

Toxicology

Occupational exposure of foundry workers assessed by the urinary concentrations of 18 elements and arsenic species



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ABSTRACT

Background: Some raw materials applied in Fe foundry industries may contain potentially toxic elements. Thus, foundry worker's occupational exposure is a constant health concern.

Method: In this study, 194 urine samples from foundry workers were analyzed by inductively coupled plasma mass spectrometry for biomonitoring of Al, As, Ba, Cd, Co, Cr, Cs, Cu, Fe, I, Mn, Ni, Pb, Sb, Sn, Se, U and Zn. Moreover, arsenic speciation was performed in representative samples of production sector workers (group A) and administration sector workers (group B).

Results: Concentrations of As, Pb, Cd, Cu, Cs, I, Sb in urines from group A were higher than those found for group B. Samples of group A presented Cs, Ni, Mn, Pb, U and Zn concentrations higher than values reported for exposed workers assessed by other studies. Forty-four samples from group A exceed As-reference limits. Group A had approximately seven times more inorganic As (as arsenite) and 14 times more organic As (as dimethyl As) than group B. A statistically significant difference was observed in the elemental concentration in the workers' urine by the time in the function. Moreover, alcohol consumption is probably influencing the urine concentration of As, Ba, Cd, Co, Cu, Fe, I, Se and Zn.

Conclusion: The monitored foundry workers are exposed to potentially toxic elements and more attention must be given to their health. Therefore, workplace safety conditions must be improved, and constant biomonitoring is necessary to ensure workers' health.

1. Introduction

Environmental contaminants are present in many workplaces leading to a health concern. These contaminants may be biological, physical, or chemical, such as metals that can be harmful to the health of workers, especially above the limits preconized by the legislation [1,2]. Some health effects include cancer and neurological damages [3]. Occupational exposure to As, Cd and Pb is a significant concern due to its toxicity and presence in several working environments [4].

Among work environments with a high risk of occupational exposure are foundry/smelted industries. From one smelting industry to

another, many variables differ, such as the furnace type, sand casting process and type of metal used. However, they have a common characteristic: the risk of exposure to hazardous metal fumes and particles [3]. Approximately 5% of alloys formulations employed in foundries may contain levels of Pb, Cd, As, Mn, I, P and Ni [5]. Evaporation, condensation and oxidation processes are responsible for the metal fumes production, exposing workers by inhalation of fumes and dust [6,7]. Thus, biomonitoring is mandatory in many countries.

Worldwide, several studies have provided evidence of the correlation between the presence of inorganic contaminants on human fluids and occupational exposure of workers from metal production industrial

Abbreviations: ACGIH, american conference of governmental industrial hygienists; NR 7, regulatory norm number 7; IARC, international agency for research on cancer; DMA, dimethyl arsenic acid; MMA, monomethylarsonic acid; CPE, collective protection equipment; PPE, personal protection equipment; FUNDACENTRO, jorge duprat figueiredo foundation for safety and occupational medicine; ICP-MS, inductively coupled plasma mass spectrometry; HPLC, high-performance liquid chromatography; CRM, certified reference materials; GM, geometric mean; PCA, principal component analysis; RV, reference values of normality; IBMP, maximum permissible biological indexes; BEIs, biological exposure indices; LOD, limit of detection; t-As, total As; o-As, organic As species; i-As, inorganic As species

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plants [8–13] and the most common elements monitored were As, Cd, Co, Cr, Cu, Ni and Pb. Campo et al. [14] have analyzed urinary levels of 12 metals (As, Ba, Cd, Cu, Co, Cr, Mn, Ni, Tl, V, Pb and Zn) from 89 workers from an electric steel foundry in Tunisia and reported values above biological limits values for Cd. These authors emphasized that other elements, even at low concentrations, such as Mn, Zn, As, Ba, Tl, and Pb were significant predictors of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) that is considered a pre-mutagenic lesion indicator and a biomarker of DNA oxidation. Therefore, monitoring a wild range of inorganic contaminants on biological samples from occupational exposure might provide additional knowledge in this field and can be used for evaluating correlation or the trends among them.

In Brazil, despite the importance of the metal production industry for the economy, information regarding foundry worker's health is scarce [15]. There are few studies regarding biomonitoring foundry workers [5,15], mostly monitoring a limited number of elements and, as far as we know, none assessing As species. Santos et al. [15] have evaluated smelter workers' exposure to Cd, Pb, Mn and Ni, finding significant differences between exposed and nonexposed groups for all the analyzed elements. Peixe et al. [5] have found positive linear correlations between Pb, Cd and Mn concentrations in the air and the biological matrixes of foundry workers.

The American Conference of Governmental Industrial Hygienists (ACGIH) defines biomonitoring as the assessment of exposure to chemicals present in workplaces by measuring a determinant in a biological specimen from a worker [1]. Urine is a fluid commonly employed for biomonitoring [8,16,17] due to its natural, easy access. Moreover, according to the Brazilian Regulatory Standard Number 7 (NR 7) from the Ministry of Labor and Employment, urine is the biological fluid more appropriate for analysis of several elements, such as As, Cd and Cr [18,19].

According to Liu et al. [3], workers exposed to Cd, Cr, Ni and Mn in foundries are at risk of developing lung cancer and impairment of neurological and behavioral function. Studies report a correlation between smelting work and the incidence of bladder cancer [20]. Other studies indicate an increased risk of lung cancer, stomach cancer and an association between cancer mortality and exposure to carcinogens in smelting work [21]. Since 1986, the International Agency for Research on Cancer (IARC) classifies occupational exposure during the casting process of Fe and steel as a Group 1 carcinogen, causing lung cancer [7].

Exposure to As can occur through food, environment, or occupational sources [22]. Excretion of As is reported to occur through urine [23]. For As, different toxicities between species make the total element content not enough to evaluate the risk. Arsenic speciation is considered a reliable strategy to identify sources of As exposure in humans [16]. In the inorganic form of arsenite (As^{3+}) and arsenate (As^{5+}), As has higher toxicity, being a human carcinogenic according to the IARC. Foundry workers, mines and chemical industries workers may be occupationally exposed to As [23,24]. The organic species of As, such as dimethyl arsenic acid (DMA) and monomethylarsonic acid (MMA), are considered less toxic [23].

Therefore, this study aimed the determination of essential (Fe, Mn, Co, Cu, Zn, I) and potentially toxic elements (Al, Cr, Ni, As, Cd, Sn, Sb, Cs, Ba, Hg, Pb and U) in the urine of foundry workers. Moreover, As speciation was performed in samples that presented higher levels of this element. Finally, a statistical approach was used to evaluate if occupational exposure affected the urinary elemental composition.

2. Materials and methods

2.1. Sample collection

This study was conducted with workers (men) from a metal smelting industry in the state of São Paulo. The raw materials employed in the factory consisted of ferrous (Fe) and non-ferrous metal alloys (Al, Cr,

Cu, Mg, Mn, Ni, Sn, Zn and others). Due to the variety of raw materials, there is a diversity of elements that may be present in metallic fumes such as As, Cd, Fe, Mn, Ni, Pb and Sn. Concerning factory conditions, there are large fans installed in the production area, apparently used to dissipate the heat. However, an undesirable secondary effect is re-suspension of the dust deposited on the factory floor, which increases the exposure of workers to chemical agents. The facilities have some Collective Protection Equipment (CPE) installed, such as hoods with previous air treatment in order not to pollute the environment. On the other hand, it was observed that the most workers do not use Personal Protection Equipment (PPE) with filters for metal fumes, even being offered by the company.

The workers were recruited according to their function, comprising two groups: A-) production workers (workers with a higher risk of exposure); B-) administrative workers (workers presumably less exposed). Sample collection was conducted in partnership with Jorge Duprat Figueiredo Foundation for Safety and Occupational Medicine (FUND-ACENTRO - Brazilian Ministry of Labor), resulting in 194 urine samples (Group A 180 samples and Group B 14 samples). It is important to emphasize that it was not possible to choose equal sample sizes for groups A and B. There were fewer workers in the administrative sector than in the production sector, beyond the difficulties of recruitment. So, it was chosen to work with unequal sample sizes.

Before each collection, workers were asked to sign a Free and Informed Consent Term and they responded to interview-administered questionnaires covering dietary habits, lifestyle and residential and work history. Collections were carried out at the beginning of the work shift, when workers arrived at the factory. For collecting, storing and measurements of trace elements in urine samples, it was used the guidelines of the Centers for Disease Control and Prevention (CDC) - Laboratory Procedure Manual [25]. The participants received the orientation not to use the first urine discharge and they were instructed to collect urine in lot screened metal-free 50 mL Falcon tubes. After collection, samples were fractionated in two Falcon tubes of 15 mL, one of them for urine creatinine dosage (by the Albert Einstein Israelite Hospital, São Paulo, Brazil), and the second tube was stored frozen at $-20^{\circ}C$ until analysis by ICP-MS. The project was evaluated and approved by the Ethics Review Board under protocol number 62547416.7.0000.0064 9.

2.2. Sample preparation and analysis

Reagents used were of analytical grade, except HNO_3 , which was previously purified by Savillex™ DST-1000 sub-boiling distillation system (Minnetonka, USA). Triton X-100 was purchased from Sigma-Aldrich (St. Louis, MO, USA). High purity de-ionized water (resistivity 18.2 M Ω cm) used throughout the experiments was obtained by the Elga water purification system (ELGA, Ubstadt-Weiher, Germany). Solutions were stored in high-density polyethylene bottles. They were cleaned by soaking in 15 % v v⁻¹ HNO_3 65 % (Synth, São Paulo, Brazil) for 24 h, rinsing five times with high purity water and dried in a class 100 laminar-flow hood (FilterFlux, São Paulo, Brazil). The VITROS creatinine slides and the VITROS Chemistry Products Calibrator kit 1 (Ortho-Clinical Diagnostics, NY, USA) were used for creatinine determination.

The concentration of trace elements in urine was measured by inductively coupled plasma mass spectrometry (ICP-MS 7900, Agilent Technologies, Hachioji, Japan), according to Freire et al. [26]. High-purity argon (99.999 %, White Martins, Brazil) was used for plasma generation (15 L min⁻¹) and as an auxiliary (1.2 L min⁻¹) and nebulizer gas (1.01 L min⁻¹). The isotopes monitored were ²⁷Al, ⁵²Cr, ⁵⁵Mn, ⁵⁷Fe, ⁵⁹Co, ⁶⁰Ni, ⁶³Cu, ⁶⁶Zn, ⁷⁵As, ¹¹¹Cd, ¹¹⁸Sn, ¹²¹Sb, ¹²⁷I, ¹³³Cs, ¹³⁷Ba, ²⁰²Hg, ²⁰⁸Pb and ²³⁸U. Helium (99.999 %, White Martins, Brazil) was used as a collision cell gas to minimize spectral interferences for Al, Cr, Mn, Fe, Ni, Cu, Zn and As (5 mL min⁻¹ for He-mode and 10 mL min⁻¹ for High Energy He-mode).

Calibration solutions for ICP-MS were daily prepared over the range of 1–50 $\mu\text{g L}^{-1}$ from multi-element standard solutions containing 1000 mg L^{-1} of each element (Perkin Elmer, Norwalk, CT, USA). Calibration was performed by matrix-matching, by spiking a pool of human urine in each calibration solution (1 + 19 dilution of the urine). The base human urines used for preparing the pool were collected from healthy adult volunteers with no medicine intake. Yttrium, Rhodium and Germanium 1000 mg L^{-1} (Perkin Elmer, Norwalk, CT, USA) were used for the preparation of internal standards solution. The following elements showed better recovery when corrected with each internal standard: Al, Cr, Ni, Pb, Sn and Zn with Ge; As, Ba, Co, Cs, Fe, Mn, Sb and U with Y; Cd, Cu, I and Se with Rh.

Samples were prepared in triplicate according to the method described by Freire et al. [26]. Urine samples (500 μL) were pipetted into (15 mL) conical tubes. Then, the volume was made up to 10 mL with the diluent solution containing 0.4 % v/v HNO_3 + 0.005 % v/v Triton X-100. Samples were direct analyzed by ICP-MS for the determination of total concentrations of 18 elements.

Aiming to correct possible variations in the analyte concentration for elements whose concentration may depend on the urine volume or dilution, the urinary creatinine adjustment was performed. The enzymatic analysis of creatinine is a widely used biochemical method [27]. In the present study, creatinine was determined by an enzymatic method using the VITROS creatinine slides in the Department of Special Chemistry Diagnostic and Preventive Medicine of Albert Einstein Israelite Hospital. One drop (6 μL) of the urine sample was added in the slide and was distributed over the diffusion layer. After, the slide was incubated at 37 °C for 5 min. The last change in reflex density was measured at two-time points at a wavelength of 670 nm. The difference in reflex density is proportional to the creatinine concentration present in the sample.

For As speciation, calibration standards were prepared using stock solutions containing arsenobetaine (AsB), As^{3+} , As^{5+} (Aldrich, St. Louis, USA), monomethylarsonic acid (MMA) and dimethyl arsenic acid (DMA) (Fluka, St. Louis, USA). Arsenic speciation analysis was performed by using high-performance liquid chromatography (HPLC, Agilent Infinity II 1290, Waldbronn, Germany) coupled to the ICP-MS. For separation, an anion exchange column (PRP-X100, 5 μm , 4.6 \times 150 mm, Hamilton, Reno, NV, USA) was used. Operational conditions were settled according to Batista et al. [28]. Briefly, the isocratic mobile phase consisted of 10 mmol L^{-1} $\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$ (98 % v v⁻¹) and methanol (2% v v⁻¹) at pH 8.5. The injection volume was 100 μL . Data evaluation was performed using MassHunter® software (Agilent Technologies, Waldbronn, Germany). Urine samples were selected for As speciation based on total As concentration (determined by ICP-MS), filtered in cellulose filter (0.2 μm , Sartorius, Germany) and direct analyzed by HPLC-ICP-MS.

Accuracy was checked through the analysis of Certified Reference Materials (CRM). For total element determination, the CRM Toxic Elements in Freeze-Dried Urine (Standard Reference Material® 2670a, NIST, Gaithersburg, MD, USA) was chosen. For As speciation, the CRM As Species in Frozen Human Urine (Standard Reference Material® 2669, NIST, Gaithersburg, MD, USA) was analyzed. Once there was no information about Fe concentration in CRMs used in this study for accuracy evaluation, a recovery test was performed in blanks of base urine by spiking this element at the concentration of 50 $\mu\text{g L}^{-1}$.

Table S1 (supplementary material) presents certified values for both Low and High levels of NIST 2670a and values found throughout this study. The *t*-test showed that all measured elements (considering mean and standard deviation) were within acceptable ranges of CRMs (not statistically different at 95 % confidence interval), except Se (high level) and Cr (low level), which were not statistically different at 99 % confidence interval. In general, the relative standard deviation was lower than 10 %. For Fe, the urine from healthy volunteers was spiked, presenting 102 % of recovery.

2.3. Statistics

In the present study, the dataset corresponded to a matrix of 194 individuals versus 18 elements. The dependent variables were the elemental concentrations in urine. The assessed hypothesis is that among groups A and B, the elemental content in the urine was affected by occupational exposure.

Data was evaluated considering minimum, maximum, average, standard deviation, geometric mean (GM) and percentile 95 of elemental concentration by groups. Data normality was tested using P–P plots, and Kolmogorov-Smirnov & Lilliefors. Statistical differences between groups A (*n* = 180) and B (*n* = 14) were evaluated by *t*-test with uneven number of subjects. Even though the unbalance sample size is undesired in most experimental models, the characteristic of the study groups did not allow an equal number of subjects in each group. The operational area workers outnumbered the administrative group. Working with an equal amount of subjects would reduce group A to 14 individuals, removing several of the potentially more exposed workers from the study. Under these conditions, the authors preferred the risk of an unbalanced statistical study and the restrictions on the data assessment that this unbalance design imposed. The confidence interval was 95 %.

Statistical exploratory analysis was a valuable tool to identify associations between samples and variables. In this study, principal component analysis (PCA) was applied to discriminate groups of individuals or elemental association. To perform PCA, variables were auto-scaled to correct differences in the concentration range of each element. The variables used in the PCA were As, Pb, Cd, Co, Cr, U, Al, Mn, Fe, Ni, Cu, Zn, Se, Cs, Ba, I, Sn and Sb. PCs were considered significant for eigenvalues ≥ 1.0 . Factor loadings which indicate the strength of each parameter's influence within a component were considered for values ≥ 0.6 . Principal components were plotted by group and by alcohol consumption. Statistical tests were performed using Statistica (version 8.0, Stat Soft, Tulsa, OK, USA).

2.4. Regulatory values

Among evaluated elements, only Cd, As, Co, Cr and U had regulatory values in urine samples. Thus, the mean concentrations of those elements were compared to the reference values allowed by Brazilian regulation [18] and by ACGIH [1].

The Brazilian regulation established reference values of normality (RV) as possible values to be found in non-exposed populations. Maximum permissible biological indexes (IBMP) correspond to the maximum value that would not cause damage to the health of occupationally exposed individuals [18]. The ACGIH establishes biological exposure indices (BEIs) as values above which would pose risks to workers' health and well-being [1].

For analytes that do not have regulatory limits in current legislation, the values obtained in the present study were compared with the scientific literature on populations not exposed and occupationally exposed to metals.

3. Results and discussion

3.1. Elemental concentration by group

The applied questionnaires provided a detailed description of the studied population, which is shown in Table S2. All participants were men, age between 19 and 57 years (mean: 35.4 \pm 8.4), of which 17 declared themselves smokers (8.8 %) and 88 (45.4 %) assumed to consume alcoholic beverages. The time they have worked in the company ranged from 2 months to 25 years.

A summary of data from the analysis of 194 urine samples, including the instrumental limit of detection (LOD), mean, minimum and maximum values found for groups A (production workers) and B

Table 1

Trace element analysis: summary of 18 element concentrations and creatinine corrected concentrations in urine for groups A (workers of the production sector) and B (workers of administration sector) of foundry industry.

Element	LOD	% < LOD	Group A (n = 180)				Group B (n = 14)			
			Mean ± SD ($\mu\text{g L}^{-1}$)	C_{\min} ($\mu\text{g L}^{-1}$)	C_{\max} ($\mu\text{g L}^{-1}$)	Mean ± SD ($\mu\text{g g}_{\text{creatinine}}^{-1}$)	Mean ± SD ($\mu\text{g L}^{-1}$)	C_{\min} ($\mu\text{g L}^{-1}$)	C_{\max} ($\mu\text{g L}^{-1}$)	Mean ± SD ($\mu\text{g g}_{\text{creatinine}}^{-1}$)
Al	2.28	57.7	34.5 ± 78.7	6.28	664	35.9 ± 98.7	40.0 ± 8.7	33.8	46.1	347 ± 57.1
As	0.07	0.5	12.4 ± 11.5 ^a	0.98	103	8.65 ± 6.79	3.34 ± 1.58	0.93	7.27	5.44 ± 6.75
Ba	0.06	8.2	3.86 ± 3.75	0.50	27.9	2.85 ± 2.77	2.92 ± 1.92	0.67	8.74	4.08 ± 3.52
Cd	0.01	15.5	0.18 ± 0.10 ^a	0.05	0.66	0.11 ± 0.06	0.15 ± 0.09	0.06	0.38	0.13 ± 0.10
Co	0.004	0.5	0.52 ± 0.22 ^a	0.05	1.39	0.38 ± 0.18	0.44 ± 0.31	0.06	1.44	1.37 ± 3.38
Cr	0.01	49.0	0.77 ± 1.22	0.23	10.7	0.47 ± 0.75	1.85 ± 3.42	0.30	7.96	2.84 ± 4.38
Cs	0.06	0.0	21.7 ± 9.50 ^a	2.60	50.7	15.5 ± 6.09	13.1 ± 7.50	1.94	32.7	17.3 ± 5.16
Cu	0.04	0.5	14.1 ± 24.7 ^a	0.58	297	10.5 ± 31.6	9.17 ± 7.49	1.35	49.4	41.6 ± 118
Mn	0.02	57.7	1.55 ± 3.64	0.12	24.6	1.17 ± 3.77	3.01 ± 2.85	0.49	6.11	19.7 ± 31.0
Ni	0.15	12.9	4.95 ± 6.29	0.88	48.6	3.13 ± 4.60	4.01 ± 3.88	0.86	22.6	8.63 ± 12.5
Pb	0.05	17.0	1.84 ± 2.01 ^a	0.04	19.3	1.20 ± 2.28	0.28 ± 0.25	0.04	0.94	0.89 ± 1.61
Se	1.19	40.7	20.8 ± 10.8 ^a	4.90	75.7	11.5 ± 3.60	24.5 ± 0.17	24.4	24.6	19.2 ± 2.18
U	0.001	71.1	0.02 ± 0.02 ^a	0.001	0.10	0.01 ± 0.02	<LOD	<LOD	<LOD	<LOD
Zn	1.33	0.0	577 ± 434 ^a	9.72	2980	384 ± 222	450 ± 391	39.3	1552	485 ± 252
Sb	0.004	35.6	0.11 ± 0.35 ^a	0.02	3.48	0.06 ± 0.14	0.03 ± 0.01	0.02	0.06	0.10 ± 0.20
Sn	0.05	65.5	1.59 ± 1.02	0.42	6.77	1.03 ± 1.16	<LOD	<LOD	<LOD	<LOD
I	0.82	0.0	336 ± 177 ^a	38.2	1237	241 ± 104	159 ± 117	17.5	447	186 ± 77.5
Fe	0.68	25.8	87.7 ± 555	9.62	10,336	40.5 ± 84.6	84.4 ± 183	13.8	746	22.7 ± 12.1

^a statistically significant difference between groups A and B (*t*-test, 95 % confidence interval); LOD: limit of detection.

(administrative workers) is shown in Table 1. For all elements except Al, Mn, U and Sn, most samples presented values above the LOD, as we can see in Table 1. Results for all elements were expressed in both creatinine uncorrected ($\mu\text{g L}^{-1}$) and creatinine corrected ($\mu\text{g g}_{\text{creatinine}}^{-1}$) concentrations.

Morton et al. [29] investigated the effectiveness of creatinine adjustment for 31 elements in urine by using mathematical modeling. Creatinine adjustment was beneficial for 22 elements, including Ba, Cd, Co, Cs, Cu, Ni, Se and Zn, reducing intra-individual variability due to urine dilution. For other elements, such as Al, As, Cr and Pb, creatinine correction can be avoided since it resulted in no significant difference in intra-individual variability [29].

Nevertheless, presenting both values is essential since some regulatory limits in Brazil and abroad are expressed by creatinine corrected, while others appear as creatinine uncorrected concentrations (Table 2). Besides that, using the two units facilitates comparison with previously published studies, as we can see in Tables 3 and 4.

The mean concentrations (creatinine uncorrected) of As, Ba, Cd, Co, Cs, Cu, Ni, Pb, U, Zn, Sb, Sn, I and Fe for group A were higher than in the group B (Table 1). On the other hand, Se, Cr, Mn and Al were higher in group B. Except for Al, the other elements whose concentration was higher in group B (Se, Cr and Mn) are essential for humans.

The maximum concentration found in group A was higher than that found in group B for 17 elements. Only the maximum concentration of Co, which is an essential element, was higher in group B. Considering creatinine corrected concentration, values found for the elements As, Pb, U, Sn, I and Fe in the group A were higher than those found in the

group B (Table 1).

The *t*-test between groups indicated a statistically significant difference for As, Pb, Cd, Co, Cu, U, Zn, Cs, I, Sb and Se, considering creatinine uncorrected values. Except for Se, the elemental content was higher in group A than in the group B. Among those elements, As, Cd and Pb are of significant concern. It is known that the processes occurring in furnaces release Cd and Pb fumes in the environment [15]. Long-term exposure to Cd is related to the development of lung cancer and may also increase the risk of kidney and prostate cancers. Because of that, the IARC has classified Cd as carcinogenic to humans [34–36]. Lead is one of the most critical elements in occupational exposure. This metal causes various damages to the neurological, hematological, metabolic and cardiovascular systems. The IARC recognizes inorganic Pb and its compounds as carcinogenic to humans [36,37].

Box plots showing the distribution of elemental concentrations by groups are represented in Fig. 1. While the distribution in group B, in general, remains more homogeneous, in group A it is possible to perceive the presence of many outliers for most elements, which in this case can represent occupationally exposed subjects. The potentially toxic elements As (Fig. 1a) and Pb (Fig. 1c) presented a remarkably different distribution between the two groups, with very few outliers between group B when compared to group A. For the element Fe (Fig. 1b), the main used in the metal smelting industry, although both groups have presented a similar mean, the group A has many subjects represented by outliers, which is not the case in the group B.

Table 2

Biological Exposure Indices (BEI), Reference Values (RV), Maximum Permissible Biological Indexes (IBMP) and elemental concentration values in groups A (workers of production sector) and B (workers of administration sector) of foundry workers.

Element (unit)	BEI (ACGIH)	RV (MTE)	IBMP (MTE)	Group A ^a	Group B ^a
As ($\mu\text{g L}^{-1}$)	35			12.4 (0.98–103)	3.34 (0.93–7.27)
As ($\mu\text{g g}_{\text{creatinine}}^{-1}$)		10	50	8.65 (1.17–44.3)	5.44 (2.36–27.7)
Cd ($\mu\text{g g}_{\text{creatinine}}^{-1}$)	5	2	5	0.11 (0.04–0.35)	0.13 (0.05–0.36)
Co ($\mu\text{g L}^{-1}$)	15			0.52 (0.05–1.39)	0.44 (0.06–1.44)
Cr ($\mu\text{g L}^{-1}$)	25			0.77 (0.23–10.7)	1.85 (0.30–7.96)
Cr ($\mu\text{g g}_{\text{creatinine}}^{-1}$)		5	30	0.47 (0.06–6.87)	2.84 (0.21–10.4)
U ($\mu\text{g L}^{-1}$)	200			0.02 (0.001–0.10)	<LOD

^a Values are expressed in mean (minimum - maximum).

Table 3

Comparison between trace elements levels in the urine for production workers (this study) and non-exposed populations. Values presented in $\mu\text{g L}^{-1}$. GM: Geometric mean; 1: Brazilian population; 2: UK population; 3: German population.

Element	This study (n = 180) 95 th percentile	This study (n = 180) GM	Batista et al. [30] ¹ (n = 412) 95 th percentile	Rocha et al. [31] ¹ (n = 175) GM	Morton et al. [29] ² (n = 132) 95 th percentile	Heitland et al. [32] ³ (n = 87) GM
Al	87.7	18.0	17.5	–	25.7	–
As	28.7	9.37	–	15.2	152	13
Ba	9.73	2.92	5.3	–	8.42	1.4
Cd	0.39	0.15	0.83	–	0.52	0.17
Co	0.93	0.47	3.7	0.26	1.04	0.18
Cr	1.41	0.56	–	2.94	0.79	0.13
Cs	40.2	19.2	18.7	–	9.30	4.4
Cu	23.5	10.5	18.4	29.7	19.3	8
Mn	5.02	0.59	4.4	1.16	0.46	0.06
Ni	15.6	3.20	4.2	2.00	6.35	0.30
Pb	5.17	1.20	2.96	–	7.63	0.6
Sb	0.22	0.06	2.14	–	0.26	0.04
Se	41.0	18.4	98.9	–	33.4	12
Sn	3.33	1.36	12.4	–	2.44	0.84
U	0.08	0.01	0.06	–	–	0.004
Zn	1542	437	–	279	730	207

3.2. Regulatory limits

In this study, most samples (150 / 194) agreed within the RV established on Brazilian regulation [18] for Cd, As, Co, Cr and U, as presented in Table 2.

Nevertheless, the mean concentration of As (creatinine corrected) in group A was 1.6 times higher than group B mean. Besides that, 44 samples from group A (24.4 %) presented As values above the RV, probably linked to occupational exposure. On the other hand, only one sample from group B presented As concentration above the RV. For Cr, the mean concentration of the group B was higher than that found for the group A. Additionally, two samples exceeded the RV for Cr in urine, being one from group B and one from group A. This result may be related to the consumption of Cr through food, since it is an essential element present in some cereals, vegetables, and fruits. For Cd, all samples agreed with Brazilian legislation and with ACGIH established limit (Table 2).

As presented in Table 2, all samples agreed with the ACGIH established limits [1] for Cd, Co, Cr and U. However, six samples from group A presented values above the BEI ($> 35 \mu\text{g L}^{-1}$) for As, which indicates a possible occupational exposure and health risk. In group B, As concentrations (creatinine uncorrected) ranged from 0.93 to $7.27 \mu\text{g L}^{-1}$, with a mean of $3.34 \mu\text{g L}^{-1}$. In group A, the As average was $12.4 \mu\text{g L}^{-1}$,

which corresponds to 3.7 times the group B average. Group A values ranged from 0.98 to $103.4 \mu\text{g L}^{-1}$. In the case of U, all individuals from group B presented concentrations below the LOD, while group A had a mean of $0.016 \mu\text{g L}^{-1}$.

Despite the results obtained for most elements being below the values recommended by legislation, it is essential to highlight that exposure in any foundry is continuous, so long-term risks can often be underestimated.

3.3. Comparison with exposed and non-exposed populations

Table 3 shows the comparison of the values obtained for production workers (n = 180) in the present study with non-exposed populations in Brazil and other countries. Comparing with a non-exposed Brazilian population, the 95th percentile from the present study was higher than that reported by Batista et al. [30] for the elements Al, Ba, Cs, Cu, Mn, Pb and U. Moreover, the 95th percentile found for Ni in this study was 3.7 times higher than in 412 individuals studied by Batista et al. [30]. This result was linked to the Fe/Ni alloys processed in the foundry.

The GM of Ni, Co and Zn were higher than the reported values from Rocha et al. [31] for a southern Brazilian population.

Morton et al. [29] reported the 95th percentile for elements determined in the urine of a non-exposed UK population, finding values

Table 4

Comparison between trace elements levels (mean \pm SD) in urine for production workers from this study and other published data. 1: Production workers of steel mill; 2: Workers from a beryllium processing enterprise; 3: Workers from a Fe and steel industry.

Element	This study (n = 180) ($\mu\text{g L}^{-1}$)	This study (n = 180) ($\mu\text{g g}_{\text{creatinine}}^{-1}$)	Afridi et al. [8] ¹ (n = 56) ($\mu\text{g L}^{-1}$)	Ivanenko et al. [17] ² (n = 40) ($\mu\text{g L}^{-1}$)	Gil et al. [33] ³ (n = 178) ($\mu\text{g g}_{\text{creatinine}}^{-1}$)
Al	34.5 \pm 78.7	35.9 \pm 98.7	–	54.7 \pm 47.0	–
As	12.4 \pm 11.5	8.65 \pm 6.79	7.9 \pm 1.8	18.2 \pm 9.9	–
Ba	3.86 \pm 3.75	2.85 \pm 2.77	–	33.6 \pm 27.5	–
Cd	0.18 \pm 0.10	0.11 \pm 0.06	–	1.13 \pm 0.59	0.25 \pm 0.28
Co	0.52 \pm 0.22	0.38 \pm 0.18	3.56 \pm 0.6	0.91 \pm 3.43	–
Cr	0.77 \pm 1.22	0.47 \pm 0.75	–	1.81 \pm 6.88	0.95 \pm 1.89
Cs	21.7 \pm 9.5	15.5 \pm 6.1	–	4.07 \pm 2.30	–
Cu	14.1 \pm 24.7	10.5 \pm 31.6	530 \pm 50	7.96 \pm 4.42	–
Mn	1.55 \pm 3.64	1.17 \pm 3.77	2.49 \pm 0.7	1.08 \pm 1.60	0.93 \pm 4.00
Ni	4.95 \pm 6.29	3.13 \pm 4.60	–	1.43 \pm 2.07	1.67 \pm 5.09
Pb	1.84 \pm 2.01	1.20 \pm 2.28	–	1.38 \pm 1.95	22.3 \pm 29.9
Se	20.8 \pm 10.8	11.5 \pm 3.6	–	98.8 \pm 40.8	–
U	0.02 \pm 0.02	0.01 \pm 0.02	–	<LOD	–
Zn	577 \pm 434	384 \pm 222	–	252 \pm 189	–

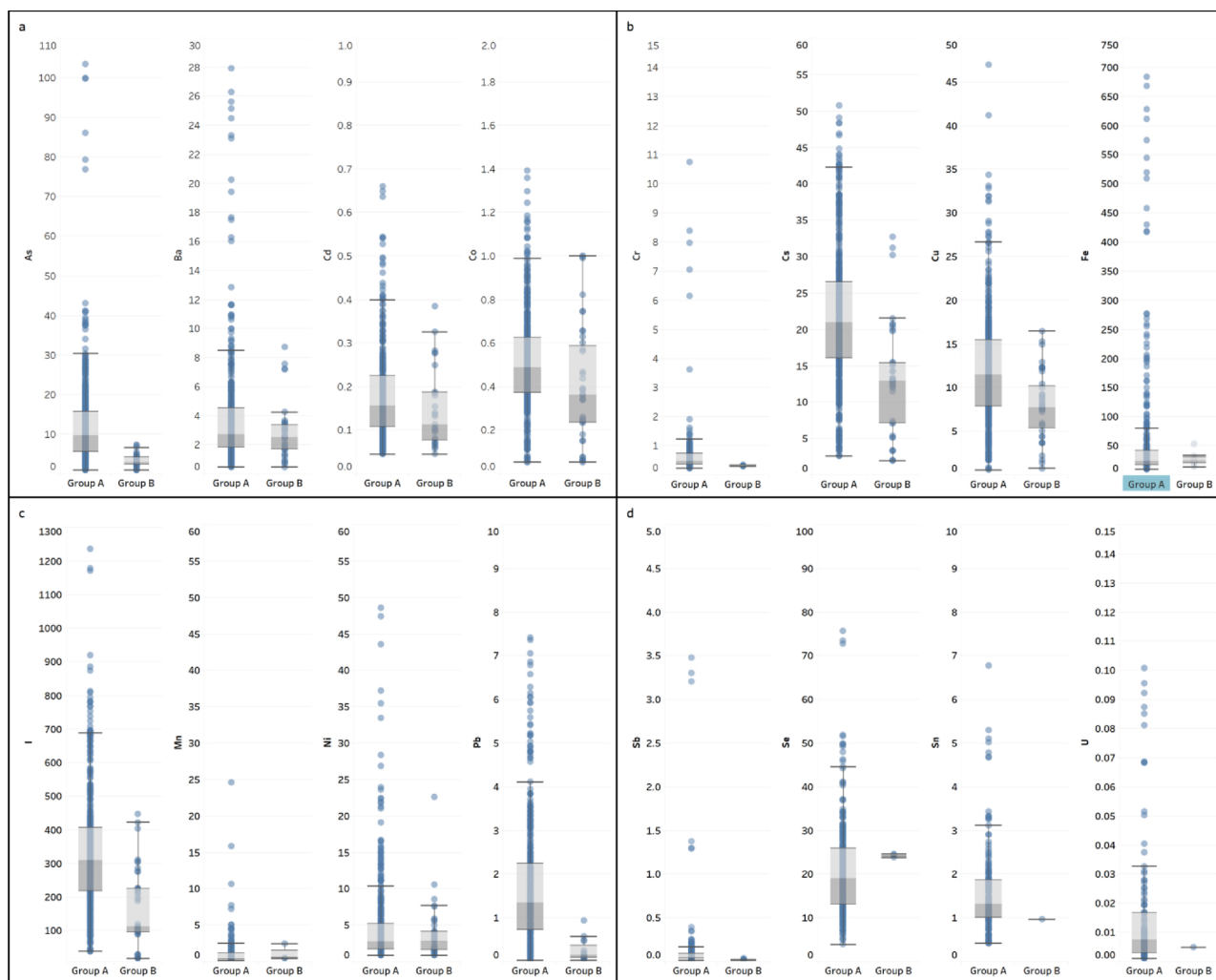


Fig. 1. Box plot with median (central lines), first and third quartiles (box), lower and higher boundaries (whiskers) and outliers (dots) for concentrations of the elements (a) As, Ba, Cd, Co, (b) Cr, Cs, Cu, Fe, (c) I, Mn, Ni, Pb, (d) Sb, Se, Sn and U by groups in urine of foundry workers. Groups: A (workers of the production sector) and B (workers of administration sector).

lower than in this study for Al, Cs, Mn, Ni, Zn, Ba, Cr, Cu, Se and Sn. In a German population, the GM reported by Heitland et al. [32] were lower than in this study for Ba, Co, Cr, Cs, Mn, Ni, Pb, U, Zn, Cu, Sb, Se and Sn.

In the present study, the elemental excretion was higher than the values observed in other populations of the world for several elements. Our results indicate that smelters are exposed to potentially toxic elements while working. These data corroborate with other studies showing that foundry workers are potentially exposed to chemicals such as Cr, Cu, Fe, Zn, Mn, Ni, Al, As, Ba, Cd and Pb, some of which are toxic or carcinogenic [3,6,21,38–40].

Table 4 presents a comparison with other occupationally exposed populations [8,17,33].

For Al, Ba, Cd, Co, Cr and Se, values found in this study were smaller than the values reported by Afridi et al. [8], Ivanenko et al. [17] and Gil et al. [33] for other exposed populations.

Concentration of As was similar to those found by Afridi et al. [8] for steel mill production workers. For Cs, Cu, Ni, Mn, Pb, U and Zn, the concentrations found in the present study were higher than those detected by Ivanenko et al. [17] for workers from a beryllium processing enterprise. For Mn and Ni, values were higher than those reported by Gil et al. [33] that investigated workers from a Fe and steel industry.

3.4. Exploratory analysis of the elemental composition of the urine

In this exploratory analysis, five principal components were found, explaining 63.09 % of all matrix variability. The graphical representation of the first three principal components is in Fig. 2. Fig. 2a and c illustrate the PCA by variables (elemental composition) and Fig. 2b and d illustrate PCA by cases (individuals, each number is associated with one worker).

Factor 1 (F1) explained 30.9 % of the matrix variability and this factor indicates the main effects on the data matrix. A positive correlation was observed between Cu (loading > 0.8), As, Zn, Cs (>0.7), Co, I (>0.6), Cd and Se (>0.5) (Fig. 2a). The association between urinary levels of Se and I was previously reported by Wang et al. [41].

Factor 2 (F2) explained 10.6 % of data variability and associated with a strong positive correlation (>0.8) Mn and Fe. These correlations were separated from the core by clusters 1 and 2 in Fig. 2a. In F1xF3 (factor 3) plot (Fig. 2c), cluster 1 shows the associations related to F3, which represents 8.70 % of data variability. High loading values were observed to Sn (>0.7), Ba, Sb and Pb (>0.6). In working population case studies, where many variability sources may be associated, three factors explain 50.2 % of the matrix variability is considered significant. PCA is a robust reduction of variability technique. However, complex systems have external variability sources that are not fully controlled, such as genetic profile, diet, general health condition, weight,

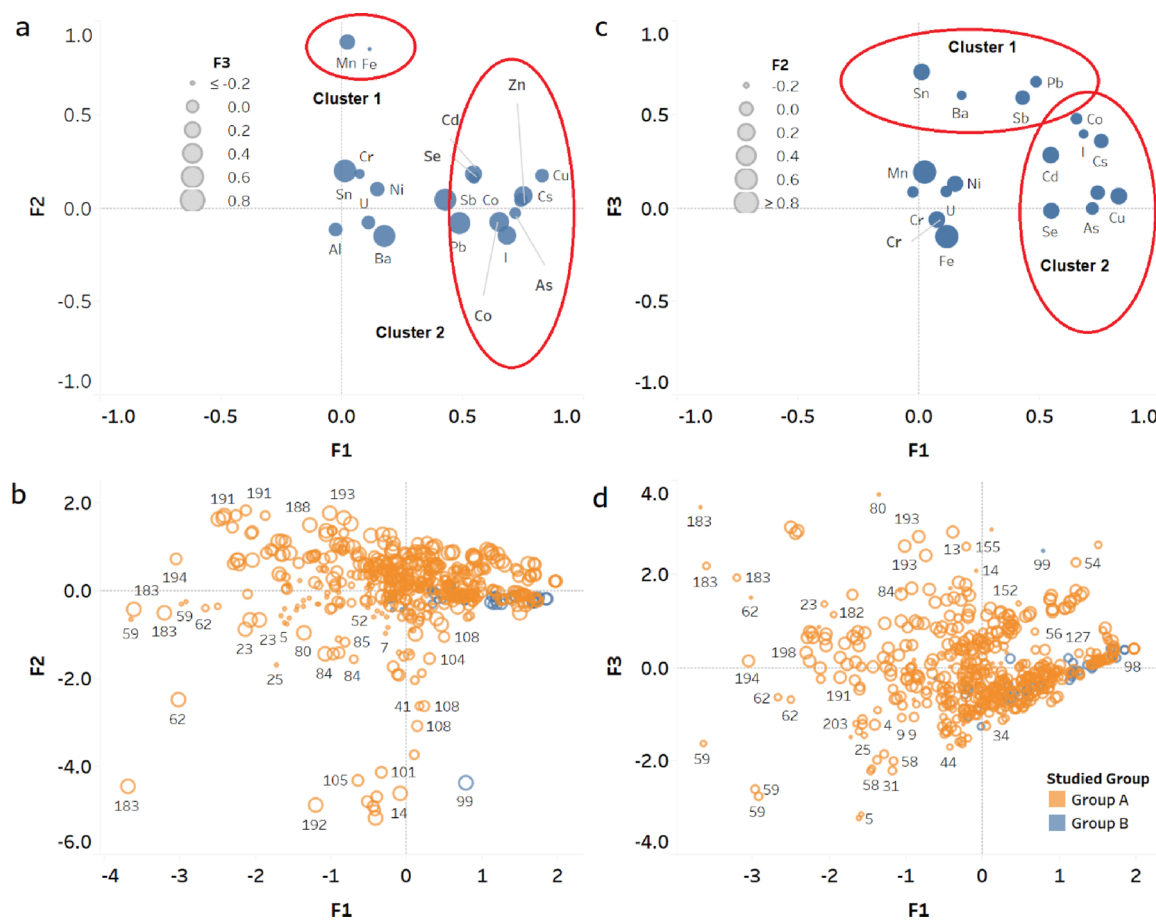


Fig. 2. Principal component analysis with (a) Factor 1 versus Factor 2 and (c) Factor 1 versus Factor 3 loading plots by elements; (b) Factor 1 versus Factor 2 and (d) Factor 1 versus factor 3 loading plots by individuals. Groups of individuals: group B (blue) and group A (orange) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

metabolic rate, etc. These variables were not accessed in the present study and could be responsible for the variability not covered by the identified factors.

The elements with loading values <0.4 associated with F1 (As, Pb, Cd, Cu, Cs, I, Sb) were also identified with a significant statistical difference between groups A and B.

Fig. 2b presents subjects with the average elemental concentration at the F1xF2 coordinates 0, 0. Among group B (blue circles, Fig. 2b), only two of them presented a significant dispersion from the average (individuals 98 and 99). Individuals from group A presented a more considerable distribution from the average concentration of elements in urine.

Individuals with a high level of As, Cu, Co, Cs, I, Zn (Cluster 1, Fig. 2a) were concentrated in the same location this cluster is located (1th and 2nd quadrants Fig. 2b). In the 4th quadrant of the F1xF2 plot (Fig. 2b), samples with a higher concentration of the elements Fe and Mn presented in cluster 2 (Fig. 2a) were observed. In the 4th quadrant of Fig. 2a, most of the subjects perform their activities for more than six years.

Fig. 2c indicates that most of the individuals excreted similar amounts of Al, Mn, Cr, Fe, U and Ni since these elements graphical representation is located at the axis intersection ($x, y = 0, 0$). Individuals from group B (blue points in Fig. 2d) presented a much smaller dispersion than group A, which may be explained by the lower number of samples. However, within group A, it was possible to observe some samples were discriminated from others by F3 ($F3 \leq -1$), as presented in Fig. 2d at the 4th quadrant.

These discriminations are associated with elements shown in cluster 1, Sn, Ba, Sb and Pb (Fig. 2c). Samples with a higher concentration of

elements presented in cluster 2 (Fig. 2c) were concentrated in 1th and 4th quadrants on the F1xF3 plot (Fig. 2d).

The exploratory analysis was applied in this study as a tool to identify possible associations between elements, thus providing evidence of a discrete or dominant source of occupational exposure. However, given the complexity of involved variables such as distinct functions, workers' age, time in function, range of raw materials, compliance with personal protective equipment use, personal habits, among others, it is difficult to define the sources of the elements clearly. Despite this fact, a common effect of some alloy or ores elements such as Fe, Mn, Zn, As, Cu, Pb, Co, Cd, Sn, Sb was observed in exposed individuals, as showed in the principal factors (F1, F2 and F3). These results suggest that occupational exposure in foundry industries may influence the elemental composition of urine.

Based on these findings, the identified elements in the exploratory analysis (Fe, Mn, Zn, As, Cu, Pb, Co, Cd, Sn and Sb) should be continuously monitored in the foundry environment and also in the periodic exam of workers (urine and blood).

3.5. Alcohol consumption and time in function

The influence of alcohol consumption and the time of work in the elemental composition of urine were assessed. It was possible to notice that, for some elements, there was an increase in the concentration with the worked years. However, after a long working time (more than five years for As, Cu and Se, for example, as shown in Fig. 3), the elimination of these elements decreased with time. This effect may be related to a decrease in renal function with age. Moreover, the kidney is the first target organ of metals toxicity due to its ability to reabsorb and

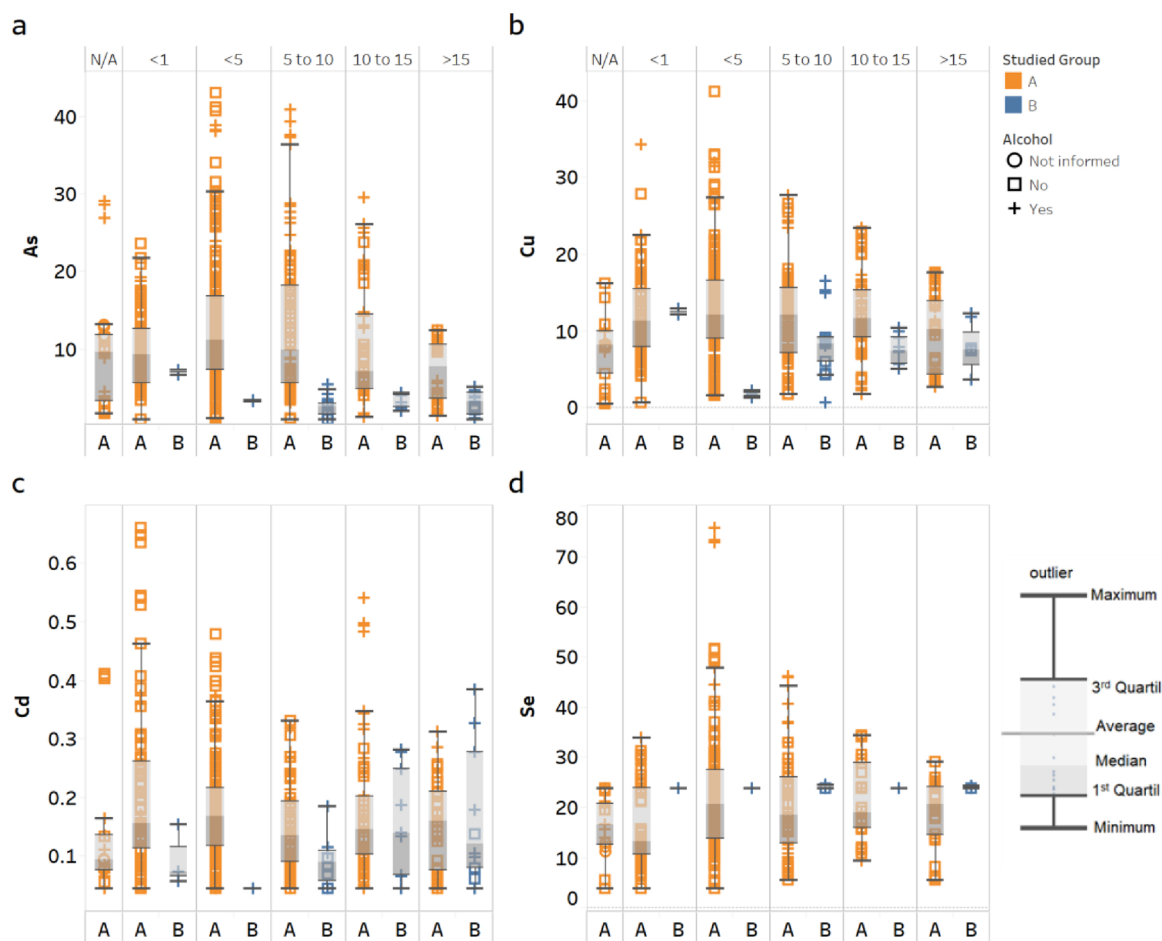


Fig. 3. Box plots with the median (central lines), first and third quartiles (box), lower and higher boundaries (whiskers) and outliers (squares and crosses) for As, Cu, Cd and Se concentrations by group and by time in function, identifying individuals who consume or not alcoholic beverages.

accumulate metals. Still, it is known that the duration of exposure can influence the extent of renal damage [42]. However, a more detailed analysis is needed to prove this theory.

For other elements, such as Cd (Fig. 3), there seems that with a short working time (<math><5</math> years), the groups A and B showed a significant difference between urine concentrations. With the increase in working time, the difference seems to decrease until disappear (>15 years). A similar effect was observed for Cu (Fig. 3), I, Ba and Co (Figure S1 in supplementary material) and Zn (Fig. 4). These results may indicate that workers from group B were initially less exposed. However, with an increase in the working years, the concentration of some elements in their urine (Cd, Cu, I, Ba, Co and Zn) becomes closer to that from group A. These findings can indicate that urine composition is affected by years of exposure in foundry industries. Again, a more detailed analysis is necessary once some other factors may influence urine concentration of metals and trace elements, namely gender, age, dietary habits and socioeconomic status [43].

Berglund et al. [43] conducted a study to assess these influences, concluding that women and children may be more vulnerable to micronutrient deficiency, as well as more subject to metal exposure. The effects of gender can be eliminated since the studied population was composed only by men. Socioeconomic status should also have little influence as all individuals have worked in the same company in similar sectors. Some essential elements such as Cu, I and Zn can be absorbed through diet [44–46], so a nutritional survey is required to prove the observed effect. On the other hand, there is evidence of air and dermal exposure to Coin metal industries [47].

Regarding alcohol consumption, a protective effect seems to be

present on those subjects who do not consume alcoholic beverages. Individuals who consume alcohol (represented by a + in Fig. 4) eliminated higher Fe and Zn concentrations in urine than those who did not drink alcohol. An increase of Fe elimination through urine could be related to blood in the urine or a compromised renal function. Oxidative stress and inflammation that are increased by alcohol consumption may influence Fe concentration in urine [48]. Nakatani et al. [49] have found a significant positive association between urinary iron and urinary oxidative stress. However, the decreased number of individuals prevent proper statistical evaluation.

Other elements were assessed, and additional results are available in the supplementary material (Figures S1 and S2). However, the effects of the time in the function and alcohol consumption were not as pronounced as in the elements represented in Figs. 3 and 4. Regarding the smoking effect, the low number of smoker's subjects was not enough for the association between smoking and elementary urine concentration.

3.6. Arsenic speciation in urine samples

The concentrations of total As (t-As) in some samples exceeded the limits established in Brazil and worldwide (Table 2). Therefore, due to differences in toxicity between organic As species (o-As) and inorganic As species (i-As), 14 representative samples were speciated by HPLC-ICP-MS, aiming to determine the As species in groups A ($n = 9$, t-As ranging from 12.6–101.0 $\mu\text{g L}^{-1}$) and B ($n = 5$, t-As ranging from 1.53 to 7.04 $\mu\text{g L}^{-1}$). Samples were chosen comprising low, medium and high t-As values for each group.

Fig. 5 illustrates the chromatograms obtained in the present study

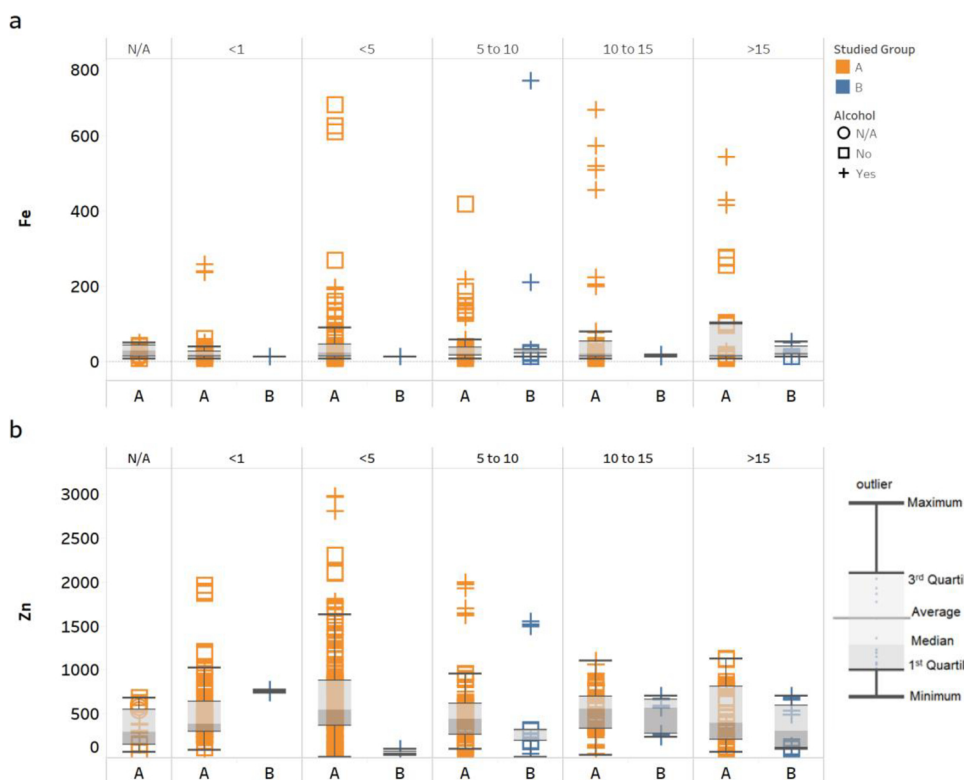


Fig. 4. Box plots with the median (central lines), first and third quartiles (box), lower and higher boundaries (whiskers) and outliers (squares and crosses) for Fe and Zn concentrations by group and by time in function, identifying individuals who consume or not alcoholic beverages.

for a standard solution at the concentration $5 \mu\text{g L}^{-1}$ of each specie (AsB, As^{3+} , DMA, MMA and As^{5+}) (Fig. 5a), for an individual from group A (Fig. 5b) and an individual from group B (Fig. 5c). Arsenic species identified in urine samples were AsB, As^{3+} , DMA and MMA

(Fig. 5b and c). Urine has a natural presence of chlorides, which form with Ar the species $^{40}\text{Ar}^{35.5}\text{Cl}^+$. This species interfered in the ^{75}As signal and was separated and identified in both group A and B chromatograms (Fig. 5b and c).

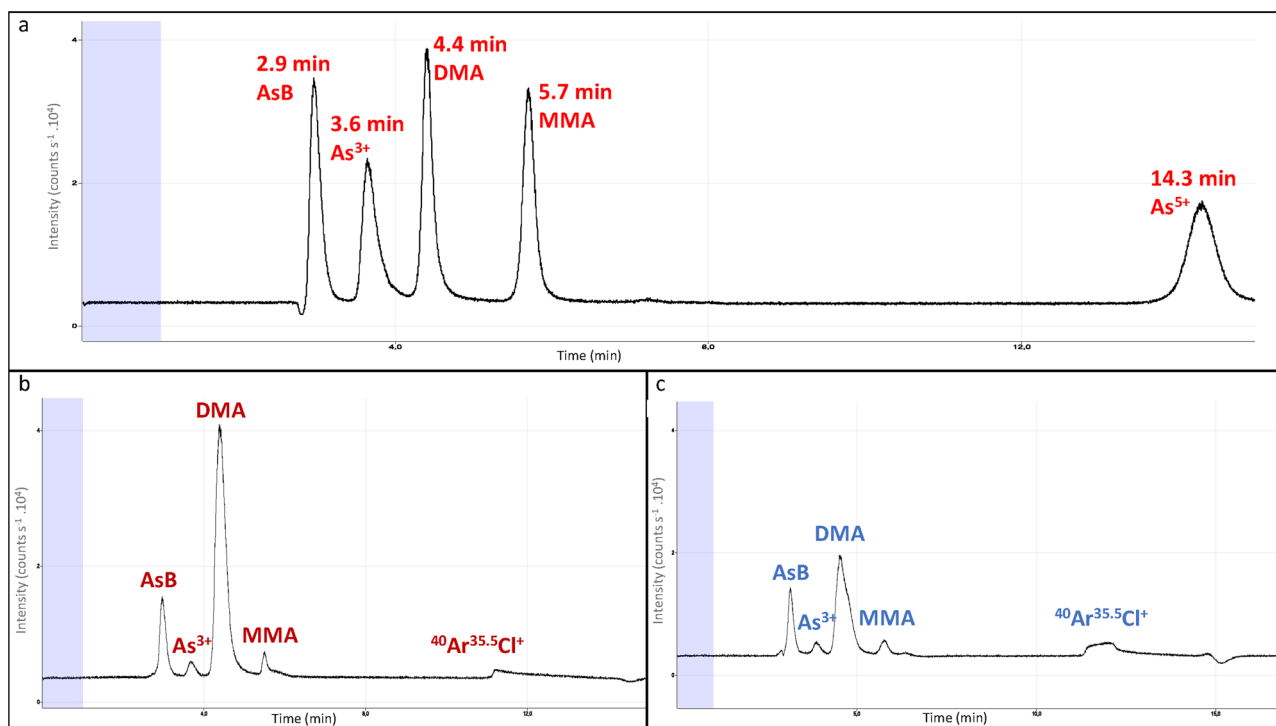


Fig. 5. Typical chromatograms obtained in the present study with the identified species. (a) chromatogram of a standard solution (above peaks are the retention time, in minutes and the corresponding species); (b) Chromatogram of an individual from the group A; (c) Chromatogram of an individual from the group B. AsB: arsenobetaine; As^{3+} : arsenite; DMA: dimethyl arsenic acid; MMA: monomethylarsonic acid; As^{5+} : arsenate.

Concentration ranges found for As species are represented in Figure S3. For group B, the concentrations ranged from 0.08 to 1.48 $\mu\text{g L}^{-1}$ (AsB), 0.07–0.32 $\mu\text{g L}^{-1}$ (As^{3+}), 1.11–4.79 $\mu\text{g L}^{-1}$ (DMA) and 0.18–0.57 $\mu\text{g L}^{-1}$ (MMA). For group A, ranges found were: 0.66–61.0 $\mu\text{g L}^{-1}$ (AsB), 0.35–2.20 $\mu\text{g L}^{-1}$ (As^{3+}), 8.04–69.3 $\mu\text{g L}^{-1}$ (DMA) and 0.51–3.59 $\mu\text{g L}^{-1}$ (MMA). Therefore, the maximum concentration of As^{3+} in group A (2.20 $\mu\text{g L}^{-1}$) was almost seven times that found in group B (0.32 $\mu\text{g L}^{-1}$). Concentrations ranges found for AsB, DMA and MMA in group A were also much higher than in group B (41 times higher for AsB, 14 times higher for DMA and six times higher for MMA).

While AsB is a dietary component derived from the consumption of fish and seafood, high levels of As^{3+} in urine may indicate exposure [22,23]. Sources of i-As in the environment include soil and rocks. Ores containing Cu or Pb contain As, so the process of casting these ores in smelting industries releases most of i-As in the form of fumes and dust, which can be inhaled by workers. Workers exposed to i-As at smelters have an increased risk of lung cancer [23].

DMA and MMA are among the final As metabolites in urine. These species are formed by reduction and methylation of inorganic forms. Thus, high DMA levels in urine can be indicative of exposure to i-As. However, DMA also can be obtained from dietary sources [22,23]. According to Morton and Leese [22], sources of DMA in urine can be challenging to interpret. On the other hand, high levels of MMA, As^{3+} and As^{5+} suggest exposure to i-As [22]. In the present study, it is more likely that DMA is coming from methylation of i-As in the body, given the difference between DMA, MMA and As^{3+} levels in groups A and B. Thus, As speciation is a useful tool to identify and monitor the prevalence and magnitude of occupational exposure in the foundry industry.

4. Conclusion

In the present study, an ICP-MS method was applied for biomonitoring of 18 trace elements in the urine of foundry workers exposed to metals. We have found elevated As, Pb, Cd, Cu, Cs, I, Sb concentrations in the urine of production workers when compared with administrative workers. Furthermore, in this study, the urine of the foundry workers had higher levels of Cs, Ni, Mn, Pb, U and Zn when compared with other occupationally exposed populations from other countries. The statistical approach indicated that the presence of Fe, Mn, Zn, As, Cu, Pb, Co, Cd, Sn and Sb in workers' urine was probably associated with occupational exposure.

Increased levels of inorganic (mainly As^{3+}) and organic (mainly DMA) As species were found in the urine of production workers, which is a concern because of the carcinogenic activity of i-As species.

The present results may indicate that foundry workers are exposed to potentially toxic elements and more attention must be given to their health. Based on our findings, these workers need to be periodically monitored to assess the risks of long-term exposure and for early detection of disease. Besides that, actions must be taken to improve industrial hygiene practices, such as improve workplace ventilation and exhaustion, and replacement or reduction of some raw materials. Continuous safety training should be provided, and personal protective equipment use should be monitored. The renal function of workers must be assessed for a better understanding of the variation in the elimination of some elements over time.

The present study was the first to investigate levels of 18 trace elements and As species in the urine of Brazilian foundry workers and our findings can contribute to the knowledge about human occupational exposure to trace elements. Therefore, future studies involving environmental and blood samples could help to improve the assessment of occupational exposure magnitude.

CRedit authorship contribution statement

Bruna Moreira Freire: Conceptualization, Methodology, Validation, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition. **Camila Neves Lange:** Validation, Formal analysis, Investigation, Writing - original draft. **Tatiana Pedron:** Methodology, Validation, Investigation. **Lucilena Rebelo Monteiro:** Validation, Formal analysis, Writing - original draft. **Livia Rentas Sanches:** Investigation, Resources. **Walter dos Reis Pedreira Filho:** Conceptualization, Methodology, Resources, Supervision. **Bruno Lemos Batista:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jtemb.2020.126593>.

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