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Research Article

Assessment of internal exposure risk from metals pollution of occupational and non-occupational populations around a non-ferrous metal smelting plant

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ABSTRACT

Non-ferrous metal smelting poses significant risks to public health. Specifically, the copper smelting process releases arsenic, a semi-volatile metalloid, which poses an emerging exposure risk to both workers and nearby residents. To comprehensively understand the internal exposure risks of metal(loid)s from copper smelting, we explored eighteen metal(loid)s and arsenic metabolites in the urine of both occupational and non-occupational populations using inductively coupled plasma mass spectrometry with high-performance liquid chromatography and compared their health risks. Results showed that zinc and copper (485.38 and 14.00 μg/L), and arsenic, lead, cadmium, vanadium, tin and antimony (46.80, 6.82, 2.17, 0.40, 0.44 and 0.23 μg/L, respectively) in workers (n=179) were significantly higher compared to controls (n=168), while Zinc, tin and antimony (412.10, 0.51 and 0.15 μg/L, respectively) of residents were significantly higher than controls. Additionally, workers had a higher monomethyl arsenic percentage (MMA%), showing lower arsenic methylation capacity. Source appointment analysis identified arsenic, lead, cadmium, antimony, tin and thallium as co-exposure metal(loid)s from copper smelting, positively relating to the age of workers. The hazard index (HI) of workers exceeded 1.0, while residents and control were approximately at 1.0. Besides, all three populations had accumulated cancer risks exceeding 1.0×10^{-4}, and arsenite (As^{III}) was the main contributor to the variation of workers and residents. Furthermore, residents living closer to the smelting plant had higher health risks. This study reveals arsenic exposure metabolites and multiple metals as emerging contaminants for copper smelting exposure populations, providing valuable insights for pollution control in non-ferrous metal smelting.

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Introduction

In recent years, there have been increasing concerns about the environmental and health impacts of toxic metals all around the world (Rakete et al., 2022; Xu et al., 2021). Certain heavy metals and metalloids, such as cadmium (Cd), lead (Pb) and arsenic (As) are highly toxic, persistent, bioaccumulating, and non-degradable, thus leading to significant environmental and public health issues (Wang et al., 2019; Zhang et al., 2017). Exposure to these toxic metals can occur through inhalation of polluted air, ingestion of polluted food, or direct contact with skin through polluted water or air. The effects of Cd, Pb and As are particularly noteworthy as these elements are known to be carcinogenic and associated with harmful effects on cardiovascular, nervous, reproductive and renal systems, and may even result in the development of cancer (Li et al., 2022; Straif et al., 2009). On the other hand, although some metals such as zinc (Zn) and copper (Cu) play a vital role in promoting human health, elevated concentrations of these elements have been found to promote systemic inflammation that leads to metabolic syndrome (Ma et al., 2020).

The output of non-ferrous metals is expected to increase consistently through 2022 in China, which also ranks as the world's top consumer and producer (MIIT, 2023). However, this large-scale production of non-ferrous metal has resulted in the continuous release of toxic metal(loid)s from smelting waste, such as combustion residues and mine tailings, leading to severe environmental pollution (Xu et al., 2021). Cu production is the most important metal in the non-ferrous metal industry in China, with its wide range of uses and huge consumption amount (Zhang et al., 2022). Metal smelting has been identified as a significant contributor to severe metal pollution in surrounding areas, especially in urban areas with dense populations (Xu et al., 2021). As, Cd, Pb, nickel (Ni), Cu, Zn and mercury (Hg) were commonly found in smelter-polluted sites (Cai et al., 2019; Li et al., 2015; Loh et al., 2016); among them, As, Pb, Hg and Cd are ranked the top seven priority substance by the agency for toxic substances and disease registry (ATSDR) of United States of America (ATSDR, 2022).

Despite the government's efforts to address the issue of contamination and facilitate the relocation of original residents, a significant portion of the population continues to reside close to scrap metal mines and operating smelters (Xu et al., 2021). Previous studies have reported higher levels of As in the urine of women living in abandoned gold (Au) smelting areas, which have a high incidence of breast cancer (Von Behren et al., 2019). The residents living near the smelting area contain higher urinary Cd than those living in the mining area (Du et al., 2020). A recent study reported that Pb-Zn smelting workers had extremely high levels of Pb in whole blood and urine in northwestern China, and found that urinary Pb is significantly correlated with $PM_{2.5}$-bound Pb rather than food and water (He et al., 2023). Although these studies did not cover a wide range of toxic metal(loid)s, they could still suggest that smelting activities can increase metal(loid) levels in residents living nearby and that environmental exposure may be a potential source. Further, workers are more steadily exposed to smelting than nearby residents. Combined with the internal exposure data of workers and surrounding residents, the extent of site restoration can be evaluated more intuitively and provide a strong scientific basis for further restoration.

As noted above, urinary Pb, Cd and As are potential biomarkers associated with environmental exposure, while urine is non-invasive and suitable for biomonitoring. Based on the comprehensive screening of various urine metal(loid)s, speciation or chemical states of some metal(loid)s is also important for comprehending its transformation, metabolism, and toxicity (Hughes, 2002; Mandal et al., 2004). Inorganic As (iAs) can be metabolized to less toxic species by methylation and predominantly excreted through urine within 3 to 4 days (Dopp et al., 2005). A low capacity for urinary As methylation is considered a major contributor to arsenic-related illnesses rather than total As (Hudgens et al., 2016; Zhang et al., 2014). Percentage of monomethyl arsenic (MMA), dimethyl arsenic (DMA), primary methylation index (PMI = (MMA + DMA)/total As) and secondary methylation index (SMI = DMA/ (MMA + DMA)) were widely used to access As methylation ability (Kuo et al., 2017; Razo et al., 1997; Zhang et al., 2014). Thus, species analysis is important for the possible As poisoned population health risks evaluation. Current studies on As speciation for Cu smelting workers and surrounding residents are little known. Thus, As metabolic profiles in the urine of non-ferrous metal smelting workers can further indicate disease occurrence under occupational exposure to As.

Current exposure studies on non-ferrous metal smelting workers are limited to multiple metal(loid)s and As species in urine, while their carcinogenic and non-risks were less studied using urinary metal(loid) levels. This study aims to: (1) characterize eighteen urinary metal(loid)s of three populations including workers (n=179) from a non-ferrous metal smelting plant (NMSP), nearby residents (n=157) and control populations (n=168) using ICP-MS; (2) analysis the As species in urine, including arsenite (As^{III}), arsenate (As^{V}), MMA^{V}, DMA^{V} and arsenic betaine (AsB) using high-performance liquid chromatography (HPLC) with ICP-MS (HPLC-ICP-MS) and assess As methylation capacity of populations; (3) identify sources and factors influencing the levels of metal(loid)s in workers; and (4) evaluate the carcinogenic and non-cancer risk associated with these populations.

1. Materials and methods

1.1. *Study population and urine sample collection*

Morning urine samples were collected from 619 adult participants in October 2020. Of the participants, 210 were current workers in a non-ferrous metal smelting plant in central China, located at 114°45′23″E, 30°04′19″N; 197 were adult residents, who lived near the smelter plant (within 5 km) and 212 were rural residents who lived approximately 30 km away from the plant. Workers, nearby residents and rural residents served as occupational populations, non-occupational populations and controls. None of the participants in this study left the local area within three months.

The urine samples were collected using plastic cups that had been pre-treated with 20% HNO_3 and rinsed with ultrapure water. Each urine sample was divided into two parts and stored in centrifuge tubes at -20°C and transported to the laboratory as soon as possible. Demographic information of the participants, occupational types, residential addresses, and smoking habits were obtained through a questionnaire. Before sampling, all participants were requested to give informed consent before sampling, and the Guangdong University of Technology's Ethics Committee (China) approved the study. After excluding outliers, the demographic characteristics of the participants are summarized in Appendix A Table S1.

1.2. *Sample preparation and instrumental analysis*

The chemicals used in this study are listed in Appendix A Table S2. For total metal analysis, urine samples were diluted with a digested solution containing 1.2% (V/V) HNO_3. 50 µg/L of Au was added to the digested solution to remove the memory effect of mercury (Hg) measurement in ICP-MS (Kim et al., 2016). The diluted urine samples were ultra-sounded for 1 hr at 45°C and centrifuged at 12000 r/min for 10 min. The supernatant of the digested sample was then stored at 4°C until ICP-MS analysis. For the analysis of five As speciation in urine, 200 µL urine samples were mixed with 800 µL of 30 mmol/L $(NH_4)_2HPO_4$ water solution (pH=8.0). After centrifugation at 12000 r/min for 10 min, the supernatant was separated and stored at 4°C until HPLC-ICP-MS analysis.

Eighteen target urinary metals were determined simultaneously using ICP-MS (Agilent 7900, Agilent Technologies, USA), including six essential trace elements: Mn (manganese), Fe (iron), Cu, Zn, Se (selenium) and Mo (molybdenum) (Ma et al., 2023), and twelve priority pollutant by ATSDR: As, Cd, Pb, Sb, Hg, V, Cr (chromium), Co (cobalt), Ni (nickel), Sr (strontium), Sn (tin) and Tl (thallium) (ATSDR, 2022). The matrix drift of ICP-MS was corrected by internal standards (scandium, yttrium, indium and bismuth).

AsB, As^{III}, DMA^{V}, MMA^{V} and As^{V} were separated using anion exchange HPLC column (Hamilton PRP100X). The mobile phase was 25 mmol/L $(NH_4)_2HPO_4$ solution (pH of 8.0) (Gilbert-Diamond et al., 2011). The targeted As species were analyzed by HPLC-ICP-MS using time-resolved analysis at m/z of 75, with gradient elution (procedure described in Appendix A Table S3). The sample injected volume was 100 µL and the column flow rate was 1 mL/min. The integration time is 12 min for As species analysis.

1.3. *Quality assurance and quality control (QA/QC)*

A procedure blank and a spiked matrix were used for every batch of 20 urine samples. The metal(loid) concentration was corrected using procedure blank. The limits of detection (LOD) of total metal(loid)s were 0.01–0.25 µg/L and the limits of quantification (LOQ) were 0.01–0.83 µg/L. LODs and LOQs of all five As species were 0.02 and 0.10 µg/L, respectively. The total metal(loid) recoveries of spiked urine samples were 85%–110%, while As species recoveries lied between 82%–97%. More detailed information on QA/QC of each target pollutant can be found in Appendix A Tables S4 and S5.

1.4. *Health risk assessment due to exposure to metals*

The health risk assessment was conducted by estimating daily intakes (EDIs) to calculate the non-cancer and carcinogenic risks (CR). Hazard quotient (HQ) was used to present the non-cancer risk of individual metal(loid)s, while hazard index to present the sum of HQs. The calculated process was defined as follows (EPA, 2018; Zhong et al., 2021):

$$\mathrm{TEDI} = \frac{C \times V}{\mathrm{BW} \times f} \times 0.001 \tag{1}$$

$$\mathrm{HQ} = \frac{\mathrm{TEDI}}{\mathrm{RfD}} \tag{2}$$

$$\mathrm{HI} = \sum_{i}^{n} \mathrm{HQ}_i \tag{3}$$

$$\mathrm{CR} = \mathrm{TEDI} \times \mathrm{CSF} \tag{4}$$

where, TEDI (µg/kg/day) is the total estimated daily intake of single metal; C (µg/L) is urinary metal concentration; V (L) represents the adult urine excreted volume per day, with 2 L/day in this study (Chen et al., 2019); BW (kg) represents the body weight; f is single urinary metal excretion factor (excretion rates); RfD (mg/kg/day) is the reference dose of metals considering non-cancer risk endpoint, while CSF ($(\mathrm{mg/kg/day})^{-1}$) is the cancer slope factor of metals considering carcinogenic risk endpoint. The calculation parameters are listed in Appendix A Tables S6–S8.

1.5. *Statistical analysis*

Outliers, defined as samples with concentrations exceeding the sum of the mean concentration plus three times the standard deviation for each metal, were excluded from the database (Quist et al., 2022). However, outliers of individual As species were not excluded again. The differences in the concentrations of target metals were assessed using the Mann-Whitney U test and the Kruskal-Wallis test. The condition that p-value < 0.05 meant a statistically significant difference. Spearman correlation was used to analyze the relationships among individual urinary metal(loid)s and demographic characteristics. Statistical analysis was performed using IBM SPSS Statistics software (13.0 version, SPSS Inc., USA).

2. Results and discussion

2.1. *Characteristics of the participants*

In this study, participants were divided into three groups: workers as the occupational exposure group, residents as a non-occupational group and rural residents as the control group. These participants were chosen based on soil metal(loid) investigation around a plant largely engaged in metal smelting and ore mining activities (Qi et al., 2023). After excluding participants with an outlier of urinary metal(loid)s, 504 participants were left for subsequent analyses. The demographic characteristics of participants were listed in Appendix A Table S1. The age of participants was 22–65 years old, while the average body mass indices of them were 24.39, 23.65 and 23.63 for workers, residents and the control population, respectively. About 86% of the workers were male, which is the general gender structure of occupational attributes of non-ferrous metal smelting. Males accounted for about 42% of both residents and the control population, which was lower than those of workers. However, to ensure a comprehensive assessment of metal(loid) exposure in the non-occupational population, the resident and control groups were structured to have a more balanced ratios of males to females compared to the workers in this study. In addition, 50% of workers and 21% of both residents and the control populations are current smokers.

2.2. Urinary metal(loid) concentrations across populations

2.2.1. Total metal(loid) concentrations

To identify potential characteristic pollutants originating from non-ferrous metal smelting activities, this study measured the levels of six essential trace elements and twelve metal(loid) pollutants prioritized by ATSDR in urine samples. The percentiles of urinary metal(loid) concentrations among three distinct populations are presented in Table 1. The geomean concentrations of essential trace elements in urine ranged from 0.02–440.36 µg/L for workers, 0.01–359.62 µg/L for residents, and 0.05–342.94 µg/L for the control population. Among the essential trace elements, Zn exhibited the highest dominance. In addition, Sr emerged as the most dominant metal(loid) in urine among ATSDR's priority list, with geomean concentrations of 146.06, 139.83 and 149.01 µg/L for workers, residents, and the control population. However, there was no significant difference in Sr between populations ($p > 0.05$, Table 1), and the potential for non-ferrous metal smelting activities of Sr was not considered and excluded in the subsequent discussion. Except that, As levels were the leading metal(loid). The geomean concentration ranges of eleven metal(loid)s were 0.01–48.36 µg/L for workers, 0.01–23.82 µg/L for residents, and 0.01–22.88 for the control population. The National Health Commission of China has provided a standard value of 38 µg/L (geomean) as a safe guideline for urinary As among the public (WS/T 665-2019). The geomean concentrations of urinary As in workers, residents and control were 48.36, 23.82 and 22.88 µg/L, respectively. Thus, workers were at risk exposed to As from NMSP based on the safe guideline values of urinary As.

Among six essential trace elements, Zn and Cu levels in workers were significantly higher than those in residents and control population ($p < 0.05$). The geomean concentrations of Zn in workers were 1.22 and 1.81 times higher than that in residents and the control population, respectively. While workers had significantly higher urinary Cu levels compared to the control population, there was no significant difference in urinary Cu levels between residents and the control population. These findings suggest that workers were exposed to higher levels of Zn and Cu, while residents were only exposed to higher levels of Zn among the essential trace elements.

Among the twelve ATSDR's priority metal(loid) pollutants, workers had significantly higher levels of As (2.03 and 2.11 times), Pb (7.03 and 7.70 times), V (2.35 and 1.65 times) and Sb (2.11 and 19.00 times) compared to both residents and the control populations ($p < 0.05$). As and Pb levels were similar between residents and the control population, which indicates that residents near NMSP may be not exposed to As and Pb originated from non-ferrous metal smelting activities. In addition, workers also had significantly higher levels of Cd and Sn compared to the control populations ($p < 0.05$), but no significant difference compared to residents. These results indicate that workers were exposed to significant levels of As, Pb, V, Sb, Cd, and Sn, while residents were exposed to significant levels of V, Sn, and Sb from non-ferrous metal smelting activities.

In addition, Pb, As, Cd, Cu, Sb and Zn median concentrations in the urine of Cu smelter workers of our study were much higher than those of workers in Zn smelters (Briki et al., 2017). Compared to the Health Effects Survey of Abandoned Metal Mines (AMS) in Korea (2013-2017), the geomean concentration of urinary As of workers in this study was higher than residents who lived within 5 km of the pit head and tailings (48.36 *vs.* 30.32 µg/L); meanwhile, residents in this study had lower urinary As (23.82 µg/L) (Seo and Hong, 2020). However, urinary Cd was shown as urinary creatinine-corrected concentrations. Thus, urinary metal(loid) concentrations of workers and residents with urinary creatinine correction were further summarized in Appendix A Tables S9 and S10 to compare to the previous studies. The geomean concentration of Cd in the urine of workers and residents in this study were 1.51 and 1.58 µg/g cr, respectively, which were lower than those of AMS in Korea (Seo and Hong, 2020). However, more comprehensive results for multiple metals, especially for copper smelter workers, are lacking.

In summary, workers were exposed to Zn, Cu, As, Pb, V, Sb, Cd, and Sn, while nearby residents were exposed to Zn, V, Sn, and Sb in urine from non-ferrous metal smelting activities.

2.2.2. As metabolic profiles

As mentioned above, As is the highest non-essential trace element in urine from non-ferrous metals smelting possibly, which metabolic profiles were further measured. Appendix A Fig. S1a shows the comparisons of five As species in urine among three groups. DMA^V was the major As species in urine. Workers had the highest concentrations of As species except for AsB, which median concentrations were 1.24, 9.96, 37.85, 5.91 and 0.93 µg/L for AsB, As^{III}, DMA^V, MMA^V and As^V, respectively. Workers had 5.79, 3.15 and 3.84 times higher As^{III}, DMA^V and MMA^V in urine compared to residents, respectively, while residents had similar levels with the control population (1.76 vs 1.62 µg/L for As^{III}, 12.01 vs 13.51 µg/L for DMA^V and 1.42 vs 1.50 µg/L for MMA^V). As^{III}, DMA^V and MMA^V accounted for almost all the mass in these five As species, ranging from 92%–98% (Appendix A Fig. S1b).

The median AsB levels in urine among the three populations were all relatively low (0.23–1.36 µg/L) in this study, and it may be ignored for total As exposure. AsB is considered nontoxic for humans and is usually excreted in the urine as its chemical prototype after consumption of shellfish, fish and certain mushrooms (Beene et al., 2022; Popowich et al., 2016; Taylor et al., 2017). The comparable concentrations of AsB ob-

Table 1 – The concentrations and percentile of urinary metal(loid)s across populations.

Metal(loid)s		Worker (n=179)			Resident (n=157)			Controls (n=168)			p-value		
(μg/L)		GM[a]	Median	25%th–75%th	GM	Median	25%th–75%th	GM	Median	25%th–75%th	W vs C	W vs R	R vs C
Essential trace element	Zn	440.35	485.38	297.84–756.65	359.62	412.10	210.96–688.63	243.94	277.10	126.35–517.68	0.00	0.04	0.00
	Mo	57.57	63.75	37.23–94.53	113.29	128.62	76.54–179.07	85.58	90.89	46.30–144.35	0.00	0.00	0.00
	Se	18.26	22.05	11.77–34.39	17.88	25.29	13.98–37.32	17.54	19.72	12.63–27.81	0.13	0.27	0.01
	Cu	12.34	14.00	8.82–17.67	3.18	9.55	4.02–16.33	9.24	9.89	6.96–15.19	0.00	0.00	0.10
	Fe	6.19	14.89	4.21–27.55	18.58	34.52	13.40–83.27	7.67	14.97	6.55–25.30	0.59	0.00	0.00
	Mn	0.02	0.01	0.00–0.23	0.01	0.00	0.00–0.26	0.05	0.14	0.00–0.43	0.00	0.12	0.00
ATSDR's priority pollutant list	Sr	146.06	164.16	93.29–242.77	139.83	158.92	88.22–238.1	149.01	169.05	103.62–257.55	0.53	0.47	0.20
	As	48.36	46.80	27.58–89.72	23.82	26.54	16.23–39.54	22.88	24.95	16.45–35.32	0.00	0.00	0.44
	Pb	7.24	6.82	3.56–14.09	1.03	1.39	0.79–2.13	0.94	1.19	0.75–1.67	0.00	0.00	0.06
	Cd	2.13	2.17	1.16–3.75	1.79	2.00	1.07–3.18	1.51	1.83	0.80–3.02	0.00	0.17	0.12
	Tl	0.58	0.58	0.39–0.89	0.61	0.65	0.45–0.92	0.51	0.60	0.34–0.85	0.50	0.28	0.10
	V	0.33	0.40	0.27–0.49	0.14	0.17	0.11–0.28	0.20	0.26	0.19–0.34	0.00	0.00	0.00
	Sn	0.23	0.44	0.14–1.02	0.08	0.51	0.00–1.06	0.01	0.00	0.00–0.23	0.00	0.06	0.00
	Sb	0.19	0.23	0.10–0.77	0.09	0.15	0.06–0.23	0.01	0.06	0.00–0.16	0.00	0.00	0.00
	Co	0.07	0.18	0.09–0.26	0.22	0.23	0.13–0.41	0.21	0.22	0.13–0.35	0.02	0.00	0.67
	Cr	0.03	0.00	0.00–1.25	0.02	0.00	0.00–0.36	0.28	0.55	0.17–1.14	0.00	0.59	0.00
	Ni	0.02	0.01	0.01–0.01	0.07	0.01	0.01–1.39	1.32	1.87	1.13–3.23	0.00	0.00	0.00
	Hg	0.01	0.00	0.00–0.04	0.01	0.00	0.00–0.12	0.01	0.00	0.00–0.13	0.84	0.31	0.50

GM: geometric mean concentration; W: worker; R: resident; C: control; ATSDR: agency for toxic substances and disease registry of U.S.

Table 2 – Arsenic (As) methylation patterns in populations.

Median (range)	Worker	Resident	Control
ΣAs (μg/L)	57.26 (3.75–544.92)	16.50 (1.08–118.48)	17.82 (0.66–72.02)
iAs%	18.20 (0.00–66.52)	11.98 (0.00–89.36)	12.02 (0.00–78.62)
MMA%	10.97 (0.39–23.00)	9.04 (0.00–23.62)	9.62 (0.00–21.38)
DMA%	70.60 (33.09–96.06)	77.43 (10.03–100.00)	78.69 (0.00–97.14)
PMI	0.82 (0.33–1.00)	0.88 (0.11–1.00)	0.88 (0.21–1.00)
SMI	0.86 (0.69–0.99)	0.89 (0.74–1.00)	0.89 (0.00–1.00)

ΣAs: Sum concentration of As^{III}, DMA^{V}, MMA^{V} and As^{V} in urine of this study; iAs%: As^{III} and As^{V}; PMI: primary methylation index; SMI: secondary methylation index.

served in both workers and residents could be attributed to the consumption of local food, as their AsB levels were significantly elevated compared to the control population. It is plausible that AsB found in seafood is a result of the transformation of arsenocholine within the body, which may be facilitated by the conversion of iAs by lower organisms, such as seaweed (Popowich et al., 2016). The present study lacks substantial evidence to establish a direct correlation between local seafood and non-ferrous metal smelting activities.

The classical metabolic pathways of inorganic As are widely acknowledged to involve repetitive reduction and oxidative methylation, ultimately leading to the formation of DMA^{V} as the final metabolite in the human body (Hayakawa et al., 2005). During the metabolic process, both inorganic and organic pentavalent As are reduced to trivalent As for further methylation with trivalent methyltransferase (Petrick et al., 2000; Zakharyan et al., 2002). In this study, all populations had low levels of As^{V}, with median concentrations of 0.00–0.93 μg/L, showing that exposed As^{V} almost entered the metabolic process. As^{III} in the urine samples may be the addition of As^{III} external exposure and metabolic intermediates of As^{V} exposure in workers. Because As in smelting slag is mainly found in the pentavalent form (As^{V} or As_2O_5) (Wang et al., 2022). Such a high concentration of iAs, in addition to indicating that workers have a high exposure to As, also suggests that workers metabolize inorganic As metabolic capacity may be overloaded.

The As methylation pattern is associated with As exposure levels, including iAs% and DMA% but not MMA% (Kuo et al., 2017), while PMI and SMI values in populations are used to reflect As methylation capacity (Zhang et al., 2014). Table 2 shows the As methylation patterns among workers, residents and control population. The median sum concentration of As^{III}, DMA^{V}, MMA^{V} and As^{V} in urine (ΣAs) were 57.26, 16.50 and 17.82 μg/L for workers, residents and controls, respectively, which were consistent with the total As concentrations in urine. Workers had a higher median iAs% value (18.20%) than residents (11.98%) and controls (12.02%). Besides, higher MMA% (10.97%) and lower DMA% (70.60%) values of workers show that they were exposed to higher As levels and their metabolic incompleteness is higher than that of non-occupational populations. Tough iAs% (11.98%) and MMA% (9.04%) of residents were slightly lower than control (iAs%: 12.02% and MMA%: 12.02%), residents may also expose higher As levels than controls with higher DMA% values (77.43% *vs*. 78.69%). The aforementioned observation indicates that despite comparable total As concentrations, or potentially lower ΣAs of residents as control, NMSP nearby residents may experience slightly higher exposure levels of As than controls.

Besides MMA% or lower DMA% values, SMI may also be a signal of increasing susceptibility to the risk of arsenicosis (Kuo et al., 2017; Zhang et al., 2014). Workers had the lowest PMI and SMI values (0.82 for PMI and 0.86 for SMI) than non-occupational populations. However, the As metabolic state of workers in this study was higher compared to Cu-smelter workers in the northeastern part of China, with PMI of 0.75 and SMI of 0.84 (Xi et al., 2011). When SMI is lower than 0.81, As dermatosis may occur (Xi et al., 2011). Combined with the high urine concentration of As and SMI, some workers may potentially develop As dermatosis, with the range of 0.69 to 0.99 in workers of this study. Thus, based on the status of As metabolism, workers may suffer from a variety of potential negative health effects due to As exposure. Residents had the same PMI and SMI as control (0.88 for PMI and 0.89 for SMI). Combined with the lower DMA% of residents than control as mentioned above, residents were at slightly higher As exposure levels, but at similar levels of risk to As exposure with control.

In all, workers had much lower As methylation capacity than residents and the control population, which suggests that workers may have higher negative health impacts. Residents may suffer slightly higher As exposure levels than control, but similar health impacts with the controls.

2.3. *Sources and influential factors of elevated urinary metal(loid) concentrations*

2.3.1. *Sources identification*

To investigate the origin of metal(loid)s in the NMSP, sources apportionment for workers was conducted through principal component analysis (PCA), and PCA results were obtained based on the correlation matrix and after varimax variance rotation (Anaman et al., 2022). Six principal components, accounting for 71% of the total contribution, were found by PCA of the total urinary metal(loid)s for workers (Appendix A Table S11). Furthermore, under PCA, each pair of metal(loid)s must be significantly correlated for identification as the same source. Appendix A Fig. S2 shows the Spearman correlation matrix of metal(loid)s in workers, and significance was indicated by an asterisk ($p < 0.05$). Fig. 1 presents the dimensional PCA results. Principal component (PC) 1 was characterized by Cd, As, Sb, Pb Tl and Sn, explaining 26% of the variance. PC 2 was dominated by Se, Cu, Zn, Mo and Sr, PC 3 by V, Ni and Hg, PC 4 by Mn and Fe, PC 5 by Cr and Mo, and PC 6 by Co. These

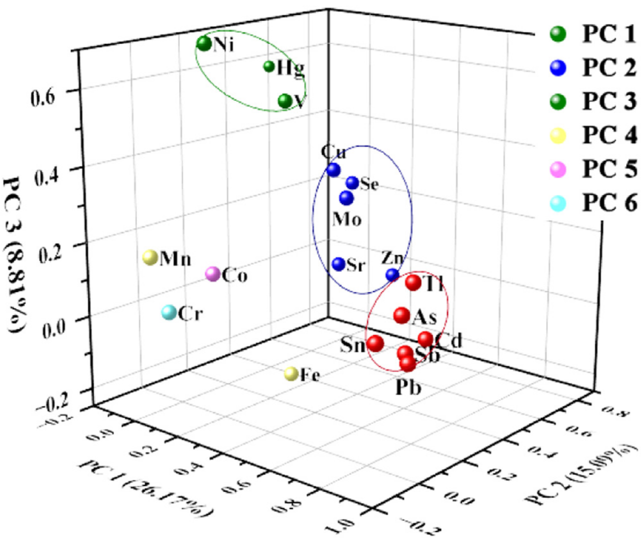

Fig. 1 – (a) Three-dimensional diagram of principal components analysis (PCA) results of metal(loid)s in urine of workers (*n* = 179). PC: principal components; the percentage in the brackets was the explained variance of relevant PCs; the metal loadings > 0.4 with significant correlation between metals were clustered into a group possibly from the same source.

PCs explained 15%, 9%, 7%, 7% and 7% of the variance, respectively (Appendix A Table S11). Hence, the urinary metal(loid)s of workers were divided into six groups based on the PCA results as described above.

The co-occurrence of Pb and Cd in various sources of pollution, particularly in non-ferrous metal smelting activities, has been documented (Zhang et al., 2022). Through our comprehensive analysis of soil metals within and close to the NMSP, it has been determined that Mn, Co, Ni, Zn, As, and Cd were co-emitted, while Co, Cu, Zn and Pb were co-emitted within the NMSP. However, As, Pb and Cd exhibit similarities in the surrounding areas (Qi et al., 2023). Additionally, lake sediments related to metal smelting activities have revealed the presence of other metals such as Tl and Sb (Wang et al., 2020). However, there is currently a lack of direct evidence to establish their relationship during metal smelting. To gain a comprehensive understanding of the sources of metal(loid)s from metal smelting activities, the total urinary metal(loid) levels of workers were compared across nine different groups based on their positions in the metal smelting process. Metal smelting involves three primary processes: smelting, extraction, and refining stages (Zhang et al., 2022). While the largest number of workers, such as smelters and furnacemen, were employed in these major smelting processes, other positions such as drivers, electricians, and welders played crucial roles in supporting metal smelting production. A comparison of metal(loid) levels in the urine of workers from various occupational categories, grouped according to their positions, is presented in Appendix A Table S12. Smelters, furnacemen, and drivers exhibited higher median concentrations of metal(loid)s on PC 1 compared to workers in other positions. Smelters, furnacemen, and drivers exhibited higher median concentrations of metal(loid)s on PC 1 compared to workers in other positions. Notably, these three positions are primarily involved in working near the smelting furnace and are in direct contact with smelting raw materials, the pollution emitted during high-temperature processes, and the residue after the furnace. As, Pb and Tl are semi-volatile heavy metal(loid)s that tend to evaporate from ore particles during high-temperature smelting (Wang et al., 2020; Zhou et al., 2021). Sb is closely associated with As due to their similar chemistry and binding properties, commonly found in the raw materials and slag of smelting (Dousova et al., 2020; Wang et al., 2022). Electricians and welders exhibited relatively high levels of Pb and Sn in their urine, likely due to the presence of Sn in solder and its release during high-temperature welding (Cheng et al., 2017; Park et al., 2015). Although air pollution control devices effectively remove some metal(loid)s during the smelting and extraction stages (Zhang et al., 2022), there were no significant differences in metal(loid)s on PC 1 among different workers, indicating that internal disordered diffusion is a characteristic of occupational exposure. Therefore, PC 1 represents the source of production processes involved in the smelting of non-ferrous metals, which includes high-temperature processes.

On the other hand, Se, Zn, Cu and Mo on PC 2 are essential trace elements commonly found in food (Ma et al., 2023). Mo, Se, and Sr on PC 2 did not exhibit characteristics of elements associated with non-ferrous metal smelting, as their concentrations in workers were not significantly higher compared to the control population (Table 1). Additionally, it is challenging to identify PC 2 as a source related to the smelting process, as the cases with the highest levels of metal(loid)s were not concentrated in one specific category of workers. Although Zn and Cu are typical pollutants from smelters (Zhang et al., 2022), it is hypothesized that the higher levels observed of essential trace elements may be due to additional exposure through the operating process and diet. Therefore, PC 2 is primarily attributed to a dietary source.

Considering the median and maximum values of V, Ni, and Hg, the exposure source of smelters, furnacemen, and drivers may be associated with PC 3. The concentrations of V, Ni, and Hg were found to be at low levels, but there were significant differences in Ni and Hg levels among occupational categories ($p < 0.05$, Kruskal-Wallis H test). Drivers had the highest levels of V and Ni, which are linked to heavy oil combustion (Czech et al., 2017; Quist et al., 2022). Hg is typically released from coal combustion, which is widely used as a fuel for smelting (Biswas et al., 2008; Wang et al., 2021). Smelters and furnacemen exhibited higher levels of Hg in their urine compared to workers in other occupations, further indicating that PC 3 is associated with fuel combustion for energy supply in smelting activities.

The elements found on PC 4–6 did not exhibit characteristic properties of non-ferrous metal smelting, as there were no significant distinctions observed between workers and the control group. The presence of both Fe and Mn primarily correlated with black metals, and these elements also serve as essential trace metals for human health. Among the various worker groups, electricians and welders had the highest concentrations of Fe and Mn in their urine. However, the levels of Fe and Mn in the urine of workers were significantly lower compared to the control group. Fe is abundant in the raw material of Cu ore, but its mass concentration in emitted flue gas is negligible (Zhang et al., 2022). Therefore, the source of Fe may be associated with the co-existence of Mn. As the control group consists of rural residents who potentially use drinking water from metal pipes or underground sources, they have a higher likelihood of exposure to Mn and Fe contamination from corroded water distribution pipes (Tong et al., 2019). Hence, PC 4 is predominantly influenced by tap water contaminated by corroded pipes. On the other hand, PC 5 and PC 6 are primarily affected by Cr and Co, respectively. Although Cr is among the top five heavy metals concentrated in a Cu smelter, its concentration significantly decreases after the smelting furnace (Zhang et al., 2022). The highest levels of Cr in urine were observed in drivers, followed by technicians, electricians, and welders, who were not directly involved in the furnace process. Interestingly, both workers and residents exhibited no significant difference in Cr levels, but their concentrations were significantly lower compared to the control group. This suggests that Cr in workers may not be associated with non-ferrous metal smelting. Regarding urinary Co impacted by PC 6, there were no consistent patterns observed across different worker groups, although the levels of Co in workers were significantly lower compared to residents and the control group. A specific source or factor may account for the lower Co levels in workers, which is also unrelated to non-ferrous metal smelting.

In summary, the urinary levels of Cd, As, Sb, Pb, Tl, and Sn in all workers were elevated due to non-ferrous metal smelting activities, likely as a result of the high-temperature processes involved. Special attention should be directed towards workers in roles such as smelters, furnacemen, and drivers, as they may be exposed to V, Ni and Hg from the fuels utilized.

2.3.2. *Influential factors*

In addition to differences in occupations within the NMSP, variations in the exposure of metal(loid)s in urine can also be attributed to interindividual differences among workers. A significant correlation was observed between gender, age, smoking habits, and certain metal(loid)s in the urine of workers ($p < 0.05$) (Appendix A Table S13). Notably, the levels of urinary Zn, Cu, and Hg were significantly higher in males compared to females across all groups (Appendix A Fig. S3), whereas urinary Co showed the opposite trend. This divergence in urinary metal levels may be attributed to physiological characteristics between males and females, as 11 out of 18 metal(loid)s showed significant correlations with gender among residents. Furthermore, the lower presence of female participants in the worker's group may explain the lower levels of Co in workers compared to residents and the control population. Only 14% of workers were females, whereas the percentage of females in the residents and control population was 58% and 58%, respectively (Appendix A Table S1). It appears that occupational exposure serves to diminish the disparity in metal exposure between males and females. Additionally, smokers exhibited significantly higher levels of urinary Zn in all three populations compared to non-smokers (Appendix A Fig. S4), indicating that smoking habits contribute to elevated urinary Zn levels. Although Cd is a toxic metal found in cigarettes, this study only observed significantly higher urinary Cd levels in smokers among workers. Therefore, gender differences and smoking habits have a limited impact on the levels of urinary metal(loid)s in workers, with occupational exposure being the primary source of metal(loid)s in the urine of workers.

Remarkably, the concentration levels of Cd, Pb, As, Sn, Sb, Tl, and Sr in urine exhibited a positive correlation with age ($p < 0.05$) among the workers (Fig. 2). Consequently, all of these metal(loid)s were categorized under PC 1, while Sr was associated with PC 2, as mentioned earlier. However, out of these elements, only the concentration of Cd exhibited a positive correlation with the duration of work in the NMSP (Appendix A Table S13). As previously stated, Cd, Pb, As, Sn, Sb, and Tl were considered potential pollutants associated with non-ferrous metal smelting. The excessive presence of these metal(loid)s in the body may result in their excretion at elevated levels. It should be noted that the clearance of these metals in the blood and their excretion in the urine vary due to the different binding states they assume within the body. For instance, Pb tends to accumulate in bones and teeth, while As accumulates in hair tissue (Cui et al., 2013). These metals maintain a dynamic equilibrium within the tissues and blood, with any excess metal(loid)s present in the blood being excreted through urine. Additionally, a positive correlation between age and urinary Cd concentration was also observed in elderly individuals (age > 65) within the general population (Lv et al., 2021). Hence, the age-related positive correlation found in urinary Cd, Pb, As, and Sb could potentially be attributed to the excessive accumulation of these metals in the body.

In general, gender differences and smoking habits were found to have a limited impact on the levels of metal(loid)s detected in urine among the workers. The primary influential factor contributing to elevated levels of metal(loid)s in the urine of workers appears to be occupational exposure to non-ferrous metal smelting, thus displaying a positive correlation with age.

2.4. *Assessment of health risks*

This study aimed to calculate the *EDIs* of the target metal(loid)s and assess both carcinogenic and non-cancer risks in both occupational and non-occupational populations. It is important to note that the estimation of risk is based on specific metal(loid) species. As^{III} was used to evaluate the health risks in this study. Some studies used As^{III} concentrations estimated by the total As may ignore the individual variation (Zhong et al., 2021). The absence of other metal speciation, such as Hg and Cr, was due to their extremely low concentration in urine, making it difficult to determine the speciation. Appendix A Fig. S5 presents the carcinogenic and non-cancer risks of three population groups exposed to metal(loid)s. The HQ followed the descending order of As^{III} > Cd > Se > Pb > Sb > Ni > Hg > Mn > Cr for workers. As^{III} resulted in higher non-cancer risks for workers (> 1.0). Taking into account the As pattern in urine discussed earlier, it can be speculated that workers with lower As methylation capacity may experience negative outcomes in terms of non-cancer risks. On the other hand, Se showed a prominent non-cancer risk for workers, following Cd. Se was considered to be a di-

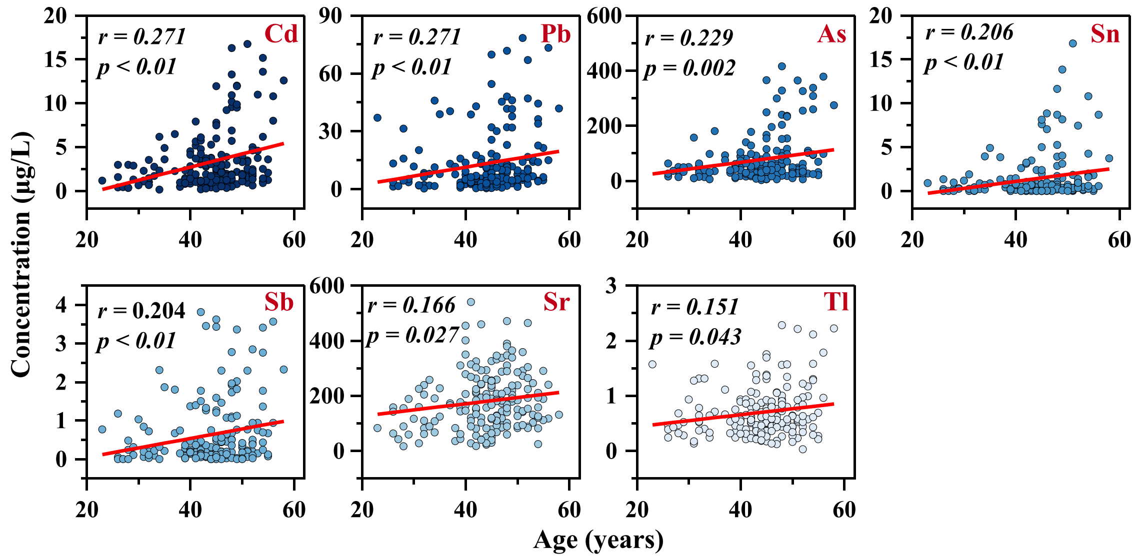

Fig. 2 – Scatter plots of Spearman correlations between age and metal(loid)s in urine of workers (*n* = 179). The red lines were the linear fitting curves; *r* represents the Spearman correlation coefficients.

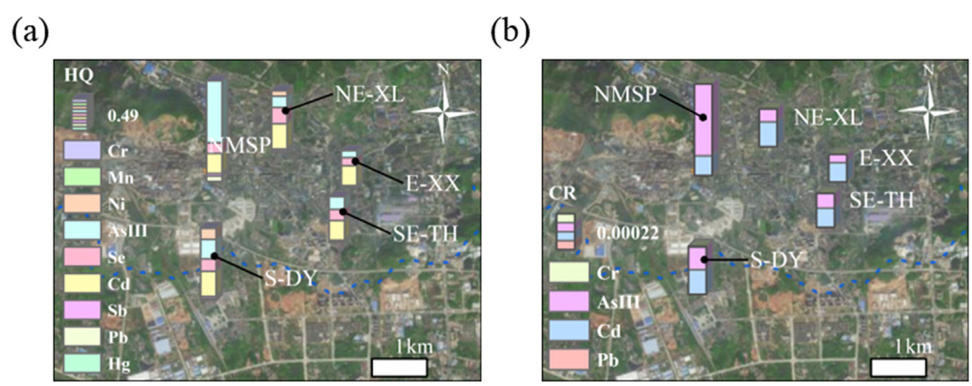

Fig. 3 – The maps of health risk assessment of residents in different locations. (a) Non-cancer risks; (b) Carcinogenic risks; NMSP: non-ferrous metal smelting plant; S-DY, residents living distributed in Daye, the southern side of the non-ferrous metal smelter plant (NMSP); NE-XL, residents living distributed in the Xialu district, the northeastern of NMSP; E-XX, residents living in the Xinxing community, the eastern of NMSP; SE-TH, residents living in Tonghua community, the southeastern of NMSP.

etary source rather than originating from non-ferrous metal smelting activities. The high non-cancer risks associated with Se suggest the need for further investigation. However, it must be noted that in this study, Se may not be characterized as a pollutant originating from non-ferrous metals smelting activities.

Concerning carcinogenic risks, it was found that As^{III} remained the primary carcinogen among workers, with a CR value exceeding 1.0E-04, which is the established unsafe limit (EPA, 1989; Hu et al., 2012). The CR values for Cd and As^{III} were both approximately 1.0E-04 for residents and control groups, indicating that they were exposed to unsafe carcinogenic risks from As^{III} and Cd. Importantly, the carcinogenic and non-cancer risks posed by Cd were similar across the three populations. When compared to the CR of Cd for general urban residents in southern China, the risk levels were found to be comparable, ranging from 1.0E-06 to 1.0E-03 (Zhong et al., 2021). In addition, the urinary Cd levels of the three populations in this study were far lower than the urinary Cd of adult residents in the Zn-Pb and Cu-smelter area (5.5 ± 3.5 μg/L) in the previous study (Du et al., 2020). This suggests that Cd exposure in these populations may pose a broader risk. While non-ferrous metal smelting does contribute to certain health risks, it is not the primary source. The cumulative CR values indicate that all populations were at risk of carcinogenic effects from these metal(loid)s. Except for Cd, As^{III} and Pb were identified as the primary risks associated with non-ferrous metal smelting activities. For the non-occupational population, both the non-cancer risks and carcinogenic risks were lower compared to workers. The trends in HQ were similar for residents and control groups (non-occupational population), with the following descending order: Cd > Se ≈ As^{III} > Sb > Pb > Ni > Hg > Mn > Cr. As the most representative metal(loid) from non-ferrous metal smelting, As^{III} had a relatively lower impact on non-occupational populations.

Although there was no significant difference between the risk of residents living near the plant and the controls, both cancer and non-cancer risks of residents who lived closer to the plant were higher (Fig. 3). The categorization of residents was based on various geographical regions, including the southern (S-DY), northeastern (NE-XL), eastern (E-XX), and southeastern (SE-TH) sides of NMSP (Appendix A Fig. S6), and the corresponding metal(loid) concentrations were shown in Appendix A Table S14. Now the residents near the NMSP were living located upwind of the plant, and the residents lived downwind of the plant had moved away (Qi et al., 2023). This can partly explain why there was no significant difference between the nearby residents and the control population. However, as residents live closer to the smelting area, there was still the possibility of increasing the health risks. Although Cd accounted for a larger portion of both the cancer and non-cancer risks, the CR and HQ of Cd for workers and all residents were at similar levels, while the greater variation was occurred in As^{III}. As is a metalloid with semi-volatile properties, giving it a higher proportion of airborne presence compared to non-volatile metals (Zhou et al., 2021). Except for the higher risks to As^{III} to NE-XL and S-DY, Ni was another important source of increased non-cancer risks of residents living closer to the NMSP. However, workers did not suffer such risks to Ni in urine. Thus, As^{III} was the main contributor to both cancer and non-cancer risks to residents. Implementing additional measures to regulate and mitigate arsenic emissions from industrial facilities can significantly diminish potential health hazards for individuals residing in proximity.

In summary, non-ferrous metal smelting activities notably contributed to the health risks associated with As^{III} in workers. Total nearby residents had similar risks compared to controls, but residents living closer to NMSP had higher both cancer and non-cancer risks.

3. Conclusions

This study examined the levels of eighteen urinary metals and five arsenic species among individuals working in the non-ferrous metal smelting industry, as well as nearby residents and the control population. The results indicate that workers had the highest levels of toxic urinary metals, followed by residents and controls. As, Pb, Cd, Sb, Tl and Sn were identified as pollutants originating from non-ferrous metal smelting activities, and all these metals showed a positive correlation with age in workers. The high-temperature smelting process was identified as the main source of these pollutants, and workers in furnace-related positions had higher levels of these metals in their urine. Health risk assessments revealed that workers were at risk of non-cancerous and carcinogenic effects from As^{III} exposure in the non-ferrous metal smelting industry. The non-occupational population seemed to suffer limited impact from metal smelting; however, residents living closer to the NMSP had higher both cancer and non-cancer risks. Except for As, most of the metals may accumulate in vivo, and further research on other biological mediators, such as blood, may uncover more emerging toxic metals to enhance more prospective environmental measures for non-ferrous metal smelting activities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jes.2023.10.003.

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