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Underestimated contribution of fugitive emission to VOCs in pharmaceutical industry based on pollution characteristics, odorous activity and health risk assessment

Qinhao Lin^{1,2}, Zhong Gao¹, Weikun Zhu¹, Jiangyao Chen^{1,2,*},
Taicheng An^{1,2}

¹Guangdong Key Laboratory of Environmental Catalysis and Health Risk Control, Guangdong Technology Research Center for Photocatalytic Technology Integration and Equipment Engineering, Institute of Environmental Health and Pollution Control, Guangdong University of Technology, Guangzhou 510006, China

²Guangdong-Hong Kong-Macao Joint Laboratory for Contaminants Exposure and Health, Guangzhou Key Laboratory of Environmental Catalysis and Pollution Control, School of Environmental Science and Engineering, Guangdong University of Technology, Guangzhou 510006, China

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ABSTRACT

Fugitive emission has been becoming an important source of volatile organic compounds (VOCs) in pharmaceutical industry, but the exact contribution of fugitive emission remains incompletely understood. In present study, pollution characteristics, odorous activity and health risk of stack and fugitive emissions of VOCs from four functional units (e.g., workshop, sewage treatment station, raw material storage and hazardous waste storage) of three representative pharmaceutical factories in comparison with other functional units. Extreme high concentration of VOCs from fugitive emission in unsealed workshop (94.87 mg/m³) was observed relative to sealed one (1.18 mg/m³), accounting for 31% and 5% of total VOCs, respectively. Fugitive emission of VOCs in the unsealed workshop mainly consisted of n-hexane, 1-hexene and dichloromethane. Odorous activity indexes and non-cancer hazard ratios of these VOCs from fugitive emission in the unsealed workshop were as high as that from stack exhaust. Furthermore, cancer risk of dichloromethane from fugitive emission and stack exhaust was up to $(1.6-1.8) \times 10^{-5}$. Odorous activity or health risk index of the VOCs from fugitive emission was up to 13 or 11 times of the corresponding threshold value, posing remarkable health threat on pharmaceutical workers. Our findings highlighted the possibly underestimated contribution of fugitive emission on VOCs in the pharmaceutical industry.

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* Corresponding author.

E-mail: chenjiangyao@gdut.edu.cn (J. Chen).

Introduction

Volatile organic compounds (VOCs) played an important role in the atmospheric chemical reaction, climatic change, growth of plants, odour source and health effect (He et al., 2019; Kansal, 2009; Shen et al., 2013). Atmospheric VOCs were originated from both natural and anthropogenic sources (Laothawornkitkul et al., 2009; Rantala et al., 2016; Chen et al., 2016; Zhang et al., 2013a; Zhang et al., 2015). Vegetation emission was an important VOC contributor of natural source (Geron et al., 2006; Tan et al., 2021; Qin et al., 2021). Several major anthropogenic sources of VOCs consisted of industrial activity, vehicle exhaust, gasoline vapor, coatings and biomass burning (Klimont et al., 2002; Zhang et al., 2021; Huang et al., 2011; Xu et al., 2021; Zhang et al., 2013b; Zhang et al., 2018). The VOC emission from anthropogenic sources currently appeared a clear increase trend, especially in China (Mozaffar and Zhang, 2020; Bo et al., 2008). From 2011 to 2013 in China, the VOC emission from industrial activity increased by an annual average growth rate of 38.3%, and it was estimated that the industrial VOC emission would reach 24 Tg in 2030 (Zheng et al., 2017). Pharmaceutical factory was one of the important VOC sources in the industrial activity (Wei et al., 2011). The total VOC emission from pharmaceutical industry was found to increase by 1.5 times, from 0.26 Tg in 2010 to 0.43 Tg in 2015, in China (Liang et al., 2017). Furthermore, with increasing in demand for medicine, the expansion on scale and amount of pharmaceutical factory in China would lead to the augment on VOC emission in the future.

Previous studied have confirmed that VOCs from pharmaceutical industry were potent odorants (Liang et al., 2021; Liao et al., 2021; Zhang et al., 2020; Hu et al., 2020; Liu et al., 2020) or posing health risk on the population (Cheng et al., 2021; Liu et al., 2017). Characterization of VOC source and chemical composition was a key step to improve their odor abatement and reduce corresponding health risk in pharmaceutical industry. Stack exhaust and fugitive emission were two VOC sources in pharmaceutical industry. Cheng et al. (2021) reported that the concentration of VOCs from the stack exhaust in the pharmaceutical workshop was up to 33.7 mg/m³, and their main constituents included ethanol and dichloromethane. Complex species of VOCs from stack exhaust in pharmaceutical workshop have also been reported in many studies (He et al., 2015; Cheng et al., 2021; Yang et al., 2019a). Sewage treatment station was another stack exhaust of VOCs in pharmaceutical industry (He et al., 2015). However, health risk of pharmaceutical workers and nearby residents was vulnerable to the VOCs from fugitive emission than stack exhaust, since of fugitive emission was close to the ground.

Leak of equipment or poor performance on leak detection and repair system in pharmaceutical industry would lead to significant fugitive emission of VOCs in pharmaceutical industry (Ren et al., 2016). Due to difference in fugitive degrees in pharmaceutical industries, the concentration of VOCs from fugitive emission highly varied. Cheng et al. (2021) reported that the levels of VOCs from fugitive emission ranged from 0.8 to 21.1 mg/m³ within five pharmaceutical production lines, and the dominant species consisted of toluene,

dichloromethane, ethanol, methanol and acetone. The fugitive emission of VOCs from wastewater treatment facilities varied from 0.1 to 17.3 mg/m³, and their component included chlorobenzene, 2-butanone, vinyl chloride, acetone chloroethylene and chloroform (Ren et al., 2016). However, available studies always only considered the contribution of stack emission to total VOCs (stack and fugitive emissions), leading to uncompleted understand of the real pollution profile of VOCs in pharmaceutical industry, especially in some old pharmaceutical factories with high leakage degree of VOCs (Yang et al., 2015). Furthermore, few studies focused on VOCs from fugitive emission in other functional units, such as raw material storage and hazardous waste storage. These units might show different fugitive emissions of VOCs (Yang et al., 2015). Differences in fugitive degrees and functional units in pharmaceutical industry complicated the contribution of fugitive emission to total VOCs emission, therefore odorous as well as health risk. Identification of pollution characteristic, odorous activity and health risk of VOCs within pharmaceutical functional units from varying fugitive degree industries would help to accurately assess the role of fugitive emission in total VOC pollution and corresponding health effect.

In this study, the pollution characteristic, odorous activity and health risk of fugitive emission of VOCs from four functional units including workshop, sewage treatment station, raw material storage and hazardous waste storage were performed in differently fugitive degrees emission for three representative pharmaceutical factories. Additionally, the analysis of VOCs profile from stack exhaust in workshop and sewage treatment station of three pharmaceutical factories was compared with that of fugitive emission. At the same time, effects of stack exhaust and fugitive emission on pollution characterization, odorous activity index and health risk of ambient VOCs in factory boundary were also evaluated.

1. Experimental

1.1. Sampling sites

The investigation area was located in a large-scaled industry park of Southwest China. The park mainly consisted of pharmaceutical, steel and other chemical factories (e.g., rubber factory). A total of nine pharmaceutical factories were operated in the park, and they were classified into three categories based on the production environment. For the first category, VOC leakage was always observed from almost all functional units, due to opened production condition and poor performance on leak detection and repair. The factories belonging to the second category possessed relatively sealed working condition for most functional units, leading to partial fugitive emission of VOCs. The strictest sealed working condition was found in factories of the third category, where aseptic workshops were applied. Then, three pharmaceutical factories corresponding to opened, normally sealed and highly sealed conditions were selected to evaluate the contribution of VOCs from fugitive emission to the total VOCs. These factories were named as Factory A, Factory B and Factory C, respectively (Fig. S1).

VOCs were sampled from four functional units of the pharmaceutical factories, including workshop, sewage treatment station, raw material storage and hazardous waste storage (Fig. S2). Moreover, the central position of each factory was also selected as control point. The fugitive emission of VOCs was sampled from these sites, except workshop of the Factory C. In addition, VOCs of stack exhaust from workshop and sewage treatment station were also collected in all studied factories. This kind of VOCs was first treated by combined processes of alkali washing, paraffin and activated carbon absorptions in workshop or of alkali washing and activated carbon absorption in sewage treatment station, and then discharged to the air. Furthermore, another twelve sampling sites were performed for analysis of ambient VOCs in the surroundings around the factories to assess the potential effect of VOC diffusion on the atmospheric pollution in neighboring areas (Fig. S1). The information of longitude and latitude for these sites were listed in Table S1. The distances between site 1, site 2 and Factory A were nearly 10 m. The distances between site 6, sites 7, site 8, site 9 and Factory C were nearly 10 m. Other sites away from the three factories were above 50 m. The ambient temperature during the sampling period ranged from 24 to 39 °C. The dominant wind pattern in the sampled site was from northwest to southeast. Moreover, malodorous VOCs from fugitive emission and stack exhaust in the factories and adjacent region were simultaneously measured using electronic nose (E-nose) to compare the odorous activity of different VOCs.

1.2. Measurement and analysis of VOCs

VOCs samples were collected by cleaned 2.7 L Summa canisters (ENTECH Instruments Inc., Silonite™) and the measurement was performed within 15 days after samples collected by using an Entech 7200 pre-concentrator (Entech Instruments Inc., CA, USA) combined with an gas chromatography-mass spectrometry (7890B GC-5977B MS, Agilent Technology, USA). All samples were detected for twice to obtain an average value. A detailed description of VOCs analysis procedures was given in the Supplementary Information and has been published in our previous study (Chen et al., 2021).

The VOC concentrations were quantified using internal standard calibration method which was estimated using standard samples Photochemical Assessment Monitoring Stations (PAMS) and TO-15 (Linde Spectra Environment Gases, USA). Four kinds of VOCs including 1,4-difluorobenzene, chlorobenzene-d5, bromochloromethane, and 4-bromofluorobenzene (Linde Spectra Environment Gases, USA) were used as internal standards. The calibration curves were achieved by running diluted standards of gradient volume plus high purity nitrogen in an identical way as the field samples. Relationship values (R^2) for calibration curves ranged from 0.95 to 1.00 for VOCs, suggesting that integrated peak areas of different VOCs were proportional to their concentrations. A total of 60 VOC species was measured in this study, and were classified into five categories including alkane, alkene, aromatics, halogenated and oxygenated compounds, and their constituents and method detection limits measured in this study were listed in Table S2.

1.3. Odorous activity evaluation

The odor threshold value of an odor substance was that the lowest concentration of an odor can be smell by at least three trainers. In order to reduce the uncertainty of odor threshold among individuals, triangle odor bag method has been used to calculate odor threshold value of a known substance (Nagata and Takeuchi, 2003). The odor thresholds of an odor substance were found elsewhere (Lee et al., 2013; Nagata and Takeuchi, 2003; Wu et al., 2015). Due to level of an odorous substance unable to directly assess odorous strength, an empirical equation was used to convert the concentration of each odorous substance into an odorous activity index, as shown in Eq. (1) (Nie et al., 2020):

$$OAI_i = C_i/OD_i \quad (1)$$

where, OAI_i is the odorous activity index of an odorous substance i , C_i and OD_i referring to the concentration and odor threshold value of an odorous substance i , respectively. Odor thresholds of odorous substances in this study were listed in the Table S3.

1.4. E-nose detection

Malodorous VOCs from fugitive emission and stack exhaust were also analyzed using the AIRSENSE PEN3.5 E-nose (Schwerin, Germany). The E-nose consisted of 10 metal oxide sensors, which could distinguish from different VOCs. For instance, These sensors sensitive to VOCs were as follows: Sensor 1, aromatic compounds; Sensor 2, broad range and nitrogen oxides; Sensor 3, aromatic compounds and ammonia; Sensor 4, hydrogen gas; Sensor 5, aromatic and aliphatic compounds; Sensor 6, broad range and methane; Sensor 7, inorganic sulfur and sulfur-containing organic compounds; Sensor 8, broad range and alcohol; Sensor 9, sulfur and chlorinate compounds; Sensor 10, methane and aliphatic organic compounds. The gases were introduced into the E-nose with a flow rate of 400 mL/min for 120 sec, and the sensor response was recorded. Principal component analysis (PCA) was allowed to discriminate the malodorous VOCs from various sources using the Winmuster software (Schwerin, Germany).

1.5. Exposure risk assessment

The health risk through inhalation of VOCs was assessed using the non-cancer hazard ratio (HR) and lifetime cancer risk (LCR) (Ramirez et al., 2012). The non-cancer and cancer risk assessments were calculated by using Eqs. (2)-(4) (Chen et al., 2021):

$$EC_i = (CA_i \times ET \times ED \times EF)/(AT \times 365 \times 24) \quad (2)$$

$$HR_i = EC_i/RfC_i \quad (3)$$

$$LCR_i = EC_i \times 1000 \times UR_i \quad (4)$$

where, EC_i and CA_i represent the exposure and ambient concentrations (mg/m^3) of an substance i , respectively, ET referred

Table 1 – VOC concentration in different functional units of three factories (mg/m³).

Locations	Emissions	Factory A	Factory B	Factory C
Workshop	SE ¹	209.69	20.57	7.37
	FE ²	94.87	1.18	*
Sewage treatment station	SE	115.78	17.13	67.97
	FE	8.51	0.30	0.55
Raw material storage	FE	1.23	0.59	0.21
Hazardous waste storage	FE	17.77	30.53	0.42
Central position	FE	65.68	0.26	0.36

*: No measurement of VOCs in this study. ¹: SE represents stack exhaust. ²: FE refers to fugitive emission.

to exposure time per day (8 hr per day), ED and EF referred to exposure duration (30 years) and exposure frequency (250 working days per year), AT represented average lifetime (70 years), RfC_i and UR_i were the reference concentration and the unit risk of a substance *i*. In this study, ET, ED and AT values were obtained from the literature (Li et al., 2020). RfC_i (mg/m³) and UR_i ((μg/m³)⁻¹) values are listed in Table S4, which were provided from the Environmental Protection Agency of the United States (<https://www.epa.gov/iris>) and some previous studies (Chen et al., 2021; Cheng et al., 2021).

2. Results

2.1. Pollution characteristics of VOCs from stack and fugitive emissions in Factory A

The total concentrations of VOCs from stack and fugitive emissions in workshop of Factory A were 209.69 and 94.87 mg/m³, respectively (Table 1). Clearly, the latter contributed to 31% of the total VOCs, suggesting important source of VOCs from fugitive emission in the workshop. Among four groups of VOCs, alkane compounds dominated in the VOCs from stack (70%) or fugitive (80%) emission (Fig. 1). However, alkane compounds from the stack exhaust mainly consisted of n-hexane and 3-methylpentane, while n-hexane was the primary alkane compound from the fugitive emission. Moreover, alkene (i.e., 1-hexene) represented 18% of VOCs from stack emission and this proportion significantly reduced to 2% for fugitive emission of VOCs. Halogenated compounds (i.e., dichloromethane) accounted for 9% and 17% of VOCs from stack and fugitive emissions, respectively. In this factory, VOCs generated inside the chemical reactors of the workshop firstly collected by pipelines, then transported and processed via adsorption or acid-alkali washing methods, and finally stack exhaust released into the atmosphere. Fugitive emission of VOCs in the workshop might be directly originated from volatilization of raw materials during feeding process or leak of pipelines and valves during pharmaceutical production processes. This difference likely led to the diversity in VOC species between stack and fugitive emissions, although they were collected in the same workshop.

The total concentration of VOCs from fugitive emission in the sewage treatment station was 8.51 mg/m³, which was significantly smaller than the level from stack exhaust (115.78 mg/m³) (Table 1). The VOCs from fugitive emission

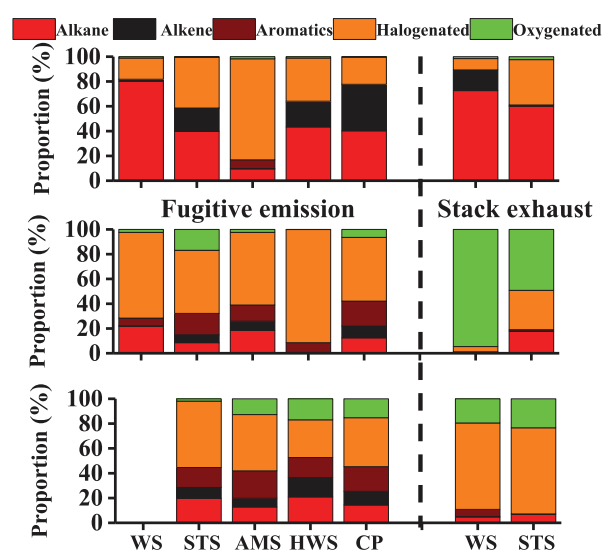


Fig. 1 – Proportions of alkane, alkene, aromatics, halogenated and oxygenated compounds in three pharmaceutical factories (Up–Factory A, Middle–Factory B, Down–Factory C). WS (workshop), STS (sewage treatment station), AMS (raw material storage), HWS (hazardous waste storage) and CP (central position).

only represented 7% of the sum of that from stack and fugitive emissions. However, lower levels of 3-methylpentane (0.19 versus 1.56 mg/m³) and 1-hexene (0.52 versus 1.38 mg/m³) from stack exhaust than fugitive emission were obtained. This further supported the fact that VOCs leaked from sewage treatment station was minor.

The total VOC concentrations from fugitive emission in the raw material storage and hazardous waste storage were 1.23 and 17.77 mg/m³, respectively (Table 1). Hazardous waste storage reserved the stack exhaust-processed active carbon or paraffin materials, leading to a relatively high concentrated fugitive emission of VOCs due to volatilization of these hazardous wastes. Furthermore, abundant n-hexane, 3-methylpentane and 1-hexene were detected in the hazardous waste storage, which was similar to that from stack exhaust in the workshop or sewage treatment station. Further comparison revealed extreme high concentrated VOCs from fugitive or stack emission in the workshop and sewage treatment station, suggesting that these two functional units were the main

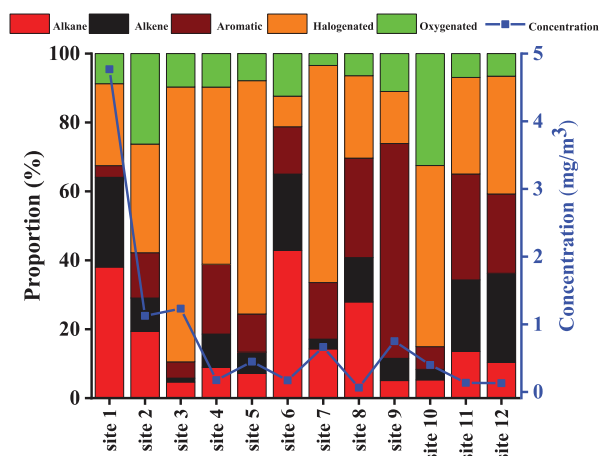


Fig. 2 – Proportions of alkane, alkene, aromatics, halogenated and oxygenated compounds in the surrounding sites of three pharmaceutical factories.

contributing sources for VOCs emission in Factory A. Moreover, the much higher contributing ratio of fugitive emission in total VOCs from the workshop than sewage treatment station indicated severer leakage of VOCs from the former.

In addition, a high value (65.68 mg/m^3) of VOCs was detected in the central position of Factory A (Table 1). n-Hexane, 1-hexene and dichloromethane contributed to over 95% of VOCs in this site. Diffusion from stack emission of the workshop likely resulted in the high level of VOCs in central position. This was because that the concentration of 1-hexene (23.89 mg/m^3) in the central position was far higher than that from other functional units (below 5 mg/m^3), but lower than that from stack emission (34.57 mg/m^3) of the workshop. However, the contribution of fugitive emission from the workshop to the central position should not be completely ignored, due to high values of n-hexane and dichloromethane from fugitive emission. Moreover, n-hexane (1.74 mg/m^3), 1-hexene (1.18 mg/m^3) and dichloromethane (1.08 mg/m^3) also showed relative high values in the adjacent region (sites 1 and 2) of the Factory A (Fig. 2). This suggested that VOC emission from the Factory A had obvious effect on its surrounding atmospheric environment. Above 80% of oxygenated compounds in the sites (sites 1, 2 and 3) near to the Factory A included methyl-tert-butyl ether. This proportion was significantly higher than that in the three factories (0-30%). Increase in oxygenated compounds in the sites near to the Factory A may be affected by other pollution sources, rather than the local emission from pharmaceutical industries.

2.2. Pollution characteristics of VOCs from stack and fugitive emissions in Factory B

In Factory B, fugitive emission resulted in total VOC concentration of 1.18 mg/m^3 in workshop, which was about 6% of that from stack exhaust (20.57 mg/m^3) (Table 1). Comparing with stack exhaust, fugitive emission was a minor contributor to VOCs in the workshop of the factory. In addition, the oxygenated compounds (e.g., tetrahydrofuran) contributed to 95% of VOCs from stack exhaust, while 70% of

fugitive emission of VOCs contained halogenated compounds (e.g., dichloromethane) (Fig. 1). This finding was similar to the VOC pollution profile between stack exhaust and fugitive emission in the workshop of Factory A. These results further emphasized diversity in VOC distribution between stack exhaust and fugitive emission, although they were seemingly originated from the same workshop.

A significant reduction in concentration of VOCs from fugitive emission (0.30 mg/m^3) was obtained in comparison with that from stack exhaust (17.13 mg/m^3) in the sewage treatment station (Table 1). Approximate 50% of VOCs from stack exhaust included oxygenated compounds and this proportion dropped to 20% for VOCs from fugitive emission (Fig. 1). On the contrary, much higher proportion of aromatic compounds was found from fugitive emission (16%) relative to stack exhaust (1%). These results suggested that leaked VOCs from sewage treatment station played a non-negligible contribution in the total VOC emission from this functional unit of Factory B.

A high concentration of VOCs from fugitive emission (30.53 mg/m^3) was observed in the hazardous waste storage (Table 1). Dichloromethane was found to be a dominated constitute in this functional unit, accounting for over 90% of the total VOCs from fugitive emission. This pollutant might be preferentially originated from volatilization of used active carbon or paraffin materials for sewage treatment station than workshop, because of far higher concentration dichloromethane in the stack exhaust from the former (5.17 mg/m^3) than the latter (0.87 mg/m^3). Although high levels of VOCs from stack exhaust in the workshop and sewage treatment station or from fugitive emission in the hazardous waste storage, a low concentration of VOCs (0.26 mg/m^3) was measured in the central position of Factory B (Table 1). This result implied that VOC diffusion after discharged from functional units in Factory B showed a minor effect on VOC pollution in the surrounding atmospheric environment.

2.3. Pollution characteristics of VOCs from stack and fugitive emissions in Factory C

About 7.37 mg/m^3 of VOCs was detected from stack exhaust in the workshop (Table 1). The halogenated and oxygenated compounds accounted for 68% and 22%, respectively (Fig. 1). The total concentration of VOCs from stack exhaust in the sewage treatment station was 67.97 mg/m^3 , which was 123 times of that from fugitive emission (0.55 mg/m^3). At the same time, much higher proportion of oxygenated compounds was found from stack exhaust (26%) than fugitive emission (5%) in the sewage treatment station. Oppositely, alkane and aromatic compounds showed higher percentages from fugitive emission (13%-20%) compared with stack exhaust (below 6%). These findings suggested an unimportant role of fugitive emission in the total VOC emission from the sewage treatment station of Factory C.

The total concentration of VOCs from fugitive emission was found to be less than 1.00 mg/m^3 in the raw material storage, hazardous waste storage and central position (Table 1). The low concentrated VOCs detected in the central position at least suggested that a highly sealed workshop efficiently reduced fugitive emission of VOCs. The lowest level (0.06 mg/m^3) of ambient VOCs was found near the factory (Fig. 2). How-

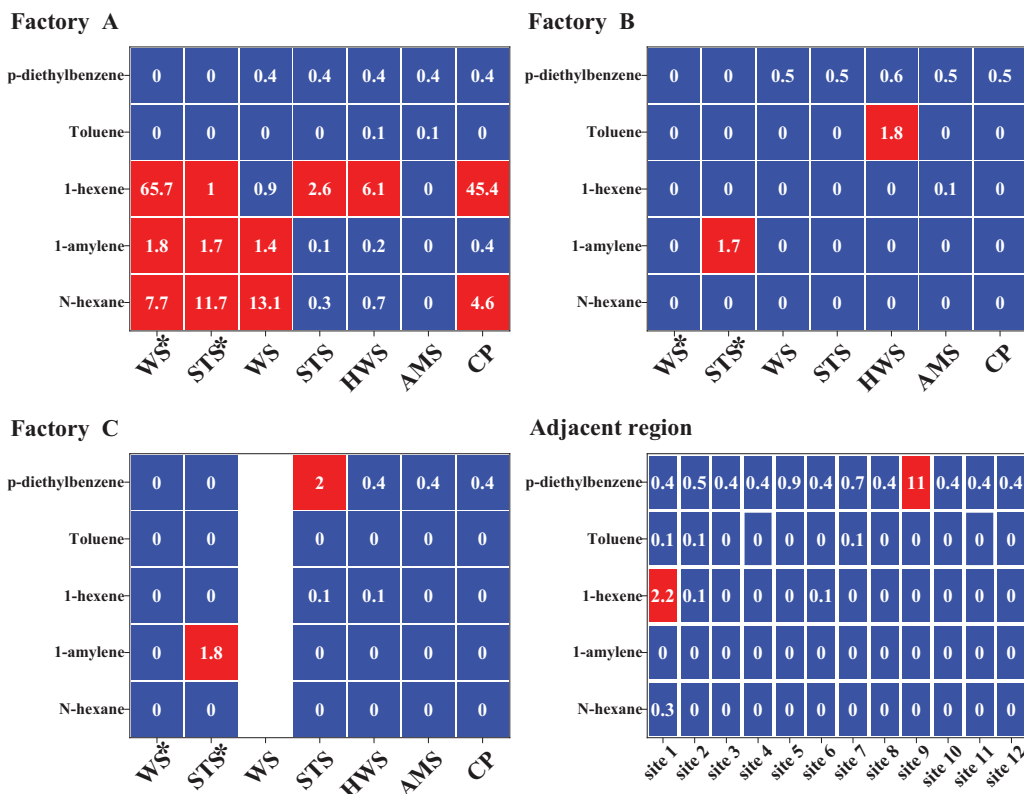


Fig. 3 – Odorous activity index of VOCs from stack and fugitive emissions in three pharmaceutical factories and their adjacent region. Blue and red colors refer to the odorous activity index below and above 1, respectively. WS* and STS* represent stack exhaust in the workshop and sewage treatment station, respectively.

ever, another site near Factory C still remained a relatively high value of ambient VOCs (0.75 mg/m³) (Fig. 2). Moreover, the main constituent of ambient VOCs in the site consisted of aromatic compounds, which differed from the observation of VOCs inside the factory, dominated by halogenated or oxygenated compounds. This difference indicated a negligible contributing role of VOC emission from Factory C to VOC pollution at ambient atmospheric environment nearby.

2.4. Odorous characteristics of VOCs in three factories

The odorous activity index of individual compound above 1 was considered as be perceived by human, while that below 1 was deemed as the odorless of individual compound (Nie et al., 2020). Fig. 3 showed the odorous activity index of detected VOCs. The odorous activity index exceeding 1 for VOCs from stack exhaust in workshop was only observed in Factory A, and these VOCs included n-hexane, 1-amylene and 1-hexene. The odorous activity indexes of n-hexane and 1-amylene from fugitive emission in workshop of Factory A were 13 and 1 (Table S5), very close to 8 (n-hexane) and 2 (1-amylene) from stack exhaust. These two VOCs from stack exhaust in sewage treatment station of Factory A also showed odorous activity indexes of over 1. In this same functional unit of Factory A, the odorous activity index over 1 was also observed for 1-hexene from fugitive exhaust. Moreover, odorous activity index of n-hexane or 1-hexene above 1 was found

from fugitive emission in hazardous waste storage and central position.

In Factory B, all VOCs in workshop from stack emission showed odorous activity indexes of below 1. However, the odorous activity index of 1-amylene from stack emission in sewage treatment station exceeded 1. Conversely, there was no exceeding odorous activity index threshold for VOCs from fugitive emission in the sewage treatment station. Presence of toluene in hazardous waste storage of Factory B also led to the odorous activity index of total VOCs higher than 1. As for Factory C, the odorous activity index above 1 in the sewage treatment station was found attributing from 1-amylene and p-diethylbenzene for stack exhaust and fugitive emission, respectively. The odorous activity index in the rest functional units of Factory C was lower than 1.

The PCA analysis of E-nose data are further shown in Fig. 4. The first (PC1) and second (PC2) principal components represented 80% and 10% of the total variation, indicating more important role of PC1. In Factory A, VOCs from stack exhaust in workshop and sewage treatment station differed from other functional units in the PC1. It was also found that aliphatic organic compounds was positively relation with the PC1 (Fig. S3), supporting the contribution of n-hexane and 3-methylpentane to odor in workshop or sewage treatment station, as discussed previously. In Factory B and Factory C, VOCs from stack exhaust in sewage treatment station was separated from other functional units in the PC1. Inorganic sulfur and

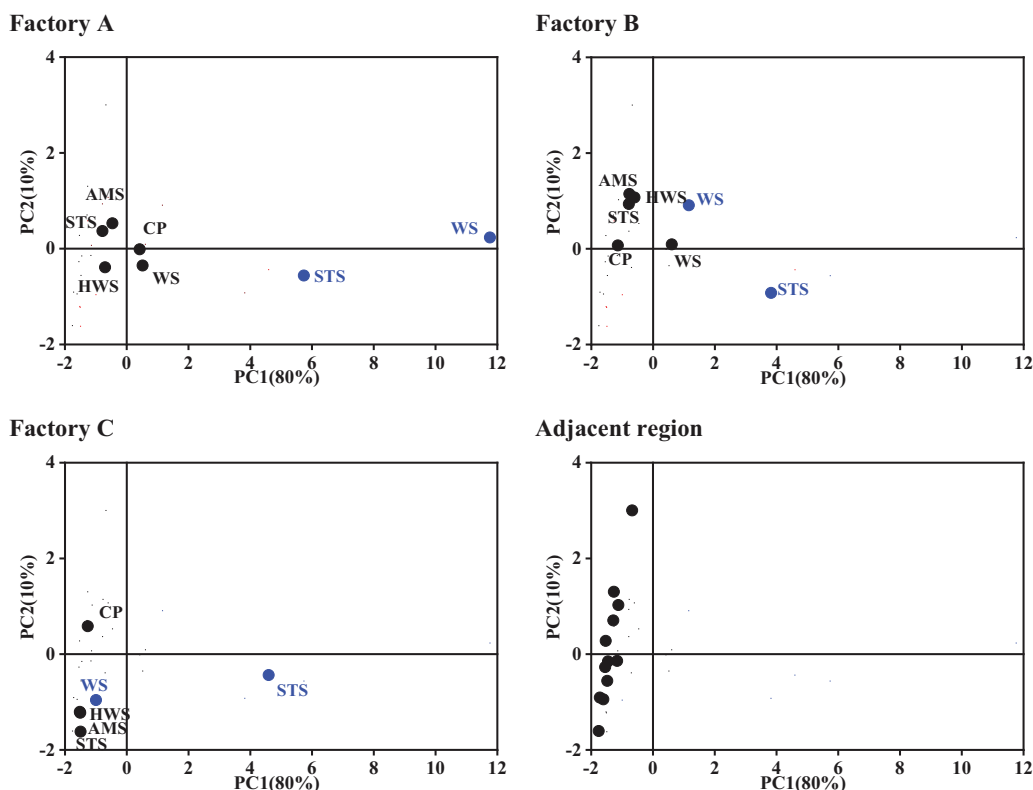


Fig. 4 – The PCA results of VOCs from stack and fugitive emissions in three pharmaceutical factories and their adjacent region measured by E-nose. Blue color represents stack exhaust.

sulfur-containing organic compounds were also positively related with the PC1 (Fig. S3). Notably, VOCs from stack exhaust in sewage treatment station of three factories showed similar feature in the PC1 (Fig. 4), suggesting that the odor was also affected by sulfur-containing compounds, though they were not measured in this study.

2.5. Non-cancer and cancer risk assessment of VOCs in three factories

Fig. 5 displays HR values of VOCs from stack or fugitive emission in three factories and adjacent region. HR value above 1 was exceeding the benchmark of non-cancer risk level (Hoddinott and Lee, 2000). The HR values of n-hexane and dichloromethane from stack exhaust in workshop and sewage treatment station of Factory A were 6 and 3, respectively (Table S6). n-Hexane (HR value of 11) and dichloromethane (HR value of 3) from fugitive emission in workshop and central position of Factory A also showed high HR values. In Factory B, HR value exceeding 1 was only measured on dichloromethane (HR value of 5) from the hazardous waste storage. Dichloromethane (HR value of 8) and 1, 2-dichloroethane (HR value of 3) from stack exhaust in sewage treatment station of Factory C exceeded the benchmark of non-cancer risk level. These findings suggested that n-hexane and dichloromethane had relatively high non-cancer risks for workers in the studied pharmaceutical factory.

The HR value exceeding 1 was found for acrolein at many sites of three factories. Additionally, the HR value of acrolein

greater than 1 was observed in the adjacent region of the three factories, while other compounds showed HR values below 1. A common feature of acrolein above the benchmark non-cancer risk level had also been reported in many regions, such as industrial, urban and suburban areas (Li et al., 2020; Yang et al., 2019b; Zheng et al., 2020). Therefore, acrolein above the benchmark of non-cancer risk level in this study was likely due to its relatively high background level.

LCR values of VOCs from stack or fugitive emission in three factories and adjacent region are shown in Fig. 6. The LCR value greater than 10^{-6} was considered as the benchmark of cancer risk level (McCarthy et al., 2009). Both dichloromethane and ethylbenzene from stack exhaust in three factories exceeded the benchmark of cancer risk level. For fugitive emission in the workshop, LCR value of dichloromethane only in Factory A showed potential cancer risk (1.6×10^{-5}) (Table S7). In addition to dichloromethane and ethylbenzene, chloroform, p-dichlorobenzene, 1,2-dichloroethane and 1,2-dichloropropane from fugitive emission in all functional units as well as central position of both Factory A and Factory B also exceeded cancer risk level. Moreover, the decrease in cancer risk levels of benzene, ethylbenzene, dichloromethane and 1,2-dichloropropane from fugitive emission in Factory C was found. In addition, these constituents measured in adjacent region of three factories also displayed LCR values higher than benchmark of cancer risk level. Higher level of dichloromethane from fugitive emission in Factory A was compared with that in the adjacent region, as previously discussed. It suggested that dichloromethane in the adja-

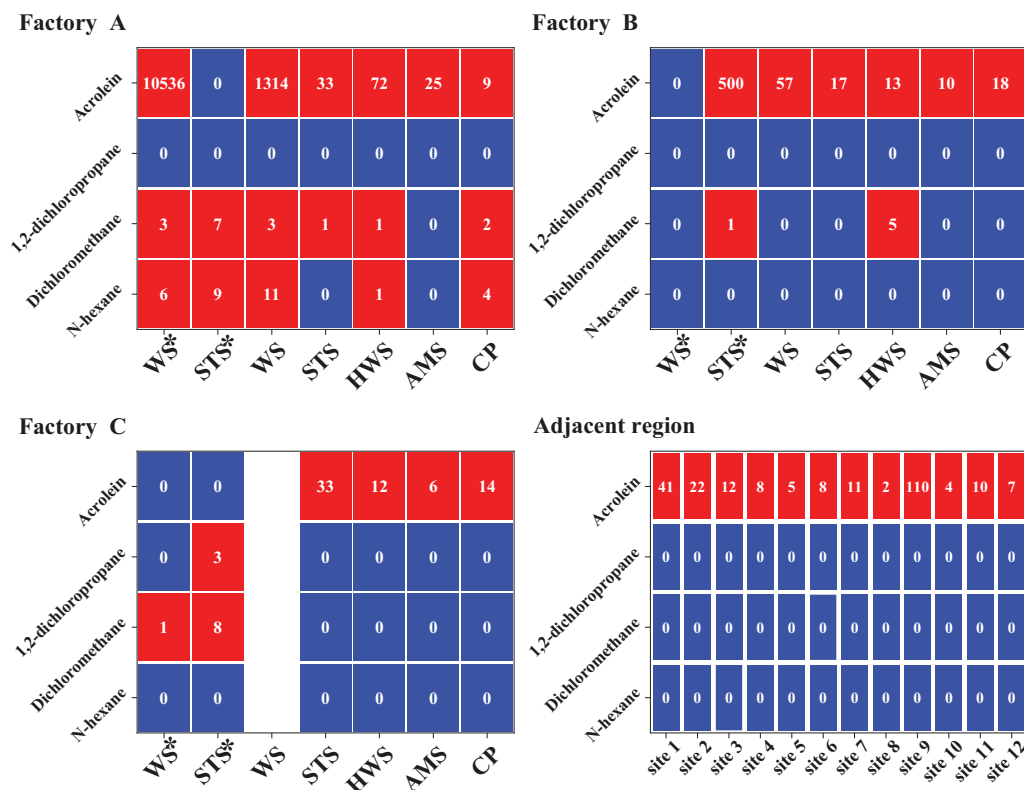


Fig. 5 – Hazard ratio (HR) values of mainly VOCs from stack and fugitive emissions in three pharmaceutical factories and their adjacent region. Blue and red colors refer to the HR below and above 1, respectively. WS (workshop), STS (sewage treatment station), AMS (raw material storage), HWS (hazardous waste storage), CP (central position). WS* and STS* represent stack exhaust in the workshop and sewage treatment station, respectively.

cent region was mainly originated from Factory A, in turn, increase in its cancer risk. Concentration of other VOCs (e.g., chloroform, 1,2-dichloropropane and p-dichlorobenzene) in Factory A, Factory B or Factory C was comparable to that in the adjacent regions of the three factories (Table S8). Relatively high background level of these VOCs in this studied region looked likely to increase their cancer risk levels.

3. Discussion

Our result showed that VOC compositions were highly dependent on pharmaceutical factories. Alkane, alkene and halogenated compounds dominated in Factory A, while proportions of aromatics and oxygenated compounds were found to increase in other two factories. Wide variety of raw materials and complex production processes would lead to changes in VOC compositions in different pharmaceutical factories and made it complicated to determine the VOC characteristics (Cheng et al., 2021). Moreover, the difference in VOC species between stack exhaust and fugitive emission in the same workshop further highlighted the complicated source of VOCs in the pharmaceutical factory.

Abundant n-hexane, 3-methylpentane, 1-hexene and dichloromethane were released from stack exhaust in the workshop of Factory A. These compounds also showed high

concentrations in the central position of the same factory. On the contrary, although high levels of VOCs from stack emission (i.e., oxygenated compounds) were detected in Factory B and Factory C, low concentrated these VOCs species were observed in the central position of two factories. Extreme high level of VOCs from stack exhaust in the workshop of Factory A (209.69 mg/m³) relative to Factory B (20.57 mg/m³) and Factory C (7.37 mg/m³) might lead to large amounts of VOCs in the workshop spreading into the central position of Factory A. The improvement of treatment process for VOCs from stack emission in the workshop was motivated to reduce amount of VOC emission.

Moreover, fugitive emission of VOCs in the workshop of Factory A represented 31% of total VOCs, and this proportion reduced to 5% in Factory B. Therefore, VOCs from fugitive emission in the workshop of Factory A would further increase the pollution level of VOCs in the central position. Previous study pointed out that the concentration of VOCs from fugitive emission in pharmaceutical factory were ten times of the background (Chen et al., 2017). Furthermore, fugitive emission of industrial activity became the most significant source of VOCs in China (Simayi et al., 2021). The improvement of production processes, airtightness of equipment, pipelines and valves, leak detection and repair system were the effective methods to reduce fugitive emission of VOCs, contributing for more than 40% of the total reduction (Simayi et al., 2021). Therefore, it was expected that the complete airtightness of

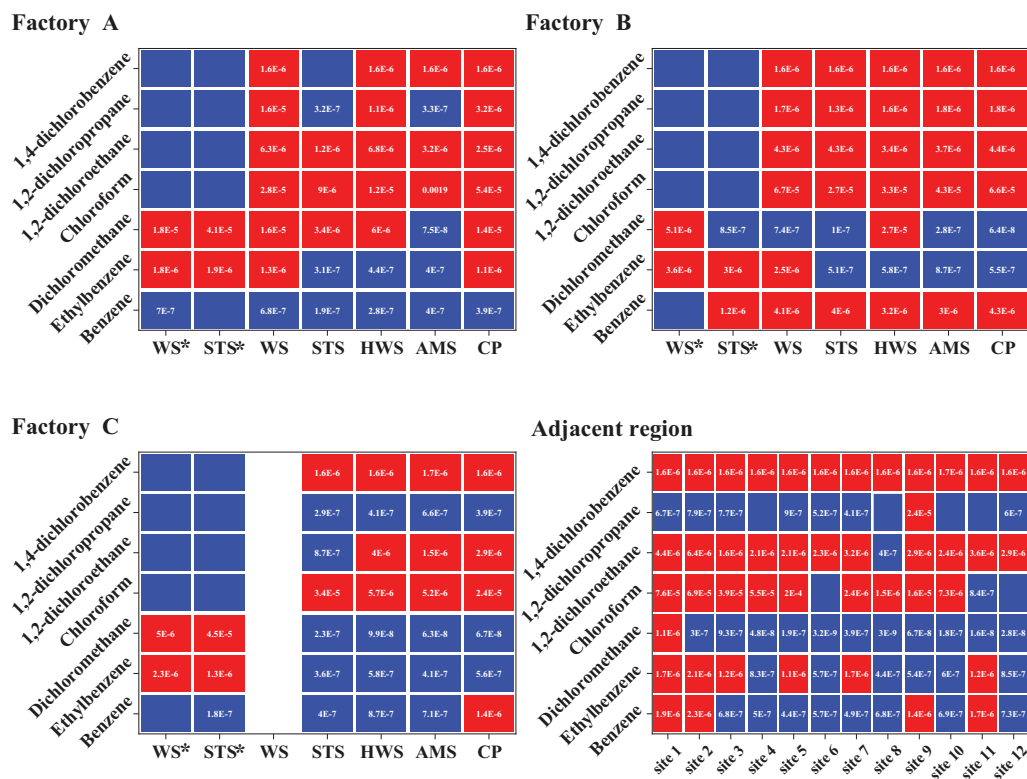


Fig. 6 – Lifetime cancer risk (LCR) values of VOCs from stack and fugitive emissions in three pharmaceutical factories and their adjacent region. Blue and red colors refer to the HR below and above 10^{-6} , respectively. WS (workshop), STS (sewage treatment station), AMS (raw material storage), HWS (hazardous waste storage), CP (central position). WS* and STS* represent stack exhaust in the workshop and sewage treatment station, respectively.

the equipment or lines in the workshop of Factory A might reduce the total VOC emission by up to 40%.

The odorous activity index of VOCs from stack emission was above 1 in the sewage treatment station of Factory B and Factory C, due to the presence of 1-amylyene. However, odorous activity index of 1-amylyene was below 1 in the central position of the two factories and their adjacent region. This suggested a minor contribution of VOCs from stack emission to the odorous activity index in the boundary of the two factories. In addition to 1-amylyene, high levels of n-hexane and 1-hexene from stack emission in the sewage treatment station and workshop also led to exceed their odorous activity index threshold in Factory A. Moreover, odorous activity index of n-hexane and 1-hexene were also found above 1 in the central position of Factory A and its adjacent region. It was unlikely resulted from sewage treatment station emission because the odorous activity indexes of both n-hexane and 1-hexene from fugitive emission in the sewage treatment station of Factory A were below 1. It should be noted that some compounds (e.g., H_2S) from sewage treatment station might enhance odor (Godio et al., 2018), though they were not measured in this study. Additionally, odorous activity index above 1 of VOCs from fugitive emission in the workshop of Factory A included n-hexane and 1-hexene. This might also increase odorous activity index of VOCs in the central position of Factory A and its adjacent region. Therefore, the odorous activity index of VOCs in the boundary of Factory A would be affected

by not only stack exhaust from the workshop, but also fugitive emission from the workshop. Previous studies showed that odorous feature of VOCs in the pharmaceutical factory could be attributed to varying constitutes including acetaldehyde, m-xylene, acetone, acetaldehyde, 1-propanol, acetone, benzaldehyde, and 2-methylisoborneol (Yang et al., 2015, 2019b). The diversity in odorous constitutes within difference pharmaceutical factories was due to wide variety of raw materials and complex production processes, as pervious discussed. Yang et al. (2015) performed the quantitative analysis of the VOCs using TO-15 gas standards. Yang et al. (2019b) used gas standards including PAMS and a mixture of oxygenated VOCs and halocarbons to obtain characteristic of VOCs. In this study, the TO-15 and PAMS gas standards were used to calibrate concentration of VOCs. The difference in using gas standards may also lead to the varying constitutes of VOCs in the pharmaceutical factories.

HR values of n-hexane and dichloromethane in the central position of Factory A exceeded non-cancer risk level, mostly resulted from the diffusion of stack exhaust and fugitive emission in the workshop, as discussed previously. HR values of n-hexane and dichloromethane from stack emission were above non-cancer risk level in the sewage treatment station of Factory A. However, this feature was not found in the VOCs from fugitive emission. These results indicated that contribution of sewage treatment station to HR values of n-hexane and dichloromethane in the central position was minor. There was

not observed that the exceeding non-cancer risk level of n-hexane and dichloromethane in the adjacent region of Factory A. This suggested that non-cancer risk of n-hexane and dichloromethane only existed inside Factory A. Similarly, exceeding cancer risk levels of dichloromethane and chloroform in the central position of Factory A was likely due to the diffused VOCs from the workshop. However, such feature was not observed in Factory B and Factory C. Other study found that mainly toxic VOCs in the pharmaceutical factory also included chloroform (Cheng et al., 2021). Their results also showed that fugitive VOCs in functional unit was more harmful to the employees than stack VOCs (Cheng et al., 2021). These findings emphasized that toxic VOCs from fugitive emission in the pharmaceutical factory cannot be ignored, especially in workshop.

4. Conclusions

The characteristics, odorous activity index and health risk of VOCs were performed in the workshop, sewage treatment station, raw material storage and hazardous waste storage as well as adjacent regions of three representative pharmaceutical factories. Workshop was the main contributor to VOC emission. The main components of VOCs in the workshop consisted of n-hexane, 1-hexene, dichloromethane and some oxygenated (e.g., tetrahydrofuran) compounds, but their proportions depended on factories. Extreme high concentrations of VOCs from stack and fugitive emissions in the workshop led to the increase in odorous activity index and health risk of VOCs in the workshop, interior or adjacent region of Factory A. This feature was not found in other two factories, mostly due to better on treatment technology for stack exhaust and on airtightness of equipment, pipelines and valves of their workshops. These diversities highlighted that fugitive emission should be taken into account except for stack exhaust, in order to reduction on emission, odorous activity index and health risk of VOCs in the pharmaceutical factory.

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Appendix A Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jes.2022.03.005.

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