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Carcinogenic and non-carcinogenic health risks of arsenic exposure in drinking water in the rural environment

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ABSTRACT

Carcinogenic and systemic health effects of arsenic exposure in drinking water are well documented. This study estimated the risk associated with chronic consumption of water with high concentrations of arsenic in children and adults living in six Andean locations, in Chile. Concentrations of arsenic in the drinking water were analyzed between 2014 and 2017 based on health authority reports and data collected during this study. Average daily arsenic intake was estimated, and systemic (HQ) and deterministic carcinogenic risk (CR) indices were calculated using U.S. Environmental Protection Agency methodology. Threshold values of HQ>1 and CR> 1 x 10–4 were considered to indicate high risk of adverse health effects. Four of the locations (Chucuyo > Putre > Humapalca = Visviri) had high concentrations of arsenic in the water, at levels 6.3–57.6 times the norm of 0.01 mg/L, Zapahuira and Belén, had values just below the threshold. Extremely high HQ values were estimated in children, at 1.3–119.8 times the threshold. Furthermore, CR values were several orders of magnitude (3.06–10790.6) above the tolerable value among all age strata. The locations studied have a high risk of adverse health effects from exposure to arsenic in drinking water. It is urgent to implement mitigation measures to improve water quality in these communities and to carry out probabilistic studies to provide more accurate assessment of exposure.

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INTRODUCTION

Arsenic (As) is ubiquitous in nature, constituting nearly 0.0001% of the earth's crust. The organic forms of the element are relatively benign, but inorganic As is highly toxic to humans. Because As is found naturally in the environment, exposure may occur through food consumption, air intake, or skin contact. The greatest source of exposure is drinking water (Bundschuh *et al*., 2010). An estimated 140 million people in 50 countries are at risk due to consumption of water with As concentrations above the 10 µg/L limit suggested by the World Health Organization (WHO) (Ravenscroft *et al.,* 2009). Many people around the world are exposed to high concentrations of inorganic As in drinking water. The populations at highest risk live in the Pacific Ring of Fire. This arc includes Southeast Asian nations such as India, Taiwan, Bangladesh, and Vietnam, as well as the west coast of the United States, Chile, and Argentina in the Americas. This exposure is associated with the geological features and orogenic processes characteristic of these areas, such as volcanic eruptions and tectonic plate movements (Bundschuh *et al.,* 2012b; Bundschuh *et al.,* 2010). Subterranean rivers and streams with a volcanic/mountainous source tend to have high concentrations of this element. In Latin America, water contaminated with As of natural origin has been identified in at least 20 countries, with an estimated 14 million persons exposed, especially in Andean regions (Bundschuh *et al.,* 2012a). Populations in northern Chile and Argentina, populations have historically been subject to As exposure. Most of the freshwater in these regions has a common lithogenic source (sulfide mineral) in the Andes Range, where As concentrations far exceed the worldwide norm of 0.01 mg/L (WHO, 1993). In this rural region, groundwater is the main source of drinking water; the monitoring carried out since 2005 shows high heterogeneity in As concentrations, averaging between 50 and 500 µg/L (Amaro *et al.,* 2014). There are many localities and communities in this Altiplano region that these waters supply and are therefore at risk, especially the most vulnerable age groups such as children and pregnant mothers. Approximately 70% of the localities in this region of northern Chile are very dispersed and isolated, particularly the communes of Putre and General Lagos (where the studied localities are located) (Fig. 1). Not all communities have adequate rural drinking water systems that meet Chilean standards. Arsenic may be found in both surface and subterranean water due to dissolved minerals, erosion, and disintegration of rocks and atmospheric depositions. The trivalent: As(III) and pentavalent arsenate: As(V) forms of inorganic As may be found in these waters, depending on environmental conditions. The toxicity of As(III) is several times greater than that of As(V), due to greater cell uptake (Ratnaike, 2003). Ingesting elevated concentrations of As in drinking water is

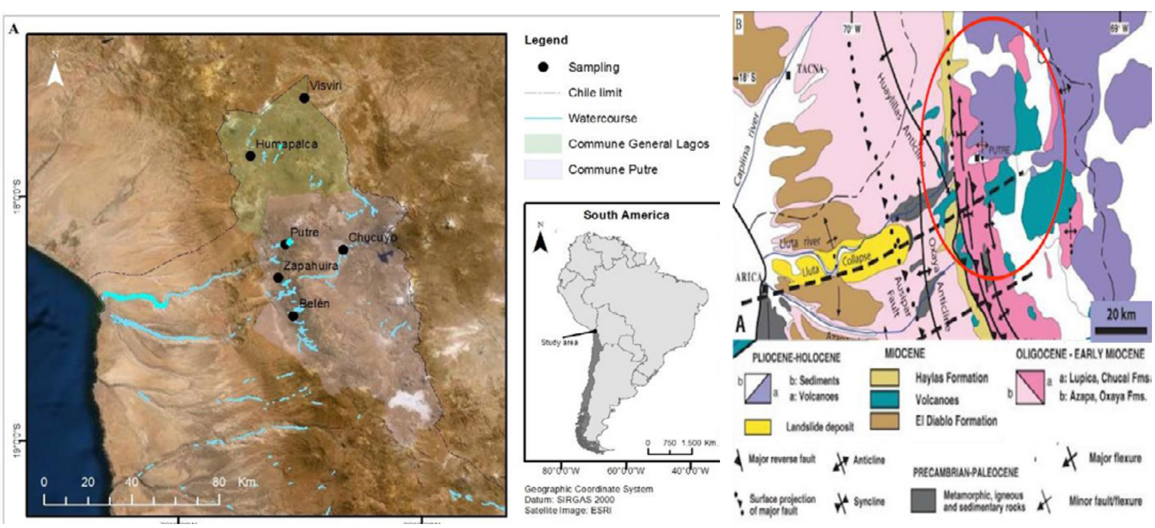

Fig. 1: A) Geographic locations of the Altiplano communities studied; Province of Parinacota, Chile B) Geological map of Putre (red circle shows the area studied) (Garcia *el al*., 2011)

associated with numerous adverse health effects in humans, including skin, lung, bladder, prostate, liver, and other cancers, as well as systemic problems, such as dermatological, circulatory, reproductive, neurological, and cardiovascular diseases (Huang *et al.,* 2015). It has also been reported that As exposure in pregnant women may increase infant mortality due to higher rates of spontaneous abortion and fetal and newborn deaths (Bloom *et al.,* 2014). Many epidemiological studies carried out in Chile since the 1990s have shown a strong association between chronic As exposure and various health problems in local pediatric and adult populations, including infant and fetal mortality, lung cancer (Soza-Ried *et al.,* 2019; Steinmaus *et al., 2014*), liver cancer, kidney cancer (Ferreccio *et al*., 2013; Yuan *et al.,* 2010), breast cancer (Smith *et al.,* 2014) and bladder cancer (Fernández *et al.,* 2019; Fernández *et al*., 2012), especially in the northern cities where As concentrations in surface and subterranean water are very high (Tapia *et al.,* 2019). Other studies have described a link between As exposure and incidence of dermatological, cardiovascular (Hall *et al.,* 2017; Román *et al.,* 2011), neurological, hormonal (Valdes Salgado *et al.,* 2019; Castriota *et al.,* 2018), and immunological problems (Yu *et al.,* 2018). The last 10 years of research in Chile have focused on epidemiological studies related to health effects from chronic exposure to high doses of arsenic in water, in the years (1970s) prior to the implementation of the guidelines recommended by the WHO. Case studies and controls, cohort and cross-sectional studies have reported sufficient evidence of the association with the presentation of various types of cancer (Roh *et al.,* 2018). Recent research adds to the causal mechanisms such as metabolism and genetic-environmental interactions that influence the response of individuals (Vicuña *et al.*, 2019; Soza-Ried *el al.,* 2019; de la Rosa *et al.*, 2017). The objective of this study is to estimate the carcinogenic and non-carcinogenic risks associated with chronic exposure to arsenic in drinking water among the inhabitants of six rural locations in the northern Altiplano of Chile in 2017.

MATERIALS AND METHODS

Study areas

Six locations in the Chilean Altiplano were studied, Belén, Chucuyo, Humapalca, Putre, Visviri, and Zapahuira. These towns are located in the Putre and General Lagos communes (Parinacota province, Arica y Parinacota region) (Fig. 1 A). These communities are located 2400–4900 meters above sea level in a mountainous and volcanic regions (Tapia *et al.,* 2019). The area where the localities under study are located, includes part of the intermediate depression of the Putre Valley, the pre-mountain range, and the Altiplano of the Arica and Parinacota Region. The Andes Range was formed by tectonic and volcanic action combined with morphological processes derived from alluvions since the Mioceno (Fig. 1 B). The water supply to these areas originates from sources in the Andes Range. Local economic activities include agriculture, cattle farming, and tourism related to the historical and cultural heritage of these areas. The population is largely of Aymara ethnicity and includes roughly 2400 inhabitants, according to the 2002 census (32% female). Putre is the most populous of the six locations, with 1977 inhabitants (ERD, 2018). The climate is characterized as high-altitude desert steppe with scarce precipitation.

Water sampling

Between May and August 2017, three drinking water samples were collected from each location. Table 1 indicates the geographic locations, dates,

Table 1: Sampling locations; Parinacota province, Chile

Location	Date	Sampling site	Altitude (meters)	UTM coordinates
Belén	13-06-2017	Elementary school	3.253	N 7957979.00 E 445637.50
Chucuyo	08-05-2017	Police station	4.408	N 7985606.89 E 465995.84
Humapalca	25-08-2017	Elementary School	3.982	N 8027997.22 E 425530.65
Putre	13-06-2017	Municipal center	3.500	N 7887975.69 E 440808.74
Visviri	25-08-2017	Town square	4.094	N 8054569.91 E 448951.94
Zapahuira	08-05-2017	Restaurant	3.313	N 7972245.25 E 437828.66

UTM: Universal Transverse Mercator

and sites of the sampling performed. Samples were collected according to the standardized protocols described in Chilean water sampling norms 409-1. Samples were collected directly from the tap. The water was allowed to run for at least 5 minutes before the sample was collected in a 1-L sterile polyethylene flask with a nitric acid preservative. The samples were stored in coolers with gel cooling packs during transport from the sampling location to the laboratory; each sample was clearly identified and labeled. The following parameters were measured: temperature, pH, and electrical conductivity. Total As concentration was determined using hydride generation atomic absorption spectrometry in the laboratory of the Universidad de Tarapacá, Arica, according to the APHA Standard Methods for the Examination of Water and Wastewater (APHA, 2012). The calibration curve for arsenic was linear over the range of 0 to 40 µg/L; the correlation coefficient was r^2 = 0.9808. The limit of detection method (LDM) for arsenic was 0.0003 mg/L. The sanitary authority of the region monitors the water quality, for which it takes periodic samples and sends them to the laboratory of the University of Tarapacá for analysis. The results of the concentrations of As for the years 2014 to 2016 were requested via the Transparency Law from the Regional Health Ministry's Drinking Water Surveillance Program in the Arica y Parinacota region. The present study began in 2017, so the existing information was used for the previous years. These results were used to for the health risk calculations described below.

Evaluation of human health risk

Daily As intake was calculated as As consumed in drinking water, and deterministic risk was then calculated according to the methods published by the U.S. Environmental Protection Agency (USEPA, 1989). Average daily As exposure through drinking water intake was calculated as LADD (Lifetime Average Daily Dose) in mg/kg/day, according to Eq. 1.

$$LADD_{ing} = \frac{C_{water} \times IR \times EF \times ED}{BW \times AT} \quad (1)$$

Where, C_{water} is As concentration in the drinking water (mg/L); *IR* is the intake rate of the contaminated medium (in this case, average daily water consumption) (L/day); *EF* is exposure factor, or frequency of daily exposure (days/year); *ED* is exposure duration (years); *BW* is body weight (kg); and *AT* is averaging time, or period over which exposure is averaged (days).

Non-carcinogenic and carcinogenic risks

Non-carcinogenic risk (hazard quotient, or HQ) was calculated using the *LADD* coefficient and ingestion reference dose RfD_{ing} (mg/kg-day) for As using Eq. 2.

$$HQ = \frac{LADD}{RfD_{ing}} \quad (2)$$

Carcinogenic risk (cancer risk, or *CR*) was calculated as the product of *LADD* and CSF_{ing}, which is the ingestion cancer slope factor for As (mg/kg/day), and the age-dependent adjustment factor *ADAF,* using Eq. 3 (USEPA, 2011).

$$CR = CSF_{ing} \times LADD_W \times ADAF \quad (3)$$

Interpretation of HQ and CR

An *HQ* value >1 indicates a high probability of adverse systemic effects from chronic ingestion of water contaminated by As, and a value below the threshold indicates a low probability of such effects. There is no safe level of exposure for carcinogenic agents. Instead, the EPA has established "tolerable" or "acceptable" risk levels of 10^{-4} or 10^{-6}; that is, lifetime exposure will not produce more than 1 cancer case per 10,000 inhabitants or 1 case per 1,000,000 inhabitants in the population (Asante-Duah, 2017). Values above these limits represent an increased risk of cancer as compared to expected rates. Table 2 presents the parameters used to estimate *LADD, HQ,* and *CR* for adults and children.

Data analysis

Descriptive statistics were calculated including measures of central tendency and range. Comparisons of mean As concentration among locations were performed using non-parametric statistics. The threshold for statistical significance was set at p<0.05. LADD was calculated according to median concentration, as the distribution of this variable was not normal. HQ and CR were calculated with Excel. Statistical analyses were performed using Stata V12 software. Graphs were constructed with GraphPad Prism V6 software. Graphs are presented on a logarithmic scale due to the magnitudes of the results.

RESULTS AND DISCUSSION

As shown in Table 3, median total As concentrations ranged from 0.007 to 0.576 mg/L in the locations studied, in descending order: Chucuyo > Humapalca > Putre > Visviri > Zapahuira > Belén. In Chucuyo, Humapalca, Putre, and Visviri, concentrations exceeded the Chilean norm of 0.01 mg/L by 6.3 to 57.6-fold, respectively (Fig. 2a). The values for Belén and Zapahuira, values were slightly below the norm, at 0.7- and 0.9-fold. Fig. 2b clearly shows the differences in As concentration by location as well as the variations observed over time.

Arsenic concentration by location was fairly constant over the period analyzed, except for a significant decrease in Chucuyo in 2016. In that year, concentrations were similar to those observed in Putre; however, by 2017, concentrations returned to values similar to those observed in 2014 and 2015. More than 85% of the samples analyzed showed As concentrations above the current WHO norm for human drinking water (0.01 mg/L). The highest concentrations were in Chucuyo, Humapalca, Putre, and Visviri, which are located in mountainous areas. The water sources in this mountainous geographic region are generally natural and are affected by the mineral deposits, thermal springs and volcanic rock found in the zone. The water is also affected by the precipitation patterns typical of high-altitude mountainous regions, including summer lightning storms that promote acid rain, mobilizing As and increasing its concentration in the water supply (Tapia *et al.*, 2019). There are many localities and communities in this Altiplano region that these waters supply and are therefore at risk, especially the most vulnerable age groups such as children and pregnant mothers. Approximately 70% of the localities in this region of northern Chile are geographically very dispersed and isolated, particularly the communes of Putre and General Lagos (where the studied localities are located). Not all communities have adequate rural drinking water systems that meet Chilean standards. Table 4 shows the HQ and CR values for each age group studied. As indicated, HQ values were greater than 1 for both pediatric age strata, with the highest risk among children under 2 years

Table 2: Parameters used to estimate daily average arsenic ingestion and associated health risks in adult and pediatric populations

Parameter		Units	Children		Adults	Reference
			< 2 y	2 to 17 y	> 18 y	
C_{water}	Concentration of arsenic in water	(mg/L)				
ED	Exposure duration	years	2	17	70	(USEPA, 1989)
EF	Exposure frequency	(days/year)	365	365	365	(USEPA, 1989)
IR_{ing}	Intake rate of drinking water	(L/day)	1.25	1.25	2.2	(USEPA, 1989)
BW	Body weight	(kg)	10	30	70	(USEPA, 1989)
AT	Averaging time	(days)				(USEPA, 1989)
	AT carcinogenic 70*365	(days)	25550	25550	25550	
	AT non-carcinogenic	(days)	ED*365	ED*365	ED*365	
ADAF	Age-dependent adjustment factor		10	2	1	(USEPA, 2011)
RfD_{ing}	Ingestion reference dose for arsenic		mg/kg/day		3.00E-04	(Asante-Duah, 2017)
CSF_{ing}	Ingestion cancer slope factor for arsenic		mg/kg/day		1.50E+00	(Asante-Duah, 2017)

Y: years

Table 3: Arsenic* concentrations (mg/L) in the drinking water of the locations studied

Location	2014	2015	2016	2017	Average	SD	Median	P25	P75	CV (%)	Median / Norm
Belén	0.005	0.004	0.033	0.008	0.013	0.0138	0.007	0.004	0.020	110.17	0.7
Chucuyo	0.602	0.581	0.080	0.570	0.458	0.2525	0.576	0.325	0.591	42.82	57.6
Humapalca	0.046	0.057	0.165	0.068	0.084	0.0547	0.063	0.051	0.116	65.16	6.3
Putre	0.070	0.090	0.066	0.066	0.073	0.0115	0.068	0.066	0.080	17.73	6.8
Visviri	0.063	0.062	0.064	0.060	0.062	0.0017	0.063	0.061	0.063	2.74	6.3
Zapahuira	0.005	0.005	0.012	0.050	0.018	0.0216	0.009	0.005	0.031	19.92	0.9

Data for 2014–2016 from the Arica Regional Health Ministry; p-value X^2 =0.007; SD: standard deviation; P25: 25th percentile; P75: 75th percentile; CV: coefficient of variation; * LDM= 0.0003 mg/L

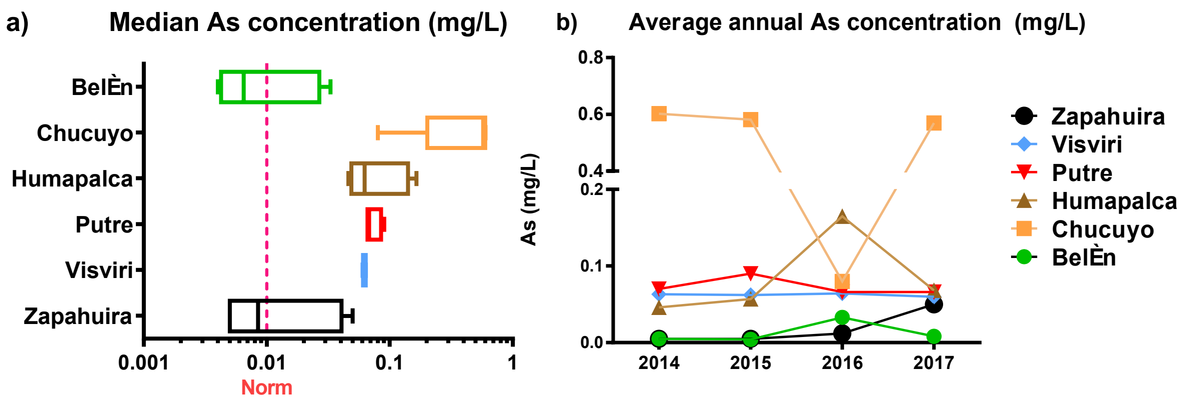

Fig. 2a): Median and b) average annual arsenic concentration in the water of the Altiplano communities studied, Parinacota province, Chile

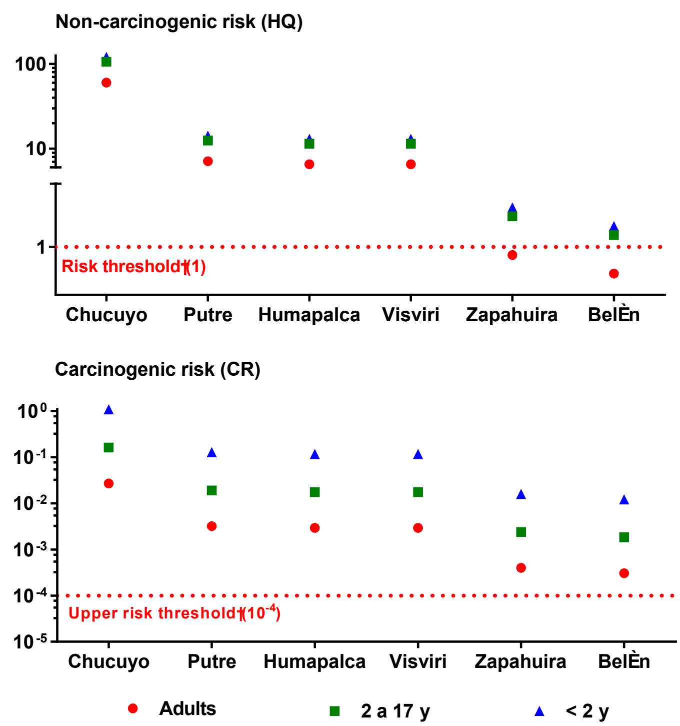

Fig. 3: Non-carcinogenic and carcinogenic risk associated with exposure to arsenic in the water of the Altiplano communities studied, Parinacota province, Chile

of age in all locations. Only the populations of Belén and Zapahuira were below the threshold considered “safe” for adults (HQ<1). HQ values in the locations studied were, in descending order: Chucuyo > Putre > Humapalca = Visviri > Zapahuira > Belén, for all age groups. The CR analysis indicated an elevated risk associated with As exposure in all age groups studied according to the reference levels of 1 x 10^{-4} suggested by the U.S. EPA. Estimated values were very high, with results by location in descending order as follows: Chucuyo > Putre > Humapalca = Visviri.

The values for Zapahuira and Belén were within the reference limits, attributable to As concentrations significantly below those of the other four locations.

Table 4: Non-carcinogenic and carcinogenic risk associated with chronic exposure to arsenic in drinking water in the locations studied, Parinacota province, Chile

Location	Children		Adults
	<2 years	2 to 17 years	>18 years
Non-carcinogenic risk (HQ)			
Belén	1.35	1.19	0.68
Chucuyo	119.90	105.79	60.29
Humapalca	13.02	11.49	6.55
Putre	14.17	12.50	7.12
Visviri	13.02	11.49	6.55
Zapahuira	1.77	1.56	0.89
Carcinogenic risk (CR)			
Belén	1.22E-02	1.83E-03	3.06E-04
Chucuyo	1.08E-00	1.62E-01	2.71E-02
Humapalca	1.17E-01	1.76E-02	2.95E-03
Putre	1.28E-01	1.91E-02	3.21E-03
Visviri	1.17E-01	1.76E-02	2.95E-03
Zapahuira	1.59E-02	2.39E-03	4.01E-04

HQ: Hazard quotient; risk threshold of 1; CR: Cancer risk; risk threshold of 1.00×10^{-4}

Fig. 3 shows the risks evaluated and their respective HQ and CR thresholds. The estimated risks associated with As exposure in the locations studied were significantly above safety thresholds for both systemic (non-carcinogenic) and carcinogenic health problems, especially in the locations located in mountainous zones rather than the foothills of the Andes Range.

The results indicate that these groups are susceptible to illnesses attributable to exposure to this element, especially various cancers. The individuals most vulnerable to the presence of arsenic in the drinking water are children under 2 years of age. Therefore, protecting this pediatric population should be a priority in terms of health policies implemented to mitigate the problem. It is well established that there are critical windows of exposure during gestation and early childhood in which children are highly susceptible to the effects of environmental toxins, with significant long-term effects (Leith Sly and Carpenter, 2012). Research in northern Chile has shown elevated lung and bladder cancer incidence among adults who had been exposed to As-contaminated drinking water during gestation, indicating that deleterious effects may appear as late as 40 years after exposure to As levels similar to those reported in the present study (Young *et al.,* 2018; Steinmaus *et al.,* 2013). This phenomenon is not completely understood, and more research is needed to clarify the impact of prenatal exposure as well as the interactions among environmental, genetic, and epigenetic factors (Bailey and Fry, 2014; Bjorklund *et al.,* 2018). Moreover, recent studies have suggested that modern Andean populations of Aymara ethnicity show an elevated tolerance to As as a result of positive selection, mediated by a specific enzymatic methylation that enhances resistance to the impact of the contaminated water (Arriaza *et al.,* 2018; Tapia *et al.,* 2019; Vicuña *et al.,* 2019; De Loma *et al.,* 2019).

CONCLUSION

This study is evaluated the potential adverse health risks of arsenic intake through water consumption in individuals living in rural areas of the Chilean Altiplano. It is concluded that in at least four of the six locations studied there is a high systemic risk of suffering from diseases related to chronic arsenic exposure, if its inhabitants continue consuming water with the concentrations determined during this study. The concentrations of As in human drinking water in these locations exceeded the Chilean standard of (0.01 mg/L) by 6.3 to 57.6 times Chucuyo, Putre, Humapalca and Visviri have very high systemic exposure to arsenic in children, with values between 1.2 to 119.9 times above threshold (HQ >1). Carcinogenic risk values were 3.06 to 10790.6 times above the upper tolerance limit (1×10^{-4}). To validate these results probabilistic risk studies should be carried out, which consider the variability and uncertainty of the exposure, especially with regard to water consumption in these rural populations. Their condition of isolation and greater vulnerability of these communities makes focused investments imperative, such as rural drinking water systems to supply them with quality water, which implies investigating the use of As removal techniques that can be applied in rural areas that do not have abatement systems for this element. Finally, epidemiological surveillance and environmental monitoring by the health authority is essential, as well as direct work with the communities involved.

AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. D. Mahan formulated the study goals and aims, environmental monitoring, data processing and analyses; O. Waissblut performed the laboratory analyses; D. Cáceres analyzed the study data and interpretation and manuscript writing.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript. The ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been completely observed by the authors.

ABBREVIATIONS

%	Percentage
<	Less than
=	Equal
>	Greater than
>=	Greater or equal than
ADAF	Age-dependent adjustment factor
APHA	American Public Health Association
As	Arsenic
As(III)	Trivalent arsenic
As(V)	Pentavalent arsenic
AT	Averaging time
BW	Body weight
CR	Cancer Risk
CSF_{ing}	Ingestion cancer slope factor
CV(%)	Coefficient of variation
C_{water}	Concentration of arsenic in water
ED	Exposure duration
EF	Exposure frequency
Eq.	Equation
ERD	Regional Development Strategy
ESRI	Economic and Social Research Institute
et al.	"and others" in latin
Fig.	Figure
GraphPad Prism	Scientific 2D graphing and statistics software
HQ	Hazard quotient
ing	Ingestion
IR_{ing}	Intake rate of drinking water
kg	kilogram
Km	Kilometre
L	Litre
L/day	Litre per day
LDM	Limit of Detection Method
LADD	Lifetime average daily dose
m.a.s.l.	Metres above sea level
mg/kg/day	Milligrams per kilogram of body weight per day
mg/L	Miligrams per liter
N	North

P<0.05	Probability that the null hypothesis is rejected
P25	Percentil 25th
P75	Percentil 75th
pH	Hydrogen potential of a solution
RfD_{ing}	Ingestion reference dose
SD	Standard Deviation
SIRGAS	Geocentric Reference System for the Americas
Stata	Syllabic abbreviation of the words statistics and data
µg/L	Micrograms per liter
U.S.	United States
USEPA	United States. Environmental Protection Agency
UTM	Universal Transvers Mercator
V12	Version number 12
V6	Version number 6
W	west
WHO	World Health Organization
X^2	chi square statistic
y	year

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