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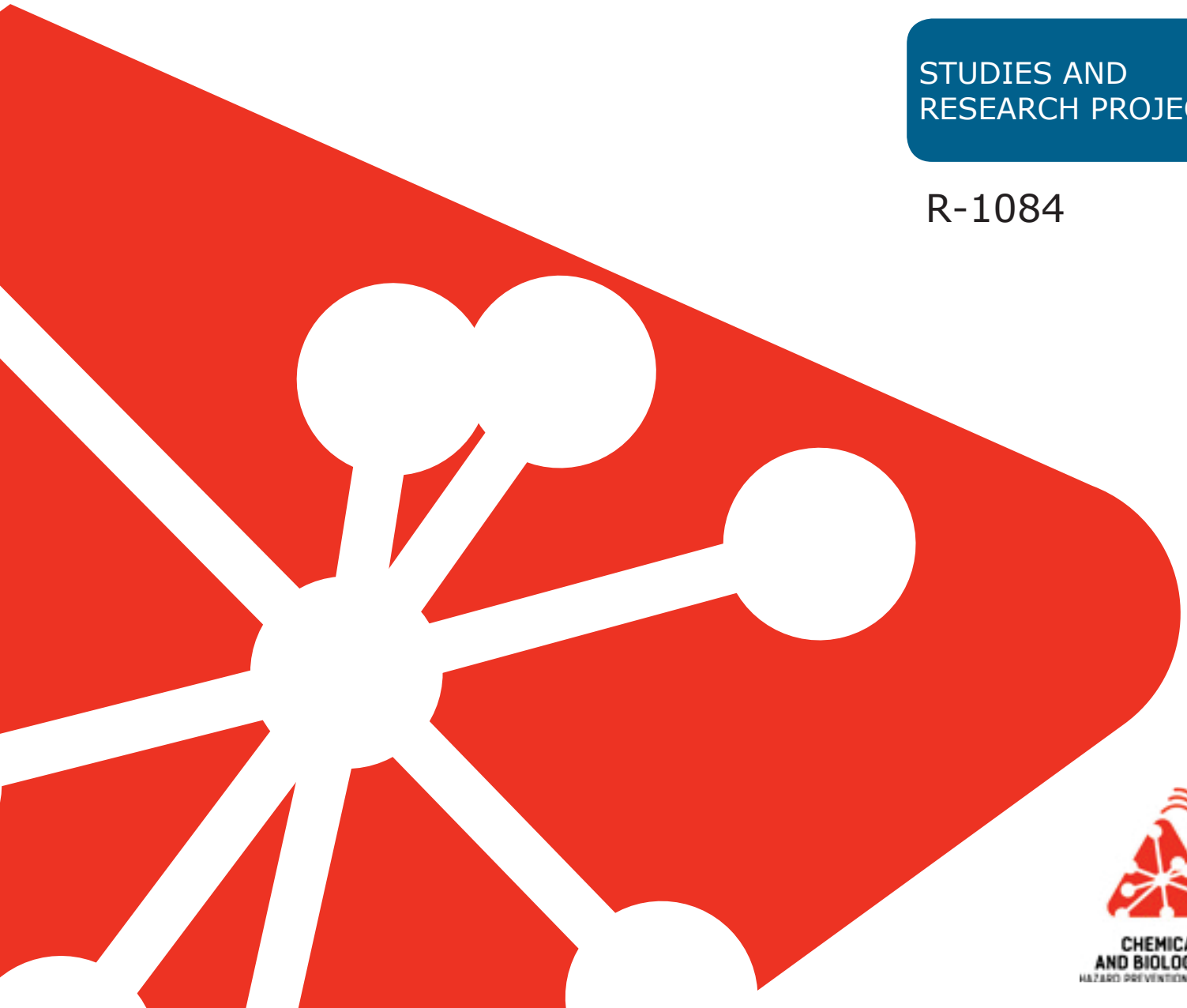

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ABSTRACT

Air quality is a key aspect of occupational health and safety. Moulds and associated chemicals are some of the contaminants to which workers can be exposed. These microorganisms are responsible for numerous health problems (disease or discomfort), including acute allergies, asthma, sinusitis/rhinitis, headaches, environmental hypersensitivity, irritations and inflammation.

Monitoring for fungi is traditionally done using direct evaluation methods or quantitative PCR (polymerase chain reaction). These approaches, however, require a complex sampling procedure that must be carried out by highly experienced personnel, as well as access to the contaminated premises for extensive periods of time and costly technical resources. It also takes a relatively long time to get results.

A new approach involves measuring volatile organic compounds emitted specifically by microfungi in the workplace. However, direct measurement of these microbial volatile organic compounds (MVOC) raises issues similar to those of the traditional approach. The suggested alternative this paper describes is an approach based on measuring MVOCs in the biological matrices of exposed workers, before and after a work shift. This biomonitoring would be complementary to existing approaches.

The study included a literature review to document current knowledge and evaluate the utility of this approach. Measurement of MVOCs in biological matrices and of MVOC levels in indoor air and their specificity are discussed. In addition, 548 MVOCs emitted by numerous species of mould were collected. Based on a close examination of several parameters (health-related parameters, emission frequency, physicochemical and pharmacokinetic parameters, etc.), this number was reduced by 96% to 20 MVOCs that were selected for a biomonitoring approach. Lastly, recommendations are given for implementation of this approach in practice, and suggestions for further study are made.

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LIST OF ACRONYMS AND ABBREVIATIONS

BTEX	Benzene, toluene, ethylbenzene and xylene
CAS	Chemical Abstracts Service databank registry number
F_{nle}	Volume fraction of neutral lipids in erythrocytes
F_{nlp}	Volume fraction of neutral lipids in plasma
F_{nlt}	Volume fraction of neutral lipids in tissue
F_{pre}	Volume fraction of binding proteins in erythrocytes
F_{prp}	Volume fraction of binding proteins in plasma
F_{prt}	Volume fraction of binding proteins in tissue
F_{we}	Volume fraction of water in erythrocytes
F_{wp}	Volume fraction of water in plasma
F_{wt}	Volume fraction of water in tissue
GC-FID	Gas phase chromatography – flame ionization detection
GC-IMS	Gas phase chromatography – ion mobility spectrometry
GC-MS	Gas phase chromatography – mass spectrometry
GC-MSxMS	Gas phase chromatography – two-dimensional mass spectrometry
GCxGC-TOFMS	Two-dimensional gas phase chromatography – time-of-flight mass spectrometry
HC	Hydrocarbon
H_{cc}	Henry's law constant
HS-SPME	Headspace – Solid phase microextraction
HS-trap	Headspace trap sampler
LC	Liquid phase chromatography
MVOC	Microbial volatile organic compound
P_{ba}	PC blood: air

P_{bw}	PC blood: water
PC	Partition coefficient
PCR	Polymerase chain reaction
P_{ew}	PC erythrocyte: water
P_{ow}	PC n-octanol: water
P_{prw}	PC protein: water
P_{pw}	PC plasma: water
PT	Purge and trap method
PTR-MS	Proton transfer reaction mass spectrometry
P_{tw}	PC tissue: water
P_{vap}	Saturation vapour pressure
SIFT-MS	Selected-ion flow-tube mass spectrometry
SMILES	Simplified molecular input line entry specification
SPME	Solid phase microextraction
$T_{½}$	Blood half-life
T_{bp}	Boiling point temperature
Vd_{ss}	Apparent volume of distribution at steady state
V_e	Volume of erythrocytes
VOC	Volatile organic compound
V_p	Volume of plasma
V_t	Volume of tissue

1. INTRODUCTION AND STATE OF KNOWLEDGE

1.1 Occupational health and safety issue, and traditional approach to assessing fungal exposure

Indoor air quality is a key aspect of occupational health and safety (OHS). Air may contain a complex mixture of pollutants, such as carbon monoxide, ozone, radon, volatile organic compounds (VOCs), fine particulate matter and microorganisms. Moulds are one of the types of microorganisms associated with this issue. While moulds are useful and are developed for their benefits in the food (e.g., cheese) and pharmaceutical (e.g., antibiotics) industries, for instance, they are also known to be responsible for various health problems (Borchers, Chang and Gershwin, 2017; Hurraß et al., 2017). Among the thousands of recognized species of mould, only a small proportion are known to pose a risk of infection. On the other hand, all moulds are potential allergens and may be hazardous to people who are sensitive to them. Some species, such as *Alternaria* spp.*, Aspergillus* spp.*, Acremonium* spp.*, Aureobasidium* spp.*, Chaetomium* spp.*, Cladosporium* spp.*, Fusarium* spp.*, Penicillium* spp.*, Stachybotrys* spp.*, Ulocladium* spp. and *Wallemia* spp.*,* are of greater concern when it comes to indoor air quality (Korpi, Jarnberg and Pasanen, 2009; Pieckova and Jesenska, 1999; Schuchardt and Strube, 2013).

Scientists have long known about the ability of moulds to metabolize organic matter while at the same time producing metabolites such as mycotoxins and microbial volatile organic compounds (MVOCs) (Korpi et al., 2009). These microorganisms also produce compounds containing spores, glucane (a polysaccharide) and ergosterol (a sterol synthesized by the microorganisms from sugars), among other things. Depending on the predisposition of the individuals exposed to these metabolites and/or compounds (e.g., compromised immune system, age), they could suffer adverse health effects. A number of studies have reported various illnesses or discomfort, including acute allergies, asthma, sinusitus/rhinitus, headaches, environmental hypersensitivity, irritations and inflammations (Borchers et al., 2017; Hurraß et al., 2017). Given that all these problems can compromise workers' health, it is particularly important to monitor contamination from moulds and related indoor air quality problems.

To monitor indoor air quality for mould contamination, methods of assessing fungal flora in the air have been developed over the years. While these methods are mostly based on visual or microscopic examinations, counting spores and/or cultures in specific media, other alternative approaches have been emerging that focus on using quantitative PCR (Borchers et al., 2017; Mensah-Attipoe and Täubel, 2017; Shorter et al., 2016). These methods involve sampling protocols that require taking samples representative of environments despite variable levels of moulds in the air. Some of them depend on the growth of microorganisms and entail analysis turnaround times that can extend to several weeks.

1.2 Alternative for assessing fungal exposure?

In recent years, a growing interest in MVOCs has raised questions about the potential capacity of moulds to produce specific volatile compounds. Studies have found that the profile of the volatile organic compounds released is characteristic of the fungal species and its stage of development (Fiedler, Schütz and Geh, 2001; Hussain, Tian, He and Lei, 2010; Lemfack, Nickel, Dunkel, Preissner and Piechulla, 2014; Lemfack et al., 2018). This specificity is a key parameter that could be useful in investigating indoor air quality. MVOCs have thus emerged as potential markers of the presence of microbes (Kuske, Romain and Nicolas, 2005; Wilkins and Larsen, 1995).

The MVOC exposure profile could be determined either through measurements taken in the workplace (Jakubowski, 2012) using efficient sampling methods (Claeson, Sandstrom and Sunesson, 2007; Garcia-Alcega et al., 2017; Matysik, Herbarth and Mueller, 2009; Schuchardt and Kruse, 2009), or by a different approach focusing on the analysis of biological matrices (e.g., blood plasma and urine) from people currently exposed or who have been exposed to MVOCs. This approach would have the advantage of circumventing potential problems related to sampling MVOCs in the air.

The distribution of xenobiotics in human tissues and from one biological matrix to the next varies with their physicochemical and pharmacokinetic characteristics (Heinrich-Ramm et al., 2000). The following parameters are generally used in this connection: the partition coefficient (PC) n-octanol: water (P_{ow}), Henry's law constant (H_{cc}), PC blood: air (P_{ba}), apparent volume of distribution at steady state (Vd_{ss}) and blood half-life. The constant H_{cc} is the concentration ratio between air and water of a gas (e.g., MVOCs) at equilibrium. It indicates the hydrophilic or volatile nature of the compound. P_{ow}, on the other hand, is the compound's concentration ratio between n-octanol and water at equilibrium. It is essentially an indicator of a neutral molecule's degree of lipophilia. P_{ba} is the concentration ratio of the compound in the blood and in the air at equilibrium. It is an indicator of the ability of a compound to be absorbed through inhalation. Vd_{ss} indicates the tendency of a molecule to accumulate in human tissue. The higher the Vd_{ss}, the greater the accumulation of the molecule in human tissue. This parameter is proportional to the blood half-life ($T_{1/2} = \frac{0.693 \times \mathrm{Vdss}}{\mathrm{clearance}}$), which is an indicator of the time it takes to eliminate a chemical from the body. The longer a chemical remains in the body, the easier it should be to detect in the biological matrices following a certain amount of exposure. The Vd_{ss} can therefore be used to assess the potential for persistence of MVOCs in the body.

The scientific literature contains a number of examples that emphasize the importance of biological analysis for volatile organic compounds. As a result, given the mould/MVOC specificity relationship, it is possible that these compounds can play the role of markers of fungal presence, thereby paving the way for a new approach to assessing exposure to mould (Matysik, Herbarth and Mueller, 2009).

2. RESEARCH OBJECTIVES

The goal of this research project was to produce an overview of the current state of knowledge in order, firstly, to assess whether an approach using microbial volatile organic compounds as biomarkers of exposure to mould can be regarded as an alternative solution or only as a complement to direct monitoring of mould in the indoor air of occupational environments. A further goal was to make it easier to choose potential MVOCs for this approach. For these purposes, the specific objectives were the following:

i) Conduct a literature search for associations between mould and MVOCs, as well as for methods of detection in the air and in biological matrices

ii) Assess the scope and limitations of this approach by carrying out a critical analysis of various aspects, including specificity, MVOC concentrations, methods and favourable combinations of these compounds

iii) Search or determine the physicochemical and pharmacokinetic parameters for the volatile organic compounds of interest

Note that only the MVOCs that could be found in the indoor air of a workplace were studied. MVOCs associated with pulmonary infections from mould were not covered in this study.

3. METHOD

To achieve the objectives set for this project, the chosen work procedure was divided into three main parts: (i) search for relevant information in the literature on the association between mould and MVOCs and on the identification of the MVOCs; (ii) collect physicochemical and pharmacokinetic parameter values for these compounds; (iii) choose potential MVOCs suitable for this biomonitoring approach.

3.1 MVOCs and their sources

The first part consisted in finding data published in the scientific literature, using databases or search engines, including PubMed, SciFinder, mVOC database (Lemfack et al., 2014), Toxline and Google Scholar. An exhaustive search was conducted using logical combinations of the following English keywords: exposure, mold*/mould*, microb*, fung*, volatile, organic, compound*, VOC*, indoor, building*, environment, damp*, detection, method, biomarker*, human, biomonitoring, blood, urine, air, worker*, etc.

Based on the data collected, MVOCs of interest were identified on a preliminary basis.

3.2 Properties of MVOCs

In the second part of the process, a second exhaustive study was conducted, this time with the goal of compiling the physicochemical and pharmacokinetic parameters of the MVOCs identified in the first part. As in the first stage, tools such as PubChem, SciFinder, Toxline, Medline and GoogleScholar were used with specific keywords to search for the following parameters: PC n-octanol: water (log P_{ow}), Henry's law constant (H_{cc}), PC blood: air (P_{ba}), apparent volume of distribution at steady state (Vd_{ss}) and blood half-life ($T_{½}$) (Peyret, Poulin and Krishnan, 2010).

When measured values of a compound's log P_{ow} and H_{cc} were neither accessible nor available in the literature, estimates were calculated with Estimation Program Interface software, release 4.1 (U.S. EPA, 2017) using the compound's CAS (Chemical Abstracts Service) registry number or its molecular structure in SMILES (Simplified Molecular Input Line Entry System) notation.

In the case of P_{ba}, the algorithm published by Peyret et al. (2010) was used, assuming that the affinity to blood is dictated primarily by solubility in lipids and water (two of the components of blood). In short, given that most collected MVOCs are neutral in a physiological pH range of 7–7.4, the PC blood: air can be estimated with the help of equations 1 to 4, drawn from the research of Poulin and Krishnan (1996) and Peyret et al. (2010):

$$P_{pw} = F_{wp} + (P_{ow} \times F_{nlp}) + (P_{prw} \times F_{prp}) \quad (1)$$

$$P_{ew} = F_{we} + (P_{ow} \times F_{nle}) + (P_{prw} \times F_{pre}) \quad (2)$$

$$P_{bw} = (0.67 \times P_{pw}) + (0.33 \times P_{ew}) \quad (3)$$

$$P_{ba} = P_{bw} / H_{cc} \quad (4)$$

where P_{pw} = PC plasma: water; P_{ew} = PC erythrocyte: water; P_{prw} = PC protein: water; P_{bw} = PC blood: water; F_{wp}, F_{nlp} and F_{prp} are respectively the volume fractions of water, neutral lipids and binding proteins in plasma; and F_{we}, F_{nle} and F_{pre} are respectively the volume fractions of water, neutral lipids and binding proteins in erythrocytes.

Assuming a negligible affinity between binding proteins in blood and neutral MVOCs, the value of P_{prw} can therefore be ignored (P_{prw} = 0). The values of F_{wp}, F_{nlp}, F_{prp}, F_{we}, F_{nle} and F_{pre} (Table 1) are taken from the literature (Peyret et al., 2010).

The Vd_{ss} of the MVOCs was estimated using the approach documented by Poulin et al. (2001) which is incorporated into Poulin's VssPREDICTOR 3.0 software (2001). Basically, this approach consists in estimating PC tissue: water (P_{tw}) of all body compartments, and to use these values to measure Vd_{ss} as follows:

$$P_{tw} = F_{wt} + (P_{ow} \times F_{nlt}) + (P_{prw} \times F_{prt}) \quad (5)$$

$$Vd_{ss} = V_p + \left(V_e \times \frac{P_{ew}}{P_{pw}}\right) + (\sum V_t \times P_{tw}) \quad (6)$$

where P_{tw} = PC tissue: water; F_{wt}, F_{nlt} and F_{prt} are respectively the volume fractions of water, neutral lipids and binding proteins in tissue; and V_p, V_e and V_t are respectively the volumes of plasma, erythrocytes and tissue. The Vd_{ss} of MVOCs were estimated with Poulin's VssPREDICTOR 3.0 software (2001), which uses equations 1 to 6. The volumes and tissue compositions in water and lipids used for these estimates are shown in Table 1. With these estimated parameters, the MVOCs could be prioritized based on their capacity for absorption through inhalation and their tendency to accumulate in human tissue.

Another kinetic parameter of interest is plasma half-life. A search in bibliographical databases such as PubChem, SciFinder, Toxline, Medline and GoogleScholar was conducted using specific English keywords: half-life, clearance, biotransformation, kinetics, etc.

Taking all the collected information into consideration, conclusions have also been drawn about the ease of biological detection of this family of compounds following relatively extended exposure, with a view to possible targeting of potential MVOCs.

Table 1 Volume fractions in tissue and blood, and tissue volumes

	Volume fraction (F)						Tissue volume
	Neutral lipid	Phospholipid		Water	Protein		Fraction of body weight (L/kg)
		Neutral	Acid				
Tissues							
Tissue cells							
Adipose tissues	0.954	0.002	0.0005	0.035	0.008		0.076
Liver	0.0427	0.0253	0.0056	0.527	0.192		0.037
Muscle	0.0099	0.0094	0.0017	0.636	0.178		0.404
Interstitial fluid							
Adipose tissues	0	0	0	0.89	0.010*	0.0003**	
Liver	0	0	0	0.89	0.014*	0.0005**	
Muscle	0	0	0	0.89	0.015*	0.0003**	
Blood							
Erythrocytes	0.0012	0.0034	0.0005	0.63	0.327		0.037
Plasma	0.0015	0.0008	0	0.96	0.029*	0.0060**	0.045

*Albumin

**Lipoprotein

The information presented above is taken from tables in Peyret et al. (2010) and Poulin, Patrick and Theil (2002).

3.3 MVOC selection

After assessing all the information, a final choice of the MVOCs of interest was made. The appropriateness of the biomonitoring approach was then weighed: Is it an alternative solution or an approach that complements direct monitoring of mould? The necessary tools and the strategy/method to be followed for this approach are set out and discussed below.

4. RESULTS AND DISCUSSION

4.1 MVOCs emitted

The initial literature search turned up a total of 548 MVOCs emitted by 87 species of mould that developed on as many as 36 different substrates. All of the MVOCs were screened on the basis of emitting fungal species and on the basis of substrate used in the studies. An examination of this inventory reveals some interesting observations.

4.1.1 Role of growth substrate in MVOC emissions

Several studies have looked at the specificity of MVOC emissions by mould (Gerritsen et al., 2017; Konuma, Umezawa, Mizukoshi, Kawarada and Yoshida, 2015; Micheluz et al., 2016; Neerincx et al., 2016; Schuchardt and Kruse, 2009; Schuchardt and Strube, 2013). Most of the studies were conducted in the lab under controlled conditions (e.g., in vitro or using cultures in very small-scale chambers), rarely in the field in occupied indoor premises. In their study, Gerritsen et al. (2017) observed that the MVOC profiles were distinct for each strain of *Aspergillus* evaluated. In another study, done in connection with the bioproduction of ochratoxin A by three strains of *Aspergillus carbonarius*, Zhang et al. also observed a specific MVOC emission profile for one of the strains (Zhang, Cheng, Ma and Li, 2017). They also established a correlation between the emission of certain MVOCs and the production of mycotoxins.

The species of mould, age and type of growth substrate (development/culture medium) seem to have an influence on the type and concentrations of MVOCs produced. For instance, Fiedler et al. (2001) have observed that emission profiles and intensity were characteristic of the species, but also that they varied with the mould's growth substrate. For example, when the species *Penicillium expansum* develops on an agar medium, 2-methyl-1-butanol or 3-methyl-1-butanol is emitted, but when it develops on construction lumber, those two volatile compounds are no longer detectable; rather, the compounds that are present in this case are 2-butanone, 2-pentanone, 2-hexanene, 2-heptanone and 2-octanone (Fiedler et al., 2001). These emission characteristics can be so specific that *Aspergillus versicolor* was identified in a mixed culture of several moulds simply by the signature of its sesquiterpenes (a class of terpenes synthesized by microorganisms) (Fiedler et al., 2001). It should be noted, however, that some MVOCs are emitted far less specifically, as they can be produced by two species of the same genus (e.g., *Trichoderma* spp.) or by two different genera and that a variation can even be observed within the same species. For instance, 3-methylfuran is not systematically produced by *Aspergillus versicolor*, as it was detected in only 42% of the 19 MVOC emission studies reviewed (Matysik, Herbarth and Mueller, 2008).

The role played by the growth substrate becomes yet more noticeable when it comes to the intensity of MVOC emissions. Emission rates drop sharply when nutrient-poor materials, of which indoor spaces are generally constituted (e.g., wallpaper), are used instead of nutrient-rich agar media (Matysik et al., 2008). Matysik et al. (2009) analysed MVOC emissions produced by seven species of mould. They compared emissions from cultures on agar media with those from mould-contaminated housing. In their study, they identified some 40 volatile compounds, some of which they attributed specifically to moulds. For instance, 1,3-dimethoxybenzene is emitted solely by *Aspergillus versicolor*, methylfurans, ketones and dimethyl disulphide are associated with the

presence of moulds of the *Penicillium* and *Aspergillus* genera, and 2-nonanone is emitted only from wallpaper infected with mould. Nevertheless, the measured concentrations are weighted averages over the entire sampling period, so the time profile of the emissions cannot be established.

4.1.2 Specificity and MVOC-mould association

At present, gaps can be seen in the associations reported in the literature. For example, 2-pentylfuran is an MVOC that, according to one study, is produced specifically by *Aspergillus fumigatus*, while in other studies, it is reported as also being emitted by other species of *Aspergillus* and even by other genera of mould. The case of 3-octanone is very similar. In a recently published review of the literature (Garcia-Alcega et al., 2017), researchers did a critical analysis of reported mould-MVOC associations. Their analysis was based on the only database dedicated exclusively to MVOCs (Lemfack et al., 2014). In the review, they reported new, more specific associations between moulds and emitted MVOCs (Table 2), thereby noting the huge number of gaps in the literature with respect to poorly established or overestimated associations (specificities). Databases designed to contain reliable information on mould-MVOC associations would certainly be of real help in identifying moulds found in contaminated places. Despite these shortcomings, a number of observations can be made.

So, despite great specificity in the case of some MVOCs, others can originate from either fungal or bacterial sources. This is the case of 2-hexanone and of 3-methyl-1-butanol (Lemfack et al., 2014). Bacteria and moulds develop in similar growth conditions (Bos, Sterk and Schultz, 2013; Cumeras et al., 2016; Kim et al., 2007; Korpi et al., 2009) and since the presence of bacteria in an indoor environment, like that of moulds, can represent a health hazard, it does not appear essential, at first glance, in a context of identifying MVOCs of interest as biological markers, to eliminate a compound solely for this reason.

Besides being of microbial origin, MVOCs can also come from several other sources, such as building materials, furniture, cosmetics, maintenance products and fragrances (Caron and Gallego, 2009; Choi, Schmidbauer and Bornehag, 2016; Dinh et al., 2015; Dunkel et al., 2009a, 2009b; Heinrich-Ramm et al., 2000; Kuske et al., 2005; Masuck, Hutzler and Luch, 2011; Schleibinger, Laussmann, Bornehag, Eis and Rueden, 2008; Ye et al., 2017). Substances such as 3-methyl-1-butanol, ethyl acetate, 2-ethyl-1-hexanol, cyclohexanone, methyl isobutyl ketone, β-pinene and limonene can actually be emitted by nonmicrobial sources and so they alone cannot be regarded as appropriate markers (Matysik et al., 2009; Schleibinger et al., 2005).

Table 2 Associations between moulds and specific MVOCs, as reported by Garcia-Alcega et al. (2017)

Mould	Specific MVOC	CAS No.
Aspergillus flavus	cis-2-Octen-1-ol	26001-58-1
Aspergillus fumigatus	2,4-Pentadione (Acetylacetone)	123-54-6
	3-Methyl-1,3-pentandione	110-13-4
	p-Mentha-6,8-dien-2-ol, acetate	97-42-7
Aspergillus versicolor	Trimethyl nonanoate of methyl	**
	1-(3-Methylphenyl)-ethanone	585-74-0
Aspergillus candidus	3-Cyclohepten-1-one, isomer	1121-64-8*
Emericella nidulans	beta-Fenchol	470-08-6
	2-Methyl-butanoate of methyl	868-57-5
	4,4-Dimethyl-pentenoate of methyl	**
Penicillium clavigerum	Bicyclooctan-2-one	2716-23-6
Penicillium crustosum	2-Ethyl-5-methylfuran	1703-52-2
	(S)-gamma-Hexalactone	695-06-7
	Isopropylfuran	10599-59-4
Penicillium cyclopium	2-Methyl-2-bornene, isomer	72540-93-3*
	delta-2-Dodecanol	10203-28-8
	4-Methyl-2-(3-methyl-2-butenyl)-furan	**
Penicillium roqueforti	beta-Patchoulene, isomer	514-51-2*
	beta-Elemene, isomer	33880-83-0*
	(1,1-Dimethylethyl)-2-methylphenol	98-27-1
	2-Methylpropyl butanoate	539-90-2
	alpha-Selinene	473-13-2
	1-Methyl-4-(1-methylethyl) benzene (p-cymene)	99-87-6
	2-methyl-2-methylpropyl propanoate (or 2-methyl-3-methylbutyl propanoate or isobutyric acid)	**
	alpha-Chamigrene	19912-83-5
Paecilomy cesvariotii	3,5,7-Trimethyl-2E,4E,8E-decatetraene	**
	2-Methyl-2,4-hexadiene	28823-41-8
	delta-4-Carene	29050-33-7
Trichodema pseudokoningii	2-Methyl-pentane	107-83-5
Muscodor crispans	2,3-Dimethylhexane	584-94-1
	N-(1-methylpropyl)-formamide	53798-89-3
	1,2-Dimethyl-3,5-bis(1-methylethenyl)-cyclohexane	**
Alternaria alternata	6-Methylheptanol	1653-40-3
Rhizopus stolonifer	1-Octene	111-66-0
	3-Methyl-3-buten-1-ol	763-32-6

*CAS given for substance and not isomer

**CAS could not be found

4.2 Detection of MVOCs

4.2.1 In the air

The detection of MVOCs in ambient air has been examined in the literature (Garcia-Alcega et al., 2017). A variety of sampling techniques are used for volatile compounds. They include the use of activated charcoal or thermal desorption tubes, electronic noses, impingers and cyclones. However, using thermal desorption tubes is the preferred collection technique because of its high sensitivity. In addition, it's also a quick method that does not require any sample preparation prior to the analytical detection stage (Garcia-Alcega et al., 2017). For the analysis or quantification of volatile compounds, the use of gas phase chromatography – mass spectrometry (GC-MS) is recommended, as it can reach fairly low detection limits (of the order of pg/m^3) at relatively low cost, while at the same time providing results quickly (Garcia-Alcega et al., 2017).

The range of MVOC concentrations reported in the air varies considerably, depending on several parameters (Table A 1, Appendix A), including the degree of ventilation of the premises (Malta-Vacas, Viegas, Sabino and Viegas, 2012), the state of development of the mould, the mould concentrations on the premises, the type of place (housing, industrial facility, etc.) and the extent of the damage (infiltration, moisture, etc.) (Araki et al., 2009; Araki et al., 2012; Choi et al., 2016; Choi, Schmidbauer and Bornehag, 2017; Elka et al., 1999; Garcia-Alcega et al., 2017; Kim et al., 2007; Korpi et al., 2009; Matysik et al., 2009; Persoons, Parat, Stoklov, Perdrix and Maitre, 2010; Ryan and Beaucham, 2013; Sahlberg et al., 2013; Schleibinger et al., 2008; Schuchardt and Kruse, 2009; Schuchardt and Strube, 2013). MVOCs were detected at very low levels – 0.24 ng/m^3 – virtually at the quantification limit of the method used, but also at levels as high as 904 µg/m^3 for 1-octen-3-ol in environments with moisture problems. It has also been reported that a minimum MVOC concentration in the air must be exceeded before a location can be regarded as having fungal contamination. For example, 1-octen-3-ol, dimethyl disulphide or 3-methylfuran, regarded as markers of fungal growth, must be present at minimum concentrations of 50 ng/m^3 before a situation can be considered to be a contamination problem, as concentrations measured in outdoor air have never exceeded these levels (Garcia-Alcega et al., 2017).

4.2.2 In biological matrices

When the physicochemical and pharmacokinetic parameters and exposure duration are favourable, the concentration levels measured in the ambient air can produce a concentration increase in the biological matrices of people exposed. For example, an MVOC having greater affinity with blood than with air (i.e., $P_{ba} > 1$) will see its blood concentration at steady state reach a level equivalent to the ambient concentration multiplied by the value of P_{ba}.

The significance of the biological analysis of VOCs has been noted a number of times in the literature. Using post-work shift blood samples, it has been shown that higher VOC blood concentrations were measurable among workers exposed to volatile compounds contained in JP-8 jet fuel, compared with a group of nonexposed workers (Maule, Proctor, Blount, Chambers and McClean, 2016). However, besides the fact that this approach has the disadvantage of being invasive, it should also be emphasized that the determined VOC blood concentration would seem to depend greatly on individual VOC elimination kinetics (Janasik, Jakubowski, Wesolowski and

Kucharska, 2010). Blood plasma analysis has also already been used to confirm VOC exposure, under real conditions, in the general population (Aranda-Rodriguez et al., 2015; Blount et al., 2006; Lemire et al., 2004), as well as among workers (Maule et al., 2016; Romieu et al., 1999).

Some scientists opt to examine biological matrices that can be sampled less invasively, at least physically (e.g., urine) (Kim, Moon, Park, Lee and Hong, 2011). Toxicokinetic modelling of urinary biomarkers can also serve to quantify exposure to parent VOCs quite effectively (Marchand, Aranda-Rodriguez, Tardif, Nong and Haddad, 2016). The specificity or sensitivity of this method could be affected, however, as a result of interference caused by natural physiological processes or by digestion of food additives, for instance (Janasik et al., 2010). Analysis of nonmetabolized VOCs excreted in the urine is considered to be a more reliable method (Antonucci, Vitali, Avino, Manigrasso and Protano, 2016; Hakkola, Saarinen and Pekari, 2001; Imbriani and Ghittori, 2005; Janasik et al., 2010; Saarinen, Hakkola, Pekari, Lappalainen and Aitio, 1998; Vainiotalo, Kuusimaki and Pekari, 2006; Vainiotalo, Pekari and Aitio, 1998). In other studies, researchers opted to examine the analytical detection of VOCs in exhaled breath (Amann et al., 2014; Cao and Duan, 2006; Caro and Gallego, 2009; Castellanos, Xifra, Fernandez-Real and Sanchez, 2016; Storer, Curry, Squire, Kingham and Epton, 2015; Tang, Liu and Duan, 2015) or in saliva (Amann et al., 2014; Milanowski, Pomastowski, Ligor and Buszewski, 2017). In the case of exhaled breath, however, the lack of standardized procedures and the presence of water in the matrix are major drawbacks (Cao and Duan, 2006; Tang et al., 2015). Furthermore, for these two types of matrices, it is essential to be able to distinguish between the exogenous and endogenous sources of the detected VOCs (Cao and Duan, 2006; Pleil, Stiegel and Risby, 2013; Tang et al., 2015).

Last, analytical methods for determining VOC concentrations in different matrices have already been developed, especially ones based on GC-MS (Table 3).

Table 3 Different analytical methods for detecting and quantifying VOCs in biological matrices

Matrix	Method	Reference
Blood	SPME-GC-MS	(Blount et al., 2006; Janasik et al., 2010; Maule et al., 2016)
	PT-GC-MS	(Lemire et al., 2004)
	GCxGC-TOFMS	(Dubois et al., 2017)
	SPME-GC-MSxMS	(Aranda-Rodriguez et al., 2015)
Exhaled breath	GC-MS	(Cao and Duan, 2007; Giardina and Olesik, 2003; Kim, Jahan and Kabir, 2012)
	SPME-GC-MS	(Bajtarevic et al., 2009; Kim et al., 2012)
	GC-FID	(Kim et al., 2012; Sanchez and Sacks, 2003)
	GC-IMS	(Kim et al., 2012; Lord, Yu, Segal and Pawliszyn, 2002)
	PTR-MS	(Bajtarevic et al., 2009; Kim et al., 2012)
	GC-PTR-MS	(Karl et al., 2001; Kim et al., 2012)
	SIFT-MS	(Abbott, Elder, Španel and Smith, 2003; Kim et al., 2012; Spanel, Davies and Smith, 1999; Storer et al., 2015)
Urine	SIFT-MS	(Abbott et al., 2003)
	SPME-GC-MS	(Antonucci et al., 2016; Janasik et al., 2010; Vainiotalo et al., 2006)
Saliva	GC-MS	(Milanowski et al., 2017)
	HS-Trap-GC-MS	(Amann et al., 2014)

4.3 Physicochemical properties and estimates of toxicokinetic properties of MVOCs

The results of the determination of the physicochemical and pharmacokinetic parameters (Heinrich-Ramm et al., 2000) are presented in Table A 2 (Appendix A). Considerable variation in the hydrophilic and lipophilic characteristics of the MVOCs surveyed can be seen. The H_{cc} range varies between 2.48×10^{-10} and 1.15×10^{4}, whereas that of log P_{ow} varies between 0.24 and 7.05. The two constants H_{cc} and P_{ow} are used in estimating P_{ba}.

When someone is exposed to a gas continuously at a given concentration, his blood concentrations reaches a ceiling after a certain length of time. At that point, steady state is achieved and the concentration in the blood will, at its maximum, be equivalent to the concentration in the air multiplied by the P_{ba}. The body's metabolism will reduce this maximum concentration by a quarter of its maximum value if the substance is strictly biotransformed by the liver, i.e., the proportion of the cardiac output received by the liver (~ 25%). The higher the P_{ba}, the greater the absorption by inhalation. The range of estimated P_{ba} values goes from 9×10^{-2} (dimethylarsane) to 4×10^{9} ((2E,4E)-2-methyl-hexa-2,4-dienoic acid (2'R,3'S)-isoleucinol amide). These values are given in Table A 2.

Since the half-life is proportional to the Vd_{ss}, it is to be expected that a substance having a high tissue distribution would have a longer plasma half-life. The MVOCs surveyed have Vd_{ss} values ranging between 0.5 and 28 L/kg (Table A 2).

4.4 Targeting potential MVOCs

In order to target the most relevant MVOCs for the purpose of assessing mould exposure through biological monitoring, the decision tree shown in Figure 1 was followed. Five screening levels (1 to 5) were used to reduce the number of MVOCs of interest and thereby concentrate only on those having the optimum properties for evaluating the biological marker approach.

The 548 MVOCs identified in the initial bibliographic search are associated with a high number of different mould species and strains. To simplify the results, all strains of a given species were grouped together. The five screening levels were then applied to the resulting groups.

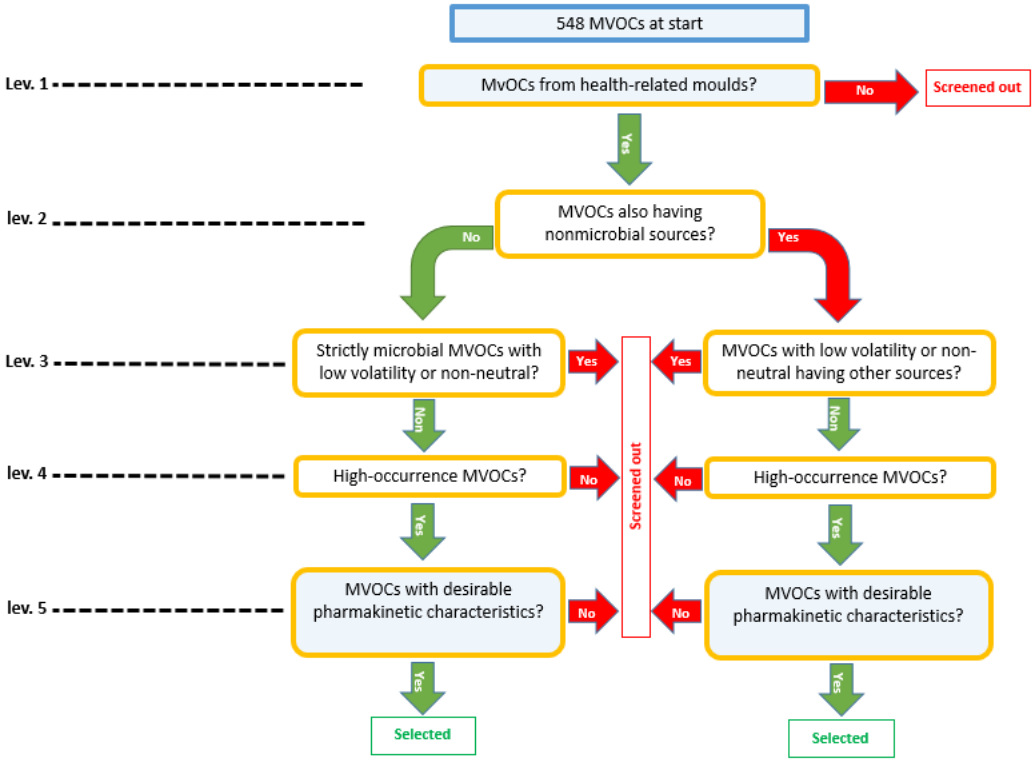

Figure 1 Strategy for selecting potential MVOCs, showing five screening levels

Level 1 targets species of interest in indoor environments. It made sense to focus on emissions of species most commonly found in the environment and especially occupied indoor spaces, including *Alternaria* spp., *Aspergillus* spp., *Acremonium* spp., *Aureobasidium* spp., *Chaetomium* spp., *Cladosporium* spp., *Fusarium* spp., *Penicillium* spp., *Stachybotrys* spp., *Ulocladium* spp. and *Wallemia* (Korpi et al., 2009; Pieckova and Jesenska, 1999; Schuchardt and Strube, 2013). A total of 218 MVOCs, i.e., 40% of the moulds, were screened out at this first stage.

The second screening level was then applied to the remaining 330 MVOCs. The purpose of this stage was to identify VOCs that were not strictly microbial in origin. As mentioned earlier, VOCs can come from a number of other sources, such as building materials, furniture, cosmetics, maintenance products, fragrances, etc. (Caro and Gallego, 2009; Choi et al., 2016; Dinh et al. ,

2015; Dunkel et al., 2009a, 2009b; Heinrich-Ramm et al., 2000; Kuske et al., 2005; Masuck et al., 2011; Schleibinger et al., 2008; Ye et al., 2017). MVOCs from nonmicrobial sources were removed from the main list, reducing the number of MVOCs to 195, a further winnowing out of 41%. At this point, 9 additional substances, cited in the literature as being emitted by moulds, but unidentified or misidentified, were also excluded, bringing the remaining number of MVOCs to 186.

Applying the third screening level required taking two conditions into account: an MVOC's degree of ionization (represented by its pK_a) and its volatility. To simplify estimates of toxicokinetic properties, only MVOCs neutral in a physiological medium having pH 7–7.4 (like blood) were considered. Under these conditions, the interactions between neutral MVOCs and biological components, such as acidic phospholipids and some proteins, can be disregarded (Peyret et al., 2010; Poulin and Theil, 2000). An MVOC's volatility, represented by its boiling point temperature (T_{bp}) and its saturation vapour pressure (P_{vap}), is also an important parameter, which is considered at this third screening level. The lower the T_{bp} (high P_{vap} relative to atmospheric pressure), the higher its proportion in the gas phase in the air will be. From the point of view of volatility, and despite the known adsorption of less volatile compounds on particles and the exposure that can result, only the most volatile compounds were selected as potential markers. To apply screening level 3, the T_{bp} threshold was set at 250°C. As a result, 49 MVOCs were screened out at this stage (44 compounds with very low volatility and 5 non-neutral ones), lowering the number of remaining MVOCs by a further 26%, to 137.

Further reduction in the number of MVOCs was achieved by considering the occurrence of MVOC emissions. An in-depth examination revealed that some products are emitted more often by mould species. The occurrence of emissions provided the basis for a fourth screening level (level 4). Only volatile compounds having been emitted by 5 species or more were considered for the last stage, thus zooming in on 21 MVOCs out of 137 (a reduction of 85%). Some MVOCs can be very specific to one or two fungal species and so were excluded at this level. These MVOCs that have been set aside could, however be useful at later stages of the research, when the time comes to identify fungal or microbial species contaminating the workplace. The MVOCs included in the final selection for this project were chosen for detection of general contamination.

Nevertheless, among the 135 MVOCs excluded at level 2 because they were from nonmicrobial sources, 34 not only had high occurrences, but were also neutral at pH 7–7.4 and relatively volatile (T_{bp} < 250°C), which justified reconsidering them as potential biomarkers. Possible nonmicrobial sources of these 34 MVOCs are indicated in Table A 3 (Appendix A). The combination of the 21 MVOCs remaining at level 4 and the 34 MVOCs recovered from level 2 brought the number of selected MVOCs to 55 (tables 4 and 5) out of the 548 identified at the start (a 90% reduction).

Table 4 High-occurrence MVOCs having no known nonmicrobial source

MVOC	CAS No.	Code	Hcc	P_{ba}	Vd_{ss} (L/kg)
2-Butylfuran	4466-24-4	B3	5.67E-01	7.43E+00	16.99
Chalcogran (Z)	38401-84-2	B8	2.77E-04	8.75E+03	11.97
Conophthorin	68108-90-7	B9	2.77E-04	8.75E+03	11.97
3-Pentanol	584-02-1	C6	8.09E-04	1.08E+03	0.96
2-Hexanol	626-93-7	C8	9.97E-04	9.34E+02	1.91
2-Heptanol	543-49-7	C10	2.27E-03	5.00E+02	4.35
2-Octanol	123-96-6	C12	5.03E-03	3.91E+02	9.93
3-Octanol	589-98-0	C13	1.27E-03	1.26E+03	7.92
E-2-Octen-1-ol or 2-Octen-1-ol	18409-17-1	C22	1.12E-03	1.25E+03	6.52
(Z)-oct-5-en-1-ol	64275-73-6	C24	1.12E-03	1.25E+03	6.52
5-Octen-2-ol	55968-41-7	C27	1.12E-03	1.17E+03	5.90
3-Nonen-1-ol (Z)	10340-23-5	C29	1.48E-03	1.71E+03	12.41
1-Penten-3-ol	616-25-1	C30	4.04E-04	2.15E+03	0.89
2-Penten-1-ol (Z)	1576-95-0	C31	4.77E-04	1.82E+03	0.89
2-Nonanone	821-55-6	E8	1.50E-02	1.86E+02	13.30
6-Undecanone	927-49-1	E18	9.16E-03	8.42E+02	21.33
1,3-Octadiene	63597-41-1	F9	1.17E+01	1.07E+00	23.74
Hexyl formate	629-33-4	H2	4.05E-02	2.76E+01	4.16
Pentyl hexanoate	540-07-8	H21	6.92E-02	4.16E+02	26.13
Hexan-4-olide or 4-Ethylbutan-4-olide or gamma-Caprolactone	695-06-7	H26	7.39E-03	1.16E+02	0.65
Methylpyrazine	109-08-0	I3	8.99E-05	9.49E+03	0.59

Table 5 High-occurrence MVOCs having a nonmicrobial source

MVOC	CAS No.	Code	Hcc	P_{ba}	Vd_{ss} (L/kg)
Ethyl acetate	141-78-6	H4	5.48E-03	1.57E+02	0.69
Heptane	142-82-5	A1	8.17E+01	7.94E-01	27.16
2-Methylfuran	534-22-5	B1	2.43E-01	3.91E+00	2.18
2-Pentylfuran	3777-69-3	B4	7.53E-01	1.49E+01	23.29
Ethanol	64-17-5	C1	2.04E-04	4.17E+03	0.56
1-Propanol	71-23-8	C2	3.03E-04	2.82E+03	0.60
1-Pentanol	71-41-0	C4	5.31E-04	1.69E+03	1.35
2-Pentanol	6032-29-7	C5	6.05E-04	1.44E+03	0.95
1-Hexanol	111-27-3	C7	6.99E-04	1.43E+03	2.85
1-Heptanol	111-70-6	C9	7.68E-04	1.87E+03	6.80
1-Octanol	111-87-5	C11	1.00E-03	2.25E+03	11.26
2-Methyl-1-propanol	78-83-1	C15	4.00E-04	2.15E+03	0.70
2-Methyl-1-butanol	137-32-6	C18	5.76E-04	1.52E+03	1.05
3-Methyl-1-butanol	123-51-3	C19	5.76E-04	1.51E+03	0.92
1-Octen-3-ol	3391-86-4	C23	9.45E-04	1.49E+03	6.61
3-Hexen-1-ol (Z)	928-96-1	C33	6.33E-04	1.43E+03	1.54
2-Ethyl-1-hexanol	104-76-7	C35	1.08E-03	1.48E+03	7.92
Dimethyl disulfide	624-92-0	D3	4.95E-02	1.89E+01	1.93
Acetone	67-64-1	E1	1.43E-03	5.95E+02	0.56
2-Butanone	78-93-3	E2	2.28E-03	3.74E+02	0.60
Cyclopentanone	120-92-3	E4	4.09E-04	2.09E+03	0.61
2-Pentanone	107-87-9	E5	3.42E-03	2.52E+02	0.76
2-Hexanone	591-78-6	E6	6.91E-03	1.28E+02	1.15
2-Heptanone	110-43-0	E7	6.91E-03	1.45E+02	2.85
2-Octanone	111-13-7	E12	7.68E-03	1.53E+02	4.75
3-Octanone	106-68-3	E13	5.31E-03	2.04E+02	3.80
Cyclohexanone	108-94-1	E15	3.68E-04	2.34E+03	0.72
Xylene	1330-20-7	G1	2.12E-01	1.36E+01	13.60
beta-Myrcene	123-35-3	J2	2.63E+00	8.21E+00	25.51
Limonene or alpha-Limonene	138-86-3	J6	1.30E+00	4.06E+01	26.97
Hexanal	66-25-1	K1	8.71E-03	1.07E+02	1.96
2-Octanal, (E)	2363-89-5	K2	3.00E-03	4.57E+02	6.34
Decanal	112-31-2	K3	7.36E-02	1.21E+02	22.15
2-Heptenal	2463-63-0	K4	2.19E-01	4.64E+00	3.03

The last level (level 5) for the selection of MVOCs to be prioritized for the identification of mould exposure biomarkers is based on pharmacokinetic properties, pulmonary absorption capacity (P_{ba}) and bioaccumulation capacity (Vd_{ss}). The idea in this case is to target substances that have a tendency to become concentrated in the blood at the time of exposure and therefore to have one of the highest P_{ba} levels among remaining substances. Compounds having a $P_{ba} \geq 100$ were selected (Figure 2).

Furthermore, it would be interesting to identify substances that are quickly eliminated from the body and others that have a tendency to bioaccumulate. With no information on clearance, Vd_{ss} was chosen to assess persistence in the human body, as it was the most indicative parameter available. A compound with a high Vd_{ss} will tend to accumulate in body tissue (e.g., fats) and will be less available for biotransformation; a Vd_{ss} value of ≥ 10 L/kg was chosen. As for compounds that can be eliminated faster, compounds having a $Vd_{ss} \leq 1$ L/kg were selected. The MVOCs indicated in the shaded sections of Figure 2 are those that meet the two established pharmacokinetic criteria, and they are listed in Table 6. Two of the compounds included in the list of MVOCs having known nonmicrobial sources in Table 6 are ethanol and acetone. They were excluded, however, as it is well known that they are formed endogenously in the human body (Garner et al., 2007; Raman et al., 2013). Possible nonmicrobial sources of these MVOCs are listed in Table A 3.

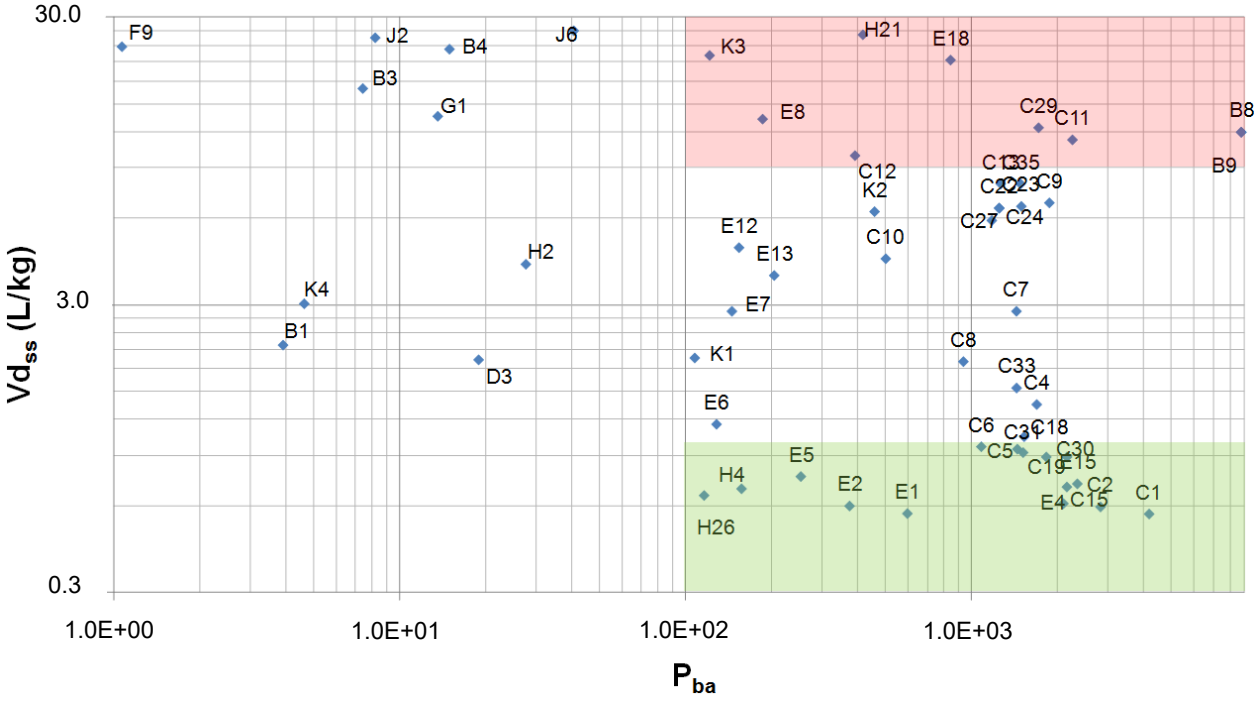

Figure 2 Graphic presentation of pharmacokinetic properties (Vd_{ss} and P_{ba}) of the 55 MVOCs selected at level 4 (see tables 4 and 5 for the codes assigned to the MVOCs)

The area shown in red contains the MVOCs selected for their strong affinity with blood and their high capacity for bioaccumulation. The area in green contains substances having a strong affinity with blood and a low capacity for bioaccumulation (i.e., little chance of being persistent).

Table 6 Remaining MVOCs selected for their pharmacokinetic properties

Bioaccumulative potential	Without other known source	Other known source
Bioaccumulable	Chalcogran (Z) 2-Octanol 3-Nonen-1-ol (Z) 2-Nonanone 6-Undecanone Pentyl hexanoate	1-Octanol Decanal
Nonbioaccumulable	3-Pentanol 1-Penten-3-ol 2-Penten-1-ol (Z) Hexan-4-olide	Ethanol* 1-Propanol** 2-Pentanol 3-Methyl-1-butanol** Acetone* 2-Butanone** Cyclopentanone 2-Pentanone Cyclohexanone** Ethyl acetate**

*Substances to be excluded because present endogenously in the human body

**Substances regulated under the Quebec Regulation Respecting Occupational Health and Safety

The chart in Figure 3 shows the final results of the MVOC selection process, with a total of 20 MVOCs chosen, and indicating the screening out of MVOCs at each stage (levels 1–5). The initial 548 substances were reduced by 96% to arrive at the final 20 MVOCs. Among the MVOCs selected, some also have nonmicrobial sources. They have not been excluded, as at this stage, the frequency and levels that can be expected from these compounds originating from a microbial source in relation to other sources is not well established. Even though potential sources may be nonmicrobial, it is possible that the presence of these MVOCs at high concentrations may still be indicative of mould.

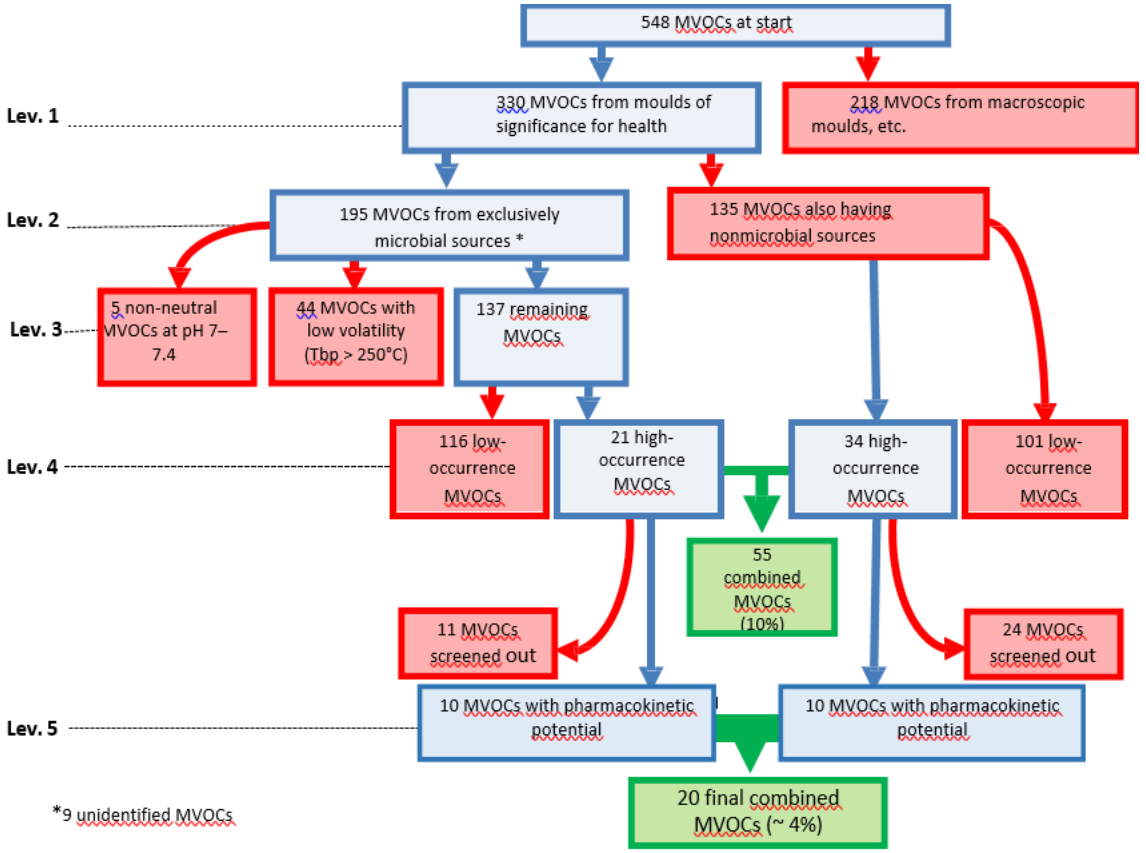

Figure 3 Final results of MVOC selection

4.5 Recommendations

MVOCs are compounds that can be measured in the air and in biological matrices (e.g., blood) using experimental procedures, including GC-MS as an analytical method. Extraction by means of solid phase microextraction (SPME) in the headspace is easy to implement for VOCs in biological matrices and should also be applicable to MVOCs in a biomonitoring context. Compared with other methods, it does not require any sample preparation other than warming, and it is cleaner for the apparatus, as only volatile substances adsorbed onto the fibre are injected into the column for separation and detection. Furthermore, for many of the compounds listed in Table 6, methods using GC-MS have already been developed and are in use (Beck, Mahoney, Cool and Gee, 2012; Fiedler et al., 2001; Marten, Córdoba, Benito, Aranda and Asensio, 2003; Matysik et al., 2009; Sahlberg et al., 2013; Schleibinger, 2002).

As no invasive sampling is required, urine would obviously be the ideal matrix, in terms of worker comfort. Unfortunately, given the lack of information on MVOC kinetics (elimination in urine) and the lipophilic character of MVOCs, the biological matrix to be explored first, with a view to initiating the development of MVOC biomarkers, must be blood. The reasons are that (i) this matrix is fairly easily accessible, despite the invasive sampling required, (ii) the use of the blood matrix is a common practice that is based on already optimized experimental procedures, (iii) the properties (Vd_{ss}, lipophilicity, P_{ba}) of the selected unchanged MVOCs assume that concentrations in blood will be higher than in other frequently used matrices (urine, exhaled breath, saliva). Subsequent kinetic studies should focus on assessing the urinary concentrations of the unchanged MVOCs and identifying their metabolites. SPME, which is the technique generally used for analysing VOCs in blood, is also suitable for urine analysis. As a result, if levels are measurable, the urinary matrix is definitely an option worth considering.

When exposed by inhalation, gases are easily absorbed into the blood and get distributed according to their affinity with tissues. Regardless of the volatile compound, in the event of extended exposure, the VOC will reach concentrations proportional to its P_{ba}. The selected substances all have an estimated P_{ba} of greater than 100, which means that if steady state is reached when blood is sampled, the MVOC concentration should approach a value that is 100 times or more than that in inhaled air. Since P_{ba} values have only been estimated so far, it would be useful to measure them experimentally for the selected MVOCs.

To conduct biomonitoring in the workplace for this type of compound, blood samples would have to be taken from workers before and after their shifts. This is because workers may be exposed outside the workplace. The difference in blood MVOC levels between shifts could provide important information on the place of exposure. For instance, an increase in levels would suggest exposure at work, while a drop would appear to indicate another source.

In addition to other MVOCs, products that have the potential to be bioaccumulated could provide additional information about exposure. Sampling spread out over several workdays could help confirm exposure to mould in the workplace as blood levels rise over the course of the week. With no information about half-lives at this point, it is hard to establish a precise strategy in this respect. Pharmacokinetic studies will be necessary to characterize the half-lives of the selected products and thereby enable more accurate interpretation of exposure to MVOCs.

Should the use of an MVOC having a possible source other than mould be confirmed, it would be important to avoid jumping quickly to conclusions, and instead to determine accurately the possible nonfungal sources present (e.g., food, carpet, solvents, paints, waxing products, deodorants, perfumes). In the list given in Table 5, some volatile compounds are regulated by the Quebec Regulation Respecting Occupational Health and Safety. These substances, which are also given off by nonmicrobial sources, can frequently be found in the ambient air of workplaces. As a result, they should not be used alone in the biomonitoring process, but rather in association with other MVOCs that are more specific to fungal and bacterial flora. In addition, for certain substances, just because no other source has been identified in this review of the literature does not mean that there are no other possible sources.

As the ultimate goal of this study is to select MVOCs having good potential to be biomarkers, it is pertinent to document what is currently known about the methods of assessing these compounds in the air. A survey of information about the sampling in the air and analysis of the compounds listed in tables 4 and 5 is presented in Table A 3. Any procedure involving the use of a chemical compound for biomonitoring must be based on the best possible characterization of exposure to it, especially by inhalation in this context. Therefore, the fact that, for some compounds, methods of assessment of concentrations in the air are already recognized or well established could favour certain compounds over others for use as biomarkers.

The list of compounds remaining after the various levels of selection in this report have been applied should be taken as a suggestion of initial MVOCs for the development of this biomonitoring approach to assessing mould exposure and should not be regarded as restrictive. Refinement of this approach could well require the addition of MVOCs that have not been prioritized here. For instance, the substances that were detected in several species of mould were prioritized here, but it might be beneficial to add MVOCs specific to a given species of mould in the analysis of blood (or urinary) MVOCs. That could provide additional information that would be very useful in identifying fungal species that contaminate the workplace.

It should be noted that the anticipated MVOC concentration levels in the workplaces targeted by this study could be well below the VOC levels usually found in many workplaces. Since data to correlate the MVOC concentrations in the air with the quantity of MVOCs absorbed by workers following exposure through inhalation would be necessary, determining the presence and quantities of these MVOCs would have to be done by air concentration assessment methods having optimum sensitivity and specificity for the expected low levels. Typical industrial hygiene methods do not usually offer the required performance level for quantifying these concentration levels, which would seem to approach the environmental background noise coming from other sources in some cases, or which would have to be evaluated in a context close to the quality of the indoor air. In this regard, whole-air analysis methods, such as vacuum cans or thermal desorption tubes with GC-MS, could be recommended for this type of assessment.

Just as for air, GC-MS analytical methods used for biological matrices generally allow several analytes per sample to be analysed, and that should be given preference as part of an approach designed to find an association between the presence of MVOCs in the blood and that of moulds in the workplace. The greater the number, specificity and concentrations of MVOCs in the blood, the greater the confidence in fungal contamination. Association studies would be required, of course, in order to validate an approach of this kind.

Experimental validation of this concept would obviously be necessary. Validation would require carrying out the following steps:

i) In-depth study of MVOC concentrations and their emission rates based on parameters such as mould age, as well as degree of prevalence in the workplace, which would help to define concentration thresholds for considering fungal contamination

ii) Developing toxicokinetic models to establish the distribution of MVOCs in biological matrices, so that matrices can be chosen based on the volatile compound being considered

iii) Study of MVOC metabolites with a view to possibly using other matrices, such as urine, for which sampling is not invasive

iv) Validation of toxicokinetic models for mould exposure biomarkers, with exposure under controlled laboratory conditions

v) In-depth field studies under real conditions to validate the biomonitoring approach

vi) Experimentation on animals, or even on humans, to determine whether these MVOCs pose a nonnegligible risk of toxicity

All these steps would help provide a better understanding of (i) the connection between the presence of microorganisms and MVOC concentrations in the air and (ii) the connection between concentrations in the air and those in biological matrices (Kim et al., 2007). It would then be possible to draw up standard sampling and analysis protocols, while ensuring the quality and robustness of the results obtained.

5. CONCLUSION

The first step in this assessment of the current state of knowledge involved identifying 548 MVOCs. All of them came from emissions of many different species of mould. On the basis of several screening criteria (e.g., health significance, physicochemical parameters, occurrence), this number was reduced as part of a process to make an informed selection of the MVOCs that had the greatest potential as biological markers. An examination of the corresponding (estimated or experimental) pharmacokinetic parameters led to more specific targeting, by further reducing the number of MVOCs selected, and the establishment of a final list of 20 MVOCs (which meant that the initial number of MVOCs identified was reduced by 96%). Some MVOCs are specific to mould, whereas others have nonmicrobial sources, which means caution must be exercised when deciding whether or not to use them as biomarkers. Furthermore, in light of their parameters, the MVOCs from nonmicrobial sources represent potential candidates for biomonitoring or for complementing direct monitoring of moulds.

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APPENDIX A
SUPPLEMENTARY TABLES

Table A 1 Concentrations of certain MVOCs in various types of indoor environments

MVOC	Concentration range (ng/m^3)	Type of environment	Method	LOD (ng/m^3)	LOQ (ng/m^3)	Reference
1-Octen-3-ol	ND–7000	Buildings without moisture problems				(Garcia-Alcega et al., 2017)
	5240–11800	Homes				(Garcia-Alcega et al., 2017)
	ND–904000	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
	300–6000	Manufacturing facilities				(Garcia-Alcega et al., 2017)
2-Octen-1-ol	ND–14000	Buildings without moisture problems				(Garcia-Alcega et al., 2017)
	12400–79600	Homes	GC-MS	0,1-2	~2xLOD	(Ryan and Beaucham, 2013)
	1560–266000	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
2-Heptanone	ND–1200	Buildings without moisture problems				(Garcia-Alcega et al., 2017)
	10000–26500	Homes	GC-MS	0,1-2	~2xLOD	(Ryan and Beaucham, 2013)
Carveol	8000–15700	Homes	GC-MS	0,1-2	~2xLOD	(Ryan and Beaucham, 2013)
3-Octanol	ND–40	Buildings without moisture problems				(Garcia-Alcega et al., 2017)

MVOC	Concentration range (ng/m^3)	Type of environment	Method	LOD (ng/m^3)	LOQ (ng/m^3)	Reference
	4400–16300	Homes	GC-MS	100-2000	~2xLOD	(Ryan and Beaucham, 2013)
	<LOQ–92	Homes	GC-MS	LOQ/3	44	(Araki, A. et al., 2009)
	ND–8860	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
gamma Terpineol	4800–17600	Homes	GC-MS	100-2000	~2xLOD	(Ryan and Beaucham, 2013)
alpha Terpineol	4600–27400	Homes	GC-MS	100-2000	~2xLOD	(Ryan and Beaucham, 2013)
2-Nonanone	3800–11800	Homes	GC-MS	100-2000	~2xLOD	(Ryan and Beaucham, 2013)
2-Methylfuran	2600–10900	Homes	GC-MS	100-2000	~2xLOD	(Ryan and Beaucham, 2013)
3-Methylfuran	<1–160	Schools	GC-MS	1		(Kim, J. L. et al., 2007)
	ND–1800	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
Geosmin	ND–50	Buildings without moisture problems				(Garcia-Alcega et al., 2017)
	2800–9500	Homes	GC-MS	100-2000	~2xLOD	(Ryan and Beaucham, 2013)
	ND–550	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
2-Pentanol	3400–5900	Homes	GC-MS	100-2000	~2xLOD	(Ryan and Beaucham, 2013)
	<LOQ–3823	Homes	GC-MS	LOQ/3	102	(Araki, A. et al., 2009)

MVOC	Concentration range (ng/m^3)	Type of environment	Method	LOD (ng/m^3)	LOQ (ng/m^3)	Reference
	<1–320	Schools	GC-MS	1		(Kim, J. L. et al., 2007)
	ND–1400	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
Dimethyl sulfide	1700	Homes				(Garcia-Alcega et al., 2017)
	ND–1700	Manufacturing facilities				(Garcia-Alcega et al., 2017)
Dimethyl disulfide	<10–710	Schools	GC-MS	1		(Kim, J. L. et al., 2007)
	16–90	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
	ND–263000	Manufacturing facilities				(Garcia-Alcega et al., 2017)
2-Heptanone	<LOQ–1518	General housing	GC-MS	LOQ/3	130	(Araki, A. et al., 2009)
	32–750	Schools	GC-MS	1		(Kim, J. L. et al., 2007)
	ND–97	Buildings with moisture problems				(Garcia-Alcega et al., 2017)
2-Methyl-1-butanol	<1–37	Schools	GC-MS	1		(Kim, J. L. et al., 2007)
3-Methyl-2-butanol	ND–160	Buildings without moisture problems				(Garcia-Alcega et al., 2017)
	3600	Homes				(Garcia-Alcega et al., 2017)
	190–1190	Buildings with moisture problems				(Garcia-Alcega et al., 2017)

ND: not detected

LOD: limit of detection

LOQ: limit of quantification

Table A 2 Experimental or estimated physicochemical and pharmacokinetic parameters of identified MVOCs (195 MVOCs from exclusively microbial sources and 34 reconsidered MVOCs having possible nonmicrobial sources)

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
Heptane	142-82-5	A1	8.17E+01	7.94E-01	27.16
Lignocerane or tetracosane	646-31-1	A2	1.15E+04	1.64E+05	27.89
Heptane, 2,4-dimethyl	2213-23-2	A3	1.63E+02	3.55E-01	27.06
Naphthalene, decahydro-, cis-	493-01-6	A4	1.92E+01	1.20E+00	25.67
2-Methylfuran	534-22-5	B1	2.43E-01	3.91E+00	2.18
Isopropylfuran	10599-59-4*	B2	4.27E-01	4.16E+00	8.94
2-Butylfuran	4466-24-4	B3	5.67E-01	7.43E+00	16.99
2-Pentylfuran	3777-69-3	B4	7.53E-01	1.49E+01	23.29
2-Heptylfuran	3777-71-7	B5	1.33E+00	7.70E+01	27.44
2-Ethyl-5-methyl-furan	1703-52-2	B6	3.55E-01	5.91E+00	10.58
4-Methyl-2-(3-methyl-2-butenyl)-furan	†	B7	8.63E-01	3.05E+01	25.96
Chalcogran (Z)	38401-84-2*	B8	2.77E-04	8.75E+03	11.97
Conophthorin	68108-90-7*	B9	2.77E-04	8.75E+03	11.97
Dihydroedulan I	63335-66-0	B10	1.71E-02	1.76E+03	26.21
Isobutyl methyl ether	625-44-5	B11	9.03E-02	9.88E+00	1.29
Isopentyl methyl ether	626-91-5	B12	1.09E-01	8.98E+00	2.57
Ethanol	64-17-5	C1	2.04E-04	4.17E+03	0.56
1-Propanol	71-23-8	C2	3.03E-04	2.82E+03	0.60
2-Propanol 1-Propano	***	C3			
1-Pentanol	71-41-0	C4	5.31E-04	1.69E+03	1.35
2-Pentanol	6032-29-7	C5	6.05E-04	1.44E+03	0.95
3-Pentanol	584-02-1	C6	8.09E-04	1.08E+03	0.96
1-Hexanol	111-27-3	C7	6.99E-04	1.43E+03	2.85
2-Hexanol	626-93-7	C8	9.97E-04	9.34E+02	1.91
1-Heptanol	111-70-6	C9	7.68E-04	1.87E+03	6.80
2-Heptanol	543-49-7	C10	2.27E-03	5.00E+02	4.35
1-Octanol	111-87-5	C11	1.00E-03	2.25E+03	11.26
2-Octanol	123-96-6	C12	5.03E-03	3.91E+02	9.93
3-Octanol	589-98-0	C13	1.27E-03	1.26E+03	7.92
delta-2-Dodecanol	10203-28-8	C14	3.94E-03	1.80E+04	27.23

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
2-Methyl-1-propanol	78-83-1	C15	4.00E-04	2.15E+03	0.70
3-Methyl-propanol	71-36-3	C16	3.60E-04	2.39E+03	0.75
2-Propyl-1-pentanol	58175-57-8	C17	1.27E-03	1.26E+03	7.92
2-Methyl-1-butanol	137-32-6	C18	5.76E-04	1.52E+03	1.05
3-Methyl-1-butanol	123-51-3	C19	5.76E-04	1.51E+03	0.92
3-Methyl-2-butanol	598-75-4	C20	7.15E-04	1.23E+03	1.03
cis-2-Octen-1-ol	26001-58-1	C21	1.12E-03	1.25E+03	6.52
E-2-Octen-1-ol or 2-Octen-1-ol	18409-17-1	C22	1.12E-03	1.25E+03	6.52
1-Octen-3-ol	3391-86-4	C23	9.45E-04	1.49E+03	6.61
(Z)-Oct-5-en-1-ol	64275-73-6	C24	1.12E-03	1.25E+03	6.52
3-Octen-2-ol	57648-55-2*	C25	1.12E-03	1.17E+03	5.90
cis-3-Octen-1-ol	20125-84-2	C26	1.12E-03	1.25E+03	6.52
5-Octen-2-ol	55968-41-7*	C27	1.12E-03	1.17E+03	5.90
Octa-1,5-dien-3-ol	83861-74-9*	C28	8.31E-04	1.43E+03	4.82
3-Nonen-1-ol (Z)	10340-23-5	C29	1.48E-03	1.71E+03	12.41
1-Penten-3-ol	616-25-1	C30	4.04E-04	2.15E+03	0.89
2-Penten-1-ol (Z)	1576-95-0	C31	4.77E-04	1.82E+03	0.89
3-Methyl-1-buten-1-ol	27214-40-0*	C32	3.20E-03	2.82E+02	1.46
3-Hexen-1-ol (Z)	928-96-1	C33	6.33E-04	1.43E+03	1.54
2-Hexen-1-ol	2305-21-7	C34	6.33E-04	1.43E+03	1.52
2-Ethyl-1-hexanol	104-76-7	C35	1.08E-03	1.48E+03	7.92
5-Methyl-2-hexanol	627-59-8	C36	9.55E-04	1.11E+03	3.53
5-Methyl-5-hexen-3-ol	67760-89-8	C37	8.40E-04	1.25E+03	3.47
Trimethylcyclohexanol	116-02-9*	C38	4.68E-04	4.37E+03	10.32
6-Methylheptanol	26952-21-6	C39	3.76E-03	4.26E+02	7.92
Hexahydrofarnesol	6750-34-1	C40	9.21E-03	1.59E+05	27.86
2,4-Di-tert-butylphenol	96-76-4	C41	1.53E-04	1.42E+06	27.70
Dichlorophenol	87-65-0*	C42	1.26E-05	1.30E+05	8.13
Phenylethanol	1517-69-7	C43	1.05E-05	8.49E+04	1.21
2−Phenylethanol	60-12-08*	C44	1.05E-05	8.44E+04	1.13
Nerolidol	142-50-7	C45	7.40E-03	9.07E+04	27.83
Myrtenol	515-00-4	C46	2.85E-04	1.11E+04	14.52
Terpineol	98-55-5	C47	4.99E-04	7.06E+03	15.45

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
1,10-Dimethyl-9-decalinol	†*	C48	4.83E-04	1.16E+04	19.21
Geosmin	19700-21-1*	C49	4.83E-04	1.25E+04	19.77
beta-Fenchyl alcohol	470-08-6*	C50	1.13E-03	2.58E+03	13.75
Verticillol	†	C51	5.02E-03	7.69E+06	27.89
Methanethiol	74-93-1	D1	1.28E-01	6.74E+00	0.71
Dimethyl sulfide	75-18-3	D2	6.58E-02	1.31E+01	0.79
Dimethyl disulfide	624-92-0	D3	4.95E-02	1.89E+01	1.93
Acetone	67-64-1	E1	1.43E-03	5.95E+02	0.56
2-Butanone	78-93-3	E2	2.28E-03	3.74E+02	0.60
3-Methyl-2-butanone	563-80-4	E3	3.98E-03	2.16E+02	0.73
Cyclopentanone	120-92-3	E4	4.09E-04	2.09E+03	0.61
2-Pentanone	107-87-9	E5	3.42E-03	2.52E+02	0.76
2-Hexanone	591-78-6	E6	6.91E-03	1.28E+02	1.15
2-Heptanone	110-43-0	E7	6.91E-03	1.45E+02	2.85
2-Nonanone	821-55-6	E8	1.50E-02	1.86E+02	13.30
6-Methylheptan-2-one	928-68-7	E9	8.35E-03	1.26E+02	3.42
4-Methyl-6-hepten-3-one	26118-97-8	E10	6.22E-03	1.60E+02	2.77
3-Cyclohepten-1-one isomer	***	E11			
2-Octanone	111-13-7	E12	7.68E-03	1.53E+02	4.75
3-Octanone	106-68-3	E13	5.31E-03	2.04E+02	3.80
5-Octen-3-one	†	E14	7.35E-03	1.35E+02	2.77
Cyclohexanone	108-94-1	E15	3.68E-04	2.34E+03	0.72
4-Methyl-3-hexanone	17042-16-9	E16	6.29E-03	1.45E+02	1.65
2-Undecanone	112-12-9	E17	2.60E-03	6.96E+03	25.03
6-Undecanone	927-49-1	E18	9.16E-03	8.42E+02	21.33
Acetoin or 3-Hydroxybutanone	513-86-0	E19	4.20e-4	2.03E+03	0.56
1-(3-Methylphenyl)-ethanone	585-74-0	E20	4.43E-04	2.37E+03	3.42
Geranylacetone	3796-70-1	E21	3.71E-02	8.88E+02	26.37
Bicyclooctan-2-one	2716-23-6*	E22	1.62E-03	6.66E+02	3.74
4-(3-Butenyl)-1,2,3,6,7,7a-hexahydro-7a-methyl-5H-inden-5-one	†	E23	4.33E-03	1.14E+04	26.90

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
(e)-5-Acetyl-2,2-dimethyl-1-(3'-methyl-1',3'-butadien-1'-yl)bicyclo[2,1,0]pentane	†	E24	5.60E-03	4.92E+03	26.05
2,3,4-Trimethyl-4-hydroxy-1,4-dihyronaphthalenone	†	E25	2.22E-08	5.25E+07	4.61
2,4-Pentadione	123-54-6	E26	9.61E-05	8.90E+03	0.61
3-Methyl-1,3-pentandione	***	E27			
1-Hexene	592-41-6	F1	1.47E+01	2.92E-01	17.15
3-Methyl-1-heptene	4810-09-7	F2	2.58E+01	6.56E-01	24.83
2,4,6-Trimethyl-1-nonene	144043-16-3	F3	9.47E+01	1.51E+01	27.86
2-Propenylidene-cyclobutene	52097-85-5	F4	3.28E+00	8.77E-01	13.60
2,4-Hexadiene	5194-50-3*	F5	7.82E+00	2.22E-01	8.70
2-Methyl-1,3-pentadiene	926-54-5*	F6	7.82E+00	2.84E-01	11.13
2-Methyl-2,4-hexadiene	28823-41-8*	F7	1.23E+01	3.62E-01	17.45
1,3-Octadiene (cis)	63597-41-1*	F8	1.17E+01	1.07E+00	23.74
1,3-Octadiene	63597-41-1*	F9	1.17E+01	1.07E+00	23.74
1,3-Octadiene (trans)	63597-41-1*	F10	1.17E+01	1.07E+00	23.74
Octadiene (isomers)	***	F11			
1,3,5-Heptatriene	17679-93-5	F12	6.30E+00	4.96E-01	14.37
1,3,6-Octadiene (isomers?)	1002-33-1	F13	1.17E+01	1.07E+00	23.74
2,4,6-Octatriene (isomers?)	15192-80-0	F14	9.88E+00	6.91E-01	20.58
2,6,-Dimethyl-2,4,6-octatriene	3016-19-1*	F15	2.43E+01	3.06E+00	27.26
Cyclooctatriene	29759-77-1	F16	6.39E+00	1.65E+00	22.99
(E)-Oct-3-ene	14919-01-8	F17	3.05E+01	5.55E-01	24.83
Nonatriene	603959-49-5	F18	1.11E+01	2.03E+00	25.61
Tridecadiene	21964-48-7*	F19	5.01E+01	7.88E+01	27.88
Tetradecene	1120-36-1*	F20	1.41E+02	1.98E+02	27.89
Pentadecene	13360-61-7*	F21	1.88E+02	2.77E+02	27.89
3,5,7-Trimethyl-2E,4E,8E-decatetraene	†	F22	48	3.13E+01	27.87
Xylene	1330-20-7	G1	2.12E-01	1.36E+01	13.60
Benzène, 1,3,5-tris (1-methylethyl)-	717-74-8	G2	1.62E+00	1.98E+03	27.88
Trimethylnaphthalene	17057-91-9*	G3	2.89E-02	3.16E+03	27.38
Chlorophenyl butene	3047-25-4*	G4	3.14E-01	2.05E+01	20.18

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
1-Chloro-4-(trifluoromethyl)benzene	98-56-6	G5	1.42E+00	4.53E+00	20.18
Dichlorostyrene	50852-77-2	G6	5.85E-02	9.76E+01	19.36
1-Methoxy-3-methylbenzene	100-84-5	G7	1.44E-02	1.04E+02	7.19
Chloromethyl anisole	824-98-6*	G8	5.07E-03	3.00E+02	7.39
4-Ethylanisole	1515-95-3	G9	1.91E-02	1.39E+02	12.85
4-Allylanisole	140-67-0	G10	1.89E-02	2.64E+02	18.35
1-Hexene, 2-(P-anisyl)-4-methyl-	†	G11	3.25E-02	1.11E+04	27.78
Dimethylanisole	874-63-5*	G12	1.59E-02	1.84E+02	13.75
Chloroanisole	2845-89-8*	G13	9.65E-03	2.27E+02	10.99
Dichloroanisole	1984-59-4*	G14	7.15E-03	4.60E+02	14.83
Trichloroanisole	54135-82-9*	G15	5.30E-03	4.55E+03	25.77
Pentachloroanisole	1825-21-4	G16	2.91E-03	1.36E+05	27.79
Dibromoanisole	74137-36-3*	G17	2.07E-03	2.93E+03	19.77
Tribromoanisole	607-99-8*	G18	8.24E-04	5.24E+04	26.75
Bromochloroanisole	50638-46-5*	G19	3.85E-03	1.51E+03	19.50
Bromodichloroanisole	174913-23-6*	G20	2.85E-03	8.09E+03	25.67
Chlorodibromoanisole	174913-47-4*	G21	1.53E-03	2.95E+04	26.80
Iodanisole	766-85-8*	G22	3.02E-03	1.37E+03	16.84
1,3-Dimethoxybenzene	151-10-0	G23	7.71E-04	1.40E+03	3.74
Dichlorodimethoxybenzene	50375-04-7*	G24	4.23E-04	8.47E+03	15.60
Trichlorodimethoxybenzene	102312-34-5*	G25	3.14E-04	5.76E+04	25.03
2,5-Dimethoxytoluene	24599-58-4	G26	8.51E-04	1.64E+03	6.52
Dibutyl maleinate	105-76-0	H1	3.10E-05	6.81E+05	25.45
Hexyl formate	629-33-4	H2	4.05E-02	2.76E+01	4.16
Formic acid heptyl ester	112-23-2	H3	5.37E-02	3.12E+01	8.36
Ethyl acetate	141-78-6	H4	5.48E-03	1.57E+02	0.69
p-Mentha-6,8-dien-2-ol acetate	97-42-7	H5	3.70E-02	7.61E+02	26.09
Propanoic acid 2-methyl-2-methylpropyl ester??	***	H6			
2-Methylpropyl 2-methylbutanoate	2445-67-2	H7	3.92E-02	7.46E+01	13.75
Isobutyric acid methyl ester	547-63-7	H8	1.26E-02	6.97E+01	1.03
Dimethyl hexanoic acid - methyl ester	813-69-4*	H9	3.92E-02	1.20E+02	17.90

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
Ethyl propionate	105-37-3	H10	1.03E-02	8.52E+01	0.96
2-Methylpropanoic acid methylethyl ester	617-50-5	H11	2.23E-02	4.79E+01	3.63
3-Methylbutanoic acid ethyl ester	108-64-5	H12	2.23E-02	4.96E+01	4.04
3-Methylbutanoic acid methyl ester	556-24-1	H13	1.68E-02	5.62E+01	2.08
3-Methylbutanoic acid methyl ethyl ester	32665-23-9	H14	2.96E-02	5.14E+01	7.39
2-Methyl-butanoic acid methyl ester	868-57-5	H15	1.68E-02	5.56E+01	1.93
Trimethylnonanoic acid methyl ester	†*	H16	1.22E-01	1.33E+03	27.62
3-Methylbutyl butanoate	106-27-4	H17	3.92E-02	8.53E+01	14.98
3-Methylbutanoic acid i-pentylester	659-70-1	H18	5.21E-02	1.39E+02	20.96
Propanoic acid, 2-methyl-3-methylbutyl ester	2050-01-3	H19	3.92E-02	7.46E+01	13.75
2-Methylbutyric acid - isopentyl ester	27625-35-0	H20	5.21E-02	1.39E+02	20.96
Pentyl hexanoate	540-07-8	H21	6.92E-02	4.16E+02	26.13
3-Methyl-2-butenoic acid ethyl ester	638-10-8	H22	1.23E-02	8.64E+01	3.58
2-Methyl-2-butenoic acid ethyl ester	5837-78-5	H23	1.23E-02	8.64E+01	3.58
4,4-Dimethyl-pentenoic acid methyl ester	16812-85-4*	H24	1.39E-02	9.31E+01	5.74
Butan-4-olide	96-48-0	H25	2.15E-06	3.95E+05	0.56
Hexan-4-olide or 4-Ethylbutan-4-olide or gamma-Caprolactone	695-06-7	H26	7.39E-03	1.16E+02	0.65
2-Furancarboxylic acid methyl ester	611-13-2	H27	1.42E-03	6.09E+02	0.81
6-Pentyl-alpha-pyrone	27593-23-3	H29	6.12E-02	1.82E+01	4.10
1-Octen-3-ol ethyl ester (?)	2442-10-6***	H30	3.88E-02	1.66E+02	20.18
Ethenamine, N-methylene	38239-27-9	I1	3.47E-01	2.62E+00	1.56
Pyrazine	290-37-9	I2	1.19E-04	7.16E+03	0.56
Methylpyrazine	109-08-0	I3	8.99E-05	9.49E+03	0.59
Ethylpyrazine	13925-00-3	I4	1.00E-04	8.57E+03	0.68
2-Butanone oxime	96-29-7*	I5	4.23E-04	2.03E+03	0.66
alpha-Terpinene	99-86-5	J1	1.49e1	1.73E+00	25.91

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
beta-Myrcene	123-35-3	J2	2.63E+00	8.21E+00	25.51
beta-Cubebene	13744-15-5	J3	1.20e1	1.58E+02	27.87
alpha-Himachalene or 1H-Benzocycloheptene, 2,4a,5,6,7,8,9,9a-octahyro-3,5,5-trimethyl-9-methylene-,(4as-cis)-	3853-83-6*	J4	2.82E+01	9.92E+01	27.88
beta-Himachalene or Himachalene	1461-03-6*	J5	3.93E+01	7.98E+01	27.88
Limonene or alpha-Limonene	138-86-3	J6	1.30E+00	4.06E+01	26.97
Elemene	33880-83-0*	J7	4.04E+01	3.80E+02	27.89
beta-Elemene (isomers)	***	J8			
2-Methyl-2-bornene (isomers)	72540-93-3?	J9	5.81E+00	1.28E+01	27.26
alpha-Muurolene	10208-80-7	J10	3.33E+01	6.52E+01	27.87
gamma-Curcumene	†	J11	6.39e1	2.46E+02	27.89
Germacrene D ou (-)-Germacrene D	37839-63-7*	J12	4.59E+01	2.98E+02	27.89
trans-Calamenene	†	J13	7.14E-01	3.49E+03	27.88
cis-Calamenene	†	J14	7.14E-01	3.49E+03	27.88
Zonarene	†	J15	3.20E+01	9.15E+01	27.88
1,4-Cadinadiene	16729-01-4	J16	3.93E+01	7.45E+01	27.88
Calarene	17334-55-3	J17	7.96E+00	2.17E+02	27.87
alpha-Amorphene	†	J18	3.33e1	6.52E+01	27.87
Cadinene	†	J19	2.82e1	9.25E+01	27.88
beta-Selinene	17066-67-0	J20	2.39e1	1.41E+02	27.88
delta-Guaiene	3691-11-0	J21	3.33e1	1.06E+02	27.88
(+)-Aromadendrene or Aromadendrene	489-39-4	J22	1.2e1	1.58E+02	27.87
alpha-Panasinsene	56633-28-4	J23	7.96	2.32E+02	27.87
Trichodiene	28624-60-4	J24	28.2	5.20E+02	27.89
alpha-Bergamotene or Bicyclo[3,1,1,] hept-2-ene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-	17699-05-7	J25	33.3	1.56E+02	27.88

MVOC	CAS No. *multiple isomers	Code given	Hcc at 25°C **	P_{ba}	Vd_{ss} (L/kg)
alpha-Cedrene or 1H-3a, 7-Methanoazulene, 2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-,[3r-(3a,3ab,7b,8aa)]	469-61-4	J26	7.96	9.68E+01	27.84
Epi-bicyclosesquiphellandrene	54274-73-6*	J27	2.30E+01	1.13E+02	27.88
Bicyclo[4,4,0]dec-1-en,2-isopropyl-5-methyl-9-methylene-	150320-52-8	J28	3.33E+01	1.06E+02	27.88
6,10,11,11-Tetramethyl-tricyclo[6,3,0,1(2,3)]undec-7-ene	†	J29	1.06E+01	4.58E+02	27.88
beta-Sesquiphellandrene	20307-83-9*	J30	4.59E+01	2.98E+02	27.89
alpha-Ylangene	14912-44-8	J31	7.96E+00	9.04E+01	27.84
beta-Ylangene	20479-06-5	J32	1.20E+01	7.21E+01	27.85
Chamigrene	18431-82-8*	J33	2.82E+01	5.20E+02	27.89
alpha-Chamigrene	19912-83-5	J34	3.33E+01	3.66E+02	27.89
beta-Chamigrene or Spiro[5.5]undec-2-ene,3,7,7-trimethyl-11-methylene-,(-)-	18431-82-8*	J35	2.82E+01	5.20E+02	27.89
alpha-Longipinene or Longipinene	5989-08-02*	J36	7.96E+00	4.43E+01	27.77
Kaur-16-en-like	***	J37			
Diterpenes	***	J39			
Hexanal	66-25-1	K1	8.71E-03	1.07E+02	1.96
2-octanal, (E)?	2363-89-5	K2	3.00E-03	4.57E+02	6.34
Decanal	112-31-2	K3	7.36E-02	1.21E+02	22.15
2-Heptenal	2463-63-0	K4	2.19E-01	4.64E+00	3.03
2,6,10-Trimethylundeca-5,9-dienal	24048-13-3	K5	8.96E-02	3.43E+03	27.76
4-Methyl-3-penenoic acid	504-85-8	L1	7.22E-05	1.33E+04	2.31
Cyclohexanisothiocyanate	1122-82-3	L2	2.31E-01	2.62E+01	19.77
Dimethyl selenide	593-79-3	L3	7.03E-02	1.21E+01	0.60
Arsine, dimethyl-	593-57-7	L4	1.04E+01	8.98E-02	1.93
Trimethylarsine	593-88-4	L5	5.99E+00	1.91E-01	4.41
Dimethyl tellurite	593-80-6	L6	?		1.08
(2E,4E)-2-Methyl-hexa-2,4-dienoic-acid-(2'R,3'S)-isoleucinol-amide	†	L7	2.48E-10	4.39E+09	3.86

*CAS number found for one of the isomers
**When a search did not turn up a value for the constant H, it was estimated
***Compounds cited in the literature as being emitted by moulds, but not identified, or compounds whose names are wrong
†Compounds whose CAS numbers could not be found

Table A 3 Nonmicrobial sources for the 34 high-occurrence MVOCs (level 4)

MVOC	Nonmicrobial source	Reference
1-Octen-3-ol	Paints, essential oils, artificial flavours	(Schleibinger, Hans, Keller and Rüden, 2004; Wieslander and Norback, 2010)
3-Methyl-1-butanol	Varnishes, solvents	(Matysik, S. et al., 2009; Schleibinger, Hans et al., 2004)
3-Octanone	Waxes, waxing products, varnishes, scents and scented products (sprayers, diffusers, candles)	(Knöppel and Schauenburg, 1989; Schleibinger, Hans et al., 2004; Uhde, Erik and Schulz, 2015; Wieslander and Norback, 2010)
2-Heptanone	Fats, coconut fat, varnishes, solvents	(Schleibinger, Hans et al., 2004)
2-Methyl-1-butanol	Varnishes, solvents	(Schleibinger, Hans et al., 2004)
Ethanol	Waxes, waxing products, detergents, surface coatings (solvents), scents and scented products (sprayers, diffusers, candles), furniture coatings, laundry detergents	(Knöppel and Schauenburg, 1989; Salthammer, 1997; Steinemann, 2015; Uhde, Erik and Schulz, 2015; Wieslander and Norback, 2010; Yu and Crump, 1998)
2-Methyl-1-propanol	Flavours, paints, waxes, waxing products, detergents, varnishes, solvents, air purifiers	(Schleibinger, Hans et al., 2004; Wieslander and Norback, 2010)
2-Pentanone	Tobacco smoke	(Sampson et al., 2014)
2-Hexanone	Glues, nail polish removers, solvents, paints	(Chin et al., 2014)
Ethyl acetate	Paints, rugs/carpets, household cleaning products, deodorants, surface coatings (solvents), laundry products	(Bari, Kindzierski, Wheeler, Héroux and Wallace, 2015; Matysik, S. et al., 2009; Steinemann, 2015; Yu and Crump, 1998)
Limonene or alpha-Limonene	Softeners, dish and window cleaners, vinyl flooring, rugs/carpets, deodorants, scents and scented products (sprayers, diffusers, candles), wood, coatings, photocopiers, furniture coatings, laundry products, air purifiers	(Bari et al., 2015; Destaillats, Maddalena, Singer, Hodgson and McKone, 2008; Salthammer, 1997; Singer et al., 2006; Steinemann, 2015; Uhde, E. and Salthammer, 2007; Uhde, Erik and Schulz, 2015; Yu and Crump, 1998)
3-Methylfuran	Tobacco smoke, cooking fumes	(Schleibinger, H., 2002; Schleibinger, H. et al., 2008)

MVOC	Nonmicrobial source	Reference
2-Pentylfuran	Linoleum, cooking fumes	(Schleibinger, H. et al., 2008; Yu and Crump, 1998)
2-Octanone	Waxes, waxing products, furniture coatings	(Knöppel and Schauenburg, 1989; Salthammer, 1997; Wieslander and Norback, 2010)
1-Pentanol	Vinyl flooring, furniture coatings	(Salthammer, 1997; Yu and Crump, 1998)
1-Hexanol	Waxes, waxing products, vinyl flooring	(Knöppel and Schauenburg, 1989; Wieslander and Norback, 2010; Yu and Crump, 1998)
Acetone	Waxes, waxing products, deodorants, household cleaning products, linoleum, rubber flooring, rugs/carpets, walls and ceilings, UV-hardened coatings, photocopiers, furniture coatings, laundry products	(Bari et al., 2015; Destaillats et al., 2008; Knöppel and Schauenburg, 1989; Salthammer, 1997; Steinemann, 2015; Uhde, E. and Salthammer, 2007; Wieslander and Norback, 2010; Yu and Crump, 1998)
1-Propanol	Tap water, cleaners, household cleaning products, deodorants	(Bari et al., 2015)
2-Pentanol	Paints, varnishes, solvents	(Schleibinger, Hans et al., 2004)
Hexanal	Nylon rugs/carpets, PVC flooring, building materials, scents and scented products (sprayers, diffusers, candles), photocopiers, furniture coatings	(Bari et al., 2015; Destaillats et al., 2008; Salthammer, 1997; Uhde, Erik and Schulz, 2015; Yu and Crump, 1998)
1-Heptanol	PVC rugs/carpets	(Yu and Crump, 1998)
1-Octanol	Rugs/carpets, vinyl flooring, scents and scented products (sprayers, diffusers, candles)	(Uhde, Erik and Schulz, 2015; Yu and Crump, 1998)
2-Ethyl-1-hexanol	Paints, rugs/carpets, PVC flooring, wall coverings, computers, photocopiers, furniture coatings	(Destaillats et al., 2008; Matysik, S. et al., 2009; Salthammer, 1997; Yu and Crump, 1998)
Dimethyl disulfide	Tobacco smoke, artificial flavours (beer, coffee, white cabbage)	(Blomberg and Widmark, 1975; Schleibinger, Hans et al., 2004)
2-Butanone	Waxes, waxing products, wall coverings, rugs/carpets, scents and scented products (sprayers, diffusers, candles), photocopiers, furniture coatings, laundry detergents	(Destaillats et al., 2008; Knöppel and Schauenburg, 1989; Salthammer, 1997; Steinemann, 2015; Uhde, Erik and Schulz, 2015; Wieslander and Norback, 2010; Yu and Crump, 1998)

MVOC	Nonmicrobial source	Reference
Cyclopentanone	Furniture coatings	(Salthammer, 1997)
Cyclohexanone	Paints, rugs/carpets, building materials, scented consumer goods, surface coatings (solvents), vinyl flooring, plastic walls, UV-hardened coatings, computers, furniture coatings	(Bari et al., 2015; Destaillats et al., 2008; Matysik, S. et al., 2009; Salthammer, 1997; Uhde, E. and Salthammer, 2007; Yu and Crump, 1998)
Xylene	Paintings, rugs/carpets, walls and ceilings, coating solvents, computers, photocopiers, furniture coatings	(Destaillats et al., 2008; Salthammer, 1997; Wieslander and Norback, 2010; Yu and Crump, 1998)
Heptane	Paints, adhesives, rugs/carpets, furniture coatings	(Bari et al., 2015; Salthammer, 1997; Yu and Crump, 1998)
3-Hexen-1-ol (Z)	Scents and scented products (sprayers, diffusers, candles)	(Uhde, Erik and Schulz, 2015)
beta-Myrcene	Waxes, waxing products, scents and scented products (sprayers, diffusers, candles)	(Knöppel and Schauenburg, 1989; Uhde, Erik and Schulz, 2015; Wieslander and Norback, 2010)
2-Octanol, (E)	Scents and scented products (sprayers, diffusers, candles), linoleum, laquers, furniture coatings	(Salthammer, 1997; Uhde, E. and Salthammer, 2007; Uhde, Erik and Schulz, 2015)
Decanal	Rugs/carpets, scents and scented products (sprayers, diffusers, candles), linoleum, laquers, furniture coatings	(Salthammer, 1997; Uhde, E. and Salthammer, 2007; Uhde, Erik and Schulz, 2015; Yu and Crump, 1998)
2-Heptenal	Laquers, resins, furniture coatings	(Salthammer, 1997; Uhde, E. and Salthammer, 2007)