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Research Article

VOC emitted by biopharmaceutical industries: Source profiles, health risks, and secondary pollution

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ABSTRACT

The biopharmaceutical industry contributes substantially to volatile organic compounds (VOCs) emissions, causing growing concerns and social developmental conflicts. This study conducted an on-site investigation of the process-based emission of VOCs from three biopharmaceutical enterprises. In the workshops of the three enterprises, 26 VOCs were detected, which could be sorted into 4 classes: hydrocarbons, aromatic hydrocarbons, oxygen-containing compounds, and nitrogen-containing compounds. Ketones were the main components of waste gases, accounting for 44.13%–77.85% of the overall VOCs. Process-based source profiles were compiled for each process unit, with the fermentation and extraction units of tiamulin fumarate being the main source of VOC emissions. Dimethyl heptanone, vinyl acetate, diethylamine, propylene glycol methyl ether (PGME), and benzene were screened as priority pollutants through a fuzzy comprehensive evaluation system. Ground level concentration simulation results of the Gauss plume diffusion model demonstrated that the diffusivity of VOCs in the atmosphere was relatively high, indicating potential non-carcinogenic and carcinogenic risks 1.5–2 km downwind. Furthermore, the process-based formation potentials of ozone and secondary organic aerosols (SOAs) were determined and indicated that *N*-methyl-2-pyrrolidone, dimethyl heptanone, and PGME should be preferentially controlled to reduce the ozone formation potential, whereas the control of benzene and chlorobenzene should be prioritized to reduce the generation of SOAs. Our results provide a basis for understanding the characteristics of VOC emission by biopharmaceutical industries and their diffusion, potentially allowing the development of measures to reduce health risks and secondary pollution.

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Introduction

China is a major producer of active pharmaceutical ingredients (APIs), such as antibiotics and vitamins. The Chinese biopharmaceutical industry has developed rapidly since 2015, with an annual growth rate of approximately 20%. However, fermentation, extraction, and other processes during the manufacturing of pharmaceutical products generate odorous organic waste gases. As many of these gases are released into the environment, the biopharmaceutical industry has become a significant source of volatile organic compound (VOC) pollution.

VOCs are compounds that have a high vapor pressure and low water solubility. Many VOCs are human-made chemicals that are used and produced in the manufacture of paints, pharmaceuticals, and refrigerants. The diverse processes used to manufacture pharmaceutical products result in complex and diverse VOC emissions. Ethyl acetate and acetone, oxygen-comprising VOCs, account for 26.63% and 8.80%, respectively, of the VOCs emitted by the pharmaceutical industries (Li et al., 2014). Benzene, toluene, methylene chloride, chloroform, and ethanol are common components of chemical pharmaceutical waste gas (Li et al., 2014). He et al. (2015) established biopharmaceutical VOC source profiles and found that ketones (e.g. acetone) account for more than 50% of the VOCs from different processes, and the emission ratio of alkanes (e.g. *n*-pentane) in the extraction unit ranges from 12.90% to 16.04%.

VOCs pose a substantial threat to human health because of their carcinogenicity, teratogenicity, and mutagenecity (Massolo et al., 2010; Rumchev et al., 2007; WHO, 2000). They can also cause respiratory tract irritation and central nervous system damage (Durmusoglu et al., 2010). Numerous studies have investigated the chronic toxicity and carcinogenic risks of VOCs from different sources, such as motor vehicle exhausts (Wang et al., 2020), industrial processes (Zheng et al., 2020), waste treatment (Nair et al., 2019; Zhang et al., 2020), wastewater treatment (Saber et al., 2020; Yang et al., 2019), and indoor human settlements (Dai et al., 2017). However, there have been few reports on the characteristics and risks of VOCs from the biopharmaceutical industry.

Fugitive VOCs from pharmaceutical processes can cause occupational exposure risks to workers, while VOCs emitted through the chimney can affect the health of nearby residents after atmospheric dispersion. Therefore, elucidating the diffusion patterns of pollutants is essential for health risk assessments. Simulations of the ground-level concentrations of pollutants dispersed and diluted through the mixing action of turbulence can be used as a critical reference for evaluating diffusion-based health risks. Air quality models, such as the Gauss plume models, community multiscale air quality models, and comprehensive air quality models with extensions, have been wildly applied to simulate the transportation and diffusion of air pollutants. Studies on the spatial diffusion of VOCs from multiple sources (Lin et al., 2021) have verified the risks of VOC diffusion. For example, Wang et al. (2021a) showed that the impacts of VOCs can reach up to 16 km from the emission source on heavy pollution days. Zhang et al. (2020) used computational fluid dynamics under an unsteady state to simulate the diffusion of VOCs from industrial parks and observed that VOC concentrations outside and inside an industrial park were 13.0% and 24.2% higher than background values, respectively.

The adverse impacts of VOC pollution also include associated contributions to secondary pollution, such as the formation of tropospheric ozone (which causes photochemical smog) and secondary organic aerosols (SOAs; the main component of total aerosol mass) (Ramírez et al., 2012; Williams and Koppmann, 2007). According to Huang et al. (2014) and Guo et al. (2014), VOCs are critical for the formation of haze. In 2020, the 90th percentile average value of the maximum 8 h ozone concentration in 337 cities in China was 138 $\mu g/m^3$, showing a 12.6% increase from the level in 2015 (Zhang, 2021), with VOCs playing a crucial role in this increase. Huang at al. (2014) investigated the proportion of organic matter in fine particulate matter ($PM_{2.5}$) in four representative cities in China and found that organic aerosols accounted for 30%–50% of overall $PM_{2.5}$ on average Generally, anthropogenic VOC emissions from the industrial sector (especially solvent use and processes) account for nearly half of ozone generation and approximately 60% of SOA formation in most Chinese provinces (Wu et al., 2017b). Although the composition and concentration level of VOCs varies considerably by source, aromatic compounds and ketones are often the main contributors to ozone formation and SOA production from VOCs (Ma et al., 2021; Lv et al., 2021; Gao et al., 2021).

There have been few studies on VOCs emitted by the biopharmaceutical industry. However, odour pollution from the production of antibiotic APIs has become increasingly prominent and led to increasing public complaints. The pharmaceutical industry requires a variety of raw materials and complex production processes. Moreover, the intermittent and irregular emissions of exhaust gases increase the complexity of VOC emissions (Liu et al., 2019). This study aimed to investigate the emission characteristics, health risks, and environmental impacts of gaseous pollutants from three biopharmaceutical enterprises by identifying and quantifying the chemicals from different phases (fermentation and extraction). The assessment of health risks involved the potential risks to surrounding residents after diffusion. The environmental impact evaluation included forecasting potential effect areas and quantitatively estimating ozone and SOA. The results of this study are expected to provide a scientific basis for the pollution control and risk management of VOCs emitted by biopharmaceutical industries.

1. Materials and methods

1.1. *Biopharmaceutical enterprises description*

We selected three biopharmaceutical enterprises in a biomedical industrial park in Ningxia province, China, for investigation. The three biopharmaceutical enterprises, NW-1P, NW-2P and NW-3P, mainly produce veterinary antibiotic and veterinary APIs, including tylosin tartrate, tiamulin fumarate, and Vitamin B12 (VB12). Profiles of biopharmaceutical enterprises are shown in Table 1. Waste gases were expelled from work-

Table 1 – Profiles of biopharmaceutical enterprises.

Enterprises	NW-1P		NW-2P		NW-3P	
Main products	tylosin		tiamulin fumarate		VB12	
Workshop	fermentation	extraction	fermentation	extraction	fermentation	extraction
Mission mode	organized emission in high stack					
Waste gas emission (m^3/hr)	12000	2500	12000	50000	6000	5000
Chimney geometric height (m)	25	25	25	25	25	25

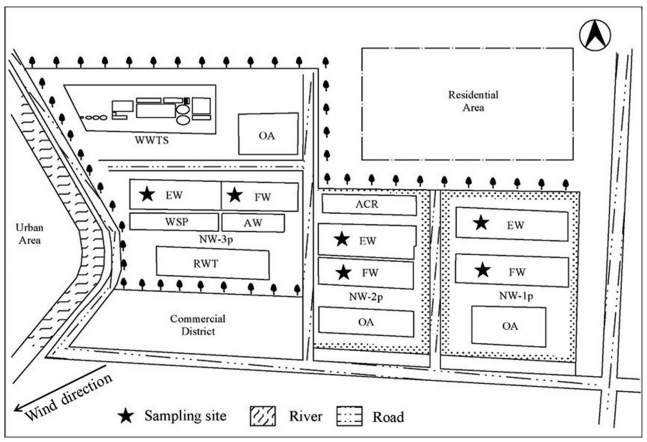

Fig. 1 – Schematic diagram of sampling sites. FW: fermentation workshop; EW: extraction workshop; OA: office area; WSP: water supply plant; AW: Additive workshop; RWT: recirculating water treatment; ACR: air compressor room; WWTS: waste water treatment station.

shop chimneys using a forced draft fan. VOCs were sampled from the access hole on the chimney of each workshop. A schematic diagram of the sampling sites is shown in Fig. 1.

1.2. *VOC sampling and analysis*

Air samples were collected by a passive gas sampling apparatus (DL-6800C, China), which consisted of a vacuum pump and closed pressure vessel. The external gas collection pipe was connected to a TEDA bag (Hede, Dalian, China), with a volume of 20 L in the pressure vessel. When the vacuum pump was running, with the internal air being pumped out, the container gradually entered a negative pressure state. The target gases entered the TEDA bag through a vacuum nozzle due to the differential pressure. The vacuum pump was then turned off until the pressure reached equilibrium to obtain a single collection. Duplicates were conducted at each sampling site. After sampling, the bags were transported to the lab within 24 hr for analysis. The sampler was easy to operate, reliable in quality, and stable in performance, making it suitable for collecting VOCs and odorous gases from ambient air and pollution sources. The working principle of the air sampler and procedures have been described in a previous study (Wu et al., 2017a). Twice on-site investigations were carried out in July and October, with the pharmaceutical plant in normal production at the time of sampling. Samples were obtained at 6, 32, 57, 95, 120, and 140 hr of fermentation, respectively, covering one production cycle. Three parallel samples were collected at each sampling site.

Qualitative and quantitative analyses were conducted using an FTIR Continuous Gas Analyzer spectrometer (MultiGas^{TM} 2030, MKS Instruments, Inc., USA) equipped with a gas cell with a 5.11 m effective path. LN2-cooled MCT was utilized as the detector. The gases entered the spectrometer at a flow rate of 1000 mL/min, which was controlled using a mass flowmeter (S49-33 M/MT, Metron, Beijing). Before analysis, the system had to be stabilized for at least 1 hr. The spectra were acquired continuously, and the concentration of each compound was processed (Wang et al., 2017). During gas detection, the gas bag was connected to the FTIR spectrometer through the gas circulation pump, and the gas was continuously entered into the FTIR spectrometer for scanning more than 100 times. The scanned result was compared with the standard database to obtain the final result.

The pollutant emission flux was calculated by the following equation:

$$G = \frac{Q \times C_i \times 3600}{1000} \quad (1)$$

where, G (g/sec) is the emission flux of the pollutant i in the exhaust gas per unit time; Q (m^3/hr) is the emission of the stack exhaust gas per unit time; and C (mg/m^3) is the measured concentration of a pollutant.

1.3. *Fuzzy synthetic evaluation system*

The fuzzy comprehensive evaluation system provides a scientific method to simplify the monitoring of biopharmaceutical VOCs (Sivret et al., 2016). The system screens and prioritises key compounds to specify a priority list of pollutants for control. These include the threshold limit value index (TLVI; ratio of chemical concentration to threshold limit value), odour threshold index (OTI; ratio of chemical content to odour threshold), chemical content, detection rate, mean lethal dose (LD_{50}), carcinogenicity, volatility, and level of attention (Cheng et al., 2019). The obtained fuzzy comprehensive index (FSI) is equivalent to the pollutant score, and compounds with higher scores are considered to have higher priority for control.

$$FSI_i = \sum_{i=1}^{8} w_{j,i} \cdot F_{j,i} \quad (2)$$

$$\sum_{j=1}^{8} w_{j,i} = 1 \quad (3)$$

where, I refers to a certain compound, i=1,2...,8; $w_{j,i}$ is the weight coefficient for factor $F_{j,i}$. F_1, and F_2 are the concentration level and the olfactory effect, and the weight coefficient is 0.2; F_3, F_7, and F_8 are the detection rate, public attention, and volatility, respectively, and the weights are 0.1; F_4, F_5, and F_6 (TLVI, Carcinogenicity and LD_{50}) are factors related to health effects, and the weights are 0.1 (Cheng et al., 2019; Yang et al., 2019; Khan and Sadiq, 2005).

1.4. *Atmospheric diffusion model*

Considering meteorological, topographic, and emission data, a Gauss plume model was used to determine pollutant dispersion into the atmosphere. The terrain of the industrial park was classified as 'plain', and the chimney emission was classified as 'organized emission in high stack', which is regarded as the average plume of a continuous point source. The basic formula for diffusion and the assumption of distribution is shown in Text S1.

Daily wind speed data at 10 m in height were obtained from the database of Wheat A Big Data Information company (Ningbo, China). Meteorological conditions, including temperature, humidity, wind speed, and irradiance were recorded using a humidity and temperature meter (GM1361, Benetech Shenzhen, China), Anemometer (HD2303.0, Delta OHM, Italy), and irradiance meter (HD2302.0, Delta OHM, Italy), respectively. The simulation was based on the pollutant emission concentration and emission source intensity of each workshop chimney and local weather monitoring data (temperature, wind speed, and wind direction) for one year. Wind speed and direction are crucial for simulating and calculating the spatial diffusion and distribution of pollutants, respectively, and the wind direction rose diagram was plotted, as shown in Fig. S1. The dominant wind directions were northeast and north.

1.5. *Health risk evaluation*

The health effect evaluation included noncarcinogenic and carcinogenic risk assessments, which were calculated using Eqs. (4) and (5), respectively (Wang et al., 2021c; USEPA, 2022)

$$H_{Q_i} = C_i \times IR \times EF \times ED/(BW \times AT \times RfD_{-inh}) \quad (4)$$

$$CR_i = C_i \times IR \times EF \times ED \times SF_{-inh}/(BW \times LT) \quad (5)$$

where, H_{Q_i} and CR_i were the assessed indexes for noncarcinogenic and carcinogenic risk of species i; C_i (mg/m^3) is the concentration of pollutant; IR (m^3/day) is the inhalation rate; EF is the exposure frequency, days/year; ED is the exposure duration, years; BW (kg) is the average body weight; AT (days) is the averaging time for noncarcinogenic effect, days; LT is the averaging lifetime for carcinogenic effect; RfD_{-inh} (mg/(kg•day)) is the inhalation reference dose, which represents the level of the daily dose of a substance to which a human could be exposed with no adverse health effects observed; and SF_{-inh} (mg/(kg•day))$^{-1}$ is the inhalation slope factor, which is the slope of the dose-response curve under extreme low exposure. The values of the relevant parameters involved in the computational evaluation process in this study are shown in Text S1.

1.6. *Estimation of secondary pollution formation potential*

1.6.1. *Estimation of ozone formation potential (OFP)*

In this study, the propylene equivalent (Propy-Equiv) concentration method and MIR weighted concentration method (Atkinson, 2000) were applied to assess the ozone formation potential (OFP), calculated as follows:

$$C_{Prop-Equiv} = C_c \times K_{OH}/k_{Propy,OH} \quad (6)$$

where, $C_{Propy\text{-}Equiv}$ (ppm) is the Propyl-Equiv concentration of a certain chemical; C_C (ppmC) is the carbon atom concentration of a certain chemical; K_{OH} and $k_{Propy,OH}$ are the chemical reaction rate (cm^3/(molecule·sec)) in different conditions. The values of K_{OH} and $k_{Propy,OH}$ used in this study were obtained from Atkinson and Arey (2003).

$$C_{i,MIR} = MIR_i \times C_{j,ppbv} \times M_i/M_{O_3} \quad (7)$$

where, $C_{i,MIR}$ (ppmv) is the MIR-weighted concentration of a certain chemical; MIR_i (g O_3/g VOCs) is the MIR coefficient of species i ; $C_{i,ppmv}$ (ppbv) is the concentration of a certain chemical; and M_i and M_{O3} are the relative molecular mass of species i and O_3, respectively. The MIR coefficients for the corresponding compounds were obtained from previous studies (Venecek et al., 2018; Xiong and Du, 2020)

Source reactivity (SR) was used to evaluate the ozone generation capacity of different emission sources (Yuan et al., 2010; Ma et al., 2021), calculated as:

$$SR = \sum_{i=1}^{n} F_i \times MIR_i \quad (8)$$

where, SR (g/g) is the amount of ozone generated at 1 g of VOC emission, and Fi (%) is the mass fraction of species i.

1.6.2. *Estimation of SOA formation*

The formation potential of an SOA (SOAP) represents the tendency of an SOA to form when a certain compound enters the ambient atmosphere. Currently, a method based on the fractional aerosol coefficient (FAC), which was proposed based on Grosjean's smog chamber experimental results (Daniel, 1992; Daniel and John, 1989), is widely used to calculate the SOAP. The method used in this study is expressed in Eq. (8):

$$SOAP_{ij} = \omega_{ij} \times FAC_i \quad (9)$$

where ω_{ij} (g VOCs)$^{-1}$ is the mass fraction of VOC species i in workshop j, g VOC species i and FAC_i (%) is the fractional aerosol coefficient of VOC species i, which was obtained from Grosjean's copious smog chamber experimental results (Daniel, 1992; Daniel and John, 1989).

2. Results and discussion

2.1. *Emission characteristics of VOCs*

2.1.1. *VOC emissions*

In total, 26 VOCs were detected in the samples collected from the fermentation workshops (FW) and extraction workshops

(EW) of three pharmaceutical enterprises producing tylosin, tiamulin, and vitamin B12 (VB12). The identified VOCs could be divided into four groups: hydrocarbons, aromatic hydrocarbons, oxygen-containing compounds (e.g. ketones, lipids, amines, ethers, aldehydes, alcohols, and acids), and nitrogen-containing compounds. Oxygen-containing compounds were the most abundant VOC category, accounting for 70.08%–89.65%, followed by nitrogen-containing compounds (7.55%–25.42%), and aromatic hydrocarbons (0.33%–5.23%). For the pharmaceutical industry in this study, lower concentration production of VOC in FW compared with that the concentration of EW. A lower concentration of VOCs was produced in the fermentation stage than in the extraction stage. The fermentation stage involves seed culture and multi-stage fermentation while the extraction stage involves lengthy and complex processes, such as filtration, refining, crystallisation, organic extraction, centrifugation and washing, leading to increased VOC production. The VB12 production line emitted the highest concentration of all pollutants, with total chemical concentrations of 4985.87 and 5890.03 mg/m^3 at FW and EW, respectively, whereas the tylosin production line emitted the lowest TCC of pollutants, with 3556.54 and 4401.15 mg/m^3 in the FW and EW, respectively. However, process-based pollutant emissions were more related to the emission fluxes than to the concentration level. The largest calculated emission fluxes of FW and EW originated from the production of tiamulin fumarate, at 20.56 and 51.13 g/sec, respectively. Considering the concentration and flux of pollutants, the enterprise of tiamulin fumarate showed the highest emissions. High concentrations of *N*-methyl-2-pyrrolidone (M-Pyrol), dimethyl heptanone, and methyl isobutyl ketone were detected in FW and EW (Fig. 2). As a representative ketone, the detected concentration of M-Pyrol in FW (889.29–2621.34 mg/m^3) was usually higher than that in EW (657.41–936.59 mg/m^3). Dimethyl heptanone was detected in all pharmaceutical processes at concentrations ranging from 332.36 to 1116.82 mg/m^3. Methyl isobutyl ketone was only observed in the production of tiamulin and VB12, at concentrations of 442.81 mg/m^3 (FW) and 886.49 mg/m^3 (EW) for tiamulin and 328.87 mg/m^3 (FW) and 473.12 mg/m^3 (EW) for VB12. The characteristic contaminant detected in FW for tiamulin was 2-pentanone, with a concentration of 365.94 mg/m^3. Ketones are frequently reported in the air quality monitoring of pharmaceutical enterprises. Near a biopharmaceutical plant in a biomedicine park in East China, the concentrations of acetone and methyl ethyl ketone in the atmosphere were 23.4 and 13.8 μg/m^3, respectively (Pan et al., 2011). A series of reports by the Office of Air Quality Planning and Standards of Environmental Protection Agency (EPA) VOCs addressed ketone emissions from the production of synthetic pharmaceutical products (USEPA, 1978). These reports indicated that ketones, such as acetone and methyl isobutyl ketone, are commonly released and volatilised during pharmaceutical extraction and liquid storage in American industries (Zobel and Feird, 1978).

The proportion of lipids in the off-gases released from the fermentation and extraction processes was 11.96%–19.74% and 2.55%–17.06%, respectively. Isobutyl acetate, vinyl acetate, and *n*-butyl acetate were the main lipid components. Amongst them, the concentration of butyl acetate in the fermentation and extraction stages of tylosin was the highest, at 469.80 and 358.49 mg/m^3, respectively. Propylene glycol methyl ether (PGME), the main ether substance, contributed 3.45%–16.75% and 8.45%–23.74% of the total VOCs emitted from the fermentation and extraction stages, respectively (Fig. S2).

Amongst the detected aromatic hydrocarbons in this study, benzene and chlorobenzene had the highest concentrations at 44.61–110.73 and 12.31–102.09 mg/m^3, respectively. A similar phenomenon was observed in a study by Chen et al. (2020), in which the benzene concentration in the exhaust tube of a fermentation biopharmaceutical company reached 182.67 mg/m^3. Diethylamine was the main nitrogen-containing compound, accounting for 7.55%–11.15% and 8.45%–23.74% of the total VOCs in the fermentation and extraction stages, respectively.

Amongst the investigated pharmaceutical processes, VB12 production released the greatest variety of VOCs, especially during fermentation. For instance, 2,4-toluene diisocyanate, ammonia, acetaldehyde, hexanal, and *n*-butyl acetate were detected only during the production of VB12, at concentrations of 19.70, 39.45, 125.97, 106.32, and 498.84 mg/m^3, respectively. Methyl acrylate and 2,4-toluene diisocyanate were detected only in the extraction stage of VB12 production at concentrations of 341.94 and 51.59 mg/m^3, respectively. In previous research, the concentration of ammonia detected in the fermentation off-gas from erythromycin, tetracycline, and tylosin production ranged from 0.068 ± 0.014 to 1.000 ± 0.430 mg/m^3 (Yang et al., 2020). According to Cheng et al. (2021), acetaldehydes account for approximately 1.2% of the total VOCs in the enrofloxacin production line, consistent with our results.

2.1.2. *Causes for VOC generation*

The final products of the three pharmaceutical enterprises investigated in this study were primarily antibiotics and vitamins, and their main production processes were similar. Soybean oil, soybean meal, corn meal, yeast powder, beet sugar, maltose, and glucose were used as raw materials for the culture medium, and the products were extracted from the fermentation broth after bacterial fermentation. Tylosin, tiamulin, and VB12 were produced by *Streptomyces*, *Trichoderma*, and *Clitopilus passeckerianus* (or *Pseudomonas*), respectively.

During the fermentation process, the protein and amino acids in the raw materials undergo decarboxylation and deamination reactions via the action of microorganisms to generate the corresponding primary amines. These amines are biologically oxidised to aldehydes and ammonia. In the fermentation stage of tylosin, citric acid is typically added to the fermentation broth to adjust the pH; this can lead to the denaturation and decomposition of protein substances, which is a potential production pathway for amines. The synthesis of tiamulin involves the introduction of sulfonic acid groups or sulfonyl chloride groups into organic molecules containing benzene rings and the introduction of amino groups (-NH_2) into organic molecules to generate amines (Ren et al., 2013; Trivedi et al., 2005). Benzene and chlorobenzene detected in the exhaust gas are intermediate products of the sulfonation reaction, and diethylamine can also escape during the amination reaction. Aerobic or anaerobic reactions can be used

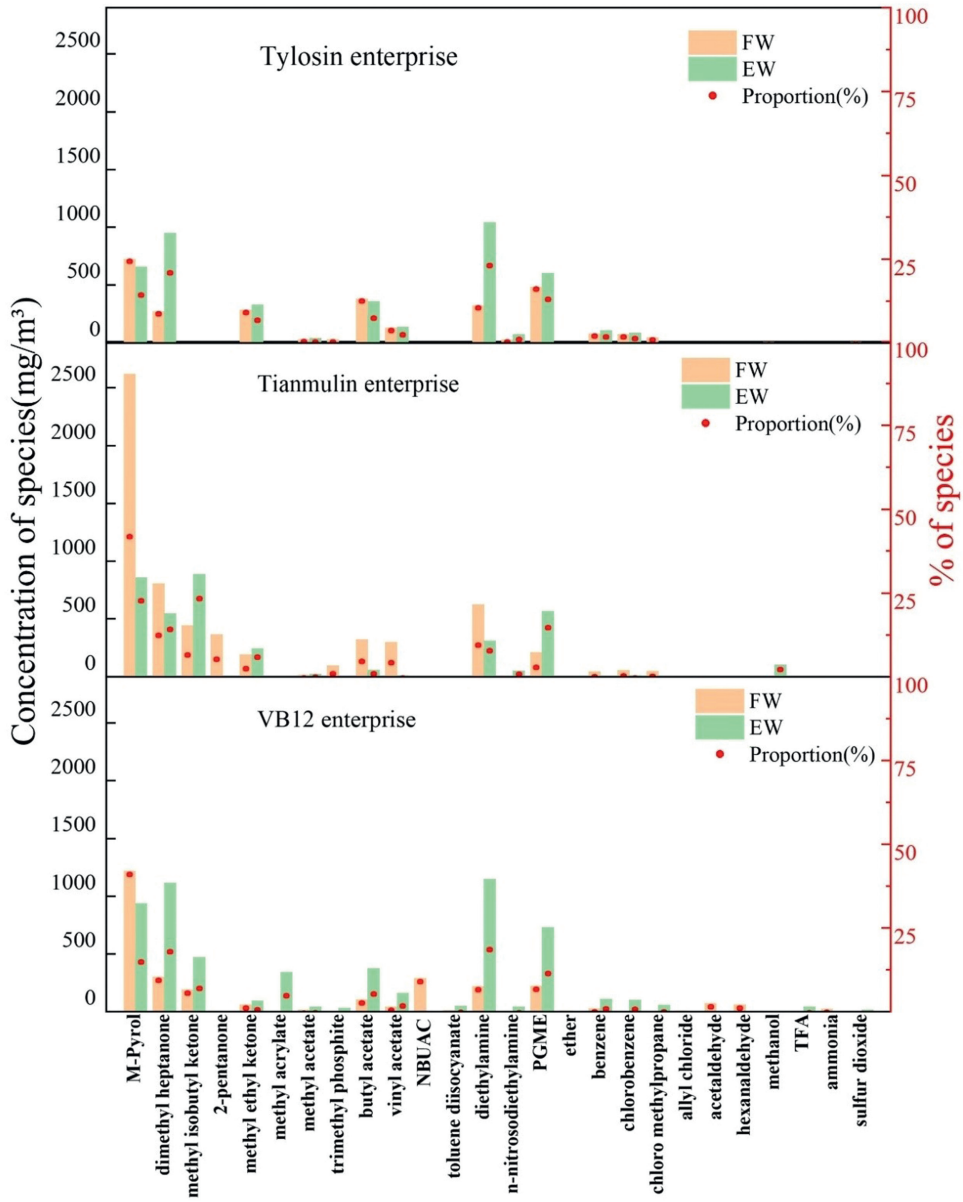

Fig. 2 – Chemical profiles of six VOC sources derived from the individual workshop of biopharmaceutical industry. Columns indicate concentrations and scatter (·) indicates the proportion of pollutants.

for the synthesis of VB12 (Xia et al., 2015), and reactions that can occur during the fermentation process include the formation of acetic acid and propionic acid, generation of benzene products by the cracking and substitution of macrocyclic organic matter, and the production of acetaldehyde and hexanal through acid-catalysed oxidation.

Environmental conditions, such as temperature and pH, can influence the emissions of odour and VOCs. Ammonia and amines exist more easily in the gaseous phase under alkaline conditions (pH > 9) than under acidic or neutral conditions. In the investigated VB12 production system, 5,6-dimethylbenzimidazole was used in the anaerobic fermentation system, ammonia was used to adjust the pH, and methyl (-CH_3) and hydroxide (-OH) groups were introduced into the reaction system, thereby promoting the volatilisation of amines. The temperature of the fermenter was maintained at 30 °C, which promoted the volatilisation of low molecular weight organic matter to the vapour phase.

The solid–liquid separation of the fermentation broth and residue was conducted using a plate and frame filter. Compared with other solid–liquid separation equipment, the plate and frame filter provide a superior separation efficiency and high solid content residue. The mixed liquid flows through the filter medium (filter cloth) and the solids gradually accumulate on the filter cloth. The filtrate permeates the filter cloth as a clear liquid, which is transported to the extraction workshop to be refined into the finished product. M-pyrrole, methyl isobutyl ketone, dimethyl heptanone, methyl ethyl ketone, and other ketones are widely used in this refining process. Methanol is a typical additive, and methyl acrylate and

Table 2 – Prioritization of VOCs.

Rank	Pollutants	tylosin		tiamulin		VB12	
		FW	EW	FW	EW	FW	EW
1	M-pyrol	2.6	2.5	2.6	2.2	2.6	2.2
2	Dimethyl heptanone	3	3.4	3.0	3.0	3.0	3.2
3	Methyl isobutyl ketone	0.9	0.9	3.1	3.1	2.7	2.8
4	2-Pentanone	0.7	0.7	2.2	0.9	0.8	0.6
5	Methyl ethyl ketone	3	2.8	2.8	2.6	2.4	2.4
6	Methyl acrylate	1.2	1.5	1.0	1.0	1.5	3.1
7	Methyl acetate	2	2.2	1.8	1.8	1.8	2.0
8	Trimethyl phosphite	2.8	1.1	2.6	1.2	1.2	2.6
9	Butyl acetate	2.9	2.7	2.5	1.8	2.4	2.5
10	Vinyl acetate	3.5	3.5	3.3	2.4	3.1	3.3
11	NBUAC	1	1	0.9	0.8	2.2	1.4
12	2,4-Toluene diisocyanate (TDI)	0.7	0.7	0.6	0.5	2.3	2.7
13	Diethylamine	3.2	3.6	3.0	3.0	3.0	3.4
14	n-Nitrosodiethylamine	2.4	2.6	1.8	2.4	1.8	2.4
15	Pgme	3.4	3.4	3.0	3.0	3.0	3.0
16	Ether	0.9	0.9	0.7	0.7	2.2	2.1
17	Benzene	3.4	3.6	3.0	1.9	3.2	3.4
18	Chlorobenzene	2.9	2.9	2.9	2.6	1.5	3.2
19	1-Chloro-2-methylpropane	1.6	0.7	1.6	1.0	1.0	2.0
20	Allyl chloride	0.8	0.8	0.6	0.6	2.4	1.2
21	Acetaldehyde	1.5	1.5	1.3	1.3	3.5	1.9
22	Hexanaldehyde	0.8	0.8	0.5	0.5	1.7	1.1
23	Methanol	1.6	1.6	1.6	2.4	1.4	1.4
24	Trifluoroacetic acid	0.9	0.9	0.6	0.6	1.1	1.6
25	Ammonia	2.7	2.9	2.3	2.3	3.2	1.8
26	Sulfur dioxide	2.7	2.8	2.4	2.6	1.6	2.9

butyl acetate are used as extractants. These substances are VOCs that can be detected in the exhaust gases of EW.

2.2. *Prioritisation of VOCs*

The fuzzy comprehensive evaluation system was used to screen the priority compounds for pollution control. The comprehensive evaluation results are listed in Table 2. The results indicated that dimethyl heptanone, vinyl acetate, diethylamine, PGME, and benzene were the most common priority pollutants from the FW and EW of the three bio-fermentation pharmaceutical enterprises. The FSI values of these compounds were all above 3.0, and they presented high chemical concentrations, detection rates, olfactory effects, toxicity and health effects, volatility, and public concern. Dimethyl heptanone is the priority VOC generated during the production of tylosin and VB12, whereas methyl isobutyl ketone is the priority VOC generated during the production of tiamulin. The VOC emissions from VB12 production were more complex. Acetaldehyde (FSI = 3.5) and ammonia (FSI = 3.2) from FW and methyl acrylate (FSI = 3.1) and chlorobenzene (FSI = 3.2) from EW also showed high scores (FSI > 3.0).

Dimethyl heptanone is commonly used as an organic solvent in biopharmaceutical processes. The concentration of dimethyl heptanone observed in this study (332.36 to 1116.82 mg/m^3) far exceeded the threshold limit value of 25 ppm proposed by the American Conference of Governmental Industrial Hygienists. Long-term exposure to high concentrations of irritating gases poses health risks. Vinyl acetate, diethylamine, and PGME were defined as the priority VOCs for control because of their very low odour threshold and serious olfactory effects. Benzene was selected as a priority compound because of its potential chronic toxicity and cancer risk to on-site workers and surrounding communities. The pollution and health risks of benzene are widely known, and it is on the list of priority control chemicals issued by the Ministry of Ecology and Environment of China. Furthermore, benzene is a priority pollutant according to the EPA Clean Air Act and the Canadian Environmental Protection Act. Benzene emissions are strictly restricted by China's Pharmaceutical Industry Air Pollution Emission Standards and some local pollutant emission standards for pharmaceutical industries (including those for pharmaceutical firms in Shanghai, Zhejiang, Hebei, and Tianjin).

2.3. *Diffusion of VOCs*

The simulation of pollutant diffusion was oriented toward the priority biopharmaceutical pollutants, which were identified according to the results of the fuzzy comprehensive evaluation system. The simulation results from the Gauss plume model showed that the maximum x-axis ground-level concentrations appeared at 300–400 m downwind. Dimethyl heptanone, PGME, benzene, and chlorobenzene showed peak values for the x-axis ground-level concentrations after the diffusion from the EW of the VB12 production process, reaching

72.80, 47.74, 7.22, and 6.65 μg/m³, respectively. The maximum peaks for vinyl acetate and diethylamine diffused from the FW of tiamulin and EW of tylosin were 38.45 and 37.26 μg/m³, respectively. In a previous study, the maximum concentrations of benzene and chlorobenzene in the surrounding environment of a biopharmaceutical workshop were 6.7 ± 1.6 and 3.7 ± 0.6 μg/m³, respectively (Pan et al., 2011).

Based on the average values of the ground concentration of the six priority VOCs in different directions and distances, a spatial distribution map was plotted with the respective concentrations (Fig. 3). The results showed that the emitted VOCs can cause serious environmental pollution and health risks in the range of 200–2000 m downwind from the workshops. Referring to the prevailing local wind direction, the probability of VOCs spreading in the southwest to south direction is considerable, at frequencies of 0.24 and 0.18, respectively. The diffusion of dimethyl heptanone caused the most serious pollution risks to the surrounding environment, with a ground-level concentration of 1.73 ± 0.09 μg/m³ at 5 km downwind from the industrial park. The ground-level concentrations of PGME and vinyl acetate gradually decreased to below 1 μg/m³ after 3 km downwind. The ground-level concentrations of benzene and chlorobenzene rapidly decreased to below 1 μg/m³ after 1 km downwind. The pollutant concentration at a certain spatial point in the Gauss model is a function of location, effective source height, and wind. Therefore, the intensity of the pollution source directly determines the degree of pollution, and wind can affect the diffusion and dilution of pollutants (Weiner and Matthews, 2003).

2.4. *Exposure and health risk*

Some of the observed VOCs (such as benzene, chlorobenzene, *N*-nitrosodiethylamine, and 2,4-toluene diisocyanate) were odorous and potentially harmful to human health. The excessive inhalation of such gases can cause dizziness, conjunctival congestion, respiratory diseases, and other inflammatory reactions, whereas long-term exposure may lead to cancer (Palmiotto et al., 2014). Amongst the 26 VOCs detected in this study, the compounds that can cause chronic toxic effects (non-carcinogenic risk) were methyl isobutyl ketone, methyl ethyl ketone, vinyl acetate, 2,4-toluene diisocyanate (TDI), *N*-nitrosodiethylamine, PGME, benzene, chlorobenzene, allyl chloride, and acetaldehyde. The observed carcinogenic compounds were *N*-nitrosodiethylamine and benzene.

2.4.1. *Non-carcinogenic risk*

Non-carcinogenic risk was assessed based on the exposure concentration in the VOC potential-affected area, that is, the maximum ground-level concentration of compounds that can cause chronic toxic effects after atmospheric diffusion from each source. The calculation of the ground concentrations was based on the simulation of the Gauss plume model and the most probable diffusion conditions (dominant wind direction: northeast, wind speed = 3.37 m/sec, frequency = 0.24). The chronic toxic risk was then obtained according to the calculation utilizing the average ground-level concentrations of non-carcinogenic compounds.

The results showed that *N*-nitrosodiethylamine was the compound responsible for the most considerable non-carcinogenic health risk, with hazard quotient (H_{Qi}) values of 1.03–16.29 detected 150–2000 m downwind. This was followed by 2,4-toluene diisocyanate, that presented an H_{Qi} of 1.25–8.61 detected 150–1500 m downwind (Fig. 4a). When $H_{Qi} > 1$, long-term exposure is likely to cause chronic health hazards (Zhang et al., 2018). The H_{Qi} of all remaining non-carcinogenic compounds at 0–10 km downwind was less than 1 and did not pose significant chronic toxicity or health effects. However, the cumulative chronic hazard index should be further investigated. VOC monitoring should be long-term and dynamic, and the non-carcinogenic risk assessment of a single compound and the accumulated effects of multiple compounds are both important references for VOC monitoring projects.

2.4.2. *Carcinogenic risk*

Similarly, carcinogenic risk was derived from the ground concentrations of carcinogenic compounds after distribution under the most probable spread condition. In this study, the primary carcinogens found in the biopharmaceutical process were *N*-nitrosodiethylamine and benzene. Fig. 4b, c shows the variations in cancer risk (CR_i) with distance. *N*-nitrosodiethylamine posed the most serious carcinogenic risk. The CR_i ranged from 1.21×10^{-4} to 2.19×10^{-2} as detected 100–5000 m downwind, with the maximum risk estimated to occur at 300 m. The CR_i of benzene ranged from 4.66×10^{-6} to 2.24×10^{-5} detected 150–2000 m downwind. For $CR_i < 1.0 \times 10^{-6}$, the risk is considered 'negligible'; for $CR_i > 1.0 \times 10^{-4}$ and $> 1.0 \times 10^{-3}$, the risk is considered 'unacceptable' and 'significant', respectively (Yang et al., 2019; Zhang et al., 2018). Based on the above results, we observed that long-term exposure to VOC pollution from the biopharmaceutical industries could significantly increase the probability of cancer in susceptible individuals. To reduce the health risks associated with such pollutants, more rigorous monitoring and regulation should be implemented.

2.5. *Effect of VOCs on secondary pollution formation*

VOCs in the atmosphere are precursors to photochemical reactions. In the presence of sunlight (mainly ultraviolet rays) irradiation, VOCs, airborne nitrogen oxides, and other suspended chemicals can generate ozone, peroxynitrophthalein, aldehydes, and other substances through a series of chemical reactions, resulting in the formation of photochemical smog and thus contributing to secondary pollution.

2.5.1. *Ozone formation potential*

VOCs are important precursors for near-ground ozone formation; however, the wide range of reactions for each chemical with hydroxyl radicals (Table S2) and the non-linear relationship between ozone accumulation and VOCs make the quantitative characterisation of their influence on ozone generation difficult. In general, source reactivity is a good evaluation index for the ozone generation capacity of different emission sources (Yuan et al, 2010). According to previous studies, ozone-generating capacity can be classified into three grades according to the SR value: high-activity, $SR > 3$; medium-activity, $1 < SR < 3$; and low activity, $SR < 1$ (Ma et al., 2021). In this study, the *SR* values for various production lines in the biopharmaceutical industries ranged from 1.77 to 2.49, with the

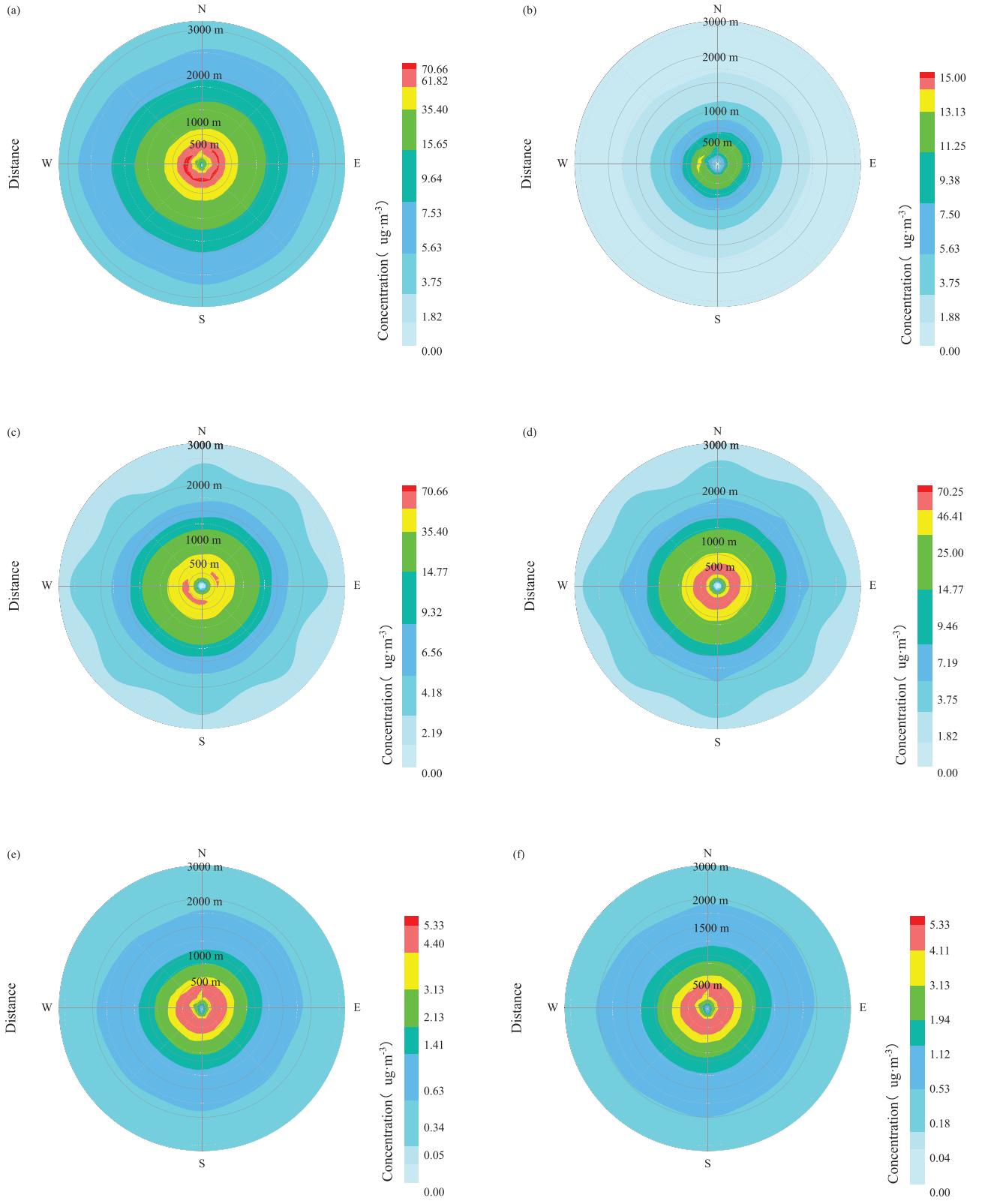

Fig. 3 – Concentration spatial distributions of VOCs. (a) dimethyl heptanone, (b) vinyl acetate, (c) diethylamine, (d) PGME, (e) benzene, and (f) chlorobenzene.

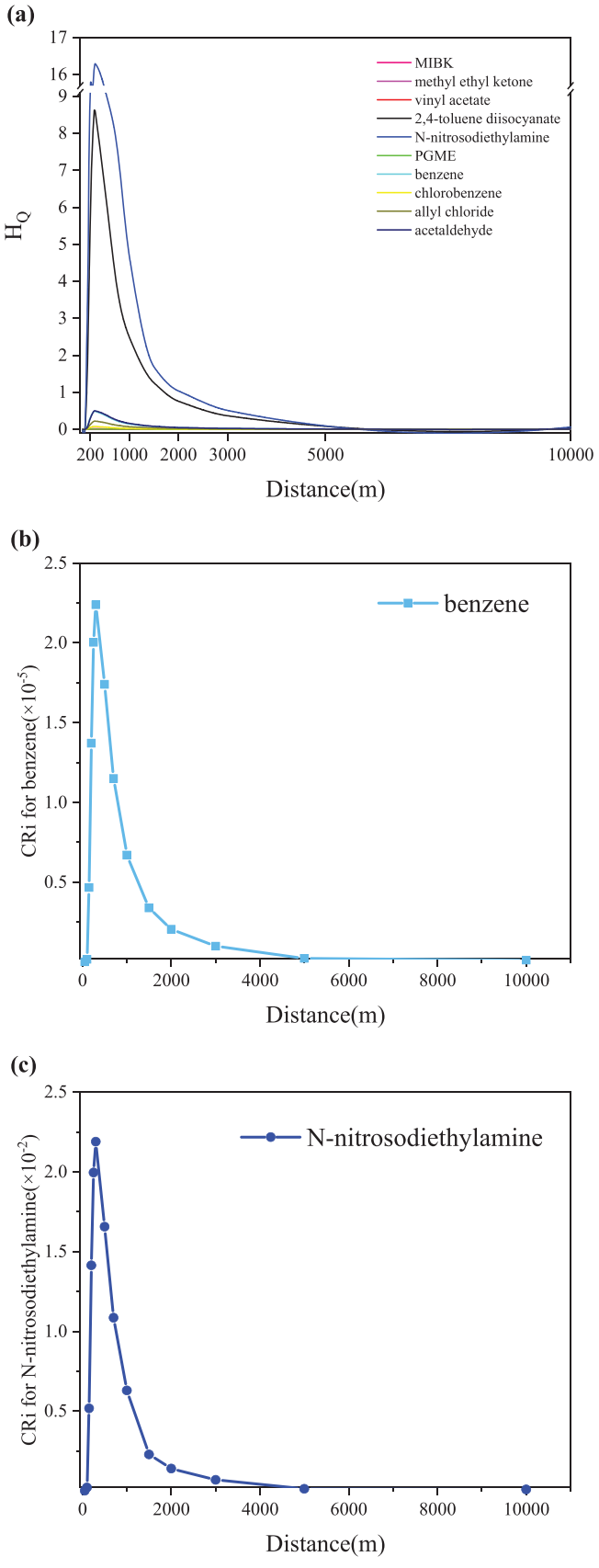

Fig. 4 – The variation of H_Q with distance: (a) the H_Q for all non-carcinogenic non-carcinogenic compounds; (b) CR_i for benzene; (c) CR_i for N-nitrosodiethylamine.

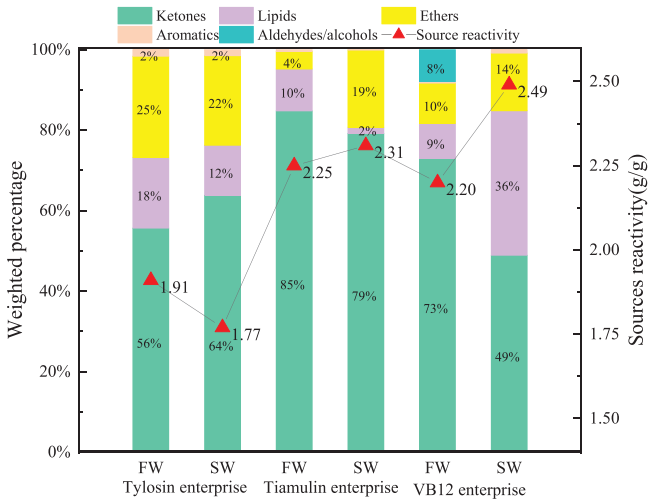

Fig. 5 – Overall VOC composition contributions of MIR-based OFP and sources reactivity in 3 biopharmaceutical enterprises.

VB12 production line having the highest *SR* of 2.20–2.49 (Fig. 5). In contrast, the tylosin production line had the lowest *SR* (1.77–1.91), owing to low ketone emissions, which are key components of ozone formation. Overall, the ozone-generating capacity of ozone pollution sources from the biopharmaceutical industry was classified as medium-activity.

Furthermore, the Propyl-Equiv and MIR methods were applied to identify and quantify the impact of pollutants on the formation of 26 compounds generated during fermentation and extraction processes in the three biopharmaceutical enterprises. Fig. 6 shows the overall VOC component contribution of OFP in the fermentation and extraction workshops of three biopharmaceutical enterprises. The results indicated that oxygenated compounds (including ketones, lipids, ethers, aldehydes, and alcohols) contributed to almost all the ozone generation potential for the industrial off-gases from the biopharmaceutical companies. Ketones had the highest MIR-weighted concentration and were the most dominant photochemically active component of the biopharmaceutical process, with contributions of 48.93%–84.41% for the ozone generation potential, followed by lipids (1.51%–35.89%) and ethers (4.37%–25.14%). Similar results for the OFP contribution scale were obtained using the Propyl-Equiv method (Fig. S3).

Of all the 26 VOCs emitted from the biopharmaceutical industry, 21 were classified as active species with potential for ozone generation. When considering the mechanistic reactivity of a single chemical, M-PYROL was rated as the greatest contributor to ozone formation, with an average MIR weighted concentration of 2.32×10^3 ppmC, approximately 32.47% of the total OFP. Dimethyl heptanone and PGME ranked second and third, accounting for 20.47% and 15.46% of the total OFP, respectively. In comparison, when considering kinetic activity based on the Propyl-Equiv method, M-PYROL presented the highest OFP with an average contribution of 54.46%, followed by dimethyl heptanone (14.72%), methyl isobutyl ketone (14.39%), and PGME (5.84%). Of these substances, seven

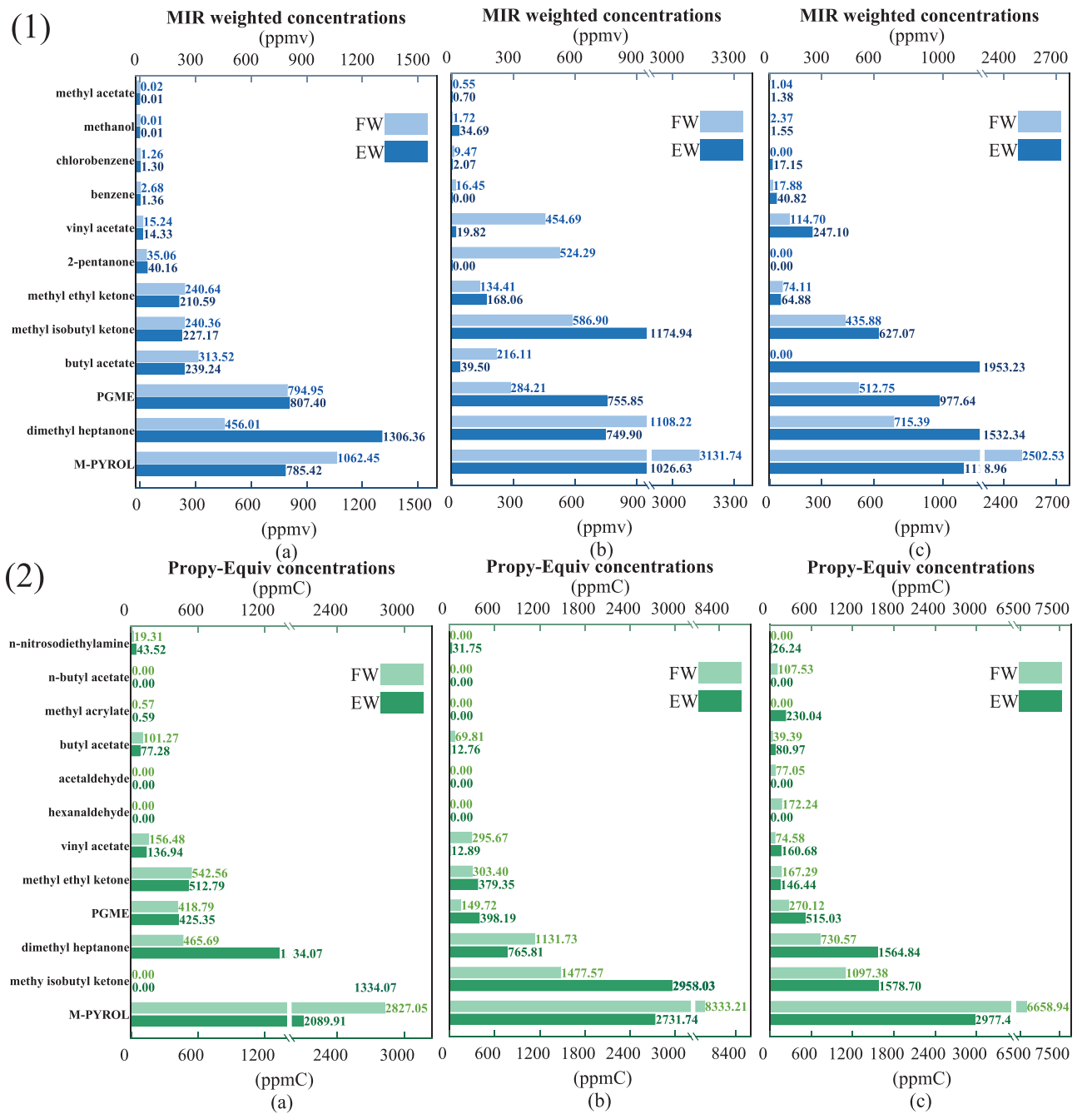

Fig. 6 – The MIR/Propy-Equiv weighted concentrations and contribution scale. (1) MIR weighted concentrations and scale; (2) Propy-Equiv weighted concentrations and scale; (a) tylosin enterprise; (b) tiamulin enterprise; (c) VB12 enterprise.

of the top 10 ozone-forming active species obtained by the MIR and Propyl-Equiv methods were identical, differing only in their rank order, indicating that both methods were suitable for quantifying the OFP of VOC emissions from stationary sources. Overall, the highest cumulative potential for ozone formation was caused by VOCs emitted from the production of VB12, particularly during the extraction process. Ozone formation because of the VOCs emitted from the production line for antibiotic-based pharmaceuticals was relatively low.

During the quantitative evaluation of ozone formation by VOCs emitted from the biopharmaceutical industry by different methods, 10 photochemical active substances were found to co-occur in both antibiotics and vitamin (VB12) production processes, suggesting the occurrence of near-ground-level ozone generation caused by biopharmaceutical industrial waste gas emission. These compounds were dimethyl heptanone, M-Pyrol, PGME, methyl ethyl ketone, vinyl acetate, butyl acetate, chlorobenzene, benzene, methanol, and methyl acetate. Our results highlighted the significant contribution of M-PYROL, dimethyl heptanone, vinyl acetate, and butyl acetate to the generation of ozone. These compounds are industrial solvents widely used in the fermentation, synthesis,

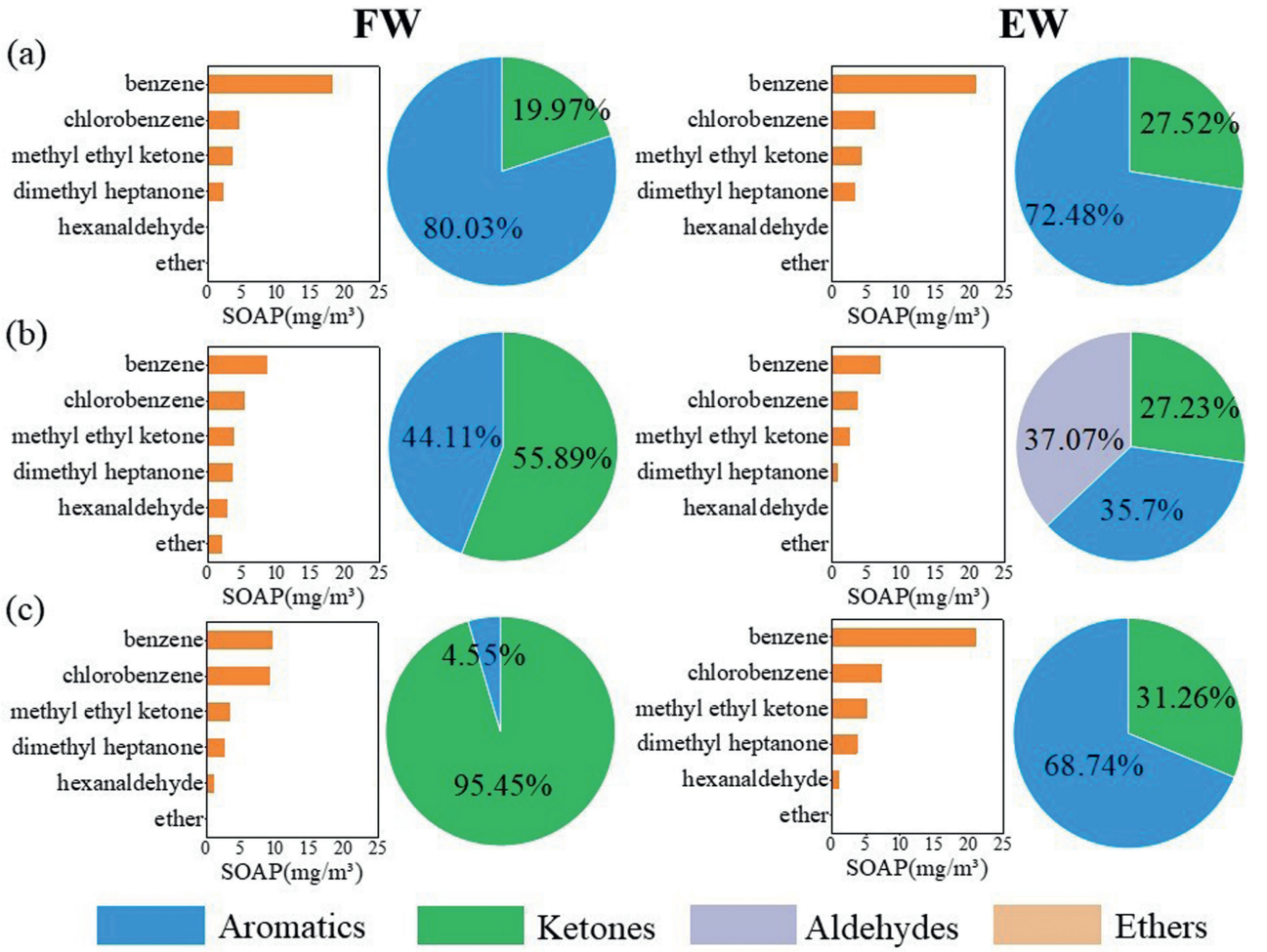

Fig. 7 – Composition of SOAP and key active species released from the biopharmaceutical industry. (a) tylosin enterprise; (b) tiamulin enterprise; (c) VB12 enterprise; FW: fermentation workshop; EW: extraction workshop.

extraction, and refining procedures of pharmaceuticals and can easily volatilize and escape in the gaseous form. To reduce ozone pollution, biopharmaceutical industries should closely consider the storage and use of organic solvents, reduce volatilisation, and enhance solvent recovery. Meanwhile, specific pollutants produced in the VB12 fermentation plant, such as acetaldehyde, should be considered for control.

2.5.2. *SOA formation potential*

Owing to their low vapour pressures, certain secondary organics can form SOAs through processes such as nucleation, condensation, and gas-particle distribution. Studies have shown that organic matter accounts for 50%–70% of the $PM_{2.5}$, of which a significant portion is produced by the photochemical conversion of VOCs (Wang et al., 2021b; Huang et al., 2014; Zhang et al., 2007).

Fig. 7 shows SOAPs and the contribution of VOCs corresponding to the different pharmaceutical production lines. The clearest result of the SOAP evaluation was the dominance of aromatics and ketones in all emission sources. The aromatics contributed the vast majority of SOAP from the emission sources of the tylosin production line, with a contribution ranging from 73.18% to 80.02%. Analogously, aromatics contributed a relatively large amount to SOAP (36.68%–68.73%) from the VB12 production line. Specifically, the key active species for these emission sources were benzene and chlorobenzene. In contrast, the SOAP from the production line producing tiamulin was mainly caused by ketones, with a contribution of 55.90%–95.42%, and the main active substances included methyl ethyl ketone, methyl isobutyl ketone, and dimethyl heptanone. Therefore, using SOAP activity evaluation, the major active species that should be prioritized for management in the biopharmaceutical sector were identified as benzene, dimethyl heptanone, chlorobenzene, and methyl isobutyl ketone.

The effect of VOCs on SOA was not only measured in terms of the potential generation capacity but also in terms of the absolute amount of SOA pollution that may be caused by individual emission sources, which was directly related to emissions from the various pollution sources. Therefore, the measured SOA pollution for each pharmaceutical workshop was estimated and is shown in Fig. S4. The results showed that the studied pharmaceutical industry generated approximately 754.23–5,919.99 kg of SOA per year from each emission

source. The tiamulin production workshops tended to generate more SOA and were the most polluting enterprise, whereas the VB12 workshops produced the lowest level of SOA pollution. Furthermore, considering the annual production of the three main pharmaceutical products in this study (Tylenol: 6000 ton/year; Tylenol 2000 ton/year; and VB12: 20 ton/year), the VOC-induced potential SOA generation per unit mass of pharmaceutical products in the biopharmaceutical industry were 0.62, 4.31, and 151.19 g.SOA/kg product, respectively. In summary, our findings confirmed that the emissions from the pharmaceutical industries are major causes of SOAs and have a non-negligible impact on ambient air quality.

2.6. *Recommendations and strategies for VOC control*

Recommendations and strategies for controlling pollutants in biopharmaceutical industries are proposed, taking into account considering the characteristics of VOCs VOC emissions, atmospheric dispersion, exposure and health risks, contribution to ozone, and SOA formation. (1) Promote technological upgradation and explore the use of non-halogenated hydrocarbons, non-aromatic hydrocarbon solvents, or less reactive solvents as alternatives to organic solvents. (2) Strengthen the recovery of solvents in the gas phase to reduce VOC pollution, thereby achieving source reduction. (3) Identify priority pollutants for control based on the process characteristics of the pharmaceutical plant in order to establish suitable exhaust gas treatment units. In the biopharmaceutical plants studied here, ketones and aromatic hydrocarbons are were identified as the priority pollutants that should be controlled in the biopharmaceutical plants investigated in the present study. They must be treated prior to emission to reduce the risk of secondary air pollution and the health effects on the surrounding population.

3. Conclusions

In this study, the biological fermentation and extraction processes in the pharmaceutical manufacturing system were the primary sources of VOCs, particularly oxygen-containing compounds. Dimethyl heptanone, vinyl acetate, diethylamine, PGME, and benzene were identified as the main pollutants that must be regulated. The simulation of gaseous pollutant diffusion in the atmosphere demonstrated that serious environmental pollution and health concerns may develop within 200–2,000 m of the industrial park. The significant noncarcinogenic and carcinogenic risks were mainly attributed to N-nitrosodiethylamine, 2,4-toluene diisocyanate, and benzene. The VOC emissions from the VB12 production process had a relatively high potential for secondary pollution. M-Pyrol, dimethyl heptanone, and PGME were the most reactive substances in OFP, whereas benzene and chlorobenzene were the most reactive for SOAP. We hope our study can help lay a foundation for VOC pollution control in the biopharmaceutical industry and support integrated countermeasures for the management of air pollutants in industrial parks.

Declaration of Competing Interest

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

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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.2022.10.022.

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