Heavy Metals in Indoor Dust in China: Occurrence, Source, and Health Risk

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Abstract

Exposure to heavy metals in indoor dust may affect human health and has gained increasing attention in recent years. However, the occurrence, sources, and health risks of heavy metals in indoor dust in China are still poorly understood, thus leading to certain knowledge gaps. This review systematically discussed the pollution characteristics and the associated health risks of heavy metals in indoor dust in China. Results show that the heavy metals in indoor dust in China are more serious than that in other countries with concentration distribution patterns of $Zn > Mn > Pb > Cu > As > Cr > Ni > V > Co \approx Cd > Hg.$ Mining and smelting activities, electronic waste recovery, and industrial production can increase heavy metal concentrations in indoor dust in sampling cities. Due to the variation of sources, significant spatial differences are observed among different regions and between rural and urban homes. Results from source apportionment show that mining activity and traffic are the dominant sources of indoor heavy metals. In comparison with adults, children have higher non-carcinogenic and carcinogenic risks due to more frequent ingestion of indoor heavy metals. Residents in South China are suffering from high carcinogenic risks due to high As occurrence levels. Children in South, East, and Southwest China are suffering from non-carcinogenic risks due to Pb exposure. To our theme, more studies, especially in rural homes, involved with more kinds of microenvironments are welcomed in the future. Meanwhile, in the premise of setting a standard guideline for a consistent target heavy metal, activity patterns should be considered when estimating the health risk. Results from this study are expected to provide crucial information for policymakers and researchers to alleviate indoor heavy metal pollution.

Keywords Heavy metals · Indoor dust · Source apportionment · Health risks

Highlights

- The occurrence, sources, and health risks of heavy metals in indoor dust in China are systemically reviewed.
- Serious indoor heavy metal pollution is caused by specific sources such as e-waste recycling and traffic emissions.
- Children had higher health risks than adults due to more indoor heavy metal exposure.
- Residents in South China suffered from carcinogenic and noncarcinogenic risks.

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Introduction

Heavy metals are widely existed in environmental media including atmosphere, water, soil, and dust. Different from other pollutants that can be quickly removed from environment through physical, chemical, biological, or self-purification processes, heavy metals are difficult to degrade in the environment [1]. Generally, heavy metals are toxic and have adverse effects on both ecosystem and human health. For example,

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long-term accumulation of mercury can damage the normal function of the lung, nerves, and vision of humans [2]. High lead level in the blood can influence the behavior and cognitive abilities of children and damage the central nervous system and kidney function of adults [3]. Anthropogenic activity, such as solid fuel combustion and mining activity, is recognized as the main source of heavy metals globally [4]. Heavy metal pollution is of great concern in recent decades due to rapid urbanization and industrialization, putting serious threats to both ecological environment and human health.

Heavy metals in indoor dust are raising concerns since people spend approximately 80% of their time indoors [5, 6]. Hwang et al. [7] confirmed that the contribution of chemical exposure in indoor dust was significantly higher than that in outdoor dust, and the difference could be as high as 1000 folds. Heavy metals in outdoor environments can enter indoors through ventilation and dust/soil on human body [8, 9]. Internal emissions (e.g., smoking and cooking) also act as major contributors to heavy metals in indoor dust [10, 11]. Yoshinaga et al. [12] reported that heavy metals, such as Cd, Cu, Pb, and Zn, in indoor dust were 10 times higher than that in outdoor dust. The main pathways of human exposure to heavy metals include oral intake, inhalation, and skin contact [11]. Indoor dust with small size can be re-suspended in the air and adhere to food and then enter into the human body through dietary intake. Children are more susceptible to indoor heavy metal pollution than adults since they are easier to exposed to indoor dust on furniture and children's toys [13].

Various negative health outcomes associated with heavy metal exposure in indoor dust have been frequently reported in previous studies. For example, Yadav et al. [14] reported that the carcinogenic risks due to exposure to heavy metals in dust for both adults and children in four major cities in Nepal were one order of magnitude higher than the acceptable level. Bian [15] observed that the blood lead levels of children ranged from 75.0 to $325.0 \ \mu g/L$, with 87% of them being over 100 $\mu g/L$ in rural households. Furthermore, a positive correlation between blood lead level and lead exposure concentrations was also reported. The results above indicated an urgent need to control indoor heavy metal pollution on the stand of human health protection.

China is facing serious heavy metal pollution in multiple environmental media in the last decades due to rapid urbanization and industrialization, thus threatening human health to certain extent. However, most of available studies are focused on heavy metal pollution in outdoor environment and its associated health effects, whereas a systematic understanding of heavy metal pollution in indoor dust is still unavailable. Herein, we systematically discussed the current status of heavy metal pollution in indoor dust with the special foci on the occurrence, sources, and health risks. Furthermore, the knowledge gaps and future research priorities are identified. Results from this study can fill in the data gap in indoor heavy metal pollution and are beneficial to the mitigation strategy formulation for policymakers.

Methods

Literature Review

Both English and Chinese literatures were peer-reviewed from different databases. Search engines including Web of Science (www.webofscience.com) and China National Knowledge Infrastructure (CNKI) were used to collect pertinent peer-reviewed articles published up to May 2023. The search terms were ("Indoor" or "household" or "indoor pollution" or "indoor environment") AND ("dust") AND ("heavy metals"). After searching the electronic databases, a total of 151 papers in English and 84 papers in Chinese met the selection criteria. Then, papers that were not closely related to the main objectives of this review were removed. Finally, 70 literatures were read in full-text and used for further analysis. The same data selection criteria were used to extract data from all papers. The data selection criteria included the following: (1) the sampling sites belonged to China; (2) the dust was collected in indoor environments such as residential homes and offices; (3) the concentrations of heavy metals were detected with proper data quality control. Information including paper title, journal name, sampling and publication year, authors, province, locations (home, office area, school, and kitchen), fuel type, and heavy metal concentrations were extracted from all papers for further analysis. Data from 88 sampling cities were collected, covering 20 provinces, 4 municipalities directly under the central government, 2 autonomous regions, and 1 special administrative region.

For better illustration, China is divided into seven regions following previous studies as follows: East China, South China, North China, Central China, Northeast China, Northwest China, and Southwest China, respectively [16]. Table S1 provides detailed information of the data extracted from selected papers (specific sampling area, locations, heavy metal types, and references).

Health Risk Assessment

Heavy metals in indoor dust can enter into human body mainly through ingestion, inhalation, and dermal contact [17]. Eight heavy metals including Cu, Zn, Pb, Hg, Ni, Cd, As, and Cr are selected for health risk assessment. The health risks of heavy metals in indoor dust to adults and children are calculated through the human health evaluation model of the United States Environmental Protection Agency (US EPA), including noncarcinogenic risk and carcinogenic risk [18].

The average daily exposure dose of heavy metals through ingestion, inhalation, and dermal contact are calculated as follows, respectively [19, 20]:

$$ADD_{inh} = \frac{C \times inhR \times EF \times ED}{PET \times BW \times AT}$$
(1)

$$ADD_{ing} = \frac{C \times ingR \times EF \times ED}{BW \times AT} \times 10^{-6}$$
(2)

$$ADD_{der} = \frac{C \times AF \times SA \times ABS \times EF \times ED}{BW \times AT} \times 10^{-6}$$
(3)

where *C* is the concentration of heavy metals in indoor dust, mg/kg. ADD_{inh} , ADD_{ing} , and ADD_{der} represent heavy metal exposure doses by inhalation, ingestion, and dermal contact (mg·kg⁻¹·d⁻¹), respectively. Other parameters used in the calculation are shown in Table S3.

The Hazard Index (HI) is used to assess the non-carcinogenic risk of heavy metals in indoor dust, which is calculated by the sum of the Hazard Quotient (HQ) caused by different exposure pathways [21]. The HI values less than or equal to 1 indicate little or no non-carcinogenic risks, while HI values higher than 1 indicate non-carcinogenic risks [22]. The calculations are calculated as follows:

$$HQ = \frac{ADD_{ing/inh/der}}{RfD}$$
(4)

$$HI = \sum_{i=1}^{n} HQ_i$$
(5)

Carcinogenic risk (CR) is used to evaluate the carcinogenic risk of heavy metals in indoor dust to human body. TCR means total carcinogenic risk, which is the sum of the carcinogenic risk of three exposure pathways [18]. The CR or TCR > 10^{-4} , < 10^{-6} , and in the range of 10^{-6} to 10^{-4} indicate that heavy metals in indoor dust have carcinogenic risk, no carcinogenic risk, and acceptable risk, respectively [22]. For carcinogenic metals such as Ni, Cd, As, and Cr, the carcinogenic risks are calculated as follows [23••]:

$$CR = ADD_{ing/inh/der} \times SF$$
(6)

$$TCR = \sum_{i=1}^{n} CR_i$$
(7)

Results and Discussion

Occurrence of Heavy Metals in Indoor Dust

Concentrations

As plotted in Fig. 1, the pattern of average concentration of heavy metals in indoor dust in China shows the decreasing trend of Zn > Mn > Pb > Cu > As > Cr > Ni > V > Co \approx Cd>Hg. The average concentrations of Zn and Mn are 1052.19 and 536.21 mg/kg, respectively, significantly higher than that of other heavy metals, while the concentration of Hg is only 0.96 ± 0.82 mg/kg, nearly 1 to 2 orders of magnitude lower than that of other heavy metals in indoor dust. Zn is the most abundant heavy metal in indoor dust, and its highest concentration is observed in an indoor e-waste manual dismantling workshop in Shanghai (12,503.00 mg/ kg) [24], following by Huize County, Yunnan Province (6888.20 mg/kg), where a lead and zinc smelting plant is located [25], and Hong Kong (5,100.75 mg/kg) [26], where the sampling site is near an electronic waste recycling plant. Similarly, the highest indoor concentration of Hg (5.47 mg/ kg) is found in workshops near the e-waste recycling planting in Hong Kong [26], following by residential homes near a lead and zinc smelting plant in Huize, Yunnan Province (3.10 mg/kg). It is reasonable to infer that the concentration of heavy metals in indoor dust is largely affected by specific emission sources since mining and smelting activities, electronic waste recycling, and industrial production contribute significantly to the accumulation of heavy metals in indoor dust [27]. In addition, the concentrations of Cu and Pb in industrial cities such as Guangzhou (693.33 mg/ kg and 862.00 mg/kg, respectively) are relatively higher than that in other regions in China. In industrial cities, emissions from industrial activities are the dominant sources of heavy metals. For example, the production of Cu can release many copper-containing particles into the surroundings, and Pb is mainly yielded from automobile manufacturing and the thermoelectric industry [28]. Results above indicate the important role of emission sources on indoor heavy metal pollution, which influences not only pollution levels but also the types of heavy metal in indoor dust.

To better illustrate the indoor heavy metal pollution in China, we compared the indoor heavy metal pollution in China with that in other countries, including Riyadh, Saudi Arabia [29], Ottawa, Canada [30], Istanbul, Turkey [31], Giza and Cairo, and Egypt [32]. (details in Table S2). China owes the highest indoor Cd pollution (10.05 mg/ kg), 2.37 and 12.56 times of Ottawa, Canada (4.24 mg/ kg), which had the second highest indoor Cd concentration, and Istanbul, Turkey (0.80 mg/kg), where indoor Cd concentration was the lowest, respectively. The indoor Cu





concentrations in the UK [33], Tokyo and Hiroshima, Japan [12], and China are all high, of 301, 304, and 323.66 mg/ kg, respectively. It is widely known that Cu is mainly emitted from engine component wear, fuel combustion, and oil spills. In addition, industries such as metal plating, electroplating, and papermaking can also release copper into environment [11, 34]. Although industrial structure and development levels in different countries are varied, severe Cu pollutions in indoor dust are all observed. The concentration of Pb in Australia is 85.20 mg/kg [35], 80.25% lower than that in China (431.36 mg/kg). This is probably due to the Australian government limits the lead amount in wall paints, which is an important source of lead [36]. The concentration of Ni in indoor dust is close among developed countries, which is 53.10 mg/kg in the UK [33], 52.90 mg/kg in Riyadh, Saudi Arabia [29], 53.60 mg/kg in Ottawa, Canada [30], and 59.60 mg/kg in Tokyo and Hiroshima, Japan [12], respectively, and all of these are significantly lower than that in China (102.91 mg/kg). Indoor Ni is mainly emitted from coal burning [37], which is extensively used as domestic and industrial energy in China [38], consequently resulting in severe indoor Ni pollution. Interestingly, the concentration of Zn in Christchurch, New Zealand, is as high as 10,400 mg/kg, much higher than that in other countries including China [39]. This is possibly due to the wide application of carpets in New Zealand, since the damage of carpets will release considerable Zn into indoor environments [39, 40]. Due to limited studies on indoor heavy metal pollution, it is difficult to consider some influencing factors such as sampling time and coverage of sampling area, which may affect the accuracy of the comparison results to some extent. Therefore, more future studies are expected to supplement the data gap and clarify regional differences in indoor heavy metal pollution.

Spatial Variation

Four typical heavy metals (Cr, Cu, Pb, and Zn) that are frequently measured in most selected papers are discussed in this section. The distribution of these four heavy metals in the seven regions is plotted in Fig. 2. The distribution patterns of heavy metals in indoor dust are Zn > Pb > Cu > Crin Southwest China, Zn>Cu>Pb>Cr in Central China, and $Zn > Cu \approx Pb \approx Cr$ in North China, indicating significant spatial differences in indoor heavy metal pollution. The concentrations of Zn in Southwest and South China are significantly higher than that in other regions. Similarly, Pb concentrations are also highest in Southwest and South China, 9.66 and 9.34 times of that in Northeast China, where the Pb concentration is lowest (92.55 mg/kg), respectively. In addition, the concentrations of Cu and Cr in South China are 800.70 mg/kg and 182.77 mg/kg, respectively, both higher than that in other regions. The high occurrence levels of Cu and Cr in South China are mainly caused by the e-waste recycling industry in South China, since electronic equipment contains relatively high levels of Pb and Cu, as well





as other heavy metals, and improper treatment can cause severe heavy metal pollution [41, 42]. Meanwhile, heavy metals such as Zn, Pb, Cu, and Cr can be released during e-waste dismantling [43]. Previous studies have proved that due to e-waste pollution, coastal cities in South China, such as Guangzhou and Hong Kong, have become "hot spots" of heavy metal pollution [44]. Southeast China is another region with severe heavy metal pollution, which may be attributed to mining and smelting activities. For example, lead and zinc mining and smelting in Huize County, Yunnan Province, have made major contributions to high indoor concentrations of Zn and Pb in Southwest China [25, 45•]. Such significant spatial differences of heavy metal pollution in indoor dust indicate that more concern should be paid in regions with strong emission sources on the stand of human health protection.

Difference Between Urban and Rural Homes

Generally, the potential sources are varied between urban and rural homes, thus resulting in differences in indoor heavy metal pollution in these two areas. For better comparison, studies conducted in urban and rural homes in the same city and measured the same heavy metals are selected. Finally, six typical cities, which are Taiyuan, Dalian, Shanghai, Wuhan, Chengdu, and Lanzhou, meet the selection criteria and are used for discussion here to give some new insight for future studies.

The distribution characteristics of heavy metals in indoor dust from urban and rural homes in these six cities

are shown in Fig. 3. As shown in Fig. 3, Zn is the dominant heavy metal in indoor dust both in urban and rural homes, accounting for more than 50% of total. While the proportions of Cd and Hg in urban and rural homes are both less than 1%. The concentrations of Zn, Pb, and Cu in urban areas are significantly higher than those in rural areas. For example, Zn concentrations in urban areas (387.26 mg/kg) are about twice that in rural areas (194.69 mg/kg). Huang et al. [46] also found that the concentration of Cu was 97.61 mg/kg in urban areas, more than twice that in rural



Fig. 3 The concentrations and percentages of individual heavy metals in urban and rural households in six cities

areas (42.19 mg/kg) in Taiyuan. However, the concentrations of the other four heavy metals (As, Ni, Cd, and Hg) showed little difference between urban and rural areas. The indoor Pb concentration may be related to motor vehicle emissions. It was found that the concentrations of Pb in school dust near major roads (617.58 mg/kg) were much higher than those near smaller roads (170.89 mg/ kg) [47]. Studies also showed that although leaded gasoline has been banned, Pb may still be related to transportation sources [48]. The above reasons may explain the high occurrence of indoor Pb in urban area. Saeedi et al. [49] suggested that Zn and Cu were related to the burning of fossil fuels such as gasoline. In addition, another important source of Zn is zinc-containing tire wear and the latex paint that were commonly used by residents for wall painting [50]. Huang et al. [46] confirmed that Cu could be released from industrial and traffic industries. Similarly, Wei et al. [51] found that dominant sources of Cu were traffic and industrial activities in Urumqi, Xinjiang Province. The above reasons indicate that due to the developed transportation and industries, the heavy metals in urban dust may be higher than that in rural areas.

Source

Methods for Source Apportionment

Source apportionment plays an important role in pollution emission identification and the following mitigation plan implementation [52]. At present, the commonly used source apportionment methods of heavy metals in dust are positive matrix factor (PMF) and principal component analysis (PCA) [25]. PMF is a mathematical method based on the receptor model to quantitatively analyze the source of pollutants using sample composition, calculate the error of each chemical component in the dust using the weight, and then determine the main sources and their contribution through the least square method [53]. PCA is a statistical method based on orthogonal transformations to convert multiple variables into a set of mutually orthogonal vectors (i.e., principal components) that retain most of information of the original variable, which is usually expressed as a linear combination of the original variables [54]. PCA can reflect the spatial distribution of pollutants, especially heavy metals, and thus identify the sources [55]. Both PMF and PCA are based on factor analysis, and source apportionment can be performed without source component spectrum [56]. Compared with PMF, PCA can determine the contributions of each factor and describe variables with minimal information loss and is frequently used to identify pollution sources of soil or sediment, as well as indoor dust [25]. Almost all the selected papers use PCA method for source apportionment.

The Sources of Heavy Metals in Indoor Dust

The source apportionment results of heavy metals in indoor dust in four typical cities reported in previous studies are selected for comparison (see Fig. 4). The sources of heavy metals in indoor dust vary in different regions. For example, in Huainan City and Chengdu City, the dominant source is traffic emission, with the contributions of 20.60% and 37.10%, respectively (Fig. 4a, d). In Huize City and Tongling City, both of which have mining industries, the heavy metals in indoor dust are closely related to local mining activities with contributions of 34.62% and 42.00%, respectively (Fig. 4b, c). Similarly, He et al. [57] confirmed that e-waste recycling activities had the largest impact on the accumulation of heavy metals in local indoor dust in Guangzhou City with a contribution of 52%, and traffic source was another important source with a contribution over 20%. Other emission sources, such as the erosion and wear of tires and alloys, corrosion of automobile parts, the municipal road facilities, and the combustion of oil fuel, could also cause the accumulation of various heavy metals in indoor dust [11]. In addition, some studies have found that biomass fuel combustion in rural indoor environments also contributes to heavy metal exposure. For example, Yaparla et al. [58] found that biomass burning was the main source of heavy metals in rural household dust in India, accounting for 56.94% of the total variance. However, there are no available results on the impact of biomass burning on heavy metal pollution in indoor dust in China, which is an interesting research priority in the near future.

In addition to anthropogenic sources, such as mining activities, traffic, and coal combustion, natural source also acts as an important source of heavy metals in indoor dust. For example, As, Co, and V in Huainan City; Co in Tongling City; and Cr in Chengdu City are all came from natural sources, and these heavy metals are associated with the geological composition and primary minerals [11, 59, 60]. Interestingly, the sources of the same heavy metal vary largely in different regions. For example, Cu is mainly from traffic sources in Huainan City and Chengdu City [11, 59]; while in Huize City and Tongling City, it is mainly from secondary minerals and mining activities, respectively [45•, 60]. Similarly, Cr is mainly from anthropogenic sources (e.g., traffic sources, metal items in households, and paints) in Tongling City and Huainan City [59, 60], while natural source is the main source of indoor Cr in Chengdu City [11].

Health Risk Assessment

In this section, the non-carcinogenic risks of Cu, Zn, Pb, Hg, As, Cr, Ni, and Cd, as well as the carcinogenic risks of As, Cr, Ni, and Cd, are discussed. The non-carcinogenic risks and carcinogenic risks to children and adults caused by different heavy metals in the seven regions in China are shown in Table S5 and Fig. 5.



Fig. 4 Sources of heavy metals in indoor dust in four typical cities. Data is obtained from previous literatures [11, 45•, 59, 60]

The main exposure pathway to heavy metals is ingestion [23••]. Children have more frequent finger sucking and pica than adults [11], thus leading to one order of magnitude higher carcinogenic and non-carcinogenic risks for most heavy metals for children than adults (Table S5). Among the seven regions, the HI values of As and Pb for children (1.29 and 1.63, respectively) in South China and the HI values of Pb for children in Southwest and East China (1.69 and 1.32, respectively) all exceed the standard level set by the US EPA (HI > 1) [22], highlighting the high non-carcinogenic risks for children. The TCR values of As for adults and children in South China are 2.96×10^{-4} and 5.78×10^{-4} , respectively, exceeding the safe level set by EPA [22], implying that residents in this region suffer from carcinogenic risk due to As exposure. This is partly due to common e-waste recycling activities here. Zheng et al. [61] reported the high Pb levels in the hair of residents in South China (14.97 mg/kg), especially for workers who were occupational exposure to e-waste (40.07 mg/kg). Wittsiepe et al. [62] also reported that the blood lead levels of workers and residents in Ghana near the e-waste recycling area were 53.67% higher than that of people who were not directly contacted with e-waste recycling. The high non-negligible health risks associated with e-waste recycling activities suggest an urgent need to control e-waste recycling. The carcinogenic risks for adults and children in other regions, apart from As in South China, are in the acceptable risk range $(10^{-6} \text{ to } 10^{-4})$.

The contributions of different heavy metals to carcinogenic and non-carcinogenic risks in the seven regions are shown in Fig. 5. As and Pb dominate the non-carcinogenic risks for both adults and children in China, while Cr and As dominate the carcinogenic risks. Similarly, Yu et al. [63] reported that As accounted for 54 to 90% of non-carcinogenic risks for atmospheric heavy metal exposure, while Cr accounted for 96 to 99% of carcinogenic risks, which is consistent with this study. The contribution of the same heavy metal to non-carcinogenic risk varies significantly among different regions and between adults and children. For example, the proportion of As to the HI for adults is 72% in South China, while it is only 7% in East China. The contribution of Pb to the HI for children in Central China is 54%, but is only 28% for adults. In contrast, the contributions of different heavy metals to cancer risk are similar among different



Fig. 5 Contributions of different heavy metals to non-carcinogenic and carcinogenic risks in China

regions and between adults and children. Figure 5c, d shows that As and Cr are the two main contributors to cancer risk in all regions with contributions of 99%. The above results suggest that reducing exposure to heavy metals of Pb, Cr, and As can significantly reduce the associated health risk.

Conclusion and Future Priorities

In this review, we systematically discuss the occurrence, sources, and health risks of heavy metals in indoor dust in China. Results show that Zn, Mn, and Pb are major indoor heavy metals. Mining and smelting activities, electronic waste recovery, and industrial production can increase heavy metal concentrations in indoor dust in the sampling cities, and the variations of these sources result in significant spatial differences. In most regions, mining activities and traffic are the dominant sources. People are exposed to heavy metals mainly through ingestion. Exposure causes carcinogenic risk for children and adults in South China, and Pb exposure causes noncarcinogenic risk for children in East, South, and Southwest China. In most regions, carcinogenic and non-carcinogenic risks of heavy metals exposure are in the acceptable range.

Based on previous studies, we systematically reviewed the pollution characteristics and associated health risks of heavy metals in indoor dust. The severe indoor heavy metal pollution indicates that there is an urgent need to mitigate heavy metal pollution in indoor dust. Given the limitations of available studies, several priorities should be paid attention to in the future. Firstly, given the large spatial variations of indoor heavy metal pollution in China, studies involving more regions and larger sample sizes are needed. Secondly, people stay in a variety of microenvironments, focusing only on residential homes that may cause great biases in the health risk assessment of heavy metal exposure [64]. Some microenvironments, such as offices, should be the focus of future research since people also stay for a long duration in these microenvironments [65]. Thus, the combination of the activity patterns with indoor heavy metal pollution may be helpful for accurate calculation of indoor heavy metal exposure for health risk assessment. Thirdly, more heavy metals should be included in future studies. Previous studies have always focused on regular heavy metals, and some heavy metals such as Hg are

rarely measured. However, Hg is a highly toxic heavy metal, which should be paid more attention to. Last but not the least, a standard guideline for a consistent target pollutant is urgently needed, which ensures future studies can focus on the same heavy metals for a better comparison.

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Data Availability Data will be made available on request.

Compliance with Ethical Standards

Competing Interests The authors declare no competing interests.

Conflict of Interest The authors declare no conflict of interests.

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