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Heavy metals bound to fine particulate matter from northern China induce season-dependent health risks: A study based on myocardial toxicity☆

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ABSTRACT

Substantial epidemiological evidence has consistently reported that fine particulate matter ($PM_{2.5}$) is associated with an increased risk of cardiovascular outcomes. $PM_{2.5}$ is a complex mixture of extremely small particles and liquid droplets composed of multiple components, and there has been high interest in identifying the specific health-relevant physical and/or chemical toxic constituents of $PM_{2.5}$. In the present study, we analyzed 8 heavy metals (Cr, Ni, Cu, Cd, Pb, Zn, Mn and Co) in the $PM_{2.5}$ collected during four different seasons in Taiyuan, a typical coal-burning city in northern China. Our results indicated that total concentrations of the 8 heavy metals differed among the seasons. Zn and Pb, which are primarily derived from the anthropogenic source, coal burning, were the dominant elements, and high concentrations of these two elements were observed during the spring and winter. To clarify whether these heavy metals in the locally collected $PM_{2.5}$ were associated with health effects, we conducted health risk assessments using validated methods. Interestingly, Pb was responsible for greater potential health risks to children. Because cardiovascular disease (CVD) is a main contributor to the mortality associated with $PM_{2.5}$ exposure, we performed experimental assays to evaluate the myocardial toxicity. Our *in vitro* experiments showed that the heavy metal-containing $PM_{2.5}$ induced season-dependent apoptosis in rat H9C2 cells through a reactive oxygen species (ROS)-mediated inflammatory response. Our findings suggested that heavy metals bound to $PM_{2.5}$ produced by coal burning play an important role in myocardial toxicity and contribute to season-dependent health risks.

1. Introduction

With the rapid economic development, industrial expansion and urbanization in China during the last few decades, increasingly frequent incidents of haze or smog episodes characterized by high fine particulate matter ($PM_{2.5}$) levels and reduced visibility have been reported at the national scale in this country (Liu et al., 2013; Zhang et al., 2012). As both the total amounts and the proportions of $PM_{2.5}$ have increased in Chinese cities, the adverse health effects of this major urban air pollutant have attracted increasing concern due to its influence on not only cardiorespiratory system but also cerebrovascular events (Stafoggia et al., 2014). These two conditions constitute two major causes of high rates of hospitalization and mortality (Ito et al., 2011; Zheng et al., 2015). The World Health Organization (WHO) has reported that ambient air pollution was responsible for 3,700,000 deaths in 2012, including 16% of the lung cancer deaths, 11% of the chronic obstructive pulmonary disease-related deaths, 29% of the heart disease and stroke deaths, and approximately 13% of the deaths that were due to respiratory infections (Lee et al., 2014). Lelieveld et al. (2013) calculated a global mortality of approximately 773,000/year due to respiratory disease, 186,000/year due to lung cancer and 2,000,000/year due to cardiovascular disease (CVD) resulting from exposure to anthropogenic $PM_{2.5}$ (Lelieveld et al., 2013). Obviously, CVD is a key contributor to mortality. A substantial body of epidemiological studies have provided consistent evidence that exposure to $PM_{2.5}$ is associated with an increase in cardiovascular mortality (Crouse et al., 2012; Madrigano et al., 2013). A previous study by the Women's Initiative (WHI) reported a 24% increase in the risk of a cardiovascular event [hazard ratio (HR) = 1.24; 95% confidence interval (CI), 1.09–1.41] and a 76% increase in the risk of death from

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CVD (HR = 1.76; 95% CI, 1.25–2.47) for each 10 μg/m^3 change in the $PM_{2.5}$ level (Miller et al., 2007). Chen et al. (2008) found that long-term exposure to $PM_{2.5}$ increases the risk of cardiovascular mortality by approximately 12–14% per 10 μg/m^3 increase in the $PM_{2.5}$ level (Chen et al., 2008). Moreover, Hoek et al. (2013) concluded that per 10 μg/m^3 increase in $PM_{2.5}$ exposure is associated with 11% (95% CI 5, 16%) for cardiovascular mortality (Hoek et al., 2013). Specifically, increasing evidences have shown that CVDs such as acute myocardial infarction (MI) and heart failure (HF) are associated with a sustained loss of cardiac cells through apoptosis (Hilfiker-Kleiner et al., 2006; Ale et al., 2013). Therefore, the potential risk of myocardial toxicity caused by $PM_{2.5}$ exposure should received more attention.

$PM_{2.5}$ is a complex mixture of extremely small particles and liquid droplets that include various components including acids (such as nitrates and sulfates), organic chemicals, heavy metals, and soil or dust particles (Yue et al., 2015). Although heavy metals account for only a small fraction of the $PM_{2.5}$, they not only are non-biodegradable when adherent to particles but also can bioaccumulate through the food chain and contribute to the toxicity of $PM_{2.5}$ (Fang et al., 2013; Abuduwaili et al., 2015). In earlier studies, Chen and Lippmann (2009) reported an association between PM-bound metals and potential health effects (Chen and Lippmann, 2009). Moreover, Niu et al. (2013) reported that specific metals might be important components that are responsible for the $PM_{2.5}$-induced cardiovascular effects (Niu et al., 2013). The Comparative Toxicogenomics Database (CTD) revealed that air pollutants that are composed of particulate metal ions are associated with cardiac arrhythmia, myocardial ischemia, myocardial infarction, stroke, and thrombosis (Meng et al., 2013). These findings suggested that heavy metal-containing $PM_{2.5}$ plays an important role in the myocardial toxicity-associated health risks.

$PM_{2.5}$ is highly heterogeneous, and various characteristics of the materials from different pollution sources induce differences in corresponding biological effects. We postulated that the myocardial toxicity-associated health risk resulting from heavy metal-containing $PM_{2.5}$ might depend on the characteristics of these pollutants, particularly in northern China, where the coal-based heating systems used in spring and winter have become the dominant sources of $PM_{2.5}$ (Song et al., 2015). Huang et al. (2011) reported that $PM_{2.5}$ from coal-burning heat sources caused the increase of mortality; among these, CVDs accounted for approximately 46% (Huang et al., 2011). However, few studies have examined the relationship between the heavy metal-containing $PM_{2.5}$ produced by coal burning and CVDs. Thus, the aims of the present study were to analyze the concentrations and sources of heavy metals in $PM_{2.5}$ in Taiyuan, a typical coal-burning city in northern China, assess the associated health risks, and determine the potential biological responses based on myocardial toxicity.

2. Materials and methods

2.1. Collection of $PM_{2.5}$ samples

Sampling was performed between 2012 and 2013 in Taiyuan, a city in northern China. The $PM_{2.5}$ samples were collected onto quartz filters (Φ90 mm, Munktell, Falun, Dalarna, Sweden) with PM middle-volume air samplers (TH-150CIII, Wuhan, China). Subsequently, 1/8 of the filters from each season were used for the heavy metal measurement, and another 1/8 of the filters were used for the *in vitro* experiments. The details of the $PM_{2.5}$ collection and filter treatment are provided in the text of the Supporting Information (SI).

2.2. Determination of heavy metals in $PM_{2.5}$

The concentrations of 8 heavy metals (chromium (Cr), nickel (Ni), copper (Cu), cadmium (Cd), lead (Pb), zinc (Zn), manganese (Mn) and cobalt (Co)) in the $PM_{2.5}$ were determined using inductively coupled plasma-mass spectrometry (ICP-MS). The detailed procedures are presented in the text of the SI.

2.3. Calculation of the enrichment factor (EF)

The enrichment factor (EF) is an important indicator for the quantitative assessment of the levels and sources of heavy metal pollution, and this value is calculated as indicated below (Liu et al., 2012b):

$$EF = \frac{(C_i/C_{ref})_{samples}}{(B_i/B_{ref})_{baseline}}$$

where EF is the enrichment level of a certain heavy metal, C_i is the measured concentration of heavy metal i in the $PM_{2.5}$ (mg/kg), C_{ref} is the measured concentration of the reference element (mg/kg), B_i is the background value of heavy metal i in the local region (mg/kg), and B_{ref} is the background concentration of the reference element in the same region (mg/kg). In this study, Al was used as the reference element because the steel factories present in Taiyuan could produce significant amounts of Fe and the filters used for collection are made of quartz, which has a high content of Si. The background values of Cr, Ni, Zn, Mn, Cu, Cd, Pb and Co in the local region (B_i) were 68.48, 28.7, 83.6, 600, 26.7, 0.2208, 24.9 and 13 mg/kg, respectively (Li et al., 2014a,b).

2.4. Principal component analysis (PCA)

Principal component analysis (PCA), a method that describes variables with a minimum loss of information, is commonly used to evaluate the specific sources of pollutants (Zhao et al., 2006). The concentration data obtained for each congener in the sample analysis was expressed as a fractional part of the total and normalized to a sum equal to 100. This normalization minimizes the influence of the total concentration and permits the comparison of compositional similarities among samples. The eigenvectors were normal-varimax rotated to facilitate the interpretation of the results (Sakurai et al., 1998). The statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc.).

2.5. Non-carcinogenic risk assessment of heavy metal-containing $PM_{2.5}$

$PM_{2.5}$ primarily induces health risks to humans by three routes: ingestion, inhalation, and dermal contact. In the present study, we adapted the health risk assessment models of the U.S. EPA to evaluate the health risks of the heavy metals. The average daily doses through ingestion (ADD_{ing}) (mg/kg/day), inhalation (ADD_{inh}) (mg/kg/day), and dermal contact (ADD_{dermal}) (mg/kg/day) were calculated as follows (Cao et al., 2015):

$$ADD_{ing} = C \times \frac{IngR \times EF \times ED}{BW \times AT} \quad (1)$$

$$ADD_{inh} = C \times \frac{InhR \times EF \times ED}{PEF \times BW \times AT} \quad (2)$$