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Pulmonary bioaccessibility of trace metals in $PM_{2.5}$ from different megacities simulated by lung fluid extraction and DGT method

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Abstract

Atmospheric fine particulate matters ($PM_{2.5}$) pose significant risks to human health through inhalation, especially in the rapidly developing China due to air pollution. The harmful effects of $PM_{2.5}$ are determined not only by its concentrations and hazardous components from diverse sources, but more by their bioavailable fractions actually absorbed by human body. To accurately estimate the inhalation risks of airborne metals, a physiologically based bioaccessibility method combining Simulated Lung Fluid (SLF) extraction and Diffusive Gradients in Thin-films (DGT) approaches was developed, representing the dissolution of particulate metals into lung fluid and the subsequent lung absorption of free metal cations in solution, respectively. The new method was used to compare the lung bioaccessibility of typical trace metals in $PM_{2.5}$ from three China megacities (Shanghai and Nanjing in the east, Guangzhou in south) during heavy pollution seasons. Generally, the SLF bioaccessibility (%) simulating the solubility of particulate metals in alveolar lung fluid was in order of Ni>Cd>Mn>>Pb, while the succeeding DGT bioaccessibility representing labile metal fractions in solution phase absorbed directly by lung was lower and ranked as Ni~Mn>Cd>>Pb, thus Ni and Cd posed relatively higher potential risks owing to their high air pollution level and higher pulmonary bioaccessibility. Due to varied particle sources such as coal combustion and traffic emissions, some airborne metal concentrations (Pb, Ni) showed inconsistent spatial patterns with bulk $PM_{2.5}$ concentrations, and also varied bioaccessibility in different regions. The framework for $PM_{2.5}$ pollution risk assessments should be refined by considering both aerosol components and associated pollutants' bioaccessibility.

Keywords: Atmospheric particulate pollution; Heavy metals; Inhalable bioaccessibility; Gamble's solution; Diffusive Gradients in Thin-films technique

1. Introduction

Air pollution is an important environmental issue around the world (Saffari et al., 2014; Momtazan et al., 2018), especially for atmospheric fine particulate matters ($PM_{2.5}$) which pose significant risks to human health through inhalation in the rapidly developing countries like China (Cheng et al., 2016; Jin et al., 2017; Zhao et al., 2016). Generated from a wide range of sources, the airborne PMs may contain numerous hazardous components (Philip et al., 2014; Van Winkle et al., 2015; Xie et al., 2018), including toxic trace metals (Badaloni et al., 2017; Goudarzi et al., 2018; Gavett et al., 2003; Lippmann et al., 2006), which play an important role in the development of pulmonary and cardiovascular diseases (Charrier and Anastasio, 2015; Chen et al., 2018; Idani et al., 2018), and some of which are also carcinogenic (Galindo et al., 2018), such as cadmium (Cd), nickel (Ni), and lead (Pb). The effective control of ambient air pollution requires detailed knowledge of the spatial distribution and potential risks of inhalable PMs and their hazardous compositions. However, most current air quality standards and abatement strategies are generally based on the total PM concentration with deficient consideration of the key toxic components (Jin et al., 2017). Moreover, due to chemical speciation and matrix effects, only a certain fraction of the pollutants in inhaled PMs is finally bioavailable to human (Leclercq et al., 2017; Luo et al., 2011; Palleschi et al., 2018; Uzu et al., 2011). Therefore, total ambient PMs and metal concentrations cannot accurately estimate the health risks, and the human bioavailability of airborne metals becomes a significant issue in air pollution assessment.

To assess the bioavailability of air PM-associated metals, various Artificial/Simulated Lung Fluids (SLF) have recently been developed as an *in vitro* tool to predict inhalational bioaccessibility, a significant step further from traditional water solubility tests (Hernández-Pellón et al., 2018; Wiseman, 2015). Using these methods, the lung bioacessibility of various metals from different aerosol sources can be evaluated (Charrier et al., 2014; Kastury et al., 2018; Zereini et al., 2012). However, trace metal speciation in the solution phase of lung fluid was rarely considered, such as the bioavailability of free metal ions and those complexed with organic and inorganic ligands. In the present study, we also investigated the dissolved metal speciation in lung fluid using Diffusive Gradients in Thin-films (DGT) technique (Davison and Zhang, 1994). The DGT technique was typically proposed as a convenient speciation tool to assess bioavailable trace metals (free metal ions plus labile species) in water and soil environments (Davison 2016). It is of good value to assess the absorption of bioaccessible metals using the DGT as a model to simulate human alveolar sac walls.

In this study, trace metals in urban $PM_{2.5}$ of three representative megacities of China during pollution seasons were analysed by the distinctive stepwise physiologically based bioaccessibility method of SLF extraction and DGT. The primary objectives were: (1) to develop lung bioaccessibility methods for accurately estimating the human health risks of airborne metals in $PM_{2.5}$; and (2) to compare the pulmonary bioaccessibility of various trace metals in $PM_{2.5}$ from different cities.

2. Materials and methods

2.1. Study areas and $PM_{2.5}$ sampling

Because different cities have various pollution patterns (sources, levels, and compositions) and consequent health risks due to urbanization, geographical distribution and meteorology, the trace metals in $PM_{2.5}$ of three typical megacities were compared, including Shanghai and Nanjing in the Yangtze River Delta (YRD) of eastern China, and Guangzhou in the Pearl River Delta (PRD) of southern China (Fig.

1). The pulmonary bioaccessibility of trace metals in PM2.5 from these different cities will be investigated in details. Both the YRD and PRD are populous regions with dynamic economy and significant air pollution, and had been identified as "hotspot" regions in the national plan for regional pollution control (Luo et al., 2017). Shanghai is the largest industrial and commercial city in China, which is a coastal megalopolis bordering on East China Sea. Nanjing is an important industry (i.e., steel smelting, petrochemical and automobile manufacturing) and transportation center, with a north monsoon climate. Guangzhou close to the South China Sea is a megalopolis in South China with a subtropical monsoon climate.

The 24-h $PM_{2.5}$ samples (8:00 am - 8:00 am) during the same pollution seasons were collected at an urban site of each city by the high volume (1000 L min^{-1}) samplers, using quartz microfiber filters (8 x 10 in., PALL, USA; pre-baked at 500 ^{o}C for 6 h). Sampling stations were mainly located in university campus to represent the general urban ambient air. A total of 18, 21, and 13 daily samples were collected from October 2013 to February 2014 at Shanghai, Nanjing, and Guangzhou, respectively. After weighing, the loaded filters were then cut into subsamples by ceramic scissors for different chemical analyses.

2.2. Metal concentration analyses and bioaccessibility evaluations

2.2.1. Metal contents in $PM_{2.5}$

The $PM_{2.5}$ samples were analyzed for trace metal concentrations (Cd, Mn, Ni, Pb) (Luo et al., 2014; Ming et al., 2017). Samples were digested by being immersed in concentrated HNO_3-$HClO_4$ acids with a progressive heating program and finally dissolved in 5% (v/v) high-purity HNO_3. Procedural blanks, sample replicates, and standard reference materials (NIST SRM 1648a, urban PM) were randomly inserted for quality control. The metal concentrations were determined by Inductively Coupled Plasma-Optical Emission Spectrometer (ICP-OES, Agilent 720) and ICP-Mass Spectrometer (ICP-MS, Agilent 7700) for low level concentrations when needed. The concentrations of trace metals in reagent blanks were <1% of the average analyte concentrations, and their recoveries in the SRM ranged from 96 to 110%.

2.2.2. Pulmonary bioaccessibility of $PM_{2.5}$ bound trace metals by SLF extraction

Besides total metal concentrations in air PMs, metal speciation was also investigated using physiologically based *in vitro* pulmonary bioaccessibility tests. Gamble's solution was used for the determination of solubility profiles of metals in $PM_{2.5}$ to simulated alveolar lung fluids, typically mimicing the surfactant fluids released by type II alveolar cells. The composition (g L^{-1}) of freshly prepared Gamble's solution (Midander et al., 2007) included $MgCl_2$, 0.095; NaCl, 6.019; KCl, 0.298; Na_2HPO_4, 0.126; Na_2SO_4, 0.063; $CaCl_2·2H_2O$, 0.368; $C_2H_3O_2Na$, 0.574; $NaHCO_3$, 2.604; $C_6H_5Na_3O_7·2H_2O$, 0.097; and the pH was maintained at 7.4 (37 °C). The mixture of 1/4 filter $PM_{2.5}$ subsample and 60 mL SLF was rotated at 200 rpm for 24 h at 37 °C. Following the extraction, 5 ml of the supernatant was decanted and filtered through a 0.22 μm cellulose acetate disk filter, and diluted with 0.1 *M* HNO_3 prior to analyses using ICP-MS.

2.2.3. Acute bioaccessibility of soluble metals in lung simulated by DGT

Furthermore, the DGT technique was used as a speciation tool to determine the labile trace metals (free cations and those complexes that can dissociate easily) dissolved in artificial human lung fluids, which represents the fraction absorbed efficiently by lung. DGT is based on the selective dissociation, diffusion and accumulation of metal species within a layer of hydrogel and Chelex resin, and measures concentrations of labile trace metals (Davison and Zhang, 1994). In summary, loaded DGT devices (LSNM for metal cations in solution, provided by DGT Research Ltd, Lancaster, UK, theory and parameter values are available at http://www.dgtresearch.com/) were immersed and deployed in the remained 55 mL of SLF-$PM_{2.5}$ mixture for another 4 h (rotated at 150 rpm and 37 °C). After system retrieval, DGT resins were eluted in 1 mL of 1 *M* HNO_3 for 24 h. Eluates were diluted by 0.1 *M* HNO_3 and analyzed by ICP-MS for metal concentrations, which were converted into the mass of metal accumulated on the resin and then into the DGT-labile metal concentrations in SLF extracts calculated by the theory equations based on the Fick's first law of diffusion (see Supplementary Materials). Finally, in addition to the lung fluid soluble metals by SLF extraction, the acutely bioaccessible fractions among them in lung were also determined. Bioaccessibility (Kastury et al., 2018) was expressed as the percentage of bioaccessible fraction (BAF%) of each metal relative to its total concentration in the $PM_{2.5}$ sample.

2.3. Statistics

The statistical analysis was performed using SPSS Statistics 21 and plotted by Origin Pro 2017. The values represented in the box plot summarizing data distribution included the 1st, 5th, and 25th percentiles, the median, arithmetic mean, and the 75th, 95th, and 99th percentiles. Principal component analysis (PCA) was conducted for metal source classification in the $PM_{2.5}$ samples.

3. Results and discussions

3.1. Intercity differences of $PM_{2.5}$ and associated trace metal concentrations

For air PM pollution, the average daily $PM_{2.5}$ levels during the investigated pollution season of the three megacities [the YRD (Nanjing > Shanghai) > the PRD (Guangzhou)] were 123±59.2, 96.9±46.2, and 71.4±31.7 μg m^{-3}, respectively (Figs. 2a and 3), being higher than the China Air Quality Standard (75 μg m^{-3}) and the WHO guideline (25 μg m^{-3}). It showed a spatial pattern of higher urban $PM_{2.5}$ pollution in the eastern China than in southern China during the cold season, and the coastal cities were lower than nearby inland cities.

As regards the airborne metals, the overall average concentrations of $PM_{2.5}$ bound trace metals was in order of Pb (115±82.5) > Mn (50.8±33.0) > Ni (12.4±7.2) > Cd (6.16±5.22 ng m^{-3}). In comparison with the currently available international guidelines (WHO and Europe) and threshold values of Pb (500), Mn (150), Ni (20), and Cd (5 ng m^{-3}) in air, the mean concentrations of $PM_{2.5}$-associated Cd in Nanjing (8.02±5.90) and Shanghai (6.37±5.04 ng m^{-3}) exceeded the guideline (Fig 2a), and Cd in Guangzhou and Ni in Shanghai also showed exceeding levels in some days. For the spatial comparisons of various metals in different cities, airborne Cd and Mn showed a similar pattern to $PM_{2.5}$ of the YRD (Nanjing > Shanghai) > the PRD (Guangzhou), but dissimilarly, the pattern was Nanjing > Guangzhou > Shanghai for Pb, and the YRD (Shanghai > Nanjing) > the PRD (Guangzhou) for Ni. These metals with same concentration pattern to the $PM_{2.5}$ were mainly due to the role of air particle mass loadings, and might be from similar sources. However, those metals showing inconsistent patterns implied an additional role of different $PM_{2.5}$ sources on particle compositions, such as Pb and Ni. It could be illuminated by their distributions of metal weight contents (mg kg^{-1}; Fig. 2b) - metals accumulated in $PM_{2.5}$, that average Pb was highest in Guangzhou (PRD) and Ni was highest in Shanghai (the coastal YRD), in contrast to the pattern of Cd and Mn. Airborne Pb and Ni should have higher Pb or Ni concentrated particle emission inputs in these corresponding cities, respectively, such as coal combustion and vehicle traffic or oil combustion. These sources factors might also influence their chemical speciation and human bioaccessibility.

3.2. Pulmonary bioaccessibility of various trace metals in $PM_{2.5}$ by SLF and DGT

For the concentrations of lung bioaccessible metals associated with $PM_{2.5}$, the overall means were in order of Mn > Ni > Pb > Cd for both SLF and DGT (Fig. 3). The data contrasted starkly to the pattern of total metal concentrations, of which Pb was the highest, indicating the importance of metal bioaccessibility and the low pulmonary bioaccessibility of Pb. A reason is that the phosphate in SLF (Gamble's solution) might decrease the Pb solubility in the neutral solution due to precipitation (Li et al., 2016). As shown in Fig. 4a, the median bulk pulmonary bioaccessibility by SLF% was Ni (22.9) > Cd (14.9) > Mn (11.9) >> Pb (1.8 %), and the acute pulmonary bioaccessibility by DGT% ranked as Ni (6.7) ~ Mn (6.7) > Cd (4.8) >> Pb (0.50 %), respectively. According to these results, the SLF bioaccessibility denoting the $PM_{2.5}$ metals dissolved into lung fluid for Ni was relatively high (>20%), while Pb was very low (<2%). Although general higher values than present study, similar orders were reported in Spain that the average metal bioaccessibility of PM_{10} in Gamble's solution followed the Cd (39.3) > Mn (34.1) > Pb (14.8 %) at an industry impacted site of, and Mn (23.0) > Cd (22.0) > Pb (11.4 %) at the urban site (Hernández-Pellón et al., 2018), that indicated comparable SLF solubility of Mn and Cd higher than Pb. The SLF bioaccessibility of Ni in $PM_{2.5}$ near a Fe-Mn smelter of France was also reported higher than Cd and Mn, though varied with wind directions (Mbengue et al., 2015). For the DGT bioaccessibility denoting the free metal cations in lung fluid that would be absorbed directly, all of them were lower (<7%). By further analysis of the proportions of DGT-labile metals in SLF, the DGT/SLF was Mn (61.9) > Ni (41.0) > Cd (32.4) > Pb (29.2 %), indicating that airborne Ni, Mn and Cd were inclined to be released into liquid phase and absorbed directly and rapidly after the $PM_{2.5}$ was inhaled into the lungs. Since total airborne Ni and Cd concentrations had exceeded the air quality guidelines, combined with the pulmonary bioaccessibility (%), their inhalation health risks should be higher than Pb.

By further analysis of intercity differences (Fig. 4b), the SLF bioaccessibility of airborne Pb and Mn were higher in the YRD cities (Shanghai, Nanjing) than the PRD (Guangzhou), and for Ni it was highest in Shanghai, but for Cd it was highest in the PRD. Furthermore, as part of SLF extraction, the DGT bioaccessibility of airborne metals in the YRD weakened (Fig. 4c). These results might be mainly related to the differences in the sources of airborne metals and the influences of other particulate components in different regions. Such as the percentages of DGT-labile metals in SLF (Fig. 4d), all of Shanghai were lowest, which might be due to the higher contents of organic aerosol components as organic complexing ligands of metals in lung fluid for $PM_{2.5}$ in Shanghai (Wang et al., 2017). Of course, since Gamble's solution measures particulate metal bioaccessibility after $PM_{2.5}$ enters alveolar-interstitial fluid in the lung, if the dynamic dissolution was evaluated by lower pH extractions such as artificial lysosomal fluids (ALF, pH 4.5) that mainly mimics inhalation bioaccessibility in macrophages (Hernández-Pellón et al., 2018; Kastury et al., 2017; Li et al., 2016), or further artificial gastric juice (pH 1.5) for particles removed from the respiratory tract which are mainly swallowed and thereby reaching the gastrointestinal tract (Kastury et al., 2018; Puls et al., 2012), the human bioaccessibility of these airborne metals would be higher for health risks.

3.3. Effects of particle sources on bioaccessibility and health risks of airborne metals

Besides the metal self-characteristics on its solubility and complexation, the particle properties also influence the speciation and bioaccessibility of $PM_{2.5}$ bound metals, in particular PM components from different sources (Hernández-Pellón et al., 2018). If all the particles in various regions are from same percentages of sources, their metal contents in $PM_{2.5}$ should also be the same. The different results in Fig. 2b indicate their varied sources in different cities. According to the source apportionment results of each city's $PM_{2.5}$ released by the Chinese Ministry of Environmental Protection in 2015, the three primary sources were mobile emissions (including traffic and oil combustion), industrial production, and coal combustion for Shanghai (29.2, 28.9, 13.5% of local sources); industry (coal combustion was 27.4%, and industrial production was 19.0%), and motor vehicle exhaust (24.6%) for Nanjing; industry (coal combustion was 20.6%, and industrial process was 11.5%), and motor vehicle exhaust (21.7%) for Guangzhou, respectively. Other major $PM_{2.5}$ sources include dust of construction, road, and soil, regional pollutant transport, and others such as biomass burning, agricultural and natural sources.

Based on the source identification by PCA, the relationships among airborne metals in each city and their possible main sources were illuminated in Table 1. The rotated component matrix (loadings) of PCA contains estimates of the correlations between each of the variables and the estimated components, that help to determine what the components represent. For these cities, Mn and Pb were mainly in a PC possibly of traffic sources, while Cd and Ni were in the other PC of coal combustion and/or industry sources. Moreover, Ni in Shanghai was also attributed to oil combustion, and Mn and Pb in Guangzhou were possibly contributed by coal combustion or industry and Cd by traffic. Therefore, corresponding to the lung bioaccessibility, airborne Ni from oil combustion and Mn from traffic showed both higher particulate accumulation and SLF bioaccessibility, Cd and Pb from traffic showed lower accumulation but higher bioaccessibility; while Mn and Ni from coal combustion showed both lower accumulation and SLF bioaccessibility, Cd and Pb from coal combustion showed higher accumulation despite lower bioaccessibility (Figs. 3,4). Considering the ambient air concentrations of these lung bioaccessible airborne metals, the aerosol pollution sources of industrial (including coal combustion) and traffic emissions posed the significant human health risks, especially the coal Cd and traffic Ni.

3.4. Implications, limitations, and directions

As results above show, most of the analyzed metals had moderate lung bioaccessibility in SLF, with a significant variability between metals and samples, implying different health risks. Such variability might be induced by the different contribution from $PM_{2.5}$ and associated metal emission sources, impacted by both meteorological conditions and anthropogenic emission patterns. By incorporating the bioaccessibility of all harmful metals into exposure assessment calculation and inhalation risk characterization, the human health risks of $PM_{2.5}$ bound metals could be assessed reasonably. Results above suggest the potential risks of airborne Ni and Cd in eastern China megacities that should be controlled of special concern for air quality management, but the comprehensive evaluation for these regions needs analyzing more samples and metals.

For health risk assessments of $PM_{2.5}$, the *in-vitro* chemistry methods could be a streamlined and inexpensive alternative for those in-vivo animal or in-vitro cell toxicological tests. The stepwise physiologically based method of SLF extraction and DGT simulating the dissolution of particulate metals in human lung fluid and subsequent acute absorption by lungs provide a useful tool to assess the pulmonary bioaccessibility. It could be supported by the anion DGT (e.g., dichromate) or the newly developed simultaneous DGT measurements of cations and anions (Wang et al., 2017) for more metal species, and simulated gastric juice for evaluating metal bioaccessibility via the gastrointestinal route. To mimic various conditions inside the human respiratory system with standard methodologies, the further study of inhalable metal bioaccessibility and its application to the exposure concentration estimation and health risk assessments is recommended.

4. Conclusions

Various sources of aerosols render the $PM_{2.5}$ composition and its associated trace metal concentrations vary spatially and temporally, thus influencing the human bioaccessibility of each hazardous airborne metal after inhalation and thereby posing diverse risks to human health. Results of this work highlight the necessity of better evaluating the potentially hazardous effects from inhalable metal exposures. To accurately assess the human health risks of ambient air $PM_{2.5}$ and airborne metals, a framework considering both aerosol components and associated metal bioaccessibility should be developed, beyond mere atmospheric concentrations of $PM_{2.5}$. As basis, standardized and systematic methods for sequential bioaccessbility tests of inhalable metals in all body processes are needed.

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Supplementary materials

The supplementary data related to this article is available at xxx.

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