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Characterisation of volatile organic compounds in hospital indoor air and exposure health risk determination

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\textbf{A R T I C L E I N F O}

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Cancer risk
Healthcare workers

\textbf{A B S T R A C T}

Several volatile organic compounds (VOCs) have impacts on human health, but little is known about the concentrations of VOCs in the hospital environment. This study characterised VOCs present in clinical assessment rooms. More than 600 samples of air were collected over 31 months (2017–2020) at two hospital sites in Leicester, United Kingdom, and analysed by comprehensive two-dimensional gas chromatography, making this the largest hospital environment database worldwide on VOCs and first such UK study. The most abundant VOCs found were 2-propanol, ethyl chloride, acetone and hexane, with respective mean concentrations of 696.6 \(\mu\)g/m\(^3\), 436.5 \(\mu\)g/m\(^3\), 83.9 \(\mu\)g/m\(^3\) and 58.5 \(\mu\)g/m\(^3\). Acetone, 2-propanol and hexane concentrations were 4, 9 and 30-fold higher respectively compared to similar studies performed in other hospitals. Our results showed that the most frequently detected VOCs, with the highest concentrations, were most likely released by healthcare activities, or related to ingress of vehicle emissions. Hazard quotient (HQ) and cancer risk (CR) were calculated to identify the potential risk of VOCs exposure to the health of healthcare workers. No HQs were measured above 1, compared to inhaled US EPA and OEHHA health guidelines for non-cancer chemicals. For both hospitals, trichloroethylene CR were calculated above 1E-06 by using inhaled US EPA cancer risk values, leading to possible risks to healthcare workers with long-term exposure. More studies of this type, including measurements of VOCs such as formaldehyde that we were unable to include in this study, are needed to better characterise exposures and risks, both to healthcare workers and patients.

1. Introduction

Indoor air is composed of a complex mixture of particles and gases, including chemical pollutants. The common pollutants studied in hospital indoor air include particulate matter, carbon monoxide, carbon dioxide, and ozone. Little is known about volatile organic compound (VOC) composition or abundance within this environment. VOCs are a class of chemical pollutant of particular interest [1,2], emitted by a wide range of activities, materials (e.g. building materials, decoration, furniture) [3] and factors, from both inside [4] and outside the building (e.g. vehicle emissions) [2]. When combined, these influencing factors result in a modified VOC composition, and are common to the majority of public and private buildings. However, hospital indoor air has additional VOC emissions owing to the activities carried out within the hospital buildings, including anaesthetic gases, disinfectant, hand sanitiser, pharmaceuticals and cleaning products [5,6]. These multiple emission sources can lead to the presence of high concentration of VOCs indoors.
VOC exposure can lead to various negative health effects [7-13], such as eye, nose or throat irritation, and headache in the short-term [7] but more hazardous long-term effects may also occur from certain VOCs. In the United Kingdom (UK), to regulate the workplace exposure of VOCs, short and long-term exposure limits have been defined, by the Health and Safety Executive (HSE) [14]. Recently UK Health Security Agency (UKHSA) published indoor air quality guidelines on 11 VOCs of concern for their potential health impact in the general population [7]. This guideline includes benzene, formaldehyde and trichloroethylene, all classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC). This list also classified, styrene and tetra-chloroethylene as probable carcinogens, and carbon tetrachloride, acetaldehyde and ethylbenzene as possible carcinogens [8]. Some VOC exposures are linked to respiratory symptoms, such as 2-ethyl-1-hexanol which can lead to exacerbation of asthma symptoms [9] and naphthalene to respiratory tract lesions [10]. VOCs can produce health effects by direct contact, especially through skin contact as well as through inhalation. Diethyl phthalate and limonene exposure can lead to skin irritation [11,12], whereas 2-propanol may induce skin allergic reactions in some individuals [13].

Characterisation of VOCs composition and abundance in hospital indoor air is important, especially for healthcare workers who are constantly exposed to this complex VOC mixture through both inhalation and skin contact. LeBouf et al. [15] reported that healthcare workers were exposed to higher total VOC (TVOC) concentration than other hospital workers. Indeed, nursing assistants and practical nurses were respectively exposed to a personal TVOC concentration at 9200 μg m⁻³ and 8700 μg m⁻³, compared to clinical laboratory technicians who were exposed to a personal TVOC concentration of 2000 μg m⁻³ [14].

Several studies have examined the impact of indoor air quality on healthcare workers [16-20]. Hellgren et al. [17] reported that hospital staff have more symptoms than the office workers in the same hospital. The most commonly reported symptoms were irritation of the nose (25% of the participants), hands (24%) and eyes (23%), and fatigue (21%) at the paediatric admissions unit (LRI1 n = 52 samples) and the second at the paediatric respiratory physiology laboratory (LRI2 n = 31 samples), of the Department of Respiratory Medicine, Thoracic Surgery, Clinical Immunology and Allergy of LRI. 530 room air samples were collected in two testing rooms of the Respiratory Biomedical Research Centre (GGH1 n = 132 samples; GGH2 n = 347 samples) and in one testing room of the Clinical Decisions Unit (GGH3 n = 51 samples) of GGH.

2.2. Sampling procedure

One litre of room air was actively sampled onto Tenax/TA with Carbograph LTD sorbent tubes (Hydrophobic, Markes International Ltd Llantrisant, UK) using a battery-operated pump (Escort Pump, Sigma Aldrich), operated at 500 mL/min at a height of 1.5 m above the ground. The healthcare workers collecting samples were instructed to clean their hands with soap and water, not hand sanitiser before putting on gloves. The sorbent tubes were pre-conditioned for 2.5 h at 330 °C in 50 mL/min CP grade N₂ (BOC). The VOC samples collected on tubes, along with control blank tubes, were immediately capped (brass caps, Markes International Ltd, Llantrisant, UK) and analysed within 2 months.

2.3. GCxGC

2.3.1. Internal standard addition

An internal standard solution was prepared from 2000 μg mL⁻¹ toluene-d₈ and phenanthrene-d₁₀ certified reference solutions (Sigma Aldrich, Dorset, UK) and n-octane-d₁₈ (D, 99% Cambridge Isotope Laboratories, Tewksbury, US). The deuterated materials were combined and diluted in methanol to give a final concentration of 20 μg mL⁻¹ per analyte. Before analysis, the samples were loaded with the internal standard solution using the calibration solution-loading rig (CSLR, Markes International Ltd, Llantrisant, UK). A 0.6 μL aliquot of internal standard solution was injected onto the tube in a stream of nitrogen at a flow rate of 100 mL min⁻¹ for 2 min, purging the excess solvent [23].

2.3.2. Calibration standards

A 100 μg mL⁻¹ multi component air standard (47537-U Sigma Aldrich, Dorset, UK) was diluted in methanol to give final concentrations of 100, 50, 25, 10, 5, 2.5, 1 and 0.5 μg mL⁻¹. A multi component air standard mixture was done to target the most abundant VOCs detected in the samples, including ethyl chloride, isopropylsulfonyl chloride, 2-methylbutane, hexamethyldisiloxane, cyclooctane, octanol, hexanal, isoprene, diethyl-phthalate, octamethylyclosiloxane, naphthalene, 2-ethyl-1-hexanol and benzaldehyde (Sigma Aldrich, Dorset, UK). Each individual sample was diluted in methanol to give final concentrations of 100, 50, 25, 10, 5, 2.5, 1 and 0.5 μg mL⁻¹. Standards were loaded onto sorbent tubes into a stream of N₂ (zero grade, BOC) at 100 mL min⁻¹ and purged for 2 min.

2.3.3. TD-GC × GC-MS/FID analysis

Analysis by two-dimensional gas chromatography was carried out on an Agilent 7890A gas chromatograph, with a G3486. A Capillary Flow Technology flow modulator and three-way splitter plate coupled to a flame ionisation detector and a HES 5977B quadrupole mass spectrometer with election ionisation (Agilent Technologies Ltd, Stockport, UK). Full details of the method and performance are given in Wilde et al. [24].

Briefly, the column configuration was a Rxi-5Sil MS 30 m × 0.25 mm x 0.25 μm primary column (Thames Restek Ltd, Saunderton, UK) and a DB-WAX 4 m × 0.25 mm x 0.25 μm as the secondary column (Agilent Technologies Ltd, Stockport, UK). The GCxGC was interfaced with a Markes TD-100xrt thermal desorption autosampler (Markes International Ltd, Llantrisant, UK). Tubes were pre-purged with carrier gas for 1 min at 50 mL min⁻¹ and then desorbed at 300 °C for 5 min with a
flow of 50 mL min$^{-1}$ onto a ‘hydrophobic, general’ trap (Markes International Ltd, Llantrisant, UK) held at –10 °C. The trap was then purged for 2 min at 2 mL min$^{-1}$ before being heated at the maximum heating rate to 300 °C for 5 min with a split flow rate of 2 mL min$^{-1}$.

Data were acquired in MassHunter GC-MS Acquisition B.07.04.2260 (Agilent Technologies Ltd, Stockport, UK) and the data were processed by using GC Image™ v2.6 along with Project and Image Investigator (JSB Ltd, Horsham, UK), following the protocol developed by Wilde et al. [25].

### 2.4. Volatile organic compounds

Only VOCs meeting the frequency of observation threshold with concentrations above their limit of detection (LOD) for more than 50% of the samples were included in the analysis, corresponding to 36 VOCs (Table 1). Experimental LOD were defined as three standard deviations above the mean signal from 22 field blanks. These 36 VOCs included the most abundant VOCs detected in the samples, and the VOCs identified as having an impact on human health. The LOD for the 36 VOCs are summarised in the Supplementary Table 1.

The term TVOC in this study is defined as the sum of the 36 VOCs detailed in Table 1. The method used for this study allowed a quantification of VOCs with a number of carbons between three and 16. VOCs have been regrouped depending of their emission sources. “Outdoor VOCs” measured in the indoor air samples were traffic emission derived cyclopentane, hexane, toluene, 2-methylbutane, m/p-xylene, o-xylene, octane and heptane based on Sheepers et al. [2]. “Anaesthesia VOCs” corresponds to the only anaesthetic measured, ethylchloride [26]. “Cleaning products VOCs” regroups limonene and alpha-pinene based on Steinemann et al. [27]. “Alcohol-based product VOC” corresponds to

<table>
<thead>
<tr>
<th>VOCs</th>
<th>LRI concentration (µg·m$^{-3}$)</th>
<th>GGH concentration (µg·m$^{-3}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohols</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Propanol</td>
<td>696.6 (1275.7)</td>
<td>307.2 (644.7)</td>
</tr>
<tr>
<td>2-Ethyl-1-hexanol</td>
<td>11.2 (10.2)</td>
<td>14.92 (7.5)</td>
</tr>
<tr>
<td>Ketones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td>78.6 (95.2)</td>
<td>83.96 (178.2)</td>
</tr>
<tr>
<td>2-Butanone</td>
<td>5.2 (3.4)</td>
<td>4.67 (2.1)</td>
</tr>
<tr>
<td>4-Methyl-2-pentanone</td>
<td>0.7 (0.1)</td>
<td>0.7 (0.2)</td>
</tr>
<tr>
<td>Aromatic hydrocarbons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>m/p-Xylene</td>
<td>1.5 (2.4)</td>
<td>0.7 (0.6)</td>
</tr>
<tr>
<td>o-Xylene</td>
<td>0.2 (1.5)</td>
<td>0.3 (0.5)</td>
</tr>
<tr>
<td>Steryrene</td>
<td>&lt; LOD</td>
<td>0.6 (0.7)</td>
</tr>
<tr>
<td>Toluene</td>
<td>1.3 (3.1)</td>
<td>2.7 (2.2)</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>2.7 (0.9)</td>
<td>3.1 (1.9)</td>
</tr>
<tr>
<td>Aliphatic hydrocarbons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hexane</td>
<td>58.3 (58.17)</td>
<td>58.5 (77.3)</td>
</tr>
<tr>
<td>Heptane</td>
<td>1.3 (2.3)</td>
<td>1.1 (0.6)</td>
</tr>
<tr>
<td>Octane</td>
<td>&lt; LOD</td>
<td>5.1 (10.1)</td>
</tr>
<tr>
<td>Cyclcopentane</td>
<td>14.9 (18.2)</td>
<td>49.3 (48.2)</td>
</tr>
<tr>
<td>2-Methylbutane</td>
<td>9.2 (8.9)</td>
<td>26.8 (22.9)</td>
</tr>
<tr>
<td>2,4-Dimethylpentane</td>
<td>&lt; LOD</td>
<td>1.8 (1.2)</td>
</tr>
<tr>
<td>2,2,4-Trimethylpentane</td>
<td>1.4 (4.4)</td>
<td>0.9 (0.8)</td>
</tr>
<tr>
<td>Aldehydrals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hexanal</td>
<td>3.7 (1.0)</td>
<td>7.6 (4.2)</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>1.5 (1.8)</td>
<td>2.8 (2.8)</td>
</tr>
<tr>
<td>Octanal</td>
<td>6.4 (2.2)</td>
<td>11.7 (6.2)</td>
</tr>
<tr>
<td>Nonanal</td>
<td>&lt; LOD</td>
<td>5.7 (3.3)</td>
</tr>
<tr>
<td>Terpenes and terpenoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limonene</td>
<td>3.33 (5.7)</td>
<td>2.2 (4.5)</td>
</tr>
<tr>
<td>Isoprene</td>
<td>65.4 (56.2)</td>
<td>89.5 (176.5)</td>
</tr>
<tr>
<td>Alpha-pinene</td>
<td>1.0 (3.2)</td>
<td>1.0 (3.2)</td>
</tr>
<tr>
<td>Halogenated hydrocarbons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>1.1 (0.9)</td>
<td>4.1 (3.2)</td>
</tr>
<tr>
<td>Tetrachloroethylene</td>
<td>&lt; LOD</td>
<td>0.4 (0.4)</td>
</tr>
<tr>
<td>1,1,1-Trichloroethane</td>
<td>1.1 (0.4)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>2.0 (5.2)</td>
<td>1.7 (4.6)</td>
</tr>
<tr>
<td>1,2-Dichloroethylene</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.3)</td>
</tr>
<tr>
<td>1,2-Dichloropropane</td>
<td>0.2 (0.1)</td>
<td>0.25 (0.1)</td>
</tr>
<tr>
<td>Ethyl chloride</td>
<td>436.5 (1295.5)</td>
<td>37.7 (36.2)</td>
</tr>
<tr>
<td>Isopropylsulfonyl chloride</td>
<td>49.2 (23.5)</td>
<td>48.2 (21.3)</td>
</tr>
<tr>
<td>Ethers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>2.3 (4.3)</td>
<td>1.9 (0.9)</td>
</tr>
<tr>
<td>Diethyl phthalate</td>
<td>11.1 (8.1)</td>
<td>12.7 (11.9)</td>
</tr>
<tr>
<td>Siloxanes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octamethyldicyclosiloxiane</td>
<td>6.2 (4.6)</td>
<td>12.6 (28.6)</td>
</tr>
<tr>
<td>Hexamethyldisiloxane</td>
<td>63.2 (481.4)</td>
<td>5.3 (12.2)</td>
</tr>
</tbody>
</table>

Table 1

VOC concentrations measured at both hospitals during the study. Mean, medium (Med), standard deviation (SD), 25th percentile (25th p.) and 75th percentile (75th p.) concentrations were calculated from the sums of all the rooms’ concentration in Leicester Royal Infirmary (LRI) and Glenfield General Hospital (GGH). Minimum (Min) and maximum (Max) values regrouped all the rooms’ concentration in each hospital.
VOC arithmetic mean and 95th percentile (worst-case scenario) concentration of the VOC at which no adverse health effect is expected. The Assessment (OEHHA) for chronic inhalation exposure limit value were concentrations were compared to the Inhalation Unit Risk (IUR) defined between concentrations were determined using an unpaired non-parametric Mann-Whitney test to compare two parameters.

2.6. Exposure risk determination

Samples were collected during 2 min over 31 months at different moments of the day during the EMBER study [21]. For exposure risk determination, VOC concentrations obtained were assumed as representative of a continuous inhalation exposure. For this reason, VOC concentrations were compared to the Inhalation Unit Risk (IUR) defined by United States Environmental Protection Agency (US EPA) to calculate cancer risk (CR). For consistency, US EPA guideline for continuous inhalation and California Office of Environmental Health Hazard Assessment (OEHHA) for chronic inhalation exposure limit value were applied to calculate hazard quotient (HQ).

2.6.1. Hazard quotient

HQ is the ratio of the exposure concentration of a VOC to the concentration of the VOC at which no adverse health effect is expected. The VOC arithmetic mean and 95th percentile (worst-case scenario) concentrations for each hospital were used as the exposure concentrations. The inhalation exposure limit values defined by US EPA and OEHHA were used as the concentration at which no adverse health effect is expected.

(1) HQ = (mean or 95th percentile concentration x exposure factor)/ US EPA or OEHHA inhalation exposure limit value

(2) Exposure factor = (8/24 h) x (5/7 days) x (40/70 years)

The hazard quotient calculation is based on the Centre for Disease Control and Prevention formula (formula 1). The HQ corresponds to the mean VOC or 95th percentile (worst-case scenario) concentrations multiplied by the exposure factor, divided by the US EPA or OEHHA inhalation exposure limit value. The exposure factor corresponds to a usual UK life work time corresponding to 8 h per day, 5 days per week over 40 years (formula 2).

2.6.2. Cancer risk

CR was determined by multiplying the mean or 95th percentile concentration of a VOC by its IUR. The VOC arithmetic mean or 95th percentile concentration for each hospital were used as the exposure concentration. IUR defined by US EPA was used.

(3) CR = mean or 95th percentile concentration x inhalation unit risk

3. Results

3.1. VOCs composition of hospital air

More than 500 VOCs were identified in the samples; however, only 36 VOCs were quantified above their limit of detection (as defined by three standard deviations above the mean signal from 22 field blanks) (Sup Table 1). 30 of the 36 VOCs quantified were detected in all the room air samples, including all the VOCs classified as alcohols, ketones, phthalates and siloxanes.

Table 1 shows the indoor air VOC concentrations measured in all the rooms of each hospital. The 10 VOCs with the highest concentration at both hospitals were, with an arithmetic mean (±SD) at LRI and GGH, 2-propanol (696.6 ± 1275.7 and 307.2 ± 644.6 μg m⁻³), ethyl chloride (436.5 ± 1295.4 and 37.6 ± 35.2 μg m⁻³), acetone (78.6 ± 95.2 and 83.9 ± 178.2 μg m⁻³), isopropene (65.44 ± 56.2 and 89.50 ± 176.5 μg m⁻³), hexane (58.34 ± 58.17 and 58.5 ± 77.3 μg m⁻³), isopropylsulfonyl chloride (49.2 ± 23.5 and 48.2 ± 21.3 μg m⁻³), cyclopentane (14.9 ± 18.2 and 49.4 ± 48.2 μg m⁻³), 2-ethyl-1-hexanol (11.23 ± 10.2 and 14.93 ± 7.5 μg m⁻³), diethyl phthalate (11.1 ± 8.1 and 12.7 ± 11.9 μg m⁻³) and hexamethyldisiloxane (63.2 ± 481.4 and 5.3 ± 12.2 μg m⁻³). Whereas six of the 36 VOCs had a mean concentration under 1 μg m⁻³ at both hospitals, these VOCs were mainly hydrocarbons.

The majority of the VOCs concentrations were similar between the hospitals with a few notable exceptions. The main differences were for hexamethyldichloride and ethyl chloride with mean concentrations in LRI that were 12 and 11 times higher, respectively, when compared to GGH.

3.2. Changes in VOCs composition by season

Fig. 1 shows the impact of the seasonality on the total VOC (TVOC) concentrations in all the hospitals rooms. TVOC concentration varied between 634.2 ± 682.9 μg m⁻³ during summer to 1089.0 ± 1582.8 μg m⁻³ during winter (Fig. 1A). TVOC concentration was significantly lower during the summer compared to the other seasons (P < 0.0001), no other significant differences were found.

The concentration of VOCs emitted by alcohol-based products during summer was also significantly lower compared to the other seasons (P < 0.0001) (Fig. 1B). The concentration of VOCs emitted by alcohol-based products was higher in winter (564.8 ± 1245.9 μg m⁻³) compared to autumn (410.0 ± 719.9 μg m⁻³), spring (306.3 ± 406.6 μg m⁻³) and summer (152.8 ± 268.4 μg m⁻³). The percentage of VOCs emitted by alcohol-based products on TVOC concentration present in the rooms varied depending of the season (Fig. 1D). The highest percentage was during winter (51%), followed by autumn (42%) then spring (32%) and summer (24%).

The concentration of VOCs emitted by outdoors activities were lower than the concentration of VOCs emitted by alcohol-based products. The VOCs released by outdoors activities represented between 13 and 18% of the TVOC concentration (Fig. 1D). Summer (18%) had the highest percentage followed by autumn (17%), while winter and spring were lower, respectively 13 and 14% of the TVOC concentration. The highest concentration of the VOCs emitted by outdoors activities was during autumn (164.4 ± 137.0 μg m⁻³), then winter (1401.3 ± 79.6 μg m⁻³) followed by spring (1256.5 ± 84.1 μg m⁻³) and summer (1077.9 ± 92.1 μg m⁻³) (Fig. 1C). The concentrations over the seasons were similar but the summer concentration was significantly lower than other seasons (P < 0.0001 compared to winter and autumn, P = 0.0196 compared to spring) and autumn’s concentration was significantly higher (P < 0.0001 compared to summer, P = 0.0004 compared to spring and P = 0.0234 compared to winter).

The percentage of VOCs emitted by anaesthesia, compared to TVOC, changed depending on the season (Fig. 1D), the percentage in summer (17%) was more than 3 times higher compared to winter (5%). The percentages of spring and autumn were similar, respectively 11 and 10%. VOCs emitted by cleaning products represented a very low percentage of TVOC concentration measured in the hospitals. The percentages were equal to or lower than 1% of TVOC for all the seasons. The VOCs emitted by mixed sources and VOCs emitted by alcohol-based products were the main sources of emission which contaminate the room air (Fig. 1D). Depending on the season, alcohol-based products emitted more VOCs than mixed sources. In winter and autumn, the percentage of VOCs emitted by alcohol-based products (respectively 51% and 42%) were higher than VOCs emitted by mixed sources (both 31%). However, in spring and summer, the VOCs emitted by mixed sources were higher, respectively 43% VS 32% and 41% VS 24%.

3.3. Variation of VOC composition between locations

Fig. 2 presents the impact of the room location and activities on the VOCs emitted in the LRI and GGH rooms. The percentage of VOCs emitted by anaesthesia, compared to TVOC, was significantly lower in the ICU rooms compared to mixed rooms (P < 0.0001) (Fig. 2A). The percentage of VOCs emitted by cleaning products was significantly higher in the ICU rooms compared to mixed rooms (P < 0.0001) (Fig. 2B). The percentage of VOCs emitted by cleaning products represented a very low percentage of TVOC concentration measured in the hospitals. The percentages were equal to or lower than 1% of TVOC for all the seasons. The VOCs emitted by mixed sources and VOCs emitted by alcohol-based products were the main sources of emission which contaminate the room air (Fig. 1D). Depending on the season, alcohol-based products emitted more VOCs than mixed sources. In winter and autumn, the percentage of VOCs emitted by alcohol-based products (respectively 51% and 42%) were higher than VOCs emitted by mixed sources (both 31%). However, in spring and summer, the VOCs emitted by mixed sources were higher, respectively 43% VS 32% and 41% VS 24%.
VOC concentrations. The results showed that the TVOC concentration in LRI was at least 1.5 times higher than in GGH (Fig. 2A). At LRI 2, TVOC concentration was significantly higher than GGH1 (p = 0.0299) and GGH3 (p = 0.0010), but not significantly higher than LRI 1. The lowest concentration was in GGH 1 (738.5 ± 483.4 μgm⁻³) followed by GGH 3 (755.3 ± 1056.4 μgm⁻³), than GGH 2 (844.1 ± 825.0 μgm⁻³), after that LRI 1 (1420.6 ± 2121.8 μgm⁻³) and LRI 2 (1733.3 ± 2395.8 μgm⁻³), which means that TVOC concentration varied more between the hospitals than within the same hospital.

The concentration of VOCs emitted by anaesthesia was significantly higher in LRI compared to GGH (P < 0.0001 for LRI 1 and 2 compared to GGH’s rooms). The highest concentration in LRI (LRI 1490.3 ± 1439.0 μgm⁻³) was 14 times higher compared to the lowest concentration in GGH (GGH 1 35.4 ± 16.7 μgm⁻³) (Fig. 2B). The concentration of VOCs emitted by anaesthesia was higher in LRI 1 (346.4 ± 976.0 μgm⁻³) compared to GGH 2 (38.6 ± 43.0 μgm⁻³) and GGH 3 (36.8 ± 16.2 μgm⁻³). VOCs emitted by anaesthesia represented 39% of TVOC concentration in LRI 1 that was 7 times higher compared to the GGH’s...
rooms where VOCs emitted by anaesthesia represented 5% of the TVOC concentration for all the rooms (Fig. 2D). Even in LRI 2 where the concentration corresponded to 19% of the TVOC concentration, the percentage was 3 times higher than in GGH’s rooms.

VOCs from alcohol-based products represented high sources of emission in all rooms (Fig. 2D) accounting for around half the TVOC concentration in LRI 2 (50%), GGH 1 and GGH 3 (both 47%). The percentage in LRI 2 and GGH 2 were lower, respectively 41 and 33%. The concentration of VOCs emitted by alcohol-based products was higher in LRI compared to GGH. The highest concentration was in LRI 2 (889.5 ± 1478.6 μg m⁻³), then LRI 1 (581.6 ± 1107.9 μg m⁻³), followed by GGH 1 (358.9 ± 428.9 μg m⁻³), GGH 3 (345.6 ± 851.4 μg m⁻³) and GGH 2 (282.0 ± 675.3 μg m⁻³).

VOCs composition of GGH indoor air was more varied compared to the air at LRI which was dominated by VOCs from alcohol-based products and anaesthesia (Fig. 2D). Outdoor activities represented only 6% of the TVOC concentration and VOCs from mixed sources correspond to 18 (LRI 1) to 25% (LRI 2) of the TVOC concentration. The percentage of VOCs from mixed sources was, however, higher at GGH. The maximum was at GGH 2, representing 43% of the TVOC concentration, followed by GGH 3 (37%) and GGH 1 (30%). VOCs from outdoor activities represent 17 (GGH 1) and 20% (GGH 2) of TVOC concentration, but the percentage in GGH 3 was twice as low (10%). For all the rooms, VOCs from cleaning products represented less than 1% of the TVOC concentration.

3.4. Healthcare worker VOC exposure

Table 2 shows the means of the VOCs mean and 95th percentile in all rooms of each hospital compared to the United States Environmental Protection Agency (US EPA) for continuous inhalation and California Office of Environmental Health Hazard Assessment (OEHHA) for chronic inhalation exposure limit value for these VOCs, and the calculated hazard quotients. Fig. 3 compares the hazard quotients for each hospital, obtained by using the mean concentration (Fig. 3A) or 95th percentile concentration (Fig. 3B). Continuous and chronic exposures were selected for these guidelines, because even if the collection time was short (2 min), the samples were collected at different days, times of the day and over a long period (31 months), so the mean and 95th percentile concentrations were considered as representative of a continuous level of exposure in these hospitals.

LRI mean and 95th percentile concentrations for ethyl chloride were above the US EPA inhalation exposure limit for continuous inhalation exposure. Naphthalene was quantified at a concentration above the US EPA inhalation exposure limit for continuous inhalation exposure for the mean concentration of GGH, and 95th percentile concentrations of LRI and GGH (Table 2).

In both hospitals, no HQ for mean concentration was above 1 (Table 2 and Fig. 3A). The three higher inhaled HQ for mean concentration were ethyl chloride in LRI (HQ = 0.59) and naphthalene in GGH (HQ = 0.14) and LRI (HQ = 0.12). No HQ for 95th percentile concentration was measured above 1 in GGH, but in LRI, the HQ for ethyl chloride 95th percentile concentration as measured to 2.44 (Table 2 and Fig. 3B).

Table 3 shows the trichloroethylene cancer risk calculated for each hospital mean and 95th percentile concentrations. All the CRs were above 1E-06. The CRs measured in GGH were higher compared to ones measured in LRI. The highest CR was the CR for the 95th percentile concentration in GGH at 1.20E-04 (Table 3).

4. Discussion

VOCs were analysed in more than 600 samples in clinical assessment rooms between 2017 and 2020 at two hospital sites in Leicester, United Kingdom. Thirty of the 36 VOCs investigated were found to be present in
Fig. 3. Hazard quotients for targeted VOCs in Leicester Royal Infirmary (LRI) (orange line) and in Glenfield General Hospital (GGH) (blue dot) for mean (A) and 95th percentile (B). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Targeted VOCs mean and 95th percentile concentrations measured at both hospitals during the study compared to the United States Environmental Protection Agency (US EPA) Inhalation Unit Risk, and calculated cancer risk (CR) for the mean and 95th percentile concentrations over the study period in Leicester Royal Infirmary (LRI) and Glenfield General Hospital (GGH).

<table>
<thead>
<tr>
<th>VOC</th>
<th>LRI Mean concentration (μg m⁻³)</th>
<th>LRI 95th percentile concentration (μg m⁻³)</th>
<th>GGH Mean concentration (μg m⁻³)</th>
<th>GGH 95th percentile concentration (μg m⁻³)</th>
<th>U.S. EPA Inhalation Unit Risk</th>
<th>Cancer risk LRI Mean</th>
<th>Cancer risk GGH Mean</th>
<th>Cancer risk LRI 95th percentile</th>
<th>Cancer risk GGH 95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichloroethylene</td>
<td>1.1</td>
<td>4.1</td>
<td>4.1</td>
<td>29.3</td>
<td>4.1 E-06</td>
<td>4.59E-06</td>
<td>1.69E-05</td>
<td>1.69E-05</td>
<td>1.20E-04</td>
</tr>
</tbody>
</table>

every sample. 2-propanol, ethyl chloride, acetone and hexane were the most abundant VOCs. Hospital activities and season influenced the VOC concentrations measured.

4.1. Comparison of VOCs concentration to previous studies

The VOC with the highest mean concentration measured in both hospitals was 2-propanol (696.9 μg m⁻³ in LRI and 307.2 μg m⁻³ in GGH (Table 1)). This result is in accordance with previous studies [1,28], however the mean concentrations found in LRI and GGH were at least 6 times higher than those found in French hospitals (between 9.8 and 47.9 μg m⁻³) studied by Baures [28] et al. and Bessonneau et al. [1]. The main source of 2-propanol in hospital is alcohol-based hand sanitiser, which is recommended by 2012 NICE Guidance [29] to be preferably used to decontaminate hands. Whisk hand sanitiser dispensers were present in all the sampling location. However, healthcare workers taking samples were specifically instructed to use soap and water as an alternative. WHO accepts two alcohol-based hand sanitiser formulations in its guideline on hand hygiene in health care [30]. The first one is mainly composed of ethanol and the second of 2-propanol. In the French hospitals studies [1,28], high concentration of ethanol was measured which suggests that the first formulation was used in these hospitals. Due to the system of detection used during this study, ethanol could not be quantified. However, regarding the high concentration of 2-propanol quantified, the second formulation seems to be used at LRI and GGH.

In accordance with previous studies [1,18,28,31,32], acetone and various silicones were also among the most abundant VOCs measured in both hospitals, together with aldehydes. A large range of sources emit these VOCs in hospital environment, including building materials and occupants, personal care products, decoration materials and pharmaceutical products [33–35]. Acetone, octanal and benzaldehyde mean concentrations in both hospital were higher than those seen in dwellings and offices [34,36]. Acetone mean concentrations were respectively at least 7 and 15 times higher compared to private [34] and public [36] buildings.

Terpene VOCs, limonene and alpha-pinene concentrations were similar to those reported in European hospitals concentrations [1,18,28]. These terpenes are mainly emitted by cleaning products and fragrances [37]. The concentration of limonene and alpha-pinene in LRI and GGH were three times lower compared to European public buildings [38]. These results may indicate adherence to pre-existing directives to reduce this type of pollution in hospitals environment. NHS suggests to its healthcare workers to not wear perfume to avoid patient discomfort [39].

4.2. Seasonality

Previous studies have investigated the impact of seasons on VOC concentrations and profile in hospital environments [28,40,41]. Seasonal changes and habits (e.g. traffic, illnesses, natural ventilation etc.) are factors to consider to understand the change of indoor VOC concentrations over seasons. Lee et al. demonstrated an increase of VOC concentrations in winter, without giving any hypothesis to explain this increase [41]. In this study, TVOC concentration was also highest in winter and significantly lower in summer compared to the other seasons (Fig. 1A). This decrease could be explained by the lower concentration of VOCs emitted by alcohol-based products in summer, which were halved compared to other seasons (Fig. 1B). Baures et al. found similar results [28], however no hypothesis has been proposed to explain this decrease. As the NHS reported constant number of hospitalisations over the seasons in this study [42–44], a reduction in the number of hospitalisations during summer cannot explain this decrease. A hypothesis to explain the reduction of alcohol-based VOCs, mainly emitted by hand-sanitiser, may be due to a lower prevalence of seasonal illnesses during summer. Visitors and patients are actively encouraged to sanitise their hands on entry to the hospital during the winter season to reduce disease transmission so are more likely to use hand-sanitiser.

Another hypothesis to explain the decrease of TVOC concentration in summer could be the increase of natural ventilation during this season. During summer, occupants are more likely to open windows to create additional ventilation to the mechanical ventilation. All the rooms studied were equipped with mechanical ventilation, set up at 6 air changes per hour according NHS guidance [45]. The impact of natural ventilation can be determined by focusing on VOCs from outdoor...
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workers were exposed to different VOC composition and concentrations depending on the season (Fig. 1). Healthcare workers were more exposed to VOC from alcohol-based products in autumn and winter, as opposed to summer and spring when the main exposure was from mixed emission sources (Fig. 1D). In contrast, outdoor activities and cleaning products emitted a constant amount of VOCs over the seasons. A previous study conducted in an European hospital found the opposite result for a VOC (α-pinene) emitted by cleaning products, the concentration during winter was eight times higher compared to summer [28].

4.3. Spatial variations

Several studies have considered the impact of clinical interventions and activities on the modification of VOC concentrations and composition by collecting samples in different wards and rooms in hospitals [1,2, 28,31,40,41,46]. All these studies concluded that VOC concentrations and profiles were impacted by the specific activities taking place in the rooms. Similar results were observed in this study, with different VOC concentrations and profiles measured between the rooms and hospitals. Higher TVOC concentrations in LRI rooms were observed compared to those at GGH (Fig. 2A). This difference TVOC concentration can mainly be explained by the significantly higher concentration of anaesthetic-related VOCs and higher concentration of VOCs from alcohol-based products in LRI rooms compared to that found in GGH rooms (Fig. 2B and C). The clinical interventions and activities taking place in the buildings where the samples were collected can explain these differences. In GGH, short-term interventions (e.g. physiotherapy, orthodontics and clinical research activities) occur in the buildings where the samples were collected. In contrast, in LRI, the buildings contained several intervention wards, including respiratory physiology department and theatres, although present on different floors. However, due to NHS ventilation regulations [45], the cleanest air originates in theatres before passing into less clean areas, including the sampling rooms. This cascade ventilation system may explain the higher concentration of anaesthetic and alcohol-related VOCs in LRI compared to GGH.

Another difference observed between the two hospitals was the concentration of VOCs from outdoor activities, with higher concentrations in GGH than LRI. The main differences between the GGH and LRI sites are the presence of a heliport and a closer car park in GGH, which may explain the higher concentration of VOCs from outdoor activities. Furthermore, difference between rooms in the same hospital was also observed, outdoor activities VOCs concentration were higher in GGH and 2 compared to GGH3. This difference is readily explained by the fact that these two rooms are in the same building unlike GGH3 that is in another building. The building housing GGH1 and 2 is closer to the roads and heliport compared to the GGH3 building.

In this study, healthcare workers in LRI and GGH were exposed to different VOC profiles and concentrations depending on the activities taking place inside and outside their hospitals (Fig. 2D). Healthcare workers in LRI were more exposed to VOCs from anaesthesia, but in comparison healthcare workers in GGH were exposed to higher concentrations of VOCs from outdoor activities. However, in both hospitals, healthcare workers were in contact with a high percentage of VOCs from alcohol-based products.

4.4. Human health impact

As previously noted, 2-min samples were collected over a long period at different times of the day. While averaging times are not directly comparable to those used for USEPA and OEHHA limit values. However, the values obtained were reasonably representative of background concentrations and could be used to estimate continuous inhalation exposure. USEPA and OEHHA limit values correspond to the VOC concentration where no health issues are likely to occur for a lifetime exposure. Two VOCs were quantified at a concentration above the US EPA inhalation exposure limit value: naphthalene and ethyl chloride. The inhalation exposure limit value fixed by US EPA for naphthalene is 3 μg m⁻³ [47], but the mean concentration quantified in GGH was slightly higher, 3.1 μg m⁻³ (Table 2). The 95th percentile concentration measured in GGH and LRI were also above the limit, at respectively 5.2 and 4.4 μg m⁻³ (Table 2). Ethyl chloride was measured at a mean concentration four times higher compared to the US EPA guideline [48], and the 95th percentile was 17 times higher (Table 2). However, the British occupational exposure limit relating to an 8-h averaging period is 134 mg m⁻³ [7], higher than concentrations measured in this study (with different sampling strategies). Given our results, workers identified as directly exposed/working with ethyl chloride might be considered for occupational exposure monitoring.

To evaluate potential health hazards to building occupants that may occur from continuous inhalation of background exposure to VOCs in both hospitals, illustrative hazard quotients were calculated using the US EPA and OEHHA inhalation exposure limit values. HQ could not be calculated for all the VOCs quantified during this study, owing to the absence of US EPA and OEHHA inhalation exposure limit value for VOCs without proven human toxicity. HQs were calculated for the mean concentration, representing the background exposure, and with the 95th percentile concentration, representing the worst-case scenario.

None of HQs calculated with the mean concentrations were above 1 (Table 2 and Fig. 3A). The results suggested that no negative impacts on the health of healthcare workers are likely to occur due to continuous inhalation exposure of VOCs in both hospital environment. HQs in healthcare environments have already been calculated by Colas et al. [49]. Similar results were observed with no HQs measured above 1. The largest HQ measured in that study were for ethylbenzene, acetone and 2-ethyl-1-hexanol, all had a HQ above 0.01 measured in several healthcare environments [49]. In this study, five different VOCs had a HQ measured above 0.01 in both hospitals, including 2-propanol, hexane, ethyl chloride, naphthalene and 1,1,1-trichloroethylen (Table 2). The three largest HQs measured in this study were above 0.1, ethyl chloride in LRI (HQ = 0.59) and naphthalene in LRI (HQ = 0.12) and GGH (HQ = 0.14).

Considering the worst-case scenario using the 95th percentile, no HQs in GGH were above 1, suggesting that the health of healthcare workers at GGH are likely to not be negatively impacted due to work-life exposure. However, the HQ obtained for ethyl chloride with the 95th percentile concentration in LRI was above 1, at 2.44 (Table 2 and Fig. 3B). Based on the Centre for Disease Control and Prevention (CDC), these results means that ethyl chloride concentrations in these rooms at LRI exceed the health guideline for non-cancer chemicals. In this situation, CDC encourages health assessors to “conduct an in-depth toxicological effects analysis”, to identify the exposure source of ethyl chloride and also to identify workers who might be exposed by considering occupational exposure monitoring. Ethyl chloride is used in medicine as an anaesthetic, owing to its capacity to produce a profound anaesthesia in less than 4 min [28]. This is the reason why acute inhalation can lead to unconsciousness and lack of muscle coordination, but at high levels ethyl chlorinations of VOCs from anaesthesia can induce unconsciousness and drunkenness [50]. However, chronic exposure can induce liver effects and neurological symptoms (including tremors, involuntary eye movement, ataxia and speech difficulties) [51].

The International Agency for Research on Cancer (IARC) classified three VOCs as carcinogenic to humans, formaldehyde, benzene and trichloroethylene. Formaldehyde (CH₂O) was not quantified during this study because the sorbent tubes used were not able to capture such a small VOC. Benzene concentrations quantified were below the limit of
detection in 65% of samples, so benzene was not included as part of this study. Trichloroethylene was quantified and Cancer Risk (CR) was calculated to assess cancer risk due to exposure to these VOCs (Table 3), using Inhalation Unit Risk (IUR), defined by US EPA for this VOC for a long-life exposure. The British workplace exposure limit for trichloroethylene has not used because the value is not specific to cancer risk [7], in contrast to the IUR from the US EPA. Trichloroethylene is linked to the development of several cancers, including non-Hodgkin’s lymphoma, renal cell carcinoma and livers tumours [52]. According to WHO [10], the main route of exposure is inhalation; ingestion will be a greatly reduced contributor in environments such as hospitals. In hospital indoor air, the main sources of trichloroethylene are building materials [34]. Trichloroethylene CRs were measured with mean concentrations at 4.59 E−06 in LRI and 1.69E−05 in GGH (Table 3). Both were above 1E−06 that signifies that possible risks from long-term exposure were present in both hospitals, based on US EPA guideline [53]. For the worst-case scenario using the 95th percentile, CR measured in GGH was greater than 1E−04 (CR = 1.20E−4) (Table 3), in this case according to US EPA guideline [53]. “remediation may be desirable” due to identified risks. If exposure is only or mainly in the workplace, this would correspond to a limited time period across the life-time, reducing risks. However, as a carcinogen, there is a requirement to keep trichloroethylene exposure “as low as reasonably practicable”. Further monitoring could help evaluate whether this is a pervasive environmental pollutant and/or whether occupational monitoring could be considered if some healthcare workers are directly exposed.

4.5. Implications

This study is the first to compare the VOC levels in UK hospital environments to exposure guidelines, to be able to examine potential health risks for healthcare workers. The monitoring conducted as part of another study was not designed to reflect/assess occupational or even long-term environmental exposures, but has highlighted some areas of potential exposure that could be further investigated with targeted sampling strategies.

This study provides primary evidence towards improving governmental recommendations and guidelines on the hospital environment. Previous changes have resulted in the improvement of healthcare workers health, e.g. the reduction of latex exposure and the abandon of glutaraldehyde-based disinfectant were associated with a reduction of occupational asthma [54]. Healthcare workers should be offered education on chemical pollution emitted by the products used daily. Regarding the results of this study, a simple and healthier alternative to reduce TVOC concentration and the exposure to 2-propanol could be to suggest that healthcare workers favour washing their hands with soap instead of hand sanitiser. It is likely, following the COVID-19 pandemic, that concentration of 2-propanol has increased since this study was conducted and further monitoring may be required. Implementing or improving ventilation systems to reduce TVOC concentration should be considered by the NHS. Healthcare workers have reported significantly fewer symptoms (e.g. irritated and runny nose, dry throat and facial skin) in hospitals with good ventilation compared to workers in hospital with poor ventilation [16]. The NHS should investigate the potential sources of emissions of trichloroethylene, which is potentially carcinogenic with long-term exposure and identify healthcare workers exposed to these sources to reduce as much as possible potential occupational-related risks.

Improvement of the indoor environment is important for healthcare workers’ health but also for health of patients. Health risks for groups with additional susceptibility (e.g. workers with pre-existing respiratory disease, patients) were not considered in this study. Further investigations should be performed to find out the impact of VOC concentrations on the recovery of hospitalised patients.

4.6. Limitations of the study

The study used convenience samples, using the same sampling time as that for the breath measurements. Whilst each 2-min active sample in this study may not capture the full variation of VOC concentrations throughout the day, hundreds of samples were collected over an extended period (4 years) at randomised times, to provide a more representative mean VOC concentration for each location. Active sampling has the advantage over longer term sampling strategies (e.g. passive sampling) that all components can be quantified without the need for sorbent specific uptake rates, and has been used extensively to profile indoor air VOCs in other studies [55-59]. Secondly, the sorbent tube used were those designed for breath measurements and did not permit us to detect and quantify VOCs of interest with high volatility, such as formaldehyde and acetaldehyde. Thirdly, the short sampling time used, may mean we may have under-estimated concentrations of some VOCs if these were fluctuating. Fourthly, no repeated set-time samples were collected unlike several papers focused on hospital indoor environment, owing to the fact that indoor air samples were convenience samples collected during a larger observational study [21, 22], according patients and healthcare workers availabilities. To finish, information regarding the specific healthcare activities taking place in the rooms before the samples were collected was not available. Further, the time of sample collection was recorded but not preserved in long-term records and therefore not available for most samples used in this study. However, we were able to use the measurements to make inferences about hospital exposures for a wide range of VOCs and to inform the design of follow-up studies.

5. Conclusions

This study is the first to characterise VOC concentrations in UK hospitals, quantifying 36 VOCs in five different rooms in two hospitals, and to identify potential impact on the health of healthcare workers. This study is also the largest reported database worldwide on the hospital environment. The two VOCs found in highest concentrations in the indoor air of these hospitals were 2-propanol and ethyl chloride, both related to healthcare activities. This study showed that VOC concentrations were significantly lower in summer and influenced by hospital activities, with variations depending on site and room location. No negative impacts on the health of healthcare workers were likely to occur due to background exposure of VOCs. However, at high (95th percentile) concentration, ethyl chloride exceeded environmental health guidelines for non-cancer chemicals. In addition, in both hospitals, possible cancer risks were identified relating to potential long-term background exposure. More studies of VOCs, ideally also including formaldehyde measurements, are needed to better characterise VOC exposure in healthcare settings and consequent evaluation of risks to healthcare workers and patients.

CRediT authorship contribution statement

Thiphanie P. Riveron: Writing – original draft, Visualization, Software, Formal analysis. Michael J. Wilde: Writing – review & editing, Validation, Software, Methodology, Investigation, Conceptualization. Wadah Ibrahim: Methodology, Investigation, Conceptualization. Liesl Carr: Investigation. Paul S. Monks: Resources, Methodology, Funding acquisition, Conceptualization. Neil J. Greening: Supervision, Resources, Methodology, Conceptualization. Erol A. Gaillard: Writing – review & editing, Resources, Methodology, Conceptualization. Chris F. Brightling: Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. Salman Siddiqui: Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. Anna L. Hansell: Writing – review & editing, Supervision, Resources. Rebecca L. Cordell: Writing – original draft, Validation, Supervision, Methodology, Investigation,
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

Data will be made available on request.

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Appendix A. Supplementary data

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References
