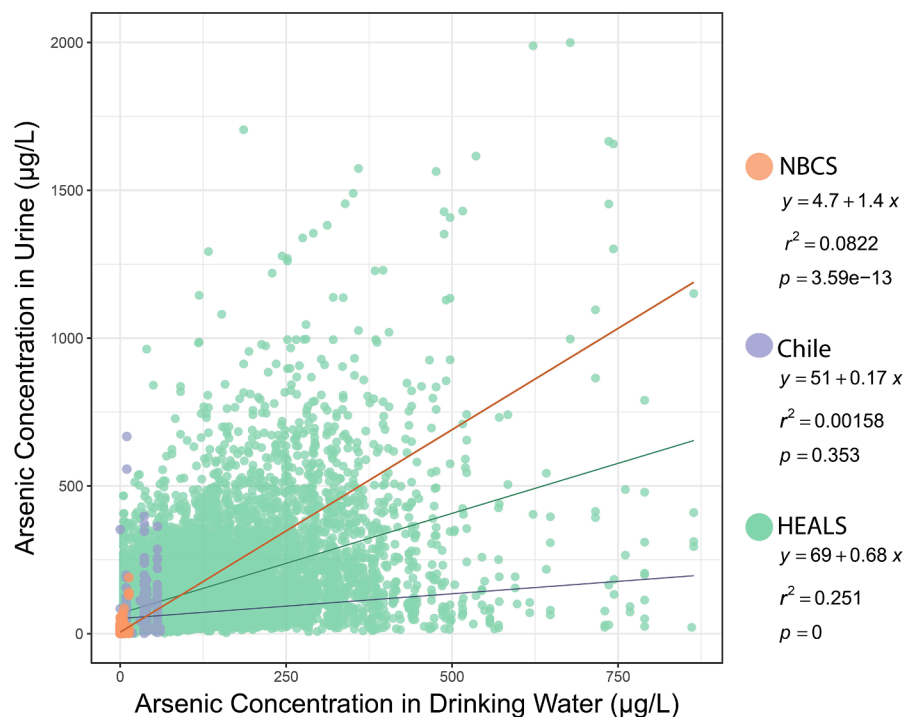

Fig. 3. Concentrations of UAs as a function of primary water As concentration for the three study populations. Also displayed are the regression lines for each cohort and the corresponding univariate regression parameters.

(Fig. 3). The univariate linear regression reveals that about 8% of the variance in UAs could be explained by WAs. A slope of 1.4 and positive intercept suggest that perspiration and respiration as well as other sources other than water might contribute to the UAs concentration.

The range of 16 distinct WAs concentrations in Northern Chile is intermediate compared to WAs in the HEALS and NBCS cohorts. Univariate least squares regression of UAs on WAs indicates a statistically insignificant slope of 0.14 (SE 0.17) with an intercept of 54 μg/L (SE 6.60), with only 0.2 % of variance in the outcome explained. This suggests that the measured WAs concentrations have no discernable relationship with measured total UAs concentrations, that other sources may play a role, or that the water measures available do not reflect the As concentrations in the water people are drinking (no water samples were collected in the participants' homes).

3.2. Relation of excretion to intake of as across populations

3.2.1. Contribution of other wells and rice to HEALS exposure
Under the simplest scenario, the intake of As is calculated solely from the measured water intake and the As concentration in the participant's primary well. For this and the other two scenarios, the excretion of As is alway the same based on UAs and urinary creatinine, augmented by 6% to account for the estimated loss of As to stool. Regression of As excretion as a function of As intake under this scenario produces a slope of 0.41 and an intercept of 180 μg/d, along with an r^2 of 0.22 (Fig. 4a). To be consistent with mass-balance, the slope and and intercept should be close to one and zero, respectively. The simplest model of exposure clearly underestimates the amount of As excreted for this population and doesn't account for considerable exposure at the low end of WAs concentrations.

The large quantity of rice consumed on a daily basis in Bangladesh and the relatively high As content of rice in general, is the most obvious explanation for the large intercept in the relation between excretion and intake of As. Using the average As content measured in rice of Araihazar and applying the quantities of rice reportedly consumed by men and women in the area indeed reduces the intercept of the relation between As excretion and intake from 180 μg/d to 120 μg/d (not shown). However, this still leaves an additional source of As that is particularly important at the low end of intake from water that is unaccounted for.

The model of Huhmann et al. (2021) applied to the same HEALS baseline data argues that participants obtain a significant proportion of their water from wells other than their primary well. When this proportion is taken into account by assuming, for lack of better individual data, the average As concentration for the entire area, the slope of the As excretion and intake relation rises from 0.41 to 0.57 and the intercept is reduced further from 120 μg/d to 80 μg/d (Fig. 4b). For a participant with a primary well containing 5 μg/L (the average for the lowest quartile), this means the actual exposure from drinking well water is closer to 40 μg/L. Correspondingly, for a participant with a primary well containing 300 μg/L (the average for the highest quartile), the actual exposure is reduced to 230 μg/L. In other words, drinking from non-primary wells leads to a convergence of exposure at both ends of the spectrum towards the mean WAs of surrounding wells.

3.2.2. Contribution of home dust to NBCS exposure
Under the simple scenario when only water is considered, regression of As excretion as a function of As intake produces a slope of 0.69 and an intercept of 7 μg/d, along with an r^2 of 0.08 (Fig. 4c). This scenario underestimates the As intake and suggests that additional sources of As besides WAs contribute to As excretion.

Using the assumptions described previously, individual-level daily home dust As ingestion was estimated to range from 0.017 to 27.5 μg with an average of 0.48 μg based on a 0.0062 m^2/day mean daily home dust ingestion rate for adults and a mean of 34% As bioavailability. We find that home dust As alone explains 29% of the variance in UAs and it is significantly associated with UAs (not shown). After adding home dust

as an additional As intake, regression of As excretion as a function of As intake increases the slope from 0.69 to 0.93, reduces the intercept from 7 to 5.4 ug/d, and increases r^2 from 0.08 to 0.17 (Fig. 4d).

3.2.3. Contribution of food to Chile exposure
Under the simple scenario when only water is considered, regression of As excretion on As intake produces a slope of 0.08 and an intercept of 61 μg/d, along with an r^2 of 0.002 (Fig. 4e). The low slope, goodness of fit, and high intercept in UAs concentration extrapolated for drinking water with 0 μg/L As concentration all suggest exposure misclassification, some of which could potentially be attributable to dietary sources of As. Including the best available estimate of As intake from food, however, only slightly raises the slope to 0.11 and reduces the intercept to 57 μg/d.

4. Discussion

In the three different case populations considered here, drinking water intake alone, while reflected to some extent in UAs excretion, was insufficient to achieve mass-balance. Our analysis confirms that health studies considering arsenic intake from drinking water only may considerably underestimate total arsenic exposure and therefore overestimate the health effects relative to dose, particularly so at the low end of the range of exposures. In the case of HEALS, adjustment of exposure due to drinking from multiple wells has the opposite effect at the high end of the range of exposure and will lead to an underestimate of the health effects relative to a dose based on drinking water from a single well (Huhmann et al., 2021).

Correcting each intake with additional exposure routes specific to each population significantly improved the match between As intake and excretion for two out of the three studied populations. In the case of HEALS, additional wells and rice brought the slope of the linear regression of As excretion as a function of intake closer to one and the intercept closer to zero (Fig. 4a, b). The finding is consistent with previous results using a slightly different approach applied to HEALS (Huhmann et al., 2021). In the case of NBCS, results show that home dust As probably contributes to the balance between As intake and excretion by lifting the slope closer to 1, reducing the intercept, and increasing r^2 as well (Fig. 4c, d). The likely role of in-house dust has not previously been reported by previous studies of the NCBS cohort. In the case of Chile, a dietary source specified by individual food surveys did not bring the slope of the As excretion as a function of intake much closer to the mass-balance (Fig. 4e, f).

The extent to which mass-balance for As is satisfied across all three populations so far did not take into account the additional uncertainty in the daily excretion rate of creatinine. Because of the way it is modeled, adding this source of variability does not change the slope or intercept of any of the As intake and excretion relationships but does reduce the proportion of the variance explained by the intake (Fig. 5). The simulations show that the outcomes in terms of variance and slope are less well constrained in the case of NBCS compared to HEALS, whereas the residual intercept in daily As excretion is much smaller than for HEALS (Fig. 6).

4.1. Potential sources of residual error

4.1.1. HEALS
In the case of HEALS, the largest unknown is the As content of wells occasionally used by the participants beyond their own primary well. The intercept in As excreted remaining after taking into account the As content of rice may reflect primarily this form of exposure misclassification. In the extreme case, random reassignment of the primary well to all participants will yield a slope of zero and an intercept that corresponds to the average As content of all wells multiplied by the average volume of water consumed. The so-called neighboring well model of Huhmann et al. (2021) was an attempt to do so by considering the
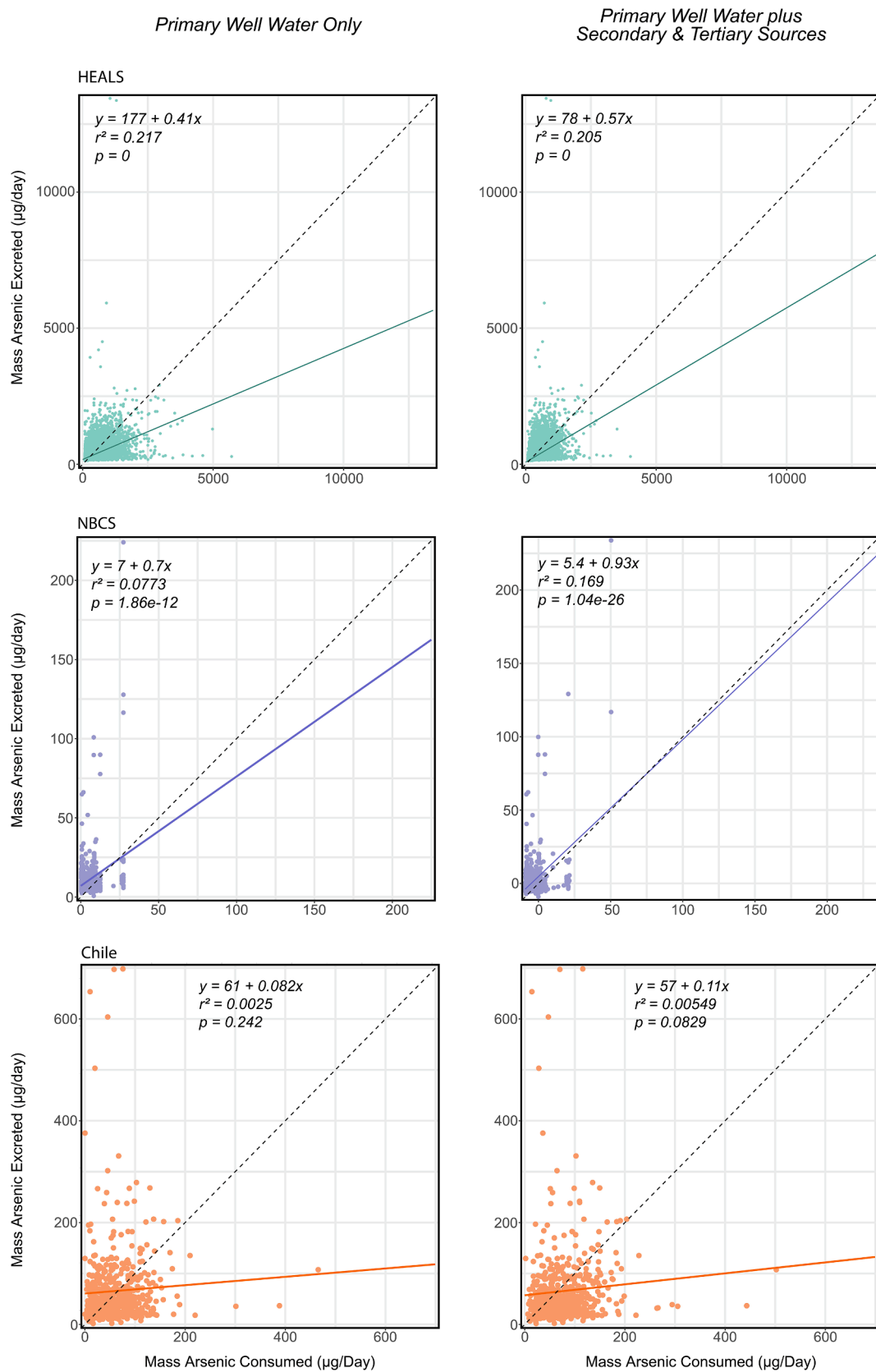
Fig. 4. Daily mass of As excreted as a function daily As intake for the three study populations considering in HEALS (a) primary well only and (b) primary and secondary well as well as rice in HEALS; NBCS (c) primary water source only and (d) primary water source and house dust; Chile (e) primary water source and (f) primary water source and seafood. Also shown in each panel is the one-to-one line corresponding to mass-balance.
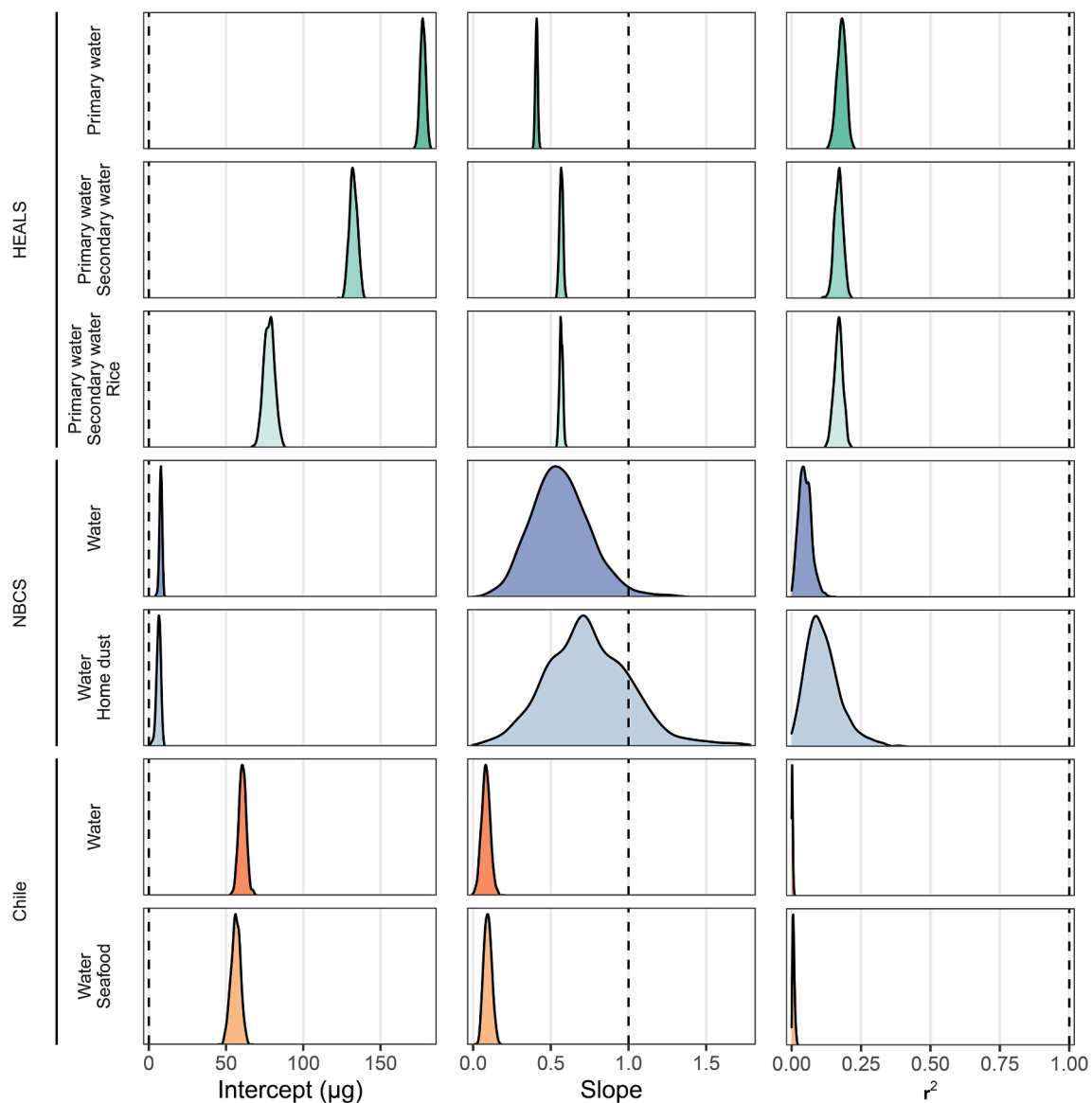
Fig. 5. Distribution of intercept, slope, and r² for the three study populations resulting from the Monte-Carlo simulations.

average As content within a radius of 20–100 m of the primary well. This additional feature suggests that women in particular obtain a fraction of their secondary water from neighboring wells but this did not markedly increase the fit of the model to the data. Systematic variations in the As content of rice consumed by specific cohort participants might be an additional, although secondary, source of misclassification of exposure given the relative magnitudes of average intake from water and rice in the study area.

4.1.2. NBCS

In the NBCS cohort, several sources may account for unexplained variations or residual error in the mass balance equation. First, WAs concentrations are derived from EPA 6-year average water quality data based on the PWS reported by participants, which might be subject to errors. However, since it has been reported that about 30% of Navajo Nation residents lack access to a PWS (Hoover et al. 2017) or at least a reliable water supply, it remains unclear if the reported PWSs are a long-term water source for the participants, which adds uncertainty to the WAs estimate. Second, residents in Navajo Nation also use unregulated water sources for non-drinking purposes such as cooking and bathing (Hoover et al. 2017). This was not captured in the data although 15 of

the NBCS participants included in this analysis reported drinking un-regulated well water. A previous study in Arizona found that for people who drank water from a PWS with As concentrations less than the US EPA Maximum Contaminant Level of 10 ug/L, only 7% of As intake was from water; while for people who drank water from water sources with As concentrations exceeding 10 ug/L, about 40% of As intake was from water (Kurzius-Spencer et al. 2014).

Third, NBCS does not have reliable individual-level data on food or water/beverage consumption as the other two cohorts. US average drinking water consumption data was used in the analysis rather than individual-level water consumption. Food is another source of As which was included in the other two cohorts. However, food data was not included in NBCS analysis due to missingness and a low percentage of participants consuming common foods with high As (e.g. rice, fish, and seafood) because these foods are not traditional dietary components of the Navajo Nation population (Hoover et al. 2020). A previous study also found that NBCS participants had lower seafood consumption when compared with NHANES samples (De La Rosa et al. 2020).

Fourth, home dust As concentrations were measured in terms of mass per surface area rather than mass in the air. The intake rate of this dust can significantly vary with daily activities and this was not taken into
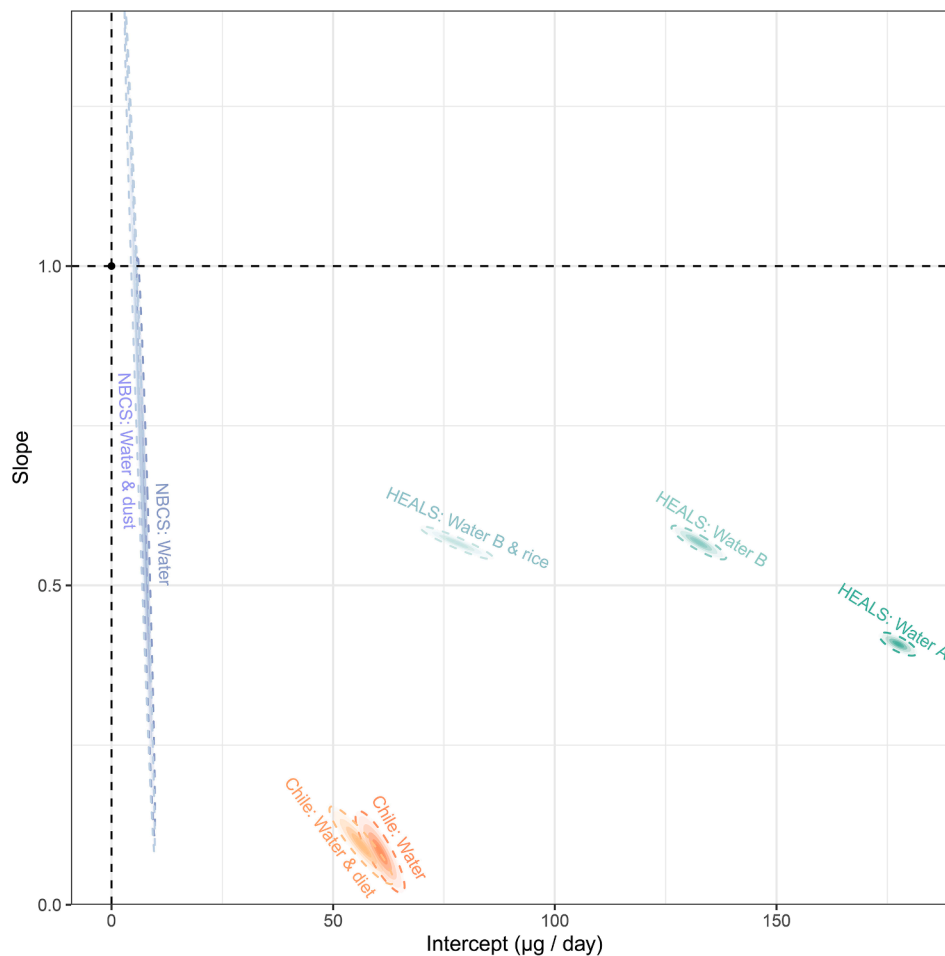
Fig. 6. Distribution of intercept, slope, and r^2 for the three study populations resulting from the Monte-Carlo simulations shown as contour plots.

account (Wilson et al. 2016). On the other hand, the deviance in As loading was < 1% for the 90% of participants with more than one dust measurement. However, the hand-to-mouth transfer or mechanistic-based approach for home dust ingestion tends to underestimate home dust ingestion (USEPA, 2017). While acknowledging the potential limitations of this mechanistic-based approach, it was the only alternative approach due to the lack of concentration of home dust As and was suggested by previous literature (USEPA, 2017) when only dust data in mass per surface area rather than dust concentration data are available. Because the only As home dust data available in the present study is characterized as As mass per surface area ($\mu g/m2$), total home dust loading ($mg/m2$) is not available in the present study. Therefore, it was not possible for us to calculate the As concentration ($\mu g/mg$) and the suggested ingestion rate for soil and dust using mg/day was not applicable/used. Moreover, although it is useful to compare the dust intake from the mechanistic approach against that from the mass-based approach, reliable soil As data near residences are also not available in the NBCS study area.

Using Monte-Carlo simulation, we simulated a lower range of bioavailability (8%-61%) rather than 100% bioavailability in home dust. Although it slightly reduced the home dust intake contribution when compared with results using 100% bioavailability, the overall pattern remains the same. It is worth noting that assuming 100% As home dust bioavailability might bring NBCS results closer to mass balance since we used the hand to mouth intake (mechanistic-based) model, which tends to underestimate the As intake from dust (USEPA, 2017).

Respirable nanoparticles with metals in ambient (outdoor) air derived from abandoned uranium mines in the Navajo Nation were

considered for the analysis (Zychowski et al. 2018). For lack of direct measurements, we used a modeled environmental risk index map (30-meter resolution) of potential AUM exposure based on proximity and other factors (Bunnell et al. 2010; Lin et al. 2020). The average intake of As from ambient air of 0.24 ± 0.07 $\mu g/day$ calculated by multiplying the daily air inhalation rate of 20 m^3/day (USEPA, 2017) by ambient air As concentration (average: 12 ± 3.4 ng/ m^3) is very small relative to the other sources, however. This helps explain why there is only a weak association between UAs and As intake from ambient air and results remain unchanged when including ambient As to the mass balance model.

It is also worth noting that results from NBCS are affected by a few points of with particularly high concentrations of UAs and home dust As (Fig. 4). Removing these data points decreases the r^2 of regression analysis results, although both water and home dust remain significant. There is, however, no justification for ignoring data reflecting the high end of As exposure. Two participants from the same home with high home dust As concentrations also show high UAs concentrations. More participants would have to be recruited for further validation of home dust as source of As exposure in this population.

4.1.3. Chile

Several potential sources of variability could explain the persistently low correlation of estimated As intake and excretion in the Chile cohort. Arsenic excretion in this cohort is estimated from a single early morning urine sample for each subject, and could thus be subject to increased measurement error, bias associated with the time of day (though our approach to estimate 24 h excretion based on creatinine may have addressed anomalous concentration effects), as well as temporal

variability associated with variable daily intake of As in food and water. WAs concentrations were estimated in a highly temporally and spatially aggregated fashion, and may misrepresent individual exposures. Notably, Nielsen et al. (2010) reported a best-case Spearman correlation coefficient of only 0.29 between As concentrations drawn from municipal water quality records and concentrations measured in-situ in the United States. Furthermore, our seafood As concentration estimates are subject to error based on estimating the proportion of various types of seafood consumed based on a survey in a different region of Chile, then mapping these proportions onto As concentrations measured several years later in the United States. We also note that variation in individual meals or subjects' preferences for different types of seafood are likely to have created scatter around the average concentrations we calculated.

5. Conclusions

Our testing for mass-balance of As in the human body sheds new light on the exposure of three distinct populations. In the case of a large rural population in Bangladesh, considering additional wells and rice as source of As brought the slope the relation of the As excretion as a function of intake close to one and the intercept close to zero, but uncertainties clearly remain. For the Navajo Nation cohort, the mass-balance exercise identified a hitherto unrecognized and significant source of As in the form of house dust. Whereas the slope of the As excretion as a function of intake was closer to one than for the other populations, it was also the least well constrained because of the scatter in the data. Nevertheless, results suggest that home dust is one crucial exposure pathway of As, especially considering other research findings about respirable nanoparticles bearing metals found in the air from single mine sites across the Navajo Nation (Zychowski et al. 2018). Potential exposure to As via nanoparticles from abandoned mine waste across Navajo Nation warrants further study. Finally, applying the mass-balance criterion to the Chile population showed that considering As intake with fish and shellfish as estimated in the study could not explain the large deviation of the slope of the relationship of As excretion as a function intake as well as the large intercept.

Funding

CRediT authorship contribution statement

Daniel Beene: Data curation, Investigation, Writing – original draft, Visualization. **Philip Collender:** Data curation, Investigation, Writing – original draft, Visualization. **Andres Cardenas:** Supervision, Writing – review & editing. **Charles Harvey:** Conceptualization, Methodology. **Linden Huhmann:** Conceptualization, Methodology. **Yan Lin:** Data curation, Investigation, Writing – original draft. **Johnnye Lewis:** Supervision, Writing – review & editing. **Nancy LoIacono:** Data curation. **Ana Navas-Acien:** Supervision, Writing – review & editing. **Anne Nigra:** Data curation, Investigation, Writing – original draft, Visualization. **Craig Steinmaus:** Supervision. **Alexander van Geen:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107371.

References

Abdul, K.S., Jayasinghe, S.S., Chandana, E.P., Jayasumana, C., De Silva, P.M., 2015. Arsenic and human health effects: a review. Environ. Toxicol. Pharmacol. 40 (3), 828–846. https://doi.org/10.1016/j.etap.2015.09.016. Epub 2015 Sep 30 PMID: 26476885.

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 (2), 191–205. https://doi.org/10.1038/sj.jea.7500449. PMID: 16160703.

Borgoño, J.M., Venturino, H., Vicent, P., 1980. Estudio clínico epidemiológico de hidroarsenicismo en la II Region (1977) [Clinical and epidemiologic study of arsenicism in northern Chile (author's transl)]. Rev. Med. Chil. 108 (11), 1039–1048. Spanish. PMID: 7244449.

Broecker, W.S., Peng, T.H., 1982. Tracers in the Sea. Eldigio Press, New York, pp. 1–690.

Bunnell, J.E., Garcia, L.V., Furst, J.M., Lerch, H., Olea, R.A., Suitt, S.E., Kolker, A., 2010. Navajo coal combustion and respiratory health near shiprock, New Mexico. J. Environ. Public Health 2010. https://doi.org/10.1155/2010/260525.

Chen, Y., Ahsan, H., Parvez, F., Howe, G.R., 2004. Validity of a food-frequency questionnaire for a large prospective cohort study in Bangladesh. Br. J. Nutr. 92 (5), 851–859. https://doi.org/10.1079/bjn20041277. PMID: 15533275.

Cleland, B., Tsuchiya, A., Kalman, D.A,, Dills, R., Burbacher, T.M., White, J.W., Faustman, E.M., Mariën, K., 2009. Arsenic exposure within the Korean community (United States) based on dietary behavior and As levels in hair, urine, air, and water. Environ. Health Perspect. 117 (4), 632–638. doi: 10.1289/ehp.11827. Epub 2008 Dec 8. PMID: 19440504; PMCID: PMC2679609.

CONAMA, 2000. Technical Information Sheet: Analysis of Human Exposure to Arsenic in Large Cities (Study No. 21–0022–002).

De La Rosa, V.Y., Hoover, J., Du, R., Jimenez, E.Y., MacKenzie, D., Lewis, J., 2020. Diet quality among pregnant women in the Navajo Birth Cohort Study. Matern. Child Nutr. 16, 1–13. https://doi.org/10.1111/mcn.12961.

Díaz, O.P., Leyton, I., Muñoz, O., Núñez, N., Devesa, V., 2004. Maria Angeles Súñer, Dinoraz Vélez, and Rosa Montoro. Contribution of Water, Bread, and Vegetables (Raw and Cooked) to Dietary Intake of Inorganic Arsenic in a Rural Village of Northern Chile. J. Agric. Food Chem. 52 (6), 1773–1779. https://doi.org/10.1021/jf035168t.

El Masri, H.A., Hong, T., Henning, C., Mendez, W., Hudgens, E.E., Thomas, D.J., Lee, J.S., 2018. Evaluation of a physiologically based pharmacokinetic (PBPK) model for inorganic arsenic exposure using data from two diverse human populations. Environ. Health Perspect. 126 (7). doi: 10.1289/EHP3096.

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 (6), 673–679. doi: 10.1097/00001648-200011000-00010. Erratum in: Epidemiology 2001 Mar;12(2):283. PMID: 11055628.

Garelick, H., Jones, H., Dybowska, A., Valsami-Jones, E., 2008. Arsenic pollution sources. Rev. Environ. Contam. Toxicol. 197, 17–60. https://doi.org/10.1007/978-0-387-79284-2_2.

Gomella, L.G., Haist, S.A., 2007. Chapter 9. Fluids and electrolytes. In: Clinician's pocket reference: The Scut Monkey. 11th ed. Gomella and Haist editors. New York: McGraw-Hill.

Gonzales, M., Shah, V., Bobelu, A., Qualls, C., Natachu, K., Bobelu, J., Jamon, E., Neha, D., Paine, S., Zager, P., 2004 May. Concentrations of surface-dust metals in Native American jewelry-making homes in Zuni Pueblo. New Mexico. Arch Environ Health. 59 (5), 245–249. https://doi.org/10.3200/AEOH.59.5.245-249.

Hall, E.M., Acevedo, J., López, F.G., et al., 2017. Hypertension among adults exposed to drinking WAs in Northern Chile. Environ Res. 153, 99–105. https://doi.org/10.1016/j.envres.2016.11.016.

He, Y., Zheng, Y., Assessment of in vivo bioaccessibility of As in dietary rice by a mass balance approach. Sci Total Environ. 408 (6), 1430–1436. doi: 10.1016/j.scitotenv.2009.12.043. Epub 2010 Jan 13. PMID: 20071009; PMCID: PMC2828880.

Hoover, J., Gonzales, M., Shuey, C., Barney, Y., Lewis, J., 2017. Elevated arsenic and uranium concentrations in unregulated water sources on the Navajo Nation. USA. Expo. Heal. 9, 113–124.

Hoover, J.H., Erdei, E., Begay, D., Gonzales, M., Jarrett, J.M., Cheng, P.-Y., Lewis, J., Team, N.S., others, 2020. Exposure to uranium and co-occurring metals among pregnant Navajo women. Environ. Res. 190, 109943.

Huhmann, L.B., Harvey, C.F., Navas-Acien, A., Graziano, J., Slavkovich, V., Chen, Y., Argos, M., Ahsan, H., van Geen, A., 2021. A mass-balance model to assess arsenic exposure from multiple wells in Bangladesh. J. Expo Sci. Environ. Epidemiol. doi: 10.1038/s41370-021-00387-5. Epub ahead of print. PMID: 34625714.

Huhmann, B.L., Harvey, C.F., Navas-Acien, A., Graziano, J., Parvez, F., Chen, Y., Argos, M., Ahmed, A., Hasan, A.K.M.R., Ahsan, H., van Geen, A., 2019. Changes in arsenic exposure in Araihazar, Bangladesh from 2001 through 2015 following a blanket well testing and education campaign. Environ. Int. 125, 82–89.

Hunter, C.M., Lewis, J., Peter, D., Begay, M.-G., Ragin-Wilson, A., 2015. DIRECT FROM ATSDR: the Navajo birth cohort study. J. Environ. Health 78 (2), 42–45.

Ix, J.H., Wassel, C.L., Stevens, L.A., et al., 2011. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clin. J. Am. Soc. Nephrol. 6 (1), 184–191. https://doi.org/10.2215/CJN.05030610.

Kurzius-Spencer, M., Burgess, J.L., Harris, R.B., Hartz, V., Roberge, J., Huang, S., Hsu, C.-H., O'Rourke, M.K., 2014. Contribution of diet to aggregate arsenic exposures—an analysis across populations. J. Expo. Sci. Environ Epidemiol. 24, 156–162.

Lin, Y., Hoover, J., Beene, D., Erdei, E., Liu, Z., 2020. Environmental risk mapping of potential abandoned uranium mine contamination on the Navajo Nation, USA, using a GIS-based multi-criteria decision analysis approach. Environ. Sci. Pollut. Res. 27, 30542–30557. https://doi.org/10.1007/s11356-020-09257-3.

Mantha, M., Yeary, E., Trent, J., Creed, P.A., Kubachka, K., Hanley, T., Shockey, N., Heitkemper, D., Caruso, J., Xue, J., Rice, G., Wymer, L., Creed, J.T., 2017. Estimating inorganic arsenic exposure from U.S. Rice and total water intakes. Environ. Health Perspect. 125 (5), 057005. doi: 10.1289/EHP418. PMID: 28572075; PMCID: PMC5726353.

Melak, D., Ferreccio, C., Kalman, D., et al., 2014. Arsenic methylation and lung and bladder cancer in a case-control study in northern Chile. Toxicol. Appl. Pharmacol. 274 (2), 225–231. https://doi.org/10.1016/j.taap.2013.11.014.

Muñoz, O., Bastias, J.M., Araya, M., Morales, A., Orellana, C., Rebolledo, R., Velez, D., 2005. Estimation of the dietary intake of cadmium, lead, mercury, and arsenic by the population of Santiago (Chile) using a Total Diet Study. Food Chem Toxicol. 43 (11), 1647–1655. https://doi.org/10.1016/j.fct.2005.05.006.

Muñoz, O., Zamorano, P., Garcia, O., Bastías, J.M., 2017. Arsenic, cadmium, mercury, sodium, and potassium concentrations in common foods and estimated daily intake of the population in Valdivia (Chile) using a total diet study. Food Chem. Toxicol. 109 (Pt 2), 1125–1134. doi: 10.1016/j.fct.2017.03.027. Epub 2017 Mar 16. PMID: 28322969.ID: 15975702.

Nermell, B., Lindberg, A.L., Rahman, M., Berglund, M., Persson, L.A., El Arifeen, S., Vahter, M., 2008. Urinary As concentration adjustment factors and malnutrition. Environ. Res. 106 (2), 212–218. https://doi.org/10.1016/j.envres.2007.08.005. Epub 2007 Sep 27 PMID: 17900556.

Nielsen, S.S., Kuehn, C.M., Mueller, B.A., 2010. Water quality monitoring records for estimating tap water arsenic and nitrate: a validation study. Environ. Health: Global Access Sci. Source, 9, 4. Doi: 10.1186/1476-069X-9-4.

Nigra, A.E., Chen, Q., Chillrud, S.N., Wang, L., Harvey, D., Mailloux, B., Factor-Litvak, P., Navas-Acien, A., 2020. Inequalities in Public Water Arsenic Concentrations in Counties and Community Water Systems across the United States, 2006-2011. Environ. Health Perspect. 128 (12), 127001. doi: 10.1289/EHP7313. Epub 2020 Dec 9. PMID: 33295795; PMCID: PMC7724967.

Özkaynak, H., Xue, J., Zartarian, V.G., Glen, G., Smith, L., 2011. Modeled of soil and dust ingestion rates for children. Risk Anal. An Int. J. 31, 592–608.

Perrier, E., Rondeau, P., Poupin, M., Le Bellego, L., Armstrong, L.E., Lang, F., Stookey, J., Tack, I., Vergne, S., Klein, A., 2013. Relation between urinary hydration biomarkers and total fluid intake in healthy adults. Eur. J. Clin. Nutr. 67 (9), 939–943. doi: 10.1038/ejcn.2013.93. Epub 2013 May 22. PMID: 23695204; PMCID: PMC3778844.

Pomroy, C., Charbonneau, S.M., McCullough, R.S., Tam, G.K.H., 1980. Human retention studies with 74As. Toxicol. Appl. Pharmacol. 53, 550–556.

Popkin, B.M., D'Anci, K.E., Rosenberg, I.H., 2010. Water, hydration, and health. Nutr. Rev. 68 (8), 439–458. https://doi.org/10.1111/j.1753-4887.2010.00304.x.

Rivara, M.I., Cebrián, M., Corey, G., Hernández, M., Romieu, I., 1997. Cancer risk in an arsenic-contaminated area of Chile. Toxicol. Ind. Health 13 (2–3), 321–338. https://doi.org/10.1177/074823379701300217. PMID: 9200798.

Roffey, S.J., Obach, R.S., Gedge, J.I., Smith, D.A., 2007. What is the objective of the mass balance study? A retrospective analysis of data in animal and human excretion studies employing radiolabeled drugs. Drug Metab. Rev. 39 (1), 17–43. https://doi.org/10.1080/03602530600952172. PMID: 17364879.

Sancha, A.M., O'Ryan, R., 2008. Managing hazardous pollutants in Chile: arsenic. Rev. Environ. Contam. Toxicol. 196, 123–146. PMID: 19025095.

Steinmaus, C.M., Ferreccio, C., Romo, J.A., et al., 2013. Drinking water arsenic in northern chile: high cancer risks 40 years after exposure cessation. Cancer Epidemiol Biomarkers Prev. 22 (4), 623–630. https://doi.org/10.1158/1055-9965.EPI-12-1190.

USEPA, 2010. Relative Bioavailability of Arsenic in Soils at 11 Hazardous Waste Sites using an In Vivo Juvenile Swine Method (EPA OSWER Directive #9200.0-76).

USEPA (1994) Determination of trace elements in waters and wastes by inductively coupled plasma-mass spectrometry. Method 200.8 Revision 5.4. https://www.epa.gov/sites/default/files/2015-06/documents/epa-200.8.pdf.

USEPA, 2017. Soil and Dust Ingestion (Chapter 5). Expo. Factors Handb. 2011 Ed. EPA/600/R, 1–100.

van Geen, A., Ahsan, H., Horneman, A.H., Dhar, R.K., Zheng, Y., Hussain, I., Ahmed, K. M., Gelman, A., Stute, M., Simpson, H.J., Wallace, S., Small, C., Parvez, F., Slavkovich, V., LoIacono, N.J., Becker, M., Cheng, Z., Momotaj, H., Shahnewaz, M., Seddique, A.A., Graziano, J.H., 2002. Promotion of well-switching to mitigate the current arsenic crisis in Bangladesh. Bull. World Health Org. 81, 732–737.

van Geen, Y., Zheng, R., Versteeg, M., Stute, A., Horneman, R., Dhar, M., Steckler, A., Gelman, C., Small, H., Ahsan, J., Graziano, I.H., Ahmed, K.M., 2003. Spatial variability of arsenic in 6000 tube wells in a 25 km2 area of Bangladesh. Water Resour. Res. 39 (5), 1140. https://doi.org/10.1029/2002WR001617.

White, P.D., Van Leeuwen, P., Davis, B.D., Maddaloni, M., Hogan, K.A., Marcus, A.H., Elias, R.W., 1998. The conceptual structure of the integrated exposure uptake biokinetic model for lead in children. Environ. Health Perspect. 106 (Suppl 6), 1513–1530. doi: 10.1289/ehp.98106s61513. PMID: 9860910; PMCID: PMC1533456.

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. An Int. J. 19, 158–188.

Wilson, R., Mitchell, I., Richardson, G.M., 2016. Estimation of dust ingestion rates in units of surface area per day using a mechanistic hand-to-mouth model. Hum. Ecol. Risk Assess. 22, 874–881. https://doi.org/10.1080/10807039.2015.1115956.

Wolle, M.M., Stadig, S., Conklin, S.D., 2019. Market basket survey of arsenic species in the top ten most consumed seafoods in the United States. J. Agric. Food Chem. 67 (29), 8253–8267.

Zaldívar, R., 1974. Arsenic contamination of drinking water and foodstuffs causing endemic chronic poisoning. Beitr Pathol. 151 (4), 384–400. https://doi.org/10.1016/s0005-8165(74)80047-8. PMID: 4838015.

Zychowski, K.E., Kodali, V., Harmon, M., Tyler, C.R., Sanchez, B., Ordonez Suarez, Y., Herbert, G., Wheeler, A., Avasarala, S., Cerrato, J.M., et al., 2018. Respirable uranyl-vanadate-containing particulate matter derived from a legacy uranium mine site exhibits potentiated cardiopulmonary toxicity. Toxicol. Sci. 164, 101–114.

Further reading

Tan, S.Y., Praveena, S.M., Abidin, E.Z., Cheema, M.S., 2016. A review of heavy metals in indoor dust and its human health-risk implications. Rev. Environ. Health 31, 447–456. https://doi.org/10.1515/reveh-2016-0026.

Yager, R.R., 1998. Quantifier guided aggregation using OWA operators. Int. J. Intelligent Sys. 11 (1), 49–73.