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Discovery of emerging sulfur-containing PAHs in $PM_{2.5}$: Contamination profiles and potential health risks

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ABSTRACT

We reported the discovery and identification of emerging sulfur-containing polycyclic aromatic hydrocarbons, namely polycyclic aromatic sulfur heterocycles (PASHs), in $PM_{2.5}$ collected from two typical regions of China, Taiyuan and Guangzhou. Until now, there is no research on contamination status, sources and potential health risks of this unexpected group of organic contaminants in $PM_{2.5}$. High atmospheric concentrations (ng m^{-3}) and significant time-dependent variations were determined in $PM_{2.5}$ of Taiyuan from 2017 to 2018. Coal combustion/secondary formation and traffic emission/secondary formation were apportioned as possible pollution sources for the $PM_{2.5}$-bound PASHs in Taiyuan and Guangzhou, respectively. Dithiothreitol and cell viability assays were applied for evaluations of PASH-induced reactive oxygen species (ROS) production and cell toxicity based on the determined real exposure levels for adults. The results illustrated that PASHs in $PM_{2.5}$ possibly caused oxidative stress and inhibition of human bronchial epithelial cells in seriously polluted regions such as Taiyuan, suggesting that the pollutant-induced health concerns may need more investigations. This study provides new insights into $PM_{2.5}$ pollution, and is beneficial for the development of effective contamination control strategies and reduction of risks on public health.

1. Introduction

The pollution of air fine particulate matter ($PM_{2.5}$) has drawn considerable attention in recent years (Li et al., 2017). Because of its small aerodynamic diameter ($\leq$ 2.5 μm) and complicated components, $PM_{2.5}$ can be inhaled by people and deposited deeply in the lungs, resulting in respiratory system dysfunctions (Song et al., 2019; Zhao et al., 2014). $PM_{2.5}$ also can pass through the alveolar epithelial fenestrated barrier after inhalation and participate in the pulmonary circulation, which may lead to cardiac injury (Qi et al., 2019). The epidemiological researches demonstrated that $PM_{2.5}$ exposure was significantly related to increased mortality around the world, including the premature mortality in the United States and the infant mortality in Africa (Dedoussi et al., 2020; Heft-Neal et al., 2018). The major compositions of $PM_{2.5}$, such as organic materials, elemental carbon, inorganic salts, water-insoluble elements and biological fractions (e.g., amino acids, antibiotic resistance genes (ARGs) and bacteria), can cause adverse effects on human health (Wang et al., 2006; Song et al., 2017; Xie et al., 2019; Liu et al., 2019; Zhang et al., 2019a). Organic pollutants in $PM_{2.5}$, like polycyclic aromatic hydrocarbon (PAHs), polybrominated diphenyl ethers and 2,3,7,8-tetrachlorodibenzo-p-dioxin, are toxic to cells and can induce genetic mutations (Kong et al., 2010; Cao et al., 2018; Zhang et al., 2017b; Lin et al., 2019). Inhalable $PM_{2.5}$-bound ARGs may create a clinical resistome in human body with negative effects on the clinical therapy of diseases (Xie et al., 2019). However, there are still unexpected $PM_{2.5}$-bound pollutants making thorough investigations on mechanism of $PM_{2.5}$ exposure-induced harmful effects difficult. Therefore, in addition to the research on the known components, it is crucial to conduct further studies focusing on the emerging contaminants in $PM_{2.5}$.

Polycyclic aromatic sulfur heterocycles (PASHs), the sulfur-containing PAHs, are an important type of organic pollutants found in

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different environmental matrices. The usage of flotation agent, insecticide, herbicide and dye in the industrial and agricultural production could release PASHs in the environment but people believed that environmental PASHs were majorly derived from incomplete combustion of fossil matter and natural gas (Manzano et al., 2017). Lately, 1-methylphenanthro[4,5-bcd]thiophene and 6,8-dimethyl-benzo[*b*]naphtho[2,3-*d*]thiophene were detected in snow and lake sediments from the Athabasca oil sands region in Canada (Manzano et al., 2017). Dibenzothiophene and their alkyl homologs were detected in soil and sediment samples from Beijing, China (Zhihuan et al., 2008; Li et al., 2012). Given the ubiquity of PASHs in the environment, it is reasonable to believe that such contaminants can also be found in $PM_{2.5}$. However, rare studies investigated the pollution status and spatial distributions of PASHs in $PM_{2.5}$. A few works recorded toxicities induced by pure chemicals of PASHs, and found that dibenzothiophene and naphtho[1,2-*b*]thiophene exhibited the inhibition of the bacteria respiration and potential mutagenicity (Alves and Paixao, 2011; Pelroy et al., 1983). Nevertheless, the health effects of personal exposure to $PM_{2.5}$-bound PASHs have not yet been documented. To better understand the possible health risks, the origins of PASHs should also be precisely traced. The above-mentioned research gaps of $PM_{2.5}$-bound PASHs motivated us to perform a systematic investigation.

China is one of the countries that suffer from serious $PM_{2.5}$ pollution in recent years, especially for urban areas (Zhang and Cao, 2015). Located in North and South China, respectively, the cities of Taiyuan and Guangzhou have significantly different economic and industrial structures, and are both hit by serious $PM_{2.5}$ pollution. Taiyuan is a typical industrial city with 4 million population. Heavy industry especially coal-driven industry is the backbone of Taiyuan's industrial production (Fu et al., 2009; Tang et al., 2014). Guangzhou has 14 million population and is one of the most developed areas in China (Chen et al., 2020a). In this study, the accurate contamination levels as well as pollution sources of $PM_{2.5}$-bound PASHs in these two representative megacities were investigated and compared for the first time. The *in vitro* toxicity experiments for PASHs in real $PM_{2.5}$ samples, including the examinations of reactive oxygen species (ROS) production and cell viability, were conducted. It was found that $PM_{2.5}$-bound PASHs in Taiyuan might lead to obvious oxidative stress and human bronchial epithelial cell toxicity. The preliminary toxicological outcomes revealed the possible adverse implications of region-specific exposure for human health.

2. Materials and methods

2.1. Sampling

The sampling sites were located at Guangdong University of Technology (Guangzhou, China, 23° 2′ 34.44′ N, 113° 24′ 19.08′ E) and Shanxi University (Taiyuan, China, 37° 47′ 42.70′ N, 12° 34′ 52.51′ E). ADS-2062E medium volume air samplers (AMAE (Shenzhen) Co., Ltd, China) used for sampling were placed on the roof of the 8-story building of School of Environmental Science and Engineering (Guangdong University of Technology) and the 5-story building of Institute of Environmental Science (Shanxi University). Samples were collected for 23.5 h daily at the flow rate of 0.1 m^3 min^{-1}. Quartz fiber filters (90 mm diameter) from Whatman were used for $PM_{2.5}$ collection. All quartz fiber filters were pre-conditioned at 550 °C for 5 h in order to avoid contamination prior to sample collection. After collection of $PM_{2.5}$, filters were wrapped with aluminum foil and sealed in a zipped bag. All $PM_{2.5}$ sample filters were kept at − 80 °C for further analysis of PASHs and PAHs. 40 $PM_{2.5}$ filters in Guangzhou and 42 $PM_{2.5}$ filters in Taiyuan were collected between May, 2017 and April, 2018 (12 months).

2.2. Chemicals and materials

Fourteen PASHs, including Dibenzothiophene (DBT), 1-, 2-, 3- and 4-methyldibenzothiophene (1-, 2-, 3-, 4-MDBT), 1,4-, 4,6- and 2,8-dimethyldibenzothiophene (1,4-, 4,6- and 2,8-DMDBT), tribenzothiophene (TBT), 7-methylbenzo[*b*]naphtho[2,3-*d*]thiophene (7-M[2,3-*d*]T), benzo[*b*]naphtho[1,2-*d*]thiophene (BbN[1,2-*d*]T), benzo[*b*]naphtho[2,3-*d*]thiophene (BbN[2,3-*d*]T), 2-nitrodibenzothiophene (2-NDBT) and 2,8-dinitrodibenzothiophene (2,8-DNDBT), were selected as target analytes. The information of commercial suppliers of above pure chemicals were listed in the Supporting Information.

16 PAHs, including naphthalene (NAP), acenaphthylene (ACY), acenaphthene (ACE), fluorene (FLU), anthracene (ANT), phenanthrene (PHE), fluoranthene (FLT), pyrene (PYR), chrysene (CHR), benz(a)anthracene (BaA), benzo(b)fluoranthene (BbF), benzo(k)fluoranthene (BkF), benzo(a)pyrene (BaP), indeno(1,2,3-cd)pyrene (IcdP), benzo(g,*h*,i)perylene (BghiP) and dibenz(a,h)anthracene (DBA), were selected as chemical markers for source apportionment. The commercial information of the standard was also listed in the Supporting Information.

Dimethyl sulfoxide (DMSO), dithiothreitol (DTT), diethylene triamine pentaacetic acid (DTPA) and 5,5′dithio-bis(2-nitrobenzoic acid) (DTNB) were acquired from Sigma Aldrich (St. Louis, MO, USA). A cell counting kit-8 (CCK-8) assay kit was purchased from Beyotime institute of Biotechnology (Beijing, China). LHC-9 medium was bought from Thermo Fisher Scientific (USA). Human bronchial epithelial cells (BEAS-2B cells) were obtained from Conservation Genetics CAS Kunming Cell Bank, Chinese Academy of Sciences.

2.3. Analytical methods

The analytical methods for PASHs with acceptable recoveries (67.6–120.8%) and limit of detections (LODs: 0.052 pg m^{-3} - 1.673 pg m^{-3}) have been detailed in our previous work (Zhang et al., 2020). Briefly, ultrasonication and silica gel column chromatography were applied for extraction and purification of PASHs in $PM_{2.5}$ sample filters, respectively. The extracts were analyzed by Agilent 7890B gas chromatography (Agilent Technologies Inc., USA) equipped with Xevo TQ-S triple-quadrupole mass spectrometer (Waters Corporation., UK). Positive atmospheric pressure chemical ionization (APCI) mode was used. The parameters of gas chromatography and mass spectrometry were presented in Table S1. For analysis of source marker PAHs in $PM_{2.5}$, the methods were same as what were described in our previous work with satisfactory recoveries (72.1–107%) and LODs (0.021 pg m^{-3} - 0.404 pg m^{-3}) (Zhang et al., 2019b). For another source indicator, NO_2, the concentrations were obtained from China National Environmental Monitoring Centre (CNEMC).

2.4. DTT and cell viability assay

The DTT assay was performed using previous methods with slight modifications (Chen et al., 2020a; Ma et al., 2018). The solvent of each 150 μL sample extract was replaced by 150 μL acetonitrile (ACN). Then, 0.5 mmol L^{-1} DTT solution (50 μL), potassium phosphate buffer (pH 7.4, 850 μL) containing 1 mmol L^{-1} diethylene triamine pentaacetic acid (DTPA) and 150 μL of a solution of the sample in ACN were mixed in a 1.5 mL tube. The mixed solution was vibrated and incubated in a dry bath at 37 °C for 90 min. When the reaction was complete, 1.0 mmol L^{-1} DTNB (100 μL) was added; the absorbance at 412 nm of the solution was then immediately determined with an ultraviolet–visible (UV–Vis) spectrophotometer (Hewlett, CA, USA). Pure ACN (150 μL) was used as a control group. The DTT assay experiment was also performed for the PASH standard at 0.01 ng, 0.05 ng, 0.1 ng, 0.5 ng, 1 ng, 5 ng, 10 ng, 50 ng, 100 ng, 500 ng, 1 μg, 5 μg and 10 μg following the same procedures. The calculation of PASH-catalyzed DTT activity and corresponding explanation were provided in the Supporting Information.

For cell viability assay, the BEAS-2B cells were grown in LHC-9 serum-free medium and maintained in a humidified incubator at 37 °C with 5% CO_2. A number of 1.0×10^4 cells/100 μL medium was seeded in 96-well plates and incubated at 37 °C for 24 h. 150 μL of PASH extract from Taiyuan $PM_{2.5}$ samples and 500 μL of PASH extract from

Guangzhou $PM_{2.5}$ samples were dried by nitrogen purging and re-dissolved in DMSO (10 μL). The control groups of cells were exposed to pure DMSO. Cell viability assay was performed with CCK-8 assay kit. The control and each exposure group had six replicates. After exposure, the suspension was replaced with fresh medium (100 μL) containing CCK-8 (10 μL), followed by 1.5 h incubation at 37 °C. The absorbance was determined at a wavelength of 450 nm by a Victor3TM microplate reader (PerkinElmer Inc., MA, USA). The cell viability assay was also used to test the pure PASH chemicals at different concentrations (0.05, 0.1, 0.25, 0.5, 1, 5, 10, 25 and 50 μg mL^{-1}) in 200 μL of medium. 2,8-DNDBT were not tested at the concentration levels of 25 and 50 μg mL^{-1}.

2.5. Statistical analysis

Statistical treatments, including Mann-Whitney test (*U*-test, $p < 0.001$), principal component analysis (PCA, $p < 0.01$), Spearman correlation analysis and regression analysis ($p < 0.05$), were performed using IBM SPSS statistics 19.

3. Results and discussion

3.1. Contamination levels of $PM_{2.5}$-bound PASHs in Taiyuan and Guangzhou

Taiyuan is a coal-driven heavy industrial city and Guangzhou is a city with light industry and manufacturing. They have different economic structures, representatives of northern and southern China, and both faced serious $PM_{2.5}$ pollution in recent years. As shown in Table 1, 100% detection frequencies of fourteen $PM_{2.5}$-bound PASHs were reported in Taiyuan between May, 2017 and April, 2018, and the average concentrations of individual PASH ranged from 18.8 pg m^{-3} (2-NDBT and 7-M[2,3-*d*]T) to 689 pg m^{-3} (BbN[2,3-*d*]T). In Guangzhou, only BbN[1,2-*d*]T and BbN[2,3-*d*]T could be detected in all samples and the lowest detection rate was 8% (7-M[2,3-*d*]T) (Table 1). 1-MDBT, 7-M[2,3-*d*]T and 2,8-DNDBT with low detection rates were excluded in the further source apportionment analysis. The lowest and highest ambient mean concentrations for individual PASH were 0.2 pg m^{-3} (7-M[2,3-*d*]T) and 26.9 pg m^{-3}(1,4-DMDBT), respectively. Compared to the well-known $PM_{2.5}$-bound organic contaminants, such as PAHs and their derivatives, chlorobenzenes and dioxins, the pollution levels of PASHs in Taiyuan were not low (Zhang et al., 2017b, 2019b, 2018; Chen et al., 2020b). The health concerns may be induced by large dosage of inhaled $PM_{2.5}$-bound PASHs, which will be discussed in Section 3.3.

The significant atmospheric concentration differences of the pollutants ($p < 0.001$) were found between two sampling sites based on Mann-Whitney test (*U*-test) (Table 1). The special time-dependent annual variations of total determined $PM_{2.5}$-bound PASHs' concentrations were observed in Taiyuan (Fig. 1). An obvious increase appeared from Dec, 2017 to Feb, 2018 in both annual variations based on sampling date and month (Fig. 1a and c). TBT, BbN[1,2-*d*]T and BbN[2,3-*d*]T were predominant $PM_{2.5}$-bound PASHs in all sampling months (Fig. 1c). The findings were strongly correlated with specific time/region-dependent pollution sources of PASHs in Taiyuan and is further explored in Section 3.2 below. On the contrary, although the total monthly $PM_{2.5}$-bound PASH concentrations were higher in May/Aug, 2017 and Feb, 2018 in Guangzhou (Fig. 1d), there were no significant changes in the daily values (Fig. 1b), suggesting PASHs in Guangzhou had relatively stable and low atmospheric concentrations. The major PASHs in $PM_{2.5}$ were DBT, 4-MDBT and 4,6-DMDBT in Guangzhou (Fig. 1d). Taken together, Taiyuan featured the more serious pollution status of $PM_{2.5}$-bound PASHs.

3.2. Source apportionments of $PM_{2.5}$-bound PASHs in Taiyuan and Guangzhou

In previous studies, PASHs were found in soil and snow that may be released from incomplete combustion of sulfur-containing fossil matter and natural gas (Thuß et al., 2000; Soontjens et al., 1997). However, there was no literature on the source apportionments of the PASHs in $PM_{2.5}$. In order to define the origins of PASHs in $PM_{2.5}$ from Taiyuan and Guangzhou, both PCA and Spearman correlation analysis were applied in the present study.

3.2.1. Define quantities of pollution sources by PCA analysis

PCA was widely used to assess the contributions from different pollution sources through reconstruction of the database of the measured compositions (Sarkar and Khillare, 2013). Using PCA, multiple variables can be reduced to a small number of factors and each factor could be regarded as a possible emission source (Chen et al., 2020a). In this way, quantities of possible PASH sources in $PM_{2.5}$ were defined. The PCA results were shown in Fig. 2a and b. Two factors were found through analyzing $PM_{2.5}$ samples from Taiyuan (Fig. 2a) with acceptable Kaiser-Meyer-Olkin (KMO) value (0.848). Factor 1 accounted for 73% of the whole variance. The detected PASHs (except 2-NDBT and 2,8-DNDBT) had high load (> 0.75) in factor 1. Factor 2 explained 9% contributions of the total variance with high load of 2-NDBT (0.84) and 2,8-DNDBT (0.88). Accordingly, there may be two possible sources (coal combustion and secondary generation) for the measured $PM_{2.5}$-bound PASHs in Taiyuan.

In Guangzhou, due to the low detection rates of 1-MDBT (60%), 7-M[2,3-*d*]T (8%) and 2,8-DNDBT (38%), PASHs in $PM_{2.5}$, with the exception of above three compounds, were analyzed by PCA in order to fulfill

Table 1
Atmospheric concentrations (pg m^{-3}) of $PM_{2.5}$-bound PASHs in Taiyuan and Guangzhou.

Compounds (pg m^{-3})	Taiyuan (n = 42)				Guangzhou (n = 40)				
	Min	Max	Mean	Detection rate	Min	Max	Mean	Detection rate	*U*-test[1] p-value
DBT	1.5	2663	242	100%	1.5	63	17	73%	< 0.001
4-MDBT	15.9	3648	359	100%	0.3	27.2	7.5	75%	< 0.001
2-/3-MDBT	2.2	1006	120	100%	0.2	5.7	1.9	70%	< 0.001
1-MDBT	0.2	1034	100	100%	0.3	3.5	1.3	60%	< 0.001
4,6-DMDBT	42.9	4482	602	100%	0.7	14.2	5.6	85%	< 0.001
2,8-DMDBT	4.1	1367	124	100%	1.3	23.5	9.9	70%	< 0.001
1,4-DMDBT	1.4	1079	117	100%	0.2	202	26.9	83%	< 0.001
TBT	0.6	294	44.2	100%	1.1	55.1	14.8	80%	< 0.001
2-NDBT	0.1	141	18.8	100%	0.03	6.7	2.1	78%	< 0.001
BbN[1,2-*d*]T	37.4	1772	357	100%	0.4	20	5.9	100%	< 0.001
BbN[2,3-*d*]T	50.7	4503	689	100%	1.5	28.8	9.5	100%	< 0.001
7-M[2,3-*d*]T	1.5	123	18.8	100%	0.1	0.3	0.2	8%	< 0.001
2,8-DNDBT	0.3	160	42.0	100%	0.8	3.5	1.5	38%	< 0.001
∑PASHs[2]	290	21,126	2796	–	4.4	241	80.8	–	–

U-test[1]: Two-tailed Mann-Whitney *U*-test — test of significant difference of concentration level for individual PM2.5-bound PASH between Taiyuan and Guangzhou.
∑PASHs[2]: Total concentration of 14 PASHs in each sampling day.

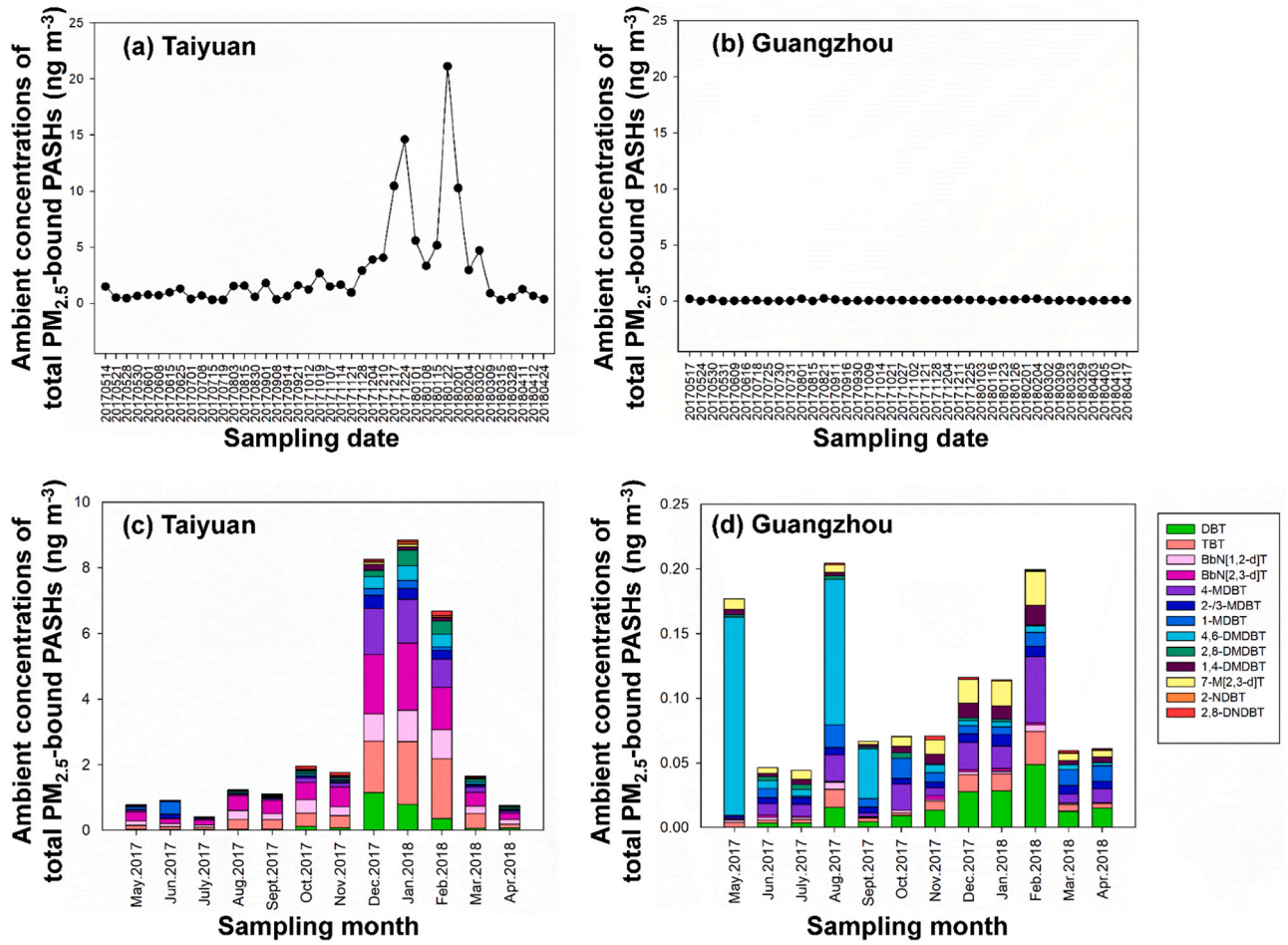

Fig. 1. Sampling date/month-based annual variations of total $PM_{2.5}$-bound PASH concentrations in Taiyuan (a/c) and Guangzhou (b/d).

the requirements of KMO and Bartlett's test (Zhang et al., 2017). The results also revealed two factors (Fig. 2b) and the KMO value was 0.765. Factor 1, which had 49% contributions to the whole variance, was mainly attributed to PASHs (with high load greater than 0.82) except 2-NDBT. Factor 2 (21%) was only dominated by 2-NDBT (0.78). Therefore, PASHs in $PM_{2.5}$ from Guangzhou also had two possible pollution sources (traffic emission and secondary generation). Generally, researchers often use marker pollutants, the compounds from specific emission sources, to ascertain which sources the factors represent (Chen et al., 2020a; Wang et al., 2014). However, no study had determined the specific sources of the individual $PM_{2.5}$-bound PASHs until now.

3.2.2. *Identify pollution sources by Spearman correlation analysis*

PAHs in $PM_{2.5}$ were usually applied as pollution markers to help identify the environmental sources of contaminants in $PM_{2.5}$ with knowledge of local pollution characteristics (Zhang et al., 2019b; Wang et al., 2011a; Jin et al., 2017). Generally, the low molecular weight PAHs (e.g., NAP and ACY) were indicators of biomass burning (Wang et al., 2014), the medium molecular weight PAHs (e.g., PHE and PYR) come mostly from coal combustion (Zhang et al., 2019b) and the high molecular weight PAHs (e.g., BaP and BghiP) were markers for traffic emission (Wang et al., 2011a).

On the basis of the reported possible origins in soil and sediments, PASHs were expected to have similar pollution sources, such as coal burning (Andersson et al., 2006) and vehicle exhaust (Fraser et al., 1998), with their structure-like PAHs. Consequently, the Spearman correlation between the determined PASHs and source marker PAHs in $PM_{2.5}$ may indicate the possible pollution sources of $PM_{2.5}$-bound PASHs. The concentrations of PAHs (Table S2) and PASHs were measured using the same $PM_{2.5}$ samples. In Taiyuan, the ambient mean concentrations of the source marker PAHs in $PM_{2.5}$ were from 0.19 to 17.3 ng m^{-3} (Table S2). All PASHs and PAHs were covered in the Spearman correlation analysis. In Guangzhou, 11 PASHs were participated in the correlation analysis. 14 PAHs in $PM_{2.5}$ were also included in the correlation analysis except undetected ACY and ACE. The range of their atmospheric average concentrations were between 0.6 and 2.31 ng m^{-3} (Table S2).

Results of the Spearman correlation analysis between $PM_{2.5}$-bound PASHs and PAHs in Taiyuan and Guangzhou were presented in Fig. 2c and d and detailed correlation coefficients and significances were listed in Tables S3 and S4. As indicated in Fig. 2c, higher positive correlation coefficients between PASHs (except 2-NDBT and 2,8-DNDBT) and ANT/ PHE/ FLT/ PYR in $PM_{2.5}$ from Taiyuan could be found with $p < 0.01$ (Table S3). In light of the local pollution characteristics, these PAHs were thought to be mainly emitted by coal combustion (Zhang et al., 2019b; Yan et al., 2017), implying that PASHs (except 2-NDBT and 2,8-DNDBT) in $PM_{2.5}$ may be also primarily emitted by the same source. The result is reasonable because combustion of sulfur-containing coal with high metamorphic grade is generally used in most industrial production in Taiyuan and PASHs are major type of the organic sulfur in this type of coal, leading to the emission of PASHs in atmosphere (Andersson et al., 2006; Li et al., 2014). Meanwhile, compared to other types, the burning of the coal with high metamorphic grade could release more PASHs (Hu et al., 2004). Therefore, the large usage would make the coal combustion-emitted $PM_{2.5}$-bound PASHs remain at high contamination levels for the whole year in Taiyuan, and also could explain the phenomenon that the total ambient concentrations had higher values

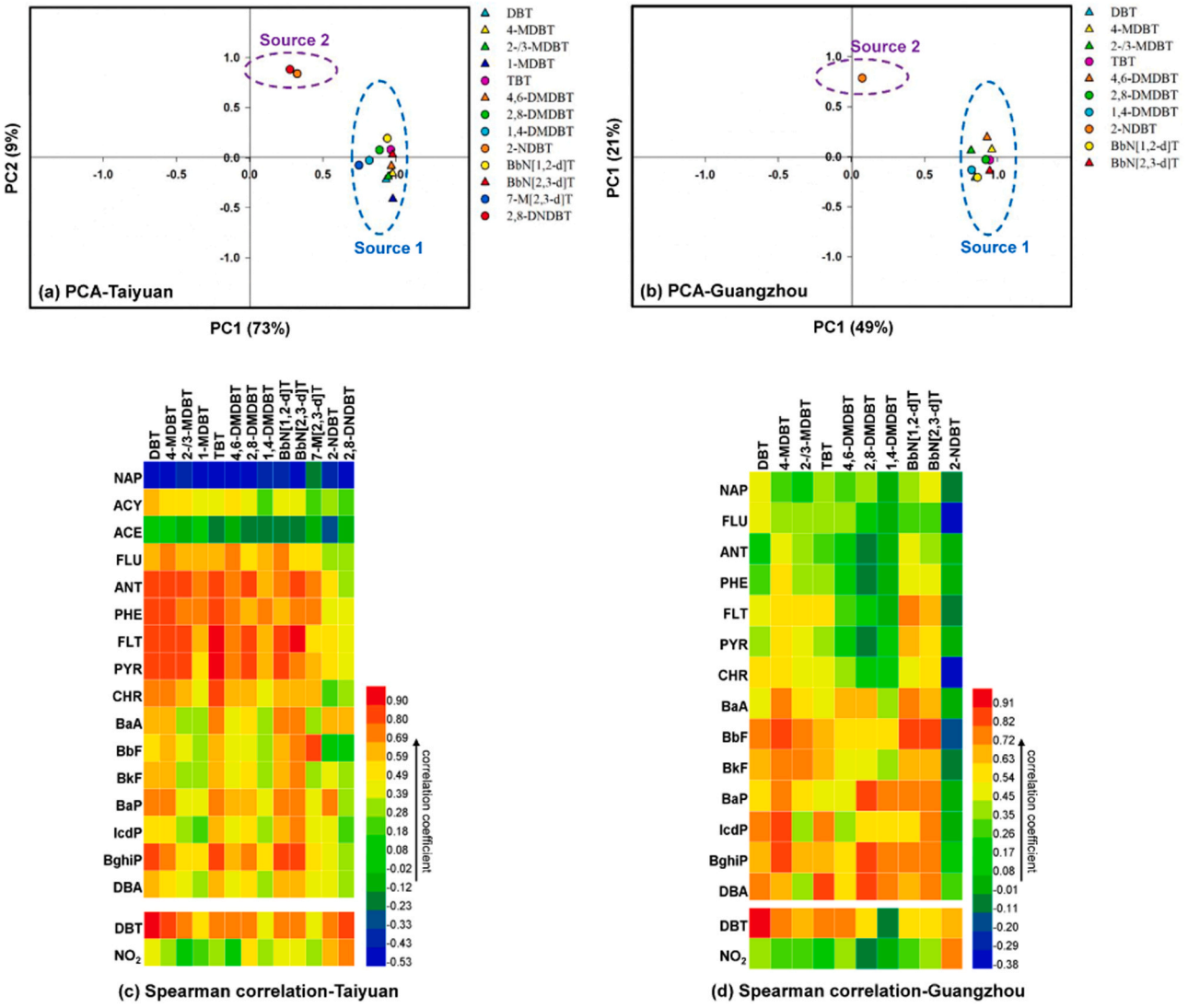

Fig. 2. PCA ordination plots of $PM_{2.5}$-bound PASHs (a/b) and Spearman correlation coefficient heat map between $PM_{2.5}$-bound PASHs and PAHs/DBT/NO_2 (c/d).

between Dec, 2017 and Feb, 2018 (Fig. 1a and c). During these months, besides industrial usage, additional coal would be burnt for home heating in Taiyuan (Zhang et al., 2018), thereby creating the concentration peaks.

2-NDBT and 2,8-DNDBT may not come from the primary emission because they had a weak or even negative correlation with PAHs in $PM_{2.5}$ from Taiyuan (Table S3). However, significant positive correlations ($p < 0.01$) were observed between 2-NDBT and DBT (0.752)/NO_2 (0.680), and between 2,8-DNDBT and DBT (0.798)/NO_2 (0.697) (Fig. 2c and Table S3). The NO_2 concentrations were listed in Table S2. Additionally, the linear relationships were also investigated (Fig. 3a–d) and the positive regression coefficients (R) were obtained ranging from 0.42 to 0.62. Considering the chemical structures of 2-NDBT and 2,8-DNDBT, the above results indicated a secondary photochemical reaction might be a possible means of generation, which is similar to the nitro-PAHs formation in $PM_{2.5}$ (for details please refer to Supporting Information) (Zhang et al., 2018; Lin et al., 2015). $PM_{2.5}$-bound 2-NDBT and 2,8-DNDBT may come from the reaction of DBT, NO_2 and free radicals (e.g., OH· and NO_3·) in atmosphere.

In Guangzhou, as shown in Fig. 2d, a relatively high positive correlation was observed between $PM_{2.5}$-bound PASHs (except 2-NDBT) and PAHs with high molecular weight (BbF, BkF, BaP, IcdP, BghiP, and DBA). These PAHs may mostly come from the traffic emission in Guangzhou (Wang et al., 2011b), indicating that the source of PASHs (with the exception of 2-NDBT) may be the same. Guangzhou is a highly developed city with about 3 million motor vehicles in China (Chen et al., 2020a). PASHs are major type of organic sulfur in gasoline and diesel oil (Wang et al., 2011b; Jha et al., 2019). Therefore, combustion of them could emit PASHs in vehicle exhaust. However, in recent years, gasoline and diesel oil with less sulfur were more frequently used, which may be the reason why $PM_{2.5}$-bound PASHs had lower concentrations in Guangzhou than in Taiyuan. For 2-NDBT, the similar phenomenon was observed with $PM_{2.5}$-bound 2-NDBT/2,8-DNDBT in Taiyuan. Significant positive correlation ($p < 0.01$) between 2-NDBT and DBT (0.669)/NO_2 (0.745) (Table S4), and corresponding linear regression coefficients (0.58 and 0.64) (Fig. 3e and f) illustrated that secondary formation may be the main origin of $PM_{2.5}$-bound 2-NDBT in Guangzhou. The source apportionment results coincided with the quantities of sources obtained by PCA shown in Fig. 2a/b and could explain the significant difference of contamination levels between two sites.

3.3. *Potential health risks for human exposure to $PM_{2.5}$-bound PASHs*

The researches on health risks of $PM_{2.5}$-bound PASHs inhaled by human were not yet reported. In order to preliminarily evaluate the adverse health effects, *in vitro* toxicity experiments, including oxidative

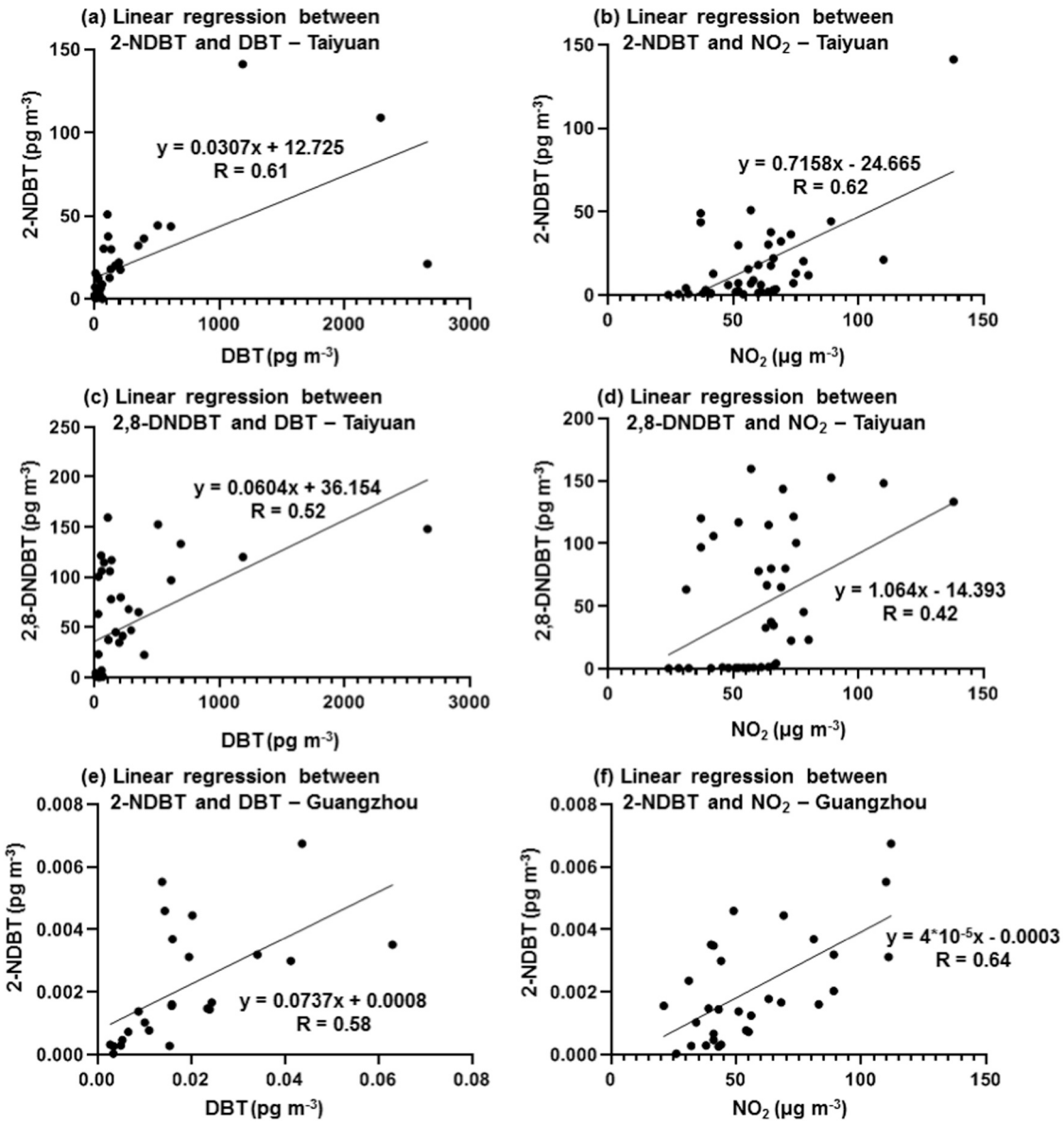

Fig. 3. Linear regressions between $PM_{2.5}$-bound 2-NDBT/2,8-DNDBT and DBT/NO_2 (a–e) in Taiyuan and Guangzhou.

stress and cell viability examinations, were conducted by DTT and CCK-8 assays, respectively.

3.3.1. *Oxidative stress induced by PASHs in $PM_{2.5}$*

Oxidative stress is a critical index of the harmful cardiorespiratory effects induced by $PM_{2.5}$ and can be effectively evaluated by assessing the formation of reactive oxygen species (ROS) using a cell-free DTT assay (Song et al., 2020; Senthilkumar et al., 2014). The DTT activities of each PASH extract from real Taiyuan $PM_{2.5}$ samples were determined and shown in Fig. 4a$_1$. It was found that no obvious DTT activities were induced by PASH extracts from samples in Guangzhou (compared to control groups, absorbance changes were all less than 1%), probably because of the excessively low concentrations. Consequently, the Guangzhou data were not given. In Fig. 4a$_1$, the similar annual variations of DTT activities and total concentrations of $PM_{2.5}$-bound PASHs in Taiyuan were observed. In particular, from Dec, 2017 to Feb, 2018, considerably high values were noticed for both DTT activities and the total concentrations of $PM_{2.5}$-bound PASHs. A positive linear relationship (R = 0.77) between them was also found as shown in Fig. 4a$_2$, suggesting that PASHs in $PM_{2.5}$ may have promotional effects on the induction of oxidative stress.

In order to validate the results from analyzing real samples, the different dosages of pure PASH chemicals were tested using the DTT assay. The amount used was based on possible annual inhaled PASH of adults (Table 2) and calculated by following Eq. (1) from USEPA (USEPA, 1989):

$$\text{Annual } PM_{2.5}-\text{bound PASHs intake} = IR \times T \times EF \times C \quad (1)$$

where IR is the inhalation rate (0.83 $m^3\ h^{-1}$), T is the exposure time in 1 day (4 h day^{-1}), EF is the annual exposure frequency (350 days per year) and C is the atmospheric concentration of PASHs in $PM_{2.5}$. Other than C, these constants were obtained from the USEPA (USEPA, 1989). For the individual PASH, the annual adult intake varied from 0.03 ng (2-NDBT in Guangzhou) to 5.2 μg (BbN[2,3-*d*]T in Taiyuan). For total amount, the values were from 5.08 ng (Guangzhou) to 24 μg (Taiyuan) (Table 2). The PASH standard chemicals with the amounts ranging from 0.01 ng to 10 μg (0.00001, 0.00005, 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 5 and 10 μg) were used. For the mixture of pure chemicals, the dosage series (0.0014, 0.007, 0.014, 0.07, 0.14, 0.7, 1.4, 7, 14, 70 and 140 μg) was the combination of individual standard

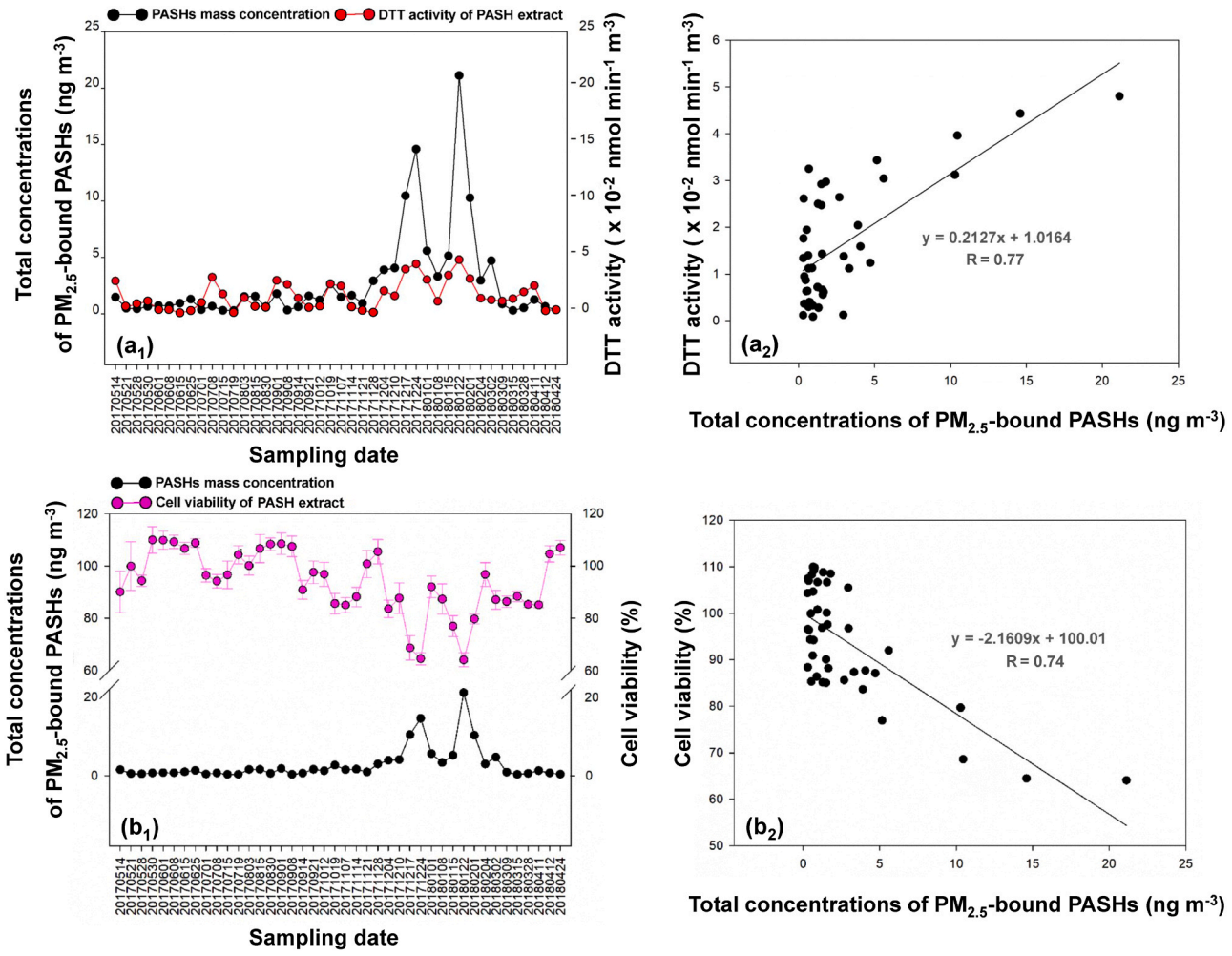

Fig. 4. Annual variations' comparisons and linear relationships of total concentrations of $PM_{2.5}$-bound PASHs and associated DTT activity (a_1/a_2)/cell viability (b_1/b_2) in Taiyuan.

Table 2
Minimum and maximum annual adult intake of $PM_{2.5}$-bound PASHs in Taiyuan and Guangzhou.

PASHs	Taiyuan		Guangzhou	
	Atmospheric concentration (pg m^{-3})	Annual exposure dosage (ng)	Atmospheric concentration (pg m^{-3})	Annual exposure dosage (ng)
Minimum (Std[1])	0.1 (2-NDBT)	0.12	0.03 (2-NDBT)	0.03
Maximum (Std)	4503 (BbN[2,3-*d*]T)	5232	202 (1,4-DMDBT)	235
Minimum ($\sum^2$)	290	337	4.37	5.08
Maximum ($\sum$)	21,126	24,548	241	280

Std[1]: Single PASH standard.
$\sum^2$: Total 14 PASHs.

(0.0001–10 μg). However, there was no DTT consumption when the exposure dosages of mixed and most individual standard chemicals were less than 0.07 and 0.01 μg, respectively. Pure DBT, 1,4-DMDBT and BbN[1,2-*d*]T did not consume DTT until their dosages were 0.05 μg. Therefore, only the linear relationships between effectual experimental dosages of PASHs and the percent of absorbance decrease (versus control) induced by DTT consumption were investigated. With the increase of the standard dosages, all the absorbance decrease became more pronounced. The pure PASH chemicals with the relatively strong DTT activities were shown in Fig. 5a_1–a_7. The DTT activities of other PASH standards were listed in Fig. S1. The results suggested that PASHs in $PM_{2.5}$ may lead to oxidative stress with potential adverse effects. For example, as shown in Fig. 5a_1, when the exposure dosage of the standard mixture was 14 μg (each single PASH being 1 μg), the absorbance decrease was more than 30%, implying the significant likelihood of inducing oxidative stress.

3.3.2. *Cell toxicity caused by PASHs in $PM_{2.5}$*

The toxicities of PASHs in real $PM_{2.5}$ samples were examined using a CCK-8 assay as the indicator of cell viability. The human bronchial epithelial (BEAS-2B) cell viabilities of PASH extracts from Taiyuan $PM_{2.5}$ samples were shown in Fig. 4b_1, where a possible negative correlation was found between the total concentrations of PASHs and cell viabilities. Particularly from Dec, 2017 to Feb, 2018, the cell viabilities became lower compared to other sampling days with the higher total concentrations. Meanwhile, in Fig. 4b_2, a negative linear relationship ($R = 0.74$) could be observed, indicating that PASHs in $PM_{2.5}$ with high concentration may cause cell inhibition. In Guangzhou the relationship was not obvious (Fig. S2), probably because the concentrations were too low to induce toxicities.

PASH standard chemicals were also examined for validating their effects on BEAS-2B cell viabilities. The exposure levels (0.05, 0.1, 0.25, 0.5, 1, 5, 10, 25 and 50 μg mL^{-1} in 200 μL medium, which are equivalent to exposure dosages of 0.01, 0.02, 0.05, 0.1, 0.2, 1, 2, 5 and 10 μg)

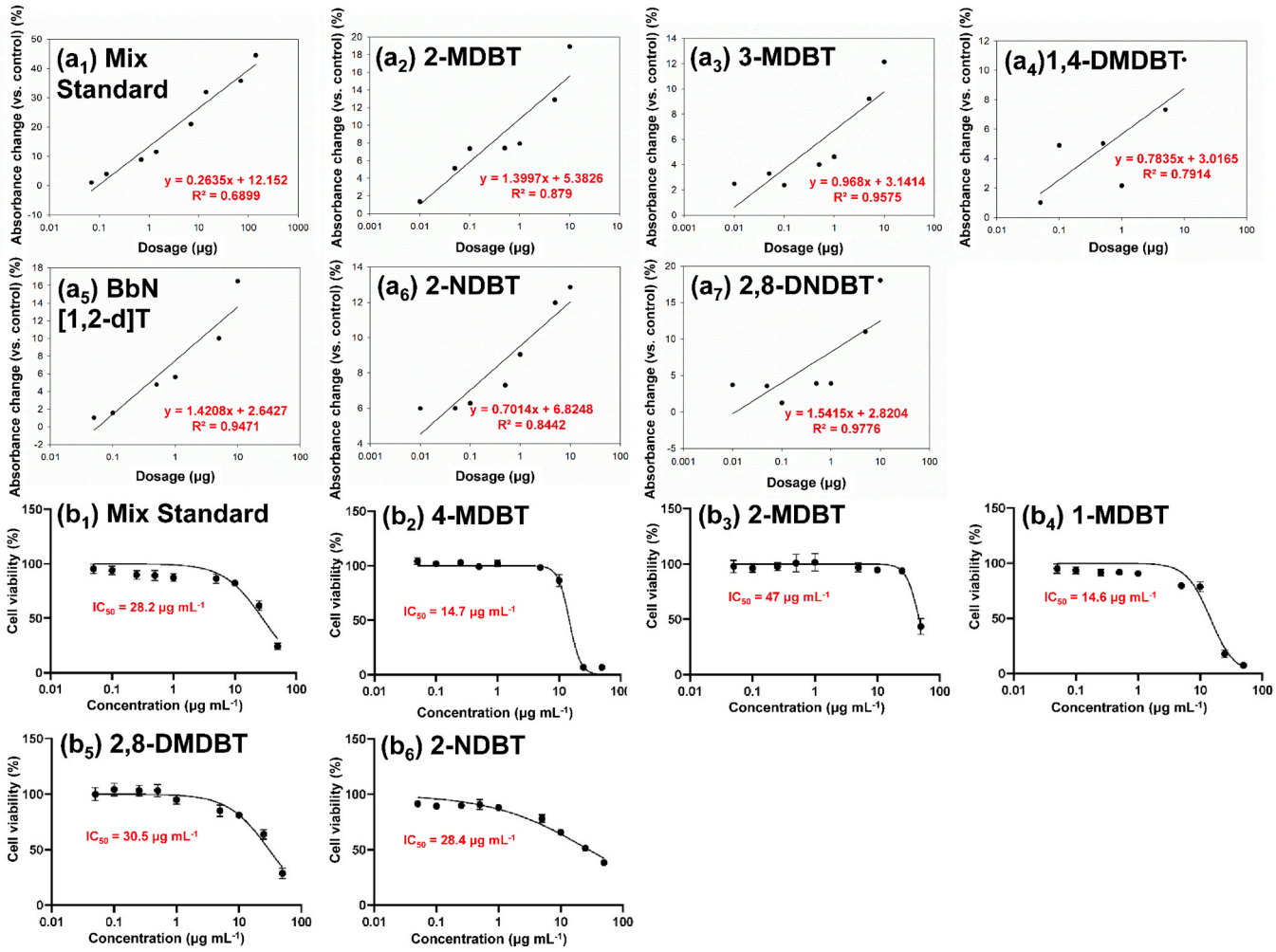

Fig. 5. The relatively strong DTT activities (a_1–a_7) and obvious dosage-survival curves (b_1–b_6) of pure PASH chemicals.

were also selected based on the adult inhalation dosage of $PM_{2.5}$-bound PASHs (Table 2). According to the dose-survival curves in Fig. 5b_1–b_6, obvious dose-dependent cell viabilities of mix standard, 4-MDBT, 2-MDBT, 1-MDBT, 2,8-DMDBT and 2-NDBT could be seen, and their half maximal inhibitory concentrations (IC_{50}) were also presented. For other pure PASH chemicals in Fig. S3, the cell viabilities of DBT, BbN[1,2-*d*]T and TBT were not lower than 50% with the increase of the concentrations, but they also exhibited obvious downward trends. Except above three compounds, other individual PASHs in Fig. S3 did not have clear relationship with the cell viabilities. However, as shown in Fig. 5b_1, the toxicity of mix standard was clear, indicating the individual PASH standards with unobvious toxicities may have adverse effects when the cells are subject to co-exposure as in previous works (Li et al., 2020; Wang et al., 2020).

Due to the similar structures of PASHs and PAHs, their cell toxicities are comparable. Some $PM_{2.5}$-bound PAHs have obvious toxicities on BEAS-2B cells. The PYR could suppress BEAS-2B cells (cell viability = 90%) at 2 μg mL^{-1} (Koike et al., 2014). BaP, a well-known carcinogen in $PM_{2.5}$ (Zhang et al., 2016), induced inhibition of BEAS-2B cells (cell viability = 85%) at about 3.8 μg mL^{-1} (Ovrevik et al., 2010). Compared to PYR and BaP, the individual PASHs with obvious toxicity (Fig. 5b_2–b_6) had similar or even lower fatal dosages for BEAS-2B cells. 4-MDBT led to 14% cell inhibition at 10 μg mL^{-1}; 2-MDBT induced 10% cell inhibition at 10 μg mL^{-1}; 2,8-DMDBT resulted in 19% cell inhibition at 10 μg mL^{-1}; 1-MDBT caused 20% cell inhibition at 5 μg mL^{-1}; 2-NDBT led to 10% cell inhibition at 0.5 μg mL^{-1}. As indicated in Table 1, except 2-NDBT, other four PASHs (4-, 2-, 1-MDBT and 2, 8-DMDBT) had high ambient contamination levels (ng m^{-3}) in Taiyuan $PM_{2.5}$ samples, which were similar to PYR and BaP with real determined concentration levels indicated in Table S2. Therefore, it was reasonable to anticipate those PASHs posing toxicities in $PM_{2.5}$. The results implied that the potential health risks of PASHs in $PM_{2.5}$ should not be overlooked, especially in seriously polluted regions such as Taiyuan in China.

4. Conclusions

The discovery of PASHs in $PM_{2.5}$ may open a new area of research not only because of their relatively high levels but also due to the obvious toxicity and potential risk to human health. In the present study, the environmental occurrence, distributions and potential adverse effects of the emerging PASHs in $PM_{2.5}$ from typical regions of China were investigated for the first time. It was found that, compared to Guangzhou, Taiyuan had higher contamination levels. The regional variations had significant correlations with local industrial and economic structures, suggesting different pollution sources of $PM_{2.5}$-bound PASHs. The results of *in vitro* assays indicated that $PM_{2.5}$-bound PASHs in Taiyuan may lead to toxicities because of their high concentrations. It was noticed that the toxicological studies for real samples did not consider the possible effects of other particle components. The research on combined toxicity of $PM_{2.5}$ compositions is still a challenge now. However, these limitations do not undermine the value of the preliminary evaluations of pollutant-induced health risks in this work, and more investigations on ambient pollution of $PM_{2.5}$-bound PASHs should be

carried out.

CRediT authorship contribution statement

Yanhao Zhang: Methodology, Formal analysis, Investigation, Writing - original draft. **Yuanyuan Song**: Methodology, Data curation. **Yi-Jie Chen**: Formal analysis, Investigation. **Yanyan Chen**: Formal analysis, Investigation. **Yan Lu**: Resources. **Ruijin Li**: Resources, Project administration. **Chuan Dong**: Resources, Conceptualization. **Di Hu**: Resources. **Zongwei Cai**: Writing - review & editing, Conceptualization, Resources, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare there is no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2021.125795.

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