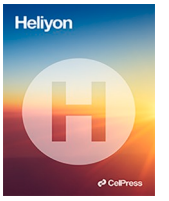
Heliyon 10 (2024) e25310

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

New health index derived from oxidative potential and cell toxicity of fine particulate matter to assess its potential health effect

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ARTICLE INFO

Keywords:
Fine particles
Toxicity
Mass concentration
$PM_{2.5}$ source
Health index

ABSTRACT

Toxicological data and exposure levels of fine particulate matters ($PM_{2.5}$) are necessary to better understand their health effects. Simultaneous measurements of $PM_{2.5}$ oxidative potential (OP) and cell toxicity in urban areas (Beijing, China and Gwangju, Korea) reveal their dependence on chemical composition. Notably, acids (Polar), benzocarboxylic acids, and Pb were the chemical components that affected both OP and cell toxicity. OP varied more significantly among different locations and seasons (winter and summer) than cell toxicity. Using the measured OP, cell toxicity, and $PM_{2.5}$ concentration, a health index was developed to better assess the potential health effects of $PM_{2.5}$. The health index was related to the sources of $PM_{2.5}$ derived from the measured chemical components. The contributions of secondary organic aerosols and dust to the proposed health index were more significant than their contributions to $PM_{2.5}$ mass. The developed regression equation was used to predict the health effect of $PM_{2.5}$ without further toxicity measurements. This new index could be a valuable health metric that provides information beyond just the $PM_{2.5}$ concentration level.

1. Introduction

High concentrations of atmospheric particulate matter (PM) with an aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$) have become a global concern due to their impacts on climate change and human health [1–3]. Epidemiological and toxicological studies have suggested a strong connection between exposure to $PM_{2.5}$ and adverse effects on human health, such as increased mortality and morbidity [1,4–7]. Current regulations and political strategies for mitigating $PM_{2.5}$ pollution are based on their mass concentrations, assuming that all particles are equally toxic regardless of their varied physical, chemical, and biological properties [8,9].

However, in vivo and in vitro studies have suggested that different toxicities exist for $PM_{2.5}$ in the ambient atmosphere [7,10–13], in which the spatially and temporally varying chemical and toxicological properties of $PM_{2.5}$ from different sources can result in different human health effects. For example, despite equal mass concentrations, greater pulmonary toxic responses in mice were induced by $PM_{2.5}$ collected from California, USA, than from Shanxi Province, China, owing to their higher level of oxidized organic

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https://doi.org/10.1016/j.heliyon.2024.e25310
Received 26 December 2023; Received in revised form 18 January 2024; Accepted 24 January 2024
Available online 2 February 2024

carbon and copper content [12]. Exposure to wintertime $PM_{2.5}$ samples from Beijing, China, caused higher oxidative stress in human bronchial epithelial BEAS-2B cells than that of $PM_{2.5}$ samples from Guangzhou, China, with equal mass concentrations [13]. $PM_{2.5}$ produced from various sources in the laboratory have differential toxicities, with the highest toxicity from diesel engine exhaust particles, followed by gasoline engine exhaust particles, biomass burning (rice straw and pine stem) particles, coal combustion particles, and road dust [7].

Northeast Asia has experienced severe air quality degradation due to high $PM_{2.5}$ concentrations [14]. In China and Korea, the major sources of $PM_{2.5}$ from 1999 to 2012 were industry and combustion sources and traffic and secondary aerosol sources, respectively [15]. Hopke et al. compiled studies on source apportionment in northeast Asia published after 2014, showing that the contribution of such sources varied over the years [16]. An epidemiological study also demonstrated that spatial heterogeneity exists in the association between $PM_{2.5}$ concentration and daily mortality across countries [17]. A recent study showed that the different $PM_{2.5}$ chemical components and sources among different cities in Korea variably affected human health (mortality) [18]. This study reported that transition and heavy metals (e.g., Pb, As, Fe, and Ti) and their related sources (e.g., coal combustion, soil, and incinerators) are significantly associated with increased mortality from cardiovascular (risk ratio (RR): 1.016–1.030) and all-cause (RR: 1.010–1.016) diseases in Seoul, Korea. In Gwangju, Korea, PM sources such as mobile, oil and coal combustion, aged sea salt, and soils were significantly associated with an increase in mortality from both respiratory (RR: 1.048–1.109) and all-cause diseases (RR: 1.015).

The underlying mechanisms of the adverse health effects caused by $PM_{2.5}$ are still poorly understood. Among the few identified mechanisms, oxidative stress induced by particles due to an imbalance between oxidants such as reactive oxygen species (ROS) and cellular antioxidants is an important factor that causes inflammatory responses and membrane damage [19–24]. ROS are produced in the body by the redox-active chemical components of $PM_{2.5}$ [9,20]. Oxidative potential (OP) is used to measure the ability of particles to generate ROS and/or activate redox reactions [25,26]. Several cell-free methods (chemical assays) such as dithiothreitol (DTT), ascorbic acid, electron spin resonance, and 2,7-dichlorofluorescein assays have been used to measure the OP of $PM_{2.5}$ [24,27].

It was suggested that the OP could be used as a good indicator to estimate adverse health effects [6]. Øvrevik reviewed previous studies to assess the association between OP and biological outcomes and found a positive association between OP and redox-related responses such as intracellular ROS generation, oxidative damage to macromolecules, and antioxidant response in in-vitro cell models [28]. However, little association was found between OP and cell toxicity, inflammatory responses, or non-oxidative DNA damage. In some cases, the OP determined by chemical assays had different results from the cell-based toxicological outcomes [27–29]. Although OP can measure responses induced by intrinsically redox-active components, such as transition metals and quinones, in $PM_{2.5}$, it cannot measure responses from redox-inactive components, such as parent polycyclic aromatic hydrocarbons (PAH), which require metabolic activation in the human body to become redox-active [13,30]. However, cell-based bioassays can capture the biological responses of chemical components that are transformed from redox-inactive to redox-active by metabolic activation in BEAS-2B [13] and A549 [30] cells. Thus, OP alone cannot estimate the overall toxicity of $PM_{2.5}$, and both chemical assays and bioassays should be combined to better understand their health effects.

While cell toxicity serves as a comprehensive measure, encapsulating the overall impact on cellular health, the inclusion of OP holds significant merit. All redox-active chemical components present in $PM_{2.5}$ may not uniformly induce cell toxicity. By including the specific responses (OP) induced by redox-active components, more refined understanding of the potential health implications by fine particles can be achieved, which may not be fully captured by a broad cell toxicity assessment alone. Therefore, the measurement of various toxicity endpoints is necessary.

This study aims to develop a health index that can provide useful information on health effect of $PM_{2.5}$ beyond just the concentration level. Simultaneous measurements of the OP, cell toxicity, and chemical components, such as ions, elements, organic carbon (OC), elemental carbon (EC), and organic compounds, of $PM_{2.5}$ in urban Beijing, China, and urban Gwangju, Korea in winter 2018–2020, and summer 2019 were conducted. The differences in fine particle toxicological characteristics (OP and cell toxicity) between the two locations and seasons (winter and summer) were examined. The measured chemical components of $PM_{2.5}$ were used to determine the influencing factors and sources that affect OP and/or cell toxicity. By considering both OP and cell toxicity and their concentrations, a new health index based on $PM_{2.5}$ was developed. Subsequently, a multi-linear regression (MLR) model was developed to relate the sources to the health risk of $PM_{2.5}$ and predict its toxicity without further measurements. Furthermore, during various event days with elevated $PM_{2.5}$ mass concentrations from different sources, differences in health indices were examined.

2. Experimental methods

2.1. Sample collection

The sampling of ambient $PM_{2.5}$ was conducted in Beijing, China and Gwangju, Korea. Beijing and Gwangju sites are located at Peking University Changping campus, Beijing, China (40°14′44.6″N and 116°11′33.3″E)) and Gwangju Institute of Science and Technology (GIST) campus, Gwangju, Korea (35°13′41.1″N and 126°50′36.3″E), respectively. Details of these maps can be found in our previous studies [31,32]. A total of 202 sampling days were simultaneously conducted, with 82 winter days from each site during January 3, 2018–February 1, 2018, December 27, 2018–January 25, 2019, and December 23, 2019–January 13, 2020, and 19 summer days from each site during August 5, 2019–August 23, 2019.

In Beijing site, ambient $PM_{2.5}$ filter samples were collected using a four-channel mini-volume sampler (TH-16A, Wuhan Tianhong Instruments, China) and a high-volume sampler (TH-1000C, Wuhan Tianhong Instruments, China) with flow rates of 16.7 lpm and 1000 lpm, respectively. On the other hand, three mini-volume samplers (URG-2000-30EH, URG, USA) and two high-volume samplers (TE-6001-2.5I, Tisch Environmental, USA and HV-RW, Sibata, Japan) with flow rates of 16.7 lpm and 1200 lpm, respectively, were

used in the Gwangju site. The 24 h samples were collected on 47 mm Teflon filters (Zefluor, Pall, USA) for ion, element, and OP analyses. For OC/EC analysis and OC speciation, 47 mm and 203 mm × 254 mm prebaked quartz filters (400 °C for 4 h) (Tissuquartz 2500QAT-UP, Pall, USA) were used. Additionally, 203 mm × 254 mm glass fiber filters (A/C Glass Fiber Filter, Pall, USA) were used for cell toxicity analysis. The daily sampling times were 09:00 a.m.–08:30 a.m. (local time) at the Beijing site and 10:00 a.m.–09:30 a.m. at the Gwangju site.

2.2. Measurement and analysis

The $PM_{2.5}$ mass concentration were measured by gravimetric analysis using a microbalance (Cubis® MSA3.6P-000-DM, Sartorius, Germany) with triplicate measurements within 5 % of measurement error. The Teflon filters were equilibrated in desiccator with constant temperature (20.1 ± 3.0 °C) and relative humidity (16.6 ± 2.2 %) before and after sampling.

Water-soluble ionic species (SO_4^{2-}, NO_3^-, Cl^-, NH_4^+, Na^+, K^+, Mg^{2+}, and Ca^{2+}) were determined by using ion chromatography (850 Professional IC, Metrohm, Switzerland) with method detection limits ranging of <0.001–0.04 ppm. The Teflon filter extraction was conducted through 2 h ultra-sonication in 30 ml deionized water, maintaining a water temperature of 20 °C. The extracted solution was then filtered through a polytetrafluoroethylene syringe filter (Advantec Inc. Japan) with a pore-size of 0.45 μm to eliminate water-insoluble fractions. After ion chromatography analysis, the remaining extract was passed through a polyvinylidene fluoride syringe filter and analyzed for water-soluble organic carbon (WSOC) using a total organic carbon (TOC) analyzer (Sievers 900, General Electric, USA). To minimize the impact of inorganic carbon on TOC measurements, an inorganic carbon remover was used. The limit of detection (LOD) for the TOC was 0.067 μgC/m^3. Replicate analyses were performed for every ten samples, ensuring that the repeatability remained within a measurement error of less than 5 %.

An energy dispersive X-ray fluorescence spectrometer at Cooper Environmental Services (Portland, USA) was employed to determine 48 elements (Na, Mg, Al, Si, P, S, Cl, K, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Br, Rb, Sr, Y, Zr, Nb, Mo, Ag, Cd, In, Sn, Sb, Cs, Ba, La, Ce, Sm, Eu, Tb, Hf, Ta, W, Ir, Au, Hg, and Pb). No sample extraction was required for the elemental analysis, and the LODs ranged from 0.99 to 51.24 ng/cm^2, respectively.

OC and EC concentrations were determined with the thermal-optical transmittance (TOT) method [33] based on the National Institute for Occupational Safety and Health (NIOSH) 5040 temperature protocol [34] using a Sunset Laboratory OC-EC Analyzer (5 L, Sunset laboratory, USA). The LOD for OC and EC, determined through sucrose spike injection, was 0.2 μg/m^3. Replicate analyses and external calibration checks were performed every 10 and 15 samples, respectively. Water-insoluble organic carbon (WISOC) was calculated by subtraction of WSOC from OC.

Organic compounds were determined by extracting quartz filter samples with dichloromethane (DCM) for non-polar types and in water or methanol for polar organic compounds. Gas chromatography electron impact mass spectrometry (GC-EIMS) was used to detect the non-polar organic compounds (i.e., n-alkanes (33 compounds), cycloalkanes (5), steranes and hopanes (16), and PAHs (22), while tandem liquid mass spectrometry (LC-MS/MS) was used to measure the polar compounds (i.e., alkanoic acids (25), resin acids (8), aromatic diacids (8), alkanedioic acids (8), levoglucosan, and sterols (6)). Both of the methods have absolute detection limits ranging from 1.7 to 4.6 pg/m^3. A more detailed information about the organic speciation method can be found in Park et al. and Oh et al. [32,35].

A DTT assay [36] was used to determine the OP. The Teflon filter was extracted via sonication and shaking for 1 h and then submerged in 5 ml of deionized water. In an amber vial, 3 ml filtered extract was mixed with 14.5 ml deionized water, 5 ml 50 mM potassium phosphate buffer (pH = 7.4), and 2.5 ml 5 mM DTT. The vial was subjected to shaking and incubation at a specific time of 5, 15, 25, 35 and 45 min using a shaking incubator (37 °C, 200 rpm). After incubation, 1 ml of 1 % (w/v) trichloroacetic acid quenching agent and 1 ml of 5,5-dithiobis- (2-nitrobenzoic acid) (DTNB) were successively added to the vial. Then, 4 ml of 80 mM Tris buffer (pH 8.9) and 4 mM ethylenediaminetetraacetate was added to stabilize the mixture. The reaction of DTT with DTNB produced a yellow chromophore (5-mercapto-2-nitrobenzoic acid), which was quantified using an ultraviolet-visible (UV-VIS) spectrophotometer (Spectramax M2, Molecular Devices LCC). The DTT consumption rate was calculated using a linear regression of the plotted absorbance against time (pmol/min) as shown in Fig. S5, leading to the derivation of the mass- and volume-normalized OP with the sampled PM mass and air volume, respectively.

Samples from 88 d (35 d from the Beijing site and 53 d from the Gwangju site) were used to measure cell toxicity. Cell toxicity was measured using a neutral red uptake (NRU) assay. A549 cells (Korea Cell Line Bank, Korea) were used as the target cells. They were grown in the Roswell Park Memorial Institute 1640 medium (Gibco, UK) with 10 % Fatal Bovine Serum (Gibco, UK), 100 units/mL of penicillin and 100 μg/mL of streptomycin (Gibco, UK) in an incubator with a humidified atmosphere (5 % CO_2 and 95 % air) at 37 °C. The filter sample was extracted in methanol for 1 h using a sonicator and a shaking incubator. The $PM_{2.5}$ extract was filtered using a 0.22 μm polytetrafluoroethylene syringe filter and lyophilized in a freeze-dryer. The dried extract was re-dissolved in the cell culture medium at 1 mg/ml for the cell toxicity tests.

The A549 cells were seeded on 96-well plates at a density of 1.5×10^4 cells/well with the culture medium [7]. The 96-well plates were exposed to the humidified atmosphere at 37 °C and 5 % CO_2 for 24 h. The culture medium was then removed, and the diluted $PM_{2.5}$ extract or culture medium (negative control) was added to each well for 24 h. After 24 h exposure, the NRU solution (50 μg/mL in culture medium) was treated for 2 h. After aspirating this solution, a wash-fix solution (1 % (v/v) formalin) was added to each well. The wash-fix solution was removed within 1 min and a mixture of 1 % acetic acid–50 % ethanol was added to each well to extract the NR solution from the cells at room temperature for 15 min. Optical density was measured at 540 nm using a microplate reader (SpectraMax M2, Molecular Devices, USA). The EC_{50} value (50 % inhibition of cell growth) was calculated through the regression of the dose-response curve, and then mass- and volume-normalized cell toxicity was calculated using the EC_{50} values and sampled PM

mass and air volume, respectively.

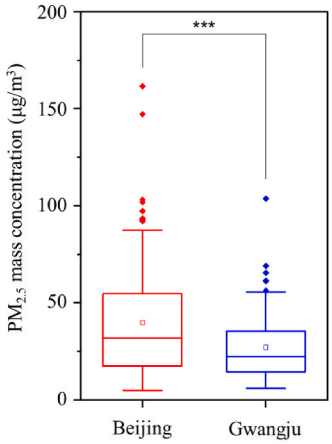
Gas (O_3, NO_2, CO, and SO_2) data were obtained from gas analyzers (models 49i, 42i, 48i, 43i, Thermo Fisher Scientific, USA) at the Beijing site and a station operated by the Korean Meteorological Administration located approximately 2 km from the Gwangju site. Meteorological data (relative humidity, temperature, wind direction, and wind speed) were collected at both sites using an Automatic Weather Station.

The US Environmental Protection Agency (EPA) positive matrix factorization (PMF) 5.0 model was used to identify the sources of the $PM_{2.5}$ (US EPA, 2014). The PMF model was run multiple times with adjustments to the factor numbers and uncertainties to obtain the optimal solutions. Detailed information on the PMF method used in this study is discussed in Oh et al. [35].

3. Results and discussion

3.1. Mass and gas concentrations

The average $PM_{2.5}$ mass concentration (39.7 ± 30.5 μg/m^3) at the Beijing site during the sampling periods was approximately 1.5 times higher than that at the Gwangju site (27.1 ± 16.6 μg/m^3), as shown in Fig. 1. This difference was more pronounced in winter and gradually decreased in summer. A higher $PM_{2.5}$ mass concentration was observed in winter than in summer at both sites. As summarized in Tables S1 and S2, the highest $PM_{2.5}$ mass concentration (62.4 ± 34.1 μg/m^3) was observed during winter in 2018 at the



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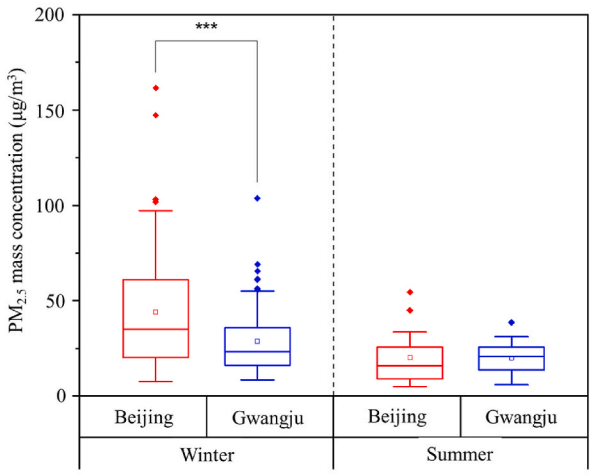


(b)

Fig. 1. Average $PM_{2.5}$ mass concentrations at the Beijing and Gwangju sites (a) during the sampling periods (winter 2018–2020 and summer 2019) and (b) in different seasons. The *** indicates $p < 0.001$.

Beijing site. The $PM_{2.5}$ mass concentrations observed during the subsequent winters decreased, likely due to the Clean Air Action Plan implemented by the Chinese government to improve air quality. The action included energy use, industrial emission, vehicle emission, and dust control. Average emissions of major air pollutants were reduced by 39 % in 2017 compared with those in 2013 [37].

The average concentrations of the gases (CO, NO_2, O_3, and SO_2) are summarized in Tables S3 and S4. The CO and NO_2 concentrations observed in Beijing were higher than those in Gwangju. The CO concentration at the Beijing site decreased by 18 % and 28 % in winter 2019 (523 ± 356 ppb) and winter 2020 (596 ± 288 ppb), respectively, compared with that in winter 2018 (724 ± 440 ppb). Significant decreases in the annual average concentrations of air pollutants, such as NO_2, CO, O_3, SO_2, $PM_{2.5}$, and PM_{10} were also observed in megacities in China from 2018 to 2020 [38]. Meanwhile, little difference was observed in the changes in $PM_{2.5}$ mass concentrations and gases during the sampling periods at the Gwangju site.

3.2. Chemical composition

Fig. 2 compares the mass fractions (%) of the major chemical components in the $PM_{2.5}$ between the two sites; the absolute concentration of the chemical component is indicated by the color. The mass fractions of the Mg^{2+} and Ca^{2+} ions, Ca, Mg, Si, Fe, and Al elements, OC, WISOC, EC, PAHs, hopanes and steranes, alkanes, and cycloalkanes were significantly higher at the Beijing site than at the Gwangju site. At the Gwangju site, the mass fractions of the NO_3^- and SO_4^{2-} ions, Ni, Cu, As, Br, Zn, and Na elements, WSOC, acids, benzo carboxylic acids, diacids, and levoglucosan were higher than those at the Beijing site. The data suggest that chemical components from fresh combustion sources and dust significantly contributed to $PM_{2.5}$ concentrations at the Beijing site, while secondary/aged sources were the more important sources affecting $PM_{2.5}$ at the Gwangju site. Biomass burning-related chemical markers (e.g., K^+ and levoglucosan) were observed in the $PM_{2.5}$ at both sites. For a detailed understanding of the major sources of fine particles, we refer readers to our prior work [35], where a thorough comparative analysis of these factors was presented.

A distinct seasonal difference was observed in the chemical components of $PM_{2.5}$ at the Beijing site, as shown in Fig. S1(a). The mass fractions of the K^+, Mg^{2+}, Ca^{2+}, and Cl^- ions, dust-related elements, PAHs, and alkanes were significantly higher in winter than in summer, whereas those of the NO_3^- and SO_4^{2-} ions, OC, WSOC, acids, diacids, and biogenic acids were higher in summer than in winter. These data suggest that fresh combustion and dust sources (desert and road dust) are predominant in winter at the Beijing site. However, the difference in chemical components between winter and summer at the Gwangju site was relatively small compared with the Beijing site, suggesting that the contributing sources to the $PM_{2.5}$ were not significantly different between the two seasons, although the level of $PM_{2.5}$ was higher in winter than in summer (Fig. S1(b)).

3.3. OP

Fig. 3(a) compares the mass-normalized OP (pmol/min/μg) of $PM_{2.5}$ at the Beijing and Gwangju sites and includes previous literature values in Asia, USA, and EU. Mass-normalized OP is an intrinsic property and informative metric that demonstrates spatial and temporal differences. Volume-normalized OP (mass-normalized OP × $PM_{2.5}$ mass concentration) additionally accounts for the exposure level and is often used for comparison with epidemiological outcomes [24]. Hereafter, OP refers to mass-normalized OP and the volume-normalized OP is represented by OP_v. The OP at the Beijing site (57.2 ± 26.8 pmol/min/μg) was significantly higher than

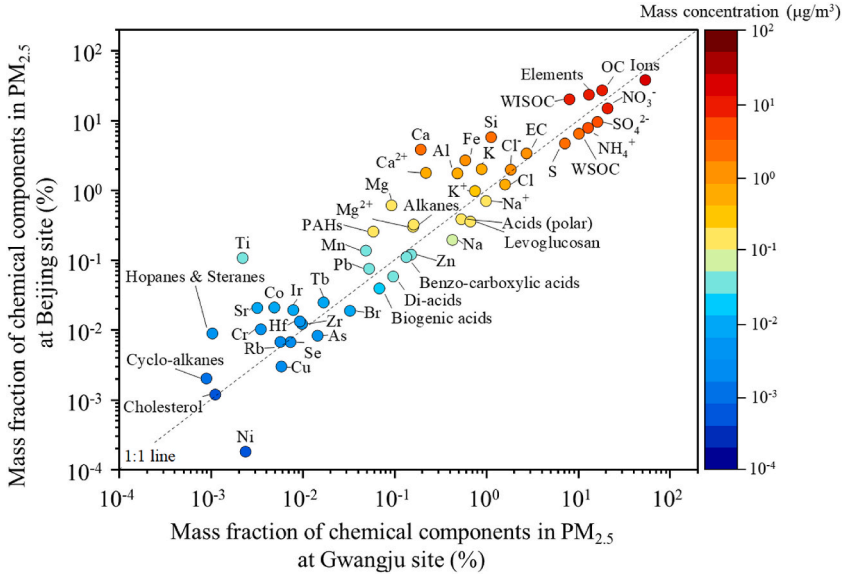


Fig. 2. Mass fractions of the chemical components of $PM_{2.5}$ at the Beijing and Gwangju sites for the entire sampling period. The color indicates the mass concentration of the $PM_{2.5}$ chemical components.

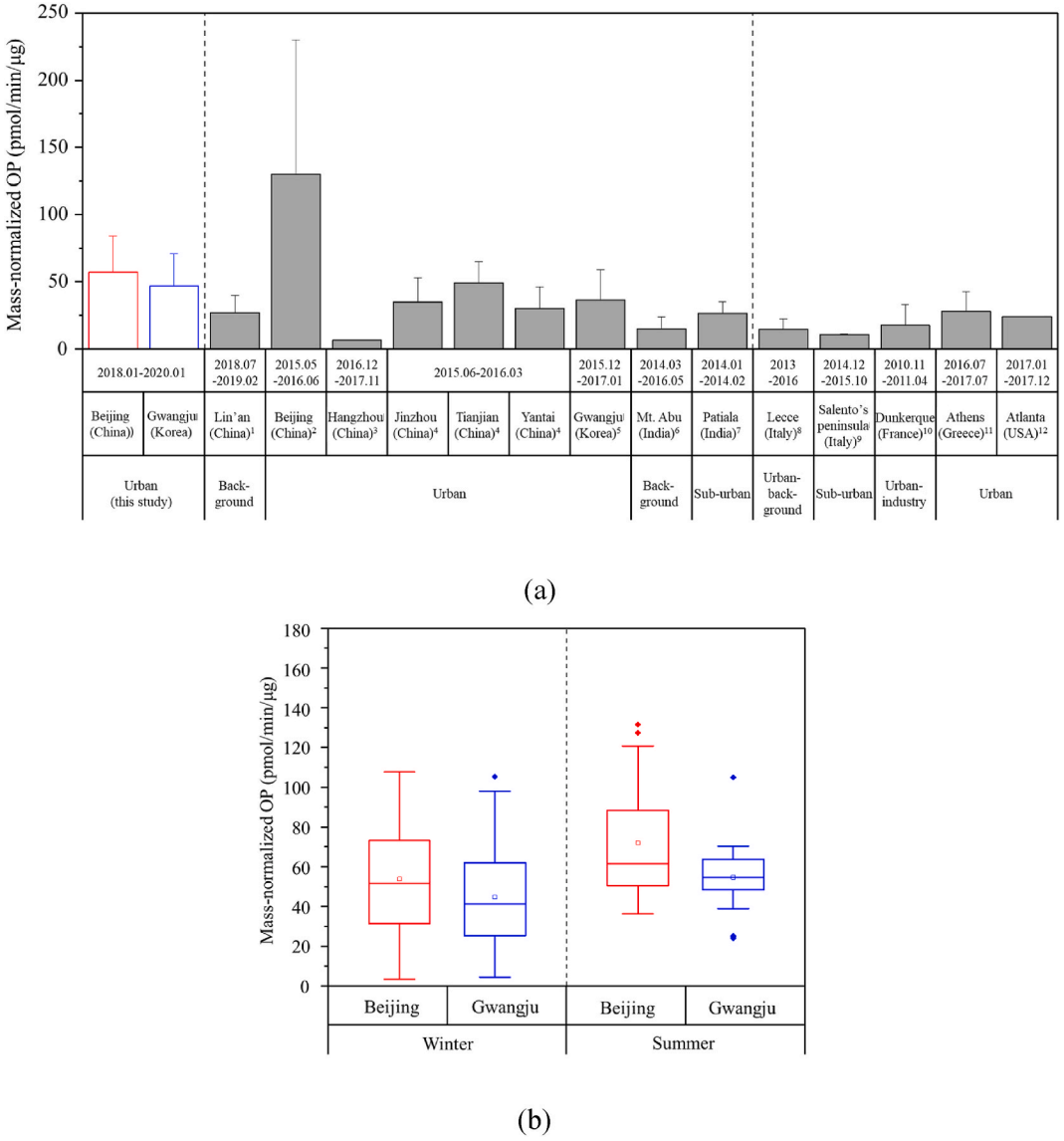


Fig. 3. OP of $PM_{2.5}$ (a) at the Beijing and Gwangju sites and from previous literature values in Asia, USA, and EU and (b) during winter and summer. The error bar represents standard deviation. [1]Li et al. [40], [2]Yu et al. [39], [3]Wang et al. [41], [4]Liu et al. [42], [5]Borlaza et al. [36], [6]Patel and Rastogi [43], [7]Patel and Rastogi [44], [8]Chirizzi et al. [45], [9]Perrone et al. [46], [10]Moufarrej et al. [47], [11]Paraskevopoulou et al. [48], [12]Gao et al. [49].

that at the Gwangju site (46.8 ± 23.9 pmol/min/μg). The OP values were comparable to those at sites other than Beijing during 2015–2016. The OP in Beijing in 2015–2016 [39] was much higher than that in 2018–2020 (this study). This may be because OP-sensitive chemical components and sources were more abundant in 2015–2016 than in 2018–2020. Higher fractions of industrial and coal combustion sources were also observed during 2015–2016 [39]. In addition, differences in the experimental setups (e.g., extraction method and initial DTT concentration) used to determine OP could exist among the studies, which could affect the OP.

The OP was somewhat higher in summer (Beijing: 72.1 ± 31.5 pmol/min/μg and Gwangju: 54.7 ± 18.8 pmol/min/μg) than in winter (Beijing: 53.7 ± 24.6 pmol/min/μg and Gwangju: 44.8 ± 24.7 pmol/min/μg), as shown in Fig. 3(b). The formation of secondary/aged organic aerosols with an increase in WSOC and acids was more pronounced in summer than in winter, leading to higher OP in summer. Aged aerosols, such as oxidized soot and aged organic compounds, also contribute to the elevated OP [25,50–52]. OP_v was higher in winter than in summer at both sites because the $PM_{2.5}$ mass concentration was much higher in winter than in summer.

3.4. Cell toxicity

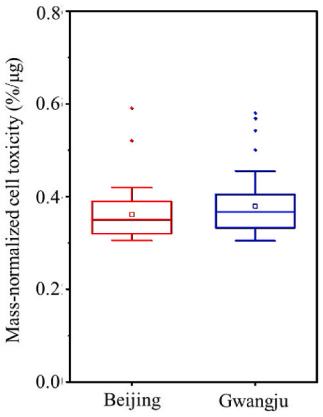
Fig. 4 shows the mass-normalized cell toxicity (%/μg) of $PM_{2.5}$ at the Beijing and Gwangju sites. The mass-normalized cell toxicity (hereafter cell toxicity) was obtained from the EC_{50} and the sampled mass, and the volume-normalized cell toxicity (hereafter cell

toxicity$_v$) was calculated by multiplying the cell toxicity by $PM_{2.5}$ mass concentration. The mass-normalized cell toxicity values did not significantly change between the two locations and seasons. Compared with OP, cell toxicity was less sensitive to different sites and seasons. The relative standard deviation of OP was 50 %, whereas that of cell toxicity was 17 % at different locations and times. This could be because cell toxicity-sensitive chemical components and sources exist in similar fractions at both sites, although their types differ. Dust and fresh combustion sources in Beijing and secondary aerosols and traffic sources in Gwangju were equally effective in increasing cell toxicity, leading to similar cellular responses to $PM_{2.5}$ at both sites. Another hypothesis is that cell toxicity is not highly dependent on the chemical components and sources of $PM_{2.5}$. However, this is unlikely because our previous study showed that cell toxicity measured using the same assay as ours varied significantly with different types of $PM_{2.5}$ produced from various sources [7].

3.5. Analysis and correlations among $PM_{2.5}$ chemical composition, OP, and cell toxicity

Correlation analyses for OP_v, cell toxicity$_v$, and concentrations of major chemical components obtained from the study sites were conducted. The chemical components with a high correlation with OP_v and/or cell toxicity$_v$ are highlighted in Fig. 5. Alkanes, acids (polar), benzo-carboxylic acids, and cholesterol in OC, K^+, Cl^-, K, As, Se, and Pb were the common species with high correlations ($r > 0.7$) with both OP_v and cell toxicity$_v$. In addition to the common species, OP_v had high correlations ($r > 0.7$) with EC, Mn, WISOC, PAHs, hopanes and steranes, and cyclo-alkanes, whereas cell toxicity$_v$ had high correlations ($r > 0.7$) with WSOC, di-acids, levoglucosan, NH_4^+, NO_3^-, SO_4^{2-}, S, Cl, Zn, and Br. Secondary species were more correlated with cell toxicity$_v$ than OP_v.

Secondary inorganic ions have not been reported to increase the OP in some studies [7,44,53]. However, OP has been correlated with secondary inorganic ions, possibly due to their covariation with redox-active organic compounds, such as WSOC [42,50]. The WSOC was moderately and strongly correlated with secondary inorganic ions at the Beijing ($0.6 < r < 0.8$) and Gwangju ($0.6 < r < 0.9$)



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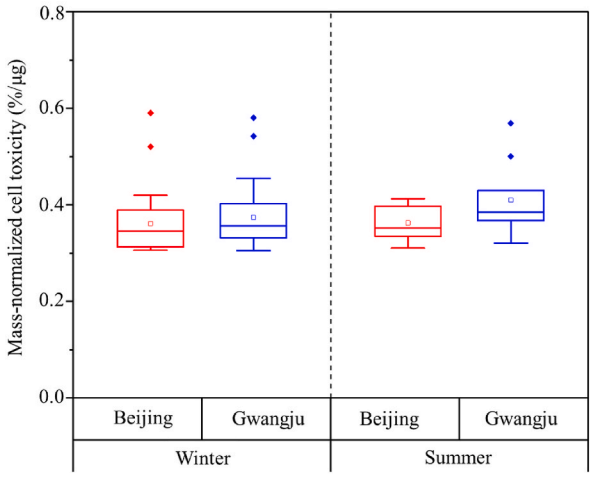


(b)

Fig. 4. Mass-normalized cell toxicity (%/μg) of $PM_{2.5}$ at the Beijing and Gwangju sites (a) during the sampling periods and (b) in different seasons.

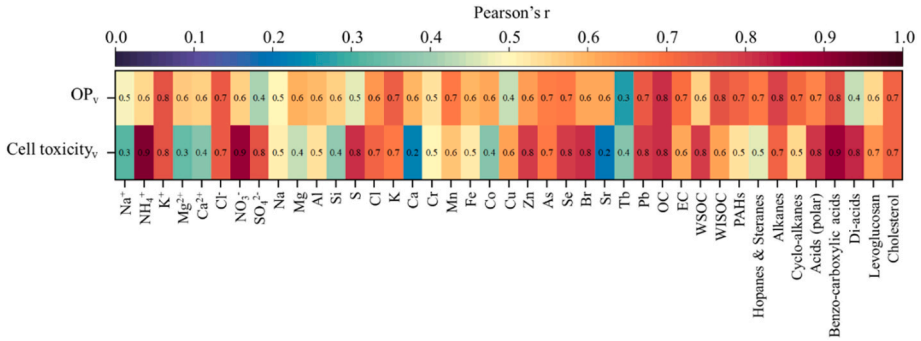


Fig. 5. Pearson's correlation coefficients among OP_v (n = 187 d), cell $toxicity_v$ (n = 90 d), and major chemical components of $PM_{2.5}$ at both sites.

sites, respectively. In other studies, secondary aerosols have been reported to contribute to an increase in OP [11] and biological responses (e.g., cell toxicity, ROS, and inflammation) [54,55]. Secondary inorganic ions can increase the solubility of metals in particles and change their pH (e.g., acidification) to indirectly affect OP [39,56,57]. Moreover, pH changes in the particles affect cell growth, causing oxidative-inflammatory responses and cardiovascular reactions [58–61].

Heavy metals are only a small fraction of $PM_{2.5}$, but they significantly influence OP and cell toxicity owing to their high carcinogenicity and low biodegradability [23]. In particular, As, Co, Cr, Cd, Pb, and Ni are classified as potential cancer agents by the International Agency for Research on Cancer (IARC) [62]. Cu and Mn can damage cell membranes, proteins, and DNA, leading to cell death [60]. Si, K, Zn, As, Se, and Pb are responsible for systemic inflammation [61]. Pb and Zn also trigger ROS generation in mitochondria, resulting in increased oxidative stress and apoptosis [63,64]. The transition metals coating the carbon surface of OC and EC affect pro-inflammatory activity and inflammatory response [65].

A principal component analysis (PCA) was also conducted to visualize chemical groups related to the OP_v and cell $toxicity_v$ (chemical components with high correlations with the OP_v or cell $toxicity_v$) during event days with high $PM_{2.5}$ concentrations. As shown in Fig. 6, PC1 and PC2 accounted for 59.0 % and 12.9 % of the total variance, respectively. Most event days were located in the positive region of PC1, except for several sulfate event days (negative region of PC1), which typically occurred in summer at both sites. The selected chemical components, OP_v, and cell $toxicity_v$ are located in the positive region of PC1, suggesting that these chemical components are related to OP_v and cell $toxicity_v$. In particular, the acids (polar), benzo-carboxylic acids, Pb, and Zn are closely located between OP_v and cell $toxicity_v$, relating to both. Dust-(Ca^{2+}, Mg^{2+}, Si, Fe, and Mn) and combustion-related (K^+, Cl^-, EC, WISOC, PAHs, hopanes and steranes, cholesterol, and alkanes) chemical components were located in the positive region of PC2. The OP_v has a slightly positive PC2 value. Secondary aerosol components (NH_4^+, SO_4^{2-}, NO_3^-, WSOC, and acids) and traffic-related (Pb, Zn, As, Se, Br, and Cu) chemical components are located in the negative region of PC2. Cell $toxicity_v$ has a negative PC2 value, suggesting that it is more affected by secondary aerosols and traffic-related chemical components.

3.6. Health index

This study developed a health index for $PM_{2.5}$ that integrated OP and cell toxicity with $PM_{2.5}$ concentration level. OP or cell toxicity

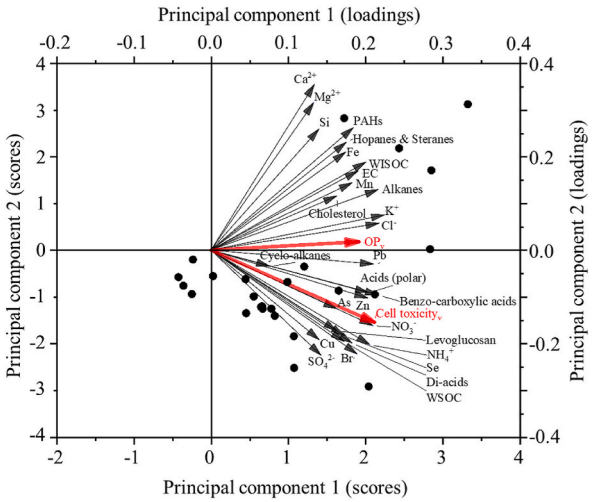


Fig. 6. PCA biplot of the selected chemical components, OP_v, and cell $toxicity_v$ during event days with high concentrations of $PM_{2.5}$.

alone cannot solely represent overall toxicity Moreover, different sensitive chemical components or groups can affect the OP and/or cell toxicity in various manners. Therefore, this proposed health index combines OP_v and cell $toxicity_v$. Because volume-normalized values were used, the index accounted for both toxicity and $PM_{2.5}$ concentration level. The min-max normalization method was first applied to standardize OP_v and cell $toxicity_v$ for all datasets. Then, individual weights of the normalized OP_v and cell $toxicity_v$ were determined using the correlation coefficient and standard deviation (CCSD) method, an objective multiple-attribute decision-making model used to determine the weights (w_1 and w_2) of attributes (e.g., endpoints) when the outcome (e.g., health index) is simultaneously influenced by multiple attributes [7,66,67]. Variability (standard deviation) and inter-relationship (correlation coefficient) of the endpoints were taken into account to determine the weights. Subsequently, the summation of the normalized OP_v and cell $toxicity_v$, which were separately weighted, resulted in a new health index (health index = $w_1 \times$ normalized $OP_v + w_2 \times$ normalized cell $toxicity_v = 0.504 \times$ normalized $OP_v + 0.496 \times$ normalized cell $toxicity_v$). This health index accounts for toxicity and concentration levels, varying from 0 to 1. Further works are needed to establish standardized normalization procedures across various sites contributing to a more universally applicable framework.

Distribution of health index data is shown in Fig. S2. The health index data show a distinct bimodal distribution, having low and high health index groups. A Gaussian mixture model was applied for the health index data. This model assumed that the dataset consisted of a mixture of Gaussian distributions [68]. The average value (0.4) in the high health index group was used as the criterion to determine the event days with a high health index (health index event days).

The temporal variation in the health index of $PM_{2.5}$ at the urban Beijing and Gwangju sites during the given sampling period (n = 84 d) is shown in Fig. 7. For comparison, daily $PM_{2.5}$ concentrations were added. The average health index in Beijing was 0.26, which was higher than that in Gwangju (0.24). The cases (days) with high $PM_{2.5}$ concentrations (i.e., $PM_{2.5}$ event days) (>50 μg/m^3) matched the high health index event days (>0.4). Notably, 64 % of the $PM_{2.5}$ event days coincided with the high health index event days. However, some days with high health indices had low $PM_{2.5}$ mass concentrations (i.e., 11 % of the health index event days). This suggests that the health index can provide additional information to $PM_{2.5}$ mass concentrations. Moreover, the health index can be further improved by integrating available toxicity data, leading to a stronger metric for determining the health effects of $PM_{2.5}$.

The MLR method was used to relate the sources of $PM_{2.5}$ to the health index derived from the measured toxicity data (OP and cell toxicity). The $PM_{2.5}$ sources were determined from the measured chemical components using the PMF method [35]. The PMF results are shown in Fig. 8 and S3. Seven major sources, namely dust (desert and road dust), traffic, combustion (biomass burning and cooking), coal combustion, secondary organic aerosols (SOA), secondary sulfate, and secondary nitrate, were derived from the PMF. In the $PM_{2.5}$ mass at the Beijing site, dust was the most dominant contributing source (26.4 %) followed by secondary nitrate (17.5 %), coal combustion (15.5 %), secondary sulfate (12.0 %), traffic (12.4 %), combustion (9.2 %), and SOA (6.8 %). At the Gwangju site, secondary nitrate (34.1 %) was the most abundant source followed by secondary sulfate (20.2 %), combustion (18.4 %), traffic (8.6 %), dust (8.5 %), SOA (6.3 %), and coal combustion (4.0 %). Some factors, including succinic acid and glutaric acid, in the source profile were assigned to the SOA. In the dust source profile, Al, Si, and hopanes and steranes were included, suggesting that the dust included desert and road dust [35]. The average contribution of the sources to $PM_{2.5}$ at both sites is shown in Fig. 8(a).

The MLR results using the health index as the dependent variable and the major sources as independent variables are shown in Table 1 (the p-value, correlation coefficient, and root mean square error (RMSE) are also included). Source selection (i.e., feature selection) was conducted using the backward elimination method in MLR [69]. This method tests all potential predictor variables and then systematically removes insignificant variables until the best-performing model is achieved. Among the seven sources resulting from the PMF, six (dust, traffic, combustion, SOA, secondary nitrate, and secondary sulfate) were selected for the optimal MLR model. The coal combustion source ($p > 0.05$) was excluded in the backward elimination method. Multicollinearity among independent variables was assessed using the variance inflation factor (VIF). If the variables are not multicollinear, the VIF is equal to 1. If the VIF is

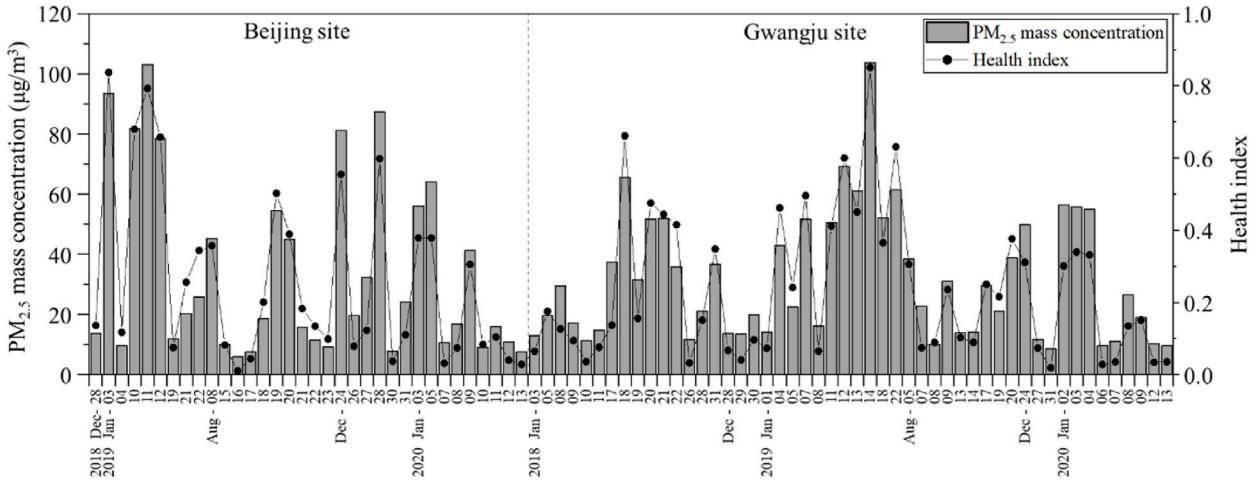
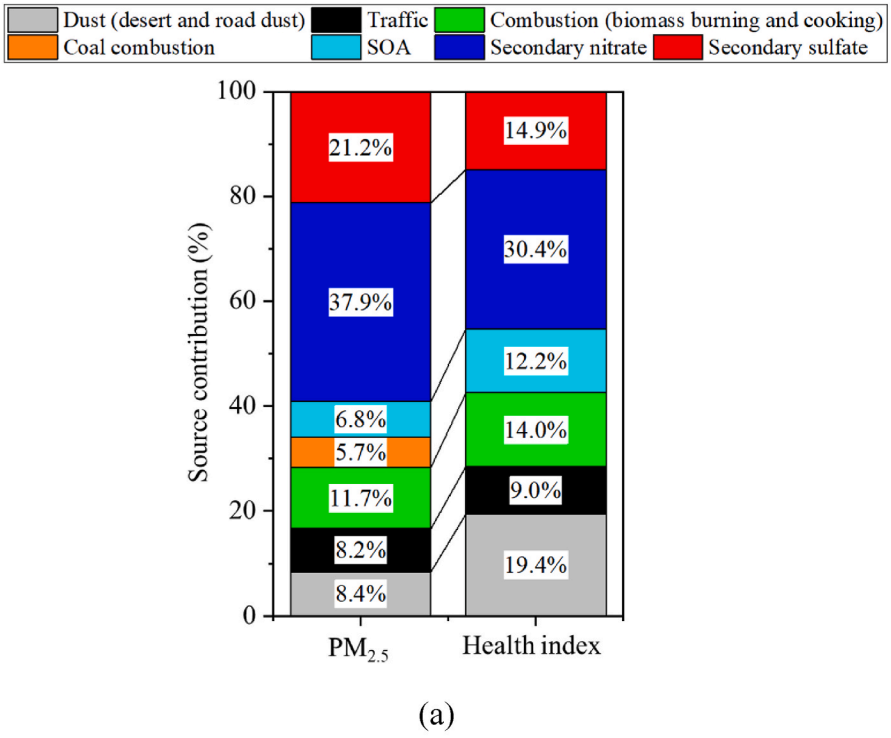


Fig. 7. Variations in the health index of $PM_{2.5}$ and $PM_{2.5}$ mass concentrations at the Beijing and Gwangju sites throughout the study period (n = 84 d).



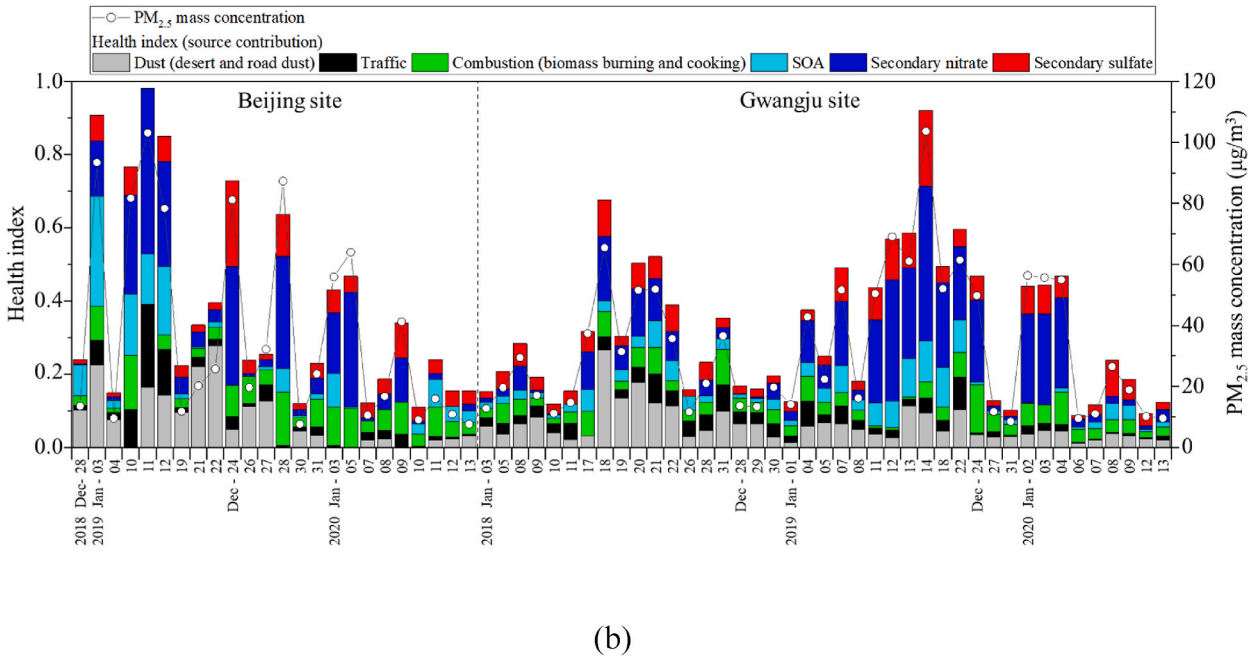


Fig. 8. (a) Average contribution (%) of sources to the $PM_{2.5}$ mass concentration and health index of $PM_{2.5}$ at all sites, and (b) time series of the health index of $PM_{2.5}$ with its contributing sources and $PM_{2.5}$ mass concentration.

near or above five, multicollinearity exists significantly among the MLR variables [70]. In this test, the VIF values of the independent variables (six sources) in the MLR model varied from 1.20 (combustion) to 2.77 (secondary sulfate). Finally, to evaluate the optimal MLR model, a 5-fold cross-validation experiment was conducted, yielding an R^2 value of 0.93.

The derived regression equation (unstandardized model) was also used to predict the health index of $PM_{2.5}$ using source apportionment data without toxicity values at the two urban sites. The modelled and measured health indices are compared in Fig. S4. The

Table 1
MLR models with the health index of $PM_{2.5}$ as the dependent variable and major $PM_{2.5}$ sources as the independent variables (n = 65 d).

Type	Equation	p-value	R^2	RMSE
Unstandardized model	Health index = −0.088 + 0.023 × dust + 0.011 × traffic + 0.012 × combustion + 0.018 × SOA + 0.007 × secondary sulfate + 0.008 × secondary nitrate	<0.001	0.94	0.06
Standardized model	Health index = 0.275 × dust + 0.156 × traffic + 0.142 × combustion + 0.229 × SOA + 0.212 × secondary sulfate + 0.464 × secondary nitrate	<0.001	0.94	0.24

results showed a good agreement, with a correlation coefficient of 0.97 and slope of 0.95.

Fig. 8(a) compares the average contribution (%) of the sources to $PM_{2.5}$ and the health index of $PM_{2.5}$ at both sites. On average, secondary nitrate was the dominant source contributing to the health index, followed by dust, SOA, secondary sulfate, traffic, and combustion. The secondary nitrate can include ammonium nitrate (inorganic nitrate) and organic-nitrate. Although the contribution of secondary nitrate to OP and cell toxicity could be small (low OP and cell toxicity of ammonium nitrate and ammonium sulfate were found in our previous study [7]), their high concentration level in $PM_{2.5}$ led to the important source in the health index. The contributions of SOA and dust (desert and road dust) to the health index significantly increased by 80 % and 131 %, respectively, compared with their contributions to $PM_{2.5}$. Also, combustion and traffic sources increased. The data suggest that the new health index accounts for differential toxicities from different sources as well as the concentration level, and that the importance of SOA, dust (desert and road dust), combustion, and traffic sources increased when the health effects of $PM_{2.5}$ with different sources were considered.

The time series of the health index of $PM_{2.5}$ with its contributing sources and $PM_{2.5}$ mass concentration are shown in Fig. 8(b). Important sources contributing to the daily health index varied significantly. As discussed before, during $PM_{2.5}$ event days, the health index also increased due to the increased exposure level. In particular, event days mainly caused by SOA or dust sources had a higher health index than sulfate or nitrate event days at similar concentration levels. In addition, the health index was high (>0.4) during certain days, even with low $PM_{2.5}$ mass concentrations (i.e., not $PM_{2.5}$ event days). During these days, the contributions of SOA and dust sources to the health index became significant. Therefore, the proposed health index can provide new information that considers differential toxicities from different sources, which could be valuable as an additional health metric beyond the $PM_{2.5}$ concentration level.

4. Conclusions

Simultaneous measurements of $PM_{2.5}$ chemical composition, OP, and cell toxicity were performed in two different urban environments. The results revealed that OP was more sensitive to different locations and seasons than cell toxicity. In particular, acids (polar), benzocarboxylic acids, and Pb were the common chemical components affecting both OP and cell toxicity. Based on the results, a health index was proposed by accounting for OP and cell toxicity and concentration levels, which were found to be useful for understanding the potential health effects of $PM_{2.5}$, compared with the $PM_{2.5}$ only. During SOA or dust (desert and road dust) event days, the health index increased significantly beyond the increased concentration level, suggesting that the health effect of $PM_{2.5}$ should be assessed by considering both toxicity and concentration levels of different sources. Also, the health index of $PM_{2.5}$ can be predicted by the derived regression model without further toxicity measurements. Furthermore, additional toxicity measurement data can be incorporated into the developed health index to improve its capability to determine the health effects associated with $PM_{2.5}$. This study makes a significant contribution to establish effective $PM_{2.5}$ abatement strategies and to mitigate health risk of $PM_{2.5}$ by revealing additional information beyond the $PM_{2.5}$ concentration level.

Data availability

Data from this study are available from the corresponding author upon reasonable request.

Funding

This research was supported by a National Research Foundation of Korea (NRF) grant from the Korean Government (MSIT; Ministry of Science and ICT) (NRF-2017M3D8A1092220, NRF-2019R1A2C3007202, NRF-2019M1A2A2103956, and NRF-2021M1A5A1065667) and by the Samsung Advanced Institute of Technology (SAIT).

CRediT authorship contribution statement

Minhan Park: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Seunghye Lee:** Writing – review & editing, Methodology, Investigation, Data curation. **Haebum Lee:** Methodology, Investigation. **Ma. Cristine Faye J. Denna:** Methodology. **Jiho Jang:** Methodology. **Dahye Oh:** Methodology. **Min-Suk Bae:** Methodology. **Kyoung-Soon Jang:** Methodology. **Kihong Park:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25310.

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