Letter to the Editor

Heavy Metal Assessment among Chinese Nonferrous Metal-exposed Workers from the Jinchang Cohort Study*

YANG Ai Min[1,2], CHENG Zhi Yuan[3], PU Hong Quan[4], CHENG Ning[5], LI Hai Yan[4], LIU Si Min[2], DING Jiao[4], LI Juan Sheng[1], HU Xiao Bin[1], REN Xiao Wei[1], ZHENG Tong Zhang[2,#], and BAI Ya Na[1,#]

Environmental exposure to heavy metals has been linked to a wide range of human health hazards. We detected the levels of 15 metals in urine samples from 500 representative sub-samples in an ongoing occupational cohort study (Jinchang Cohort) to directly evaluate metal exposure levels. Fifteen metals, namely As, Ba, Be, Cd, Cs, Cr, Co, Cu, Pb, Mn, Ni, Se, Tl, U, and Zn, were detected by inductively coupled plasma quadruple mass spectrometry. The results showed that median creatinine adjustment and geometric mean urinary metal levels were higher in the heavy metal-exposed group, except Se and Zn, than other reported general or occupational populations. Further studies should address the effects of heavy metals on human health.

China has become the largest producer and consumer of heavy metals in the world due to rapid industrialization and urbanization[1]. A large quantity of metals has been released into the environment and has had significant health implications for occupational workers; however, limited urinary metal reference data are available for metal-exposed workers. We have established a prospective cohort study among metal-exposed workers called the China Metal-exposed Workers Cohort Study (Jinchang Cohort)[2] for the purpose of evaluating the association between metal exposure and various health outcomes. In the present study, we detected levels of 15 metals in urine samples from a representative sub-sample of 500 subjects in the Jinchang Cohort to evaluate metal exposure levels among occupational workers.

A total of 500 participants working in the Jinchang nonferrous metal industry for at least 1 year were selected from the Jinchang Cohort to participate in this study. They were occupationally exposed to nickel, copper, cobalt, and other metals from various production processes, including mining, concentrating, smelting and metallurgy. These 500 workers were between the ages of 20 and 50 years and included three subgroups based on their occupation, including management and service workers, chemical and metal products manufacturing workers, and mining/smelting/refining workers.

Spot urine specimens were collected in cryogenic tubes, stored at -40 °C, and then shipped on dry ice to the Public Health School of Lanzhou University. The levels of 15 heavy metals were measured by inductively coupled plasma mass spectrometry (Thermo Scientific, Rockford, IL, USA): arsenic (As), barium (Ba), beryllium (Be), cadmium (Cd), cesium (Cs), chromium (Cr), cobalt (Co), copper (Cu), lead (Pb), manganese (Mn), nickel (Ni), selenium (Se), thallium (Tl), uranium (U), and zinc (Zn). All urine samples were completely thawed at room temperature and homogenized. Each 1 mL sample was mixed with 3.0% HNO_3 to a final volume of 2.5 mL for overnight nitrification[3]. The standard human urine reference (SRM2670A; National Institute of Standards and Technology, Gaithersburg, MD, USA) was used as an external quality control, and sample spike recoveries were used to confirm analytical recovery, which was 95%. The intra-day and inter-day coefficients of variation were ±5%.

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1. Institute of Epidemiology and Statistics, School of Public Health, Lanzhou University, Lanzhou 730000, Gansu, China; 2. Department of Epidemiology, School of Public Health, Brown University, Providence, RI 02906, USA; 3. Evidence-Based Medicine Center and Key Laboratory of Evidence Based Medicine and Knowledge Translation of Gansu Province, College of Basic Medicine, Lanzhou University, Lanzhou 730000, Gansu, China; 4. Workers' Hospital of Jinchuan Group Co., Ltd., Jinchang 737100, Gansu, China; 5. Center of Medical Laboratory of Basic Medicine College, Lanzhou University, Lanzhou 730000, Gansu, China

Urinary metal concentrations were log-transformed prior to data analysis. Descriptive statistical parameters were computed initially. We replaced the metal concentrations below the limit of detection (LOD) with LOD/2. An agglomerative hierarchical cluster analysis based on the average linkage method and a correlation matrix were also prepared. All analyses were conducted using SAS software ver. 9.4 (SAS Institute, Cary, NC, USA).

Table 1 shows the urinary metal levels of the 500 subsamples in the Jinchang Cohort study. The table shows the LODs and the proportion of results below the LOD, arithmetic (AM) and geometric mean (GM) concentrations, and median and selected percentiles. The LODs were in the range of 0.0002 μg/L (for U) to 0.1391 μg/L (for Zn) calculated from undiluted urine. All urinary metal levels, except that of Be, were higher than the LODs. The GM, AM, and median levels of urinary As were 54.68, 118.05, and 46.30 μg/g creatinine, respectively. The corresponding urinary Ni levels were 4.27, 7.21, and 3.97 μg/g creatinine, respectively. The GM values of urinary Cd, Cr, Co, Cu, Pb, Mn, and Zn were 0.53, 0.91, 0.56, 12.17, 4.06, 1.71, and 249.76 μg/g creatinine, respectively.

Inter-metal relationships provide information on metal sources and pathways. The results obtained by cluster analysis are also presented with a dendrogram where the distance axis represents the degree of association of the between-group variables (Figure 1). Many of the metals, except Be, correlated with each other. Strong positive correlations were found between Ba and Mn, Ni and Co, and Cr and Cu with Pb ($P \le 0.05$).

We compared the urinary heavy metal levels among occupational workers in the cohort with Chinese, US, and Canadian general populations, as well as Chinese coke oven workers (Table 2). The median urinary As level in nonferrous metal workers was approximately two times higher than that of the Chinese general population (65.158 *vs.* 28.434 μg/L) and 10-fold higher than levels in the Canada general population (65.158 *vs.* 11.67 μg/L). Arsenic exposure from As dust was the largest source for metal-exposed workers, which usually originates from copper and other metal smelting. The creatinine adjusted median values for Pb were about 14 times higher than those in the US general population. The GM value was also about eight-fold higher than that in the US, Canadian, and German populations[3]. Higher As and Pb levels have been found in metal-exposed workers in the Jinchang Cohort, compared with those of general and occupational populations.

The GM values for Cd were slightly higher than those in the US and Canadian populations. The 95th percentiles for urinary Cd levels in these occupational workers were less than the Occupational Safety & Health Administration (OSHA) standards (1.60 *vs.* 3.00 μg/g creatinine)[4]. The creatinine corrected median

Table 1. Creatinine Adjusted Geometric, Arithmetic Means, and Selected Percentiles of Urinary Metal Levels for Chinese Nonferrous Metal-exposed Workers (μg/g creatinine)

Metal	LOD* (% < LOD)	Geometric Mean (95% *CI*)	Arithmetic Mean (95% *CI*)	Standard Deviation	Selected Percentiles				
					5th	25th	50th	75th	95th
As	0.0182 (0.0)	54.68 (49.92-59.88)	118.05 (88.45-147.66)	336.92	13.38	26.68	46.30	93.20	403.71
Ba	0.0119 (0.0)	2.69 (2.52-2.87)	3.78 (3.29-4.27)	5.56	0.87	1.61	2.52	4.07	9.99
Be	0.0327 (27.4)	0.07 (0.06-0.08)	0.134 (0.12-0.147)	0.15	0.01	0.03	0.08	0.18	0.45
Cd	0.0007 (0.0)	0.53 (0.51-0.56)	0.65 (0.61-0.69)	0.47	0.20	0.35	0.50	0.79	1.60
Cs	0.0004 (0.0)	6.33 (6.15-6.51)	6.69 (6.48-6.90)	2.42	3.66	5.10	6.26	7.77	10.80
Cr	0.0106 (0.0)	0.91 (0.86-0.95)	1.15 (1.04-1.27)	1.31	0.41	0.61	0.81	1.23	2.75
Co	0.0020 (0.0)	0.56 (0.52-0.60)	0.78 (0.71-0.85)	0.77	0.19	0.30	0.49	0.97	2.41
Cu	0.0688 (0.0)	12.17 (11.68-12.69)	14.30 (12.82-15.77)	16.76	6.66	8.93	11.42	15.27	27.98
Pb	0.0063 (0.0)	4.06 (3.86-4.26)	4.82 (4.50-5.14)	3.65	1.82	2.83	3.81	5.50	10.89
Mn	0.0080 (0.0)	1.71 (1.60-1.82)	2.50 (2.19-2.82)	3.63	0.62	1.02	1.54	2.47	6.84
Ni	0.0475 (0.0)	4.27 (3.97-4.60)	7.21 (5.75-8.67)	16.61	1.26	2.46	3.97	6.63	16.62
Se	0.0636 (0.0)	18.47 (17.99-18.96)	19.484 (18.68-20.29)	9.20	11.91	15.30	18.28	21.62	30.83
Tl	0.0003 (0.0)	0.41 (0.40-0.43)	0.46 (0.44-0.48)	0.25	0.20	0.31	0.41	0.54	0.88
U	0.0002 (0.0)	0.09 (0.08-0.09)	0.139 (0.09-0.19)	0.61	0.04	0.06	0.08	0.12	0.24
Zn	0.1391 (0.0)	249.76 (237.25-262.34)	290.76 (276.04-305.47)	167.50	95.22	183.31	257.37	369.61	581.10

Note. * LOD: limit of detection.

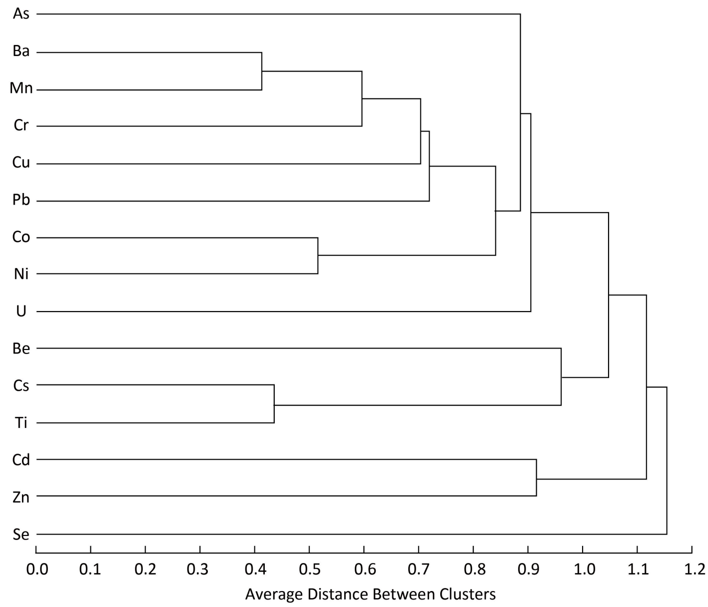

Figure 1. Dendrogram derived from the hierarchical cluster analysis of urinary heavy metals. The *x*-axis represents the degree of association for the between-group variables. The lower the value on the axis, the more significant the association.

Table 2. Comparison of Urinary Metal Levels from Chinese Nonferrous Metal Exposed Workers and other Reported Populations

Metals	Median							Geometric Mean				
	Creatinine-unadjusted (μg/L)			Creatinine-adjusted (μg/g)				Creatinine-unadjusted (μg/L)		Creatinine-adjusted (μg/g)		
	This Study (*n* = 500)	General Population[a] (*n* = 2,242)	Reference	This Study	Coke Oven Workers[b] (*n* = 1,493)	General Population[a] (*n* = 2,242)	Reference	This Study	Reference	This Study	Coke Oven Workers	Reference
As	65.158	28.434	6.09[c]/11.67[d]	46.298	2.80	2.474	6.52[c]/13.07[d]	75.44	7.09[c]/12.00[d]	54.68	2.98	8.04[c]/14.24[d]
Ba	3.427	3.775	1.19[c]/0.89[d]	2.517	1.30	0.335	1.31[c]	3.71	1.13[c]	2.69	1.38	1.29[c]
Be	0.125	-	0.01[d]	0.082	-	-	-	0.10	-	0.07	-	-
Cd	0.678	0.885	0.192[c]/0.38[d]	0.501	0.45	0.078	0.22[c]/0.39[d]	0.74	0.194[c]/0.35[d]	0.53	0.02	0.22[c]/0.42[d]
Cs	8.829	-	4.11[c]	6.263	-	-	4.29[c]	8.73	3.85[c]	6.33	-	4.36[c]
Cr	1.188	1.421	-	0.810	0.26	0.124	-	1.25	-	0.91	0.27	-
Co	0.683	0.240	0.308[c]/0.3[e]	0.409	0.02	0.021	0.327[c]	0.77	0.307[c]	0.56	0.02	0.349[c]
Cu	16.597	7.400	9.99[d]	11.416	0.73	0.640	-/10.62[d]	16.80	8.98[d]	12.17	0.78	10.86[d]
Pb	5.377	3.175	0.39[c]/0.53[d]	3.809	0.02	0.272	0.414[c]/0.5[d]	5.60	0.381[c]/0.48[d]	4.06	0.05	0.433[c]/0.58[d]
Mn	2.162	2.448	0.12[c]/0.08[d]	1.539	0.13	0.210	0.133[c]/0.09[d]	2.35	0.121[c]/0.08[d]	1.71	0.14	0.137[c]/0.10[d]
Ni	5.392	2.255	1.16[d]	3.968	0.18	0.198	1.32[d]	5.90	1.10[d]	4.27	0.18	1.34[d]
Se	26.894	7.489	53.68[d]	18.279	0.83	0.656	57.83[d]	25.48	48.86[d]	18.47	0.82	59.09[d]
Tl	0.590	0.552	0.155[c]/0.15[e]	0.406	0.05	0.047	0.164[c]	0.57	0.147[c]	0.41	0.46	0.166[c]
U	0.115	0.030	0.005[c]	0.083	0.003	0.003	0.006[c]	0.12	0.006[c]	0.09	4.49	0.007[c]
Zn	359.206	270.494	274.33[d]	257.371	31.47	23.531	323.01[d]	344.24	254.02[d]	249.48	32.36	307.11[d]

Note. [a]Chinese general population aged 18-80 years in Wuhan City (2011). [b]Chinese coke oven workers in Wuhan City (2016). [c]US general population ≥ 20 years, The Fourth National Report on Human Expose to Environmental Chemicals (2011-2012), (updated February 2015). [d]Canada general population, 6-79 years, Report on Human Expose to Environmental Chemicals in Canada, Results of the Canadian Health Measures Survey Cycle 1 (2007-2009). [e]Canada non-occupational population (*n* = 100) (2005).

Cr values were about seven times higher than those in the Chinese general population (0.810 *vs.* 0.124 μg/g creatinine). The median urinary Co level (0.683 μg/L) was about three times higher than that in the Chinese general population (0.240 μg/L). Creatinine adjusted GMs were slightly higher than those in the US population. The median urinary Ni levels in the metal-exposed workers were higher than those in the Chinese general population. Cd is emitted into the air from copper, nickel, or zinc smelters. Exposure to Co in the workplace can originate from electroplating, processing alloys, refining, or using hard metal cutting tools. The company described in this study mainly focuses on mining, smelting, and processing Ni, Cu, Co, and Zn as well as chemical processing of materials. A strong positive correlation was observed between Ni and Co. Cd and related compounds have been classified as human carcinogens (Group 1) by the International Agency for Research on Cancer (IARC)[5]. IARC has classified Co metal and other soluble Co salts as possibly carcinogens of humans.

Some metals, such as Cu, Mn, Se, and Zn, are also considered essential trace elements in humans. Workers in certain occupational settings, such as mining, smelting, welding, or the manufacture of Cu and Zn alloys and galvanized metals, may be exposed to higher amounts of Cu and Zn. In this study, median urinary Cu levels were two-fold higher than those in the Chinese general population. The GM values of Cu were roughly similar to those in the Canadian population. The normal range of concentrations for Mn is 0.97-1.07 μg/L in urine[6]. The median urinary Mn level in the metal-exposed workers was slightly lower than that in the Chinese general population (2.162 *vs.* 2.448 μg/L). Three-fold higher Se GM levels were reported among people aged 6-79 years in the Canadian Health Measures Survey (18.47 *vs.* 59.09 μg/g) compared with this study. The level at which Se toxicity occurs is difficult to determine, as Se concentration is affected by the types of protein in the diet, level of vitamin E, and the various forms of Se present in the body[7]. The median urinary Zn concentration was higher in the metal-exposed workers than that in the Chinese general population. However, the GM values were lower than those in the Canadian population (249.48 *vs*. 307.11 μg/g) and a study reported in British Columbia on non-smoking adults aged 30-65 years[8]. Exposure to high levels of Cu, Mn, Se, and Zn can affect health; however, IARC has not published reference potential carcinogenic values for Cu, Mn, and Zn.

Urinary Ba, Be, Cs, Tl, and U levels represent recent exposures, whereas Be and U concentrations in urine reflect accumulated exposure. Occupational workers can be exposed to Ba, Be, Cs, Tl, and U during mining and smelting of lead, copper, and zine ores[4]. The creatinine-adjusted median and GM values of those metals were both higher in the nonferrous metal workers than those in the Chinese and US general populations. Median Ba levels were 30 times higher in welders of barium-containing electrodes than the levels in the present study (101.7 μg/L *vs.* 3.427 μg/L); however, the welders had no obvious adverse clinical effects[9]. Urinary Be was generally undetectable in the two general populations[3]. In the present study, urinary Be levels were below the LOD of 0.0327 μg/L in 27.4% of workers. This is consistent with a survey of the US and Canadian populations. The creatinine-corrected GM value for Cs was higher than that reported for firefighters (4.08 μg/g creatinine) and residents living near a fire area (3.89 μg/g creatinine)[10]. However, evidence for an association between environmental expose to Ba, Be, Cs, Tl, and U and adverse health effects is limited. The IARC also has no human carcinogenicity ratings for Ba, Be, Cs, and U[4].

In conclusion, workers in the Jinchang Cohort had relatively high urinary metal levels compared with those in general and occupational populations, but higher urinary heavy metal levels do not necessarily mean that an adverse health effect will occur. Further studies are needed on combined metal exposures and health effects among metal-exposed workers.

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#Correspondence should be addressed to BAI Ya Na, Tel: 86-931-8915526, E-mail: baiyana@lzu.edu.cn; or ZHENG Tong Zhang, Tel: 1 (401) 863-6365, E-mail: tongzhang_zheng@brown.edu

Biographical note for the first author: YANG Ai Min, Postdoctoral Fellow, school of public health, Brown University, majoring in environmental and occupational health.

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REFERENCES

1. Fort M, Cosín-Tomás M, Grimalt JO, et al. Assessment of exposure to trace metals in a cohort of pregnant women from an urban center by urine analysis in the first and third trimesters of pregnancy. Environ Sci Pollu Res Int, 2014; 21, 9234-41.
2. Bai Y, Yang A, Pu H, et al. Cohort Profile: The China Metal-Exposed Workers Cohort Study (Jinchang Cohort). Int J Epidemiol, 2016; dyw223.
3. Heitland P, Köster HD. Biomonitoring of 30 trace elements in urine of children and adults by ICP-MS. Clin Chim Acta, 2006; 365, 310-8.
4. USCDC (US Centers for Diesease Control and Provention). Fourth National Report on Human Exposure to Environmental Chemicals. Washington DC. 2009.
5. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans-volum 58, Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry: IARC, World Health Organization, 1993.
6. ATSDR (Agency of Toxic Substances and Disease REgistry) (2000). Toxicological Profile for Manganese. Available from: www.atsdr.cdd.gov/toxprofiles/tp151.html. [2016-8-6]
7. Canada H. Guidelines for Canadian Drinking Water Quality - Supporing Documents: Selenium. Ottawa: Water Quality and Health Bureau, Safe Environments Programme. 1992.
8. Hess SY, Peerson JM, King JC, et al. Use of serum zinc concentration as an indicator of population zinc status. Food Nutr Bull, 2007; 28, 403S-29S.
9. Zschiesche W, Schaller KH, Weltle D. Exposure to soluble barium compounds: an interventional study in arc welders. Int Arch Occup Environ Health, 1992; 64, 13-23.
10. Wolfe MI, Mott JA, Voorhees RE, et al. Assessment of urinary metals following exposure to a large vegetative fire, New Mexico, 2000. J Expo Sci Env Epid, 2004; 14, 120-8.