Letter to the Editor

Occupational Exposure to Indium of Indium Smelter Workers*

DING Chun Guang[1], WANG Huan Qiang[1], SONG Han Bo[2], LI Zhi Hui[1], LI Xiao Ping[3], YE Shao Se[3], ZHANG Fu Gang[1], CUI Shi Wei[1], YAN Hui Fang[1], and LI Tao[1,#]

Case reports of indium-related lung disease in workers have raised public concern to the human toxicity of indium (In) and its compounds. However, studies evaluating the exposure or health of workers in In smelting plants are rare. Therefore, in this study, we focused on four In smelting plants, with the main objective of characterizing In in smelter plants in China and discussing the potential exposure biomarkers of In exposure. We recruited 494 subjectsat four In smelting plants in China. Personal air samples, first morning urine and spot blood samples were collected. In concentrations in samples were analyzed using inductively coupled plasma mass spectrometry. In concentrations in air samples did not exceed the permissible concentration-time weighed average, but the smelter workers had a higher internal exposure to In. Positive correlations were observed between the air In and urine In concentrations, and between the air In and blood In concentrations. This study provides basic data for the following In exposure and health risk assessment.

Indium (In) (CAS 7440-74-6) is a rare metal that is primarily used in the form of indium-tin oxide (ITO), a sintered material consisting of 90% indium oxide (In_2O_3) and 10% tin oxide (SnO_2), to produce flat panel displays. Case reports of In-related lung disease in workers that have emerged during the past decade from Japan, China, and America have raised public concern to the human toxicity of In and its compounds[1-2]. China has achieved the highest In output since 2000, accounting for over 50% of the total global refined In[3]. In this study, we focused on four In smelting plants, with the main objective of characterizing In in smelter plants in China and discussing the potential exposure biomarkers for In smelter workers.

We selected four smelting plants of different sizes and degrees of automation in different areas. Plant 4 (P4) is a small/medium-sized plant (annual production<20 tons), plant1 (P1), plant2 (P2), and plant3 (P3) are medium/large-sized plants. Workers in P2 didn’t have a fixed type of work because of the job rotation system. We identified the six main work tasks performed on the days of sampling: 1) lixiviate, 2) extraction, 3) metathesis, 4) electrolysis, 5) ingot casting, and 6) chemical examination workers. We assessed exposure using a cross sectional survey. We used questionnaires to obtain information about work tasks and the use of protective equipment on the day of sampling as well as information about lifestyle, including tobacco use and dietary habits. Personal breathing zone air samples were collected from workers over the entire shift period, with continuous sampling for three days. The blood samples were collected by registered nurses at the work places. Serum was collected in a 4 mL serum separation hose (Vacutainer SST™, BD, USA). The tubes were centrifuged at 3000 rpm for 20 min to obtain serum. The first morning urine samples (>50 mL) were collected from the participants on arrival at workplace. We stored all samples in a portable fridge at 4-6 °C until arrival at the laboratory (within 24 h), where the samples were immediately frozen at -20 °C. This study was approved by the institutional review board at the National Institute of Occupational Health and Poison Control, China CDC, and each subject gave written informed consent. All volunteers agreed to the use of their blood and urine samples for this biological monitoring survey.

Blood, serum and urine samples were analyzed by inductively coupled plasma mass spectrometry[4]. For air samples, the filters were digested in the hot

doi: 10.3967/bes2016.049

*This research was supported by the Public Welfare Special Projects of National Health and Family Planning Commission of the People’s Republic of China (No. 201402021); and The ‘Twelfth Five-Year Plan’ of the National Science and Technology Support (No.2014BAI12B01).

1. National Institute of Occupational health and Poison Control, Chinese Center for Disease Control and Prevention, Beijing 100050, China; 2. North China University of Science and Technology, Tangshan 063009, Hebei, China; 3. Guangxi Zhuang Autonomous Region Academy for the Prevention and Treatment of Occupational Diseases, Nanning 530021, Guangxi, China

block and analyzed by inductively coupled plasma mass spectrometry.

For statistical analyses, SPSS software version 20.0 for Windows was used. For observations below LOD, the value was imputed as LOD divided by the square root of 2[5]. The metal concentrations in the air samples were highly skewed, and therefore, we log (ln) transformed them and used parametric statistics to evaluate the results. We analyzed different work tasks with no stratification by plants, and used binary logistic regression analysis to exclude the effects of confounding factors for different plants. We used a simple one-way analysis of variance (ANOVA) and post-hoc test for multiple analyses to evaluate differences in air samples. We used non-parametric statistics on non-transformed data for the biomonitored results. The differences between two independent groups were assessed using the Mann-Whitney U-test, whereas the differences among multiple independent groups were assessed using the kruskal-Wallis H Test. The correlation analysis between concentrations in air samples and biological samples was estimated by computing Spearman's correlation coefficient. Statistical significance was established at P>0.05. Analytical results of urine samples with a specific gravity of <1.010 g/mL or >1.030 g/mL were excluded from statistical analysis.

In total, we recruited 494 subjects (417 smelter workers and 77 office workers) from the four In smelting plants. One Hundred and forty-six of the study participants (38.7%) were women. The age of participants ranged from 21 to 60 years (mean=39.67 years), and the work age of the participants ranged from 1 to 42 years. Among the participants, approximately 49.2% were smokers. Plants 1-3 used process ventilation, whereas P4 did not, as their building is an open workshop. All workers wore personal protective equipment during their shifts according to their company policy demands, workers in P4 wore the ordinary cotton mask, and workers in other three plants wore professional dusk mask.

We collected 190 personal breathing zone air samples from In smelting workers and 29 personal breathing zone air samples or static samples from office workers. The average sampling time was 295 min (range 120-480 min) for the samples. As shown in Table 1, the geometric mean (GM) concentrations of In in the air samples from the smelter workers in the four plants were 2.76, 0.41, 0.45, and 2.26 μg/m³, respectively. No significant difference of In concentration in smelter workers was found between P1 and P4, and between P2 and P3; the concentrations were significantly higher in P1 and P4 than those in P2 and P3 (P<0.05). In concentrations

Table 1. In Concentrations (μg/m^3) in the Collected MCE Fraction from Personal Air Sampling of Workers

Group	N	GM	GSD	MIN	MAX	*P*
P1						
Office workers	8	0.45	4.85	0.12	18.85	0.010
Smelter workers	90	2.76	4.56	0.09	69.05	
P2						
Office workers	2	0.23	1.56	0.17	0.31	0.507
Smelter workers	54	0.41	3.40	0.02	2.81	
P3						
Office workers	3	0.13	4.84	0.05	0.80	0.061
Smelter workers	31	0.45	2.71	0.03	6.71	
P4						
Office workers	2	0.82	2.59	0.42	1.60	0.379
Smelter workers	29	2.26	4.82	0.25	53.37	
Totle						
Office workers	15	0.35	4.20	0.05	18.85	0.005
Smelter workers	204	1.22	5.20	0.02	69.05	
Working Procedure						
Lixiviate workers	39	1.48	3.13	0.28	69.05	0.000
Extraction workers	18	1.06	3.79	0.14	35.91	
Metathesis workers	14	4.67	8.06	0.21	61.58	
Electrolysis workers	8	11.15	3.13	0.77	35.40	
Ingot casting workers	2	12.80	1.39	10.13	16.17	
Chemical examination workers	8	0.94	5.49	0.09	36.32	

Note. GM: geometric mean; GSD: geometric standard deviation. MIN: minimum value; MAX: maxmum value.

in the air samples from the smelter workers of P1 were significantly higher than those from the office workers (*P*<0.05), while there was no significant difference was found in other plants. In concentration in the air samples from different work tasks were significantly different (*F*=8.11, *P*<0.05). Binary logistic regression analysis was used to exclude the effects of confounding factors for different plants, and the cut point was set at 66.7% percentiles (1.73 μg/m^3). Ingot casting workers exposed the highest air In concentration (12.80 μg/m^3), but it was not calculated in the regression analysis because it has only two samples. The result indicated that metathesis workers (OR=63.25) and electrolysis workers (OR=63.52) exposed in much higher In concentration than other workers (Supplemental Table S1). However, no concentration in air samples exceeded the permissible concentration-time weighed average of 0.1 mg/m^3 (National occupational health standards GBZ 2.1).

We collected 424 blood, 430 serum, and 477 urine samples from 494 subjects. As shown in Table 2, In concentrations in blood of the smelter workers in the four plants were 0.09, 0.03, 0.05, and 0.44 μg/L, respectively, with concentrations significantly higher (*P*<0.05) for smelter workers than for office workers from P1 and P4. In concentrations in serum of the smelter workers in the four plants were 0.03, 0.12, 0.20, and 0.35 μg/L, respectively, with concentrations significantly higher (*P*<0.05) for

Table 2. Indium Concentrations (μg/L) in Blood, Serum and Urine from Workers

Group	Blood-In		Serum-In		Urine-In	
	n	GM (GSD) Range	*n*	GM (GSD) Range	*n*	GM (GSD) Range
P1						
Office workers	46	0.03 (1.76) 0.02[a]-0.25	37	0.02 (1.00) 0.02-0.02	46	0.07(2.52) 0.02-0.53
Smelter workers	212	0.09* (4.43) 0.02-4.70	225	0.03* (3.12) 0.02-3.92	255	0.2* (4.05) 0.02-17.29
P2						
Office workers	3	0.05 (4.87) 0.02-0.31	3	0.23 (3.38) 0.06-0.63	3	0.04 (2.46) 0.02-0.1
Smelter workers	54	0.03 (3.79) 0.02-3.82	54	0.12 (3.21) 0.02-3.46	54	0.05 (3.77) 0.02-1.16
P3						
Office workers	11	0.02 (1.00) 0.02-0.02	11	0.08 (2.46) 0.02-0.28	11	0.03 (2.12) 0.02-0.25
Smelter workers	44	0.05* (4.03) 0.02-3.74	45	0.20* (2.76) 0.03-3.32	46	0.10* (5.61) 0.02-10.12
P4						
Office workers	15	0.09 (2.99) 0.02-0.41	14	0.09 (4.7) 0.02-6.36	15	0.12 (4.8) 0.02-1.23
Smelter workers	48	0.44* (4.41) 0.05-30.18	42	0.35* (5.48) 0.02-39.71	48	0.27 (5.62) 0.02-11.33
Totle						
Office workers	67	0.03 (2.45) 0.02-0.41	65	0.04 (3.10) 0.02-6.36	75	0.07 (3.08) 0.02-1.23
Smelter workers	358	0.09* (5.07) 0.02-30.18	366	0.07* (4.45) 0.02-39.71	403	0.16* (4.76) 0.02-17.29
Working Procedure						
Lixiviate workers	49	0.05 (3.04) 0.02-0.62	49	0.04 (2.58) 0.02-1.14	53	0.13 (3.56) 0.02-2.24
Extraction workers	25	0.16 (4.09) 0.02-3.99	25	0.09 (5.00) 0.02-2.86	27	0.33 (3.43) 0.02-8.80
Metathesis workers	13	0.34 (11.04) 0.02-30.18	12	0.33 (10.36) 0.02-39.71	14	0.56 (4.79) 0.02-11.33
Electrolysis workers	8	1.90 (2.72) 0.60-9.12	9	0.47 (11.64) 0.02-8.05	9	1.70 (2.39) 0.29-5.51
Ingot casting workers	7	0.61 (4.72) 0.02-2.10	9	0.12 (7.97) 0.02-1.60	9	1.16 (2.69) 0.13-2.70
Chemical examination workers	21	0.05 (3.66) 0.02-0.62	20	0.04 (2.97) 0.02-0.50	23	0.09 (4.00) 0.02-1.68

Note. GM: geometric mean; GSD: geometric standard deviation. [a]LOD/$\sqrt{2}$ =0.02 μg/L. *Statistically significant difference between the groups (*P*<0.05).

smelter workers than for office workers in P1, P3 and P4. In concentrations in urine of the smelter workers in the four plants were 0.20, 0.05, 0.10, and 0.27 μg/L, with concentrations significantly higher (P<0.05) for smelter workers than for office workers from P1 and P3. No significant differences were found between males and females, smokers and nonsmokers for any biomonitored results.

For different plants, the differences of all biomonitored results from smelter workers was significant (P<0.05). Pairwise comparisons showed that the blood In in P4 was significantly higher than in other plants (P<0.05); urine In was significantly higher than that in P2 and P3 (P<0.05), the result is similar with the air In in different plants; serum In in P1 was significantly lower than that in other three plants (P<0.05). The lower air exposure but highest internal exposure for workers in P4 may be associated with its lower degree of automation and poor personal protective equipment. In P2, no significant differences were found between smelter workers and office workers (P>0.05) in air samplesor bio-samples probably because the office is too close to the workshop, and the spatial layout is not reasonable.

Among different work tasks, Kruskal Wallis Test indicated significant differences for all biomonitored results. Binary logistic regression analysis (Supplemental Table S2, S3) showed similar results for urine In and blood In, with the concentrations in electrolysis and ingot casting workers much higher than those in other task workers. For serum In (Supplemental Table S4), the concentrations in metathesis, electrolysis and ingot casting workers were higher than other workers. The tendency of In concentrations in biological samples was similar to that in air samples.

In total, In concentrations in serum and urine of the smelter workers were approximately twice as high as those of the office workers. Blood In concentrations of smelter workers in this study were much higher than those of the general population (<0.03 μg/L)[6]. The Japanese Society for Occupational Health recommended an In serum concentration of 3.0 μg/L as the exposure limit[7], the serum In concentrations in smelter workers exceeded the limit by 2.2%, with the highest value at 39.71 μg/L.

We compared the concentrations in the biological samples from the smelter workers with the concentrations in the corresponding air samples. Positive correlations were found between air In and blood In concentrations (r=0.448, P<0.01), between air In and urine In concentrations (r=0.481, P<0.01), but this tendency was not observed for serum In concentrations. The bivariate correlations between each two biomonitored results were also calculated. Blood In concentration was significantly correlated with urine In concentration (r=0.626, P<0.01); however, the correlation coefficient was 0.169 (P=0.001) between blood In and serum In concentrations and 0.052 (P=0.326) between serum In and urine In concentrations. The Japanese Society for Occupational Health recommended an In serum concentration as the exposure biomarker[7]. However, the studies[7-8] also indicated that serum In concentrations may better reflect long-term exposure rather than short-term exposure. In this study, we found that blood In and urine In concentrations appeared to increase with increasing In concentrations in the air samples, indicating that blood and urine In may better reflect recent exposure than serum In for In smelter workers.

In the study, we characterized In exposure in smelter plants in China, and discussed the potential exposure biomarkers for In smelter workers. The biomonitored results indicated that In smelter workers have a higher internal exposure to In, even though all the concentrations in personal breathing zone air samples were lower than the permissible concentration-time weighed average, which suggested that biomonitoring may play a more important role than air samples monitoring to evaluate In exposure. Correlation analysis indicated that blood In and urine In may be the potential exposure biomarker to reflect recent In exposure for smelter workers, and more evidences are needed to confirm the conclusion. This study provides basic data for the following In exposure and health risk assessment for In smelter workers.

We are greatly indebted to the study participants and to the occupational health and environmental offices who supported our work at the local level.

#Correspondence should be addressed to Professor LI Tao, Tel: 86-10-83132513; E-mail: litao@chinacdc.cn

Biographical note of the first author: DING Chun Guang, male, born in 1983, Associate Professor/Master, majoring in occupational and environmental health, chemical analysis and biomarker study.

Received: November 20, 2015;

Accepted: May 5, 2016

REFERENCES

1. Cummings KJ, Nakano M, Omae K, et al. Indium lung disease.

Chest, 2012; 141, 1512-21.
2. Omae K, Nakano M, Tanaka A, et al. Indium lung-case reports and epidemiology. Int Arch Occup Environ Health, 2011; 84, 471-7.
3. USGS (U.S. Geological Survey). Indium. Mineral commodity summaries, June 2015. http://minerals. usgs.gov/minerals/pubs/commodity/indium/mcs-2015-indiu.pdf.
4. Ding CG, Zhu C, Dong M, et al. Inductively coupled plasma mass spectrometry for the simultaneous determination of thirty metals and metalloids element in blood samples. Chin J Prev Med, 2012; 46, 745-8. (In Chinese)
5. Hornung RW, Reed LD. Estimation of average concentration in the presence of nondelectable values. ApplOccup Environ Hyg, 1990; 5, 46-51.
6. Zhang FG, Ding CG, Zhang AH et al. Study of distribution and influencing factors of gallium, indium and thallium in whole blood among population in 8 provinces in China. Chin J Prev Med, 2014; 48, 138-40. (In Chinese)
7. Nakano M, Omae K, Tanaka A, et al. Causal relationship between indium compound inhalation and effects on the lungs. J Occup Health, 2009; 51, 513-21.
8. Hoet P, De Graef E, Swennen B, et al. Occupational exposure to indium, what does biomonitoring tell us? Toxicol Lett, 2012; 213, 122-8.

Supplemental Table S1. Parameters of Binary Logistic Regression Analysis for Air In Concentrations from Different Work Tasks

workers	B	SE	Wald	*df*	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Office workers			18.19	5	0.003			
Lixiviate workers	2.74	1.14	5.78	1	0.016	15.54	1.66	145.52
Extraction workers	1.65	1.21	1.84	1	0.175	5.19	0.48	55.97
Metathesis workers	4.15	1.36	9.25	1	0.002	63.25	4.37	915.06
Electrolysis workers	4.15	1.52	7.44	1	0.006	63.52	3.21	1255.10
Chemical examination workers	-0.21	1.55	0.02	1	0.892	0.81	0.04	16.90

Supplemental Table S2. Parameters of Binary Logistic Regression Analysis for Urine In Concentrations from Different Work Tasks

workers	B	SE	Wald	*df*	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Office workers			41.34	6	0.000			
Lixiviate workers	1.37	0.51	7.31	1	0.007	3.95	1.46	10.69
Extraction workers	2.34	0.57	16.99	1	0.000	10.43	3.42	31.80
Metathesis workers	3.00	0.73	17.09	1	0.000	20.05	4.84	83.11
Electrolysis workers	4.18	1.15	13.31	1	0.000	65.49	6.92	619.59
Ingot casting workers	4.48	1.14	15.30	1	0.000	88.05	9.34	830.34
Chemical examination workers	0.28	0.69	0.17	1	0.680	1.33	0.35	5.11

Supplemental Table S3. Parameters of Binary Logistic Regression Analysis for Blood In Concentrations from Different Work Tasks

workers	B	SE	Wald	*df*	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Office workers			33.46	6	0.000			
Lixiviate workers	2.32	0.88	6.96	1	0.008	10.15	1.81	56.77
Extraction workers	4.48	0.96	21.67	1	0.000	87.84	13.35	578.06
Metathesis workers	4.55	1.07	18.19	1	0.000	94.27	11.67	761.59
Electrolysis workers	25.12	12664.41	0.00	1	0.998	81531798581.81	0.00	
Ingot casting workers	6.40	1.39	21.22	1	0.000	603.79	39.61	9203.70
Chemical examination workers	0.90	0.84	1.15	1	0.283	2.45	0.48	12.60

Supplemental Table S4. Parameters of Binary Logistic Regression Analysis for Serum In Concentrations from Different Work Tasks

workers	B	SE	Wald	*df*	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Office workers			21.01	6	0.002			
Lixiviate workers	0.76	0.67	1.29	1	0.256	2.14	0.58	7.95
Extraction workers	3.39	1.18	8.20	1	0.004	29.72	2.92	302.97
Metathesis workers	5.38	1.63	10.90	1	0.001	216.55	8.90	5270.88
Electrolysis workers	6.40	1.53	17.57	1	0.000	601.31	30.17	11982.85
Ingot casting workers	6.17	1.46	17.89	1	0.000	479.07	27.44	8365.00
Chemical examination workers	1.86	1.08	2.98	1	0.084	6.41	0.78	52.77