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Volatile organic compounds from topical drugs and medical products: Effects on air quality and healthcare environments

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ABSTRACT

Fifteen commonly used topical drugs and five medical products were evaluated using headspace Q-TOF GC/MS to assess VOCs emissions into healthcare environments and potential patient inhalation. The speciation of VOCs found in medicine products was less complex than typically found in non-medicated, cosmetic skincare products. VOCs arising from medicinal products could be classified as being related to product performance (e.g., solvent), product fragrance, and likely trace contaminants unintentionally included. The scale of emissions and resulting inhalation could be significant for products that are facially applied, and there may be some potential for wider indoor air quality effects if used regularly in poorly ventilated spaces. Emission rates from topical drugs were then quantified using SIFT-MS, focusing on the ten most abundant/commonly found species identified by Q-TOF GC/MS – 2-propanol, benzaldehyde, benzyl alcohol, cyclohexane, ethanol, menthol, methyl salicylate, phenol, and limonene and eucalyptol (representing the total of all terpene species). Emission rates were in the range 9.7×10^{-5} μg s^{-1} g $_{[product]}{}^{-1}$ to 5.9 μg s^{-1} g $_{[product]}{}^{-1}$.

Introduction

Medicinal products are highly regulated, for example in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA), EU by European Medicines Agency, and in the US by the Food and Drug Administration (FDA). Regulations apply during product development, and during licensing and production to ensure that once in use they meet applicable safety, quality, and efficacy standards[1,2]. Safety considerations for regular, intended use include possible side-effects such as allergic reactions, repeated dose toxicity, genotoxicity, and the presence of solvent residue and other impurities.

Solvents can be used and/or produced in the manufacture of pharmaceuticals and may not be completely removed during the production process. Thus, pharmaceutical manufacturers must evaluate the solvents used during synthesis and make reasonable efforts to remove them from the final product so they contain `no higher levels of residual solvents than can be supported by safety data`[3], which may mean only very small trace amounts. As most traditional medications are taken orally, this is to minimise potential oral ingestion routes. Some delivery formats of pharmaceuticals purposefully formulate with organic solvents as the vector for the effective delivery of active pharmaceutical ingredients, most notably in topically applied drugs[4,5]. Topical drugs, also known as topical medication, are pharmaceuticals applied to the surface of the body. They can be used to treat a wide range of ailments including, but not limited to, skin conditions, and come in many different forms such as creams, gels, and ointments[6,7]. Although the solvents used in topical applications are not designed to be orally ingested, they have the potential for human uptake *via* either a dermal or inhalation pathway[8]. The inhalation pathway occurs when they are volatilised (VOCs) during and after product application.

There is a growing body of work to suggest that consumer and household products are a large contributor to VOCs found in indoor air [9–16], including from topically applied cosmetics and toiletries. Recent work by Yeoman et al. [17] and Yeoman et al. [18] found emissions of solvent, fragrance, and active ingredient VOCs, such as UV blockers and moisturising agents, from sunscreens and facial moisturisers respectively. There is also the potential for contaminant VOCs (compounds which have not been purposefully added to the product as an ingredient) to be emitted. Whilst most consumer products are contributors to in - room concentrations, topical healthcare products may lead to enhanced

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exposure, being directly inhaled during use due to application in close proximity to the inhalation exposure pathway (nose and mouth). Yeoman et al. [18] found an average of 40 % of the total mass of VOCs emitted from an application of facial moisturisers were directly inhaled (although not necessarily adsorbed within the body).

As topical drugs are a necessity for treatment there is a less discretionary nature to their use when compared to topical cosmetics and toiletries, the latter being an optional and personal decision. Some groups who use topical medicines, and hence may gain exposure to VOCs derived from them, may also have a greater susceptibility to respiratory harms from air pollution, including children and the elderly. The 2013 Health Survey for England showed prescription medication usage increases with age (Fig. 5A and B)[19], at the same time the elderly have decreased lung function due to a natural decrease in thoracic cavity and reduced inspiratory and expiratory respiratory muscle strength that comes with age[20]. In contrast, children have younger, less developed respiratory systems than those of adults. They also inhale more air relative to their body, which makes their exposure dose to airborne pollutants higher[21]. Whilst children are less likely to use cosmetic skincare products, there are many topical drugs that are approved for use on children, or formulated for them specifically, such as nappy rash creams.

Whilst primary inhalation exposure affects those using the product, topical drug VOC emissions will also contribute to indoor air pollution in all enclosed spaces, including homes, social care and healthcare settings.". Indoor air pollution in hospitals affects both vulnerable patients and also staff who may experience continuous occupational exposure over long periods of time. Maio et al. (2015)[22] examined the links between air quality in nursing homes and respiratory health, and found that as the elderly spend the majority of their time indoors, they are at higher risk of inhalation exposure to indoor air pollutants. Baudet et al. [23] reported that the highest concentrations of VOCs found in healthcare facilities in France included ethanol, 2-propanol, and limonene, species that are commonly included in, and emitted from, skincare products. Given the location, however, it is plausible that they may have originated from topical drugs in addition. Similarly, Riveron et al. [24] characterised VOCs present in UK clinical assessment rooms and found 2-propanol and acetone to be the most and third-most abundant species. The source of 2-propanol was determined to be healthcare-related cleaning and sanitising products, but it was noted that acetone, along with other species detected such as siloxanes, may have originated from personal care or pharmaceutical products. Gola et al. [25], in a review found cleaning products, finishing and building materials, and furniture as sources of chemical pollutants on inpatient wards, but did not identify VOCs from medications themselves. In a similar study of the chemical products used in a French hospital, Berrubè et al. [26] concluded that alcohols (ethanol and 2-propanol) from detergents and disinfectants required priority attention in terms of chemical risk, however 25 medications and antiseptics were also identified as products emitting VOCs likely to be inhaled. These publications show emerging evidence for the scale of VOC emissions, and possible impacts, from use of topical drugs and other medical products. This paper is the first to both speciate VOCs emitted from a representative range of commonly used products and quantitatively estimate in-use emission rates (expressed as an emission per gram product used). These emission data are then used to assess the effect of location (room/building) that product application has on personal / patient inhalation and in-room potential exposure for healthcare professionals.

Methods

Product selection

Fifteen topical drugs were purchased from a large UK pharmacy. These products were off-the-shelf and did not require a prescription or a consultation from an over-the-counter pharmacist. We define a topical drug as a product designed to be applied to the skin with at least one medically active ingredient or application. The MHRA definition of a medicinal product is "Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; Any substance or combination of substances which may be used in, or administered to, human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis"(Article 1 of Directive 2001/83/EC)[27], and samples were chosen based on this guidance. This does not include products such as cosmetics with active ingredients (anti-wrinkle creams, skin serums, etc.), that are not designed for health and well-being. The products purchased are summarised in Table 1.

Experimental

The experimental methods for VOC measurement have previously been described in detail in Yeoman et al. [17].

Briefly, an initial untargeted analysis was carried out to identify the most abundant VOCs emitted across the products chosen. An Agilent Technologies (Santa Clara, CA, USA) 7200 Accurate-Mass Quadrupole-Time-of-Flight Gas Chromatography/Mass Spectrometer (Q-TOF GC/MS) fitted with a Gerstel (Gerstel, Germany) MultiPurpose Autosampler and a 2.5 mL headspace syringe was used for qualitative screening and identification of VOCs present in the headspace of the 20 products. Approximately 1 g of the 15 topical drugs and gel medical products (antimicrobial handwash and antiseptic wound cleaning spray), and approximately 0.1 mL of the liquid medical products (liquid antiseptics) were weighed in 20 mL clear glass, round-bottom headspace vials and capped with magnetic stainless-steel screw caps with 1.6 mm PTFE-faced butyl septum.

Separation was achieved using a BPX5 50 m × 0.32 mm ID 1 μm film thickness capillary column with a flow rate of 2 mL min^{-1} using helium gas. N_2 collision gas was used at a flowrate of 1.5 mL min^{-1} in the mass spectrometer, collecting data at an effective frequency of 5 Hz. The GC headspace needle was maintained at 70 °C. Samples were incubated and agitated for 5 min in a Gerstel agitator at 35 °C before a 2 mL headspace sample was taken. The GC inlet temperature was set at 330 °C with a split ratio of 10:1 and split flow of 20 mL min^{-1}. The column oven temperature was initially 40 °C, which was held for 5 min and then increased to 340 °C at a rate of 10 °C min^{-1}, amounting to a run time of 40 min. The transfer line was set to 350 °C. Data were acquired over a mass range of 28–500 amu.

GC/MS Q-TOF data were analysed using Agilent MassHunter Qualitative Analysis (version B.07.00) and the latest version of the NIST Library (MS Search v2.3) to identify compounds. The presence of nine compounds were confirmed using authentic standards using the method described previously. 2-Propanol, benzyl alcohol, and ethanol standards were run neat with no solvent delay. 3-Methylpentane, benzene, cyclohexane, eucalyptol, and toluene were prepared in ethanol and run with a 4 min solvent delay. Ethyl acetate was prepared in ethanol, and run with no solvent delay for 3.9 min (before ethanol elutes). All standards were run with a 50:1 split (100 mL min^{-1}).

To quantify the emission rates of the 10 VOC species found across the products tested that are quantifiable by on-line soft-ionisation a Voice200 Ultra SIFT-MS (Syft technologies, Christchurch, New Zealand) was used in selected ion monitoring (SIM). The VOCs targeted for this SIFT-MS analysis were chosen based on the initial GC/MS QTOF screening. Measurements were made following a methodology previously reported in Yeoman et al., [28], with the SIFT-MS instrument sampling from the headspace of a gas-tight sample vessel where the sample was placed. Targeted VOCs and the *m/z* values used to identify them for each reagent ion are listed in SI Table 1.

Approximately 1 mg of each product was weighed on a small section of filter paper and placed into a 50 mL stainless-steel gas-tight sample vessel which was thermostatted at 35 °C to simulate skin temperature. A

Table 1
Summary of topical drugs and medical products purchased and their labelled active ingredients.

	Product Type	Products Analysed	Labelled active ingredients
Topical Drugs	Itch and skin irritation relief cream	1	Crotamiton
	Medicated pain relief gel	2	Ibuprofen, diclofenac diethylammonium
	Non-medicated pain relief cream	1	Methyl salicylate, menthol, eucalyptus oil, turpentine oil
	Antifungal athlete's foot cream	2	Clotrimazole, terbinafine hydrochloride
	Antiseptic nappy rash cream	1	Zinc oxide, benzyl alcohol, benzyl benzoate, benzyl cinnamate, lanolin
	Nappy rash ointment	1	Titanium dioxide, titanium peroxide, titanium salicylate
	Thrush cream	1	Lidocaine
	Antibacterial acne cream	1	Benzoyl peroxide
	Bite and sting relief cream	2	Mepyramine maleate, hydrocortisone
	Wound antiseptic cream	1	Cetrimide, chlorhexidine digluconate
	Irritation and sunburn lotion	1	Calamine, zinc oxide
	Burn and scald relief gel	1	Carbopol Ultres 21, glycerine USP
Medical Products	Liquid antiseptic	3	Halogenated phenols, phenol, cetylpyridinium chloride, chloroxylenol
	Antimicrobial handwash	1	Chlorhexidine gluconate
	Antiseptic wound cleaning spray	1	Decyl glucoside tenside, polihexanide

gas phase headspace sample was drawn continuously from the gas-tight vessel into the SIFT-MS at a flowrate of 10 mL min^{-1} under atmospheric pressure, with the inlet to the vessel connected to a supply of high-purity N_2. The sampling lines, vessel, and instrument were operated without sample for ~ 10 min prior to the product being introduced, with this initial period used as a baseline measurement, which was later subtracted from the sample measurement data. N_2 was passed over the sample for a maximum of 180 min or until measured VOC emissions had reduced to baseline. Data acquisition lasted for this 180 min period with an ion dwell time of 100 ms per *m/z* and a cycle time of 3.6 s overall. Emission rates were calculated using SIFT-MS data acquired using Labsyft (version 1.8.1) software, and using principles described in Harding-Smith et al. Eq. 1 [29]. Briefly, the integral of the emission curve (AUC) was assumed to be equal to total VOC emission. This was averaged over the total emission time (t), which varied for each species and product, and scaled to the amount of product sampled. The sample flow rate (SFR) was calculated as 8.3×10^{-7} m^3 s^{-1}.

$$Emission\ rate\left(\mu g \quad s^{-1} g^{-1}_{[product]}\right) = \frac{AUC(\mu g \quad s \quad m^{-3}) \times SFR(m^3 s^{-1})}{t \quad (s) \times Product\ sampled(g)} \tag{1}$$

Previously calculated liquid calibration correction factors for 2-propanol, ethanol, and benzyl alcohol were applied to the data. The in-house dynamic liquid calibration system and calculation method is described in Yeoman et al. [17]. Limonene calibrations were performed using an in-house developed gas dilution unit, described in Wagner et al. [30]. Briefly, an in-house 2 ppm gravimetrically prepared gas standard containing limonene in ultrahigh purity nitrogen was diluted with zero air to generate multipoint calibrations in the concentration range of 1–100 ppbv.

Potential ambient inhalation dose calculation

In order to compare the total emission of contaminant species from the products (μg $g^{-1}_{[product]}$) with workplace exposure limits (μg m^{-3}), Eq. 2 is used to calculate a potential inhalation dose in units of μg m^{-3}.

$$Potential\ inhalation\ dose\left(\mu g \quad m^{-3}\right) = \frac{Mean\ total\ emission\left(\mu g \quad g^{-1}_{[product]}\right) \times Product\ used(g)}{Room\ volume(m^3)} \tag{2}$$

Direct inhalation dose calculation

The inhalation dose applicants will potentially directly inhale during product use is calculated using Eqs. 3 and 4.

$$Total\ mass\ emitted\left(\mu g \quad g^{-1}_{[product]}\right) = Emission\ rate\left(\mu g \quad s^{-1} \quad g^{-1}_{[product]}\right) \times Time(s) \tag{3}$$

$$Direct\ inhalation\ dose\left(\mu g \quad g^{-1}_{[product]}\right) = Total\ mass\ emitted\left(\mu g \quad g^{-1}_{[product]}\right) \times \%Potential\ inhalation\ dose \tag{4}$$

Percentage potential inhalation dose values were determined based on data from Yeoman et al. [17]. These are referred to as emission-to-inhalation ratios, representing the fraction of VOC inhaled relative to the amount emitted overall to the gas phase. Using data from Yeoman et al. [31], where experiments were conducted using a real-life product application replica, a total estimated amount inhaled when product is applied to the face was calculated to be 39 % of the total VOCs available emitted from the product.

Room exposure contour plot calculation

A contour plot has been constructed to visualise the influence of room size and ventilation on in-room concentrations of topical drug emissions using the methods described in Warburton et al. [16]. In brief, it is a one-compartment box model which assumes steady-state conditions and isotropic emission, into a well-mixed compartment. The model employed solves the ordinary differential equation (ODE) presented in Carslaw [32] to predict indoor concentrations of an emitted species. It assumes pollutant emissions occur within a well-mixed, single--compartment indoor environment, where sources are instantaneously and uniformly distributed upon emission. In discrete simulations, the solution yields a time series depicting the evolution of gas-phase concentrations over time, eventually approaching a steady-state concentration, defined by the condition dC/dt= 0.

To generate the contour plot, the model was iterated across a range of air change per hour (ACH) and room volumes. Specifically, ACH

varied from 0.1 to 10 h^{-1} in increments of 0.1 h^{-1} , while room volumes ranged from 1 m^3 to 50 m^3 in 0.1 m^3 steps. For each parameter combination, the corresponding steady-state concentration was computed and used to construct a contour plot representing the relationship between ACR, room volume, and pollutant concentration.

Oxidation reactions for 2-propanol were sourced from the Master Chemical Mechanism (MCM), which, at the time of writing, listed two gas-phase reactions with hydroxyl (OH) radicals. Indoor OH concentrations were fixed at 1×10^5 molecules·cm^{-3} . Deposition velocity—the rate at which a compound deposits onto indoor surfaces—was set to zero, reflecting the absence of available data for isopropanol deposition in the literature.

As the objective of the model was to evaluate the incremental burden of 2-propanol within an indoor environment, both the initial isopropanol concentration and its concentration in incoming air were set to zero. Thus, the modelled concentrations reflect only the contribution from indoor emission sources.

The mean emission rate for 2-propanol, calculated in μg s^{-1} $g^{-1}_{[product]}$ using SIFT-MS data, was used in the model. We assume 1 g of product is used in a single application giving an emission rate of 1.49 μg s^{-1}.

Results and discussion

Qualitative analysis—determination of volatile species using Q-TOF GC/MS

See figure 1

Topical drugs

Fig. 1 visualises the VOCs identified in the 15 topical drugs and 5 medical products analysed by QTOF-GC/MS. An initial observation is that the variety of different compounds emitted is more limited than those identified in sunscreens using the same method (Yeoman et al., 2023[17], Fig. 2). Despite the sample size in this work being smaller, there are a total of 14 non-fragrance and non-contaminant species identified, compared to the more than 30 in Yeoman et al., 2023. As topical drugs are formulated for the sole purpose of treating an ailment, they only require the active ingredient(s), solvents and preservatives. This is unlike cosmetics and toiletries, which are formulated to include several other ingredients to enhance texture, application, and scent. This differs to the results presented by Berrubè et al.'s 2015 study[26], which concluded that "*Since medicines and antiseptics are generally made up of several substances (the active ingredient and the excipients), the number of substances is approximately twice as large as that of commercial products*". The commercial products in question in the 2015 study, however, did not include cosmetics and toiletries and focussed on medical products such as disinfectants, anaesthetic gases, and pharmaceutical products. What this indicates is that topical drugs are still a complex and significant mixture of VOCs that can be present in healthcare environments, despite them being less complex than cosmetics and toiletries.

Ethanol is the most commonly used solvent for cosmetics and toiletries owing to its low cost, wide availability, and relatively low toxicity compared to other solvents[33], [34]. Somewhat surprisingly however ethanol was only identified in two of the fifteen topical drugs tested here. 2-propanol was the more common solvent and the preference for its inclusion then explains the lack of denaturants, such as t-butyl

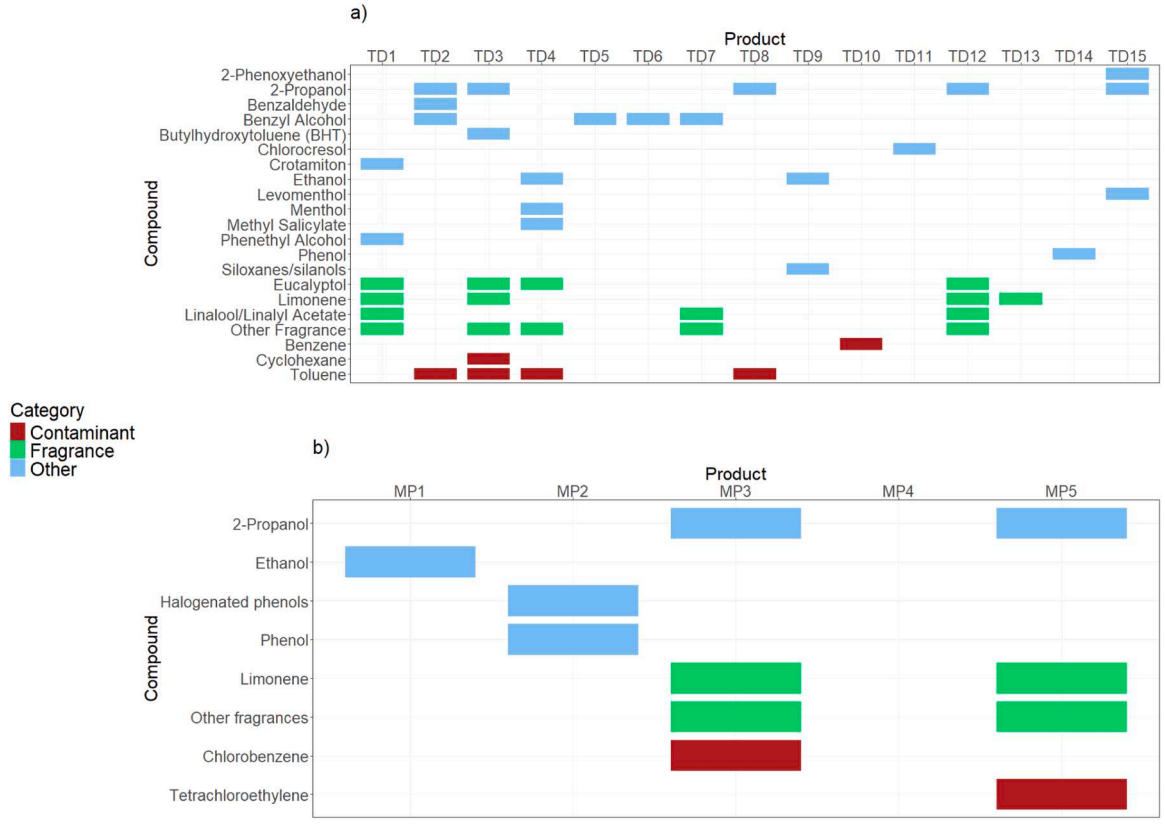

Fig. 1. All VOCs identified by QTOF-GC/MS from a) 15 topical drugs and b) 5 medical products. Contaminant species are those we do not believe have been purposefully added to the formulations as ingredients. TD1 - Itch and skin irritation relief cream, TD2 - Medicated pain relief gel, TD3 - Medicated pain relief gel, TD4 - Non-medicated pain relief cream, TD5&6 - Antifungal athlete's foot cream, TD7 - Antiseptic nappy rash cream, TD8 - Thrush cream, TD9 - Nappy rash ointment, TD10 - Antibacterial acne cream, TD11 - Bite and sting relief cream, TD12 - Wound antiseptic cream, TD13 - Bite and sting relief cream, TD14 - Irritation and sunburn lotion, TD15 - Burn and scald relief gel. MP1 - Liquid antiseptic, MP2 - Liquid antiseptic, MP3 - Antimicrobial handwash, MP4 - Antiseptic wound cleaning spray, MP5 - Liquid antiseptic.

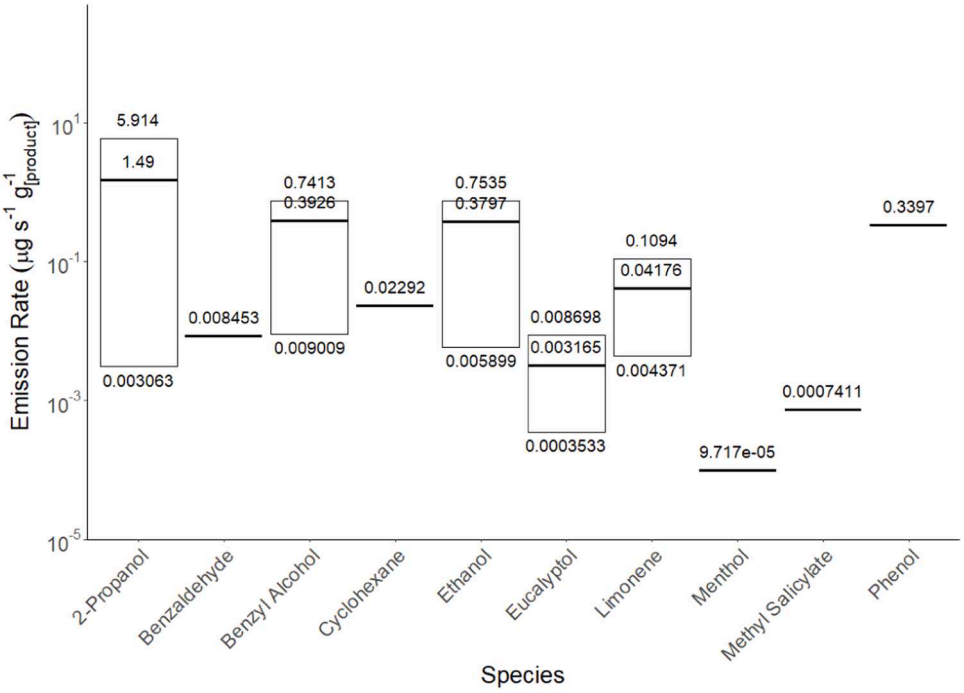

Fig. 2. Emission rates for ten of the most commonly found VOCs in 15 topical drugs thermostatted at 35 °C. Bars show the max, min, and mean emissions. Emission rates for each of the 15 topical drug products can be found in SI Table 2. CHANGE FACTOR TO RATE.Fig. 2 presents the emission rates measured using SIFT-MS for the 15 topical drugs. This analysis was not carried out on the five medical products as their formulations, in the case of MP1, MP2, MP3, and MP5 are mostly solvent and fragrance, which would have been too concentrated to measure using the instrument, and in the case of MP4 because it emits no VOCs. Together, limonene and eucalyptol represent the total of all terpene species. This is due to the limitations of SIFT-MS as a soft-ionisation technique, where terpenes and monoterpenes cannot be distinguished from one another due to having the same mass-to-charge ratio.

alcohol, that are found in cosmetics and toiletries. Only products with ethanol content require denaturing to ensure it is not fit for human consumption[35]

Products containing the bactericide benzoyl peroxide have previously been reported to also contain trace amounts of the carcinogen benzene. An independent study from 2024 reported that seven benzoyl peroxide based acne products purchased in the US, all of which were formulated differently, all emitted gaseous benzene[36]. This was attributed to thermal decomposition of benzoyl peroxide to form benzoic acid or phenyl radicals, with benzene being a potential end-product. This work confirms those observations that benzene can be emitted from products containing benzoyl peroxide.

The most prevalent contaminant VOC identified in the 15 products was toluene, being emitted from four topical drugs, three of which were a type of pain relief. All four products contain a volatile solvent, either 2-propanol or ethanol. It has been suggested previously that contaminant solvents/VOCs in products containing ethanol may originate from its purification process via distillation using entrainers and/or from the originating petrochemical feedstock[17]. This may be an explanation for the toluene found in TD4. As 2-propanol is typically synthesised by the hydration of propene[37] or the hydrogenation of acetone[38], it is not as clear where the toluene in TD2, TD3, and TD6 may have originated.

Asides from the contaminant species, there are no other unexpected compounds identified in the topical drugs. Compounds identified that are labelled as active ingredients in the products are: chlorocresol (disinfectant and antiseptic), crotamiton (general antipruritic), menthol (cooling/warming), methyl salicylate (cooling/warming). Benzyl alcohol is a solvent and preservative. 2-Phenoxyethanol, phenethyl alcohol, benzaldehyde, and butylhydroxytoluene are also used as preservatives. Phenol can be used as a topical anaesthetic, antiseptic, and disinfectant. Levomenthol is used to relieve itching. Silanols and siloxanes are commonly used to improve the texture of a product on the skin [39], [40], and are only identified in one topical drug, the nappy rash cream. All of these compounds are required for the safety and efficacy of the products These results have been summarised in Table 2.

Table 2
Medical properties of VOCs identified by QTOF-GC/MS.

Identified VOC	Properties/Use
2-Phenoxyethanol	Preservative
2-Propanol	Solvent
Benzaldehyde	Preservative
Benzene	Contaminant
Benzyl alcohol	Solvent and preservative
Butylhydroxytoluene	Preservative
Chlorocresol	Disinfectant and antiseptic
Crotamiton	General antipruritic
Cyclohexane	Contaminant
Ethanol	Solvent
Eucalyptol	Fragrance
Levomenthol	Itch relief/cooling
Limonene	Fragrance
Linalool/Linalyl acetate	Fragrance
Menthol	Cooling/warming
Methyl salicylate	Cooling/warming
Phenethyl alcohol	Preservative
Phenol	Topical anaesthetic, antiseptic, and disinfectant
Silanols and siloxanes	Improves texture of product on skin
Toluene	Contaminant

In the products that contained it, the fragrance was the most complicated VOC element of the formulation. Limonene, eucalyptol, and linalool/linalyl acetate were the most common fragrance compounds identified. `Other fragrances` consisted of between 5 and 15 different fragrance compounds. This is largely consistent with the complexity of the fragrances identified in sunscreens in Yeoman et al. Fragrance is the only component of the products not required for direct medicinal functionality and is likely added to improve the user experience, and

possibly to mask the smell of other ingredients. Fragrance compounds can in some people cause respiratory irritation[41] and other negative effects such as headaches, dizziness, and the triggering of asthma attacks when inhaled[42,43].

Medical products

Medical products have less complicated VOC formulations than topical drugs. Within the albeit small sample size of this work, we observe only seven individual VOCs and `other fragrances` emitted, two of which are likely contaminants. One product (MP4) did not emit any volatile organic ingredients at all. As this antiseptic wound spray product is advertised as being `pain-free` it has likely not been formulated with any solvents, or other volatile components, which may aggravate open wounds. As with the topical drugs, the contaminants are the only unexpected species identified.

Liquid antiseptic products need only be formulated with ingredients to effectively disinfect whatever surface they are applied to. As such, they contain solvent (2-propanol/ethanol), fragrance, and sometimes another disinfecting agent (phenol/halogenated phenols). The chlorinated contaminants are found in products containing chlorinated active ingredients. In the case of MP3 this is chlorhexidine gluconate and chloroxylenol for MP5.

Quantitative analysis—emission rates of prevalent species

The mean VOC emission rates for topical drugs tested here are broadly similar to data published for sunscreen products in Yeoman et al. [17]; the exception is ethanol which is around one order of magnitude lower in topical drugs. The most common solvent used in the topical drugs, 2-propanol, also has the widest emission range.

A likely contaminant VOC cyclohexane, whilst only identified in one product, is emitted at comparable amounts as the purposefully added ingredients. The UK short-term (15 min) workplace exposure limit for cyclohexane is 1050 mg m^{-3}, and the long-term exposure limit (8 h) 350 mg m^{-3} [44]. The same Public Health England document states inhalation exposure can cause headaches, dizziness, drowsiness, incoordination and euphoria. Using total emission data from Table 3, and assuming 1 g of product is applied in a 15 m^3 room (estimated UK bathroom size), the potential inhalation dose of cyclohexane from TD3 is very low at only 4.3 μg m^{-3}. Whilst this is significantly below both workplace occupational short- and long-term exposure limits, tolerance by some groups such as the very young, very elderly, and those with respiratory health conditions may be lower than occupational workplace assumptions[45,46]. Repeated use of the product over a long period of time would lead to an aggregate high exposure, and the health effects of long-term low-concentration inhalation exposure dose has yet to be determined. Exposure limits, where they have been found in the literature, and potential ambient inhalation dose from the other species measured by SIFT-MS can be found in Table 4. As with cyclohexane, it has been assumed that 1 gram of product has been applied in a 15 m^3 room.

Table 3
Mean total emission in μg $g^{-1}_{[product]}$ and standard deviation of ten of the most commonly found VOCs in 15 topical drugs calculated using mean data from Fig. 2 and total time of emission. The full dataset can be found in SI Table 3.

Species	Mean Total Emission (μg $g^{-1}_{[product]}$)	Standard Deviation
2-Propanol	7800	14,000
Benzaldehyde	47	
Benzyl Alcohol	3400	3200
Cyclohexane	65	
Ethanol	2800	3900
Eucalyptol	22	33
Limonene	290	400
Menthol	0.50	
Methyl Salicylate	6.5	
Phenol	3900	

Table 4
Long- and short-term exposure limits, where available in the literature, for 10 VOCs measured by SIFT-MS. Potential ambient inhalation dose for 1 g of product used in a 15 m^3 room have been calculated using mean total emission data from Table 3 and Eq. 2.

Species	Long-term exposure limit (mg m^{-3})	Short-term exposure limit (mg m^{-3})	Source	Potential ambient inhalation dose −1 g of product in a 15 m^3 room (mg m^{-3})
2-Propanol	999 (8 h)	1250 (15 min)	Health and Safety Executive (UK)[47]	5.20×10^{-1}
Benzaldehyde				3.10×10^{-3}
Benzyl Alcohol	22 (long-term not defined)	110 (short-term not defined)	Univar Solutions [48]	2.30×10^{-1}
Cyclohexane	350 (8 h)	1050 (15 min)	Health and Safety Executive (UK)[47]	4.30×10^{-3}
Ethanol	1920 (8 h)		Health and Safety Executive (UK)[47]	1.90×10^{-1}
Eucalyptol				1.50×10^{-3}
Limonene	9 (24 h)	90 (30 min)	Public Health England[49]	1.90×10^{-2}
Menthol	5289 (4 h)		European Chemicals Agency[50]	3.00×10^{-5}
Methyl Salicylate				4.30×10^{-4}
Phenol	16 (8 h)	7.8 (15 min)	Health and Safety Executive (UK)[47]	2.60×10^{-1}

Whilst none of the measured compounds reach either long- or short-term exposure limits when emitted into ambient air, as mentioned previously these limits are not designed with health-impaired/vulnerable persons in mind. Additionally, products may be used in greater quantities and in smaller spaces, such as small treatment rooms, which would increase potential ambient concentration. Direct inhalation dose, inhaled from the product on application, is independent of room size and may also be higher than literature exposure limits. This is discussed further in a subsequent section.

Emission into healthcare and home environments

The room in which any medical product is used will influence the inhalation dose an occupant is exposed to. Fig. 3 uses 2-propanol as an example, as it is commonly found in topical drugs, to illustrate the effects of room size and ventilation. As would be expected, the smaller the room and the less air changes per hour (ACH) there are, the higher the concentration of VOC a room occupant will be exposed to.

Topical drugs are most likely to be used in home bathrooms, hospital/healthcare treatment rooms, and rooms within care homes. Whilst there is no data on the average room volume and ventilation for these rooms in the UK, or similar nations, we make a conservative estimate of the concentration those within the room may be exposed to, and therefore potentially inhale. UK homes usually have ventilation rates of 2 ACH or lower, particularly if windows are not opened or mechanical extraction systems are not well maintained or turned on. We estimate a typical bathroom size to be 15 m^3. These conditions would result in in-room concentrations of around 250 μg m^{-3}. We consider this size would

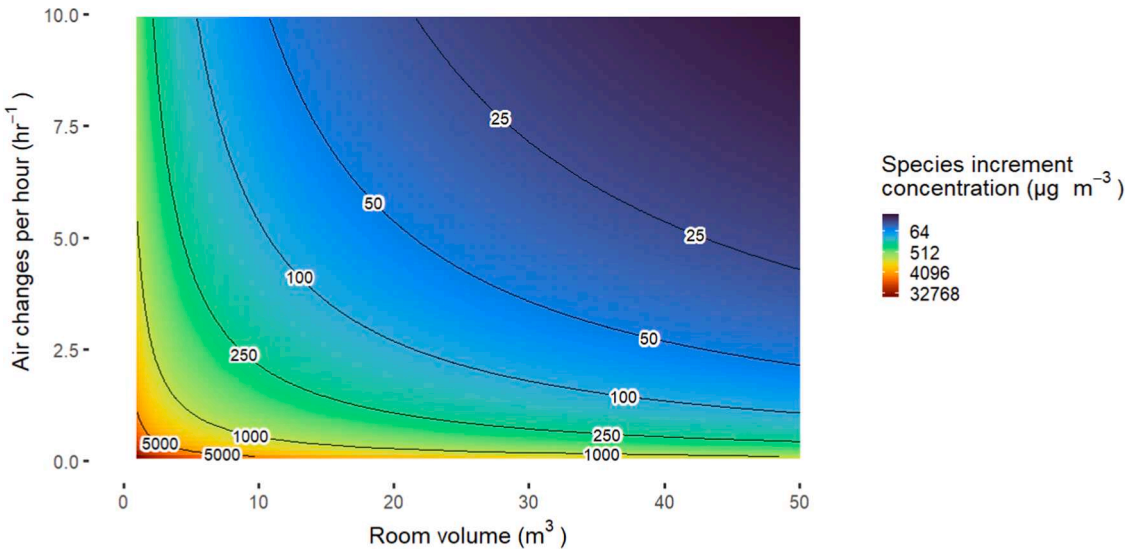

Fig. 3. Example estimates of in-room concentration increments when using tropical drugs, based on 2-propanol mean emissions calculated from SIFT-MS data in Fig. 2. Assumes 1 g of product is used, resulting in an emission rate of 1.49 µg s^{-1}.

also be typical of a larger healthcare treatment room, but that in a treatment setting a higher ACH would be used, likely with mechanical ventilation, reducing concentration as ACH increases along the y-axis of the Fig. 3. A smaller healthcare treatment room we estimate as being 5 m^3, again reducing concentrations as volume increases along the x-axis. An ACH of 2 in this environment would result in in-room concentrations of between 500 and 1000 µg m^{-3}.

Even in a larger room (50 m^3) with very high levels of extraction (10 ACH) room concentrations would not fall below 25 µg m^{-3}. It should be noted, however, that this model assumed a constant emission rate, rather than an outgassing integrated over a period of time which is likely more representative of the real world.

Fig. 4 presents a concentration time series of 2-propanol for two room scenarios, 15 m^3 bathroom/larger treatment room and 5 m^3 smaller treatment room, if 1 g of product is used at 0.5 ACH with an emission rate peaking at 1 min into the simulation and exponentially decaying completely within 1 h from the start of the simulation. This ACH was chosen to represent a `worse-case scenario` of poor ventilation which can be observed in rooms where mechanical ventilation has not been switched on and no windows have been opened/are present[51]. The emission data are based on the average 2-propanol emission profiles measured by SIFT-MS, from which the average emission rates in Fig. 2 were calculated. In the 15 m^3 room a peak concentration of just over 3 µg m^{-3} is reached, and 10 µg m^{-3} in the 5 m^3 room. In both cases there is a relatively quick decay.

Specific inhalation toxicology for the VOCs emitted from topical drugs are not well established for either long- or short-term exposure, however more generally exposure to VOCs can lead to the onset of health conditions such as asthma and chronic pulmonary diseases. Those occupying healthcare environments where these products are used may be more vulnerable to the negative effects of inhalation exposure as they are already suffering from ill-health.

Direct inhalation dose

Direct inhalation estimates for single facial application of sunscreens were made in Yeoman et al. [17], using the assumption that 39 % of total VOCs emitted from the product will be directly inhaled. Direct inhalation dose is dependent on site of application - the closer to the inhalation exposure pathway (nose and mouth) the higher the dose. As topical drugs can be used on all areas of the body we can assume that 39 % represents the highest potential direct inhalation dose (if applied to the face), and make a conservative estimate that the lowest potential direct inhalation dose may be 10 % for application to areas of the body further away from the inhalation exposure pathway (such as the feet). Fig. 5 presents the potential total direct inhalation dose of each species from 10 % to 39 %.

The greater the portion of total VOCs emitted that is directly inhaled by applicants, the less that will be released into ambient air. This outcome is positive for ambient occupiers of the space as they will be

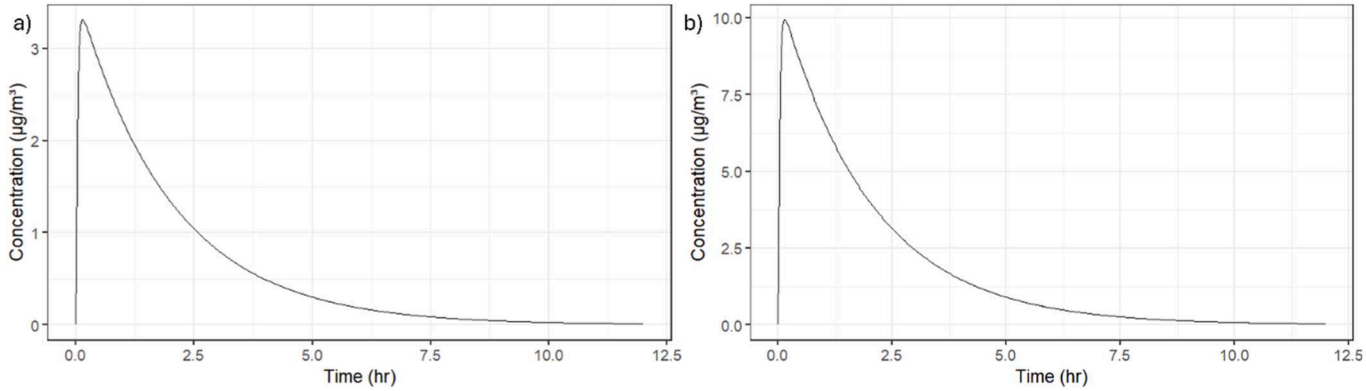

Fig. 4. Concentration time series for 2-propanol in a) 15 m^3 room and b) 5 m^3 room, assuming 1 g of product is used at 0.5 ACH.

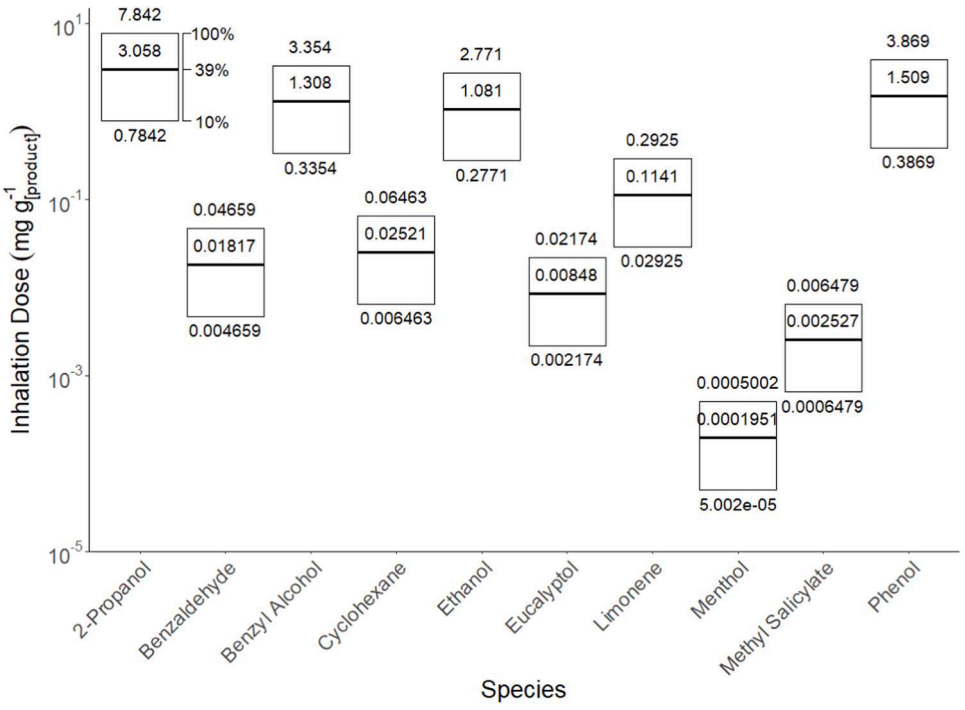

Fig. 5. Potential direct inhalation dose in mg $g^{-1}_{[product]}$ for ten of the most commonly found VOCs in 15 topical drugs using mean total emission data from Table 1. The top bar indicates 100 % of emissions, the middle 39 %, and the bottom 10 %.

exposed to lower levels, and may also reduce exposure to potentially more harmful secondary pollutants that may occur via reactions of the primary pollutants. It is, however, a negative outcome for the applicant themselves as they are exposed to a higher dose.

As direct inhalation dose is independent of room size, it is difficult to compare data from Fig. 4 to inhalation exposure limits, as seen in Table 4, which have been generated in units of mass/volume (typically mg m^{-3}). The same goes for air quality guidelines, which are also dependent on external factors such as room size and ACH. What we can interpret from the data, however, is that an applicant's direct inhalation dose will be higher and more sustained than that of someone breathing the emissions into and from ambient air in the room in which a product was applied.

Conclusions

Whilst the ingestion of VOCs and solvents in oral medication is a tightly regulated issue, the inhalation ingestion of solvents from topical medicines is rarely considered. The mixture of VOCs found in topical medicines is more limited than are found in cosmetic products, and all are likely needed for functional performance, (bar fragrances which are likely added to mask other odours). Product reformulation may not therefore be possible. In order to avoid potential harms to those using and applying the products, and occupying spaces where they are frequently used, medical professionals should be aware of the VOC inhalation risks, particularly when it concerns use by vulnerable groups and in poorly ventilated smaller treatment spaces.

More systematic assessment of the VOC emissions arising from topical medicines use should be considered, including assessment and quantification of risks before use. Clearer identification of the VOCs emission rates from these products is needed to avoid excessive concentration build-up in rooms where usage is high and/or ventilation poor should be considered, for example via better product labelling and instructions for use. Whilst in-room ventilation is likely to be well-managed in larger hospitals, other smaller healthcare facilities such as surgeries and care homes may be less controlled, particularly if they have been converted from domestic dwellings[52]. Whilst likely only a small overall source of VOCs in the context of national VOC emissions, this source should nonetheless be suitably captured in emissions inventories and emissions models used for indoor air quality, as part of national outdoor emissions inventories, and ultimately as part of international agreements to limit transboundary pollution[53].

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CRediT authorship contribution statement

Yeoman Amber M: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis. **Marvin Shaw:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation. **Martyn Ward:** Writing – review & editing, Validation, Methodology. **Thomas Warburton:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Lewis Alastair C:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

There are no declarations of interest to disclose.

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