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Differing toxicity of ambient particulate matter (PM) in global cities

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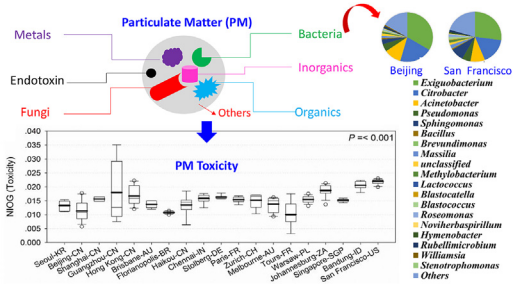
GRAPHICAL ABSTRACT



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ABSTRACT

Air quality is often assessed using particulate matter (PM) mass concentration without considering its toxicity, thus possibly leading to improper control policies or inadequate health protection. Here, we studied differences in oxidative potentials (OPs) of PM samples collected using automobile air conditioning (AC) filters from 19 global cities, as well as influences from microbial contents. Dithiothreitol (DTT) assay showed remarkable differences in the PM OPs among cities (p-values ≤ 0.001, Kruskal-Wallis test). For example, the normalized index of oxidant generation (NIOG) of PM samples in San Francisco (2.20×10^{-2}, annual average PM_{10} = 16 μg/m^3) was found to be twice that in Beijing (1.14×10^{-2}, annual average PM_{10} = 135 μg/m^3). Limulus amebocyte lysate (LAL) assay found that PM-borne endotoxin ranged from 12.16 EU/mg (Florianopolis, Brazil) to 2518.23 EU/mg (Chennai, India) among cities. Besides, culturing method and real-time qPCR revealed significant differences of up to ~100-fold in both bacterial and fungal levels among 19 cities. Spearman's correlation analysis implied that PM-borne microbes such as bacteria and fungi as well as metals could strongly influence the PM OP.

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As an example, our results in Xi'an, China further suggest that the $PM_{2.5}$ OP evolves for a particular city over the time, which is attributable to both the urbanization and air pollution control measures. This work highlights the importance in optimizing the current air quality control measures by considering the toxicity factor and its microbial constituents.

1. Introduction

Ambient particulate matter (PM) is described as a major contributor to premature mortality and shortened life expectancy (Lelieveld et al., 2015). Globally, Western Pacific and Southeast Asia are among the most affected regions, having mortality rates attributable to air pollution of 80.7 and 48.9 deaths per 100 000 in 2010, respectively (Lelieveld et al., 2015). As for current air quality assessment, PM mass concentration is generally used. For example, the 24-h ambient air quality guideline values for $PM_{2.5}$ from World Health Organization (WHO), United States and China are 25 μg/m^3, 35 μg/m^3, and 75 μg/m^3, respectively (GB3095-2012; U.S. EPA, 2012; WHO, 2005). An increase of 10 μg/m^3 in ambient $PM_{2.5}$ was shown to be statistically associated with a 9% increase in mortality risk for non-accidental causes (Yin et al., 2017). On the other hand, PM compositions were also shown to influence its toxicity, thus on the PM mass-health relationship (Strak et al., 2012; Tuomisto et al., 2008). Some other studies also showed that the toxicity of PM was source-dependent (Lippmann et al., 2013; Mcwhinney et al., 2013). However, current air quality assessment uses the same $PM_{2.5}$ mass concentration guideline value without considering its toxicity difference for all locations.

It is known that PM compositions such as organic carbon (OC), element carbon (EC), polycyclic aromatic hydrocarbon (PAHs), and transition metals are strongly associated with reactive oxygen species (ROS) (a major indicator for oxidative potential) generation in human cells (Brook et al., 2010; Huang et al., 2013; Li et al., 2003; Samake et al., 2017; Strak et al., 2012). For example, one study revealed that water-soluble V and Cr from $PM_{2.5}$ were significantly associated with the increase of DNA damage measured in blood (Sorensen et al., 2003). The PM oxidative potential (OP) was also shown to vary greatly among 20 sampling sites in Europe (Künzli et al., 2006). Likewise, it was reported by Weichenthal et al. (2016a,b) that the between-city differences on PM OP could modify the impact of $PM_{2.5}$, even at its low levels, on acute respiratory illnesses and myocardial infarction. Among others, Manzano-León et al. (2016) showed that there was an additional seasonal impact on the PM composition, which accordingly influenced its deleterious effects. On the other hand, it was reported very recently that PM-borne bacteria and fungi, in addition to causing opportunistic

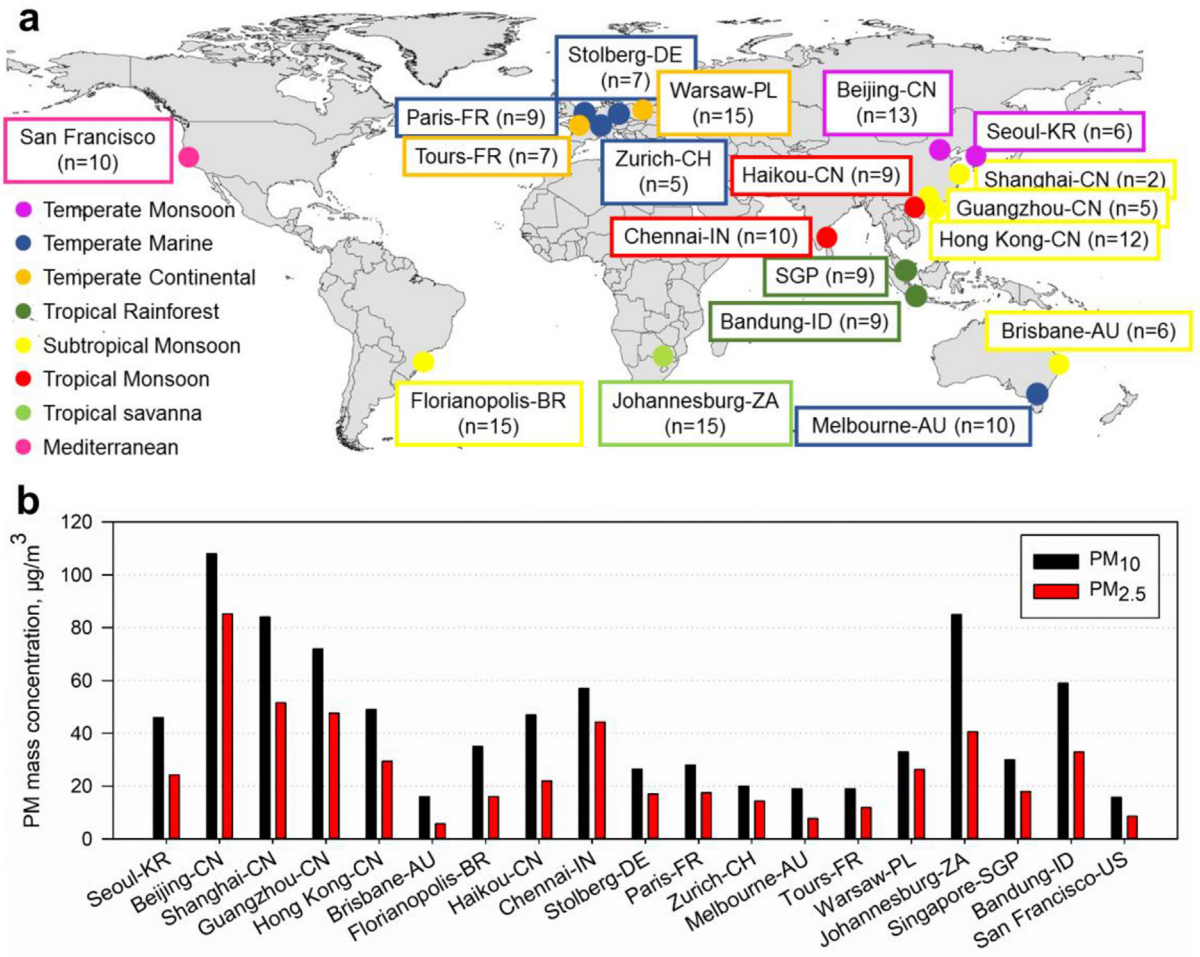

Fig. 1. (a) Automobile AC filter collection map (the map was obtained using ArcGIS 10.2 (Esri)) as also used in our previous work (Li et al., 2018); and corresponding climate zones, wherein *n* indicates the sample size for each city; and (b) cities' annual average mass concentrations of PM_{10} and $PM_{2.5}$ from the Ambient Air Pollution Database provided by WHO (2016).

infections, could modify the PM OP by interplaying with its contents (Samake et al., 2017; Vaïtilingom et al., 2011, 2013). For example, Samake et al. (2017) confirmed a cumulative effect on OP by fungal spores (*Aspergillus fumigatus*) with airborne PM, copper and 1,4-naphthoquinone (1,4-NQ), in contrast to a strong reductive effect from bacterial cells (*Staphylococcus epidermidis*). Independent of metabolism, inactivated microbes were also shown to exhibit the same OPs as viable microbes, implying their ROS generation capability (Samake et al., 2017). For example, endotoxin, as a major constituent of the outer cell membrane of Gram-negative bacteria, is thought to mediate pro-inflammatory responses, thus playing a role in various respiratory problems such as asthma, fever, shivering, arthralgia, cardiovascular diseases, and even a rapid increase in blood pressure when inhaled (Beutler and Rietschel, 2003; Suffredini et al., 1989; Takano et al., 2002; Zhong et al., 2015). Therefore, the health effects of PM to some extent, as suggested above, also depend on their biologicals in addition to metals and organics. Some other studies have shown that such constitutes of PM varied greatly across different geographical locations (Bell et al., 2007; Heinrich et al., 2003; Laden et al., 2000; Mueller-Anneling et al., 2004; Schins et al., 2004).

Accordingly, it is plausible that current air quality assessment practice could lead to improper control policies or inadequate health protection. Here, this work was conducted to address the following questions: 1) Are there any significant differences in oxidative potential (OP) per unit mass of PM among different world cities? Are there any evolutions in OP over a longer time period, e.g., 10 years, for a specific city? What are the possible influencing factors?; 2) Are there any significant differences in biological components, e.g. endotoxin, bacteria, fungi, in ambient PM among different world cities?; 3) Is the current air quality assessment of using PM mass concentration adequate or appropriate regardless of locations for protection of public health from air pollution? The corresponding information is of great help for optimizing air pollution control and understanding current air quality assessment practice drawbacks.

2. Materials and methods

2.1. Ambient PM sample collection

Global ambient PM sample collection using automobile AC filters: In this work, we utilized a previously reported automobile air conditioning (AC) filter method (Li et al., 2013) to collect ambient particulate matter (PM) samples from 19 cities in 13 countries under 8 different climate zones across the globe. The air samples used in this work were the same as those in our previous work (Li et al., 2018), but analyzed for toxicity. Fig. 1 shows **a)** these locations in the world map and corresponding climate zones as stated by Li et al. (2018), and **b)** every city's annual average mass concentrations of PM_{10} and $PM_{2.5}$ according to the Ambient Air Pollution Database provided by WHO (2016). As described previously, a total of 174 used AC filters were collected from randomly selected automobiles without considering specific times or seasons from 2016 to 2017 (Li et al., 2018). Here, grouping the AC filters based on seasons is difficult since these automobiles are located under different climatic zones and have different frequencies in replacing the AC filters. Nonetheless, different replacing frequencies would significantly affect the total PM mass, but not the PM toxicity per unit of mass for the same season. As the PM accumulates over time, the AC filters despite different brands should have similar performance with respect to their filtration efficiencies. For example, at certain point, the AC filter not just collects large particles, but also smaller ones because all the “collecting pores” of the filter are filled with particles (not many particles can pass through). Accordingly, particles of all size were collected onto the AC filter. Acquired from ClimaTemps (http://www.climatemps.com/), the meteorological conditions including annual average daily maximum and minimum temperatures, annual average relative humidity (RH) and annual precipitation in each city are presented in Table S1 (Supporting Information). In this work, the PM samples were obtained by first shaking them onto a white office paper from the automobile AC filters, then poured into a 50-mL centrifuge tube (Corning® Premium Quality, Acton, MA, USA), which were further analyzed for weight using an analytical balance (AL204IC, Mettler Toledo, Inc., Greifensee, Switzerland). The obtained 50-mL tubes, which contained the PM samples, were subsequently extracted by pre-calculated volumes of sterile deionized (DI) water (Milli-Q, Millipore, Billerica, MA, USA) to achieve a PM concentration of ~1 mg/mL. The PM extraction solutions were subsequently treated by vigorous vortexing for 15 min at a rate of 2800 rpm and then stored at −20 °C until further experiments. Here, the PM samples collected from the AC filters contained both $PM_{2.5}$ and coarse particles. In this work, we did not perform any solution-based extraction of PM from the filter, thus the filter material could have had minor interferences on the PM (If any, it could be diluted by the large volume of PM mass collected from the filter, e.g., more than 20 mg PM). In terms with the quality control, the same type of office paper was used along with a new AC filter (purchased in Beijing, China) to conduct the same procedures described above (although no visible particles obtained). The obtained 50-mL tube containing the DI water from this control AC filter was used as a negative control in all of our experiments.

Xi'an's $PM_{2.5}$ samples and pretreatment: To study the evolution of particle toxicity over the years, $PM_{2.5}$ samples from Chinese Academy of Sciences' Institute of Earth Environment over a 10-year time period in Xi'an were used for analysis in this work. As described in an earlier study (Li et al., 2018), these samples were collected over the years at an urban monitoring site which was located on the rooftop (~ 10 m above the ground) of the institute building (E 108.887°, N 34.229°), surrounded by a residential area ~ 15 km south of downtown Xi'an, Northwest China. A portable atmospheric particulate matter sampler, MiniVol® Tactical Air Sampler (TAS) (Airmetrics, Inc., Springfield, Oregon, USA), was used with a sampling flow rate of 5 L/min to collect pre-defined 24-h $PM_{2.5}$ samples. The $PM_{2.5}$ samples were collected onto quartz filters (47 mm, Whatman QM/A, England), and were further sterilized by baking at 780 °C for 3 h before use. For weighing the filter, the gravimetrical method was applied according to the protocol reported in a previous study (Cao et al., 2005). After the weight analysis, each filter sample was sealed and stored at −20 °C. A total of 72 quartz filter samples, respectively from 6th or 7th and 25th of each month (January to December) for 2004, 2009 and 2014 as listed in Supplementary Excel file S1, were selected and analyzed. Prior to all experiments, $PM_{2.5}$ samples were extracted, as described in our previous work (Li et al., 2018), from quartz filter samples by the following procedures: Firstly, each of the filters was cut into pieces, ranging from 1.4 to 2.8 cm^2 in area using a sterile cutter. Each filter piece was then placed into 2 mL of sterile purified water with 0.05% Tween 20 (Solarbio, Inc., Beijing, China) in a sterile centrifuge tube, then subjected to 20 min of sonication, followed by a vortex mixing for 40 min at 2800 rpm. $PM_{2.5}$ extraction samples were stored at −20 °C until subsequent experiments. Due to sampler malfunction, mass concentration values of $PM_{2.5}$ samples on July 25th 2004, July 25th 2009 and November 25th 2009 were not obtained. Here, automobile AC filter samples from Xi'an city were not obtained at the time of our global sample collection.

2.2. DTT assay procedure for PM toxicity

The DTT (Dithiothreitol, $HSCH_2(CH(OH))_2CH_2SH$) assay was used to analyze the oxidative potential (OP) in global ambient PM and Xi'an's $PM_{2.5}$ extraction samples. Redox-active compounds catalyze the oxygen reduction to superoxide by DTT, which is then oxidized into disulfide. The remaining thiol was used to react with 5,5′-dithiobis-2-nitrobenzoic acid (DTNB), generating a mixture of disulfide and 5-mercapto-2-nitrobenzoic acid (TNBA). The mixture was further quantified by its

absorption at 412 nm. The solutions used for DTT assay, including the buffer solution, DTT and DTNB, were prepared according to a previous work by Kramer et al. (2016). The DTT assay was carried out in a following system: 50 μL of 0.5 mM DTT, 1.0 mL of buffer solution, 200 μL of 10-fold diluted PM extraction solution (0.1 μg/μL) or 50 μL/100 μL of $PM_{2.5}$ extraction solution or 200 μL of negative control (sterile purified water with 0.05% Tween-20) or 10, 20, 30, 40, 50 μL of external standard (0.01 μg/μL 1,4-napthaquinone (1,4-NQ)) or blank (1000-fold diluted dimethyl sulfoxide (DMSO)). After well mixed, all the tubes were incubated at 37 °C for 30 min and shielded from exposure to light. 100 μL of 1.0 mM DTNB was then added to each reaction solution. The absorbance of TNBA in 200 μL of each stop solutions was measured at 412 nm using a spectrophotometer (SpectraMax M2, Molecular Devices, Inc., Sunnyvale, CA, USA). The measured ROS generation potentials were expressed as the normalized index of oxidant generation (NIOG) according to the method reported by Li et al. (2009). DTT assays for all PM samples were carried out within one day after the extraction. Additionally, the volume-normalized oxidative potential characterized by NIOG per cubic meter (pcbm) of airborne PM ($NIOG_{cpbm}$, μg 1,4-NQ/m^3) for each city including Xi'an was also calculated according to the following equation:

$$NIOG_{pcbm} = NIOG \times PM_{10} \text{ or } PM_{2.5} \text{ mass conc.} \quad (1)$$

where PM_{10} mass concentration (μg/m^3) for each city can be found in Fig. 1b. Here, we use PM_{10} mass concentration (TSP data are not available for all cities) for estimating the geographical variations in volume-normalized concentrations among 19 cities. This is reasonable since a significant linear correlation (R = 0.79–0.99, p-value < 0.0001) was detected between PM_{10} and TSP, as supported by a high PM_{10}/TSP ratio of 0.56–0.92 (Ma et al., 2017). $PM_{2.5}$ mass concentration (μg/m^3) of each $PM_{2.5}$ sample from Xi'an is listed in Supplementary Excel file S1.

2.3. Biological contents analysis

Culturable bacteria and fungi analyses: Culturable bacteria and fungi fractions in global ambient PM samples were analyzed by using lysogeny broth (LB) agar plate and Sabouraud's dextrose agar plate (Becton, Dickson and Company, Sparks, MD), respectively. The culturing conditions for bacteria and fungi were at 30 °C for 3 days and at 30 °C for 5 days, respectively, in separate incubators. For each sample three replicates were performed.

Total bacteria analysis: DNA extraction of 1 mL of global ambient PM extraction solutions (1 mg/mL) and 200 μL Xi'an's $PM_{2.5}$ extraction solutions were performed according to the manufacture's guidelines as recommended by the bacterial genome extraction kit (Tiangen Biotech, Inc., Beijing, China). DNA extracts were stored at −20 °C until the real-time qPCR assay for quantifying the total bacterial cell concentration of each PM extraction solution using a standard curve. Pure cultures of Gram-negative *Escherichia coli* (*E.coli*, ATCC 15597) purchased from American Type Culture Collection (ATCC) were used as the DNA standard templates in our experiments. The cells of *E.coli* were obtained by their culturing on Tryptic Soy Agar (TSA, Becton, Dickson and Company, Sparks, MD) plates at 30 °C for 24 h. When preparing the pure bacterial solution, 20 mL of autoclaved water was added into the agar plate and colonies of *E.coli* were gently scraped from the agar surfaces using an inoculation loop. The resulting bacterial suspension was washed three times by pouring them into a 50 mL autoclaved tube and centrifuged at a vortex rate of 7000 rpm (Eppendorf Centrifuge 5804R, Eppendorf, Hamburg, Germany) for 7 min. The final pellet of bacteria from the last centrifugation was re-suspended in the 20 mL of autoclaved water. The final achieved concentration of the pure bacterial solution was around 9.0×10^8 cells/mL (manually counted under the microscope and calculated). Then the pure bacterial solution was serially diluted by 10-10^8 times as respective standard curve samples. As described above, the DNase/RNase-free ddH_2O (Tiangen Biotech, Inc., Beijing, China) from the tube was used as the negative control in all PCR tests.

The previously reported primers and probe are used for universal qPCR assays in this work: forward primer: 5′-TCCTACGGGAGGCAGC AGT-3' (Tm = 59 ± 4 °C), reverse primer: 5′-GGACTACCAGGGTATC TAATCCTGTT-3' (Tm = 58 ± 1 °C), probe: (6-FAM)-5′-CGTATTACCG CGGCTGCTGGCAC-3'-(TAMRA) (Tm = 69 ± 9 °C) (Nadkarni et al., 2002). The qPCR assay was carried out in a 50-μL reaction mixture containing 5 μL of template DNA, 1 μL of each dNTP (2.5 mM each) (Tiangen Biotech, Inc., Beijing, China), 5 μL of 10 × PCR buffer (Tiangen Biotech, Inc., Beijing, China), 0.2 μL of Taq polymerase (2.5 U/μL) (Tiangen Biotech, Inc.), 1 μL of each primer (10 μM each) (Sangon Biotech, Inc., Shanghai, China), 1 μL of probe (10 μM each) (Sangon Biotech, Inc.) and 40.8 μL of DNase/RNase-free ddH2O (Tiangen Biotech, Inc.) using a 7300 Real Time PCR System (Applied Biosystems, Inc., Foster City, CA, USA). Cycling conditions were set as follows: 50 °C for 2 min, followed by initial denaturation at 95 °C for 10 min, then 40 cycles of 95 °C for 15s, and last 60 °C for 1 min.

Endotoxin analysis: The quantitation of endotoxin concentration in global ambient PM samples was performed by the kinetic-turbidimetric Limulus Amebocyte Lysate (LAL) assay (Associations of Cape Cod, Inc., Falmouth, MA, USA). For extracting endotoxins from particles, 10-fold diluted (using sterile DI water with 0.05% Tween 20) PM extraction solutions were subjected to vortexing for 120 min at 300 rpm, and then followed by a 20 min of sonication. Each solution was subsequently centrifuged for 10 min at 3500 rpm to remove small particles and other fragments that may interfere with LAL analyses. The supernatants were then transferred into 1.5-mL centrifuge tubes. Each supernatant was ultimately diluted 30 times using sterile DI water with 0.05% Tween 20. Endotoxin concentrations in the diluted PM extraction solutions were measured according to the manufacturer's instructions and the procedure documented in a previous study (Yao et al., 2009). As described above, the DNase/RNase-free ddH_2O (Tiangen Biotech, Inc., Beijing, China) with 0.05% Tween 20 from the tube was used as the negative control in endotoxin tests. Standards, samples, spikes, and blanks were analyzed using a microplate reader (SpectraMax M2, Molecular Devices, Inc., Sunnyvale, CA, USA) at a wavelength of 405 nm for 60 min in the kinetic mode.

Additionally, the volume-normalized concentrations per cubic meter (C_{pcbm}) of air for all the endotoxin were also estimated according to the equation below:

$$C_{pcbm} = \frac{C_{PM}}{1000} \times PM_{10} \text{ mass conc.} \quad (2)$$

where C_{PM} is endotoxin concentration per unit mass of PM, PM_{10} is the annual average mass concentration (μg/m^3) for each city (can be found in Fig. 1b).

2.4. Trace elements analysis for $PM_{2.5}$ samples

Trace elements, including P, Ca, Ti, V, Cr, Co, Ni, Cu, Zn, As, Se, Mo, Cd, Tl, Pb, Th, U, Na, Mg, Al, K, Mn, Fe and Ba for Xi'an's $PM_{2.5}$ samples were measured in 100-fold diluted (by sterile purified water with 0.05% Tween-20) $PM_{2.5}$ extraction solutions using inductively coupled plasma mass spectrometry (ICP-MS, Aurora M90, Bruker, Inc., Billerica, MA, USA). The ICP-MS was equipped with a two-channel atomizing chamber with controlled temperature at 3 ± 0.1 °C and a quartz integration quarter with the central passage size of 2.5 mm in diameter. Before analysis, all diluted $PM_{2.5}$ extraction solutions were filtered using nylon membranes (0.22 μm; Agela Technologies, Inc., Tianjin, China). A blank reagent (sterile purified water with 0.05% Tween-20) as a negative control was prepared in each run following the same procedure used for the samples. The detailed experiment procedure was followed as specified in the document of "Methods for Chemical Analysis of Silicate Rocks-Part 30: Determination of 44 Elements" (in Chinese) (GB/T 14506.30-2010). The metal analysis was not performed

for the global city PM samples.

2.5. Statistical analysis

In this work, because the data were not Gaussian-distributed, Kruskal-Wallis one-way analysis of variance (ANOVA) on ranks for multiple and non-parametric comparisons were used to analyze differences in biological contents and oxidative potentials among different cities, as well as those between heating seasons and non-heating seasons for each year in Xi'an. Friedman Test as an alternative of ANOVA for related samples was applied to analyzing the inter-annual differences in oxidative potentials, $PM_{2.5}$ mass concentrations and total bacteria during the whole year or during heating/non-heating seasons. Pearson's correlation and Spearman's correlation were performed to evaluate the associations between endotoxin/oxidative potentials with other factors. Friedman Tests were performed using SPSS 16.0 (IBM Corp. Ltd., NY, USA). Other statistical analyses were conducted using SigmaPlot 12.5 (Systat Software, Inc., Chicago, IL, USA). The results from the negative controls were shown to be below the analytical detection limits. A *p*-value of 0.05 indicates a significant difference.

3. Results and discussion

3.1. PM oxidative potential (OP) varied greatly with global cities

Fig. 2 presents (a) mass-normalized PM OPs in NIOG values and (b) calculated PM OP per cubic meter of air in $NIOG_{pcbm}$ values in different world cities. Kruskal-Wallis tests showed statistically significant differences in both NIOG and $NIOG_{pcbm}$ among 19 studied cities (*p*-value ≤ 0.001). As shown in Fig. 2a, NIOG values of PM in Beijing (1.14×10^{-2}), a city that is often frequented by haze problems, were unexpectedly found to be among the third lowest levels for all 19 cities, only 6% above Florianopolis (1.08×10^{-2}) of Brazil, and 13% above Tours (1.01×10^{-2}). However, the PM OP in San Francisco (2.20×10^{-2}) with much lower PM_{10} mass concentration of 16 μg/m^3 (Fig. 1b) was found to have the highest NIOG, about 93% higher than that of Beijing. Results of rat's exhaled breath experiment in our recently published work further confirmed above results of DTT assay (Chen et al., 2018). For example, rats from Zurich (City A), Johannesburg (City C) and San Francisco (City D) were found to produce significantly higher exhaled IL-6 levels than those from rats in the group Beijing (City B). In addition, the results of blood-borne IL-6 concentration levels were shown to agree with the results from the DTT assay (Chen et al., 2018).

Using equation (1), Fig. 2b visually shows the PM OP per cubic meter of air in $NIOG_{pcbm}$ (μg 1,4-NQ/m^3) values estimated for different world cities. It can be clearly recognized from Fig. 2b that $NIOG_{pcbm}$ was extremely high in Johannesburg, Shanghai, Guangzhou, Beijing and Bandung; other cities with high levels of $NIOG_{pcbm}$ included Chennai and Hong Kong; those with medium levels of $NIOG_{pcbm}$ included Haikou, Seoul, Warsaw, Singapore, Stolberg and Paris; the remaining cities were found to have lower levels of OP per cubic meter of air. The OP variations among locations as aforementioned were also reported in other studies (Künzli et al., 2006; Weichenthal et al.,

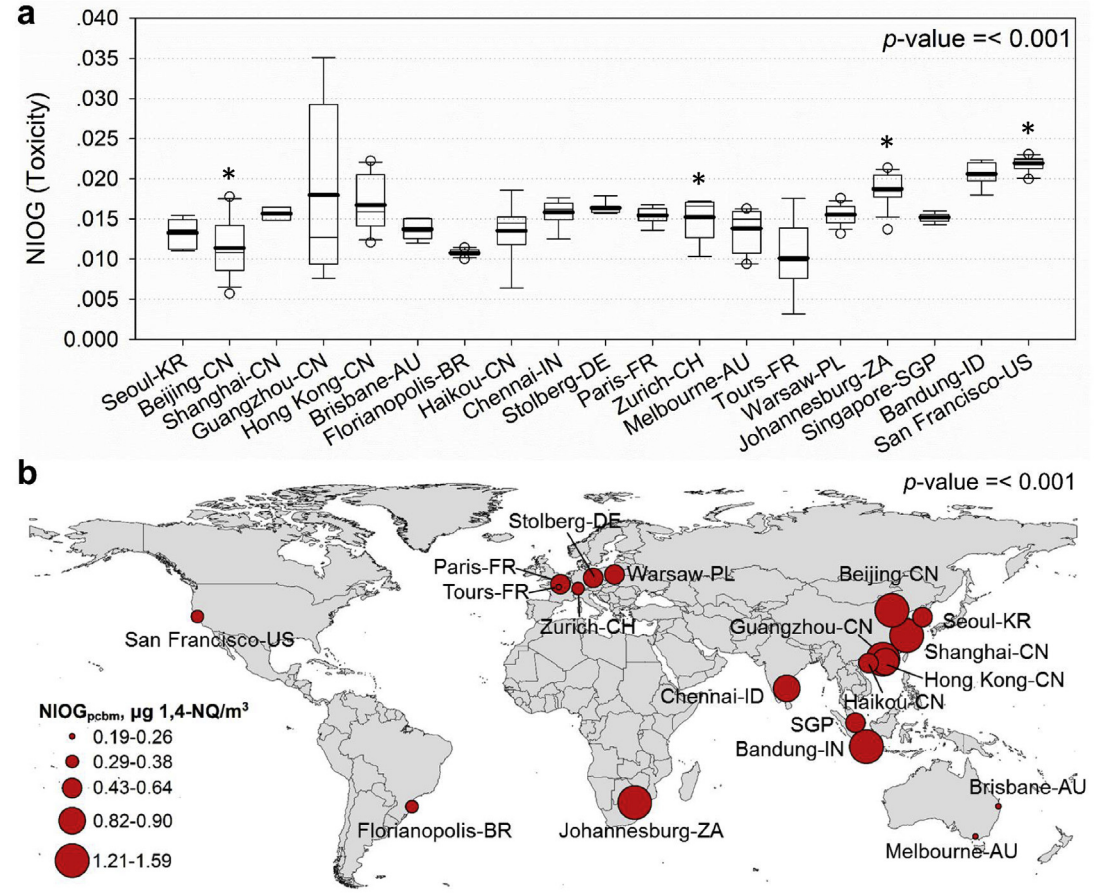

Fig. 2. (a) Boxplots of mass-normalized oxidative potentials (NIOG values); and (b) volume-normalized oxidative potential estimates ($NIOG_{pcbm}$ values) across different world cities. In (a) the upper and lower ends of the box respectively represent 75% and 25% percentiles; the vertical bars above and below respectively indicate 90th and 10th percentiles, with the upper and lower circles showing the data outside 90th and 10th percentiles; the lines inside the box are for mean (bold ones) and median values. *p*-value is the statistical result of Kruskal-Wallis Test. The toxicity values for cities marked with "*" in the figure were used to evaluate an online PM toxicity analysis method in another work (Chen et al., 2018).

2016a,b). Our results on the other hand suggest that cities with lower annual PM levels but higher PM OPs could still present health risks to those elderly, children and people with low immunity.

Our results on OP per unit mass of PM (NIOG) here might be partially explained by variations in its PM organic and inorganic components and source among different cities. For example, the relative mass percentages of $PM_{2.5}$-borne components that have strong associations with ROS generation such as OC, EC, NO_3^-, transition metals (Cu, Ni, Zn and Fe) in San Jose (close to San Francisco), California were reported as 34.7%, 6.7%, 19.2%, 0.04%, 0.05%, 0.06% and 0.81%, respectively (Wang and Hopke, 2013). However, those of OC, EC and NO_3^- in $PM_{2.5}$ in Beijing were much lower compared to San Jose, respectively, 12.5%, 3.7% and 8.4% (Zhang et al., 2013). Similarly, the relative mass percentages of OC, EC and NO_3^- in PM_{10} in Seoul were also at the low levels, respectively 15.3%, 4.5% and 12.1% (Yi and Hwang, 2014). The results from positive matrix factorization (PMF) showed that the contributions from vehicles, combustion and secondary reactions together accounted for more ambient $PM_{2.5}/PM_{10}$ in San Jose (81.8%) in comparison with Beijing (56%) and Seoul (48.1%). In contrast, fugitive dusts, generally believed to be less toxic, were reported to contribute more to PM_{10} in Seoul (34.9%) and to $PM_{2.5}$ in Beijing (16%) than to $PM_{2.5}$ in San Jose (5.1%) (Wang and Hopke, 2013; Yi and Hwang, 2014; Zhang et al., 2013). It was reported that in Beijing dust sources could contribute as much as 31–40% to PM_{10} during Asian dust storm (Liu et al., 2014a). Previous studies reported different results on source apportionment of ambient PM using different models or sampling in different seasons. For example, it was investigated using chemical mass balance (CMB) that in wintertime only the wood combustion contributed over 45% and as high as 81%, to ambient PM in San Jose, Sacramento and Modesto that are close to San Francisco (Chow et al., 1995; Kleeman et al., 2009). Vehicular emissions, incomplete combustion and secondary reactions were described to contribute larger fractions to the total generation of ROS than other sources (Charrier et al., 2015; Chung et al., 2006; Fang et al., 2015; Liu et al., 2014b; Verma et al., 2015). In addition to particle composition, a recent work showed that air samples collected into 13 different size ranges (10 nm–18 μm) for Beijing and Zürich had remarkably different size distributions and size-specific toxicity (Yue et al., 2018). This could be also true for the cities investigated here that particles collected from different cities, e.g., Beijing and Zürich, could have different size distributions, thus influencing its toxicity. Thus, it is not surprising that ambient PM samples from some cities (such as San Francisco) with low annual average PM concentration (usually termed as good air quality) were found to exhibit higher toxicity per unit of PM mass.

3.2. PM-borne endotoxin and associated microbes differed significantly among global cities

To study its influence on PM toxicity, PM-borne endotoxin levels among different world cities were analyzed and shown in Fig. 3. Kruskal-Wallis tests revealed statistically significant differences (p-values ≤ 0.001) in both mass-normalized and volume-normalized endotoxin levels among 19 different cities (no comparisons were made for any two cities here). As observed from Fig. 3a, mean values of endotoxin fractions in PM for different cities were found to vary significantly by two orders of magnitude from 12.16 ± 7.74 EU/mg

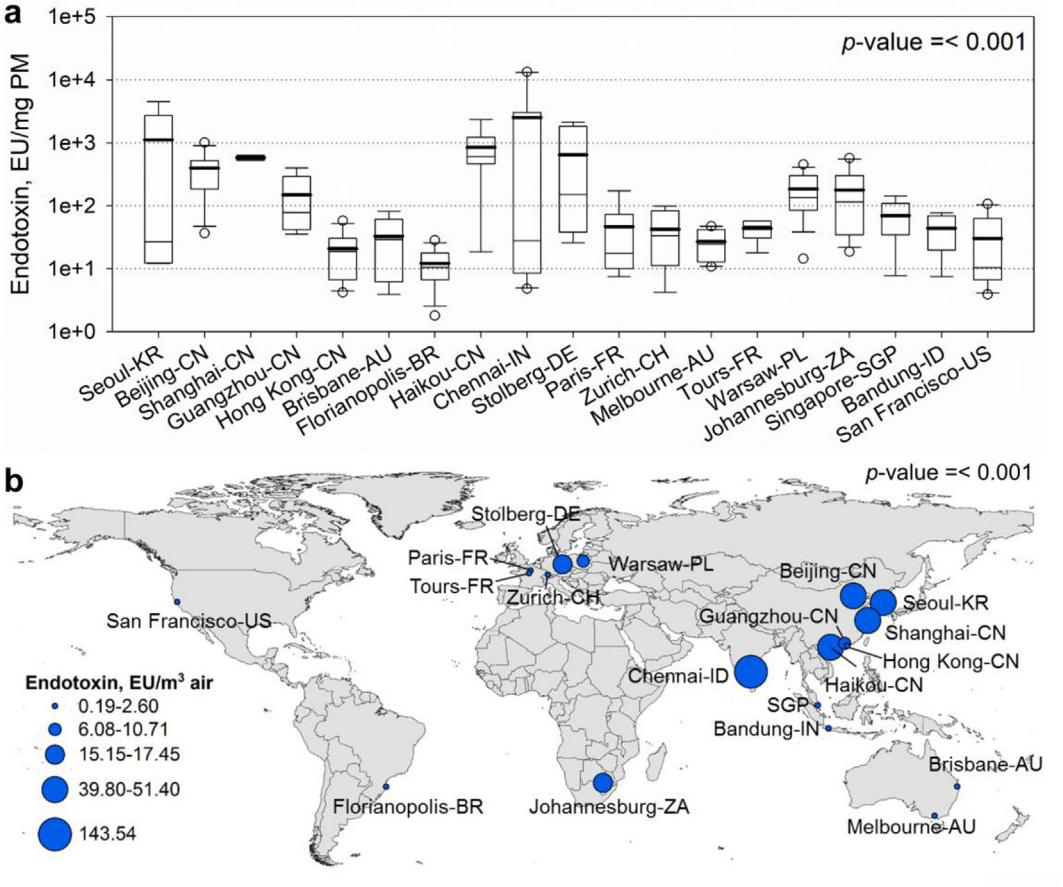

Fig. 3. (a) Boxplots of endotoxin fractions in PM (TSP); and (b) airborne endotoxin concentration estimates from dust-borne shown in (a) across different world cities (EU/m^3). In (a), the upper and lower ends of the box respectively represent 75% and 25% percentiles; the vertical bars above and below respectively indicate 90th and 10th percentiles, with the upper and lower circles showing the data outside 90th and 10th percentiles; the lines inside the box are for mean (bold ones) and median values. p-value is the statistical result of Kruskal-Wallis Test.

(mean value ± standard deviation, hereinafter) in Florianopolis, Brazil to 2518.23 ± 5229.89 EU/mg in Chennai, India. The same as Chennai, PM in Seoul (1117.3 ± 1864.48 EU/mg), Chinese mainland cities, i.e., Beijing (396.48 ± 269.83 EU/mg), Shanghai (580.50 ± 73.40 EU/mg), Guangzhou (148.80 ± 151.32 EU/mg) and Haikou (846.77 ± 692.04 EU/mg), Johannesburg (178.22 ± 187.90 EU/mg) and Warsaw (184.37 ± 130.89 EU/mg) also contained high levels of endotoxin. Stolberg, Germany was detected to exhibit a relatively high level of PM-borne endotoxin fraction of 646.41 ± 912.99 EU/mg, while other West European cities were in general found to have lower levels of mean value around 50 EU/mg PM. Other cities located in Southeast Asia, America and Australia exhibited low levels of PM-borne average endotoxin, less than 100 EU/mg as shown in Fig. 3a. The endotoxin fractions in PM partly agree with previous studies in term of its magnitude. The ambient endotoxin in San Francisco (30.21 EU/mg) in this study were relatively comparable to the PM_{10}-associated endotoxin level in Southern California (13.6 EU/mg) (Mueller-Anneling et al., 2004). The ambient endotoxin in Beijing (396.48 EU/mg) in this study, however, was much higher than the $PM_{2.5}$-borne endotoxin in Beijing (10.25 EU/mg) reported by Guan et al. (2014). The differences could partially result from different sampling methods, thus collecting different size PM samples. For example, studies showed that airborne endotoxin was detected mainly in $PM_{2.5\text{-}10}$ fraction (Heinrich et al., 2003; Schins et al., 2004; Tager et al., 2010). Nonetheless, these data suggest that same mass of PM from different cities contained different amounts of endotoxin. In addition to mass-normalized endotoxin, Fig. 3b visually presents the air volume-normalized endotoxin concentrations estimated using equation (2) for each of studied cities by considering their annual average PM_{10} levels (grouped into five levels as shown in the legend using Jenks Natural Breaks in ArcGIS 10.2). It can be clearly recognized from Fig. 3b that airborne endotoxin concentration level (EU/m^3) was extremely high in Chennai; other high levels of airborne endotoxin appeared with Seoul, Shanghai, Beijing and Haikou; cities with medium levels included Stolberg, Johannesburg, Guangzhou and Warsaw; the remaining cities were found to have relatively lower levels of airborne endotoxin. Our results here implied that people from different cities as studied here could likely have significantly different endotoxin inhalation exposure due to various factors, such as such as PM mass concentration.

To further study endotoxin-related biologicals, we analyzed bacterial contents in the PM samples. Fig. 4 presents (a) results of bacteria (both total and culturable) along with fungi fractions in PM collected from studied cities, and (b) correlations of the ratio of culturable bacteria to fungi (B/F ratio) with annual average minimum and maximum temperatures. Kruskal-Wallis tests showed statistically significant differences in all studied contents (i.e., total bacteria, culturable bacteria and culturable fungi) among different world cities with p-values of ≤ 0.001. As observed from Fig. 4a, total bacteria (1.01×10^4-

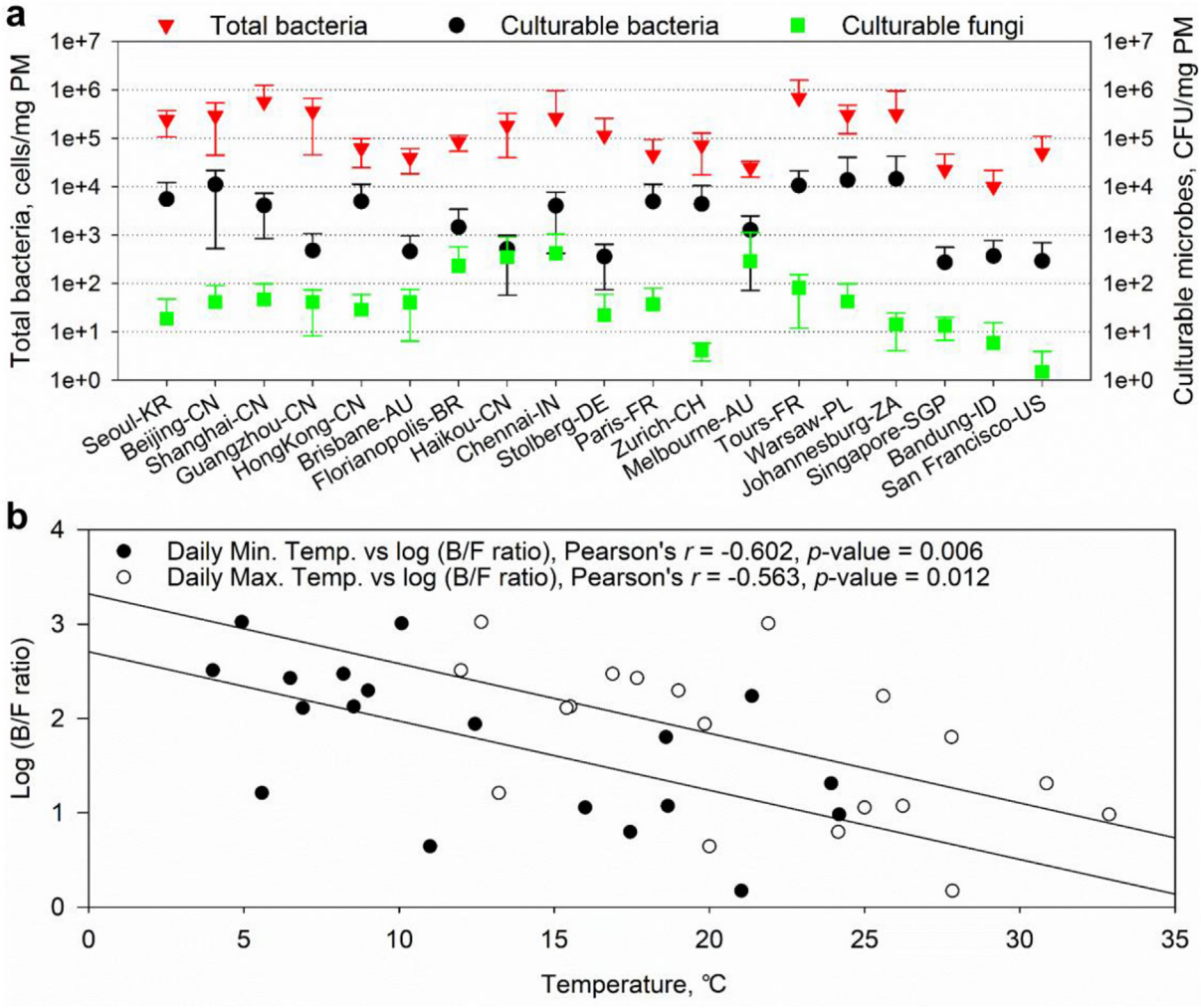

Fig. 4. (a) Average concentrations with standard deviations of total bacteria, culturable bacteria and culturable fungi in PM across 19 world cities; wherein standard deviations (error bars) were calculated from results of independent AC filter samples from each city as shown in Fig. 1; and (b) the correlation of the ratio of culturable bacteria to fungi (B/F ratio) with annual average daily minimum and maximum temperatures.

6.81 × 10^5 cells/mg), culturable bacteria (2.73 × 10^2-1.45 × 10^4 CFU/mg) and fungal (1.48–421.48 CFU/mg) were shown to vary significantly up to 100-fold among different cities, which thus could strongly influence the PM toxicity. In our recent work, it was shown that PM samples collected from global cities also had significant bacterial community structures (Li et al., 2018; https://www.ncbi.nlm.nih.gov/sra/PRJNA525745), further contributing to different toxicity of PM observed.

To explore the associations between PM-borne endotoxin fraction and different microbial fractions, we here performed Spearman's correlation analyses as shown in Table S2. Endotoxin was observed to be significantly associated with total bacteria (ρ = 0.489, *p*-value = 0.033) rather than culturable bacteria (ρ = 0.172, *p*-value = 0.475), because release of endotoxin molecule follows not only the growth of gram-negative bacteria but also mostly their cell lysis (Beutler and Rietschel, 2003; Liebers et al., 2008). On the other hand, endotoxin was shown to be positively associated both $PM_{2.5}$ (ρ = 0.560, *p*-value = 0.013) and PM_{10} (ρ = 0.459, *p*-value = 0.047) mass concentration as shown in Table S2. All above results reflected that different bacterial contents per unit of PM mass as shown in Fig. 4a and different $PM_{2.5}$ and PM_{10} mass concentration levels as presented in Fig. 1b could lead to different levels of PM-borne endotoxin for different cities.

The associations of B/F ratio with the meteorological factors are additionally listed in Table S1, including temperature (Fig. 4b), relative humidity and precipitation (Fig. S1). The results revealed only a significant, negative correlation between B/F ratio and daily minimum temperature (ρ = −0.602, *p*-value = 0.006) as well as daily maximum temperature (ρ = −0.563, *p*-value = 0.012) in this work. Our results suggested that temperature changes (minimum and maximum) affect bacteria and fungi differently, i.e., the inhibition effect for bacterial growth, in contrast to a promotion effect for fungal growth; which are consistent with some previous studies (Jones and Harrison, 2004; Lighthart and Shaffer, 1995). Our results here indicated that different meteorological conditions in different cities would influence the microbial compositions (bacteria and fungi) of PM including the endotoxin fraction, and thus the PM OP according to a recent work by Samake et al. (2017). Accordingly, sole use of PM mass concentration levels without considering PM-borne microbial contents might not be adequate for assessing the health impacts of ambient PM.

We additionally performed the Spearman's correlation analysis of PM OP here between biological fractions and $PM_{2.5}$ and PM_{10} mass concentrations. The results only showed a significantly negative association between NIOG and culturable fungi fraction in PM as shown in Table S3 (ρ = −0.481, *p*-value = 0.037). A number of recent studies has showed that PM-borne microorganisms in the atmosphere could modify the ambient OP through the biodegradation of H_2O_2 oxidants (Vaïtilingom et al., 2011, 2013). However, the specific oxidative reactivity of bioaerosols was reported to vary with the specific genera or species of microorganisms (Samake et al., 2017). Previous studies also demonstrated that endotoxin molecules could promote ROS generation both alone and in interaction with other species in PM (Di et al., 2011; Hsu and Wen, 2002; Simon and Fernandez, 2009; Takano et al., 2002). Here, the relationship between endotoxin and NIOG, shown to be statistically insignificantly correlated (ρ = 0.009, p-value = 0.968), might be possibly modified as discussed above by the different microbial community compositions reported for different cities in our recently published work (Li et al., 2018). The PM OP was also found to have no significant correlation with either $PM_{2.5}$ or PM_{10} mass concentration, which agreed with the findings in a previous study in Europe (Künzli et al., 2006). Overall, the OP of PM could be affected greatly by their chemical and biological compositions, however much work is needed to further elucidate the relevant influencing mechanisms.

3.3. $PM_{2.5}$ oxidative potential evolved significantly over a past decade in Xi'an, China

In the past years, benefiting from various control measures several major Chinese cities such as Beijing and Xi'an were observed to have declines in annual $PM_{2.5}$ mass concentration levels (Han et al., 2009; Huang et al., 2015; Wu et al., 2011; Zhang et al., 2013). In this work, as an example, we studied changes in OP for ambient $PM_{2.5}$ in 2004, 2009 and 2014 (a 10-year time period) in Xi'an, China. Fig. 5a respectively presents box plots of mass-normalized $PM_{2.5}$ OP in NIOG values, $PM_{2.5}$ mass concentrations, and estimated volume-normalized air OP in $NIOG_{pcbm}$ values during heating seasons and non-heating seasons of

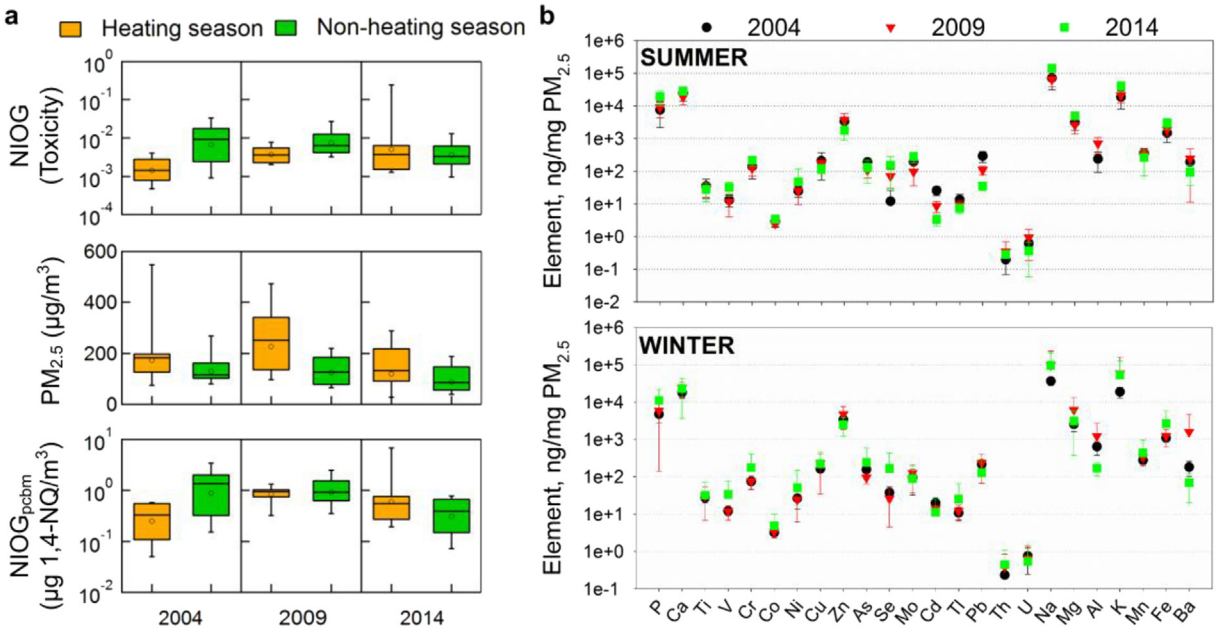

Fig. 5. (a) Boxplots of NIOG values, $PM_{2.5}$ mass concentrations and $NIOG_{pcbm}$ values in heating seasons (from 25th November to 6th or 7th March) and non-heating seasons (from 25th March to 6th or 7th November), and (b) average fractions with standard deviations in form of error bars of $PM_{2.5}$-borne trace elements in summer and winter during 2004, 2009 and 2014. In (a) upper and lower ends of the box represent 75% and 25% percentiles, respectively; the circle and line indicate geometric mean and median values, with the vertical bars showing the 90th and 10th percentiles, respectively.

2004, 2009 and 2014. The complete time series of daily $PM_{2.5}$ mass concentration observed in this work are shown in Fig. S2. Table 1 shows the statistical results on NIOG, $PM_{2.5}$ mass concentration, $NIOG_{pcbm}$ for 2004, 2009 and 2014 respectively in heating seasons and non-heating seasons. For heating seasons, Friedman Test shows that NIOG values among 2004, 2009, and 2014 differed significantly (p-value = 0.021) as observed in Table 1 with the order of: 2014 > 2009 > 2004. These data imply that $PM_{2.5}$ OP had increased over the past decade during heating seasons. In contrast, for non-heating seasons, $PM_{2.5}$ OP seemed to follow a similar pattern with the $PM_{2.5}$ mass concentration, i.e., it first slightly increased from 2004 to 2009, and then significantly decreased starting from 2009 when significant control measures have been implemented. For example, according to Xi'an Environmental Protection Bureau, the "Xi'an City motor vehicle emission prevention and control regulations" had come into force on September 1st, 2009. The regulations clearly defined the prevention and control, the determination and treatment and the related legal liabilities. Besides, Xi'an successively implemented the Tier III of China vehicle emission standard and the Tier IV of China vehicle emission standard respectively on August 1st, 2008 and June 1st, 2012 (Xi'an Environmental Protection Bureau). Surprisingly, Kruskal-Wallis Test suggested that the NIOG values in non-heating seasons were significantly higher than those in heating seasons during 2004 (p-value = 0.010) and 2009 (p-value = 0.048); and then the two seemed to be fairly equal (a turning point for $PM_{2.5}$ OP) in 2014 (p-value = 0.903). This phenomenon could be due to higher fraction of $PM_{2.5}$ from non-biogenic sources during the non-heating seasons for 2004 and 2009 as discussed above. As observed from Fig. 5a, $PM_{2.5}$ mass concentrations in heating seasons were generally higher than those in non-heating seasons all the time. Supposedly, the PM toxicity change from 2009 to 2014 during non-heating season were due to changes in $PM_{2.5}$ compositions, e.g., fewer emissions from industry and other non-biogenic emissions due to strict prevention and control policies implemented for the year of 2014. The results of $NIOG_{pcbm}$ shown in Fig. 5a imply that the overall $PM_{2.5}$ OP per cubic meter of air during the heating seasons in 2014 was shown to be 2.44 times that in 2004. For heating seasons, the $PM_{2.5}$ OP per unit volume of air ($NIOG_{pcbm}$) increased rapidly (roughly by 2.42 times) from 2004 to 2009, and then decreased by 40% from 2009 to 2014 due to strict control implementation. In contrast, for the non-heating seasons, the mean $NIOG_{pcbm}$ value in 2014 was about 1.81 times lower than that in 2004, although there was a slight increase (about 5.79%) from 2004 to 2009. These data show that the air pollution control practices have been taking effects at least during the non-heating seasons over the past decade in Xi'an, and heating significantly affects air toxicity.

These results shown above are largely attributed to the adopted changes for the energy consumption and permanent population in Xi'an as shown in Supplementary Excel file S2 obtained from Xi'an Statistical Yearbooks (2005–2015). The permanent population and the raw coal consumption mostly used in heating seasons had respectively increased by 16% and 52% from 2004 to 2009, and then continued to increase but with lower rates of 2% and 23% from 2009 to 2014. Coal combustion has been reported to be strongly associated with increased mortality risk through inducing the ROS production (Hu et al., 2014; Laden et al., 2000; Lelieveld et al., 2015), and a major contributor to the $PM_{2.5}$ during heating seasons (1–7%) than during non-heating seasons (24.1–57%) (Cao et al., 2005; Zhang et al., 2013). Here, the $PM_{2.5}$ OP in Xi'an was observed to increase by 2.53 times from 2004 to 2014 during heating seasons. In contrast to the raw coal, the usages of other energies including crude oil, gasoline and diesel had respectively decreased by 14%, 1315% and 452% from 2009 to 2014 as observed from Supplementary Excel file S2. Therefore, the $PM_{2.5}$ OP during non-heating time of 2014 was significantly lower than those in 2004 and 2009. It should be also noted that previously observed higher fractions of EC, OC and transition metals per μg of $PM_{2.5}$ during the non-heating seasons in Xi'an (Huang et al., 2012) could partially explain why $PM_{2.5}$ OP during non-heating seasons was observed to be significantly higher than those during heating seasons for 2004 and 2009. The results here imply that $PM_{2.5}$ even during the non-heating seasons should be controlled to protect elderly and children with low immunity, especially for places where non-biogenic control measures are not in place.

To further analyze the reasons for observed $PM_{2.5}$ OP changes, the metal elements of $PM_{2.5}$ samples of summer (June, July and August) and winter (December, January and February) and the total bacteria (possible toxicity modifier) in all $PM_{2.5}$ samples were analyzed, and presented in Fig. 5b and Fig. S3, respectively. Friedman Tests showed significant inter-annual differences in Cd (04 > 09 > 14), Pb (04 > 09 > 14), U (09 > 04 > 14) and Na (14 > 04 > 09) for summer (p-values = 0.007, 0.007, 0.015 and 0.042) and in Se (14 > 09 > 04) only for winter (P = 0.011), as shown in Table S4. For summer, the non-heating season, decreased levels in Cd, Pb and U, which are often used as the industrial emission markers, together with increased Na, and usually enriched in crustal materials (Calvo et al., 2013), might explain the lowest NIOG values for $PM_{2.5}$ during non-heating seasons in 2014 as discussed above. For winter, Se, one of the typical coal combustion emission marker (Calvo et al., 2013), increased from 2004 to 2014 due to the increase in population size, which had coincidence with the increased NIOG values for $PM_{2.5}$ during heating seasons as discussed above. These data indicate that changes in the oxidative potential of $PM_{2.5}$ were in part due to the changes of metal contents in the $PM_{2.5}$ samples as a result of various air pollution control measures. Certainly, these observations could also occur to other world cities other than Xi'an here if similar air pollution control measures are adopted. Spearman's correlation analyses additionally showed significant, positive associations between the $PM_{2.5}$ OP with $PM_{2.5}$-borne bacteria (ρ = 0.250, p-value = 0.038), element P (ρ = 0.346, p-value = 0.045), Cr (ρ = 0.373, p-value = 0.030) and Na (ρ = 0.459, p-value = 0.007), as shown in Table S5.

In this work, we have detected significant differences (p-values ≤ 0.001, Kruskal-Wallis test) in both microbial contents and toxicity of PM among 19 global cities. The biological components were also shown to vary greatly with geographical locations. Xi'an's samples also showed the PM OP could also evolve over the time as a result of changes from the ground activities and air pollution measures. Here, we used Xi'an as an example to study the impacts of time and season on the PM toxicity. In future studies, more samples and locations around the world can be included to improve spatial PM toxicity resolutions. The AC filter collection efficiencies as well as sample representativeness should be evaluated against other common methods. Our work just provides an

Table 1
P-values of Friedman Tests of NIOG, $PM_{2.5}$ mass concentration, $NIOG_{pcbm}$ among 2004, 2009 and 2014 in heating seasons and non-heating seasons separately, and Kruskal-Wallis Tests of those between heating seasons and non-heating seasons in 2004, 2009 and 2014, respectively.

	Friedman Tests among 2004, 2009 and 2014		Kruskal-Wallis Tests between heating and non-heating seasons		
	Heating seasons	Non-heating seasons	2004	2009	2014
NIOG	**0.021***	0.135	**0.01***	**0.048***	0.903
$PM_{2.5}$ mass conc. (μg/m^3)	0.607	**0.046***	0.121	**0.02***	0.132
$NIOG_{pcbm}$ (μg 1,4-NQ/m^3)	**0.021***	**0.019***	**0.023***	0.404	0.302

*p-value < 0.05. Numbers in the table above refer to p-values of different statistical tests performed.

overall glimpse of air toxicity differences across the global cities, and a more quantitate assessment would require both higher temporal and spatial resolution with controlled influencing factors. The results obtained herein highlight the importance in optimizing current air quality control measures by considering both biologicals and toxicity factor of PM.

Competing financial interests

The authors declare no competing financial interests in association with this study.

Declaration of interest statement

We declare that we do not have any conflicting interests with respect to the work reported here.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2019.05.048.

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