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Monitoring of Arsenic in Occupational Exposure by Utilizing Urinary Arsenic as Biomarker: A Case Study in Caletones, Chile

Oscar P Díaz Schultze[1]* and Rubén Pastene[2]

[1]*Magister Program on Integrated Management, Faculty of Environmental Science, University of Concepcion, Concepción, Chile*
[2]*Department of Chemistry of Materials, Faculty of Chemistry and Biology, University of Santiago of Chile, Santiago, Chile*

***Corresponding Author:** Oscar P Díaz Schultze, Magister Program on Integrated Management, Faculty of Environmental Science, University of Concepcion, Concepción, Chile.

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Abstract

Introduction: Arsenic (As) and As-containing compounds are human carcinogens. Exposure to As occurs occupationally in several industries, as well as environmentally from both industrial and natural sources. Inhalation is the principal route of As exposure in occupational settings.

Objective: The aim of this work, was to provide and discuss important information about occupational exposure to As, derived from a case study carried out in a copper smelting in Chile.

Materials and Methods: A group of 21 workers employed to warehousing and convey of mineral residues from a copper smelting, which contains toxic elements such as As was considered in the study. Air samples in the work-site were collected through digested and analyzed for As on a hydride generation atomic spectrometer (HG-AAS). At the end of the job-week, participants were asked to provide a first morning-void urine. These samples were filtered and diluted for total As (t-As) determination by HG-AAS. The quality assurance/quality control of the t-As levels, was checked by analyzing urine samples against certified reference material. Sampling of air in the work-site and urine collected from each of selected workers, were obtained between 2007 and 2011.

Results: Arsenic levels present in the work-site, ranging from 0.0012 to 0.092 mg/m^3. These As levels, were higher than those established by both American Conference of Governmental Industrial Hygienists (ACGIH) and Occupational Safety and Health Administration (OSHA) threshold limit value of 0.01 mg/m^3, with the exception the As levels found in samples during 2011. Arsenic concentration in urine samples exceeded the permissible exposure limit of 35 µg/g creatinine in all workers, except during 2011.

Conclusions: Arsenic levels in the work-site exceeds the threshold limit value established by both ACGIH and OSHA. Similarly, the majority of workers exceeded the permissible exposure limit. These results imply a serious risk to the health of workers.

Keywords: *Work-Site Arsenic; Biological Exposure Index (BEI); Threshold Limit Value (TLV); Arsenic Occupational Disease*

Abbreviations

As: Arsenic; t-As: Total Arsenic; i-As: Inorganic Arsenic; ACGIH: American Conference of Governmental Industrial Hygienists; OSHA: Occupational Safety and Health Administration; HG-AAS: Hydride Generation Atomic Absorption Spectrophotometry; BEI: Biological Exposure Index; TLV: Threshold Limit Value; SPSS: Statistical Product and Service Solutions; CCA: Chromated Copper Arsenate; LTB: Biological Tolerance Limit; USEPA: United States Environmental Protection Agency; ATSDR: Agency of Toxic Substances and Disease Registry; TLV: Threshold Limit Value; CAT: Chronic Arsenic Toxicity

Introduction

Arsenic (As) and arsenic containing compounds are human carcinogens. Exposure to As occurs occupationally in several industries, including mining, pesticides, pharmaceutical, glass and microelectronics, as well as environmentally from both industrial and natural sources [1]. Occupational exposures to As are mainly due to inhalation or through the dermal route, whereas the ingestion of contaminated drinking water and food (raw and cooked), is the predominant source of significant environmental exposure globally [2,3].

The toxicity of As widely varies based on route of exposure and form. Arsine gas is one of the most toxic forms and is readily absorbed into the body by inhalation. Inorganic forms of As are more toxic than organic forms. Of the inorganic As compounds, the more toxic trivalent form reacts with sulfhydryl groups causing enzyme disruption and reduced oxidative phosphorylation; the pentavalent form is less toxic and, through phosphorus substitution, and it uncouples oxidating phosphorylation [4].

Workers who produce or use As compounds in such occupations can be exposed to substantially higher levels of As [5,6]. It is rare for workers to be exposed to As alone because the exposure usually occurs in combination with other metals [7].

Occupational exposure by inhalation in copper smelters is associated with several subclinical health phenomena. The acute and subacute toxicity of As involves many organ systems including gastrointestinal, dermal, nervous, renal, hepatic, hematopoietic, cardiovascular, respiratory and ophthalmic systems [8,9]. Long-term exposure to nonlethal doses of As, has also been found to induce chronic health hazards in these organ systems. Inorganic As induces cancer of the skin and various internal organs without any specific organotropism [9,11]. The systemic involvement of As toxicity may result from the generalized distribution of ingested and inhaled As in the human body and from the direct toxic effect of inorganic As without metabolic activation. With respect to exposure biomarkers, occupational safety and health professionals have traditionally used biological monitoring as the primary integration tool for assessing chemical exposure via multiple pathways or routes of exposure [10]. After being uptaken into the human body, approximately 40 - 60% and 55 - 80% of As that is absorbed from the lungs and the gastrointestinal tract respectively, is excreted in the urine, mainly within 1 - 2 days [12,13]. For this reason, measurement of urinary As levels is generally accepted as the most reliable indicator of recent As exposure [14].

Occupational Safety and Health Administration (OSHA), promulgates and enforces regulations for toxic substances in the workplace. These regulations are enforceable by law. OSHA regulations are based on both air monitoring and biological monitoring of the worker. Air monitoring provides data on work place conditions, guides industrial hygiene measure and serves as the basis for requiring medical/biological monitoring measures the uptake of As into the body, reflects actual exposure and is used to assess health risk to workers [15].

There are few studies on occupational exposure to As, though involve a severe health risk to workers. In this study we provide and discuss important information about occupational exposure to As, as well as the possible health effects associated with As exposure.

Materials and Methods

Group selection

A group of 21 workers employed in an industry dedicated to warehousing and convey of mineral wastes generated in a gas cleaning Plant, were identified. This plant depends on a copper smelting, located in Caletones in the pre-Andean zone of the O´Higgins Region, approximately 45 km east of Rancagua city in Chile. These mineral wastes contain several toxic elements such as copper and arsenic. All these workers were considered as highly exposed to arsenicals. Data on the age of workers, duration of exposure to As, other occupational activities evolved during monitoring study were obtained by questionnaire. Urine collected from each of the selected workers exposed to As, were obtained once a year between 2007 and 2011.

Air sampling and analysis

Air samples were collected during a working day (8 hours) at the start of the week in each year at the work-site (Table 2). Environment in the work-site is characterized by the presence of abundant suspended matter surrounding of the sampling area. Airborne As was

collected on 37-mm mixed cellulose ester filters (pore size ≤ 0.8 μm). Then, air As samples were digested in a microwave device with a mixture of nitric, perchloric, and sulfuric acids in the proportion 3:1:1 by volume. Then, the digested solution was analyzed for As on a hydride generation atomic absorption spectrometer (HG-AAS) (Perkin-Elmer model 3300) equipped with an autosampler (PE AS 90) [16-18]. Air samples in the environmental were obtained once a year between 2007 and 2011.

Urine sampling and analysis

Workers were supplied a polyethylene bottle rinsed with nitric acid 5% previously. At the start of the job-week participants were asked to provide first morning-void urine directly into polyethylene bottles. Urine samples were collected the same working day of the week that the air monitoring. Concentrated hydrochloric acid, Probus P. A., 1.19 g/mL (1 mL on 100 mL urine) was added to prevent bacterial growth and to preserve As content. During transport the samples were kept on ice, and upon their arrival to the laboratory the samples were then frozen at -20°C and stored until analysis which was performed before 48 hours previous it was sampled. Urinary creatinine was measured by Jaffe method [19]. Prior to analyses, samples were filtered through a 0.45 μm syringe filter and diluted up to 5 fold with 2% nitric acid for total As (t-As) determination by HG-AAS (Perkin – Elmer, model 3300) equipped with an autosampler (PE AS 90). Throughout the analyses, the quality assurance/quality control of the t-As levels measured was checked by analyzing urine against certified reference material (MedisafeRMetalle U, Level 1, Medichem, LGC Standards) for each batch samples (certified value = 0.50 μg/mL) [2,13].

Statistical Analysis

All statistical tests were carried out using the SPSS (Statistical Product and Service Solutions) 13.0 software package. We calculated range, mean values, median, standard deviation and correlation between arsenic concentration in the air of the work-site and arsenic level measured in the urine of workers, during all the monitoring period.

Results and Discussion

Exposure to As and other work activities

The information collected regarding period of exposure to As and other tasks evolved after this monitoring study was finished, is shown on table 1.

Worker	Age (years)	Period		
		Exposure to As	Other Work Activities	
			Hydraulic Cleaning	Rain Mitigation
1	31	2007-2011	2011-2012	Not Employed
2	25	2007-2011	2011-2012	2011-2012
3	44	2007-2011	2011-2012	2011-2012
4	21	2008-2011	2011-2012	Not Employed
5	46	2007-2011	Not Employed	2012
6	54	2007-2011	2011-2012	Not Employed
7	32	2010-2011	2011-2012	2011-2012
8	34	2010-2011	2011-2012	Not Employed
9	35	2007-2011	2011-2012	Not Employed
10	46	2007-2011	Not Employed	Not Employed
11	26	2007-2011	2011-2012	Not Employed
12	24	2007-2011	2011-2012	2011-2012
13	43	2007-2011	2011-2012	2011-2012
14	48	2010-2011	2011-2012	Not Employed
15	55	2007-2011	2011-2012	2011-2012
16	27	2008-2011	Not Employed	Not Employed
17	26	2007-2011	2011-2012	Not Employed
18	27	2008-2011	2011-2012	Not Employed
19	22	2010-2011	2011-2012	Not Employed
20	29	2008-2011	Not Employed	Not Employed
21	19	2010-2011	2011-2012	Not Employed
Mean Age	34			

Table 1: *Exposure to arsenic and other occupational activities.*

The work-site where all workers were employed, corresponds a section of the gas cleaning Plant named "Arsenicals waste and harmful waste management". The majority of workers are young (mean age: 34 years, Table 1) and the majority of them have been exposed to As since 2007 until 2011 (Table 1). Hydraulic cleaning and mitigation of rain effects were another work activities evolved by workers between 2011 and 2012 (Table 1) and, both activities represent no risk for health due to the presence of As and other elements in the working environment.

Figure 1 and table 2, present the mean airborne As levels in the working-place, where all 21 workers were exposed during 2007 to 2011 with As concentrations ranging from 0.0012 (2011) to 0.092 (2007) mg As/m^3. These As levels were variable during every sampling day and every year and generally higher than both American Conference of Governmental Industrials Hygienists (ACGIH) and Occupational Safety and Health Administration (OSHA) threshold limit value of 0.01 mg As/m^3 [15,26], with the exception of the As levels found during 2011 (mean: 0.001 mg As/m^3). Noteworthy is the very high As concentration monitoring carried out in 2007 (0.092 mg As/m3), which exceeds threshold limit value by nine times. It is known that in the smelting work-site, there is a very high contamination of several toxic elements, which without preventative maintenance of the work-site can result in very high levels of As.

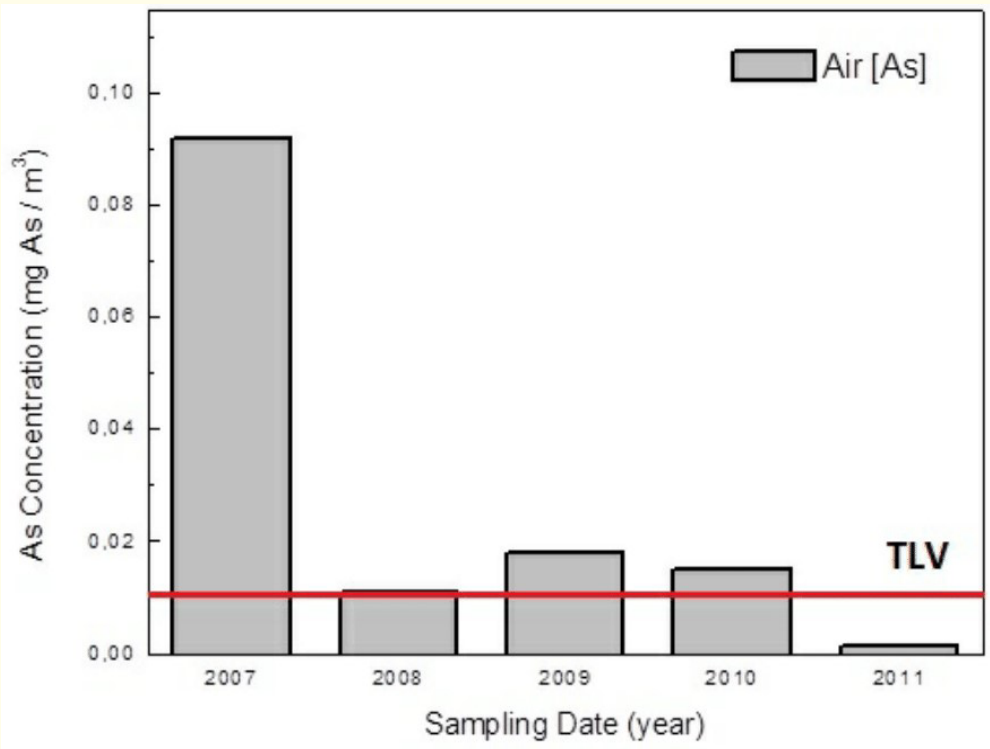

Figure 1: *Mean arsenic concentration in the work-site (TLV: threshold limit value = 0.01mg As/m^3).*

Sampling Date	No. of Samples	Mean Concentration (mg As/m^3)	Range (mg As/m^3)
August 21, 2007	3	0.092	0.083 - 0.102
June 17, 2008	3	0.011	0.004 - 0.023
November 17, 2009	4	0.018	0.013 - 0.027
October 4, 2010	4	0.015	0.006 - 0.022
May 23, 2011	4	0.0012	0.001 - 0.002

Table 2: *Concentrations of airborne arsenic in the work-place.*

Urinary arsenic levels

Figure 2, shows urinary As levels in all workers and in each year that the study was carried out.

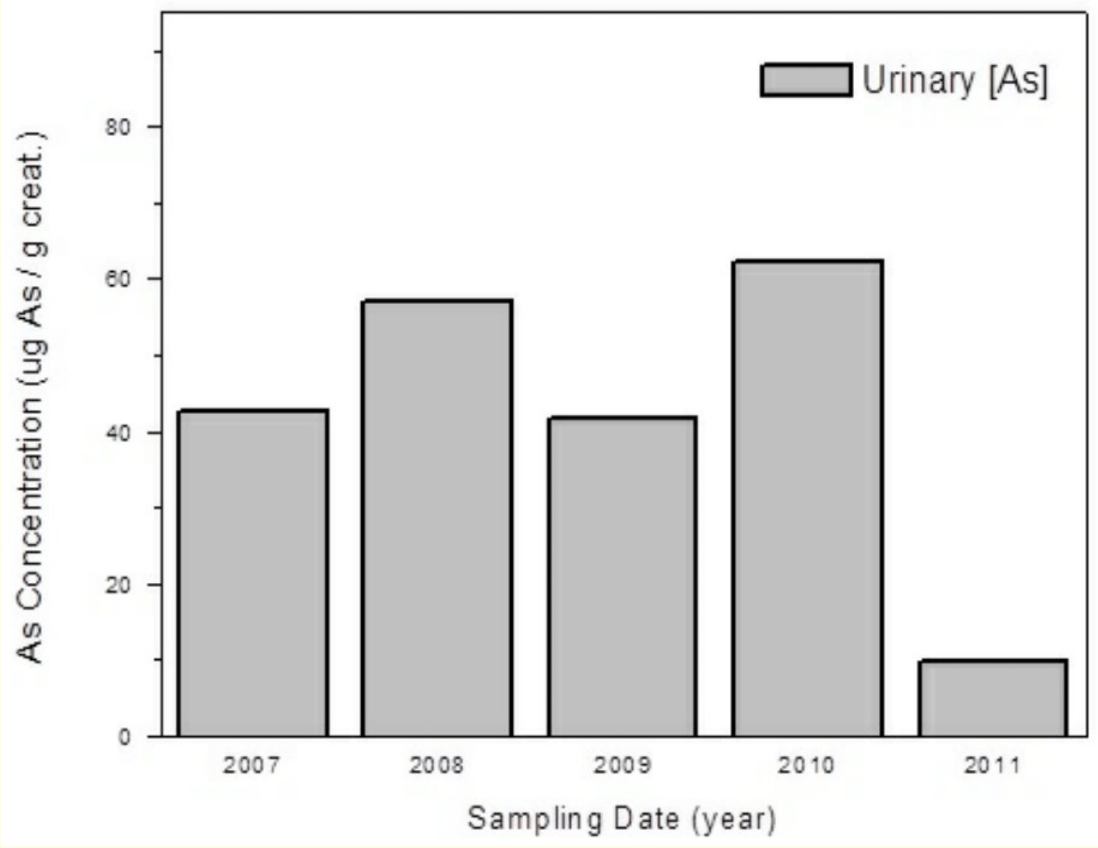

Figure 2: *Urinary arsenic levels.*

The concentrations of As in urine ranged from 19 to 65 µg As/g creatinine, with an average value of 42.6 ± 11.3 µg As/g creatinine in the samples collected during 2007. The concentrations of As in urine collected during 2008, ranged from 22 to 119 µg As/g creatinine, with an average value of 57.1 ± 28.0 µg As/g creatinine. Urine samples collected during 2009, ranged from 6 to 108 µg As/g creatinine,

with an average value of 41.7 ± 26.2 µg As/g creatinine, whereas the urine samples collected during 2010, ranged from 20 to 130 µg As/g creatinine, with an average value of 60.4 ± 34.4 µg As/g creatinine. Finally, the urine samples obtained during 2011 ranged from 1 to 44 µg As/g creatinine, with an average value of 10.8 ± 10.7 µg As/g creatinine.

These urine As concentrations are variable that demonstrated by wide ranges and high standard deviations. Nevertheless, the mean As concentrations in urine recollected in 2011, were significantly lower compared to urine samples collected during 2007, 2008, 2009 and 2010. This result could be related to very high airborne As levels measured in the work-place during the first year of the study (mean: 0.092 mg As/m^3, Table 2).

ACGIH develops Biological Exposure Indices (BEIs) as guidance values for assessing biological monitoring results. The BEI generally indicates a concentration below which nearly all workers should not experience adverse health effects [10,26].

ACGIH has developed a BEI of 35 µg As/g creatinine measured at the end of a work week. Hence, majority of workers in our study exceeded the permissible exposure limit of 35 µg As/g creatinine during all monitoring period, except during 2011. Data obtained by the questionnaire indicated that between September 2010 and July 2011, 7, 8, 14, 19 and 21 workers were employed (Table 1), thereby these workers have been slightly exposed to As and then they showed lowest As levels in urine (2, 4, 18, 5 and 12 µg As/g creatinine, respectively). By another hand, monitoring of airborne As levels were the lowest during 2011 with respect to the others years (mean: 0.0012 mg As/m^3, Table 2) mainly due that the industry carried out some plans directed to reduce As levels in the work environment, since 2010 year. This decision probably also involved reducing As levels in urine.

In table 3, As levels in the airborne and As concentrations in urine are presented in order to estimate the correlation between those parameters.

Sampling-year	Airborne As mean levels (mg As/m^3)	Urinary As mean levels (µg As/g creat.)
2007	0.092 ± 0.007	42.6 ± 11.3
2008	0.011 ± 0.0083	57.1 ± 28.0
2009	0.018 ± 0.0057	41.7 ± 26.2
2010	0.015 ± 0.006	60.4 ± 34.4
2011	0.0012 ± 0.0004	10.8 ± 10.7

Table 3: *Mean As concentrations in the airborne and urine in each sampling year.*

For As in the air of the work environment, a low correlation with urinary arsenic was found (r = 0.22). This correlation value is lower than that obtained by Pinto., *et al*. [20] who reported a linear relation up to 150 µg As/m^3 (r = 0.53). Finally, age shows not to be decisive at the moment to measure the urine As concentration (Table 1).

Arsenic has long been a cause for its adverse health effects in the form of cancer or other systemic diseases resulting from occupational and/or environmental exposure. Recent research developments have caused a special concern about As low level exposure, particularly its long-term accumulative effects on human health. This is particularly important if the found concentrations of As are higher than those reported by OSHA and ACGIH [18].

Occupational and non-occupational exposure to inorganic arsenic (i-As) may occur by inhalation at or near nonferrous smelters, residential and industrial burning of coal or pesticides manufacturing plants and by dermal contact of As-contaminated soil or use of As-containing pesticides. Estimates of As air concentrations at a Tacoma, Washington, copper smelter exceeded 1.00 µg/m^3 during certain periods of its operation [12]. This concentration was lower than that obtained in our study and only similar to that measured during

the monitoring period of 2011 (mean: 1.2 μg/m^3, Table 2). This value was the lowest in the monitoring period of this work. In Chile, the Supreme Decree 594, regulates on basic sanitary and environmental conditions in the workplace [21]. Article 56 sets a weighted permissible limit that represents the maximum value allowed for the weighted average of the environmental concentration of chemicals in the workplace during the normal working day of 8 hours, with a total of 48 hours per week, equivalent to 0.16 mg/m^3 of As and soluble compounds expressed as As. Regarding with the national regulation, all monitoring analysis fulfill with that regulation. Here, a strong disagree is observed between international and national regulations. Thus, hazardous substances involving inhalation exposures to individual contaminants still present, particularly in developing countries where regulations or enforcement may be less restrictive. It is known that the majority of regulations within developed countries are inadequate and permissive. So far, people who work close to waste sites, landfills or industrial As sources (smelting operations, coal burning, power plants) are more exposed to As contamination through air [7,10].

On the other hand, the As inhalation unit risk for cancer based on studies of occupational exposure to i-As, is 4.3 x 10^{-3} μg/m^3 [16]. So far, from data provided in table 2, all workers had inhaled As from contaminated work environment for at least four years and then, there is an increased risk of development of urinary bladder cancer and lung cancer for all of them, due to chronic exposure to As. When all the epidemiological data are considered for these two types of cancer, the findings are consistent with strong associations found in several human groups with high exposure to As [9].

As mentioned above, the threshold level value in the work environment established for both OSHA and ACGIH is 0.01 mg As/m^3 which is fulfilled during monitoring carried out in 2011 only (Table 2).

There are numerous epidemiological studies in humans; these studies have demonstrated the carcinogenic effects of i-As from inhalation exposure [22]. Long-term exposure to As results in chronic As toxicity (CAT, arsenicosis). This has been reported to occur in people who live in endemic areas with high As concentrations in water or in burning coal [22]. Arsenicosis has also been reported in people due to occupational exposure to As. Occupational exposure to As can result in reduction of methylation capacity as indicated by elevation of unmetabolised i-As in the urine [24]. Skin lesions, which include change of pigmentation (e.g. melanosis) and keratosis of the hands and feet are characteristics of chronic arsenic poisoning and usually appear after 5 - 15 years after exposure [9,25]. Chronic As poisoning may also lead to damages of internal organs the respiratory, digestive, circulatory, neural, and renal systems [9,27,28]. The most significant consequence of chronic exposure to As is the occurrence of different types of cancer in various organs especially the skin, lung, and bladder [6,28].

Often, workers are not aware that they have been exposed to As unless directly asked about their work environment and activities. A detailed occupational and environmental exposure history is a fundamental step towards acquiring information on possible exposure to As [4]. A full work history is necessary to identify jobs with possible As exposures. Ask workers about their jobs (where they work and what they do), potential exposure occurring in current and previous jobs, hygiene practices in the workplace, and use of any personal protective equipment. If the individual is employed in a job that may involve exposure to As, further questions on length of time at the job, frequency of tasks handling As materials, and descriptions of how they carry out their work, recent activities associated with As can provide important information on possible risks, use of folk remedies (e.g. "Asiatic pill", kushta, yellow root), spouse' occupation, wood arsenic-treated in the home because could contain the preservative chromated copper arsenate (CCA) is of recent interest, proximity of residence to hazardous waste sites, smelting operations and others aspects related should be asked [4,12]. In our study, some of these aspects were covered from the questionnaire.

A medical history also might help to recognize possible symptoms associated with chronic arsenic toxicity. Investigation of non-cancer disease including hypertension, cardiovascular disease, diabetes, and possibly intelligence quotient, nutritional factors such as dietary selenium or methionine and general nutritional status should be explored. The presence of other diseases can often modify the toxic

potential; for example, liver disease may modify the toxic effects of As. The presence of other carcinogenic compounds that may act as cocarcinogens with As, is a possibility and it should be inquired [29]. This feature was not included to the questionnaire and hereby is a limiting factor in this study.

The Occupational Safety and Health Administration (OSHA) promulgates and enforces regulations for toxic substances in the work-place. These regulations are enforceable by law. OSHA regulations are based on both air monitoring and biological monitoring of the worker. Air monitoring provides data on work-place conditions, guides industrial hygiene measures and serves as the basis for requiring medical/biological monitoring of workers. Biological monitoring measures the uptake of arsenic into the body, reflects actual exposure and is used to assess health risk to workers [15].

Chilean regulation [17], developed a Biological Tolerance Limit (LTB, in Spanish), as a guidance value for assessing arsenic concentration in urine. The LTB generally indicates the lowest concentration at which nearly all workers should not experience adverse health effects. Chilean regulation has developed a LTB of 220 µg As/g creatinine, therefore all biological monitoring analysis are in accordance with the law in our study. However, the urinary As levels of exposed group are being close to the BEI value published by the ACGIH (35 µg As/g creatinine) [26], it might be valid to expect any significant adverse health effects that happen to workers as established by Synczuk-Walczak., *et al* [27]. These authors, measured As levels in urine, recollected from 21 exposed workers employed in a cooper smelting factory. The concentration of total As in urine ranged from 17.4 to 434.7 µg/L (mean: 86.8 ± 86.6 µg/L), so far occupational exposure to inorganic As levels exceeding hygiene standards (TLV, BEI) generating typical disorders of peripheral neuropathy in the exposed workers.

As recommended by Ma and Le [30] and Vélez and Montoro [31], it is strongly suggested that the differences in total urinary As should also be attributed to seafood sources, such as fish, seaweed, mussels, clams, and oysters, though not to the occupational exposure source. Hence, if the total urinary As levels is used as an indicator, one must be very cautious in interpreting such conventional levels for As exposure.

In the present study, a low correlation between As concentrations in the air of environmental work site and As levels in urine was obtained (r = 0.22).This correlation value includes workers that have been working since 2007 until 2011. For i-As in the air, linear and nonlinear relation have been reported with urinary As. Enterline., *et al*. [32], reported a nonlinear relationship with higher arsenic air concentrations. The nonlinear relation was attributed to either the use of respirators by the workers at high arsenic air concentrations or changes in their arsenic storage or excretion mechanisms. Similarly, Synczuk-Walczak., *et al*. [27] have not revealed any relation between the concentrations of As in urine and As levels in the work-place air. In our study, low correlation between As in the work-place and As levels in urine can be attributed to the obligatory use of respirators by workers at high As air concentrations. In fact, Chilean regulations [21], have established the obligatory use of respirators by workers in the work-site where there are many possibilities of potential exposure to chemicals including As, solvents, photoactive polymers, and other materials. Among of them, potential occupational As exposure is one of the most significant problems [18].

Conclusion

Arsenic levels in the work-site exceed the threshold limit value of 0.01 mg As/m3 established by both ACGIH and OSHA, with the exception of the As levels found during sampling 2011 year. Likewise, the majority of workers in our study, exceeded the permissible exposure limit of 35 µg As/g creatinine, during all monitoring period, except during 2011.

In the future, speciation of urinary arsenic would be more appropriate in such cases to clearly differentiate the contribution of arsenic species in urine and to avoid further misinterpretation of the results of urinary arsenic levels.

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Conflict of Interest

There are no other conflicts of interest in the manuscript.

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