Source differences in the components and cytotoxicity of $PM_{2.5}$ from automobile exhaust, coal combustion, and biomass burning contributing to urban aerosol toxicity

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Abstract. Although air quality guidelines generally use the atmospheric concentration of fine particulate matter ($PM_{2.5}$) as the metric for air pollution evaluation and management treating all particles as equally toxic, it is inconsistent with the facts that particle toxicity are significantly related to their sources and chemical compositions. Therefore, judging the most harmful source and identifying the toxic component will be extremely helpful to optimize air quality standards and prioritize targeted $PM_{2.5}$ control strategies to more protect public health effectively. The combustions of fuels, including oil, coal, and biomass, are main anthropogenic sources of environmental $PM_{2.5}$, however, their discrepant contributions to health risks of mixed ambient aerosol pollution dominated by respective emission intensity and unequal toxicity of chemical components are still unclear. In order to quantify the differences among these combustion primary emissions, ten types of $PM_{2.5}$ from each typical source group, i.e., vehicle exhaust, coal combustion, and plant biomass burning, were collected for comparative study with toxicological mechanisms. Totally thirty type individual combustion samples were inter-compared with representative urban ambient air $PM_{2.5}$ samples, which chemical characteristics and biological effects were investigated by component analysis (carbon, metals, soluble ions) and *in vitro* toxicity assays (cell viability, oxidative stress, inflammatory responses) of human lung adenocarcinoma epithelial cells (A549). Carbonaceous fractions were plenteous in automobile exhaust and biomass burning, while heavy metals were more plentiful in $PM_{2.5}$ from coal combustion and automobile exhaust. The overall ranking of mass-normalized cytotoxicity for source-specific $PM_{2.5}$ was automobile exhaust > coal combustion > plant biomass burning > ambient urban air, possibly with differential toxicity triggers, that the carbonaceous fractions (organic carbon, OC; elemental carbon, EC) and redox-active transition metals (V, Ni, Cr) assisted by water-soluble ions (Ca^{2+}, Mg^{2+}, F^-, Cl^-) might play

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important roles in inducing cellular reactive organic species (ROS) production, causing oxidative stress and inflammation, resulting in cell injury and apoptosis, thus damage human health. Coupled with the source apportionment results of typical urban ambient air $PM_{2.5}$ in eastern China, reducing toxic $PM_{2.5}$ form these anthropogenic combustions will be greatly beneficial to public health, especially preferentially decreasing the diesel exhaust by strengthening emission standards, then lessening the coal combustion by replacement with low-ash clean coals, and depressing the crop straw burning emissions.

1 Introduction

As a mixture of multiple sources, ambient particulate matter (PM) arise from anthropogenic activities are continuously deteriorating the urban air quality, particularly in developing countries. Among these, fine PM with an aerodynamic diameter of less than 2.5 µm ($PM_{2.5}$) is recognized as a serious public health concern due to its long persistence in air, carcinogenicity and acute toxicity to humans (Al-Kindi et al., 2020). There were extensive epidemiological evidences that airborne PM can cause serious negative effects on human health, such as respiratory and cardiovascular diseases, genetic mutations, and developmental disorders (Chowdhury et al., 2022;Lelieveld et al., 2021;Smith, 2021;Clemens et al., 2017). Currently, either the world air quality guidelines or the national air quality standards use the mass concentration of $PM_{2.5}$ as the metric for $PM_{2.5}$ pollution evaluation and management, in which all particles are treated as equally toxic, however, it is inconsistent with the scientific facts that particle toxicity are significantly related to their sources and chemical compositions (Shiraiwa et al., 2017). Therefore, to identify which component(s) and source(s) of ambient PM are most harmful to health, will be very helpful to optimize air quality guidelines/standards and prioritize targeted PM control strategies to more effectively protect public health (Kelly and Fussell, 2020).

Besides natural sources like dust and sea spray, the vast majority of aerosols come from anthropogenic activities especially energy consumption, including the combustion of fossil fuels causing industrial emissions and automobile exhaust, and biomass burning (McDuffie et al., 2021;Wu et al., 2022). Finally, these diverse sources make the ambient air $PM_{2.5}$ become a complex mixture with multiple chemical components varying with time and space, which consisting mainly of sulfate, nitrate, ammonium, organic carbon (OC), elemental carbon (EC), mineral and trace metals (Bari and Kindzierski, 2016; Kelly and Fussell, 2020). The physiological mechanisms of PM-induced cell toxicity in respiratory system have been continuously investigated with some progresses (Kelly and Fussell, 2012, 2020; Shiraiwa et al., 2017; Mack et al., 2020; Li et al., 2022b), such as the metabolic activation, oxidative stress, inflammatory response, and apoptosis, focused on by current study. In brief, after inhalation and deposition onto the epithelium, redox-active materials in $PM_{2.5}$ can induce the release of reactive organic species (ROS), which cause oxidative stress (an imbalance between ROS and antioxidants, i.e., disequilibrium of the redox state of a cell) followed by inflammation and cell death. The ROS can mediate subsequent signaling pathways leading to biomolecule damage (e.g., DNA, lipid, and protein) and cellular injury, through mediating inflammatory responses including the release of pro-inflammatory cytokines like IL-6 and TNF-α by epithelial cells (Sabbir Ahmed et al., 2020; Landwehr et al.,

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2021). For instance, oxidative stress could trigger the induction of pro-inflammatory transcription factors, such as nuclear factor (NF)-κB, via the mitogen-activated protein kinase (MAPK) signaling pathway. Components adsorbed on particle surface, such as redox-active metals (transition metals, Fe, Ni, V, Cr, Cu), organic compounds (polycyclic aromatic hydrocarbons, PAHs; quinones), or even carbonaceous core of particles, are responsible for oxidative stress (Cachon et al., 2014; Sabbir Ahmed et al., 2020). The non-redox active metals (Zn, Pb, Al) can also influence the toxic effects of transition metals by exacerbating or lessening the production of free radicals. The EC may not be a directly toxic component of $PM_{2.5}$ but rather operate as a universal carrier of combustion-derived chemicals (semi-volatile organic fractions, transition metals) of varying toxicity (Kelly and Fussell, 2020). Inorganic soluble sulphates and nitrates are acidic and can interact with and influence the solubility other compositions like metal bioavailability (Fang et al., 2017; Weber et al., 2016). However, which specific components and which particular sources are the most critical factors dominating the ambient aerosols' health risks, still leave puzzles unsolved.

Past studies performed in various countries have focused on physicochemical characterization or biological effects of ambient air $PM_{2.5}$ respectively (Weagle et al., 2018;Jia et al., 2017;Wang et al., 2020). For example, the source analysis of $PM_{2.5}$ by photochemical modelling (Bao et al., 2018), chemical composition of regional $PM_{2.5}$ (Chi et al., 2022), and the mechanism of $PM_{2.5}$ toxicity was independently reported recently (Jia et al., 2020). Because differences in particle composition, sources, and toxicity appear in different urban environments (Zhao et al., 2019;Borlaza et al., 2018), the source profiles of different emission inventories were applied to elucidate aerosol pollution characteristics and control strategies. For instance, it was found that straw burning during the harvest season is a major trigger of severe air pollution in many regions (Sahu et al., 2021). Aerosols from open biomass burning in the Amazon had a stronger ability to induce ROS than laboratory-generated secondary organic aerosols (Tuet et al., 2019). The particle composition of motor vehicle exhaust was related to automobile types with various fuels, engines, and loads (Lin et al., 2020). A strong catalytic reactivity of metals in PM emitted from diesel vehicles was observed by dithiothreitol (DTT) assay (Jesus et al., 2018). Sulfate is a major component of PM from Xi'an city, western China, mainly released from residential coal combustion activities (Dai et al., 2019). Traffic was suggested playing the most crucial role in enhancing the toxicity of fine particles (Park et al., 2018). Although there were emerging studies on particle emission from single source, quantitatively comparative studies on multi-source pollutants as well as the differential composition and unequal toxicity of various sources are still limited.

The main objective of current study was to compare the chemical components and corresponding mass-normalized toxicological effects of individual $PM_{2.5}$ from various combustion sources and their unequal contributions to ambient aerosol health risks. The aim is to provide detailed guidance on the targeting and precise control of specific anthropogenic sources with prominent risks based on their pivotal toxic components. Therefore, we collected both representative ambient $PM_{2.5}$ samples from urban air and abundant typical source $PM_{2.5}$ samples from automobile exhaust, coal combustion, and plant biomass burning. Their independent profiles of chemical compositions and *in vitro* cytotoxicity (cell viability, oxidative stress, and inflammatory responses) were investigated and intercompared, to assess the differences in source-to-receptor toxicity and

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to infer the core toxic components and respective harmful contribution. The pivotal toxic components were identified based on the source-sink bi-directional composition-effect results, which were further used to assess the health toxicity contribution of various emission sources to ambient air $PM_{2.5}$, supported by its source apportionment through positive matrix factorization (PMF) model. This study could advance the understanding to quantify the complex source contribution to high-risk $PM_{2.5}$ emission oriented to public health, which is imperative for precise prevention and control of atmospheric PM pollution.

2 Materials and methods

2.1 Collection of $PM_{2.5}$ samples from primary emissions of 30 typical combustion sources and from representative ambient urban air

As the main anthropogenic sources of the ambient air $PM_{2.5}$ pollution, totally 30 types of primary $PM_{2.5}$ samples emitted directly from automobile exhaust, coal combustion, and plant biomass burning were respectively collected as follows for both chemical and toxicological analyses.

Based on the classification of automobile fuel types as well as load and tailpipe emission standards provided by the 2019 Annual Report on Environmental Management of Mobile Sources in China, a total of 10 types of vehicles were chosen for exhaust investigation. They were further categorized into 7 sub-groups, including small duty gasoline coaches (SDGCs), small duty diesel coaches (SDDCs), middle duty diesel coaches (MDDCs), heavy duty diesel coaches (HDDCs), light duty diesel vans (LDDVs), middle duty diesel vans (MDDVs), and heavy duty diesel vans (HDDVs). The detailed information of these representative local automobiles was showed in Table S1.

To cover all coal types consumed in the city, 10 representative types of coal were gathered for investigation. They were further classified into 4 sub-groups, including 2 types of honeycomb coal (HC), 3 types of anthracite coal (AC), and 2 types of bituminous coal (BC) mainly for restaurant or household use, and 3 types of industrial coal (IC) for coal-fired power plants and steel-smelting industry. The detailed characteristic analysis of these typical coals purchased from local market were showed in Table S2.

Considering the plant biomass combustion in rural areas surrounding the megacity, 10 representative types of agricultural and forestry solid wastes were gathered for investigation. Because of the high annual production of three staple food crops (rice, wheat, and corn) as well as soybean, peanut and rapeseed, their straws generated during harvest are often used as fuels in rural households. In addition, woods were also common fuels. Therefore, straws of rice, wheat, corn, soybean, peanut, rape, and sesame, corncob, branches of peach and pine, were selected as plant biomass fuels and further divided into 2 sub-groups, including 8 types of crop straw and 2 types of firewood. The detailed characteristic analysis of these typical plant biomass fuels collected from rural areas around Nanjing city were showed in Table S3.

The $PM_{2.5}$ samples directly emitted from these combustion sources were collected by dilution channel sampling method (Figure S1), using a 4-channel particulate matter dilution sampler (HY-805, Hengyuan Technology Development Co., CN).

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Each sampling included 3 parallel channels of quartz microfiber filter (Figure S2) and 1 channel of Teflon membrane filter, with diameters of 47 mm, through a size selector for $PM_{2.5}$ with a flow rate of 160 L min^{-1}. Clean air was pumped for 10 min before and after each sample was collected. Before using, the blank quartz filters were incinerated by a muffle furnace at 500 °C for 3 h to remove any possible organic matters, while Teflon filters were baked at 60 °C for 4 h. After being equilibrated in a constant temperature and humidity chamber for 24 h, the filters were weighed both before and after sampling for gravimetric measurements, then the mass of collected $PM_{2.5}$ could be calculated. The sampled filters were stored in a refrigerator at -20 °C before analysis. The quartz filter loaded $PM_{2.5}$ samples were used for carbon and ion analysis, and for toxicity tests, while the parallel Teflon filter loaded samples were used to determine metals.

As the actual mixture of various source particles in real environment, totally 16 representative ambient air $PM_{2.5}$ samples (each time lasting 23h) covering a year monthly were collected from December 2019 to October 2020 in an urban site surrounded by traffic, residential and commercial quarters of Nanjing city, Yangtze River Delta of eastern China, using a high-volume air sampler (800 L min^{-1}) with quartz microfiber filters. Detailed procedures and sample information were described in previous paper (Li et al., 2022a), but the purpose of using these air samples in current study was to compare them with the specific source samples for evaluating the chemical and toxicological contributions of the combustion primary sources to environmental aerosols pollution.

2.2 Chemical composition analysis

All collected source and ambient $PM_{2.5}$ samples were conducted various component analysis (Li et al., 2023). For the concentrations of heavy metals in particulates, samples were digested by concentrated HNO_3-$HClO_4$ acids with a progressive heating program and determined by inductively coupled plasma optical emission spectrometry (ICP-OES; Optima8000, PerkinElmer), with some elements at lower concentrations measured by ICP mass spectrometry (ICP-MS; NexIONTM300X, PerkinElmer). Blank filter, reagent blank, replicates, and standard reference material (NIST SRM 1648a, urban dust) were adopted for analytical quality control, with recoveries ranged 90-110 %. Carbonaceous species (OC and EC) in $PM_{2.5}$ were determined using a DRI-2001A OC/EC (Atmoslytic Inc., Calabasas, CA, USA). For the concentrations of water-soluble ions (WSIs), the main cations (Na^+, K^+, Mg^{2+}, Ca^{2+}, NH_4^+) and anions (NO_3^-, SO_4^{2-}, Cl^-, F^-) in $PM_{2.5}$ were measured by ion chromatography (IC, Thermo Fisher Scientific, USA), using the Metrosep C6-150/4.0 column for cations and the Metrosep A Supp 5 150/4.0 column for anions, respectively.

2.3 Preparing mass-normalized $PM_{2.5}$ suspension for cell exposure

Totally 30 source and 16 ambient $PM_{2.5}$ samples were also performed cytotoxicity tests. In order to elute the particles completely from the quartz membranes, the $PM_{2.5}$-loaded sample filter was cut into small pieces, immerged in ultrapure water and extracted six times (30 min for each) in an ultrasonic bath at 0 °C. Although the ultrasonication might impact the ROS (Miljevic et al., 2014), the inevitable systematical error was ignored in this study. The extract was then suction filtered through a 2.6 μm pore-size nylon membrane to remove possible quartz fragments, and the bulk filtrate was freeze-dried back to pure

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$PM_{2.5}$ powder. Ultimately, based on particle mass, the gathered $PM_{2.5}$ was dispersed by sterile phosphate-buffered saline (PBS) to a concentration of 400 mg L^{-1}, and then diluted to $PM_{2.5}$ suspension of 80 mg L^{-1} with serum-free Dulbecco's modified eagle medium (DMEM) medium for following *in vitro* cell exposure (Li et al., 2022a).

2.4 Cell culture and cellular toxicity tests by *in vitro* $PM_{2.5}$ exposure

Aerosol pollution can harm lung alveoli and epithelial cells, and the A549 human lung adenocarcinoma epithelial cell has long been used as a suitable epithelial alveolar model to investigate the interactions between PM and lung epithelial cells (Park et al., 2018; Li et al., 2022b). The A549 cells were cultured in RMPI-1640 medium (Gibco, USA) supplemented with 10% fetal bovine serum (FBS, Hyclone, USA) and 1% antibiotic penicillin-streptomycin (100 U mL^{-1}) at 37 °C in a 5% CO_2 incubator. After $PM_{2.5}$ exposure, cell viability and the indicators reflecting oxidative damage and inflammatory responses were determined respectively. While the cell viability assay was helpful in determining $PM_{2.5}$ dose to cells, the endogenous ROS measurements revealed the status of cellular oxidative potential after $PM_{2.5}$ exposure followed by the relative effects of ROS on various stages of cellular toxicity like inflammatory responses (Gali et al., 2019). The cell viability (metabolic activity) was evaluated by mitochondrial activity and determined by the methyl-thiazol-tetrazolium (MTT) assay (Chen et al., 2019). After trypsin action, the density of cells in the logarithmic growth phase was adjusted to 1×10^5 mL^{-1}. Cell suspensions were inoculated into 96-well plates (Costar, USA) at 100 μL per well. The blank control well (without medium and $PM_{2.5}$ suspension) and reagent control well (with medium but without $PM_{2.5}$ suspension) were set together. After incubation for 24 h and removing the cellular supernatant, various types of $PM_{2.5}$ suspension (concentration of 80 mg L^{-1}) were added to 96-well plates and incubated for 24 h. Based on pre-experiments, the oxidative stress and inflammation response sensitively under this dose, while the cell viability can keep sufficient. Fresh medium and MTT reagent (Solarbio, Beijing, CN) were added to each well and the supernatant was discarded, then 100 μL of formazan lysate was added to each well. The optical density (OD) values were measured at 490 nm using a microplate reader (Thermo MULTISKAN FC, USA). Cell viability (%) = $(OD_{treatment} - OD_{blank\ control}) / (OD_{reagent\ control} - OD_{blank\ control})$. The levels of cellular ROS production causing oxidative stress in cells, pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) production for determining the expression of genes related to the inflammatory response in the supernatant were analyzed by enzyme-linked immunosorbent assay (ELISA) kits (Jiangsu Enzyme Biotechnology Co., Ltd., CN), and OD values were measured at 450 nm (Huang et al., 2020;Pang et al., 2020).

2.5 Data analysis

The statistical analysis was performed by IBM SPSS statistics 24 and plotted by Origin 2020b software. Spearman correlation coefficients were produced by the correlation analysis. The variance was statistically significant when the statistical test level was $p < 0.05$, and extremely significant when $p < 0.01$. Statistical analyses were performed using Kruskal–Wallis test (Kruskal and Wallis, 1952).

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The source apportionment of $PM_{2.5}$ mass in urban ambient air was conducted by the receptor model PMF (EPA PMF version 5.0). Major constituents (OC, EC, Cu, Cr, Co, Ni, As, Pb, Mn, V, Na^+, K^+, Mg^{2+}, Ca^{2+}, NH_4^+, Cl^-, F^-, NO_3^-, and SO_4^{2-}) were selected as input data, and a four-factor solution was chosen as the optimal solution based on an assessment of the interpretability of the source profiles and the seasonal variability of the source contributions.

3 Results

3.1 Contributions of combustion primary sources to urban ambient air $PM_{2.5}$

As shown in Figure S3, although have been significantly improved with the national air quality in recent years, the daily $PM_{2.5}$ concentrations of representative city Nanjing still exceeded the healthy guidelines obviously, with higher urban air $PM_{2.5}$ pollution level in the cold season[23]. Four major sources of the ambient $PM_{2.5}$ were produced by the PMF model, including secondary aerosols, and primary particles of automobile exhaust, coal combustion, and plant biomass burning, which account for 34%, 27.7%, 25.2%, and 13.1% of total $PM_{2.5}$ mass concentration, respectively. Their source profiles and proportions were showed in Figure 1. Therefore, although the contribution of secondary aerosols cannot be ignored, the main anthropogenic sources of urban air $PM_{2.5}$ were primary emissions (66%) from the various fuel combustions.

3.2 Chemical compositions of different $PM_{2.5}$ from 30 combustion sources and from representative urban ambient air

Typical chemical components including carbonaceous fractions, heavy metals and WSIs of all $PM_{2.5}$ samples from both ambient urban air and 30 representative combustion primary sources (covering different categories of automobile exhaust, coal combustion, and plant biomass burning) were analyzed and compared with each other.

According to the comparisons of $PM_{2.5}$ bound carbonaceous fractions (Figure 2), automobile and biomass sourced $PM_{2.5}$ contained significantly higher total carbon (TC) content than coal combustion and ambient air, while the OC/EC ratio trend was ambient air > coal combustion > biomass burning > automobile exhaust sources. It indicated that the carbon content of ambient $PM_{2.5}$ mixture was lower and dominated by OC than that of combustion primary sources. Figures S4-S7 showed the detailed carbon fraction characteristics (contents and ratio) of $PM_{2.5}$ from each specific source. Carbonaceous fractions in automobile exhaust $PM_{2.5}$ were high but the difference between OC and EC content was small. Depending on the diverse automobile fuels, loads and tailpipe emission standards, the concentrations of carbon fractions in exhaust $PM_{2.5}$ varied widely with vehicle categories. The carbonaceous portion of $PM_{2.5}$ gradually declines as emission regulations rise, and EC likewise declines dramatically (Figure S4). However, such differences among coal types were less, except the bituminous coal with extreme high OC (Figure S5). The carbonaceous fraction of $PM_{2.5}$ from plant biomass burning differed in raw material species that tree branches source $PM_{2.5}$ generally contained higher carbon contents than those from crop straws (Figure S6).

Based on the grouped (Figure 3) and individual (Figures S8-S11) distributions of the measured heavy metals in various $PM_{2.5}$, the V concentrations of combustion sources were generally higher while Co and Mn were lower than ambient urban air.

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Coal combustion emissions carried highest levels of Pb and were enriched in Cu and As (Figure S9), while biomass burning were rich in Cr and Ni (Figure S10). However, automobile exhausts were enriched in most heavy metals, especially Cu, and Cr, Ni, V, Mn (Figure S8). Heavy metals from different types of automobile exhausts with the same emission standard varies greatly. Anthracite and industrial coal combustions contain similar heavy metals much more than bituminous coal. Generally, Pb, V, Mn, As, and Cu in branches source $PM_{2.5}$ were higher than straws, while Cr, Ni, and Co were dominant and higher in straw burning emissions. A special discovery was that corn cob burning $PM_{2.5}$ carried more heavy metals than corn straw and was the biomass with the highest emission levels of heavy metals. Correspondingly, ambient air $PM_{2.5}$ were also rich in most metals, especially Mn, Pb, and Ni, Cu, Cr. Therefore, coal combustion sources might contribute most Pb to urban ambient air, and contribute significant Cu and As with automobile exhaust emissions, while plant biomass burning and automobile sources contribute the Cr and Ni. Besides natural dust, automobile exhaust should be the main anthropogenic source of airborne Mn. Considering the PMF source apportionments of ambient aerosols, automobile exhaust should be the main source of Cr in urban air $PM_{2.5}$, and also the source for Cu together with coal combustion.

According to the comparisons of water-soluble cation and anion concentrations in various $PM_{2.5}$ (Figure 4), coal combustions contained highest SO_4^{2-} and NH_4^+, automobile exhausts had highest contents of NO_3^-, Na^+ and Ca^{2+}, while plant biomass burning sources contained highest K^+ and Cl^-, but Mg^{2+} was the lowest for all sources. However, the urban ambient air $PM_{2.5}$ contained highest NO_3^- and were also dominated by SO_4^{2-} and NH_4^+, for which NO_3^- should be mainly contributed by secondary aerosols and automobile primary source, SO_4^{2-} and NH_4^+ should be significantly from coal combustions. Besides NO_3^-, Na^+ and Ca^{2+}, automobile source $PM_{2.5}$ also had the highest F^- and Mg^{2+} concentrations than other sources. The detailed concentration distributions of WSIs in $PM_{2.5}$ from each specific source were provided in Figures S12-S14. The WSIs levels vary widely with specific source categories. $PM_{2.5}$ from LDDVs-2 had the lowest amount of WSIs compared to the other automobile exhausts (Figure S12). Similar to the metal composition, bituminous coal also had the lowest WSIs among all coals (Figure S13). Compared to branches, $PM_{2.5}$ from burning crop straws had much greater levels of K^+, Cl^-, SO_4^{2-} and less levels of F^-, NO_3^- (Figure S14).

To summarize, the overall concentrations of measured TC, cumulated heavy metals and WSIs in $PM_{2.5}$ from each source type were showed in Figure 5. Among all source emission and environmental receptor samples, the cumulated heavy metals from coal combustion was highest and automobile exhaust was higher than ambient $PM_{2.5}$, the overall carbon contents from automobile exhaust and biomass burning were both higher than ambient $PM_{2.5}$, while only the cumulated soluble ions in $PM_{2.5}$ from primary source of coal combustion was equivalent to the ambient aerosols. In a word, chemical compositions of $PM_{2.5}$ distributed much diversely and varied significantly with the specific source types of combustion emissions.

3.3 Cell viability, oxidative stress and inflammation levels exposed to various mass-normalized $PM_{2.5}$

Multiple toxicological endpoints (cell viability, oxidative stress, and inflammation) that facilitate identifying the specific particle triggering ROS and inflammatory responses resulting in cell death were evaluated for source-specific $PM_{2.5}$. After 24

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h exposure to the same dose of different $PM_{2.5}$ obtained from specific emission sources, the A549 lung cells also showed varied toxicological responses (Figure 6). The survival rate of cells exposed to automobile exhaust $PM_{2.5}$ was much lower than ambient air $PM_{2.5}$ (Figure 6.1). Automobile exhaust $PM_{2.5}$ induced the highest ROS production in cells higher than biomass burning and both sources were also much higher than ambient $PM_{2.5}$ (Figure 6.2). Coal combustion induced the highest cellular IL-6 production followed by automobile exhaust that was also higher than ambient air $PM_{2.5}$, while the $PM_{2.5}$ from automobile exhaust and biomass burning induced similarly higher cellular production of TNF-α than ambient $PM_{2.5}$ (Figure 6.3, 6.4). These results suggested that, combustion primary emission $PM_{2.5}$ had stronger ability to induce oxidative stress and inflammatory injury in lung cells than ambient air $PM_{2.5}$, thus resulted in the higher probability of apoptosis induction (Victor and Gottlieb, 2002;Wang et al., 2013). Generally, the mass-normalized $PM_{2.5}$ from primary source of automobile exhaust posed the strongest overall toxicity. Therefore, to protect public health by controlling $PM_{2.5}$ pollution, the anthropogenic combustions were key target sources, especially the most toxic automobile $PM_{2.5}$ should be reduced preferentially.

3.4 Correlations between various $PM_{2.5}$ components and toxicity endpoints

Spearman correlation coefficients between chemical compositions and cellular toxicological response indicators were applied to screen the key components of all $PM_{2.5}$ involved in cell injury (Figure 7). It was found that, the degrees of correlations varied with the toxicological mechanisms of different airborne chemicals. Based on the overall $PM_{2.5}$ samples from various sources, the pro-inflammatory cytokine IL-6 showed significantly strong positive correlations with some heavy metals (As, Pb, V, Cu), while TNF-α and oxidative stress (ROS) had similar significantly positive correlations with aerosol components of carbon fractions (EC, OC) and transtion metals (V, Cr, Ni). The TNF-α also showed positive correlation with water soluble Cl^- and K^+, and ROS correlated with F^-, Ca^{2+} and Mg^{2+}.

4 Discussion

4.1 New chemical markers for source apportionments of ambient air $PM_{2.5}$

Combustion emissions are key anthropogenic sources contributing to urban air $PM_{2.5}$, through both primary and secondary aerosols, which were 66% and 34% calculated by PMF model, respectively (Figure 1). The high concentrations of chemical markers are usually used in source analysis, such as ammonium sulfate and nitrate for secondary aerosols which are originated mainly from the gaseous precursors (e.g., NH_3, SO_2 and NO_X) (Mahilang et al., 2021), the EC, Cu, Mn, and Ni for vehicle exhaust (Srivastava et al., 2021) , the As, Pb, OC, EC, SO_4^{2-} and relatively low NO_3^-/SO_4^{2-} ratios for coal combustion (Dai et al., 2020), soluble K^+ and Cl^- for plant burning (Jain et al., 2020). The detailed chemical species of these specific source emission $PM_{2.5}$ samples also supported the results. Moreover, low OC/EC ratio of high TC content, high NO_3^-, F^-, Na^+, Ca^{2+} and Mg^{2+}, V and Mn of automobile exhaust; Pb and As, SO_4^{2-} and NH_4^+ of coal combustion; soluble K^+ and Cl^-, and high OC/EC ratio of high TC for plant biomass burning found in current study (Figures 2-5), could also be corresponding potential

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aerosol source markers. The principal aim of this paper was to assess and contrast the chemical composition and potential harmfulness of PM arising from diverse anthropogenic sources, thus natural sources, like fugitive soil dust, were not included in the source examination.

4.2 Common $PM_{2.5}$ components related to specific combustion sources

Generally, the automobile exhaust $PM_{2.5}$ had high TC content and low OC/EC value with considerable EC content (Figure 2), varying with specific vehicle types (Figure S4). The contents of the carbon fractions from diesel vehicles were higher than gasoline exhausts, and the OC/EC ratios of diesel exhausts were much lower than gasoline vehicles, owing to both considerable contents of EC and OC from diesel vehicle emission $PM_{2.5}$. Some diesel vehicles showed higher EC emissions with age, so exhaust cleaning devices for them are suggested. In addition, the amounts of OC and EC in exhausts gradually decreased with the strengthened emission standards they met (Wong et al., 2020). In $PM_{2.5}$ samples obtained from coal combustion (Figure S5), the TC contents of bituminous coals were significantly higher than that of honeycomb coals, anthracite coals, and industrial coals, because bituminous coals contain higher volatile fraction, which is composed of organic matter. Therefore, besides the way of combustion and the use of combustion stoves, the coal quality related to different coal types and origins determine the carbonaceous fractions of the PM emitted by coal combustion (Zhang et al., 2022). In the $PM_{2.5}$ samples from plant biomass combustion (Figure S6), OC contents were generally higher than EC contents, except that pine branches contained higher EC and rapeseed straw had considerable contents of EC and OC. Dominated by OC (Figure S7), the concentrations of carbonaceous fractions in urban ambient air samples varied seasonally (Flores et al., 2020;Xu et al., 2019). Combining the TC contents and OC/EC ratios, carbonaceous components in ambient $PM_{2.5}$ mainly originate from semi-volatile organic compounds (SVOCs) (Wang et al., 2018) and combustion primary emissions for OC (Kang et al., 2018), and automobile exhaust for EC (Barraza et al., 2017). Thus, to control ambient carbon aerosol pollution, besides reducing the precursor emissions of secondary organic aerosols (SOA), controlling primary aerosols especially EC from diesel vehicles were key measures.

Airborne redox-active metals are usually linked with the oxidation stress of $PM_{2.5}$. Different types of automobiles emitted diverse metal contents (Figure S8). Metal elements in automobile exhaust are primarily contributed by fuels, lubricants, and engine component abrasion. Because Mn is a common antidetonator that delays and prevents the oxidation of hydrocarbons and increases the octane number, which not only increases the thermal efficiency of the engine but also improves the emission performance of the vehicle (Cheung et al., 2010), the Mn content was greater in gasoline vehicle exhausts than in diesel vehicles. Although there are multi-sources of traffic Pb emissions such as fuel combustion and brake wear (Wang et al., 2019;Panko et al., 2019), the automobile exhaust Pb content of gasoline vehicles were greater than diesel vehicles owing to oil combustion. Moreover, for the same vehicle type (LDDVs-1 and 2; HDDVs-1 and 2; SDGCs-1 and 2), the stricter the emission standard required, the lower the exhaust metal contents. The metal contents in the $PM_{2.5}$ of trucks was higher than that of passenger cars (Wu et al., 2016). In the combustion $PM_{2.5}$ of 10 coal types (Figure S9), Pb contents were the highest

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than other heavy metals, similar to available findings (Zhang et al., 2020). The $PM_{2.5}$ metals from bituminous coal were significantly lower than other coal types, because indicated by the coal quality analysis, bituminous coal has a low ash content which is mainly derived from non-combustible minerals in coal. These findings suggested that coal maturity might be an important factor influencing the metal composition of particulates emitted from coal combustion (Shen et al., 2021;Zhang et al., 2021). Heavy metal contents in biomass burned $PM_{2.5}$ varied much widely with raw plant types (Figure S10), although dominated by Cr and Ni. Different plant species and even different plant parts differ significantly in their ability to uptake and accumulate metals from soil (Zhao et al., 2020). Moreover, because of the high enrichment factors of some metals for crop straws (Zhang et al., 2016;Sun et al., 2019), they also released more Cr, Ni, and Co during burning than fuelwoods. Total metal emissions were highest in corn cob but lowest in peanut straw burning $PM_{2.5}$. The heavy metals enriched in urban ambient air $PM_{2.5}$ demonstrated a seasonal pattern (Chen et al., 2018;Hsu et al., 2016) (Figure S11). Contents of V, Co, and As were relatively low and are less affected by seasonal changes. Accordingly, supported by the metal profiles of anthropogenic combustion sources and ambient aerosols, to control the environmental airborne heavy metal pollution, the Pb, Cu and As from honeycomb, anthracite and industrial coal combustion, Cu from vehicle exhausts and especially V from light duty diesel van with the CN.III emission standard and Mn from gasoline vehicles, Cr and Ni from biomass especially crop straws burning, should be key targets.

Epidemiological studies have also shown the mortality closely related to the WSIs such as sulfate and nitrate in aerosols (Ostro et al., 2009;Liang et al., 2022). Among the WSIs contents of various automobile exhaust $PM_{2.5}$ (Figure S12), NO_3^- and Ca^{2+} were the most abundant anion and cation, respectively. The high NO_3^- in the automobile $PM_{2.5}$ may be due to NO_x production during high-temperature combustion (Hao et al., 2019), while the high Ca^{2+} content should be related to additives in automobile fuels and calcium-based lubricants (Yang et al., 2019). Moreover, the exhaust WSIs decreased with the strengthened automobile emission standards required. Coal combustion $PM_{2.5}$ contained relatively higher SO_4^{2-} and NH_4^+ concentrations followed by Cl^- than other WSIs species (Figure S13). Among various coal types, industrial coals emitted highest SO_4^{2-} followed by honeycomb and industrial coal with also high NH_4^+, but bituminous coals emitted low WSIs which were mainly NO_3^-, F^- and Na^+, Ca^{2+}. The WSIs emission factors of honeycomb coal were generally higher than those of lump coal (Yan et al., 2020). For biomass combustion emissions (Figure S14), Cl^- and K^+ were dominant WSIs in $PM_{2.5}$ from straw-type fuels (Tao et al., 2016;Sillapapiromsuk et al., 2013), but fuelwood-type combustion emitted high NO_3^-. Plant species absolutely determine the emissions (Liao et al., 2021). Finally, there were also high levels of NO_3^-, SO_4^{2-}, and NH_4^+ in ambient air $PM_{2.5}$ (Zhang et al., 2019) (Figure S15). Consequently, implied by the WSIs species distributed in combustion primary sources and environmental $PM_{2.5}$, to control the aerosols ions pollution, the NO_3^- from vehicle exhausts and fuelwood burning; SO_4^{2-} and NH_4^+ from honeycomb, anthracite and industrial coal combustion; Cl^- and K^+ from biomass especially crop straw burning, should be principal targets, by stricter automobile emission standards or using clean coals.

4.3 $PM_{2.5}$ toxicity related to specific sources by pivotal chemical components

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The complexity of the sources and compositions of atmospheric $PM_{2.5}$ leads to different toxicological effects (Newman et al., 2020;Kelly, 2021). The toxicological effects of $PM_{2.5}$ are not comparable among different studies owing to distinct exposure concentrations, biological models, endpoints, and $PM_{2.5}$ generation methods (Park et al., 2018; Kelly and Fussell, 2020). In this study, we employed same exposure conditions and biological endpoints, in order to obtain comparable toxicity data for $PM_{2.5}$ from different sources. Our mass-normalized results demonstrated that automobile exhaust $PM_{2.5}$ induced the highest lethality and cellular ROS and TNF-α production, coal combustion $PM_{2.5}$ induced the highest cellular IL-6 production, plant biomass burning $PM_{2.5}$ induced considerable cellular TNF-α and ROS production (Figure 6). Generally, various toxicities of combustion emission primary $PM_{2.5}$ were much greater than the urban ambient air $PM_{2.5}$ (Figure 6), owing to the higher concentrations of specific toxic components in $PM_{2.5}$ from these sources. The supplementary information had included exhaustive cytotoxicity indicators from each individual source (Figure S16-S19). While the survival rate of cell exposed to CN.III emission standard $PM_{2.5}$ was the lowest and the capacity to induce cells to produce ROS was the highest for CN.IV, automobile exhaust had a similar potential to cause cells to produce inflammatory cytokines (Figure S16). The capability to induce IL-6 production in cells was highest for industrial coal $PM_{2.5}$, whereas bituminous coal had the highest survival rate of cells and TNF-α induction capacity (Figure S17). From the Figure S18 we can see that the $PM_{2.5}$ cytotoxicity of straws and branches burning was analogous, but it should be noted that the cell viability of various straw $PM_{2.5}$ differs significantly, that may be related to the raw fuel characteristics.

These possible mechanisms were implied by the overall relationships between the measured chemical components with cytotoxicity indicators of $PM_{2.5}$ from various specific sources (Figure 7). In general, both TNF-α and ROS were significantly positively correlated with carbonaceous fractions and redox-active transition metals (V, Cr, Ni), which were main contributors of automobile exhausts and biomass burning. The IL-6 was significantly positively correlated with some heavy metals (As and Pb, V and Cu), which were main contributors of coal combustion sources. Potential mechanisms include that, carbon fractions bound in $PM_{2.5}$ could be transformed into reactive metabolites and then induce ROS production in cells (Stevanovic et al., 2019), and the $PM_{2.5}$ bound transition metals could also induce ROS production through the Fenton reaction and disrupt the function of enzymes in cells (Verma et al., 2010;Sørensen et al., 2005; Zou et al., 2016). Oxidative stress can lead to inflammatory infiltration of neutrophils and stimulate immune cells to produce inflammatory cytokines, among which TNF-α and IL-6 play important roles in the inflammation development (Xu et al., 2020). Ultimately, excessive production of ROS leads to dysfunctional endoplasmic reticulum responses and dysfunctional lipid metabolism in ROS bursts can result in cell membrane damage and even cell death (Piao et al., 2018;Zhao et al., 2004). There have been some related supporting reports. For instance, the OC and EC were significantly associated with biological responses of PM from vehicle emissions collected in tunnels (Niu et al., 2020). The polar or quinone fractions of PAHs in diesel engine exhaust particles significantly contributed to the heightened toxic response (Xia et al., 2004). The $PM_{2.5}$ generated from biomass burning contained a substantial concentration of carbonaceous components. In addition, Cr and Ni in PM_{10} from straws were highly associated with ROS (Li et al., 2023). In current study, cellular ROS was also correlated with water soluble Ca^{2+}, F^-, and Mg^{2+}, which were main

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contributors of automobile exhaust $PM_{2.5}$. The Ca^{2+} controls the membrane potential and regulates mitochondrial adenosine triphosphate (ATP) production, and excessive Ca^{2+} leads to energy loss and more ROS production (Madreiter-Sokolowski et al., 2020). Moreover, the TNF-α was also positively correlated with water soluble Cl^- and K^+, which were main contributors of plant burning $PM_{2.5}$. Therefore, the accumulations of some organic matters with high carbonaceous content (OC, EC) in $PM_{2.5}$ typically from automobile exhausts and plant biomass burning, redox-active metals (V, Cr, Ni) and water-soluble anions (Cl^-, F^-) and cations (Ca^{2+}, Mg^{2+}) contributed by various combustions, might induce ROS production in cells, cause cellular damage through oxidative stress and inflammatory responses, impair cell viability and finally harm human health.

Considering the multi-endpoints measured and the $PM_{2.5}$ toxicity mechanisms mentioned above, based on the cell viability first, and then ROS followed by inflammatory markers, together with the significantly related toxic chemical composition contents (Park et al., 2018), we put forward a general sequence of overall mass-normalized toxicity for these combustion source $PM_{2.5}$ to managers. To improve the urban environmental air quality for best public health benefits by controlling aerosols pollution, considering the differential toxicity intensity of each chemical component and their contributions from various sources to ambient aerosols, preferential targets of specific primary $PM_{2.5}$ sources and bound pollutants to be controlled are suggested as following sequence: Reducing all anthropogenic combustions, especially decreasing the automobile exhaust $PM_{2.5}$ with high contents of EC, transition metals (V, Cu, Ni, Cr), and ions (Ca^{2+}, Mg^{2+}, F^-, Na^+) from diesel exhausts by strengthening the emission standards, then lessening the coal combustion with high heavy metals (As, Pb, Cu) by replacement with low-ash clean coals, and depressing the biomass burning with high OC, Ni, Cr, Cl^- and K^+ from crop straw emissions.

4.4 Limitations and perspectives

In current study, we selected A549 cell based on previous abundant experimental experiences and also because it has been used popularly in *in vitro* toxicology studies to elucidate the cellular and molecular mechanisms of PM involved in lung for many decades (Li et al., 2022b). However, recently the human normal bronchial epithelial cell BEAS-2B was preferred over the human lung adenocarcinoma epithelial cell A549. For instance, both cells were used in an aerosol study (Bonetta et al., 2017), results of which highlighted the higher sensitivity of BEAS-2B cells respect to A549 also in samples with low level of pollutants, because the $PM_{0.5}$ samples from Italian towns can induce genotoxicity in normal cells while cancer cells might be resistant to their adverse effects. Therefore, although our results are reasonable under the same exposure conditions, there were still potential limitations of A549 cells since they may be more resistant to exposure to external compounds, and the generally more sensitive BEAS-2B cells are suggested for future studies.

In toxicity assessments, cell vitality reflects the overall health of cells, encompassing factors such as cell membrane integrity, intracellular metabolic activity, and cell proliferation capacity. Decreased cellular vitality may be associated with cell damage, toxic effects, or cellular apoptosis. Inflammation markers are employed to assess the extent and nature of inflammatory reactions, including the production of cytokines and inflammatory mediators, as well as the activation status of inflammatory cells. Inflammation is a complex physiological response, typically delineated by the immune and inflammatory reactions of

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the body to stimuli such as injury or infection. Alterations in inflammation markers can indicate the intensity and nature of the inflammatory response. In this study, multiple biological responses of epithelial cells to various $PM_{2.5}$ were evaluated, including that, cell viability evaluated the mitochondrial dehydrogenase activity of the living cells, excessive intracellular ROS formation induced by $PM_{2.5}$ was responsible for oxidative stress to the cells, cytokines IL-6 and TNF-α were determined for the effect of $PM_{2.5}$ on pro-inflammatory response in cells. In general, in vitro data can be used to rank various types of particles in terms of the toxic potential including possible carcinogenicity. Each marker will help to understand the hazard and toxicity of $PM_{2.5}$. However, the toxicity of $PM_{2.5}$ may be the result of multiple components acting through disparate physiological mechanisms, with inconsistent relationships among endpoints (Park et al., 2018). For instance, in BEAS-2B cells, oxidative stress generated by H_2O_2 exposure often results in cytotoxicity rather than by stimulating cytokine/chemokine responses, sometimes no correlation between oxidative damage and cytokine/chemokine responses. Moreover, TNF-α gene was not detected in BEAS-2B cells exposed to atmospheric PM collected from Benin, but the gene expression of other inflammatory cytokines (IL-1β, IL-6, and IL-8) were significantly induced, and decreasing cell viability was highly correlated with high secretion of all studied cytokines (Cachon et al., 2014). Therefore, in the present study, it was impossible to analyze all chemicals in $PM_{2.5}$ and determine all related toxicological endpoints, so unmeasured chemicals and endpoints might also play roles in the incongruous or unexplained results, and we also can't over-explain the mechanisms just based on statistical relations. To overcome these hurdles, standardization of toxicological studies (experimental methodologies) and reporting guidelines are necessary for tracking and comparing results.

This study ranked the unequal "toxic effects" based on the same mass concentration of $PM_{2.5}$ exposure in body lung fluid system, while the "health risks" usually relating to the inhalation exposure concentration of $PM_{2.5}$ in ambient air were not calculated and evaluated quantitatively. Moreover, non-linear concentration-response functions for various endpoints and different exposure concentrations might also limit using toxicological data straightforwardly to predict health effects (morbidity, mortality) in human populations, so drawing conclusions precisely quantifying/ranking the health risks of $PM_{2.5}$ from specific sources or of individual $PM_{2.5}$ components is still not an easy task (Kelly and Fussell, 2020). Therefore, coupled with source apportionment and exposure level of ambient aerosols pollution, toxicology combined with epidemiology studies are essential for linking these factors and understanding scientific mechanisms to reach conclusions.

5 Conclusions

In current study, we found that 2/3 mass of urban ambient air $PM_{2.5}$ in a representative megacity of eastern China originated from primary sources of anthropogenic combustions including coal, automobile, and biomass. Because of the significant differences in the chemical compositions, the diverse $PM_{2.5}$ from both mixed ambient air and directly from individual combustion sources showed much differential mass-normalized *in vitro* toxicity to the human lung epithelial cells, either for the environmental aerosol samples collected from different seasons, or for the primary emissions of $PM_{2.5}$ from various specific

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source types. According to the comparative study and correlation analysis, the carbonaceous fractions (OC, EC) and redox-active heavy metals (V, Ni, Cr) assisted by water-soluble ions (Ca^{2+}, Mg^{2+}, F^{-}, Cl^{-}) might play important roles in inducing cellular ROS production, causing oxidative stress and inflammation, resulting in cell injury and apoptosis, thus damage human health. These toxic pollutants accumulated in specific-source $PM_{2.5}$ varied by the emission types and raw fuel properties. Combined with chemical composition and general cytotoxicity rank, the preferential controlling targets of specific combustion sources should be automobile exhaust (diesel vehicles with emission standards inferior to CN.IV), coal combustion (high ash and high sulfur coals), and plant biomass burning (crop straws). Although showing the synthetic effects of mixed compositions and complex sources, besides preventing the secondary aerosols from combustions, preferentially targeted reductions of these primary sources of toxic $PM_{2.5}$ direct emissions, would produce the greatest benefits for public health with improved ambient air quality. Overall, this paper provides a precise, oriented, effective, efficient, and economical composition-source-based strategies for urban aerosols pollution control. However, as a prospect, the detailed mechanisms for unequal toxicity of PM with complicated components from various sources and their quantitative contributions to the health effects of ambient air $PM_{2.5}$ mixture still need in-depth study.

Supplementary materials

There are 19 figures (Figure S1-S19) and 3 tables (Table S1-S3) in the Supporting Information.

Data availability

All raw data can be provided by the corresponding authors upon request.

Author contributions

XSL conceived and supervised the study; WH, YP, MT, HL, and ZZ collected the samples; WH, YP, MT, WL, HL, ZZ, GS, and LX analyzed the chemical compositions; WH, YP, and MT performed the toxicity tests; WH, YP, MT, and XSL analyzed the data; WH and XSL wrote the manuscript draft; XSL, WH, GS, and TM reviewed and edited the manuscript.

Competing interests

The authors declare that they have no conflict of interest.

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Captions of figures

Figure 1. The PMF factor profiles of various components and source percentages of secondary aerosol, automobile exhaust, coal combustion, and plant biomass burning contributing to the urban ambient air $PM_{2.5}$.

Figure 2. Carbon contents (mg kg^{-1}) and ratio in $PM_{2.5}$ from various specific sources (n=10 for each combustion source and n=16 for urban ambient air).

Figure 3. Heavy metal contents (mg kg^{-1}) in $PM_{2.5}$ from various specific sources (n=10 for each combustion source and n=16 for urban ambient air).

Figure 4. Water-soluble ion (WSI) contents (mg kg^{-1}) in $PM_{2.5}$ from various specific sources (n=10 for each combustion source and n=16 for urban ambient air).

Figure 5. Cumulated typical measured components (mg kg^{-1}) in $PM_{2.5}$ from various specific sources (n=10 for each combustion source and n=16 for urban ambient air).

Figure 6. Cell viability, oxidative stress and inflammation levels of human alveolar epithelial cell lines (A549) exposed to $PM_{2.5}$ suspension (80 mg L^{-1}) from various specific sources (n=10 for each combustion source and n=16 for urban ambient air).

Figure 7. Overall correlations between typical cellular toxicological responses and chemical compositions of $PM_{2.5}$ from various sources (*p < 0.05，#p<0.01; n=46).

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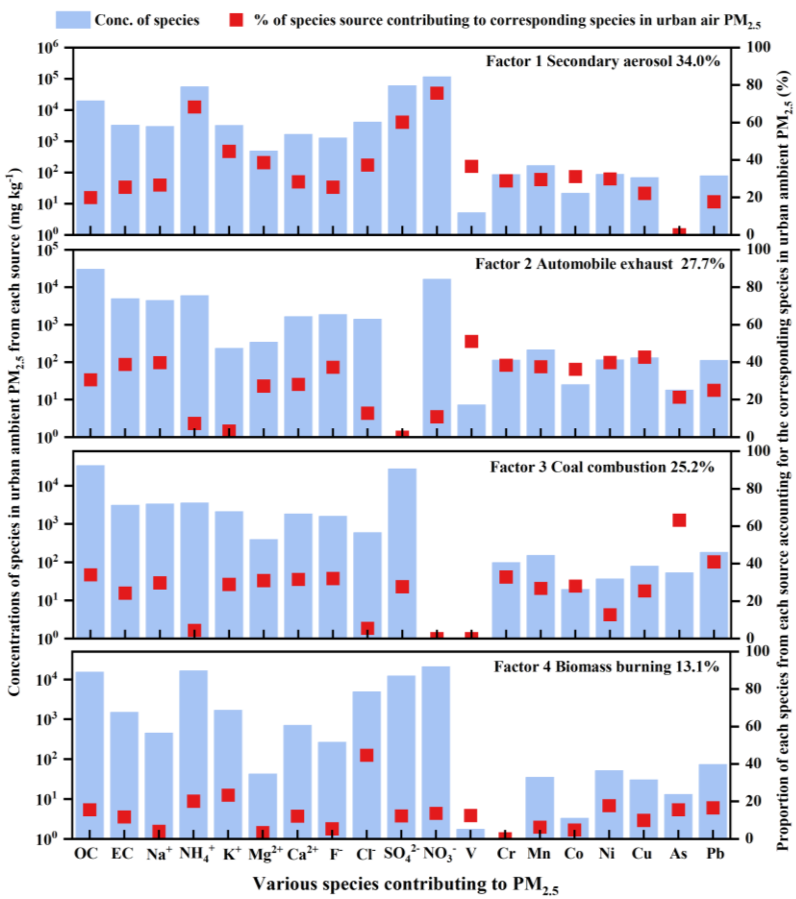

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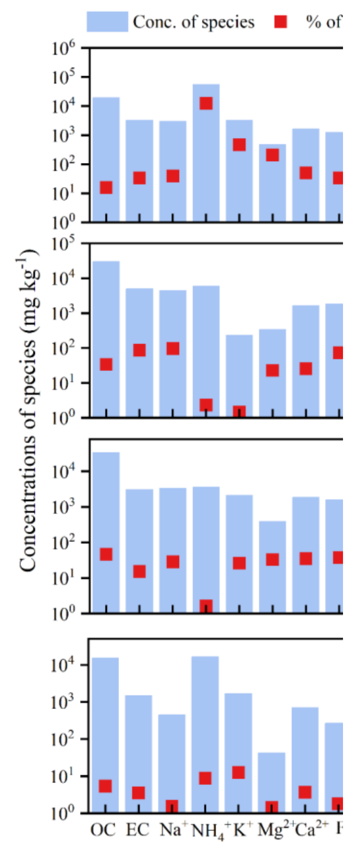

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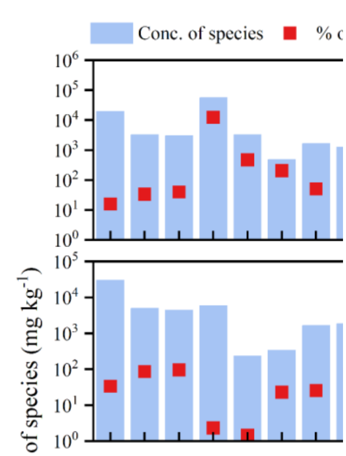


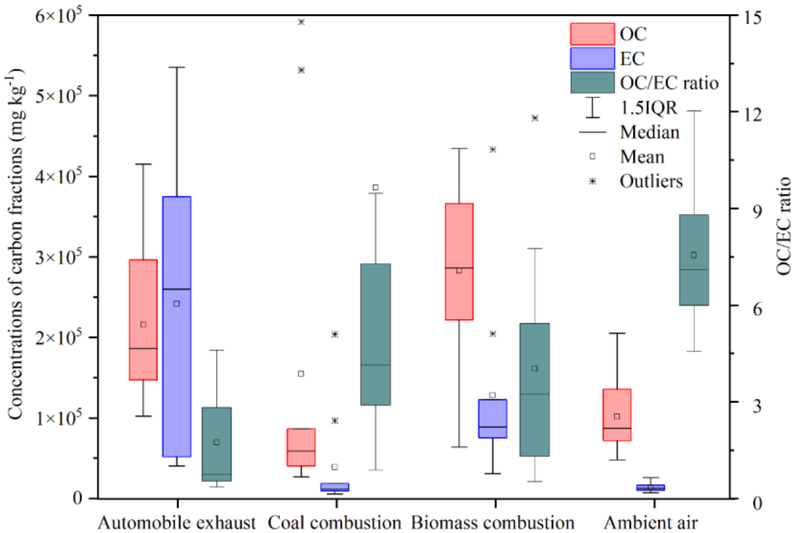
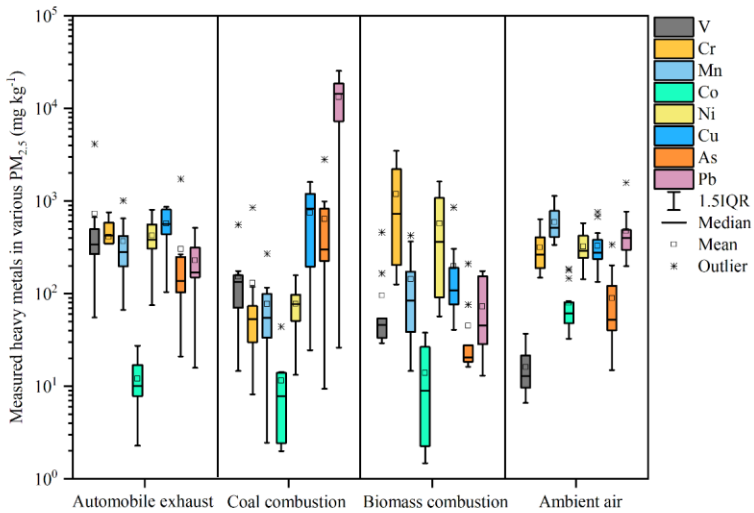


Figure 2. Carbon contents (mg kg^{-1}) and ratio in $PM_{2.5}$ from various specific sources (n=10 for each combustion source and n=16 for urban ambient air).



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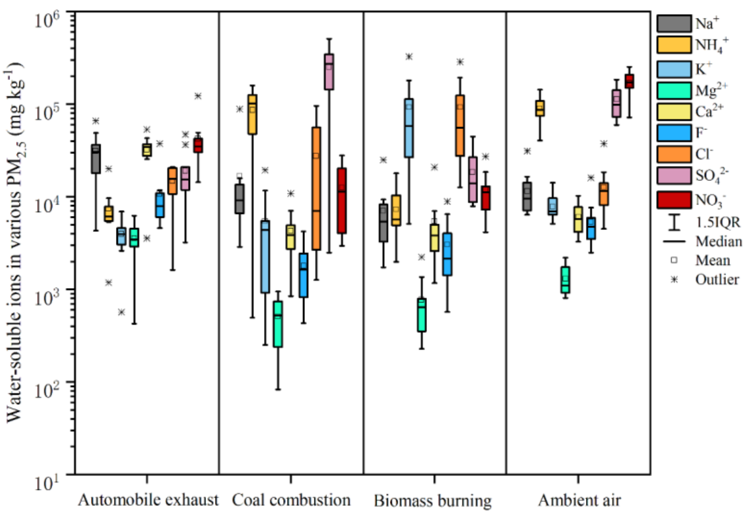

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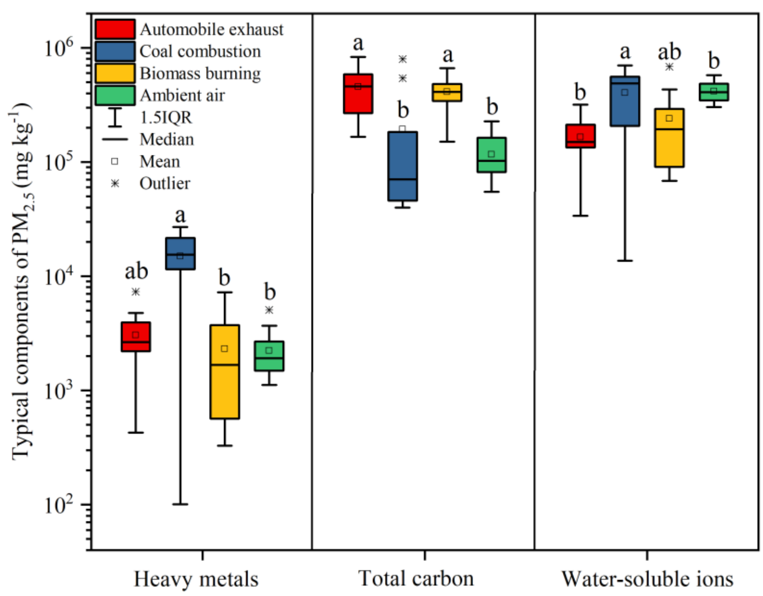
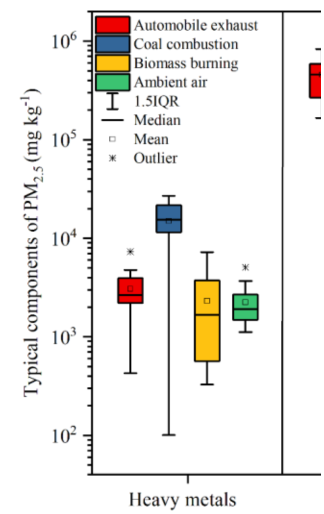


Figure 5. Cumulated typical measured components (mg kg^{-1}) in $PM_{2.5}$ from various specific sources (n=10 for each combustion source and n=16 for urban ambient air). The letters a and b are significant groups classified by Kruskal–Wallis test, $p < 0.05$.



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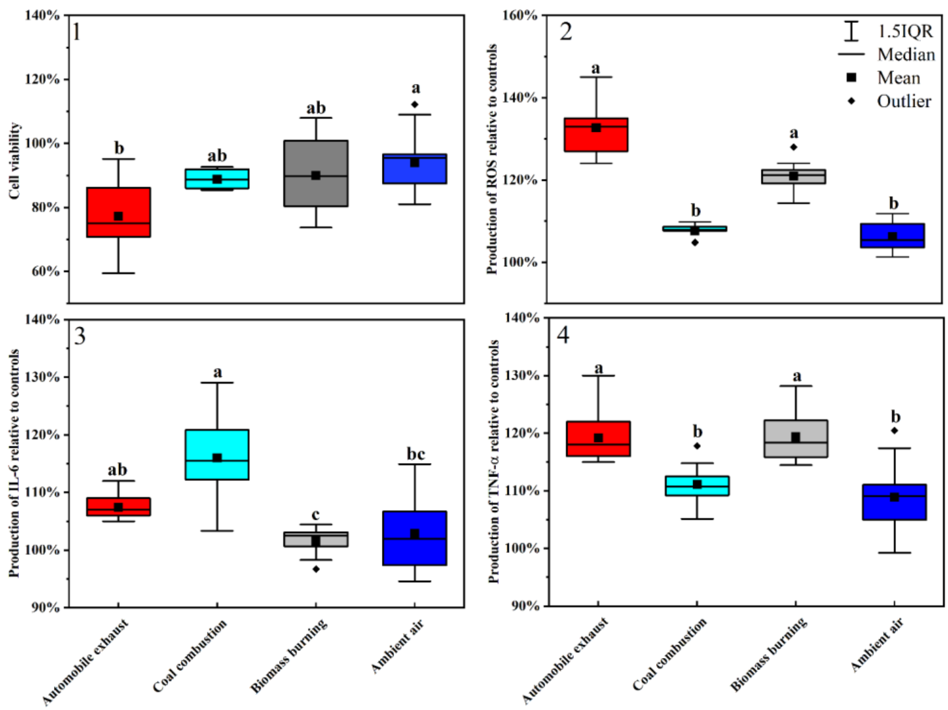

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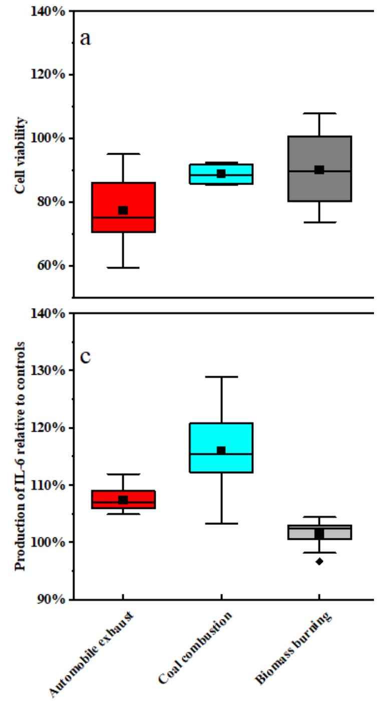

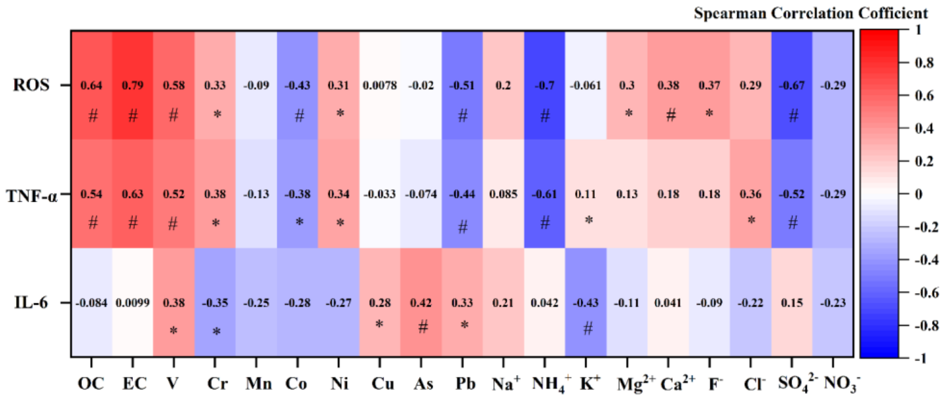

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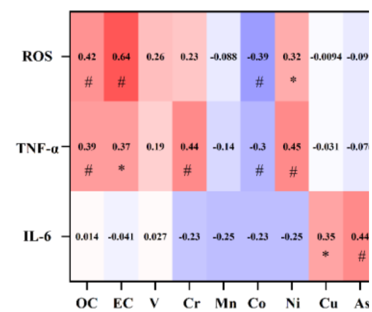

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