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Keywords:	blood lead, occupational exposure, reference value, worker, Iran

Relevant Factors of higher blood lead levels and reference values for lead-exposed workers in eastern Iran

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Abstract:

Objective: Lead is extensively used in daily life as a poisonous metal. The present investigation aimed to explore the blood lead levels and its relevant factors in workers exposed to it in Southern Khorasan, Iran.

Methods: The population of the study consisted of 630 lead-exposed workers in South Khorasan Province. Participants were selected through quota random sampling. For measuring the blood lead concentration 5 ml venous blood samples were drawn from participants (via atomic absorption kit). The measured lead concentrations were described as geometric means: 10th, 25th, 50th, 75th, 90th, and 95th percentiles as well as 95% confidence intervals (CI) of the 95th percentiles. To obtain the reference values, the rounded values of the upper limits of the 95% CIs of the 95th percentiles were employed. The analysis of data was conducted using Student t-test, Mann-Whitney U, One-way ANOVA, Kruskal-Wallis, and Spearman correlation coefficient and regression analysis

Results: Based on the findings of the current study, the mean blood lead level and the median of BLL were 6.48±8.08 and 3.9µg/dl (IQR:2.9-5.8) respectively. Of the participants, 85 (13.5%) had a BLL ≥10 µg/dl. The reference value of blood lead level in this study was 30 µg/dl and 14µg/dl for men and women, respectively. There was a significant relationship between higher BLL and age, work experience, working in printing factory and radiator repair workshop.

Conclusion: In various occupational settings lead is still the main exposure factor. The findings of this study can contribute to determining the priorities for intervention in and control of lead exposure in work environment.

Key words: blood lead, occupational exposure, reference value, worker, Iran

Strengths and limitations of this study:

- Corresponding population reference values in lead-exposed workers were determined
- To our knowledge, no study reported on adult reference lead concentrations in Iran, and few studies have been conducted in other countries as well
- Given the cross-sectional design of this study, we cannot definitely judge the reported relationships
- We cannot measure the health effect of lead poisoning and its signs and symptoms exactly

1. Introduction

Lead is a widely-used metal and a persistent poison that is extensively utilized in many industries[1] for its chemical properties. Moreover, it is also the fifth commonly used metal throughout the world[2 3]. The most important source of risk for the lead poisoning is exposure to industrial pollution. This metal is used in more than 900 industries including battery manufacturing, radiator-related sectors, ceramics, plumbing, paint industry, cable manufacturing etc. Lead can enter the body and cause poisoning through contact with any of its sources and via ingestion, inhalation or skin contact[4-6]. Lead poisoning is a major health issue in countries like Iran, and over the past decades, huge efforts have been made to reduce exposure to it. To this end, work on occupational safety and health has begun since 1946 in Iran [3].

Recently, as defined by the CDC (Centers for Disease Control and Prevention) and NIOSH (National Institute for Occupational Safety and Health), a lead level of more than 5 µg/dL is considered as high BLL in adults. The United States Department of Health and Human Services (HHS) also recommends that blood lead level in adults needs to be reduced to below 10 µg/dL[7]. In the same way, the US Occupational Safety and Health Administration (OSHA) has emphasized that workers with blood levels equal to or greater than 60 µg/dL should withdraw from their jobs until their lead serum levels decrease to below 40 µg/dl[7]. But evidence suggests that toxic effects of lead may even occur at minor and lower levels and there is no safety threshold for the lead[8]. Symptoms of lead poisoning in adults are non-specific and include short-term memory loss, lack of concentration, irritability, depressed mood, paresthesia, poor coordination, generalized abdominal pain, nausea, headache, weight loss, and weak or diminished deep tendon reflexes (DTR)[3 8-10].

As it is absorbed, lead enters the bloodstream where more than 95% of it gets bound to erythrocytes and is distributed in the liver and kidney in particular and partly stored in the bones[11]. Lead interferes with the function of the enzymes and essential cations in the cells of the body[11]. This can have adverse health outcomes for people, including nerve damage, digestive problems, liver and kidney damage, anemia, immune system weakness, infertility, developmental problems[1 12], cognitive impairment, memory loss and learning difficulties[13] and cardiovascular problems like hypertension and coronary artery disease [14 15].

Some researchers have also discussed the carcinogenic effects of lead on some systems such as stomach, lung, kidney, brain, and meninges, although the evidence has yielded conflicting results in this regard[1]. Generally, high blood levels of lead have been associated with increased mortality due to various diseases as it adversely affects body systems [16 17].

As noted earlier, lead poisoning and complication are among the threats for human health that lead to lower health status and may impose additional burdens on the health system of a society. Thus, in addition to understanding the hazards and factors that cause harm to the work environment and accordingly affect the health of workers, health authorities should seek to improve the working environment and thereby control diseases, complications and occupational injuries and ultimately guarantee the health of workers through examination, measurement and control of occupational hazards.

Considering the differences in the level of development of countries, the level of safety for workers, and the application of preventive programs in many countries, examining the lead levels in different regions can provide a complete picture of the problem. Accordingly, this study was conducted to determine the concentration of lead in blood, its related factors and to identify the reference values in lead-exposed occupational workers in South Khorasan Province, Iran.

2. Methodology

In this study, 630 lead-exposed workers were investigated in Southern Khorasan province. Workers in tile factory, rubber manufactory, mining, printing industry as well as mechanics, radiator-manufacturers and painters were examined. Upon confirmation of the research proposal by the Deputy Vice-Chancellor for Research and the Ethics Committee of the University, and after receiving a letter of introduction from the vice chancellor for research and preparing the list and address of the targeted groups, the researchers attended the workplace of the above-mentioned exposed occupational workers. After the explanation of the research objectives and according to the inclusion criteria, participants could enter the study based on quota random sampling. To this end, first the quota of each occupation proportionate to the total number of employees in the lead-exposed jobs was determined, and then individuals were chosen randomly from each of the occupations under scrutiny.

Written consent was obtained from all contributing participants of the study. Demographic data (age, gender, history of drug addiction and smoking, and work experience) were also collected from individuals. For blood tests, 5 cc venous blood samples were taken for the measurement of serum lead concentration and the relevant samples were sent to laboratory in the ice container. The level of lead in the blood sample was measured in *The Shafa Laboratory* using a graphite furnace atomic absorption system (PG instrument, AA500FG, UK). Graphite Furnace Atomic Absorption Spectrometry is a sensitive and precise method with high repeatability for measuring lead and other heavy metals in biological samples. The standard curve was drawn up with at least 5 standard concentrations and the quality control was carried out using 3 control samples of the Norwegian Sero Company. The experiments were carried out using trained technicians at the same laboratory.

SPSS 19 was used to analyze the data. First, descriptive indexes including mean, standard deviation, frequency, mean, quartile and percentiles of blood lead levels were reported for different groups. The reference value of BLL was based on the maximum limit of

95%confidence interval for the 95th percentile. Using Kolmogorov-Smirnov test, we also examined the normality of quantitative variables. In case of normalization, independent T-test and ANOVA were used, otherwise Mann-Whitney and Kruskal-Wallis tests were performed. Tukey's post-hoc test was also used to compare lead levels of the groups. A multiple logistic regression was performed to examine the relationship between variables. The significance level was set at 0.05 (5%).

Patient and Public involvement:

There were no participants involved in the development of the research and outcome measures, the study design or the recruitment to and conduct of the study.

3. Results

This study investigated 630 occupational workers who were exposed to lead (585 men (92.8%) and 45 women (7.2%)). The mean age of the participants was 36.29±8.03 (95%CI: 35.56-37.01) years. Fig 1 presents the distribution of blood lead. The mean blood lead level was 6.48±8.08 µg/dl (95% CI: 5.75-7.21) with a median of 3.9 µg/dl and inter quartile range from 2.9 to 5.8 µg/dl. Eighty-five (13.5%) individuals had a blood lead level above 10µg/dl and the lead level was below 10µg/dl in 545 (86.5%) participants. Of the participants, 188 (29.8%) and 7 (1.1%) had a BLL higher than 5 and 40 µg/dl, respectively. The blood lead level in men was significantly higher than that of women with a median of 9.0 and 3.9µg/dl, respectively. The median of blood lead was 3.7 [2.7-5.3] µg/dl in the youngest age group (<30years), 3.9 [2.9-5.9] µg/dl in the intermediate age group (30-45 years) and 4.3 [3.2-8.1] µg/dl in the oldest group (>=45 years). The reference value for blood lead in the present study for the oldest age group was 35µg/dl. The median blood lead was 3.7 [2.7-5.4]µg/dl for those with a work experience below 10 years, 3.9 [3.02-6.0] µg/dl for those with a work experience from 10 to 20 years and 4.0 [2.9-5.0] µg/dl for those with above 20 years of work experience.

The results of Kruskal-Wallis test showed that lead levels in different occupations exposed to lead were statistically significant ($\chi 2$=54.25, p<0.001). The mean blood lead for radiator maker was 22.43±13.11 µg/dl, with the median 23.2 [9.0-32.4] µg/dl and the reference value 43 µg/dl. The median blood lead was 4.9[3.2-15.8] µg/dl with the reference value of 39 µg/dl in printing factory that was significantly higher than rubber manufactory with the median 3.9 [3.1-4.9] µg/dl (p=0.004) and mechanics with the median 3.3 [2.5-4.2] µg/dl (p=0.003). The blood lead level in radiator maker was significantly higher than other occupations (p<0.001) (Table1).

The reference value for blood lead level in radiator maker in the youngest (<30years) and intermediate (30-45 years) age group was 43 and 42 µg/dl, respectively. Among the workers of the printing factory, mechanics and radiator makers, the reference level of the lead increased with enhanced work experience (Table2).

According to the multiple logistic regression with adjusting of opium use, there was a significant relationship between higher blood lead concentration with age, work experience, printing factory and radiator maker (Table 3). The results showed that by increasing work experience (OR (CI= 95%): 1.07 (1.03-1.13), p-value=0.002), there is a chance for BLL>10 µg/dl increase by 1.07 times in one year. In radiator makers compared to painters, the chance for BLL>10 µg/dl increase was up to 12.93 times (OR (CI= 95%): 12.93 (4.56-34.98), p-value=0.002). The Hosmer-Lemeshow goodness-of-fit test result was found *in*significant (x^2= 5.38, d.f= 8, *p*-value= 0.72). Thus, the null hypothesis claiming that the model fitted the data well could not be rejected. The Cox and Snell R-squared values indicated 30% that suggests that independent variables contributed to predicting the BLL>10 µg/dl

4. Discussion

The aim of this study was to determine the concentration of blood lead and its related factors in lead-exposed occupational workers in Southern Khorasan province. Based on the results, the average blood lead concentration in the subjects was 6.63±8µg/dL (minimum: 1.1 and maximum: 83.5). Of the subjects 29.8% had lead levels above 5µg/dl, 13.5% had lead levels above 10 µg/dl and 1.1% revealed lead levels higher than 40 µg/dl. The average lead level in subjects of the study was above the maximum recommended concentration by the Centers for Disease Control. According to the recent definition of CDC and NIOSH, equivalent levels of lead or more than 5 µg/dL is considered high blood levels in adults. Also, the American Occupational Safety and Health Administration (OSHA) announced that workers with blood levels equal to or above 60 or 50 µg/dL should quit work until their lead levels of serum returns to below 40 g/dl in addition to recommending that medical examinations should be performed on workers with serum blood levels ≥40 µg/dl[7] .

In a meta-analysis (2016) in Iran that investigated 34 study of occupational exposures to lead, the average blood lead concentration in Iranian workers was 42.8 µg/dl with a confidence interval of 50.49-15.35[18]. The lowest mean blood lead concentration was reported in a study in Yazd during 2006 (4.97 µg/dl)[19], whereas the highest rate was demonstrated in Tehran in 2004 (96.7 µg/dl)[20]. Alasia (2010) also found the mean lead level of 190 people with lead-exposed occupations (including welding/metal work, paint/pigment workers, radiator repairers, battery workers and petrol workers) as 50.37±24.58 µg/dL[21]. In another study, the mean lead level among a number of workers in the iron and steel industry was reported to be 43.39 ± 52.65[22].

Many studies have emphasized the high levels of lead in occupationally exposed workers compared with healthy ones, including Anetor (2002), where the mean serum concentration of lead in occupationally lead-exposure workers was shown as 56.3 ± 1.0 µg / dL versus 30.5 ± 1.4 µg / dL in the control group[23]. Also, the level of lead in a group of Korean workers was 32.0 ± 15.0 µg / dL compared to 5.8 ± 1.8 µg/dL in the control group[24]. Based on our data, no study has been conducted on the reference values of lead among adult occupational workers in Iran and the number of studies conducted in other countries is also limited. In a study, the reference values in exposed occupational workers in Taiwan were 40 and 30 µg/dL for men and women respectively. The reference values in the healthy population of the Czech Republic were 8 and 5 µg/dL, respectively for adult males and females[25].

Also, according to the NHANES (National Health and Nutrition Examination Survey) in the United States in 2007/2008, the given values were 4.4 and 3 µg/dL for men and women. Differences in levels of lead in various studies can be attributed to the difference in the study timing and grouping[26]. Based on the results of this study, there was a significant relationship between the blood lead levels and age. Moayedi (2008) found a significant relationship between age groups and high blood lead levels[27]. In Kim (2011), the mean geometric mean of blood lead in people over 40 years old was significantly higher than those under 40 years of age[28]. Kuno (2013) in the Brazilian population also confirmed the existing association revealing that older people showed 23% higher blood lead levels[29]. This association has been reported in many other studies such that older people had higher levels of lead[30-32]. Older people are exposed to more lead during their lifetime that makes it gradually precipitate in their bones in a way that about 90% to 95% of this substance is stored in calcified tissues including bones[28]. This accumulated lead in bones can act as an internal source and in conditions such as pregnancy, lactation, menopause and in some physiological or pathological conditions such as osteoporosis and bone fractures, and increased age release the lead into the bloodstream[33].

Based on the results of this study, blood lead levels in men were significantly higher. In many studies across the world, this difference was reported as being significant in the two gender groups[31 32 34-36] such that according to Kim (2011), the lead level was 30% higher in Korean men[28] and as reported in Kuno (2013), it was 50% higher in males in the Brazilian population[29].

Some reasons may explain the higher level of lead in men one of which might be that men are more likely to be exposed to this metal due to their occupation and presence in lead-exposed areas. As another argument, young women or women in the pre-menopause, for the high levels of estrogen, hold more lead in their bones, and the release of lead from the bones is slower in them compared to men. Hemoglobin levels are also higher in males. These all can be explanations for the identified association[31 32].

Another result of the present study was that a higher work experience in lead-exposed occupations could increase the risk of lead poisoning. Based on the results of a number of studies on lead-exposed occupations, the average level of lead in the blood increases with increasing work experience that is consistent with the results of the current study [22 37-39].

Based on the results of our study, among the careers investigated, repairing the car radiator and working in the printing plant increased the risk of lead poisoning significantly. Lead poisoning among radiator repairers has been reported in a number of studies as well[11 40-45]. The ingestion of lead by car radiator repairers occurs as a result of soldering. During the repair process, the radiator sections are welded together at a temperature about 900° F. The lead has a melting point of 621.5° F and a significant evaporation temperature of 900° F that results in the potential risk of workers' exposure to lead by inhalation[46].

The poor and inadequate sanitation can also increase the risk of lead poisoning. The workers usually do not take precautions such as using masks, protective gloves, and aprons, and many of them do not wash their hands before eating or eat at work[11]. In many developing countries, these shops are in the vicinity of residential homes that also increase the risk of contact with lead for other people, so preventive measures must be taken into consideration not only by these occupational workers themselves, but also by others.

In various studies, high levels of lead have been confirmed in individuals having a profession in painting[47-50]. Lead is used in paints because of its anti-corrosion properties. Since 1984, the use of lead in paint has been banned in almost all countries of the world. But a quantity of lead in a few countries is still added to the color[11 51]. This also exposes the people working with color to the risk of lead poisoning.

5. Conclusion

This research gives an estimation of the levels of blood lead in exposed workers in Southern Khorasan province, Iran by obtaining the relevant reference values. Based on the findings, there was a significant association between blood lead concentration and age, work experience, work in printing factory and radiator repair workshop. The findings of this study further necessitate taking preventive measures concerning the exposed individuals and show the need for improvement of the existing occupational and environmental exposure regulations.

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Author Contributions:

OM was the overall coordinator. SN, AA, SN, MZ, JAM, AA, HMD, MM, OM were responsible for the design and preparation of the manuscript. SS, AA, MZ, JAM, AA, HMD, MM conducted the data collection. AA designed the study's analytic strategy and helped to the interpretation of the data. SN, OM, AA made substantial contributions in drafting the manuscript and revising it critically for important intellectual content. All authors have read and approved the final version of manuscript

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Ethics approval:

The study has ethics committee approval from Birjand University of Medical Sciences

Competing interests:

The authors declare that they have no conflict of interest.

Patient consent:

Obtained.

Data sharing statement:

No additional data available.

Table 1. Blood lead level in relation to different variables and purpose reference intervals

Group	P10	P25	P50	P75	P90	P95	95%CI (p95)	RV	Mean
Age									
<30years	2.1	2.72	3.7	5.27	12.25	22.43	13.78-31.93	32	5.93
30-45 years	2.1	2.9	3.9	5.9	13.46	21.07	17.4-38.51	39	6.58
>=45 years	2.1	3.2	4.3	8.15	24.4	30.0	23.67-34.5	35	7.9
Work experience									
<10 years	2.1	2.7	3.7	5.45	14.9	28.95	21.71-34.53	35	6.04
10-20 years	2.47	3.02	3.9	6.0	10.23	16.38	10.21-23.45	24	5.55
>=20 years	2.26	2.9	4.0	5.0	12.08	23.36	9.70-38.8	39	6.80
Gender									
Male	2.1	2.9	9.0	11.7	14.34	25.06	19.52-29.59	30	8.48
Female	1.9	5.2	3.9	9.5	13.3	13.3	10.88-13.3	14	6.45
Factory									
Printing factory	2.9	3.22	4.9	15.85	27.45	36.25	23.02-38.5	39	10.65
Tile	2.01	2.7	3.55	4.7	8.79	14.26	9.15-36.94	37	5.22
Mine	2.0	2.3	4.1	8	16.2	24.52	16.2-39.02	40	7.16
Rubber	2.54	3.1	3.9	4.9	7.62	9.46	7.75-17.82	18	4.73
manufacturing	2	2.5	3.3	4.2	7.8	10.3	6.41-20.2	20	4.1
Mechanic	2.7	3.2	4.1	4.7	6.8	19	4.72-19.0	19	4.76
Painter									
Radiator maker	3.72	9.0	23.2	32.4	42.36	42.60	34.78-42.6	43	22.43
Opium use									
Yes	2.8	3.6	5.5	13.82	22.9	26.62	21.06-30.6	31	9.3
No	2.1	2.9	3.85	5.2	12.55	24.95	17.10-30.19	31	6.2
Smoking habit									
Yes	2.14	3.6	4.4	10.4	20.08	30.6	17.95-38.8	39	8.3
No	2.1	2.9	3.9	5.65	12.9	25.12	17.42-29.56	30	6.3

Table 2. Percentile, means and reference values derived for blood lead level according to factory, age and work experience groups

Factory	Age (years)	P10	P25	P50	P75	P90	P95	95%CI(P95)	RV	Mean
Printing factory	<30	2.82	3.0	3.9	16.7	27.04	29.5	19.75-29.5	30	9.82
	30-45	3.3	4.2	6.8	17.87	38.5	38.5	10.31-38.5	39	11.81
	>=45	3.0	3.0	11.1	23.4	23.4	23.4	12.71-23.4	24	12.5
Tilemaking	<30	2.03	2.7	3.4	4.55	7.2	12.66	7.2-25.21	26	4.36
	30-45	1.93	2.27	3.4	5.55	25.47	42.16	10.48-48.4	49	7.38
	>=45	2.1	3.52	4.15	8.45	10.4	10.4	6.88-10.4	11	5.43
Mine	<30	2	2.35	4.1	8.0	11.86	14.68	9.75-15.0	15	5.44
	30-45	2.0	2.3	3.9	7.5	17.72	27.12	16.71-83.5	84	7.79
	>=45	1.55	2.07	4.95	18.2	27.95	31.2	22.63-31.2	32	9.87
Rubber manufacturing	<30	2.13	2.7	3.55	4.1	8.52	35.5	4.84-36.9	37	5.30
	30-45	2.67	3.1	3.9	5.05	7.52	9.63	7.5-17.94	18	4.62
	>=45	2.68	3.15	4.0	4.95	8.12	13.27	5.0-15.4	16	4.62
Mechanics	<30	2.0	2.65	3.6	4.45	10.09	15.08	7.88-20.2	21	4.63
	30-45	1.64	2.4	3.3	4.25	6.36	9.92	4.71-10.3	11	3.68
	>=45	1.5	2.92	3.2	3.9	4.4	4.4	3.59-4.4	5	3.20
Painting	<30	2.75	3.35	3.75	4.62	6.59	6.8	4.62-6.8	7	4.04
	30-45	2.7	2.77	3.4	8.27	19.0	19.0	4.49-19.0	19	6.0
	>=45	4.6	4.6	4.7	4.8	4.8	4.8	4.71-4.8	5	4.7
Radiator making	<30	3.33	3.82	26.4	36.75	42.6	42.6	36.21-42.6	43	22.13
	30-45	8.4	9.5	20.8	28.4	42.0	42.0	24.91-42.0	42	20.68
	>=45	9.0	18.45	26.25	32.92	34.5	34.5	31.07-34.5	35	25.0
Factory	Work experience	P10	P25	P50	P75	P90	P95	95%CI(P95)	RV	Mean
Printing factory	<10	2.9	2.9	14.15	25.4	25.4	25.4	8.22-25.4	26	8.56
	10-20	2.93	3.27	4.9	14.15	27.67	37.15	21.57-38.5	39	10.33
Tile-making	<10	2.0	2.55	3.5	4.7	7.56	13.74	7.36-41.31	42	4.99
	10-20	2.05	2.47	3.15	3.8	9.5	14.5	3.8-14.5	15	3.88
	>=20	2.8	2.8	6.7	19.6	38.8	38.8	12.49-38.8	39	11.83

Mining	<10	1.99	2.2	3.4	6.07	12.25	24.38	11.62-78.83	79	11.84
	10-20	5.56	6.1	10.1	16.2	22.7	26.6	16.96-26.6	27	24.7
Rubber manufacturing	<10	2.79	3.3	3.8	4.12	4.84	32.1	4.50-36.9	37	5.20
	10-20	2.61	3.0	3.85	5.12	7.88	8.83	7.55-17.4	18	4.51
	>=20	2.22	3.0	3.95	4.95	7.79	12.54	5.56-18.0	18	4.57
Mechanics	<10	1.5	1.5	3.3	3.3	4.4	4.4	3.27-4.4	5	3.30
	10-20	2	2.5	3.3	4.12	8.0	10.45	6.77-20.2	21	4.17
Painting	<10	2.7	3.2	4.1	4.7	6.8	19.0	4.72-19.0	20	4.76
Radiator making	<10	3.8	9.0	21.6	33.5	33.5	33.5	25.6-33.5	34	22.47
	10-20	3.66	8.95	25.3	33.45	42.48	42.60	35.46-42.6	43	23.19

Table 3. Parameters of the multiple logistic regression analysis

Variable	B(SE)	OR(95%CI)	p-value
Age	0.02(0.001)	1.02(1.01-1.05)	0.04
Work experience	0.7(0.02)	1.07(1.03-1.13)	0.002
Gender			
Female	Reference		
Male	0.62(0.87)	1.85(0.26-8.15)	0.53
Factory			
Painting	Reference		
Printing factory	2.44(1.12)	11.52(7.26-28.65)	0.03
Tile-making	0.16(1.10)	1.17(0.13-10.24)	0.88
Mine	1.20(1.06)	3.32(0.41-6.36)	0.26
Rubber manufacturing	-1.63(1.20)	0.19(0.02-2.07)	0.17
Mechanics	0.06(1.16)	1.06(0.11-9.44)	0.89
Radiator making	2.56(1.14)	12.93(4.56-34.98)	0.002

Fig 1. Estimation distribution of blood lead level in the occupational exposure to lead

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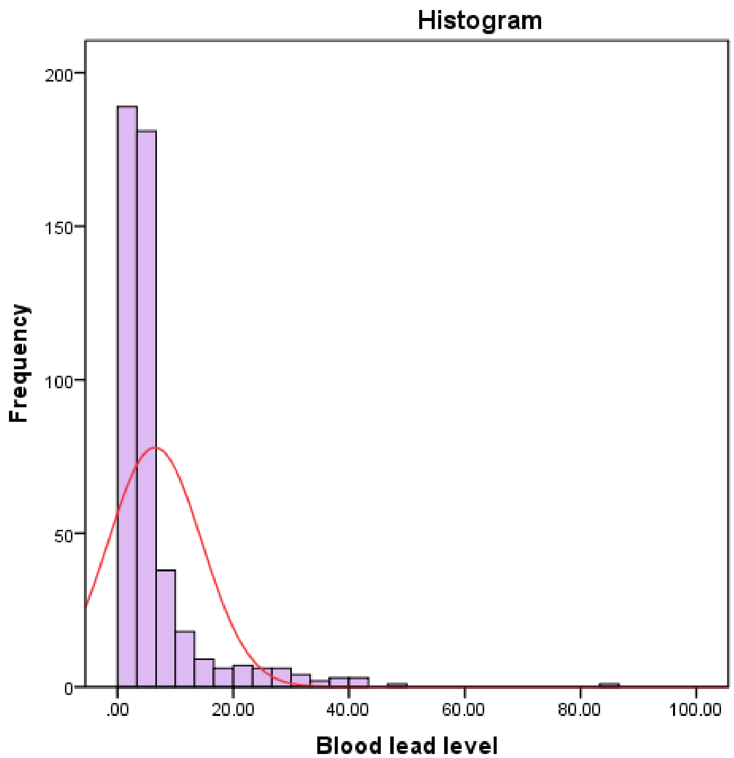

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Elevated blood lead level risk factors and reference value derivation in potentially lead-exposed workers in Iran

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Abstract:

Objective: Lead has extensive industrial uses and well described adverse biologic effects. This exploratory investigation aimed to measure blood lead levels and associated risk factors in exposed workers in Iran, and to derive appropriate reference values for blood lead in this population.

Methods: The study cohort consisted of 630 workers in potentially lead-exposed occupations. Subjects were selected through stratified random sampling. Venous blood samples were assayed by atomic absorption spectroscopy. Measured lead concentrations were described as geometric means: 10th, 25th, 50th, 75th, 90th, and 95th percentiles. To derive reference values, rounded upper limits of the 95% confidence intervals of the 95th percentiles were employed. Data analysis was conducted using Student t-test, Mann-Whitney U, One-way ANOVA, Kruskal-Wallis, Spearman correlation coefficient, and regression analysis

Results: Mean and median blood lead concentration (BLC) were 6.5±8.1 and 3.9 mcg/dL (IQR 2.9-5.8), respectively. Of subjects, 85 (13.5%) had BLC ≥10 mcg/dL. The derived reference BLC value in this study was 30 mcg/dL for men and 14 mcg/dL for women. Increasing work experience and age were associated with BLC >10 mcg/dL. Radiator manufacturers were up to 12.9 times (95%CI 4.6-35; p<0.005) more likely than painters to have BLC >10 mcg/dL.

Conclusion: Mean BLC was above the maximum recommended concentration. There was a significant relationship between higher BLC and age, working in a printing factory, and working on radiator repair. These findings can direct efforts toward reducing occupational lead exposure.

Keywords: blood lead, occupational exposure, reference value, worker, Iran

Strengths and limitations of this study:

- To our knowledge, no current literature reports on reference lead concentrations in Iran, and few studies have been conducted in other countries.
- This study was conducted on suspected lead-exposed workers, and results may not be generalizable to all workers.
- Reference values derived in this study are epidemiologic in nature, and do not imply thresholds for health effects.
- This study used random stratified sampling was used, and generalizability of the results to other populations is limited.
- This study is descriptive, does not test any theory, and provide values that are of use for future research and various public health purposes.

1. Introduction

Lead is a widely-used metal and a persistent poison that is extensively utilized in many industries for its chemical properties [1 2]. The most important risk source for lead poisoning is occupational, as it is used in more than 900 industries including battery and radiator manufacturing, ceramics, plumbing, and paint [3]. Lead exposure is toxic via ingestion, inhalation, or dermal routes [4 5]. Lead poisoning is a significant public health issue in Iran and other countries, and tremendous efforts have been undertaken to reduce occupational exposure in Iran since 1946 [3].

Over the past several decades, government agencies have been progressively lowering the upper blood lead concentration (BLC) limit considered not associated with harm. The United States Centers for Disease Control and Prevention and the National Institute for Occupational Safety and Health now consider BLC >5 mcg/dL in adults elevated. The United States Occupational Safety and Health Administration has emphasized workers with BLC ≥60 mcg/dL should be removed from the occupational exposure until BLC decreases below 40 mcg/dL [6]. Lead poisoning symptoms, although nonspecific in adults, includes short-term memory loss, irritability, depressed mood, paresthesias, poor motor coordination, abdominal pain, headache, and weight loss [3 7] .

In the body, lead distributes to labile soft tissue and stable bone compartments. Lead interferes with the function of numerous proteins and can mimic divalent cations [8]. Adverse effects include neuropathy, kidney damage, anemia, immunocompromise, cognitive impairment, and hypertension [9 10]. There is also conflicting evidence for potential carcinogenicity [2 11]. Due to its various toxic effects, elevated BLC is associated with increased mortality [12 13].

Reference values for a substance in human biological specimens, such as blood, are statistically obtained based on a series of measurements from an appropriately sampled portion of a population of interest. Reference values indicate the upper border of a detected substance in the population. There are numerous methods of deriving reference values, and the abbreviation RV95 was introduced in 2011, referring to rounded values of the upper limits of the 95% confidents intervals (CIs) of the 95th percentiles (14). Although the term reference value often refers to the range of laboratory values considered within a normal range, RV95 reference values in this study were derived as a means of comparing groups, and are not intended for the purpose of interpreting normal ranges for individual.

Given lead poisoning is an ongoing major global public health issue, and since differences in occupational exposure regulations exist between countries, examining blood lead concentrations in varying regions and among occupations can clarify the problem with granularity. The aims of this exploratory study were to measure BLC, its related factors and to identify the reference values in workers probably were exposed to this element in their current job in eastern Iran. This study on BLC in potentially lead-exposed workers can offer valuable reference data stratified by demographic and occupational factors. Given the significance of lead toxicity, it is prudent to implement biological monitoring programs for lead in this occupational population, and results from this study may assist in targeting efforts toward particular occupations.

2. Methodology

This was a cross-sectional study which enrolled 630 adult workers in 2017. Enrollment occurred in Southern Khorasan Province, Iran, of workers in tile manufacturing, radiator manufacturing, rubber production, mining, mechanics, printing, and painting. The study was approved by the university Institutional Review Board. Sample size of 630 total subjects was determined *a priori* based on prior literature, to achieve α 0.05 and β 0.2[14]. Enrollment occurred via stratified random sampling, which divided potential subjects into exclusive subgroups based on occupation, and subjects were randomly selected from each subgroup while taking into consideration of proportions and estimated sample size. (the selected number and frequency of workers in different occupations of Radiator-manufacturing, painting, mechanics, mining, rubber production, tile manufacturing and printing industry were 65(10.3%), 75 (11.9%), 80 (12.7%), 110 (17.5%), 115 (18.2%), 115 (18.2%) and 70 (11.2%), respectively.

Inclusion criteria were: age ≥18 years old, and workers with ≥3 years of experience in one of the potentially lead-exposed occupations. Subjects were not included for known pre-existing conditions (anemia, liver, kidney, neurological, gastrointestinal, or cardiovascular disease) or active treatment of lead poisoning. Written consent was obtained from all subjects.

Age, gender, work experience, cigarette smoking, and history of opium use were collected. Opium use was evaluated as a potential confounding variable given prior literature demonstrating lead contamination of opium[15]. A standardized symptom checklist instrument was utilized by trained study personnel to assess for symptoms of lead toxicity including fatigue, abdominal colic, memory loss, weakness, muscular pain, irritability, constipation, anorexia, and headache. To measure BLC, a 5 mL venous blood sample was obtained and placed on ice, then measured using graphite furnace atomic absorption spectroscopy (PG instrument, AA500FG, UK). The calibration curve was based on ≥5 standard concentrations, utilizing three control samples (Sero Company, Norway). Measurements were performed by trained technicians in the same laboratory, using the same equipment. In cases with elevated BLC >10 mcg/dL, both worker and employer were notified and referred for management.

Data were analyzed using SPSS 19 (IBM Corp, NY, USA). Descriptive indices were reported by group including mean, standard deviation, frequency, quartile, and percentiles of BLC. Reference values in this study were determined based on the rounded upper limits of the 95% confidence intervals of the 95th percentiles.[11 16-20] If the BLC or urine samples of special groups of the community (e g, children, females, and nonsmokers) clearly differs from the general population, reference values should be defined; however, if any significant relationship is observed between age and BLC, reference values are also required for some particular age groups.[17] Since the term "reference value" does not convey its method of derivation, the term RV95 was introduced in 2011 to reduce ambiguity.[11] The Kolmogorov-Smirnov test was used to examine normality of quantitative variables; if data were normally distributed then independent T-test and ANOVA were used, otherwise Mann-Whitney and Kruskal-Wallis tests were performed. Tukey's post-hoc test was used to compare BLC between groups. Multiple logistic regression was used to evaluate the relationship between demographic and occupational variables (type of occupation, duration of work experience) and BLC. P-value <0.05 was considered significant.

Patient and public involvement: Subjects were not involved in the development of the research, study design, conduct, or writing of this study.

3. Results

A total of 630 subjects were enrolled, consisting of tile manufacturing (n 115, 18.2%), radiator manufacturing (n 65, 10.3%), rubber production (n 115, 18.2%) mining (n 110, 17.5%), mechanics (n 80, 12.7%), printing (n 70, 11.2%), and painting (n 75, 11.9%). These workers were enrolled from the among the total employees in each occupation work site: radiator-manufacturing (n 619), painting (n 714), mechanics (n 762), mining (n 1048), rubber manufacturing (1095), tile manufacturing (n 1095), and printing (n 667). There were 585 men (92.8%) and 45 women (7.2%). Mean age of subjects was 36.3±8.0 (range 23-62) years. Mean years of work was 18.7±9.4 (range 5.0-28.0), and mean hours worked per week was 49.9±7.4 (range 14.0-210.0).

The major complaint among subjects was muscular pain (28.7%), followed by headaches (25.7%), irritability (19%), anorexia (14.6%), memory loss (11.4%), and abdominal colic (9.9%). Most subjects reported multiple symptoms. Figure 1 demonstrates the skewed distribution of BLC. The mean BLC was 6.5±8.1 mcg/dL, median 3.9 mcg/dL, and interquartile range (IQR) 2.9-5.8 mcg/dL. 85 (13.5%) subjects had BLC ≥10 mcg/dL, and 545 (86.5%) had BLC <10mcg/dL in participants. Of the participants, 188 (29.8%) and 7 (1.1%) had a BLC higher than 5 and 40 mcg/dL, respectively. The BLC of male subjects was significantly higher than females, with median BLC 9.0 and 3.9 mcg/dL, respectively. In the youngest age group (<30 years) median BLC was 3.7 [IQR: 2.7-5.3] mcg/dL, in the middle-aged group (30-45 years) was 3.9 [IQR: 2.9-5.9] mcg/dL, and in the oldest group (≥45 years) was 4.3 [IQR: 3.2-8.1] mcg/dL. In this study, BLC reference values were 35 mcg/dL for the oldest age group. Those with work experience less than 10 years had median BLC was 3.7 [IQR: 2.7-5.4] mcg/dL, those with work experience from 10 to 20 years had median BLC 3.9 [IQR: 3.02-6.0] mcg/dL, and those with greater than 20 years of work experience had median BLC 4.0 [IQR: 2.9-5.0] mcg/dL.

The Kruskal-Wallis test showed that lead concentrations differed between occupations ($\chi 2$=54.25, p<0.001). In radiator manufacturers, mean BLC was 22.4±13.1 mcg/dL, median 23.2 [IQR: 9.0-32.4] mcg/dL, and RV95 reference value 43 mcg/dL. In a printing factory, median BLC was 4.9 [IQR: 3.2-15.8] mcg/dL with RV95 reference value 39 mcg/dL, which was significantly higher than rubber manufacturing with median 3.9 [IQR: 3.1-4.9] mcg/dL (p=0.004), and mechanics with median 3.3 [IQR: 2.5-4.2] mcg/dL (p=0.003).

The BLC in radiator manufacturers was significantly higher than in other occupations (p<0.001) (Table 1). The BLC RV95 reference values in radiator manufacturers in the youngest (<30years) and intermediate (30-45 years) age groups were 43 and 42 mcg/dL, respectively. Among workers in the printing factory, mechanics, and radiator manufacturers, BLC RV95 reference values increased with longer work experience (Table 2).

Based on the multiple logistic regression adjusting for opium use, cigarette smoking and work experience, higher BLC was significantly correlated with age, printing factory, and radiator manufacturing (Table 3). The results showed that for each year of increasing work experience, the chance for BLC>10 mcg/dL increases by 1.07 times (OR: 1.07, 95%CI: 1.03-1.13, p=0.002). In radiator manufacturers compared to painters, it was 12.93 times more likely to have BLC>10 mcg/dL (OR: 12.93, 95%CI: 4.56-34.98, p-value=0.002). The Hosmer-Lemeshow goodness of fit test was insignificant ($\chi 2$=5.38, df= 8, p-value=0.72). Thus, the null hypothesis claiming the model fit the data well could not be rejected. Cox and Snell's pseudo-R-squared was 30%, which suggests independent variables contributed to predict the BLC>10 mcg/dL.

4. Discussion

This study aimed to explore factors related to elevated BLC in workers in eastern Iran. The results showed mean BLC was 6.5±8.1 mcg/dL (range 1.1-83.5). Mean BLC values were >5 mcg/dL in 29.8%, >10 mcg/dL in 13.5%, and >40 mcg/dL in 1.1% of subjects.

Mean BLC was above the 5 mcg/dL recommended by the Centers for Disease Control and Prevention. Further, the United States Occupational Safety and Health Administration recommend workers with BLC ≥50 (construction) or ≥60 (general industry) be removed from their occupational exposure until BLC below 40 mcg/dL, and this recommendation would apply to a portion of subjects in this study [6].

The RV95s provide a basis for identifying individuals or sub-populations with higher mean BLL. So, Individual with age of 30-45 years, work experience of 20 years or higher, Male gender, Radiator manufacturing workers, opium and cigarettes smokers with 95% confidence have higher mean BLL in comparison with other subgroup individuals.

Predicting factors of higher blood lead concentration using multiple logistic regression analysis after covariation of opium use,cigarette smoking and work experience were Age, and Radiator manufacturing occupation.

A meta-analysis in Iran that investigated 34 studies of occupational lead exposure found mean BLC in Iranian workers was 42.8 mcg/dL (95%CI 50.5-15.4) [21]. The lowest mean BLC occupationally in Iran was 4.98 mcgdL/, and the highest was 96.7 mcg/dL in Tehran in 2004 [22]. Alasia et al. found mean BLC of 190 lead-exposed workers (including welding/metal work, paint/pigment work, radiator repair, battery work, and petrol work) was 50.4±24.6 mcg/dL [23].

Many studies have emphasized the high concentrations of lead in occupationally exposed workers compared with non-occupationally exposed people, including a Nigerian study with mean BLC in exposed workers of 56.3±1.0 mcg/dL versus 30.5±1.4 mcg/dL in controls [24]. BLC in a group of Korean workers was 32.0±15.0 mcg/dL compared with 5.8±1.8 mcg/dL in controls [25]. No prior study has examined BLC reference values in workers in Iran, and the number of studies conducted in other countries are limited. In a Taiwan study, lead reference values in exposed workers were 40 and 30 mcg/dL in men and women, respectively. Reference values in the Czech Republic among non-exposed people were 8 and 5 mcg/dL, respectively, for adult males and females [26]. For potentially carcinogenic agents, or substances with no clearly defined biologic permissible concentration, RV95 may be applied in risk assessment. The German Human Biomonitoring Commission suspended lead concentration threshold values given the lack of evidence establishing safe exposure limits [11]. Inorganic lead compounds were upgraded by the International Agency for Research on Cancer as group 2A (probable carcinogens).

Some other studies based their reference value on different percentiles: such as 97.5th percentile and its 90% CI or the 90th percentile with/without its 95% CI [27-29] However, the definition and operationalization of RVs varies even more, depending on the national study.

The benchmark United States National Health and Nutrition Examination Survey has found decreasing mean BLC's, from 1.65 mcg/dL in 1999-2000 to 0.84 mcg/dL in 2013-14 [30]. Moayedi et al. found BLC was associated with age group [31]. Kim et al. also found mean BLC in people >40 years old was significantly higher than those under 40 [32]. Kuno et al. in Brazil also found older people had 23% higher BLC's [20]. The association between BLC and age has been reported in many other studies, with older people having higher lead concentrations [33 34]. Older people are exposed to more lead during their lifetime, which distributes to both the labile soft tissue and stabile bone compartments [32].

This study found BLC in males was significantly higher than females. This finding is consistent with numerous studies globally [18 33 34]. Potential explanations include occupational differences, or higher estrogen in women may increase lead distribution to the stable bone compartment with subsequent slow release [33 34]. Hemoglobin levels are also generally higher in males, and since lead is measured in whole blood this may contribute to the difference noted in multiple studies [33 34].

This study found, among occupations investigated, that working in radiator manufacturing or printing increases the risk of lead poisoning significantly. Lead poisoning among radiator manufacturers has also been reported prior literature [8 35 36]. Lead-containing solder is commonly used in radiators, and puts workers at risk of inhaling lead fumes and dust [37].

In numerous studies, high BLC has been found in painters [38 39].Lead is used in paints for its anti-corrosion properties, and since 1984 lead in household paint has been banned in most countries. However lead is still used in non-household paint, and regulations in paint vary by country [8 40].

Occupational hygiene practices modify exposure to lead, and are particularly relevant in non-industrialized countries. These practices include poor sanitation, inadequate personal protection such as masks, gloves, and aprons, eating in the workplace or lack of hand washing prior to eating [8]. Further, in developing countries these repair shops and factories are often proximate to residential homes.

5. Conclusion

This research provides an estimation of BLC in occupationally exposed workers in eastern Iran. A significant association was observed between BLC and age, and work in radiator manufacturing or a printing factory. The findings of this study demonstrate the ongoing need for further improvements in occupational regulations and adherence.

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Author Contributions:

OM was the overall coordinator. SN, AA, SN, MZ, JAM, AA, HMD, MM, OM: the study design and drafting of the manuscript. SS, AA, MZ, JAM, AA, HMD, MM: data collection. AA: analytic strategy design and interpretation of the data. SN, OM, AA, and JS: drafting of the manuscript and critically revising for important intellectual content. All authors read and approved the final version of the manuscript

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Table 1. Percentile, means and reference values derived for blood lead level according to different variables using descriptive analysis using descriptive analysis

Group	P10	P25	P50	P75	P90	P95	95%CI	RV95	Mean
Age									
<30 years	2.1	2.7	3.7	5.2	12.2	22.4	13.7-31.9	32	5.9
30-45 years	2.1	2.9	3.9	5.9	13.4	21.1	17.4-38.5	39	6.5
≥45 years	2.1	3.2	4.3	8.1	24.4	30.0	23.6-34.5	35	7.9
Work experience									
<10 years	2.1	2.7	3.7	5.4	14.9	28.9	21.7-34.5	35	6.1
10-20 years	2.4	3.02	3.9	6.0	10.2	16.3	10.2-23.4	24	5.5
≥ 20 years	2.2	2.9	4.0	5.0	12.1	23.3	9.7-38.8	39	6.8
Gender									
Male	2.1	2.9	9.0	11.7	14.3	25.06	19.5-29.5	30	8.4
Female	1.9	5.2	3.9	9.5	13.3	13.3	10.8-13.3	14	6.4
Occupation									
Printing factory	2.9	3.22	4.9	15.8	27.4	36.2	23.02-38.5	39	10.6
Tile manufacturing	2.01	2.7	3.5	4.7	8.7	14.2	9.1-36.9	37	5.2
Mining	2.0	2.3	4.1	8	16.2	24.5	16.2-39.02	40	7.1
Rubber manufacturing	2.5	3.1	3.9	4.9	7.6	9.4	7.7-17.8	18	4.7
Mechanic	2	2.5	3.3	4.2	7.8	10.3	6.4-20.2	20	4.1
Painter	2.7	3.2	4.1	4.7	6.8	19	4.7-19.0	19	4.7
Radiator manufacturing	3.7	9.0	23.2	32.4	42.3	42.60	34.7-42.6	43	22.4
Opium use									
Yes	2.8	3.6	5.5	13.8	22.9	26.6	21.1-30.6	31	9.3
No	2.1	2.9	3.8	5.2	12.5	24.9	17.1-30.1	31	6.2
Cigarette Smoking									
Yes	2.1	3.6	4.4	10.4	20.1	30.6	17.9-38.8	39	8.3
No	2.1	2.9	3.9	5.6	12.9	25.1	17.4-29.5	30	6.3

p10: 10th percentile, 95%CI: 95% confidence interval, RV: reference value

Table 2. Percentile, means and reference values derived for blood lead level according to different occupations stratified by age and work experience using descriptive analysis

Occupation	Age (years)	P10	P25	P50	P75	P90	P95	95%CI	RV95	Mean
Printing factory	<30	2.8	3.0	3.9	16.7	27.0	29.5	19.7-29.5	30	9.8
	30-45	3.3	4.2	6.8	17.8	38.5	38.5	10.3-38.5	39	11.8
	≥45	3.0	3.0	11.1	23.4	23.4	23.4	12.7-23.4	24	12.5
Tile making	<30	2.0	2.7	3.4	4.5	7.2	12.6	7.2-25.2	26	4.3
	30-45	1.9	2.2	3.4	5.5	25.4	42.1	10.4-48.4	49	7.3
	≥45	2.1	3.5	4.1	8.4	10.4	10.4	6.8-10.4	11	5.4
Mining	<30	2	2.3	4.1	8.0	11.8	14.6	9.7-15.0	15	5.4
	30-45	2.0	2.3	3.9	7.5	17.7	27.1	16.7-83.5	84	7.7
	≥45	1.5	2.07	4.9	18.2	27.9	31.2	22.6-31.2	32	9.8
Rubber manufacturing	<30	2.1	2.7	3.5	4.1	8.5	35.5	4.8-36.9	37	5.3
	30-45	2.6	3.1	3.9	5.05	7.5	9.6	7.5-17.9	18	4.6
	≥45	2.6	3.1	4.0	4.9	8.1	13.2	5.0-15.4	16	4.6
Mechanics	<30	2.0	2.6	3.6	4.4	10.1	15.1	7.8-20.2	21	4.6
	30-45	1.6	2.4	3.3	4.2	6.3	9.9	4.7-10.3	11	3.6
	≥45	1.5	2.9	3.2	3.9	4.4	4.4	3.5-4.4	5	3.2
Painting	<30	2.7	3.3	3.7	4.6	6.5	6.8	4.6-6.8	7	4.0
	30-45	2.7	2.7	3.4	8.2	19.0	19.0	4.4-19	19	6.0
	≥45	4.6	4.6	4.7	4.8	4.8	4.8	4.7-4.8	5	4.7
Radiator manufacturing	<30	3.3	3.8	26.4	36.7	42.6	42.6	36.2-42.6	43	22.1
	30-45	8.4	9.5	20.8	28.4	42.0	42.0	24.9-42.0	42	20.6
	≥45	9.0	18.4	26.2	32.9	34.5	34.5	31.07-34.5	35	25.0
Occupation	**Work experience**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**95%CI**	**RV95**	**Mean**
Printing factory	<10	2.9	2.9	14.15	25.4	25.4	25.4	8.2-25.4	26	8.5
	10-20	2.9	3.2	4.9	14.1	27.6	37.1	21.5-38.5	39	10.3
Tile manufacturing	<10	2.0	2.5	3.5	4.7	7.5	13.7	7.3-41.3	42	4.9
	10-20	2.1	2.4	3.15	3.8	9.5	14.5	3.8-14.5	15	3.8
	≥20	2.8	2.8	6.7	19.6	38.8	38.8	12.4-38.8	39	11.8

Mining	<10	1.9	2.2	3.4	6.1	12.2	24.3	11.6-78.8	79	11.8
	10-20	5.5	6.1	10.1	16.2	22.7	26.6	16.9-26.6	27	24.7
Rubber manufacturing	<10	2.7	3.3	3.8	4.1	4.8	32.1	4.5-36.9	37	5.2
	10-20	2.6	3.0	3.8	5.1	7.8	8.8	7.5-17.4	18	4.5
	≥20	2.2	3.0	3.9	4.9	7.7	12.5	5.5-18.0	18	4.5
Mechanics	<10	1.5	1.5	3.3	3.3	4.4	4.4	3.2-4.4	5	3.3
	10-20	2	2.5	3.3	4.1	8.0	10.4	6.7-20.2	21	4.1
Painting	<10	2.7	3.2	4.1	4.7	6.8	19.0	4.7-19.0	20	4.7
Radiator manufacturing	<10	3.8	9.0	21.6	33.5	33.5	33.5	25.6-33.5	34	22.4
	10-20	3.6	8.9	25.3	33.4	42.4	42.6	35.4-42.6	43	23.1

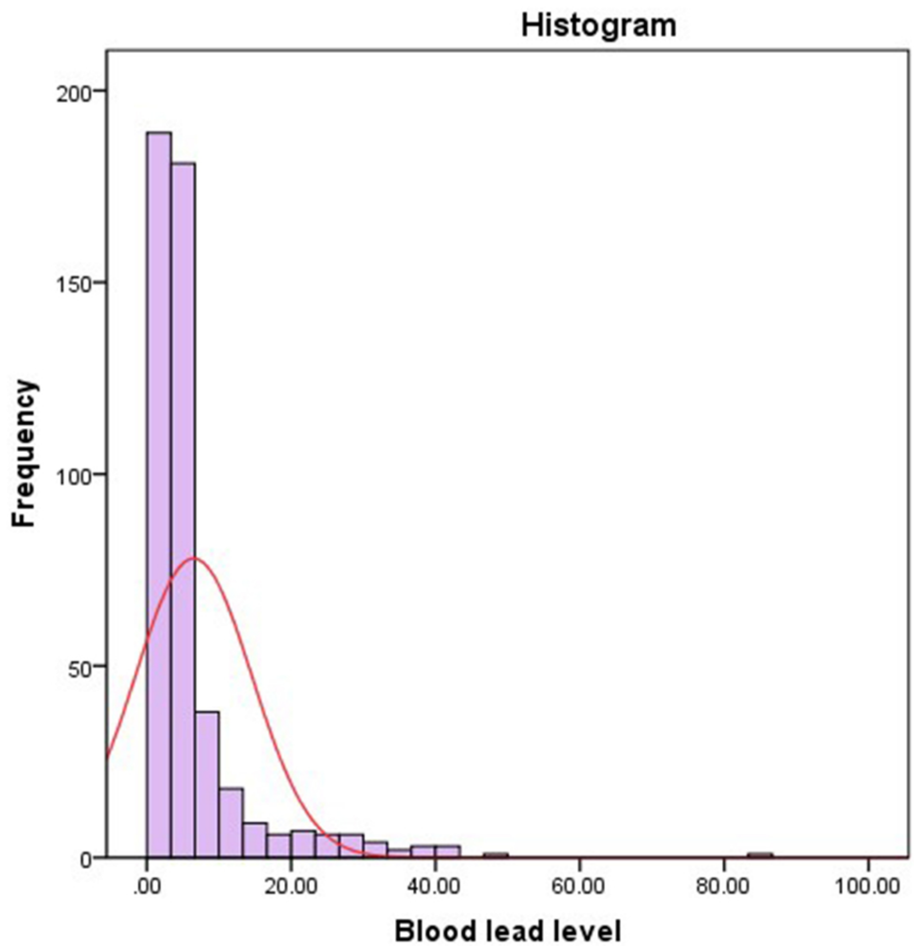
p10: 10th percentile, 95%CI: 95% confidence interval, RV: reference value

Table 3. Predicting factors of higher blood lead concentration using multiple logistic regression analysis after covariation of opium use, cigarette smoking and work experience

Variables	B(SE)	OR(95%CI)	p-value
Age	0.02(0.02)	1.02(0.98-1.05)	0.06
Gender			
Female	Reference		
Male	0.64(0.41)	1.90(0.84-6.13)	0.31
Occupations			
Painting	Reference		
Printing factory	2.21(0.99)	9.11(6.14-18.52)	0.01
Tile-making	0.13(0.89)	1.13(0.54-8.63)	0.58
Mining	0.99(0.71)	2.69(0.74-6.36)	0.11
Rubber manufacturing	-1.74(1.09)	0.17(0.08-1.25)	0.19
Mechanics	0.10(0.95)	1.10(0.45-3.58)	0.56
Radiator making	2.43(1.03)	11.35(5.32-21.35)	0.001

B(SE): coefficient (standard error), OR: odds ratio, 95%CI: confidence interval

Figure 1. Estimated distribution of blood lead level in occupational exposure to lead



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Blood lead level risk factors and reference value derivation in a cross-sectional study of potentially lead-exposed workers in Iran

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Abstract:

Objectives: This exploratory investigation aimed to measure blood lead levels and associated risk factors in exposed workers in Iran, and to derive appropriate reference values for blood lead in this population as a means of epidemiologic comparison

Design: Cross-sectional.

Setting: Manufacturing plants with potential lead-exposure in Southern Khorasan Province, Iran.

Participants: The study included 630 workers, selected through stratified random sampling.

primary and secondary outcome measures: The primary measures in this exploratory were venous blood lead concentrations and associated risk factors of age, gender, work experience, cigarette smoking, and history of opium use. Secondary measures were symptoms associated with lead toxicity. Data analyses were conducted using Student t-test, Mann-Whitney U, One-way ANOVA, Kruskal-Wallis, Spearman correlation coefficient, and regression analysis.

Results: Mean and median blood lead concentration (BLC) were 6.5±8.1 and 3.9 mcg/dL (IQR 2.9-5.8), respectively. Of subjects, 85 (13.5%) had BLC ≥10 mcg/dL. The derived reference BLC value in this study was 30 mcg/dL for men and 14 mcg/dL for women. Increasing work experience and age were associated with BLC >10 mcg/dL. Radiator manufacturers were up to 12.9 times (95%CI 4.6-35; p<0.005) more likely than painters to have BLC >10 mcg/dL. Most subjects reported multiple symptoms.

Conclusions: Mean BLC was above the maximum recommended concentration. There was a significant relationship between higher BLC and age, or working in a printing or radiator. These findings can direct efforts toward reducing occupational lead exposure.

Keywords: blood lead, occupational exposure, reference value, worker, Iran

Strengths and limitations of this study:

- To our knowledge, no current literature reports on reference lead concentrations in Iran, and few studies have been conducted in other countries.
- Generalizability to all workers may be limited by the random stratified sampling method, and by the targeting of suspected lead-exposed industries.
- Reference values derived in this study are epidemiologic in nature, and do not imply thresholds for health effects.
- This study is exploratory and not hypothesis testing. It provides data that are valuable for future research and targeting of occupational public health resources.

1. Introduction

Lead is a widely-used metal and a persistent poison that is extensively utilized in many industries for its chemical properties [1 2]. The most important risk source for lead poisoning is occupational, as it is used in more than 900 industries including battery and radiator manufacturing, ceramics, plumbing, and paint [3]. Lead exposure is toxic via ingestion, inhalation, or dermal routes [4 5]. Lead poisoning is a significant public health issue in Iran and other countries, and tremendous efforts have been undertaken to reduce occupational exposure in Iran since 1946 [3].

Over the past several decades, government agencies have been progressively lowering the upper blood lead concentration (BLC) limit considered not associated with harm. The United States Centers for Disease Control and Prevention and the National Institute for Occupational Safety and Health now consider BLC >5 mcg/dL in adults elevated. The United States Occupational Safety and Health Administration has emphasized workers with BLC ≥60 mcg/dL should be removed from the occupational exposure until BLC decreases below 40 mcg/dL [6]. Lead poisoning symptoms, although nonspecific in adults, includes short-term memory loss, irritability, depressed mood, paresthesias, poor motor coordination, abdominal pain, headache, and weight loss [3 7].

In the body, lead distributes to labile soft tissue and stable bone compartments. Lead interferes with the function of numerous proteins and can mimic divalent cations [8]. Adverse effects include neuropathy, kidney damage, anemia, immunocompromise, cognitive impairment, and hypertension [9 10]. There is also conflicting evidence for potential carcinogenicity [2 11]. Due to its various toxic effects, elevated BLC is associated with increased mortality [12 13].

Reference values for a substance in human biological specimens, such as blood, are statistically obtained based on a series of measurements from an appropriately sampled portion of a population of interest. Reference values indicate the upper border of a detected substance in the population. There are numerous methods of deriving reference values, and the abbreviation RV95 was introduced in 2011, referring to rounded values of the upper limits of the 95% confidents intervals (CIs) of the 95th percentiles (14). Although the term reference value often refers to the range of laboratory values considered within a normal range, RV95 reference values in this study were derived as a means of comparing groups, and are not intended for the purpose of interpreting normal ranges for individual.

Given lead poisoning is an ongoing major global public health issue, and since differences in occupational exposure regulations exist between countries, examining blood lead concentrations in varying regions and among occupations can clarify the problem with granularity. The aims of this exploratory study were to measure BLC, its related factors and to identify the reference values in workers probably were exposed to this element in their current job in eastern Iran. This study on BLC in potentially lead-exposed workers can offer valuable reference data stratified by demographic and occupational factors. Given the significance of lead toxicity, it is prudent to implement biological monitoring programs for lead in this occupational population, and results from this study may assist in targeting efforts toward particular occupations.

2. Methodology

This was a cross-sectional study which enrolled 630 adult workers in 2017. Enrollment occurred in Southern Khorasan Province, Iran, of workers in tile manufacturing, radiator manufacturing, rubber production, mining, mechanics, printing, and painting. The study was approved by the university Institutional Review Board. Sample size of 630 total subjects was determined *a priori* based on prior literature, to achieve α 0.05 and β 0.2[14]. Enrollment occurred via stratified random sampling, which divided potential subjects into exclusive subgroups based on occupation, and subjects were randomly selected from each subgroup while taking into consideration of proportions and estimated sample size. A flowchart of subject enrollment is illustrated in Figure 1. The selected number and frequency of workers in different occupations of Radiator-manufacturing, painting, mechanics, mining, rubber production, tile manufacturing and printing industry were 65 (10.3%), 75 (11.9%), 80 (12.7%), 110 (17.5%), 115 (18.2%), 115 (18.2%) and 70 (11.2%), respectively.

Inclusion criteria were: age ≥18 years old, and workers with ≥3 years of experience in one of the potentially lead-exposed occupations. Subjects were not included for known pre-existing conditions (anemia, liver, kidney, neurological, gastrointestinal, or cardiovascular disease) or active treatment of lead poisoning. Written consent was obtained from all subjects.

Age, gender, work experience, cigarette smoking, and history of opium use were collected. Opium use was evaluated as a potential confounding variable given prior literature demonstrating lead contamination of opium[15]. A standardized symptom checklist instrument was utilized by trained study personnel to assess for symptoms of lead toxicity including fatigue, abdominal colic, memory loss, weakness, muscular pain, irritability, constipation, anorexia, and headache. To measure BLC, a 5 mL venous blood sample was obtained and placed on ice, then measured using graphite furnace atomic absorption spectroscopy (PG instrument, AA500FG, UK). The calibration curve was based on ≥5 standard concentrations, utilizing three control samples (Sero Company, Norway). Measurements were performed by trained technicians in the same laboratory, using the same equipment. In cases with elevated BLC >10 mcg/dL, both worker and employer were notified and referred for management.

Data were analyzed using SPSS 19 (IBM Corp, NY, USA). Descriptive indices were reported by group including mean, standard deviation, frequency, quartile, and percentiles of BLC. Reference values in this study were determined based on the rounded upper limits of the 95% confidence intervals of the 95th percentiles.[11 16-20] If the BLC or urine samples of special groups of the community (e g, children, females, and nonsmokers) clearly differs from the general population, reference values should be defined; however, if any significant relationship is observed between age and BLC, reference values are also required for some particular age groups.[17] Since the term "reference value" does not convey its method of derivation, the term RV95 was introduced in 2011 to reduce ambiguity.[11] The Kolmogorov-Smirnov test was used to examine normality of quantitative variables; if data were normally distributed then independent T-test and ANOVA were used, otherwise Mann-Whitney and Kruskal-Wallis tests were performed. Tukey's post-hoc test was used to compare BLC between groups. Multiple logistic regression was used to evaluate the relationship between demographic and occupational variables (type of occupation, duration of work experience) and BLC. P-value <0.05 was considered significant.

Patient and public involvement: Subjects were not involved in the development of the research, study design, conduct, or writing of this study.

3. Results

A total of 630 subjects were enrolled, consisting of tile manufacturing (n 115, 18.2%), radiator manufacturing (n 65, 10.3%), rubber production (n 115, 18.2%) mining (n 110, 17.5%), mechanics (n 80, 12.7%), printing (n 70, 11.2%), and painting (n 75, 11.9%). These workers were enrolled from the among the total employees in each occupation work site: radiator-manufacturing (n 619), painting (n 714), mechanics (n 762), mining (n 1048), rubber manufacturing (1095), tile manufacturing (n 1095), and printing (n 667). There were 585 men (92.8%) and 45 women (7.2%). Mean age of subjects was 36.3±8.0 (range 23-62) years. Mean years of work was 18.7±9.4 (range 5.0-28.0), and mean hours worked per week was 49.9±7.4 (range 14.0-210.0).

The major complaint among subjects was muscular pain (28.7%), followed by headaches (25.7%), irritability (19%), anorexia (14.6%), memory loss (11.4%), and abdominal colic (9.9%). Most subjects reported multiple symptoms. Figure 2 demonstrates the skewed distribution of BLC. The mean BLC was 6.5±8.1 mcg/dL, median 3.9 mcg/dL, and interquartile range (IQR) 2.9-5.8 mcg/dL. 85 (13.5%) subjects had BLC ≥10 mcg/dL, and 545 (86.5%) had BLC <10mcg/dL in participants. Of the participants, 188 (29.8%) and 7 (1.1%) had a BLC higher than 5 and 40 mcg/dL, respectively. The BLC of male subjects was significantly higher than females, with median BLC 9.0 and 3.9 mcg/dL, respectively. In the youngest age group (<30 years) median BLC was 3.7 [IQR: 2.7-5.3] mcg/dL, in the middle-aged group (30-45 years) was 3.9 [IQR: 2.9-5.9] mcg/dL, and in the oldest group (≥45 years) was 4.3 [IQR: 3.2-8.1] mcg/dL. In this study, BLC reference values were 35 mcg/dL for the oldest age group. Those with work experience less than 10 years had median BLC was 3.7 [IQR: 2.7-5.4] mcg/dL, those with work experience from 10 to 20 years had median BLC 3.9 [IQR: 3.02-6.0] mcg/dL, and those with greater than 20 years of work experience had median BLC 4.0 [IQR: 2.9-5.0] mcg/dL.

The Kruskal-Wallis test showed that lead concentrations differed between occupations ($\chi2=54.25$, $p<0.001$). In radiator manufacturers, mean BLC was 22.4±13.1 mcg/dL, median 23.2 [IQR: 9.0-32.4] mcg/dL, and RV95 reference value 43 mcg/dL. In a printing factory, median BLC was 4.9 [IQR: 3.2-15.8] mcg/dL with RV95 reference value 39 mcg/dL, which was significantly higher than rubber manufacturing with median 3.9 [IQR: 3.1-4.9] mcg/dL ($p=0.004$), and mechanics with median 3.3 [IQR: 2.5-4.2] mcg/dL ($p=0.003$).

The BLC in radiator manufacturers was significantly higher than in other occupations ($p<0.001$) (Table 1). The BLC RV95 reference values in radiator manufacturers in the youngest (<30years) and intermediate (30-45 years) age groups were 43 and 42 mcg/dL, respectively. Among workers in the printing factory, mechanics, and radiator manufacturers, BLC RV95 reference values increased with longer work experience (Table 2).

Based on the multiple logistic regression adjusting for opium use, cigarette smoking and work experience, higher BLC was significantly correlated with age, printing factory, and radiator manufacturing (Table 3). The results showed that for each year of increasing work experience, the chance for BLC>10 mcg/dL increases by 1.07 times (OR: 1.07, 95%CI: 1.03-1.13, p=0.002). In radiator manufacturers compared to painters, it was 12.93 times more likely to have BLC>10 mcg/dL (OR: 12.93, 95%CI: 4.56-34.98, p-value=0.002). The Hosmer-Lemeshow goodness of fit test was insignificant ($\chi2$=5.38, df= 8, p-value=0.72). Thus, the null hypothesis claiming the model fit the data well could not be rejected. Cox and Snell's pseudo-R-squared was 30%, which suggests independent variables contributed to predict the BLC>10 mcg/dL.

4. Discussion

This study aimed to explore factors related to elevated BLC in workers in eastern Iran. The results showed mean BLC was 6.5±8.1 mcg/dL (range 1.1-83.5). Mean BLC values were >5 mcg/dL in 29.8%, >10 mcg/dL in 13.5%, and >40 mcg/dL in 1.1% of subjects.

Mean BLC was above the 5 mcg/dL recommended by the Centers for Disease Control and Prevention. Further, the United States Occupational Safety and Health Administration recommend workers with BLC ≥50 (construction) or ≥60 (general industry) be removed from their occupational exposure until BLC below 40 mcg/dL, and this recommendation would apply to a portion of subjects in this study [6].

The RV95s provide a basis for identifying individuals or sub-populations with higher mean BLL. So, Individual with age of 30-45 years, work experience of 20 years or higher, Male gender, Radiator manufacturing workers, opium and cigarettes smokers with 95% confidence have higher mean BLL in comparison with other subgroup individuals.

Predicting factors of higher blood lead concentration using multiple logistic regression analysis after covariation of opium use, cigarette smoking and work experience were Age, and Radiator manufacturing occupation.

A meta-analysis in Iran that investigated 34 studies of occupational lead exposure found mean BLC in Iranian workers was 42.8 mcg/dL (95%CI 50.5-15.4) [21]. The lowest mean BLC occupationally in Iran was 4.98 mcgdL/, and the highest was 96.7 mcg/dL in Tehran in 2004 [22]. Alasia et al. found mean BLC of 190 lead-exposed workers (including welding/metal work, paint/pigment work, radiator repair, battery work, and petrol work) was 50.4±24.6 mcg/dL [23].

Many studies have emphasized the high concentrations of lead in occupationally exposed workers compared with non-occupationally exposed people, including a Nigerian study with mean BLC in exposed workers of 56.3±1.0 mcg/dL versus 30.5±1.4 mcg/dL in controls [24]. BLC in a group of Korean workers was 32.0±15.0 mcg/dL compared with 5.8±1.8 mcg/dL in controls [25]. No prior study has examined BLC reference values in workers in Iran, and the number of studies conducted in other countries are limited. In a Taiwan study, lead reference values in exposed workers were 40 and 30 mcg/dL in men and women, respectively. Reference values in the Czech Republic among non-exposed people were 8 and 5 mcg/dL, respectively, for adult males and females [26]. For potentially carcinogenic agents, or substances with no clearly defined biologic permissible concentration, RV95 may be applied in risk assessment. The German Human Biomonitoring Commission suspended lead concentration threshold values given the lack of evidence establishing safe exposure limits [11]. Inorganic lead compounds were upgraded by the International Agency for Research on Cancer as group 2A (probable carcinogens).

Some other studies based their reference value on different percentiles: such as 97.5th percentile and its 90% CI or the 90th percentile with/without its 95% CI [27-29] However, the definition and operationalization of RVs varies even more, depending on the national study.

The benchmark United States National Health and Nutrition Examination Survey has found decreasing mean BLC's, from 1.65 mcg/dL in 1999-2000 to 0.84 mcg/dL in 2013-14 [30]. Moayedi et al. found BLC was associated with age group [31]. Kim et al. also found mean BLC in people >40 years old was significantly higher than those under 40 [32]. Kuno et al. in Brazil also found older people had 23% higher BLC's [20]. The association between BLC and age has been reported in many other studies, with older people having higher lead concentrations [33 34]. Older people are exposed to more lead during their lifetime, which distributes to both the labile soft tissue and stabile bone compartments [32].

This study found BLC in males was significantly higher than females. This finding is consistent with numerous studies globally [18 33 34]. Potential explanations include occupational differences, or higher estrogen in women may increase lead distribution to the stable bone compartment with subsequent slow release [33 34]. Hemoglobin levels are also generally higher in males, and since lead is measured in whole blood this may contribute to the difference noted in multiple studies [33 34].

This study found, among occupations investigated, that working in radiator manufacturing or printing increases the risk of lead poisoning significantly. Lead poisoning among radiator manufacturers has also been reported prior literature [8 35 36]. Lead-containing solder is commonly used in radiators, and puts workers at risk of inhaling lead fumes and dust [37].

In numerous studies, high BLC has been found in painters [38 39].Lead is used in paints for its anti-corrosion properties, and since 1984 lead in household paint has been banned in most countries. However lead is still used in non-household paint, and regulations in paint vary by country [8 40].

Occupational hygiene practices modify exposure to lead, and are particularly relevant in non-industrialized countries. These practices include poor sanitation, inadequate personal protection such as masks, gloves, and aprons, eating in the workplace or lack of hand washing prior to eating [8]. Further, in developing countries these repair shops and factories are often proximate to residential homes.

5. Conclusion

This research provides an estimation of BLC in occupationally exposed workers in eastern Iran. A significant association was observed between BLC and age, and work in radiator manufacturing or a printing factory. The findings of this study demonstrate the ongoing need for further improvements in occupational regulations and adherence.

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Table 1. Percentile, means and reference values derived for blood lead level according to different variables using descriptive analysis using descriptive analysis

Group	P10	P25	P50	P75	P90	P95	95%CI	RV95	Mean
Age									
<30 years	2.1	2.7	3.7	5.2	12.2	22.4	13.7-31.9	32	5.9
30-45 years	2.1	2.9	3.9	5.9	13.4	21.1	17.4-38.5	39	6.5
≥45 years	2.1	3.2	4.3	8.1	24.4	30.0	23.6-34.5	35	7.9
Work experience									
<10 years	2.1	2.7	3.7	5.4	14.9	28.9	21.7-34.5	35	6.1
10-20 years	2.4	3.02	3.9	6.0	10.2	16.3	10.2-23.4	24	5.5
≥ 20 years	2.2	2.9	4.0	5.0	12.1	23.3	9.7-38.8	39	6.8
Gender									
Male	2.1	2.9	9.0	11.7	14.3	25.06	19.5-29.5	30	8.4
Female	1.9	5.2	3.9	9.5	13.3	13.3	10.8-13.3	14	6.4
Occupation									
Printing factory	2.9	3.22	4.9	15.8	27.4	36.2	23.02-38.5	39	10.6
Tile manufacturing	2.01	2.7	3.5	4.7	8.7	14.2	9.1-36.9	37	5.2
Mining	2.0	2.3	4.1	8	16.2	24.5	16.2-39.02	40	7.1
Rubber manufacturing	2.5	3.1	3.9	4.9	7.6	9.4	7.7-17.8	18	4.7
Mechanic	2	2.5	3.3	4.2	7.8	10.3	6.4-20.2	20	4.1
Painter	2.7	3.2	4.1	4.7	6.8	19	4.7-19.0	19	4.7
Radiator manufacturing	3.7	9.0	23.2	32.4	42.3	42.60	34.7-42.6	43	22.4
Opium use									
Yes	2.8	3.6	5.5	13.8	22.9	26.6	21.1-30.6	31	9.3
No	2.1	2.9	3.8	5.2	12.5	24.9	17.1-30.1	31	6.2
Cigarette Smoking									
Yes	2.1	3.6	4.4	10.4	20.1	30.6	17.9-38.8	39	8.3
No	2.1	2.9	3.9	5.6	12.9	25.1	17.4-29.5	30	6.3

p10: 10^{th} percentile, 95%CI: 95% confidence interval, RV: reference value

Table 2. Percentile, means and reference values derived for blood lead level according to different occupations stratified by age and work experience using descriptive analysis

Occupation	Age (years)	P10	P25	P50	P75	P90	P95	95%CI	RV95	Mean
Printing factory	<30	2.8	3.0	3.9	16.7	27.0	29.5	19.7-29.5	30	9.8
	30-45	3.3	4.2	6.8	17.8	38.5	38.5	10.3-38.5	39	11.8
	≥45	3.0	3.0	11.1	23.4	23.4	23.4	12.7-23.4	24	12.5
Tile making	<30	2.0	2.7	3.4	4.5	7.2	12.6	7.2-25.2	26	4.3
	30-45	1.9	2.2	3.4	5.5	25.4	42.1	10.4-48.4	49	7.3
	≥45	2.1	3.5	4.1	8.4	10.4	10.4	6.8-10.4	11	5.4
Mining	<30	2	2.3	4.1	8.0	11.8	14.6	9.7-15.0	15	5.4
	30-45	2.0	2.3	3.9	7.5	17.7	27.1	16.7-83.5	84	7.7
	≥45	1.5	2.07	4.9	18.2	27.9	31.2	22.6-31.2	32	9.8
Rubber manufacturing	<30	2.1	2.7	3.5	4.1	8.5	35.5	4.8-36.9	37	5.3
	30-45	2.6	3.1	3.9	5.05	7.5	9.6	7.5-17.9	18	4.6
	≥45	2.6	3.1	4.0	4.9	8.1	13.2	5.0-15.4	16	4.6
Mechanics	<30	2.0	2.6	3.6	4.4	10.1	15.1	7.8-20.2	21	4.6
	30-45	1.6	2.4	3.3	4.2	6.3	9.9	4.7-10.3	11	3.6
	≥45	1.5	2.9	3.2	3.9	4.4	4.4	3.5-4.4	5	3.2
Painting	<30	2.7	3.3	3.7	4.6	6.5	6.8	4.6-6.8	7	4.0
	30-45	2.7	2.7	3.4	8.2	19.0	19.0	4.4-19	19	6.0
	≥45	4.6	4.6	4.7	4.8	4.8	4.8	4.7-4.8	5	4.7
Radiator manufacturing	<30	3.3	3.8	26.4	36.7	42.6	42.6	36.2-42.6	43	22.1
	30-45	8.4	9.5	20.8	28.4	42.0	42.0	24.9-42.0	42	20.6
	≥45	9.0	18.4	26.2	32.9	34.5	34.5	31.07-34.5	35	25.0
Occupation	**Work experience**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**95%CI**	**RV95**	**Mean**
Printing factory	<10	2.9	2.9	14.15	25.4	25.4	25.4	8.2-25.4	26	8.5
	10-20	2.9	3.2	4.9	14.1	27.6	37.1	21.5-38.5	39	10.3
Tile manufacturing	<10	2.0	2.5	3.5	4.7	7.5	13.7	7.3-41.3	42	4.9
	10-20	2.1	2.4	3.15	3.8	9.5	14.5	3.8-14.5	15	3.8
	≥20	2.8	2.8	6.7	19.6	38.8	38.8	12.4-38.8	39	11.8

Mining	<10	1.9	2.2	3.4	6.1	12.2	24.3	11.6-78.8	79	11.8
	10-20	5.5	6.1	10.1	16.2	22.7	26.6	16.9-26.6	27	24.7
Rubber manufacturing	<10	2.7	3.3	3.8	4.1	4.8	32.1	4.5-36.9	37	5.2
	10-20	2.6	3.0	3.8	5.1	7.8	8.8	7.5-17.4	18	4.5
	≥20	2.2	3.0	3.9	4.9	7.7	12.5	5.5-18.0	18	4.5
Mechanics	<10	1.5	1.5	3.3	3.3	4.4	4.4	3.2-4.4	5	3.3
	10-20	2	2.5	3.3	4.1	8.0	10.4	6.7-20.2	21	4.1
Painting	<10	2.7	3.2	4.1	4.7	6.8	19.0	4.7-19.0	20	4.7
Radiator manufacturing	<10	3.8	9.0	21.6	33.5	33.5	33.5	25.6-33.5	34	22.4
	10-20	3.6	8.9	25.3	33.4	42.4	42.6	35.4-42.6	43	23.1

p10: 10th percentile, 95%CI: 95% confidence interval, RV: reference value

Table 3. Predicting factors of higher blood lead concentration using multiple logistic regression analysis after covariation of opium use, cigarette smoking and work experience

Variables	B(SE)	OR(95%CI)	p-value
Age	0.02(0.02)	1.02(0.98-1.05)	0.06
Gender			
Female	Reference		
Male	0.64(0.41)	1.90(0.84-6.13)	0.31
Occupations			
Painting	Reference		
Printing factory	2.21(0.99)	9.11(6.14-18.52)	0.01
Tile-making	0.13(0.89)	1.13(0.54-8.63)	0.58
Mining	0.99(0.71)	2.69(0.74-6.36)	0.11
Rubber manufacturing	-1.74(1.09)	0.17(0.08-1.25)	0.19
Mechanics	0.10(0.95)	1.10(0.45-3.58)	0.56
Radiator making	2.43(1.03)	11.35(5.32-21.35)	0.001

B(SE): coefficient (standard error), OR: odds ratio, 95%CI: confidence interval

Figure 1. Flow diagram of subject enrollment.

Figure 2. Estimated distribution of blood lead level in occupational exposure to lead.

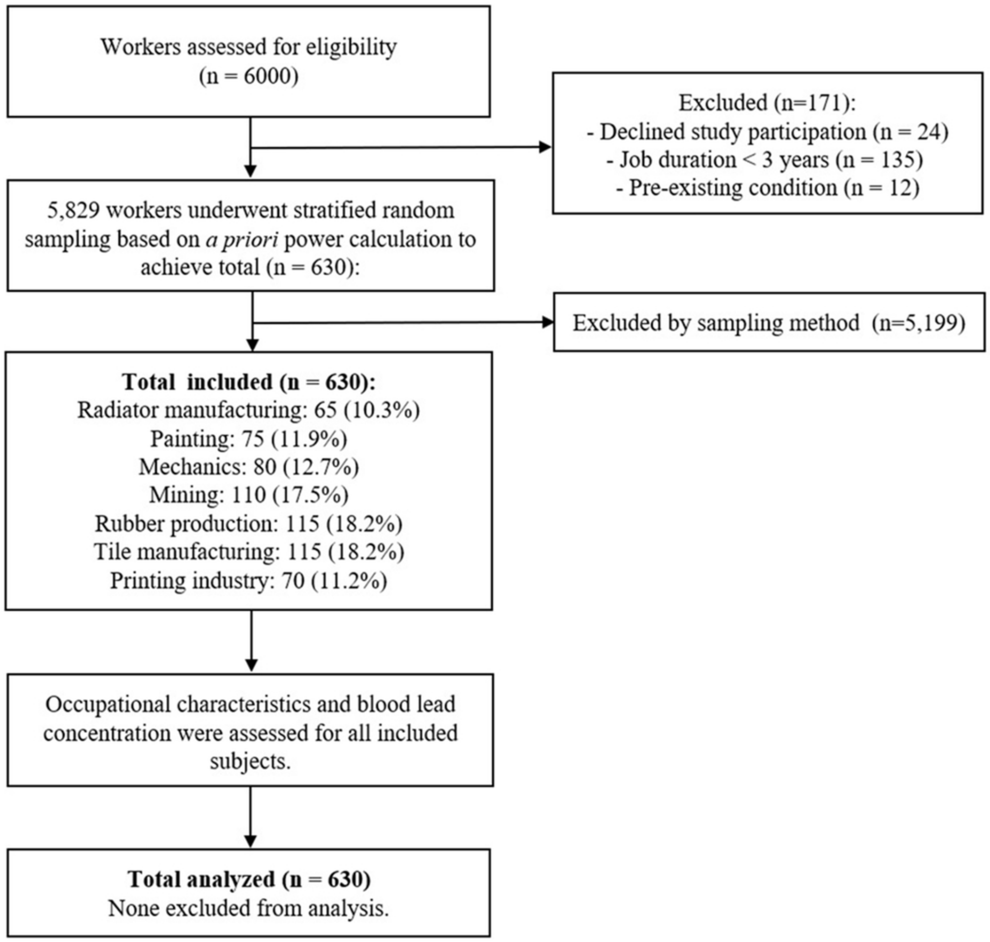

Figure 1. Flow diagram of subject enrollment.

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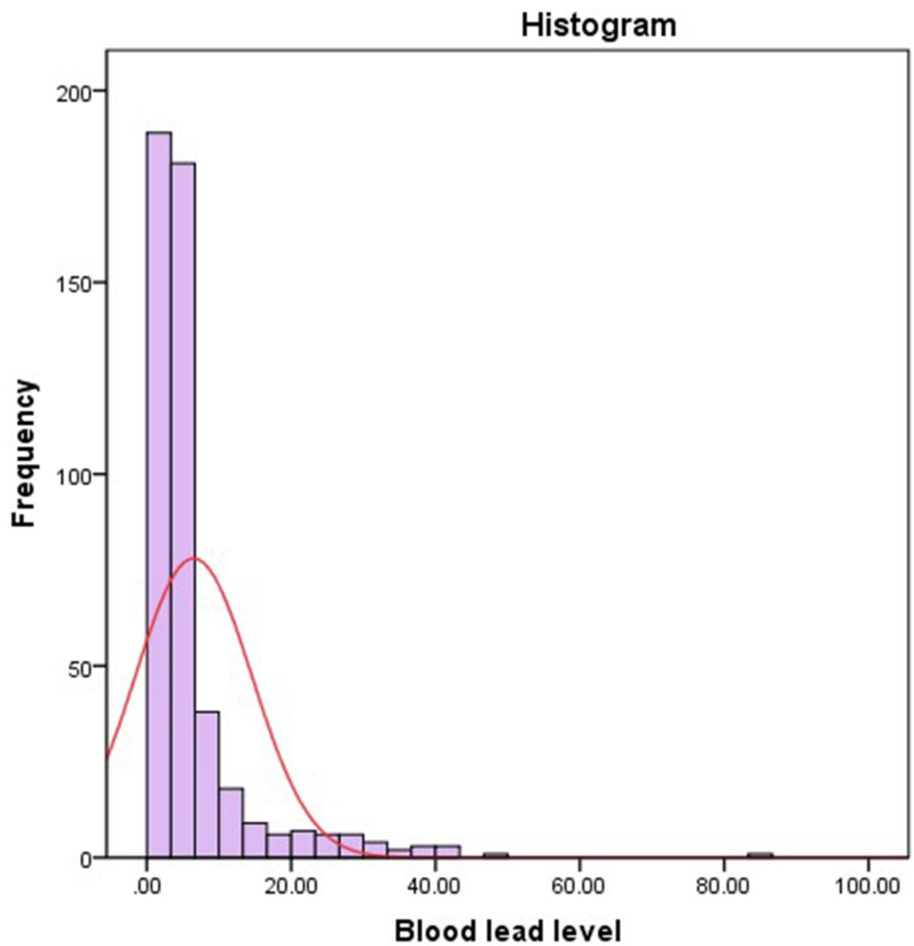

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5,6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	22
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	22
		(c) Consider use of a flow diagram	22
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	22
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9

		(*b*) Report category boundaries when continuous variables were categorized	8,9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	3
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.