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Review

A review of disrupted biological response associated with volatile organic compound exposure: Insight into identification of biomarkers

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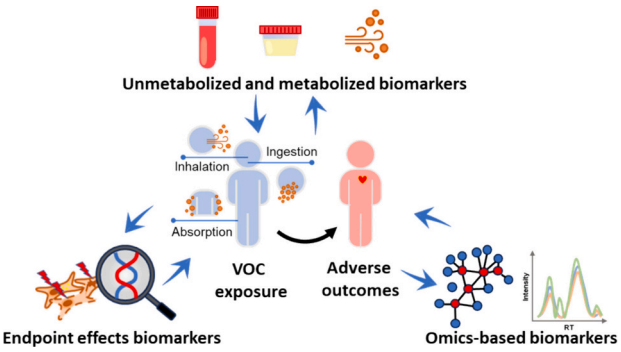
HIGHLIGHTS

- VOC exposure leads to hematological, respiratory, immune and nerve toxicity.
- Unmetabolized and metabolized VOC biomarkers in human samples are summarized.
- VOC exposure causes oxidative stress, inflammation response and DNA damage.
- Omics-based techniques reveal molecular signaling pathways exposure to VOCs.

GRAPHICAL ABSTRACT



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ABSTRACT

Volatile organic compounds (VOCs) are widespread harmful atmospheric pollutants, which have long been concerned and elucidated to be one of the risks of acute and chronic diseases for human, such as leukemia and cancer. Although numerous scientific studies have documented the potential adverse outcomes caused by VOC exposure, the mechanisms which biological response pathways of these VOC disruption remain poorly understood. Therefore, the identification of biochemical markers associated with metabolism, health effects and diseases orientation can be an effective means of screening biological targets for VOC exposure, which provide evidences to the toxicity assessment of compounds. The current review aims to understand the mechanisms underlying VOCs-elicited adverse outcomes by charactering various types of biomarkers. VOCs-related biomarkers from three aspects were summarized through in vitro, animal and epidemiological studies. i) Unmetabolized and metabolized VOC biomarkers in human samples for assessing exposure characteristics in different communities; ii) Adverse endpoint effects related biomarkers, mainly including (anti)oxidative stress, inflammation response and DNA damage; iii) Omics-based molecular biomarkers alteration in gene, protein, lipid and metabolite aspects associated with biological signaling pathway disorders response to VOC exposure. Further research, advanced machine learning and bioinformation approaches combined with experimental results are

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urgently needed to ascertain the selection of biomarkers and further illuminate toxic mechanisms of VOC exposure. Finally, VOCs-induced disease causes can be predicted with proven results.

1. Introduction

Volatile organic compounds (VOCs) are a kind of air pollutant received attention for years. During past decades, environmental levels (Mozaffar and Zhang, 2020), analysis methods (Reyes-Garcés and Gionfriddo, 2019), control technologies (Guo et al., 2021) and health effects (Ye et al., 2017) of VOCs have been comprehensively discussed. Some VOC species are categorized as carcinogens by International Agency for Research on Cancer (IARC), such as formaldehyde and benzene being classified as group I carcinogen and styrene being a IIB carcinogen. In addition, as an important part of tropospheric atmosphere chemistry, VOCs can react with oxygen components (e.g. $^{\bullet}$OH and NOx) through photochemical oxidation in the present of solar irradiation, leading to the formation of secondary organic aerosols and ozone, and further imposing health hazards (Mozaffar and Zhang, 2020).

VOCs and their metabolites are detected in human urine and blood, providing direct evidences of VOC exposure in human (Liu et al., 2022; Rafiee et al., 2018). VOCs are used in industrial, agricultural and human daily activities, several of them are contained in food, such as acrolein and acrylamide. Due to their physical properties and emission mode, VOCs widely distribute in indoor and outdoor gaseous, particulate and water phase, and easily evaporate at normal temperatures making inhalation as the main exposure route (Li et al., 2021). VOCs in outdoor environment largely originate from industrial manufacturing, combustion and leakage of transportation fuels, and biological metabolism (Adgate et al., 2004; Li et al., 2021). Occupational exposure to VOCs, such as oil refiner, traffic police and highway toll station workers might pose sever exposure risks. As the amount of time people in indoors increases, indoor air pollution makes an increasing contribution to human exposure, and also due to VOC levels typically being higher indoors than outdoors (Heeley-Hill et al., 2021). Indoor VOCs emitted from modern house products (e.g. paints, dyes, cleaners and adhesives), resident behaviors (smoking, second-hand smoke and cooking) and personal care products. About 90 % of susceptible people, including children, the infirm and the elderly, spend more time indoors, which undoubtedly increases their risk of exposure to indoor VOCs (Kuang et al., 2023).

As direct target of air pollutants, respiratory system injuries and pathologies have been frequently investigated. Epidemiological studies have found that indoor VOC exposure increases the risk of airway diseases in children and the elderly, including asthma, a heterogeneous disease attributes to chronic airway inflammation. Animal study evidence highlights that VOC exposure induces phenotypes of respiratory lesions in mice, including airway hyperresponsiveness, alveolar cell apoptosis, and emphysema (Amor-Carro et al., 2020). Hematotoxicity is also well known to be caused by VOC exposures. Typically, benzene exposure leads to chromosomal aberrations via genotoxic effects on the pluripotent hematopoietic stem cells, and further leukemia (Scholten et al., 2020; Wang et al., 2012). Traffic related VOCs are positively associated with cardiovascular health outcomes (Tsai et al., 2010). Earlier animal and human studies have pointed out that exposure to indoor VOCs, such as formaldehyde also cause a strong sensory irritation and neurobehavioral impairment effects (Norgaard et al., 2014; Pitten et al., 2000). Besides, potential immunotoxicity and endocrine-disrupting effects associated with exposure to VOCs and their metabolites are also reported (Ogbodo et al., 2022; Tachachartvanich et al., 2018; Winter et al., 2017). For example, 1,4-benzoquinone, a metabolite of benzene can suppress the function of T-cells with elevated IL-13 and Granzyme B cytokine release (Winter et al., 2017). Overall, these studies point out VOCs being acted as possible etiological factor of health risks. However, the underlying mechanisms linking chemical exposure with these adverse outcomes remain unclear and there is an urgent need for specific indicators that can identify the health risks posed by VOCs accurately.

Biomarkers is a high-throughput tool used to identify xenobiotics (e.g. pollutants, drug, food), establish dose-response relationship, assess exposure risks and associate biological responses with adverse health outcomes, which generally includes exposure, effect and susceptibility biomarkers (Jeddi et al., 2021). Environmental biomarkers emphasize a continuum between specific environmental chemical family or chemical mixture exposure and early disease outcome by assessing altered measurable biological indicators (Heffernan et al., 2014; Shen et al., 2024). When a biomarker is used to characterize environmental exposure or association with possible health impairment, it can be the compound itself, its metabolites in human specimens, physiological behavior or altered biomolecule in *in vitro*, animal and epidemiology studies (Guo et al., 2022a). It is worth mentioning that environmental biomarkers also provide advanced indicators for explaining differences in early health effects exposure to chemicals through multiple exposure routes due to individual differences such as age and gender, as well as to observe the characteristics and trends in different community over time (Chung and Herceg, 2020). As such, biomarkers enhance the understanding of the disease pathogenesis caused by environmental exposures and provide a target for the development of more precise prevention and therapy strategies. With the diversification of detection tools and analysis methods, the limit of identification of biomarkers is getting lower and more accurate, and the selection is no longer monotonous, and also more targeted.

Nowadays, the adverse outcome pathway (AOP) framework defined by European Human Biomonitoring Initiative improves the understanding of biomarkers, which integrates environmental chemical exposure information and mechanistic knowledge of a particular disease (Jeddi et al., 2021; Jin et al., 2022). To date, biased studies have documented and overview VOCs related biomarkers and biological signaling based on AOP framework. As presented in Fig. 1 and Table 1, in this review, three categories of biomarkers for assessing VOC exposure and potential health risks are summarized, i) Exposure biomarkers including unmetabolized and metabolized VOCs in human specimens (e.g. urine, blood and exhaled breath); ii) Effect biomarkers of VOCs induced key events, mainly including oxidative stress, inflammation response and DNA damage; iii) Omics-based molecular initiating events, where multiple RNAs, proteins, metabolites and lipids are served as new biomarkers. Summarily, we provide an effort to overview the characteristics of VOC exposure, etiology of health effects and disease onset caused by VOC exposure through comprehensive biomarker information.

2. Unmetabolized VOCs in human urine, blood and exhaled breath

Most VOCs have a half-life of only a few hours and tend to metabolize and transfer rapidly in the human body. Unmetabolized VOCs in human specimens have been served as potential indicator of "ADME" (adsorption, distribution, metabolism and excretion) dose, and for health risk assessment. A portion of VOCs are not metabolized after entering human body, and ultimately excrete in urine by kidney (Rafiee et al., 2019). Human urine is generally used to detect the unmetabolized VOCs, due to their non-invasiveness and easy sampling. Besides, unmetabolized VOCs are also detected in blood and exhaled breath samples in few studies. To better understand the exposure characteristics of VOCs, as well as adsorption and excretion, different biospecimens can be chosen. Benzene, toluene, ethylbenzene and xylenes (BTEX) are typical aromatic

VOCs, which largely attribute to the combustion of gasoline and diesel fuels, the nature of high volatility and lipophilicity make them more potential for human exposure (Rafiee et al., 2018). Thus, the levels of unmetabolized BTEX in human specimens are more documented, and detailed information is summarized in Table S1.

2.1. VOCs in urine

Urinary unmetabolized VOCs are served as suitable biomarker in human biomonitoring studies, since high correlation between urinary unmetabolized VOCs and VOC levels is confirmed. Globally, in identified works, the median of unmetabolized BTEX up to 7.37, 6.28, 2.47, 7.58 and 7.8 ng/mL are detected in human urine, respectively (Table S1). Numerous studies have documented exposure characteristics of exposure and non-exposure groups, especially occupational and non-occupational settings through measuring urinary unmetabolized VOCs. Higher concentrations of urinary BTEX are measured in petroleum distribution workers (Heibati et al., 2018), municipal solid waste composting facility workers (Rafiee et al., 2019) and beauty practitioners (Moradi et al., 2019), due to frequent inhalation of BTEX released from chemical production, traffic exhaust and personal care products. Besides, smoking and second-hand smoking cases are at risk of exposing to more BTEX (Cattaneo et al., 2021).

2.2. VOCs in blood

VOCs can be easily absorbed through human alveoli barrier and then distribute systemically. Blood unmetabolized VOCs represent actual dose, which are regarded as effective biomarkers of environmental exposure and closely associated with health outcomes. Blood VOC concentration reflects the bioavailability of environmental VOC exposure, since the fraction of compounds entering the blood circulatory system can directly react with various target organs and tissues (Jia et al., 2012). Measurement of VOC levels in blood provides an extrapolation basis for VOC exposure dose in occupational and general populations, as well as potential onset of diseases human posed.

Levels of BTEX in human blood are found to be associated with hematologic parameters, liver indicators, neurologic symptoms and endocrine markers. In exposure data of 3950 participants from the Canadian Health Measures Survey, increase in blood BTEX and styrene (BTEXS) are found to be associated with biomarkers of hematotoxicity, hepatotoxicity and nephrotoxicity (Cakmak et al., 2020). In an exposure study comprised of 1055 adults in the American Gulf region, blood benzene and toluene were associated with symptoms of central nervous symptom impairment and peripheral nervous system impairment, respectively (Werder et al., 2019). Decrease in testosterone hormone (TT) related to increased blood BTEX in gasoline station workers

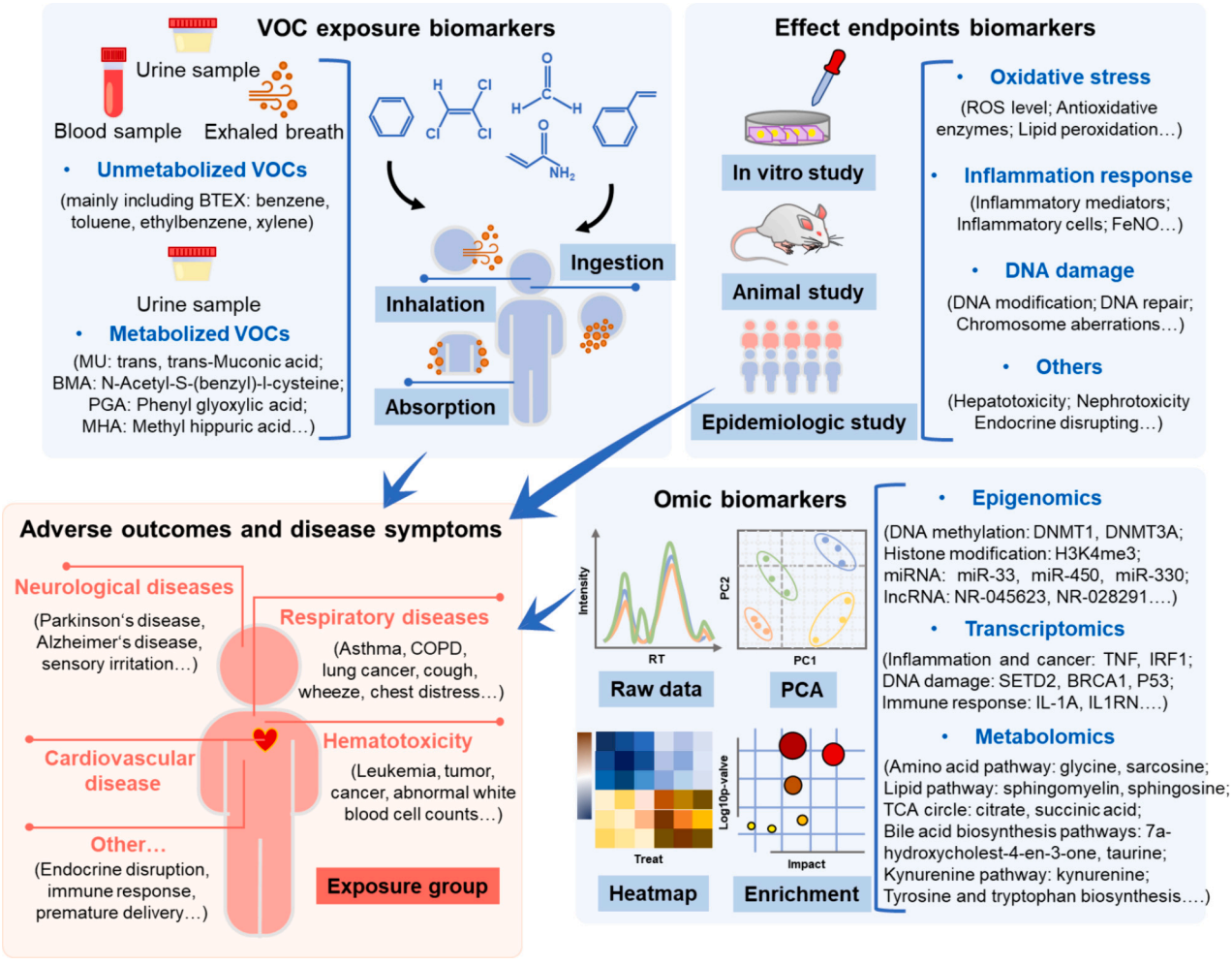

Fig. 1. Schematic illustration depicting the application of identification and determination of biomarkers in exposure and health risks prediction of VOCs to comprehensively understand adverse outcomes and disease symptoms induced by VOC exposure. Three categories of biomarkers including i) unmetabolized and metabolized VOC biomarkers in human sample (blood, urine and exhaled breath); ii) Effect endpoint biomarkers involved in oxidative stress, inflammation response and DNA damage caused by VOC exposure reported in in vitro/*vivo* and epidemiologic studies; iii) Omics and bioinformation analysis-based biomarkers revealing molecular initiation event of adverse outcomes.

provides evidence of VOCs induced endocrine dysfunction (Tanasorn et al., 2012).

2.3. VOCs in exhaled breath

It is also reported that inhaled gaseous-phase compounds can be adsorbed by fluids in respiratory tract due to octanol/water partition coefficient and water solubility, but only 30 % is absorbed during respiration (Wei et al., 2018). Exhaled breath can be sampled in suit with less invasiveness and more frequency, which is well-fitted to study the uptake of VOCs during indoor and outdoor activities. The breath aromatic VOCs, such as benzene, is found to be corrected with ambient level, and the exhaled concentration of BTEX or other aromatics are more accurate indicators of their blood concentrations than that of alcohols, acetates and ketones, because they are less water soluble (King et al., 2012). Endogenous products complicate the composition of exhaled breath, making it unclear to assess exposure levels of VOCs using the exhaled concentrations. For instance, the concentration of esters, sulfides and ketones in exhaled breath, such as methyl acetate, methyl methacrylate, carbon disulfide, 2-butanone and acetone are much higher than those in ambient air. Besides, personal medication can be a source of VOCs in exhaled breath. For example, 3-heptanone in breath may be a metabolite of valproate (Amann et al., 2014). The concentrations of VOCs in exhaled breath can also be affected by

Table 1
Inventory of biomarkers related to VOCs exposure based on in vitro, animal and human studies.

Type of biomarker	Category	Target VOCs	Biomarkers	Strengths/limitations
Exposure biomarkers	Unmetabolized VOCs	BTEX	Benzene, toluene, ethylbenzene, xylene	Urine specimen is non-invasiveness and easy sampling; blood VOC concentrations are closely associated with health outcomes; exhaled VOCs can reflect the ambient VOC exposure in real time. VOCs may diffuse from urine, blood, or exhaled breath into the atmosphere during sample collection and processing; VOCs in urine and blood generally reflect the exposure dose at a certain time due to short half-live; atmospheric VOCs and naturally produced VOCs in human may confound the determination of VOCs in exhaled breath.
	Metabolized VOCs	20 VOCs including acrolein, acrylamide, benzene, 1,3-Butadiene, *N*, *N*-Dimethylformamide, styrene, toluene, vinyl chloride, xylene	N-Acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA), trans, trans-Muconic acid (t, t-MA), N-Acetyl-S-(3,4-dihydroxybutyl)-l-cysteine (DHBMA), Methylhippuric acid (MHA), N-Acetyl-S-(benzyl)-l-cysteine (BMA), Phenylglyoxylic acid (PGA)	Urine specimen is non-invasiveness and easy sampling; metabolized VOCs are stable and specific to detect. Urinary metabolized VOCs are affected by individual differences of human volunteers and are occasionally not reliable to disease prediction.
Effect biomarkers	Oxidative stress	BTEX, formaldehyde, trichloroethylene, VOC mixture	4-hydroxy-2-nonenal-mercapturic acid (HNEMA), 8-isoprostaglandinF2α (8-isoPGF2α), malondialdehyde (MDA), protein carbonyl (PCO)	Effect biomarkers are widely verified and mature to indicate VOCs induced adverse toxic effects, providing deep understanding of early disease onset (e.g. hematological disease, lung impairment, spleen injury); these biomarkers can be easily detected in multiple specimens.
	Antioxidative response		Heme oxygenase 1 (HO-1), NAD(*P*)H quinone dehydrogenase 1 (NQO-1), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione S-transferase (GST)	
	Inflammatory	BTEX, formaldehyde, vinyl chloride, 1,3-butadiene, acetaldehyde, VOC mixture	Interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukin 6, 8, 1β (IL-6, 8, 1β), C—C motif chemokine 2 (CCL2), fractional exhaled nitric oxide (FeNO)	Most of these effect biomarkers are less effective to indicate a specific disease, since biospecimens (e.g. urine and blood) are generally used in human studies.
	DNA damage	BTEX, VOC mixture, benzene, styrene	8-hydroxydeoxyguanosine (8-OHdG), phosphorylated H2AX (γH2AX), micronuclei (MN)	
	Others	VOC mixture, benzene, 1,4-dichloro-benzene, 2,5-dimethylfuran, toluene, trichloroethylene, styrene	Alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), testosterone (TT), estradiol (E2), glycated hemoglobin (HbA1c)	These biomarkers exist reference levels and are widely verified and mature to indicate environmental pollutants induced adverse toxic effects; they are more plausible for specific health effect, including hepatotoxicity and endocrine disrupting. These biomarkers vary from human physiology, including age, gender, ethnicity and smoking status, leading to misdiagnosis and inexact risk assessment.
Omics-based molecular biomarkers	Epigenomics	BTEX, formaldehyde, benzene, toluene, aldehydes	has-miR-4478, hsa-miR-6807-5p, hsa-miR-7109-5p, hsa-miR-1185-1-3p, hsa-miR-1290, hsa-miR-6867-5p, hsa-miR-371a-5p, hsa-miR-1185-1-3p	Omics-based molecular biomarkers offer a comprehensive characteristic of disordered biological molecular (e.g. gene expression, metabolites and proteins) and deep understanding of key events (e.g. oxidative stress, inflammation response and DNA damage) associated with VOC exposure within a batch analysis. These laboratory-controlled new biomarkers are sometimes lack of persuasiveness for characterizing population exposure to VOCs and individualized prediction of exposure risk until their effectiveness is fully proved.
	Transcriptomics	Benzene, formaldehyde, toluene, hexanal, vinyl chloride, acrylonitrile, dichloromethane, trichloroethylene	C1R, IL1R1, IL1RAP, FN1, BCL2, BAX, POLD4, IFITM1, IFITM3, IFIT1, IFI213, IGSF1, RUNX3, DNMT1, DNMT3	
	Proteomics	Benzene, formaldehyde, *N*, *N*-dimethylformamide,	ApolipoproteinA-1, alpha-1-antitrypsin, complement C3, plasminogen, platelet basic protein, apolipoprotein B100	
	Metabolomics	VOC mixture, benzene, *N*, *N*-dimethylformamide, 1,3-butadiene, acrylonitrile, trichloroethylene, vinyl chloride	L-carnitine, arachidonic acid, methionine, glutamine, phenylacetic acid, uric acid, oleic acid, 10z-heptadecenoic acid, palmitoleic acid, acetylcarnitine	

physical activity, that is, an increased ventilation-perfusion ratio can decrease the VOC concentrations in alveoli.

Detection of VOCs in exhaled breath is applied in various lung diseases, which is well-known as volatilomics and garnered increasing attention in recent years. These biomarkers are metabolic productions originated from multiple signal pathways in the human body for early disease prediction and prevention (Amann et al., 2014; Xing et al., 2023). For example, aldehydes (e.g. pentanal, hexanal, octanal, and nonanal) and alkanes (e.g. ethane and pentane) can be formed via peroxidation of fatty acid, which are considered as biomarkers of oxidative stress and inflammatory process associated with asthma and chronic obstructive pulmonary disease (COPD) (Ratiu et al., 2021). It should be noted that, for human health risk prediction and assessment, measurement of atmospheric VOC levels rather than exhaled breath can be better markers for VOCs-related adverse outcomes, since such volatilomics profiling in exhaled breath is a mixture of ambient VOCs and naturally produced VOCs in human body. Besides, other air pollutants (e.g. particulate matter and perfluoroalkyl chemicals) have been proposed to be pathogenesis of lung diseases, interfering the volatilomics profiling through various signaling pathways (Wang et al., 2021).

Although the measurement of VOCs in urine, blood, and exhaled breath provides a convenient means for assessing the dose of individual external exposure, it is important to note that unmetabolized VOCs collected at a certain time point can often only represent the most recent exposure level due to the short half-life of VOCs (Rafiee et al., 2018; Watson et al., 2021). Besides, BTEX and other VOCs in these specimens are influenced by various factors. First of all, individual differences of the investigated population, such as age, gender, and body mass index, increase the possibility of significant differences or incorrect model evaluation. For example, significant difference of blood ethylbenzene, toluene, xylene and styrene levels is observed between groups 12–16 and 17–19 years old, while lower concentrations of blood toluene and xylene are found in female group (Cakmak et al., 2020). It is widely acknowledged that smoking and second-hand smoking exposure contribute to VOC levels. About 1.47, 1.21, 1.21 times higher of benzene, ethylbenzene and xylene, respectively, are observed in urine of smoker living in a metropolitan area in Milan, Italy (Cattaneo et al., 2021). The blood levels of toluene and xylene are 3.28 and 1.75 times higher in smokers in Canadian Health Measures Survey containing 3950 subjects (Cakmak et al., 2020). Ethnicity is another factor considered to be relevant to the association between health and VOC exposures. The differences in VOC levels in specimen between different ethnic groups can be explained by different levels of VOC exposure due to various sources (Konkle et al., 2020). Thus, multiple factors are needed to be considered when human exposure levels of VOCs are predicted using unmetabolized biomarkers.

3. Metabolized VOCs in human body

VOCs may diffuse from urine, blood, or exhaled breath into the atmosphere during sample collection and processing, detecting unmetabolized VOCs may underestimate real exposure levels. Therefore, stabilized metabolized VOCs can also be used as an effective biomarker to assess environmental exposure levels. Biotransformation of VOCs in human mainly through two pathways, cytochrome P450 (CYP)-dependent phase I oxidation metabolism and conjugation reaction mediated by phase II enzymes (Shen et al., 2023). Metabolism plays an important role in eliciting adverse health effects, that is, unmetabolized VOCs are usually less toxic and their undesired effects are exerted through metabolic activation catalyzed by multiple enzymes, such as CYP2E1, epoxide hydrolase and aldo-keto reductase. Some intermediates including epoxides, dihydrodiols and quinones show genotoxic and carcinogenic properties, since they can bind to DNA and proteins to form bulky adducts (Frigerio et al., 2019). Besides, quinones can generate reactive oxygen species (ROS) in cells and lead to oxidative DNA damage. Further, these active electrophilic intermediates can conjugate with endogenous compounds glutathione in mercapturic acid pathway for detoxification in a few hours, and finally excreted in urine. Due to longer physiological half-lives in human and specificity of most glutathione conjugate metabolites, these mercapturic acids in urine can be useful biomarkers for assessing VOC exposure. Total 20 parent VOCs, 23 their metabolite names and abbreviations are shown in the Table S2.

3.1. VOC metabolites in urine

All the papers published containing concentrations of 23 VOC metabolites in urine samples in this section are illustrated in Figs. 2 and S1, the detailed information is also included year of sampling, sampling area and size of participants in individual paper as presented in Table S3. Most studies are based on the population from North America, followed by participants living in Asia areas, few publications reported concentrations of VOC metabolites in urine of European population. Samples collected from U.S., China and Italy are mainly recorded, and several differences can be seen among these areas. In American, *N*-acetyl-S-(3-hydroxypropyl)-l-cysteine (3HPMA), *N*-acetyl-S-(3-hydroxypropyl-1-methyl)-l-cysteine (HPMMA) and *N*-acetyl-S-(3,4-dihydroxybutyl)-l-cysteine (DHBMA) are the dominant metabolites, with concentration ranged from 155 to 1763.7, 117–2740 and 182–742 ng/mL or ng/mg creatine, respectively. In Asian countries, HPMMA was the predominant metabolite in urine, followed by 3HPMA and mandelic acid (MA). The highest level of HPMMA with median concentration of 1644 ng/mL is found in first-morning-void urine samples collected from 406 subjects in winter in Wuhan, China (Qian et al., 2021b). Zhang et al. (2014) determined highest level of 3HPMA in urine of smoking case in Zhengzhou, China with mean concentration of 1481.3 ng/mL. In passive smoking children, geometric mean of MA (544 ng/mg of creatine) is detected in urine (Kuang et al., 2022). Dominant urinary metabolites of VOCs reported in European countries are similar to American, concentrations of HPMMA, DHBMA and 3HPMA are ranged from 18.9 to 1199.5, 76.2–479.1 and 47.9–799 ng/mL or ng/mg of creatine, respectively. 3HPMA and HPMMA, whose parent VOCs are derived from tobacco combustion and engine exhaust, are dominant metabolites among Asian, American and European countries, indicating a similar exposure pattern and source. In addition, 12 VOC biomarkers show significant difference among America, Asia and Europe countries, including AAMA, *N*-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-l-cysteine (GAMA), trans, trans-muconic acid (*t,t*-MA), *N*-acetyl-S-(n-propyl)-l-cysteine (BPMA), DHBMA, phenylglyoxylic acid (PGA), MA, *N*-acetyl-S-(2-cyanoethyl)-l-cysteine (CYMA), *N*-acetyl-S-(2-hydroxyethyl)-l-cysteine (HEMA), *N*-acetyl-S-(*N*-methylcarbamoyl)-l-cysteine (AMCC), *N*-acetyl-S-(2-hydroxypropyl)-l-cysteine (2HPMA) and *N*-acetyl-S-(benzyl)-l-cysteine (BMA) (Fig. S1). Among these VOC metabolites, the concentrations of AAMA, GAMA, *t,t*-MA, BPMA, DHBMA and PGA in urine of American are significantly higher than that in Asian and European, while MA concentrations are much higher in urine of Asian.

In addition to comprehend the characteristics of VOC exposure, metabolic biomarkers point out VOC species of concern through correlating specific health effect indicators. VOCs can easily penetrate into the depths of respiratory system, chronic exposure to high level of VOCs diminish lung function, causing symptoms such as asthma and even lung cancer. Relationships between VOC exposure and respiratory disease indicators are previously established with monitoring data of urinary metabolite levels. It is worth noting that the lung function of children and the elderly is sensitive and fragile to VOC exposure. For example, higher odd ratio for 3/4-methylhippuric acid (3/4-MHA) followed by 2-aminothiazoline-4-carboxylic acid (ATCA) and DHBMA are observed in asthmatic children, which are associated with increased 8-hydroxy-2′-deoxyguanine (8-OHdG). These indicate that m/p-xylene, cyanide and 1,3-butadiene induced DNA oxidative damage may play crucial roles in asthma pathogenesis (Kuang et al., 2021). The decline of forced expiratory volume in the first second (FEV1), an indicator of the flow block linked to increase in urinary hippuric acid and MHA, as well as

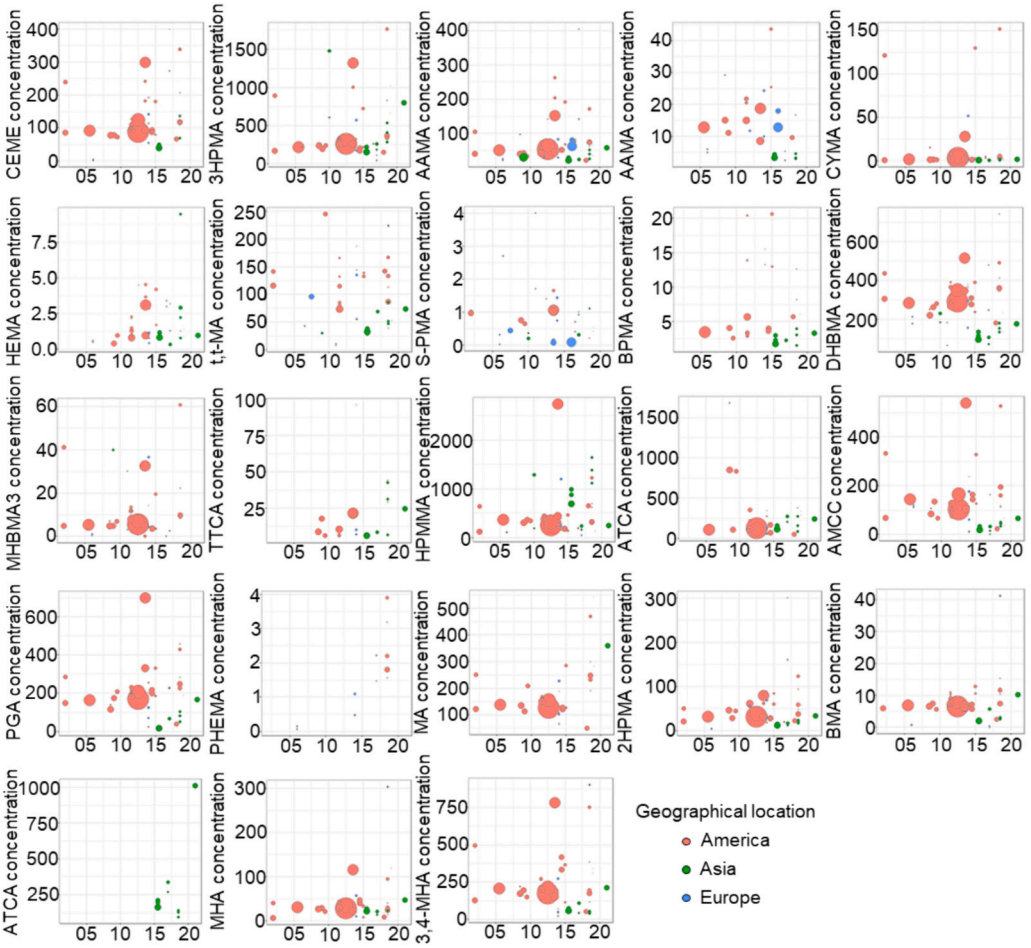

Fig. 2. Recorded geometric mean or median urinary biomarker of 23 VOCs according to the year of sample collection (from 2002 to 2021). The center of the solid circle indicates concentration value on the y-axis and median year of sample collection on the x-axis. The solid circle colored in red, blue and green represents American, European and Asian area, respectively. The size of circle is depicted according to participants included in each study. The complete and detailed data can be found in the Table S3. The unit of each sample is ng/mL or ng/mg creatine.

malondialdehyde (MDA) in elder people, implying impaired lung function by oxidative stress caused by VOC exposure (Yoon et al., 2010). Other disease onset and exacerbation, such as immunological system disorders (Dutta et al., 2013; Moro et al., 2015), cardiovascular disease (Riggs et al., 2022), sensorineural hearing loss (Pudrith and Dudley, 2019) and urothelial carcinoma (Chung et al., 2020) are also confirmed to be associated with urine VOC metabolites. Generally, these biomarkers are affected by individual differences of human volunteers and are occasionally not reliable to disease prediction. Therefore, combining effect biomarkers to indicate the occurrence and cause of symptoms is a more anticipated and optimized approach.

3.2. Factors affecting VOC metabolites in urine

The concentrations of VOC metabolites in urine reflect the amounts of ambient VOCs entering the human body through inhalation, ingestion, and dermal contact pathways. Individual differences including age (e.g. adolescents have higher metabolic capacity than children and the elder), gender (e.g. men smoke more than women, and subject to more VOCs), and health status (e.g. higher concentrations of metabolites are found in the urine of illness cases) can affect biomarker levels. In addition, differences in residence (e.g. urban and suburban housing), seasons changes, residents' lifestyles (e.g., smoking habit, indoor and outdoor work and rest time, indoor ventilation, coal burning), and daily necessities using (e.g. usage of VOCs-containing toiletries and furniture) are likely to affect exposure levels. Children and infants are vulnerable to VOCs during the growth and development due to their weak immune system and respiratory system, and higher respiratory rate than adults, but weak excretion ability (Yoon et al., 2011). Biomarker levels of 11 VOCs including acrolein, acrylamide, benzene, and toluene detected in children's urine are significantly higher than those of adults, implying children subject to higher risk of VOC exposure (Jain, 2015b). Children spend more time indoors, and tobacco smoke (e.g. secondhand smoke and smoke pollutants deposited on dust particles) or furniture release can be their main sources of VOC exposure. For the effect of gender on urinary biomarker levels, non-smoking women are less exposed to VOCs than men and eliminate VOCs from the body at a faster rate resulting in lower concentrations of metabolized VOCs. In addition, other components in tobacco, such as PAHs, can induce female smokers to produce enzymes expediting the metabolism of VOCs (Jain, 2015a). We can conclude that individual differences may affect the urinary VOC metabolites, and the levels of these biomarkers are compositely influenced by multiple factors.

Changes in lifestyle, such as gas using, affect VOC exposure levels and urinary biomarkers. Pregnant women who use firewood as raw materials for cooking show alteration in the metabolites of PAHs and VOCs in urine after 6–8 weeks of intervention with liquefied petroleum gas stoves. Among these metabolites, *N*-acetyl-S-(phenyl)-l-cysteine (PMA), HEMA and CYMA decrease by 40 %, 12 % and 37.7 %, respectively (Weinstein et al., 2020). There is a significant correlation between residential greening and VOC exposure. It is found that the VOC metabolites decrease by 22 % for every 0.1 unit increase in normalized

vegetation index, indicating that residential greening reduces VOC exposure and exposure risk (Yeager et al., 2020). Based on the above studies, metabolic biomarkers can help us to predict health risks in different lifestyles and living environments.

Occupational exposure is also one of the factors affecting the urinary biomarkers of VOCs in exposed individuals. Based on the human biomonitoring data, it is found that occupationally exposed workers such as painters (Sisto et al., 2020), dismantling worker (Liu et al., 2022), and traffic police (Borgie et al., 2014) are subject to higher concentrations of VOCs, because they are frequently exposed to solvents, industrial emissions and vehicle exhausts. For example, up to 1-order of magnitude higher of urinary PGA, MA and 3/4-MHA is found in *E*-waste recycling industrial park workers than those in other previous study, which are detected to be 1570, 2760 and 902 ng/mg of creatine (Liu et al., 2022). Therefore, more attentions need to be paid to occupational exposure groups, identify potential exposure sources and dominants pollutants, thus minimize their exposure risks.

3.3. VOC metabolites in blood and exhaled breath

Unlike unmetabolized VOC markers, these hydrophilic metabolites can be rapidly excreted by the kidneys in urine after being produced in the liver; therefore, their presence in human blood has not been reported in any monitoring studies. In the future, it is worth studying whether these environmental VOCs can be rapidly transformed into other volatile or semi-volatile compounds after entering the respiratory system and excreted from the lung with respiration, and serve as viable metabolic markers.

4. Effect biomarkers for VOC exposure

Additionally, specific indicators are also used to assess pathobiological process and endpoints following VOC exposure. These measurable results can explain the impact of VOC exposure on human health by evaluating the relationship between exposure and adverse outcomes (Pal et al., 2022). VOCs initially enter human lung through inhalation, and then transport to target organ and bind to receptors through the circulation, resulting in various toxicity endpoints. Typically, schematic representation of oxidative stress and generation of biomarkers after VOCs entering the cell as shown in Fig. 3. Briefly, VOCs are transformed into active electrophilic intermediates (e.g. phenols and quinones) catalyzed by CYP enzymes to stimulate the production of ROS in cells. Antioxidant defense system is initially turn out to be activated, mainly manifest as increased activities of reductases, such as catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH). Excess ROS tends to stimulate nuclear factor erythroid2-related factor 2 (Nrf2) to dissociate from Kelch-like ECH-associated protein-1 (Keap1) and translocate to the nucleus. As consequence, Nrf2 regulates the enzymatic defense mechanisms and mediates to produce cytokines in great quantities through antioxidant response element activation to maintain homeostasis (Sun et al., 2022b). Existing *in vivo/vitro* and epidemiology studies have demonstrated that VOCs are likely to play a critical role in incidence of diseases including asthma, COPD, leukemia and cancer. An overview of available effect biomarkers exposed to VOCs is summarized in Table S4, and these biomarkers are divided into four categories according to effect endpoints, including oxidative stress and antioxidant response, inflammatory response, and DNA damage.

4.1. Oxidative stress and antioxidative response

Oxidative stress is one of the most important subjects in environmental toxicology. Oxidative stress generates in cells due to excessive production of ROS, such as superoxide anion, $^{\bullet}OH$ and H_2O_2, further leads to protein modification, lipid peroxidation, and DNA/RNA damage (Barnes, 2016). In turn, disturbance of antioxidants (e.g. SOD, glutathione peroxidase (GSH-Px) and GSH) is beneficial to counteract and moderate chemical induced injury in lung, liver and central nervous system. Therefore, the products of cellular damage or antioxidant

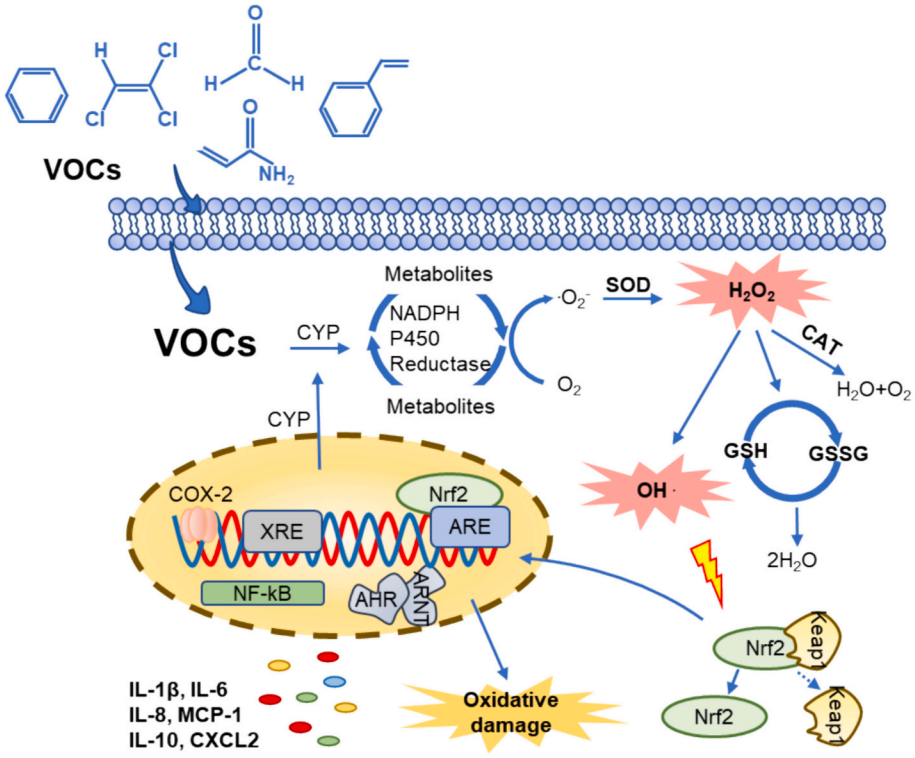

Fig. 3. Schematic representation of typical oxidative stress pathway and biomarker release after VOCs enter the cell. Nrf2 dissociate from Keap1 after stimulated by electrophilic compounds and then translocate to the nucleus. Nrf2 binds to the antioxidant responsive elements (ARE) and other specific sequences coding for conjugating/detoxification enzymes, antioxidant enzymes and stress proteins.

responses can be served as reliable indicators for assessing oxidative stress induced by VOCs.

VOCs can penetrate into cells due to lipophilicity after entering target tissues, causing instability in mitochondrial membrane potential and oxidative stress. VOC exposure (trichloroethylene, formaldehyde and BTEX) induced oxidative damage leading to multiple health effects, such as DNA damage (Jin et al., 2020), hematological disease (Wei et al., 2017), lung impairment (Murta et al., 2016) and spleen injury (Wen et al., 2016) were proved in zebrafish, Balb/c mice and Fischer rat study. These disorders commonly shown as increased production of ROS and MDA, while the activities of CAT, SOD, heme oxygenase 1 (HO-1), GSH and GSH-Px was sharply decreased, indicating enhanced oxidative damage with higher depletion of antioxidants. The *in vitro* studies also verify the effectiveness of these biomarkers and offer insight into underlying molecular mechanisms of VOCs-induced toxic effect. For example, activation of oxidative stress in the normal human lymphocyte line with dose-dependently elevated ROS and decreased NAD(*P*)H quinone dehydrogenase 1 (NQO-1) levels is proved to elicit autophagy and apoptosis exposure to 1, 4-benzoquinone (benzene metabolite), resulting in hematotoxicity (Chen et al., 2019).

Besides, the oxidative stress of VOCs on human beings has been widely reported through monitoring biomarkers in blood, urine and sputum specimen. The 90-min acute formaldehyde exposure leads to oxidative stress with increased MDA level in plasma while protein carbonyl (PCO) does not alter obviously (Augenreich et al., 2020). However, a meaningfully greater level of PCO is observed in gasoline station attendants who chronically exposure to low level of benzene (Ahmadi et al., 2019; Moro et al., 2019). Besides, it is proved that longer working time is associated with increased MDA and glutathione S-transferase (GST) levels in chronic benzene exposed workers, indicating an increased risk of oxidative damage (Costa-Amaral et al., 2019). Difference in biomarker levels depend on VOC types and exposure period, a long-term occupational exposure may lead to sever lipid and protein oxidative in human. Positive associations are observed between VOC metabolites and oxidative stress biomarkers in human urine. Based on human biomonitoring data, weighted quantile sum (WQS) regression models show *t,t*-MA presented the highest contribution to the increase of 4-hydroxy nonenal mercapturic acid (HNEMA) in non-occupational healthy adults, followed by ATCA (Qian et al., 2021a). Similarly, in the urine of 0–7 year-old healthy children, more than ten VOC metabolites are positively associated with HNEMA, and *t,t*-MA contributes the most (Song et al., 2022). Urinary levels of *N*-acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA), 2HPMA, 3HPMA, BPMA, ATCA, and HPMMA are correlated significantly with MDA, whereas 2-MHA, 3/4-MHA, and ATCA levels are correlated significantly with 8-isoprostaglandin F2α (8-isoPGF2α) (Pal et al., 2022). All above studies demonstrate oxidative damage and lipid peroxidative caused by VOC exposure in dose-response relationship, which are predictive of various diseases.

4.2. Inflammatory response

Inflammatory is a complex biological process in response to harmful stimuli, and the activation of systematical inflammation enable to alleviate cellular damage and execute initiate repair processes (Wong et al., 2016). Inflammatory response can be triggered by increased ROS mediated oxidative pathways, such as nuclear factor kappa B (NF-kB) and mammalian target of rapamycin (mTOR) signaling pathway following VOC exposures, which can explain underlying pathophysiologic pathway linking VOC exposure with increased risks of diseases.

4.2.1. Inflammatory mediators

Cytokines and chemokines are small secreted proteins synthesized and released by immune or non-immune cells response to environmental stimuli, which can mediate a variety of cellular functions, such as gene expression, immune response and inflammatory response. VOC exposure can lead to systematic inflammation in tissues and organs, contributing to abnormal immune response induced disease, such as atopic dermatitis (AD) and asthma. Formaldehyde exposure increases the mRNA expression levels of Th1 pro-inflammatory cytokines in skin, including tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β in AD Sprague-Dawley (SD) rats, suggesting exacerbated immune responses (Han et al., 2016). Similarly, elevated inflammatory chemokines in the lung of Fischer rats exposed to formaldehyde, such as C—C motif chemokine 2 (CCL2) and CCL5, accompanied with decreased GSH were found, leading to airway inflammation injury (Murta et al., 2016). However, Amor-Carro et al. (2020) found that VOC exposure is not efficient in leading inflammation cytokines. In bronchoalveolar lavage fluid (BALF) of Brown Norway rats, exposure to BTEX did not alter the concentration of IL-1α, CCL2, TNF-α, Interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4, although airway hyperreactivity in mice is observed after exposure. That is, VOCs can activate noninflammatory responses through acting with other biological pathways, such as innating immunity pathways to cause airway diseases (Amor-Carro et al., 2020). Animal studies also demonstrate VOCs, at least their metabolites, associated with aggravated liver injury. Chloroethanol (a vinyl chloride metabolite) promote inflammatory liver injury caused by dietary fatty acids in C57BL/6 J mice with increased plasma levels of IL-1β and hepatic IL-1β expression (Anders et al., 2016).

Inflammation response is reported in human studies presented a dose-dependent mode, which is helpful for forecasting and assessing health effect exposing to VOCs in different periods or through the whole life time. Greater concentrations of TNF-α and IFN-γ are detected in blood of residents living in high traffic and industrial areas compared to low traffic areas, which can be ascribed to higher BTX and styrene concentrations in former study sites (Samadi et al., 2019). A correlation analysis between exposure dose and effect biomarkers is needed to emphasize the importance of VOCs in inflammation process, due to complexity of ambient air in these areas. Cassidy-Bushrow et al. (2021) report that the serum IL-1β and TNF-α would increase when pregnant women exposed to BTEX in their first trimester and mid-pregnancy, increasing risk of preterm birth via inflammation. Population studies also provide evidences to important role inflammation response plays in pathology. In a cross-sectional pilot study with 108 obese subjects, benzene is found to be associated with serum cytokeratin 18 (CK18M30, indicator of hepatocyte death), IL-6, IL-8 and IL-1β, indicating potential risk of benzene exposure in inflammatory liver disease (Werder et al., 2020). Individuals occupationally exposed to VOCs subject to higher health risks can be explained by the interference with more inflammatory mediators in body. Significantly higher IL-8 expression is observed in lymphocytes of population exposed to VOCs (benzene and 1,3-butadiene) released from a petrochemical complex than the control side (Kampeerawipakorn et al., 2017).

4.2.2. Inflammatory cells

Inflammatory cells can be activated and recruitment into the target tissue and release abundant mediators, leading to inflammatory injury. VOCs are proved to cause abnormal activation and over recruitment of immune cells in inflammation site, and result in the emergence of immune disease (Ogbodo et al., 2022). Lung and skin are susceptible to VOCs due to inhalation and directly contact to ambient VOCs, leading to acute and chronic lung damage and even systemic inflammation. Infiltration of inflammatory cells, including eosinophils, neutrophils, and monocytes, and hypertrophy are detected in the ears of BALB/c mice treated with formaldehyde through repeated painting onto skin, indicating potent irritancy against skin (Saito et al., 2011). Similarly, dose-dependent manner of lymphocytes and macrophages is observed in BALF of Fischer rats exposed to formaldehyde using an inhalation chamber (Murta et al., 2016). Study points out the enhanced allergic airway inflammation induced by VOC exposure. Low concentration of acetaldehyde intranasal exposure leads to increased eosinophilic infiltration in the lung of *Dermatophagoides farinae* allergen-sensitized BALB/

c mice with elevated levels of inflammatory mediators (IL-5 and GM-CSF) (Kawano et al., 2012). Further, the inflammation mediators released by inflammation cells play a vital role in pathogenesis of VOC-induced inflammatory injury and immune responses.

4.2.3. Fractional exhaled nitric oxide (FeNO)

FeNO is synthesized by iNOS in the central and peripheral airway, and proposed as one of an established biomarkers for airway impairment regulated by inflammation mediators (Ricciardolo, 2014). Studies based on epidemiological investigation have confirmed that VOC exposure leads to eosinophilic airway inflammation and impaired lung function. Generally, children are susceptible to air pollution exposure due to immature pulmonary metabolic capacity, elevated FeNO accompany with increased asthma symptoms in children exposure to VOCs is confirmed in previous cross-section studies. For example, panel study shows that children living near an oil shale industry site fugitively emitted with benzene, phenol, formaldehyde and non-methane hydrocarbons, have 1.63 times higher FeNO level ($\geq$ 30 ppb) and attacks of asthma than children living far from the site (Idavain et al., 2019). Study reported that FeNO is a more sensitive and reliable biomarker to indicate the impaired lung function induced by air pollutants in asthmatic children. Kuang et al. (2020) find positive corrections between PAHs, benzene and toluene with FeNO in 334 children participated (262 asthmatic children and 72 healthy children) cohort study, while there is no significant effect on MDA.

4.3. DNA damage

It is well-known that some of VOC species, such as benzene, are classified as human carcinogen. A substantial number of cross-section studies have indicated that VOC exposure is closely related to DNA damage through oxidative stress and inflammation. Some biomarkers have been prospectively associated with genotoxicity and carcinogenesis, and their feasibility have been validated both in animal and population studies.

4.3.1. 8-Hydroxy-2′-deoxyguanine (8-OHdG)

8-OHdG is a production of DNA base modification derived from attacked guanine by $^{\bullet}$OH due to ROS level rises in intracellular upon environmental stress, and the unpaired DNA lesions seem to account for mutagenicity and cancer (Valavanidis et al., 2009). 8-OHdG can be used to indicate oxidative stress mediated DNA damage after exposing to various air pollutants. In animal studies, increased ROS and 8-OHdG are detected in tissue and BALF exposure to single or VOC mixture (Bahadar et al., 2015; Li et al., 2020; Wang et al., 2013). In population exposure monitoring researches, significant relationships are observed between urinary 8-OHdG and VOC metabolites, indicating that VOC exposure causes DNA damage. For example, VOC metabolite mixture in pregnant women is significantly related to higher levels of oxidative stress related DNA damage, among them GAMA contributes most to the mixture effect on 8-OHdG, while *t,t*-MA plays a vital role on increased HNEMA level (Li et al., 2023). Similar evidence is provided from a large-scale survey in China, where 7 VOC metabolites including CEMA, 2-MHA, 3/4-MHA, AMCC, *t,t*-MA, HPMMA and CEMA are associated with 8-OHdG (Yan et al., 2023). Besides, a six-year longitudinal study reports that urinary TGA, MA, AMCC and HPMMA contribute most to the joint effect on 8-OHdG in e-waste recycling sites children, and a declined trend in 8-OHdG level after e-waste control from 2016 to 2021, indicating reduced population exposure risks (Yu et al., 2023). Some studies have evaluated for the relationships of VOC exposure with 8-OHdG, as well as the mediating role 8-OHdG in VOC induced specific diseases, which is helpful for grasping underlying mechanism in increased disease risks, such as type 2 diabetes (Wang et al., 2023) and asthma (Kuang et al., 2021).

4.3.2. Phosphorylated form of H2AX (γH2AX)

γH2AX is the phosphorylated form of H2AX responses to DNA double-strand breaks (DSB) formation and locally increases at the site of DSB via serine-threonine kinases (Podhorecka et al., 2010). The formation of γH2AX can be used as biomarker of DSB and pre-screen of genotoxicity. Genotoxicities of VOCs and VOC-containing air pollutants (e.g. secondhand smoke, diesel exhaust gas) have been proved both in vitro and human studies through evaluating the formation of γH2AX. In vitro studies using A549 cells (Zhang et al., 2017) and keratinocytes (Dezest et al., 2017) provide evidences to increased level of γH2AX after single and VOC mixture exposure and their potential genotoxicity. In an epidemiological study comprised 141 cases occupationally exposed to BTEX with abnormal hematological parameters and 152 controls without any abnormal hematological parameters, Roshan et al. (2022) report significantly higher frequency of ATM-rs22858 and H2AX-rs7759 in cases than the controls, implying DNA damage related to hematotoxicity of BTEX.

4.3.3. Micronuclei (MN)

MN is a well-validated cytogenetic biomarker in peripheral blood lymphocytes to predict cancer risk, which is considered to be induced by the accumulation of DNA damage, chromosome aberrations and defects in the cell repair machinery (Iarmarcovai et al., 2008). The genotoxicities of VOCs have been investigated in dozens of experimental and biomonitoring studies through recording frequency of MN. For instance, strong association is reported between benzene exposure and MN in human with an increase of 0.27 % MN per parts-per-million benzene exposure (Scholten et al., 2020). Systematic review and meta-analysis provide convincing evidence of association between styrene exposure and MN frequency in monitoring genetic risk in styrene-exposed workers (Costa et al., 2016). VOC occupational exposure workers, such as gasoline station workers, painters and hairdressers are susceptible to genotoxic effects induced by increased frequency of MN. In an epidemiologic study, higher percentage with >2MNs/2000 exfoliated urothelial cells is also detected in voided urine in individuals of organic solvents and paints exposed group than unexposed group. Furthermore, methylated GSTP1 and p16INK4a promoters in individual are likely to increase MN frequency (Reddy et al., 2012).

4.4. Others

Oxidative stress and inflammation are both well confirmed and considered as common causal event resulting in occurrence or exacerbation of diseases caused by VOCs. In addition, some of the other effect biomarkers have been confirmed to predict specific adverse health outcomes. Population study shows VOC mixture exposure positively associated with hepatic injury biomarkers, including aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase (ALP) (Liu et al., 2023b; Yu et al., 2024). Besides, Wahlang et al. (2023) propose that VOCs can impact on AST and ALP in biological sex, race, and smoking status-dependent mode. Although reference levels for these biomarkers have been given in humans, they are not as specific to liver damage because other tissues also contribute to their levels (Ozer et al., 2008).

Several VOCs are reported to be endocrine-disrupting chemicals (EDCs), which can interfere with the endocrine system and lead to reproductive and developmental toxicity. TT and estradiol (E2) are major sex hormone markers in the human body and play a critical role in differentiating reproductive system function and sexual development (Wei et al., 2023). Multiple statistical models evidently suggest associations between blood benzene, 1,4-dichlorobenzene, 2,5-dimethylfuran, toluene with TT and E2. Especially, 2,5-dimethylfuran, a kind of VOCs derived from smoking, could increase TT and E2 by 213.594 ng/dL and 7.229 pg/mL, respectively, by one unit of blood 2,5-dimethylfuran (Wei et al., 2023). An in vitro study using NCI-H295R cell line reveals that trichloroethylene and its major metabolites (trichloroethanol and

trichloroacetic acid) orchestrate endocrine disruption via promoting E2 production through 17β-hydroxysteroid dehydrogenase 1 (17βHSD1) mediated steroidogenesis pathway (Tachachartvanich et al., 2018). Besides, the dysfunction of glucose metabolism is also one of the manifestations of the endocrine system disruption, and the increase of BTEXS exposure is significantly correlated with glycated hemoglobin (HbA1c) in gender-dependent manner, indicating increased risk of diabetes (Cakmak et al., 2020). In the same study, low serum creatinine is found to associated with BTEXS, which can be attribute to renal hyperfiltration (Cakmak et al., 2020).

While these effect biomarkers are population based, individual differences can lead to misdiagnosis and inexact risk assessment, since levels of these markers vary from human physiology, including age, gender, ethnicity and smoking status.

5. Use of omics technologies and potential biomarkers

In environmental toxicology, it is a fast-growing field to address biological complexity and discover new effective biomarkers. The applications of omics technologies aim to describe and quantify the changes of biomolecules (e.g. gene regulation, metabolite disorder, epigenetic change) in cells, tissues and body fluids, and provide information on the structure and function of living organisms. Omics technologies provide new means to clarify the endotypes of the emergence, development and treatment of various diseases (Brockmeier et al., 2017; Eguiluz-Gracia et al., 2018). The high throughput, low detection limit and multidisciplinary omics techniques help link early life exposure to environmental pollutants with adverse health effects and lesions in later life. In this section, a summary of works using omics technologies for biomarker identification exposure to single or multiple VOC exposures were reviewed. Fig. S2 and Tables S5-S8 show the identified biomarkers and associated pathways using different omics technologies.

5.1. Epigenomics

Epigenetic mechanisms refer to heritable change of mitosis and meiosis in gene expression rather than altering the sequence of DNA nucleotide (Chung and Herceg, 2020). Epigenetic aberration provides valid mechanistic evidence to gene dysregulation, cellular responses, and is key driver of hematological diseases and cancer induced by environmental carcinogens. Epigenetics characterize the DNA methylation, post-translational histone modification, as well as profiling of altered microRNA (miRNA) and long noncoding RNA (lncRNA) (Chung and Herceg, 2020). As showed in Table S5, numerous studies have proved VOCs play a key role in epigenetic changes leading to abnormal epigenetic modification and diseased phenotypes. Thus, the epigenetic biomarkers can be used to predict early VOC exposure induced adverse health outcomes in later life.

5.1.1. DNA methylation

DNA methylation is proposed as stable and responsive molecular predictor of environmental exposure related disease progression and cancer. Increased level of DNA methylation is observed in blood and urine samples of VOC exposed groups (Chatterjee et al., 2023; Janos et al., 2023; Sabi et al., 2020). DNA methyltransferases 1 (DNMT1), DNMT3A and DNMT3B are methyltransferases playing distinctive role in methylation activity, previous studies have reported increase in expressions of these methyltransferases after exposure to VOCs (Chatterjee et al., 2023). DNA methylation occurs in the promoter regions and gene bodies, suppressing and activating the expression of downstream genes. Generally, DNA hyper-methylation leads to downregulation of gene expression, while hypo-methylation is responsive to upregulation (Chen et al., 2017b). Investigating the correction between DNA methylation and gene expression is beneficial for accurately identify epigenetic markers of VOC exposure. Studies have characterized the relationships between DNA methylation and toxicity effects to further identify the epigenetic mechanisms of carcinogenesis related cancer, tumor and other adverse outcomes. It is found that methylated *GSTP1*, $p16^{INK4a}$ promoters in organic solvents and paint exposed car painters are more likely to have an increased MN frequency compared with unexposed individuals (Hoyos-Giraldo et al., 2016). In another epidemiology study, hypermethylated $p16^{INK4a}$ is determined to be positively correlated with chromosomal abnormalities and risk of miscarriage in BTEX exposed female gas station workers (Silvestre et al., 2020). There are also evidences that VOCs cause hyper/hypomethylate of genes involved in multiple biological signaling disorders such as dendritic complexity and abnormal patterning of synapses, cell surface receptor-linked signal transduction, JAK-STAT signaling pathway (Table S5), potentially providing biomarkers for early disease diagnosis.

5.1.2. Histone modification

Histone modification, such as histone acetylation and methylation, is served as hallmarks of chromatin organization and gene activation (Chen et al., 2017b; Portela and Esteller, 2010). Following widely adoption of epigenetics in environmental epidemiology and toxicology studies, regulation in histone marks have been reported in response to VOCs in human and in cell lines. H3K4me3 is one of an active histone mark contributing to DNA repairing, the enhanced H3K4me3 modification in buffy coats samples of low-level benzene-exposed workers is associated with the increased concentration of *S*-phenylmercapturic acid and decreased white blood cell counts (Li et al., 2018). Higher level of H3K4me3 modification is also confirmed in primary human lymphocytes and HL-60 cells exposed to hydroquinone, a metabolite of benzene (Li et al., 2018; Mancini et al., 2017). Besides, oxidative stress is suppressed by endogenous histone modification inhibitor (β-hydroxybutyrate) (Shimazu et al., 2013). Previous studies have indicated that histone modification might be a potential mechanism of oxidative stress induced by acrylamide and formaldehyde in THP-1 (Hung et al., 2021) and Beas-2B (Gonzalez-Rivera et al., 2020) cells. Taken together, these results indicate that VOCs could cause adverse health effects in human through histone modification.

5.1.3. MicroRNAs (miRNAs)

miRNA, regulator of mRNA expression, is served as novel and sensitive biomarkers in blood, cell and tissue samples for pollutant toxicology research and disease diagnosis. Regulated miRNAs related to cancer pathway are widely accepted in cell, mouse and human studies exposure to VOCs, such as BTEX and formaldehyde. Downregulated miR-33, miR-330, miR-450, miR-181a, and miR-10b are validated in A549 cells exposure to formaldehyde, accompanied by increased levels of the inflammatory mediator IL-8 (Rager et al., 2011). Toluene, ethylbenzene and xylene lead to increase in hsa-miR-483-5p, hsa-miR-718, and hsa-miR-3663-3p expressions in HL-60 cells, which are predicted to be associated with genes related to the chronic myeloid leukemia pathway, including mitogen-activated protein kinase 1 (MAPK1), cyclin dependent kinase inhibitor 1 A (CDKN1A), and tumor protein p53 (TP53) (Lim et al., 2016). VOC occupational exposure population including firefighters and painters subject to increased cancer risk with aberrant miRNA expression, such as tumor related miR-342-3p, miR-223-3p, and miR-486-3p (Dai et al., 2023; McHale et al., 2011). Downregulated 221-3p, miR-181a-5p, 342-3p, 223-3p and upregulated miR-638 are show dose-response relationship with BTEX exposure in serum samples of painting workers, which are closely related to tumor pathway and carcinogenic process (Dai et al., 2023).

VOCs induced nervous system diseases, including cognitive disorder and Alzheimer's disease, are proved to be associated with disordered miRNA expression. In human, occupational exposure to toluene is associated with upregulated miR-15a-5p, miR-15b-5p and miR-16-5p, which mediate Ras signaling pathway and induce structural abnormalities in neurons (Yu et al., 2022). Toluene exposure leads to upregulation of miR-7109-5p, miR-4478, miR-6807-5p, miR-371a-5p, miR-1185-1-3p and miR-1290 in HL-60 cell exosome, of which putative target genes (e.

g. exosome component 6 and golgin A4) are mostly related to nervous system disease (Lim et al., 2017).

Large numbers of VOCs mediated miRNAs are verified in epidemiology studies and biological models, contributing to accurate selection of biomarkers. Maternal increased miR-223 expression exposure to benzene and toluene negatively associated with Treg cell numbers in infants, indicating allergy risk in later life (Herberth et al., 2014). *In vitro* and *vivo* studies using HepG2 cells and C57BL/6 mice have proved that miR-92a-1-5p can mediate mitochondrial function and mitophagy through modulating BNIP3L (BCL2/Adenovirus E1B protein-interacting protein 3-like), which play a key role in *N*, *N*-dimethylformamide induced hepatoxicity (Xu et al., 2022). Administration miR-153-3p antagomir effectively attenuates formaldehyde induced cardiomyocyte apoptosis and fetal cardiac fibrosis in SD rats through βII-spectrin pathway (Yang et al., 2021). Thus, investigation of miRNAs is helpful to better understand the pathogeneses of disease caused by VOC exposure and potential therapeutic targets in the future.

5.1.4. Long non-coding RNAs (lncRNAs)

lncRNAs is still a relatively new area of environmental toxicology. Although lncRNAs do not encodes proteins, they can participate in the regulation and maintenance of homeostasis in organisms through multiple biological process, such as cell differentiation, apoptosis and proliferation (Hu and Yu, 2019). Perturbations of lncRNA have been detected in peripheral blood and in vitro cell samples, accounting for effect endpoints observed in human. lncRNAs NEAT1 is associated with nerve system disorder, studies suppose NEAT1 as a potential epigenome marker for neurodegenerative diseases. Yu et al. (2022) suggest that toluene exposure associated with neurological disorders, as lncRNAs NEAT1 is significantly downregulated in toluene-exposed workers and mice. As for carcinogenesis risk, a study performed on benzene-exposed workers finds that lncRNA NR-028291 and NR-045623 are important genes related to benzene hematotoxicity through immune response (Bai et al., 2014). Similarly, lymphoblastoid cell line TK-6 and workers subjected to hydroquinone and benzene result in decreased expression of lncRNA FAS antisense RNA 1 (FAS-AS1) and increased DNMT3b (Yuan et al., 2020).

5.2. Transcriptomics

Transcriptomics is a bottom-up approach to in-depth analysis of key stress response, biological processes and signaling pathways of various environmental stimulation and disease progress phenotypes from the genome-wide scale (Schirmer et al., 2010). Transcriptomics has the advantages to reveal altered endotype of lung injury, hematological disease, reproduction toxicity and nervous system damage; and to find new biomarkers exposure to VOCs in organisms. A summary of transcriptomic studies is listed in Table S6.

Genotoxicities of VOC exposures are frequently reported in transcriptome studies. Eaves et al. (2020) find that benzene is correlated with most differential gene expression in A549 cells exposed to ambient air pollutants, where inflammation and cancer pathway related TNF and interferon regulatory factor 1 (IRF1) are the two genes most obviously upregulated. Formaldehyde exposure upregulates the expression of histone cluster 1 (HIST1H2AC), SET-domain-containing 2 (SETD2) and breast cancer susceptibility protein-1 (BRCA1) in Beas-2B cells, which are involved in chromatin modifying enzymes, DNA damage response and signal transduction by p53 class mediator pathways (Gonzalez-Rivera et al., 2020). In addition, numerous studies have proved the genotoxic effects of BTEX, hexanal, formaldehyde and other VOCs on SD rats, Fischer 344 rats and human blood cells (Table S6).

Immune effect is also commonly focused, and transcriptomics expands underlying mechanisms for VOC induced immune diseases. Perturbed expressions of immune activation, development and differentiation related pathway are observed in rodent and human studies. Maternal benzene exposure results in reduced expression of several interferon-stimulated genes in placenta tissue, such as interferon-inducible transmembrane 1 (IFITM1), IFITM3, IFIT1, and IFI213 (Maxwell et al., 2023). Immune response related genes, including IL-1 A, CCL20, C-type lectin receptor 5 A (CLEC5A), interleukin 1 receptor antagonist (IL1RN), proteoglycan 2 (PRG2) are reported to be potential biomarkers in peripheral blood cells of shoe manufacturing workers occupationally exposure to benzene (McHale et al., 2011). Meanwhile, it is proposed that the immune response may be activated by upregulated expression of genes for inflammatory cytokines, such as LEPTIN, IL-10, CCL2, vascular endothelial growth factor (VEGF), and CCL12.

Two latest animal studies have demonstrated that maternal exposure to benzene during pregnancy affects disease risk to offspring. Koshko et al. (2023) find that benzene exposure during gestation of maternal C57BL/6JB mice causes alteration of hypothalamic transcriptome in male offspring, in which upregulated markers microsomal triglyceride transfer protein (MTTP), serine/threonine kinase 3 (STK3), uncoupling proteins 2 (UCP2), carnitine O-acetyltransferase prepropeptide (CARTPT) and fibroblast growth factor 2 (FGF2) are reported to involved in metabolic signaling pathways mediated central nervous system development and function. Besides, hemorrhage and abnormal organ development are also found in mouse fetuses after a maternal benzene exposure (Maxwell et al., 2023). Downregulated expressions IFITM1, immunoglobulin superfamily member 1 (IGSF1), RUNX family transcription factor 3 (RUNX3), DNMT1 and DNMT3 are all associated with inhibition of interferon pathway and abnormal T cell differentiation, which plays vital roles in immunologic response in offspring (Maxwell et al., 2023).

Transcriptomics-based biomarkers can be used to explain why exacerbating effects of VOC exposure on existing diseases. For example, vinyl chloride exposure was demonstrated to aggravate western diet caused liver injury through MLX interacting protein like (MLXIPL) and MYCN proto-oncogene, BHLH transcription factor (MYCN) regulated metabolic pathways and ribosomal processes (Liu et al., 2023a).

5.3. Proteomics

Proteomics studies make it possible to acquire biomarkers of environmental exposure and to monitor early health risks of diseases (Suhre et al., 2021). Proteomics-based studies are summarized in Table S7. Benzene is one of the typical aromatic hydrocarbon VOCs and a class I carcinogen. Few works have reported the regulated proteins in serum samples of animal and human exposure to benzene. Based on a study in BALB/c mice, Qiao et al. (2023) suggest downregulated proteins including CD22, BCL10 immune signaling adaptor (BCL10) and NF-kB p65 in spleen tissues, which are involved in immune dysfunction pathways, such as leukocyte transendothelial migration processing, B cell receptor signaling pathway, and presentation, and Th17 cell differentiation. In previous human studies, several altered proteins in serum samples are identified and validated by various biological methods (e.g., ELISA and Western Blot) (Huang et al., 2012; Zhang et al., 2018). Plasminogen, apolipoproteinA-1, alpha-1-antitrypsin (AAT) and complement C3 are proved to be upregulated in chronic benzene-poisoning subjects with aplastic anemia and pancytopenia, while platelet basic protein and apolipoprotein B100 are downregulated (Table S7). These proposed biomarkers of benzene exposure are reported to be related to pathways related to immuno- and hematotoxic effects.

Besides, studies have investigated impact of other VOC types in cell model and laboratory mice. For example, *N*, *N*-dimethylformamide exposure leads to the disturbance of metabolic process and signaling pathway in primary human hepatocytes at protein level, mainly including N-glycan biolysis, glutathione metabolism, primary bile acid metabolism and mitochondrial dysfunction (Xu et al., 2020). In Wistar rats, low concentration of formaldehyde exposure activates PI3K-AKT pathway to inhibit caspase activity and survive cells against apoptosis, where Ras and Akt proteins are accumulated; and Caspase 3 protein

decreases (Mohanty et al., 2020). There appears to be a series protein markers involved in various biochemical functions, and these functions are more likely to be affected by VOC exposure.

5.4. Metabolomics

Metabolomics is the youngest of the omics technologies which is currently adopted to identify and further quantify global profiling of both endogenous (effect biomarkers) and exogenous (exposure biomarkers) molecules in cells, tissues and biofluids with the aid of advanced detection and bioinformation analysis technology (Jeddi et al., 2021; Johnson et al., 2016). Integrating various biochemical approaches, these small molecular metabolites reveal subtle alterations in biological pathways, which provide underlying mechanisms linking with aberrant processes and phenotype of diseases under stress conditions (Johnson et al., 2016; Sun et al., 2022a). Environmental metabolomics has been carried out on exposome investigation to determine the exposure status and chemical associated health risk of individuals. Furthermore, laboratory-controlled metabolomics using animal and cell models are applied to find key molecular changes and potential biomarkers of chemical exposure related biochemical endpoints, such as oxidative stress and endocrine disruption (Beale et al., 2022). Since metabolites shape etiology of environmental pollutants-induced diseases through disordering metabolic pathways such as hematological disease, it is important to focus on disordered metabolites associated with the exposure of environmental xenobiotics, such as VOCs. A summary of metabolomic studies is listed in Table S8.

It is acknowledgeable that metabolites mediate oxidative stress is consider to contribute to imbalanced cellular homeostasis and dysfunction. Studies have shown altered levels of metabolites involved intracellular oxidation exposure to single or complex mixture of VOC *in vitro* and animal models. 1,4-Benzoquinone exposure leads to oxidative stress and system inflammation in human peripheral blood B lymphocyte cells via upregulated glycine/glycine *N*-methyltransferase/sarcosine axis, and Zhang et al. (2021) propose that elevated ratio of two amino acids sarcosine and glycine can be novel biomarker to identify benzene exposure induced metabolic disorder and potential hematotoxicity risk in human. Xu et al. (2020) report that *N*, *N*-dimethylformamide tends to cause hepatotoxicity in primary human hepatocytes through disturbing N-Glycan biosynthesis, primary bile acid biosynthesis, mitochondrial dysfunction and glutathione depletion pathways. Further, several biomarkers (including downregulated taurine, glycine, carnitine, acetylcarnitine and glutathione; and upregulated orotic acid and acetyl-spermidine) are found involved in enhanced ROS production, inflammation process and lipid peroxidation. Metabolomics studies have also demonstrated that VOC exposure causes disorders of lipid metabolism in mice and humans, and further contributes to oxidative stress and metabolic reprogramming of cancer (Guo et al., 2022b). Furthermore, an advanced lipidomic assay can be conducted to accurately assess damage and reveal the interactions between VOC exposure and organisms (Miao et al., 2023).

Sometimes, biomarkers can be differed from sample types. Wang et al. (2020, 2017) find that tryptophan and sphingosine in serum samples of workers are related to neurotoxicity caused by long-term exposure to acrylamide, while urinary anthranilic acid and β-guanidinopropionic acid also play relatively important roles. Besides, it is necessary to note that metabolism induced by environmental pollutants is differed from age, gender and lifestyle. For example, long-term exposure to petrochemical pollution (heavy metals, PAHs, VOCs) interferes metabolism of tryptophan and phenylalanine metabolism in children, while glycine, serine, and threonine metabolism in the elderly, resulting in early health effects such as oxidative stress (Chen et al., 2017a).

5.5. Multi-omics

The occurrence of an effect endpoint often involves intricate biological pathways, including gene regulation, protein synthesis, and metabolic alterations. In environmental toxicology, multi-omics profiling integration technologies are able to improve the sensitivity and accuracy of the assessment of disease risks orchestrated by environmental chemicals at multiple molecular levels, and comprehensively reveal the interactions between organisms and environmental exposure (Miao et al., 2023). Herein, multi-omics data are integrated to gain a deeper understanding of the underlying biological mechanisms responsible for the toxic effects of VOCs.

Lipids play key role in cell, tissue and organ physiology, in common with many environmental chemicals, VOC exposure interferes with lipid acid metabolism prominently. Numerous studies have demonstrated perturbated lipid acid metabolism following VOC exposure associated with multiple disordered proteins and genes. Yu et al. (2021) find that benzene exposure results in increased 1-acyl-sn-glycero-3-phosphocholine and phosphatidylethanolamine, while phosphatidylcholine and phosphatidylserine decrease in C57BL/6 mice. The results were explained as decline in the mRNA levels of phosphatidylserine synthase 1 (PTDSS1) and PTDSS2, which are key enzymes response for glycerophospholipid pathway. They also find upregulated Capase-3 and Bax/Bcl-2 ratio, which is supposed to mediate downregulated glucosylceramide and further cell apoptosis. Miao et al. (2023) demonstrate that indoor relevant VOC exposure in C57BL/6 J mice promotes the expression of diacylglycerol kinase theta (DGKQ) through FoxO transcription factors (Foxo1 and Foxo2), disturbing the interconversion of diacylglycerol and phosphatidic acid, and resulting in decreased triacylglycerol. Furthermore, Sun et al. (2016) find that, at the protein level, VOC can disturb the expressions of enzymes, turn out to regulate lipid metabolism and lead metabolic diseases. Induction of fatty acid transport and β-oxidation is observed in benzene exposed C3H/He mice with increased expression of related genes, including carnitine palmitoyl transferase 1 A, carnitine *O*-acetyltransferase (CART), acetyl-CoA acyltransferase 2, aldehyde dehydrogenase 1 family member L2, very long-chain acyl-CoA dehydrogenase (ACADVL), carnitine O-octanoyltransferase and enoyl-CoA hydratase, short chain 1. They also demonstrate increased expressions of CART and ACADVL associated with decreased white blood cell counts, indicating that benzene induce hematotoxicity through fatty acid β-oxidation pathway (Sun et al., 2018). The adverse outcomes induced by VOCs are often initially caused by their binding and activation of receptors, which leads to metabolic disorders. Peroxisome proliferator-activated receptors (PPARs) is one of the molecular targets interacts with VOCs, which can regulate fatty acid disposition and lead to multiple metabolic diseases. Fang et al. (2013) find the upregulated PPARα related genes (including ACOX1, CYP4A10, ACADM, EHHADH, ACADL and ACAA1A) being associated with trichloroethylene exposure in livers of C57BL/6 mice, which are negatively correlated with fatty acid metabolism in serum. The above results demonstrate that abnormal activation of receptor proteins after VOC exposure interferes with the homeostasis of lipid metabolism.

Summarily, enormous omics profiling offers a comprehensive characteristic of disordered biological molecular (e.g. gene expression, metabolites and proteins) and deep understanding of key events (e.g. oxidative stress, inflammation response, and DNA damage) associated with VOC exposure within a batch analysis. As a limitation, these laboratory-controlled new biomarkers obtained from high throughput omics technologies are lack of persuasiveness for characterizing population exposure to VOCs and individualized prediction of exposure risk until their effectiveness is fully proved. First, due to temporal and spatial variety of VOC exposure, human based omics study is supposed to execute with a longitudinal sampling at multiple time in a single day or during certain life stage to accurately depict an individual's exposure characteristics (Baccarelli et al., 2023). Second, with the aid of multiple analysis models and tools (e.g. geospatial methods, WQS regression

model and *R* package), integrating bulky individual information, external environmental exposure data, omics profiling in various human specimens and disease indicators is a key step to identify and obtain plausible new biomarkers associated with disease risk. Third, biomarker kinetics, including dose-response and time-response in *in vitro* cell culture and animal studies, accompanying with toxicology knowledge and *in vitro* analysis are necessary to define the suitability of a presumptive biomarker related to VOC exposure.

6. Summary and perspective

Combination of multiple biomarkers summarized herein bridges the gap between VOC exposure, disrupted biological responses and health outcomes in the occupational and general population. The concentrations of unmetabolized and metabolized VOCs in human specimens (e.g. urine, blood and exhaled breath) vary from exposure sources, individual differences and lifestyles of exposed people. Among them, blood VOCs can reflect the internal exposure dose; urinary metabolized VOCs are stable biomarkers for indicating the characteristics of external exposure and association with disease symptoms. Generally, VOCs-induced health outcomes, including hematotoxicity, respiratory toxicity, immunotoxicity and neurotoxicity can be attributed to oxidative stress, inflammation response and DNA damage. These endpoint effects related biomarkers (e.g. ROS, antioxidant enzyme activities, and lipid peroxidation products; inflammatory mediators and inflammation cells; productions of DNA damage and chromosomal abnormality) are maturely verified in cells, animals and epidemiology studies. Some of effect biomarkers are not accurate for a specific disease, since several tissues and organs undergo the same biological signaling pathway. Furthermore, disorders in omics-based biomarkers at gene, protein, lipid and metabolite aspects providing depth understanding of molecular mechanism of key biological events and pathological processes. These molecular alterations can explain the pathogenesis of VOC orchestrated diseases, and thus predict and intervene environmental burden in later life. However, such new biomarkers urge for comprehensive validation to apply in future studies.

Indeed, the health risks adversely affected by environmental exposure of individuals or special groups (e.g. occupationally exposed group and patient group) can be determined by monitoring various biomarkers. However, in epidemiological studies, even in the same subpopulation where individuals subject to the similar exposure scenario, only a small proportion of them are diagnosed with diseases related to environmental exposure, such as lung diseases (Simkovich et al., 2019). In addition, VOCs are merely one types of environmental exposures (drug, bacteria, diet, etc.) in the most subpopulations, and their contributions to an individual's health risks throughout their whole life are unclear. Therefore, it is a huge challenge to take environmental exposure characteristics (exposure source, exposure amount, etc.) and individual difference information (physiological differences, lifestyles, etc.) into consideration to determine accurate and efficient biomarkers, taking prevention as the premise, and ultimately reduce the health burden of environmental exposure. Recently, the application of exposomes can facilitate the identification of exposure, effects and omics biomarkers, as well as individual sensitivity factors related to VOC exposure over a complete lifetime in a longitudinal study. Moreover, during the verifying these plausible biomarkers through *in vitro* and *in vivo* toxicity experiments, indiscriminate testing without pre-selection or priority ranking increases cost, time and the incorrect risk assessment. Advanced machine learning and bioinformatics methods can more efficiently determine biomarkers that are most relevant to individual high exposure rates or high disease risks, or specific toxic effects in cells and animals, enabling more biomarker identification.

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CRediT authorship contribution statement

Qianyong Shen: Writing – original draft, Validation, Investigation, Data curation. **Yalin Liu:** Visualization, Validation. **Guiying Li:** Writing – review & editing, Funding acquisition. **Taicheng An:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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