

Effect of exposure time and smoking habit on arsenic levels in biological samples of metal workers in comparison with controls

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ABSTRACT: The main goal of this study was to investigate the effect of exposure time and smoking habit on arsenic levels in biological samples of workers occupationally exposed to metals in comparison with non-occupational residents in Turkey. Blood, urine and hair samples were collected from 95 metal workers at Ankara Occupational Diseases Hospital, Turkey. Similarly, 94 hair samples were taken from controls. Arsenic levels in biological samples were measured using Graphite Furnace Atomic Absorption Spectrometry (GFAAS) equipped with Zeeman background correction and Hydride Generation Atomic Absorption Spectrometry (HGAAS). In metal workers; mean hair-arsenic levels of the smokers group (2.05 ±1.97 mg As/kg) was found to be significantly higher than the mean of the hair-arsenic levels of non-smokers group 1.80±1.79 mg As/kg (p<0.05). Mean hair-arsenic levels of exposure time group (4-10 years) was found (2.34±2.21 mg As/kg) to be significantly higher than the arithmetic mean of exposure time group (1-3 years) (1.39 ±1.25 mg As/kg, p<0.01). As for the control group, mean of hair-arsenic levels in the smokers group (0.133 ±0.012 mg As/kg) was found to be significantly higher than the mean of the hair-arsenic levels of non-smokers group (0.101±0.006 mg As/kg, p<0.05). In addition, mean hair arsenic level in metal workers (1.81 ±1.79 mg As/kg) was found significantly higher than mean hair arsenic level in control group (0.115 ±0.006 mg As/kg, p=0.00). Smoking increased the hair arsenic levels significantly both in metal workers and controls. The hair arsenic levels significantly enhanced with ascending exposure time. In addition, metal workers had significantly higher hair arsenic levels than controls. However, there was no significant effect detected in terms of urine and blood arsenic levels.

KEYWORDS: Arsenic; blood; hair; urine; smoking habit; occupational exposure.

1. INTRODUCTION

As a metalloid, arsenic is a prevalent environmental toxic substance [1] which has been classified as a human carcinogenic substance, group 1, by the International Agency for Research on Cancer [2]. Arsenic exposure in humans is mostly affiliated with the use of drinking water contaminated from natural and geological origins of inorganic arsenic [3,4]. Occupational exposure to arsenic has been expressed in varied works such as smelting of metallic ore and mining, use and fabricating of agricultural goods and wood preservatives, application of animal feed additives, manufacturing of electronic semiconductors and fabricating of glass and pigment products [5-8].

Arsenic can be found in inorganic and organic forms with different valence or oxidation states in the environment [3]. It exists in natural water mostly as inorganic arsenic compounds namely As(III) (arsenite) and As(V) (arsenate), respectively. As(III) compounds are more toxic than As(V) species [9,10]. Furthermore, organic arsenic species in the pentavalent oxidation state are much less toxic than inorganic arsenic compounds since metabolism of organic arsenicals is limited [11,12]. Trimethylarsine oxide (TMAO) and tetramethylarsonium (TETRA) are the examples of moderately toxic arsenic species, while arsenobetaine (AsB) and arsenocholine (AsC) have no toxicity in mammals. From inorganic to organic forms, toxicity and mobility of As species in the body decreases in the manner As(iii) > As(v) > organo-arsenic [13-16]. Some arsenic species [17] are listed in Figure 1.

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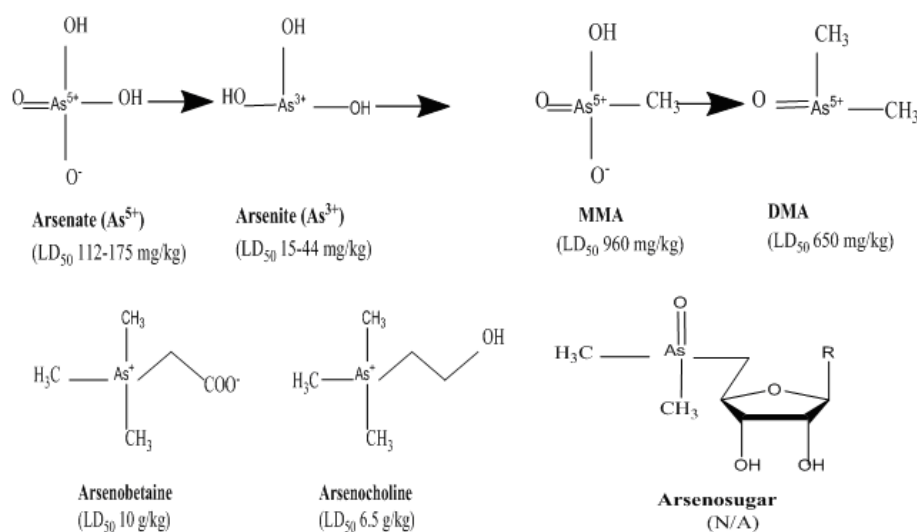


Figure 1. Some important arsenic species: common inorganic arsenicals and their metabolites are listed in top row while organic arsenicals found in sea food are listed in bottom row [17].

Arsenic shows its toxic effects on numerous tissues by binding to sulfhydryl groups of proteins [18]. Acute and chronic exposure to arsenic is related with non-cancer health effects and diverse cancer forms including skin, bladder, liver and kidney [19,20]. Earlier studies revealed that individuals who excrete less arsenic could have higher risk in terms of developing arsenic-related diseases [21]. One of the primary mechanisms of arsenic-induced genomic vulnerability is known as DNA damage that is a character of cancer cells. Past studies show that arsenic can cause DNA damage in human cell lines acting as lymphocytes, TK6 cells and human lung fibroblast cell line [18]. Likewise, Shi *et al.* (2004) revealed that chronic arsenic exposure through calcium-mediated production of hydroxyl radicals, peroxyxynitrite and hypochlorous acid can cause a significant oxidative stress-induced DNA damage [22].

Inorganic arsenic exists environmentally in soil and various sorts of rock. Particularly, it occurs in minerals and ores containing copper, lead, cobalt, silver, and gold. Arsenic trioxide is volatilized throughout smelting and concentrates in flue dust that can involve up to 30% arsenic trioxide [6]. Occupational exposure to chemicals occurs most commonly via inhalation. Hence, arsenic exposure in metal workers takes place by inhalation of industrial soil and dust [23]. Arsenic cycle [24] in the nature is summarized in Figure 2.

Measurement of arsenic in biological samples can be operated by various methods such as neutron activation, X-ray fluorescence, atomic absorption and fluorescence spectrometry, and inductively coupled plasma atomic emission and mass spectrometry (ICP-AES and ICP-MS) [25]. In our previous studies, we have developed and validated methods for arsenic determination in human biological samples by Hydride Generation Atomic Absorption Spectrometry (HGAAS) [26] and Graphite Furnace Atomic Absorption Spectrometry (GFAAS) [3]. The objective of our present study was to investigate the effect of exposure time and smoking habit on arsenic levels in biological samples of metal workers in comparison with non-occupational control group. Hence blood, urine and hair samples were taken from 95 metal workers at Ankara Occupational Diseases Hospital while 94 hair samples were taken from control group who have no known illness or exposure to interact arsenic levels in their biological samples.

2. RESULTS AND DISCUSSION

Arsenic is one of the most toxic elements. In humans, exposure to arsenic can occur via ingestion of foods and water or inhalation of dust contaminated with arsenic [27]. Total arsenic exposure is a sum of exposure to food, drinking water, soil and dust which are directly ingested, inhaled or penetrated in dermal route [28]. The lethal dose of arsenic for humans is approximately 125 mg [29].

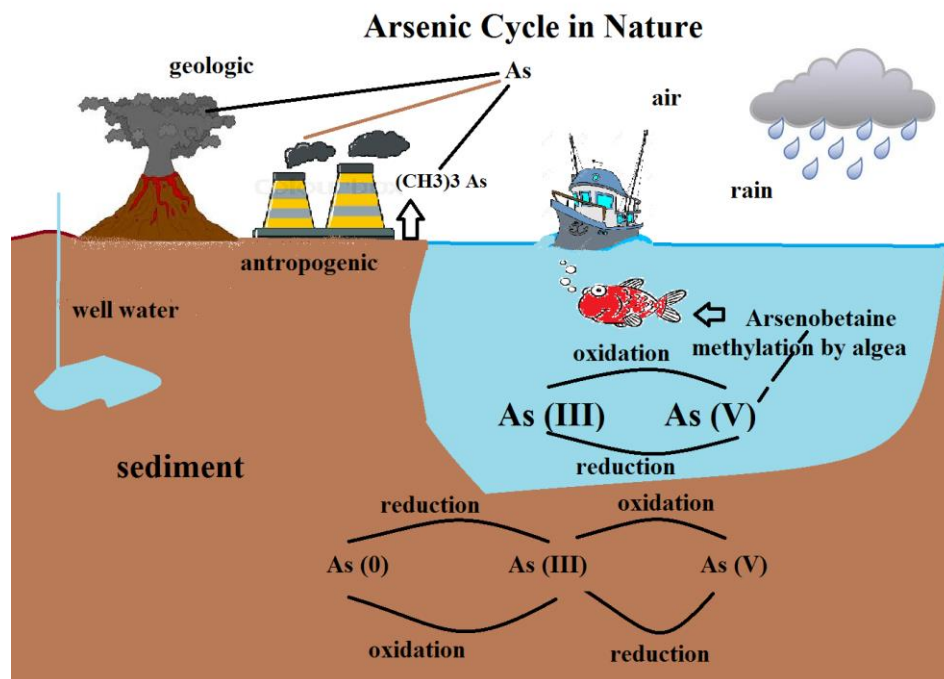


Figure 2. Arsenic cycle in the environment as a schematic diagram. This figure was redrawn with regard to the permission given on December 11, 2016 through simon@uic.edu by Prof. Dr. Simon Silver [24].

Metal mining and production, iron-steel manufacturing, medicine and cosmetics industry, use of herbicides and pesticides containing arsenic, consumption of coal, dyes, wood preserver with arsenic content are the examples of biogenic processes leading to arsenic contamination in the environment [6,30,31]. Industrial exposure to arsenic is particularly observed in developing countries such as Mexico, China and countries in Southeastern Asia. Furthermore, it was observed that people exposed to drink water contaminated with arsenic in Bangladesh were diagnosed with various cancer types especially skin cancer [32]. Occupational exposure occurs primarily via inhalation of dust or smoke contaminated with arsenic. However, in some cases, dermal or oral exposure to organic and inorganic arsenic compounds may also happen. Occupational exposure to arsenic generally takes place by inhalation of gases produced unintentionally when raw ores or metals with arsenic content are treated with acids [6].

For arsenic exposure, it is possible to achieve a more accurate estimation of total dose using biomarkers [33] particularly blood, urine and hair [3]. Urine can become a good choice in order to estimate the arsenic exposure because the main route of arsenic excretion occurs in kidneys [34]. Since inorganic arsenic is rapidly excreted from blood, arsenic levels in blood samples mainly reflect the current or comparatively high level of exposure [35]. Hair has a special potential to explain retrospective information due to arsenic exposure [36].

Mean hair arsenic levels of individuals who have no known exposure to arsenic ranged between 0.02 and 0.20 mg As/kg [37, 38]. However, mean hair arsenic levels of subjects who were exposed to drinking water highly contaminated with arsenic ranged between 3.0 and 10.0 mg As/kg [39]. Arsenic levels in human biological samples from various countries are listed in Table 1. Arsenic concentrations in blood, urine, nail, and hair of unexposed human adults are usually below 1 µg/L, 100 µg/L, 1 mg/kg and 1 mg/kg, respectively [6] as listed in Table 2.

In this research, metal workers who have an obvious exposure to arsenic were selected as a target group to compare with the controls. Effect of exposure time and smoking habit on arsenic levels in biological samples of metal workers were interpreted. Moreover, creating a database due to occupational exposure to arsenic in Turkish population was also aimed.

In the risk group (metal workers); mean hair-arsenic levels of the smokers group (2.05 ±1.97 mg As/kg) was found to be significantly higher than the mean of the hair-arsenic levels of non-smokers group 1.80±1.79 mg As/kg (p<0.05). On the contrary, no statistically significant difference was found between smokers and non-smokers groups of blood and urine samples. Statistical results due to effect of smoking habit on arsenic

levels in blood, urine and hair samples of metal workers, are summarized in Table 3. As for the control group, mean of hair-arsenic level in the smokers group (0.133 ± 0.012 mg As/kg) was found significantly higher than the mean of the hair-arsenic level of non-smokers group (0.101 ± 0.006 mg As/kg, $p < 0.05$). Arsenic is involved in tobacco naturally, and concentration of arsenic in tobacco plants are enhanced by treating them with insecticide containing lead arsenate. Therefore, smoking tobacco causes to arsenic exposure. Metal workers are under an elevated risk of developing lung cancer due to toxic metal exposure including arsenic. It is readily possible to state that metal workers who smoke are under higher risk [40, 41].

Mean hair-arsenic levels of exposure time group (4-10 years) was found (2.34 ± 2.21 mg As/kg) to be significantly higher than the arithmetic mean of exposure time group (1-3 years) (1.39 ± 1.25 mg As/kg, $p < 0.01$). Statistical results due to effect of exposure time on arsenic levels in blood, urine and hair samples of metal workers, are listed in Table 4.

As can be seen in Table 5, mean hair arsenic level in risk group (1.81 ± 1.79 mg As/kg) was found significantly higher than mean hair arsenic level in control group (0.115 ± 0.006 mg As/kg, $p = 0.00$). This result demonstrated that metal workers were under risk of dangerous arsenic exposure. Mean hair arsenic levels (1.81 ± 1.79 mg As/kg) in metal workers were above the safe limits. Arsenic content in hair samples of unexposed humans are generally below 1 mg/kg [6]. This knowledge is consisted with the mean arsenic levels in our control group (0.115 ± 0.006 mg As/kg).

According to another finding of the current study in terms of blood and urine arsenic content, there was no significant effect observed either in metal workers or controls. This situation can be expressed with the fact that arsenic can remain in the blood for 10 hours and in urine for 96 hours after exposure has finished [42].

Table 1. World-Wide reported arsenic levels in human biological samples.

Country	Biological Sample	Mean Arsenic Level ($\mu\text{g/g}$)	Reference	Reference Number
Catalonia, Spain	Lung	<0.05	Garcia et al. (2001)	[43]
Catalonia, Spain	Liver	<0.05	Garcia et al. (2001)	[43]
Catalonia, Spain	Kidney	<0.05	Garcia et al. (2001)	[43]
West Bengal	Nail	7.32	Mandal et al. (2003)	[44]
West Bengal	Hair	4.46	Mandal et al. (2003)	[44]
New York, USA	Urine	15.7	Tsuji et al. (2005)	[45]
Fort Valley, Georgia	Urine	11.6	Hewitt et al. (1995)	[46]
Fort Valley, Georgia	Hair	0.78	Hewitt et al. (1995)	[46]
Fort Valley, Georgia	Nail	0.79	Hewitt et al. (1995)	[46]
Glasgow, Scotland	Hair	0.650	Raie et al. (1996)	[47]
Platine, Germany	Urine	3.96	Gebel et al. (1998)	[48]
Platine, Germany	Hair	0.028	Gebel et al. (1998)	[48]
Nurenberg, Germany	Lung	5.5	Kraus et al. (2000)	[49]
Taiwan	Hair	0.410	Lin et al. (1997)	[50]
Bombay, India	Hair	0.475	Dang et al. (1983)	[51]
West Bengal, India	Hair	0.550	Srivastava et al. (2002)	[52]
Iran	Hair	0.073	Raire (1996)	[47]
Iceland	Hair	0.040	Raire (1996)	[47]
Mongolia	Hair	2.62	Yang et al. (2002)	[53]
Australia	Hair	5.52	Hinwood et al. (2003)	[54]
China	Hair	0.40	Zhuang et al. (1989)	[55]
China (Country-Wide)	Hair	0.571	Yang et al. (1996)	[56]
China (Tongju)	Hair	4.40	Tang et al. (2001)	[57]
China (Tongju)	Urine	0.160	Tang et al. (2001)	[57]
China (Xinjiang)	Urine	0.011	Xu et al. (2009)	[58]
China (Xinjiang)	Hair	1.680	Jin et al. (2003)	[59]
China (Xinjiang) (Control)	Hair	0.65	Jin et al. (2003)	[59]
Taiwan	Urine	0.259	Hsueh and Huang (1998)	[60]
Pakistan	Hair	1.06	Afridi et al. (2011)	[61]
Pakistan	Urine	0.04	Afridi et al. (2011)	[61]

Table 2. Normal Arsenic Levels in Human Biological Samples.

Blood	Urine	Nail	Hair
< 1 µg/L	<100 µg/L	≤ 1 mg/kg	≤ 1 mg/kg

Table 3. Statistics due to the effect of smoking habit on arsenic levels in blood, urine and hair samples of metal workers.

Smoking Habit		(n)	Mean	SD	Minimum Value	Maximum Value	p value
Blood Arsenic (µg/L)	No	27	21.53	10.96	5.21	46.93	.891
	Yes	68	21.14	13.10	3.83	52.44	
	Total	95	21.25	12.47	3.83	52.44	
Urinary Arsenic (µg/L)	No	27	5.66	4.10	1.26	17.83	.343
	Yes	68	6.74	5.30	1.29	27.54	
	Total	95	6.43	4.99	1.26	27.54	
Hair Arsenic (mg/kg)	No	27	1.16	.97	.15	3.91	.025*
	Yes	68	2.05	1.97	.06	7.90	
	Total	95	1.80	1.79	.06	7.90	

3. CONCLUSION

According to statistical analysis for blood and urine arsenic levels, there was no significant association found due to exposure time or smoking habit. However, smokers both in metal workers and controls have statistically higher hair-arsenic levels than non-smokers. Metal workers who were exposed to arsenic in ranging from 4 to 10 years had statistically higher hair-arsenic levels than workers who were exposed to arsenic ranging from 1 to 3 years ($p= 0.01$). Hence, it was observed that hair was relatively one of the best biomarkers to explain chronic long term arsenic exposure. It was found that mean hair arsenic level of metal workers were significantly higher than the controls ($p=0.00$). Therefore, it was observed that hair arsenic levels increased significantly with ascending occupational exposure as well.

4. MATERIALS AND METHODS

4.1 Instrumentation

The analysis was carried out with a dual atomic absorption spectrophotometer (AAS) system (Varian240). Arsenic measurements in hair samples were performed using a Varian AA240 atomic absorption spectrometer (Varian, Victoria, Australia) equipped with a Varian VGA 77 vapor generation system, while blood and urinary arsenic levels were determined using a Varian AA240Z atomic absorption spectrometer (Varian, Victoria, Australia), equipped with a Zeeman background correction system. A boosted-discharge hollow cathode lamp (Agilent, Australia) was used as the excitation source for arsenic. The digestion procedure for the blood and hair samples was carried out using a Mars Xpress microwave system (CEM, Matthews, NC, USA) with PTFE microwave digestion vessels.

4.2 Standard Solutions and Reagents

A 1000-µg/mL arsenic stock solution was obtained from SCP Science (Courtaboeuf, France). Triton® X-100, polyethylene glycol mono (p-1,1,3,3-tetramethylbutylphenyl) ether, was obtained from Scharlau (Barcelona, Spain). Nitric acid (HNO₃, 65%) was purchased from Merck (Darmstadt, Germany). Hydrochloric acid (HCl, 37%), sodium hydroxide (NaOH), and hydrogen peroxide (H₂O₂) were purchased from Merck (Darmstadt, Germany). Sodium borohydride (NaBH₄) was obtained from Fluka (Buchs, Switzerland) and potassium iodide (KI) from Sigma (St. Louis, MO, USA). All chemicals used were of analytical reagent grade unless otherwise specified. Ultrapure water (Human UP 900 Scholar-UV, Korea), with a resistivity of 18MΩ cm, was used to prepare the solutions for the experimental process. Argon gas with a purity of 99.999% was purchased from a local supplier (Vaşak Gaz, Ankara, Turkey). BCR-CRM 397 human hair powder (Community

Bureau of Reference BCR, Institute for Reference Materials and Measurement, Belgium) and Seronorm™ Trace Elements Whole Blood L-2 (Sero AS, Billingstad, Norway) were used as the certified reference materials.

Table 4. Statistics due to effect of exposure time on arsenic levels in blood, urine and hair samples of metal workers.

Exposure Time (Year)	(n)	Mean	SD	Minimum Value	Maximum Value	p value
Blood Arsenic (µg/L)	1-3	54	21.49	12.91	4.40	0.835
	4-10	41	20.95	12.02	3.83	
	Total	95	21.25	12.47	3.83	
Urinary Arsenic (µg/L)	1-3	54	6.45	5.35	1.29	0.967
	4-10	41	6.41	4.54	1.26	
	Total	95	6.43	4.99	1.26	
Hair Arsenic (mg/kg)	1-3	54	1.39	1.25	.06	0.01**
	4-10	41	2.34	2.21	.19	
	Total	95	1.80	1.79	.06	

Table 5. Statistics due to effect of occupational exposure on hair-arsenic levels in comparison with controls.

Occupation	N	Mean As Concentration ± SD (mg/ kg)	Minimum Value (mg/ kg)	Maximum Value (mg/ kg)	P Value
Metal Workers	95	1.81± 1.79	0.06	7.90	0.00*
	94	0.115 ± 0.01	0.021	0.312	

4.3. Study Subjects

For the risk group (metal workers); blood, urine, and hair samples were collected from 95 metal workers (volunteers) at the Ankara Occupational Diseases Hospital, Turkey. The patients ranged in age from 18-61 years. Similarly, 94 hair samples were taken from controls ranged in age from 18-74 years, who have no known illness or exposure to interact arsenic levels in their hair samples. This study was ethically approved by the Research Ethics Committee of the Medical Faculty-Ankara University (Decision Number:11-343-12/25.06.2012). Each volunteer was given a written informed consent form in accordance with the principles as established in The Declaration of Helsinki (World Medical Association, Declaration of Helsinki, 1964). The blood, urine, and hair samples were stored separately at 4 °C in vacuoner blood collection tubes, polypropylene tubes, and polyethylene lock bags, respectively, until the day of analysis.

In this study, we followed the procedures that we previously published in our earlier studies [3, 26]. In order to prepare calibration standards at the concentrations of 3.0, 6.0, 9.0, 12.0, and 15.0 µg/L, a 1000-µg/mL arsenic stock solution was diluted in 5% (v:v) HNO₃ for GFAAS analysis of blood and urine samples. All glassware was kept in 10% (v:v) nitric acid for at least one night prior to each experimental work. Prior to analysis, the biological samples (except for urine) were pre-treated using the acid digestion procedure. One milliliter of each blood sample was taken into Teflon® tubes. The microwave system (CEM Mars Xpress) was operated for digestion of the samples with 5 mL of 65% HNO₃ solution. For the urine samples, 1-mL amounts were mixed with 5 mL of 65% HNO₃ [3].

4.4 Procedure

In order to prepare calibration standards at the concentrations of 1.0, 2.0, 3.0, 4.0, and 5.0 µg/L, a 1000-µg/mL arsenic stock solution was diluted in 20% (v:v) HCl and 1% (w:v) KI for HGAAS analysis of hair samples. A 0.6% (w:v) NaBH₄ solution containing 0.5% (w:v) NaOH was used as a reductant where 5M of HCl was used as an acidifier in the hydride generation module. 100 mg amounts of hair samples were taken and washed with Triton-X, rinsed, and left standing to air dry. The same microwave digestion procedure was also applied to the hair samples [25]. All biological samples were diluted with ultra-pure water to 10 ml. The

GFAAS and HGAAS methods were tested by studying the certified reference materials of Seronorm™ Trace Elements Whole Blood Level-2 and human hair powder (CRM 397).

4.5 Statistical Analysis

Statistical analysis was performed using The Statistical Package for Social Sciences (SPSS) version 19.0 software for Windows. All results were expressed as mean±standard deviation (SD) of the mean. Normality of data distribution was evaluated with Kolmogorov-Smirnov test. Statistical significances between mean values were assessed using Student-t test while mean values of exposure time groups were evaluated using chi-square test. The statistical significance was considered as $p < 0.05$.

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