



Review

Volatolomics: A broad area of experimentation

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ABSTRACT

Chemical analysis (detection and monitoring) of compounds associated with the metabolic activities of an organism is at the cutting edge of science. Volatile metabolomics (volatolomics) are applied in a broad range of applications including: biomedical research (e.g. disease diagnostic tools, personalized healthcare and nutrition, etc.), toxicological analysis (e.g. exposure tool to environmental pollutants, toxic and hazardous chemical environments, industrial accidents, etc.), molecular communications, forensics, safety and security (e.g. search and rescue operations). In the present review paper, an overview of recent advances and applications of the volatolomics will be given. The main focus will be on volatile organic compounds (VOCs) originating from biological secretions of various organisms (e.g. microorganisms, insects, plants, humans) and resulting fusion of chemical information. Bench-top and portable or field-deployable technologies-systems will also be presented and discussed.

1. Metabolomics

Recent advances in molecular sensing technologies allow the development of analytical approaches and tools that can screen, analyse and decode phenotype variations. The outcomes of such analyses can elaborate the details of processes evolved within the metabolism of an organism. Metabolomics describes these biological processes by utilising low molecular weight (<2000 Da) compounds that are produced by cells as chemical tools during metabolism [1,2]. Metabolomics enables the characterization and screening of specific markers and their patterns to obtain sufficient information of the physiological health status of an organism, as well as during environmental and genetic changes or under stress conditions [1].

Gold standard instrumentation available for metabolomics is stand-alone or hyphenated mass spectrometry (MS), ion mobility spectrometry (IMS), nuclear magnetic resonance (NMR), high-performance liquid chromatography (HPLC), gas chromatography (GC) and Fourier transform infrared spectroscopy (FT-IR). These analytical techniques are complementary allowing qualitative, quantitative, structural and time evolving information about the metabolites [3].

The Human Metabolome Database (HMDB) [4] is considered to be the most complete collection available of human metabolites found in urine, blood and cerebrospinal fluid samples. It is an open access collection of all the available chemical, physical and biological data associated with human metabolites (>40,000) including spectral and quantitative information and their classification.

The combined knowledge of the metabolome, genome and proteome can describe an organism both chemically and biologically. However, due to past and recent climatic events, environmental and pollution factors, diet, human lifestyle and medication, the human metabolome and all the processes occurring within it may be influenced. Thus, the metabolome is a synergy of endogenously generated and exogenously introduced compounds, some of which interfere [5]. This review paper focuses on an essential part of metabolomics: the volatile-omics (volatolomics), which are mainly associated with the study of volatile emissions of final stage metabolites [6,7]. This allows a holistic approach to the volatolome from the micro-world (microorganisms e.g. bacteria) to the macro-world (e.g. insects, plants, humans). It identifies highly promising current application areas with rapid growth potential and considers a possible future orientation to-

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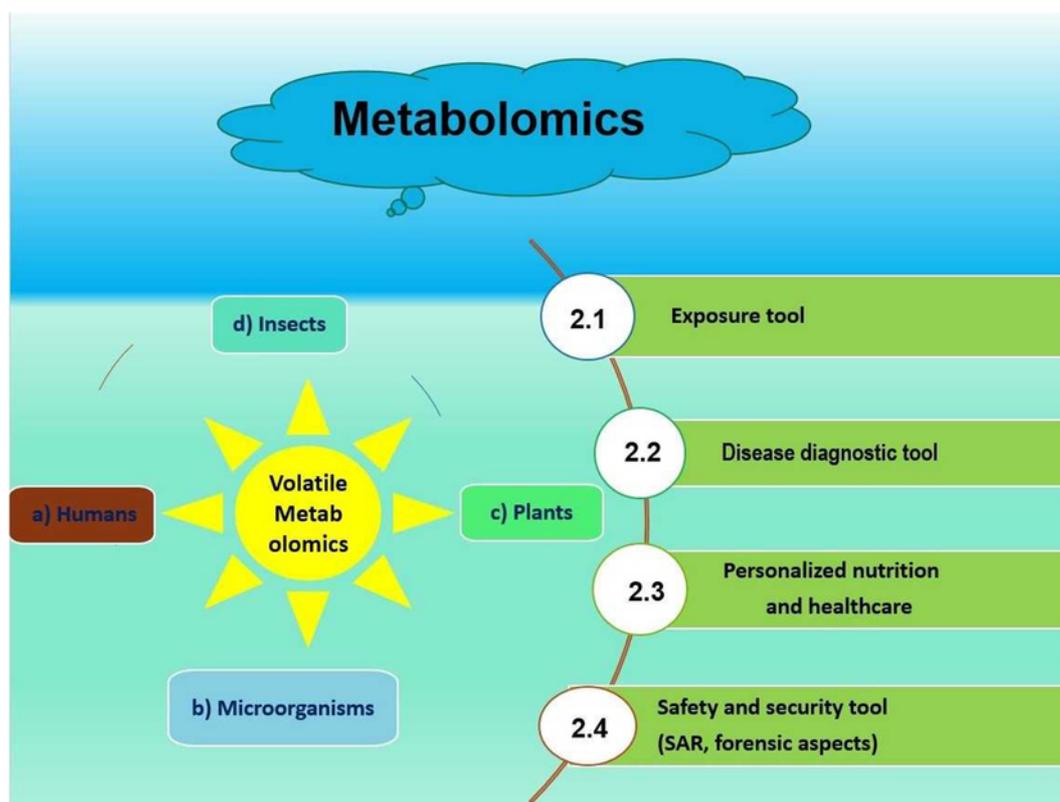


Fig. 1. Workflow illustration summarizing selective applications for volatolomics.

Table 1
Potential chemical attractants of mosquitoes [55].

1.	Carbon dioxide
2.	L-Lactic acid
3.	Octanal
4.	Nonanal
5.	Decanal
6.	Butanone
7.	3,7-Dimethyl-6-octanol
8.	1-Octen-3-ol
9.	Phenol
10.	Eicosane
11.	Diphenyl ether
12.	2-Ethyl hexanol

wards field chemical analysis, with miniaturized and portable analytical systems for real-time in-vivo metabolomic and volatolomic research (Fig. 1).

2. Volatolomics

Olfaction is one of the most important senses and processes for chemical and biological communication and interaction between humans, animals and plants. Volatolomics is a recently introduced non-invasive approach that constitutes the study of the volatile organic compounds (VOCs) that are emitted by the metabolome [6]. VOCs are low molecular weight organic compounds (<350 amu), which can transmit from the liquid phase into the gaseous phase at room temperature (25 °C) and pressure of 760 mmHg. They can be categorised in a wide range of groups depending their volatility (e.g. very VOCs, VOCs, semi-VOCs, etc.), their origin (e.g. biogenic or anthropogenic, endogenous or exogenous, etc.) and their emission source (e.g. outdoor, indoor, industrial, material, building, etc.) [8]. Traditionally, volatolomics focuses on VOCs originating from human body secretions (e.g. breath, sweat,

urine, feces, saliva, etc.) and carry information related to medical diagnostics. However, as it will be discussed below, volatolomics can cover all living organisms and is therefore a useful tool in a wide range of applications [9–13].

a) Humans

Within the human body, a complex interaction of biochemical processes continuously occurs. These processes result in volatile metabolites, which are emitted in human bodily fluids and tissues (i.e. lungs, skin, etc.). When abnormalities or changes occur, the conventional final volatile metabolic products are altered, and/or new VOCs are generated. Variations in the volatile profile of the human biochemistry can be identified in the headspace area above human skin - sweat, urine, blood, saliva, cells and directly in the exhaled air [9–13].

The human volatolome constitutes of a matrix of compounds contained within human body odor (breath and skin VOCs), which can provide diagnostic information of various diseases in an efficient and non-invasive way with the right analytical tools [14]. Due to the nature of human VOC samples, highly sensitive (low limits of detection – ppq or ppt) and accurate, highly resolving approaches-methodologies are required for sample collection and analysis.

b) Microorganisms

VOCs play a major role in intra- and inter-kingdom microbial communication [15,16]. Microorganisms can release specific VOCs that allow above- and below ground short- and long-distance interactions among themselves or with plants and insects [15,17]. These microbial VOCs are responsible for the generation of beneficial or harmful effects on other organisms, as they allow accurate communication (chemical signalling followed by message transmission and subsequent decoding) [15,16,18–21]. Microbial molecular communication using VOCs occurs

Table 2

Representative VOCs in exhaled breath, as possible diagnostic markers of various diseases [74–100].

Disease	Possible characteristic breath volatile marker	
1	Diabetes	Acetone, ethanol
2	Liver diseases	Carbonyl sulfide, carbon disulfide, isoprene
3	Pulmonary tuberculosis	Naphthalene, 1-methyl-, 3-heptanone, methylcyclohexane, etc.
4	Breast cancer	Nonane, tridecane, 5-methyl, undecane, 3-methyl, etc.
5	Lung cancer	Benzene, 1,1-oxybis-, 1,1-biphenyl, 2,2-diethyl, furan, 2,5-dimethyl, butane, sulfur compounds, etc.
6	Renal disease	Ammonia
7	Unstable angina	Octane, 4-methyl, decane, 4-methyl, hexane, etc.
8	Heart transplant rejection	Propane, 2-methyl, octadecane, octane, 5-methyl, etc.
9	Schizophrenia	Pentane, carbon disulfide
10	Acute myocardial infarction	Pentane
11	Acute asthma	Pentane
12	Rheumatoid arthritis	Pentane
13	Active ulcerative colitis	Ethane
14	Asthmatic inflammation	Nitric oxide
15	Bronchiectasis	Nitric oxide, carbon monoxide
16	Chronic obstructive pulmonary disease (COPD)	Nitric oxide
17	Cystic fibrosis	Hydrogen cyanide, ethane, propane, pentane, etc.
18	Liver diseases	Acetaldehyde, pentane
19	Anaemia	Carbon monoxide
20	Lipid peroxidation	Ethane
21	Oxidative stress	Carbon dioxide (C^{13} isotope), toluene, benzene, heptane, decane, styrene, octane
22	Hyperglycemia in type 1 diabetes	Methyl nitrate
23	Periodontal disease	Pyridine
24	Nervous system disorder	Methanol
25	Blood cholesterol	Isoprene
26	Intestinal problems	Methane

Table 3

Representative VOCs emitted from various human body sources [94–101, 121, 122, 129–138].

Body source	No of VOCs identified	Representative VOCs
Exhaled breath	874	Acetaldehyde, acetone, butanone, 1-butene, dimethyl sulfide, ethanol, ethyl acetate, ethylene, furan, hexanal, isoprene, isopropanol, methanol, methyl ethyl ketone, pentane, 1-pentene, n-propanol, etc.
Saliva	353	Ethyl alcohol, isopropyl alcohol, 1-propanol, 2-methyl-1-propanol, 1-butanol, hexanal, nonanal, 2,3-butanedione, 2-heptanone, octane, limonene, p-cymene, etc.
Skin	504	D-Limonene, α -pinene, dodecane, acetone, lactic acid, propanoic acid, toluene, nonanal, hexanal, heptanal, etc.
Urine	279	Acetone, 2-pentanone, 4-heptanone, 1H-pyrrole, 2-butanone, toluene, benzene, ethanol, hexane, 2,2-dimethyl, p-xylene, phenol, etc.
Blood	130	Acetone, isoprene, butane, 2,2,2,3-tetramethyl, toluene, phenol, etc.
Feces	381	Ethanoic, butanoic, pentanoic acids, benzaldehyde, ethanal, carbon disulfide, dimethyldisulfide, acetone, 2-butanone, 2,3-butanedione, 6-methyl-5-hepten-2-one, indole, and 4-methylphenol, etc.

between bacteria, fungi, bacteria-fungi, bacteria-fungi-plants, etc. [15]. Headspace solid phase microextraction gas chromatography mass spectrometry (HS-SPME-GC-MS) has been utilised extensively to study volatile metabolites of biocontrol fungi [22]. In addition to SPME, thermal desorption (TD) has been used for sample collection. Proton-transfer-reaction mass spectrometry (PTR-MS) has also been employed for

Table 4

Major volatile markers identified in the headspace gas area above animal and human corpses during their decomposition stages [139, 140, 142–144].

Decomposition stage	Time after death	Representative VOCs
Fresh	Up to 3 days	Hexane, octane, decane, decane trimethyl, ethanol, 2-propanol, phenol, 2-propanone, 2-butanone, dimethyl disulfide, dimethyl sulfide, dimethyl trisulfide, methyl ethyl disulfide, methyl benzene, p-xylene, o-xylene, m-xylene, styrene, D-limonene, etc.
Bloated	3–10 days	Sulfur dioxide, dimethyl disulfide, dimethyl trisulfide, indole, 1-propanol, 4-methylphenol
Active decay	10–20 days	Sulfur dioxide, dimethyl disulfide, dimethyl trisulfide, trimethylamine, methenamine, indole, carboxylic acids (e.g. acetic acid, butanoic acid, pentanoic acid, benzoic acid, etc.), ketones (e.g. 2-butanone, 2-pentanone, etc.), phenols (e.g. 4-methylphenol, etc.)
Advanced decay	20–50 days	Dimethyl disulfide, dimethyl trisulfide, indole, carboxylic acids (e.g. acetic acid, propanoic acid, 2-methylbutanoic acid, 3-methylbutanoic acid, etc.), ketones (e.g. 2-pentanone, etc.), alcohols (e.g. 2-propanol, etc.)
Skeletonization	50–365 days	Dimethyl disulfide, dimethyl trisulfide, carboxylic acids (e.g. acetic acid, propanoic acid, butanoic acid, 2-methylbutanoic acid, 3-methylbutanoic acid, etc.), 2-butanone, 2-pentanone, 2-propanol, hydrocarbons (e.g. pentane, hexane, heptane, octane, tridecane, eicosane, etc.)

on-line sniffing of volatiles produced from microbial cultures (*Escherichia coli*, *Shigella flexneri*, *Salmonella enterica*, and *Candida tropicalis*) [16].

Bohm et al. give an extensive overview of the role of VOCs in the micro-world [15]. It is noticeable that VOCs produced by bacteria can be used as biocontrol agents against plant pathogens, can boost the inhibitory activity against specific bacterial diseases, can enhance the growth of neighbouring bacteria, or even can modulate the behaviour of other bacteria against certain conditions. In the world of fungi, VOCs such as 1-octen-3-ol can modulate the development of filamentous fungi [15]. Other fungal VOCs, can regulate the growth and the establishment of their population [15]. Some other fungal species can generate VOCs with strong effect against their competitors or other antagonistic fungal species. VOCs play a major role in the fungi-bacteria communication for partner identification or to modulate the growth of a population or even to repel competitors [15]. Other microorganisms such as the nematodes *Caenorhabditis elegans* have highly developed chemo-sensory reception systems and can be used for the detection of VOCs for environmental monitoring and/or security related operations (e.g. detection of explosive-related chemicals) [23].

c) Plants

Plants are constantly exchanging information using chemical signals (biogenic VOCs) concerning their surrounding environment, including the generation of defence alarms in the case of external enemies. This can result in the activation of specific mechanisms for survival. Plant communication is performed either underground (by chemicals released by their roots and spread through the soil) or in the ambient air by specific VOCs [24–26]. Plant communication above soil is a well explored area. However, little is known about under soil communication between plants and micro and macro organisms. This is important for providing the right nutrition for optimal plant growth.

Plants have also shown that they release volatile markers, when they are affected by disease. Infectious diseases (e.g. those caused by fungi, parasitic plants, nematodes, etc.) and non-infectious diseases

Table 5
Advantages and limitations of the existing molecular technologies for volatolomics.

Technique	Advantages	Limitations
GC-MS	<ol style="list-style-type: none"> 1. Pre-concentration 2. Low LOD (ppt-ppb) 3. High sensitivity 4. High specificity 5. High selectivity 6. Accuracy 7. Qualitative & quantitative analysis 8. Commercial libraries 	<ol style="list-style-type: none"> 1. High purchase and maintenance costs 2. Require specialised personnel for operation 3. Bulky size and high weight 4. Long analysis times
SIFT-MS	<ol style="list-style-type: none"> 1. Real-time analysis 2. Low LOD (sub-ppb) 3. High sensitivity 4. High specificity 5. Self-calibration 	<ol style="list-style-type: none"> 1. Uncertain identification of analyte ions 2. Limit of quantification 3. Lack of commercial libraries
PTR-MS	<ol style="list-style-type: none"> 1. Real-time analysis 2. Low LOD (sub-ppt) 3. High sensitivity 4. High specificity 5. No sample preparation 6. Soft ionization – small number of fragments 7. No sample pre-concentration 	<ol style="list-style-type: none"> 1. Maximum measurable concentration 2. Lack of commercial libraries

Table 5 (Continued)

Technique	Advantages	Limitations
MIMS	<ol style="list-style-type: none"> 1. Near-real time analysis 2. Low LOD (ppt) 3. High selectivity 4. No sample preparation 5. Gas, liquid and soil analysis 6. Low cost 7. Low power consumption 8. Integrates with portable systems 	<ol style="list-style-type: none"> 1. Requires stable membrane temperature for reliable quantitative analysis 2. Requires temperature-programmed desorption for resolving complex mixtures
High performance MS with ambient ionization (e.g. APCI, SESI)	<ol style="list-style-type: none"> 1. Real-time analysis 2. No sample preparations 3. MS/MS capabilities 4. Low-invasive 	<ol style="list-style-type: none"> 1. Possible contamination of new samples
IMS	<ol style="list-style-type: none"> 1. Real-time analysis 2. Low LOD (ppb) 3. High sensitivity 4. High specificity 5. Fast response times 6. Portability (size & weight) 7. Robustness 	<ol style="list-style-type: none"> 1. False-positive alarms 2. Lack of performance in highly contaminated chemical environments 3. High bureaucracy for the systems with radioactive sources
E-noses [45–52]	<ol style="list-style-type: none"> 1. Fast response times 2. Low cost 3. Portability 	<ol style="list-style-type: none"> 1. Unstable results 2. Saturation effects 3. Low specificity 4. Relatively poor sensitivity

Table 5 (Continued)

Technique	Advantages	Limitations
Laser absorption spectroscopy (LAS) [163,164]	<ol style="list-style-type: none"> 1. Qualitative information 2. Near real-time measurements 3. Low instrument costs 4. Sensitivity 5. Selectivity 	<ol style="list-style-type: none"> 1. Cannot resolve complicated mixtures – identification of single (or a small combination) of molecules
Nanotechnology [8]	<ol style="list-style-type: none"> 1. High sensitivity 2. Fast response times 3. High selectivity 4. Miniaturized size 	<ol style="list-style-type: none"> 1. Cannot resolve complicated mixtures 2. Need for results cross-validation

Table 6
Commercially available portable MS-based instruments for volatolomics determination and their main characteristics.

Product	Weight (kg)	Dimensions (cm)	Mass range (Daltons)	Power (W)	Other information
MS – 200 (Kore Technology Ltd)	20	53.1 × 32.8 × 1.3	1–1000		1 spectrum every 5 min
TRIDION™ - 9 GC-MS (toroidal ion trap MS)	14.5	38.1 × 39.4 × 22.9	50–500	120	Use of solid phase micro extraction (SPME) fiber syringe as an inlet
Griffin™ 400	37	48.7 × 48.7 × 45.7	40–425	600	Transportable GC-MS
IonCam™	19	43.8 × 43.2 × 25.4	1–72 or 6–210 (according to the design)	150	
EcoSys-P	20	61.6 × 49.3 × 22.0	Up to 200–300	170	
Dq1000™ (portable quadrupole mass spectrometer)	23	66 × 19 × 38	Up to 140	390	Detection and analysis of hydrocarbons and other species in oil-based drilling operations
VapourSense500 (Q-Technologies) (portable dual filter quadrupole MS)	< 17	61.6 × 49.3 × 22	0–500 (ability to increase up to 1.000)	< 75	Simulations on dual filter QMS using the CPO3D software, showed that when a pre-filter is added to the main quadrupole analyser, ion trajectories are more stable and ion focusing is enhanced by at least a factor of two.

(e.g. caused by environmental factors such as light, oxygen, air pollution, soil composition, agrochemicals, etc.) generate characteristic VOCs [25–28]. Detection, qualitative identification and quantification of biogenic VOCs emitted from diseased plants have been previously investigated by various techniques such as gas chromatography (GC) followed by Flame Ionization Detection (GC-FID) or GC connected with MS (GC-MS). MS based methods such as direct injection (DI-) MS, atmospheric pressure chemical ionization (APCI-MS), proton transfer reaction (PTR-MS), and selected ion flow tube (SIFT-MS) have been so far applied for the rapid monitoring and quantification of VOCs [29–42].

Other technologies, appropriate for field chemical analysis of VOCs emitted by plants are the electronic nose (e-nose or EN), which has been reported for successful application in agriculture [43–52]. ENs are intelligent chemical sensor array systems, typically consisting of two major components: (a) a gas sensor array, and (b) a pattern recognition system. The most frequently used sensors are the metal oxide semiconductor (MOS) based and conducting polymer sensors. The drawbacks of MOS sensors include their high sensitivity to alcohol, the binding with substance like sulfur compounds and weak acids, and the high working temperatures. MOS are insensitive to humidity (as they are operated in temperatures between 50 °C and 400 °C) and present long self-life [45]. Polymers are cheap and operate at ambient temperatures. However, their relatively slow response times (20–40s) and temporal drift are their main drawbacks, resulting in low repeatability over long time periods [43–45].

ENs have been used to detect the causal agent of plant disease, such as fungi and bacteria. Li et al. used the Cyranose 320 chemical vapour sensing instrument to detect post-harvest fungal disease in blueberries in a controlled environment [46]. Loathawornkitkurt et al. evaluated the potential of plant volatile signature for pest and disease monitoring in cucumber, pepper and tomato plants [47]. They used the EN Bloodhound ST214 obtained from Scensive Technologies Ltd., UK, for determining its responses to VOCs released by plant leaves in experiments conducted in a greenhouse. Zhang et al. used a portable electronic nose (PEN) developed by Airsense Analytics Inc., Germany, consisting of an array of 10 MOS sensors, to measure the profile of VOCs released from wheat damaged with age and insects [48]. The authors were able to classify the different categories of wheat grains. Spinelli et al. evaluated a near infrared and EN system to detect fire blight in pear plants

[49]. It was reported that the EN system was able to provide a distinct olfactory signature required to identify that disease. Markom et al. used an EN to detect stem rot disease in oil palm plantation during field experiments [50]. The novel EOS⁸³⁵ EN (Sacmi Imola s.c.a.r.l., Italy), based on an array of six thin film MOS sensors, was used for the determination of the fingerprint of peeled tomatoes, which have been artificially spoiled with bacteria and fungi [51]. The same EN was applied to detect spoilage of maize cultivation by fungi [52].

Moreover, IMS and specifically field asymmetric – IMS (FAIMS) has been used on a tomato greenhouse for health monitoring of tomato plants [53]. Linear ion trap mass spectrometry (LIT-MS) has also been previously used by Soparawalla et al. for in situ analysis of agrochemicals residues on apples using ambient ionization and results concluded in clear distinction between organic and non-organic apples [54].

d) Insects

As mentioned above, human body odor results from the combined complex interaction of skin glands and the secreting organic compounds from the colonised bacteria of the human skin. These bacteria metabolise and transform the odorless sweat to an odorous liquid comprising of some hundreds of VOCs that disperse in the surrounding environment and mediate the attraction of insects [8,55–58]. Human detection by insects is usually a matter of time, distance and is affected by the surrounding environmental conditions, e.g. relative humidity, temperature, etc.

Mosquitoes are a worldwide threat both for human public health, as well as to plant cultivation and also industrial livestock production. Malaria, yellow fever, leishmaniasis, plague, dengue fever and typhus are representative of diseases that mosquitoes are responsible for causing and spreading. In Africa, the risk to public health is huge with >700,000 deaths per annum caused by mosquito bites [59]. Anthropophilic mosquitoes using physical and chemical cues can sniff VOCs produced by the human body and to bite. Along with dogs, rats and bees, they are considered ideal biological detectors. Previous work using GC-MS has proposed potential chemical compounds found in human body odor, which attract mosquitoes (Table 1). The role of the volatolomics in insects' world is further discussed throughout the paper at various points, such as in the agricultural and forensic applications that are followed.

2.1. Exposure tool

Human exposure to a toxic, pollutant and potential hazardous chemical environment can generate severe health issues such as lung issues, cardiopulmonary disease, neurodegenerative diseases, disorders, cancer or even death [60,61]. After exposure to extreme environments, metabolomics can be used to perform rapid toxicological analysis of affected humans [62,63]. Blood and urine samples can be collected for analysis to determine possible inflammations by measuring the chemicals themselves or their by-products or final metabolites. Inhaled toxic VOCs such as pneumotoxic metals, organometallic compounds, halogenated hydrocarbons and/or aerosols and particles and their spread in the human organs can be measured in human breath using trace-level analytical techniques (e.g. MS, IMS, etc.) [64–71]. Exhaled breath testing has been recently implemented as a safety health status monitoring tool in occupational hazard applications such as wildfires, in dangerous industrial areas and the military to protect personnel from exogenous chemical threats [62]. Chronic exposure to harmful compounds can also be measured via breath monitoring and characterization. This allows the development of toxicokinetic models, chemical toxicity prioritization, prediction models for inflammatory responses for medical doctors and first responders [70].

Commonly available instrumentation for off-line elemental analysis is based on inductively coupled plasma – mass spectrometry (ICP-MS) or electrothermal atomic absorption spectroscopy (ETAAS) [72,73]. Direct injection ICP-MS results on the total amount of an element. In some cases, speciation is required, which can be obtained by hyphenated ICP-MS techniques such as LC-ICP-MS. These techniques despite their advantageous characteristics, lack portability and time-resolving capability, which is usually > 1 h excluding sample transportation time. These generate the requirement for portable or even wearable sensing systems allowing in-situ detection capabilities of trace elements in a qualitative and quantitative way.

2.2. Disease diagnostic tool

VOCs emitted from human biological sources (e.g. breath, sweat, urine, feces, etc.) have been used for a wide range of applications including diagnostic purposes in medicine, toxicological analysis, doping control, etc. [74,75]. Exhaled breath has been extensively studied for decades and widely used for a number of health-related issues (e.g., early diagnosis of diseases, pharmacokinetic studies, substance metabolism monitoring). VOCs in human exhaled breath can provide pivotal characteristic information of human health status, of metabolic processes, of various pathological conditions (e.g. oxidative stress, lung cancer, breast cancer, prostate cancer, etc.) and disorders [76–81]. Despite the usefulness of the VOCs and the potential for reliable on-site measurements, further investigation both qualitatively and quantitatively, are still required to provide clinically established single or multi-component volatile signature/alarm patterns.

Volatile biomarkers from human secretions (e.g. breath, urine) have the potential to distinguish patients with asthma from patients with other lung diseases [76,77,80–82]. Increased levels of ethane, pentane and aldehydes have been identified in the exhaled breath of patients with asthma as possible breath markers [83]. Preliminary research has been undertaken in this direction with positive outcomes, which still requires further investigation and evaluation. However, due to the small patient sample size considered, further research is required. VOCs from human secretions have also been investigated as potential biomarkers for the detection of various types of cancer. Researchers at the University of Liverpool perform pioneer research on bowel, prostate and liver cancer [84–86]. They have developed an electronic nose (Odoreader) based on GC combined with advanced mathematical

models able to sniff VOCs from biological samples and to diagnose malignancies with high accuracy. VOCs generated from different fecal microbiotas of children with celiac disease, before and after they followed a gluten free diet and comparison with healthy children using solid-phase microextraction SPME-GC-MS, has been investigated [87]. The dental community is currently using gas-phase analytical technologies to assess, and cure halitosis produced by oral bacteria that produce volatile sulfur compounds (VSCs) such as hydrogen sulfide, methyl mercaptan, and dimethyl sulfide [88]. Research has also been done in the correlation of VSCs with the progression of periodontal disease [89]. The Zurich Exhalomics [90] project, combines three non-invasive technological approaches: secondary electrospray ionization (SESI)-MS, quantum cascade laser-based vibrational spectroscopy and chemical sensors with aim to detect and monitor characteristic volatile biomarkers in as many as possible breath detectable diseases. Table 2, presents a selection of representative VOCs in exhaled breath, which have been identified and linked with various diseases and can act as possible diagnostic markers [91–100].

Conventional chemical analysis of VOCs in biological samples is accomplished with laboratory testing using bulky and heavy analytical systems, as well as time-consuming and cost-demanding complex processes performed by specially trained personnel. There is also lack of standardized repeatable protocols for sample collection, transportation, storage and analysis. Thus, current and future trends are oriented towards field chemical analysis (FCA) as an advanced solution for rapid decision making and situational awareness outside the laboratory, at the point-of-analysis (e.g. in a medical centre or for point-of-care diagnostics).

2.3. Personalized nutrition and healthcare

The process of nutrition involves the consumption, assimilation and bioprocessing of food resources for energy production, growth and repairing processes of the human body. Nutrition balance also involves the processes of catabolism and excretion. With the rapid increase of new dietary intakes or diet styles, new metabolic risks may appear. In addition, and despite the technological improvements in the food industry, there is an increasing requirement for customized and personalized nutrition due to different dietary needs. For example, the dietary needs for an athlete are different from an office worker or a diabetic person should follow a different diet lifestyle from a non-diabetic. Sometimes, even in the same target group of people, different subgroups have different nutrition needs, e.g. a bodybuilding athlete has different dietary needs from a runner. Thus, new food products (e.g. dietary supplements, pills, powders, energy bars, etc.) are being developed with high speed for assisting human wellbeing or improving health and their effects on the human organism need to be tested with high precision and with smart and accurate ways [101,102]. Metabolomics and specifically breath volatolomics could be a new non-invasive approach for screening potential indicators of metabolic risks arising from new food products or from different diets.

Existing monitoring methodologies for food products' biotransformation available in the market include demanding and time-consuming clinical studies using mostly blood and urine analysis. Alternatively, on-line exhaled breath analysis could be used as a non-invasive tool for the determination of volatile breath markers associated with the metabolism of existing or new food products (e.g. 3D printed products enriched with bioactive ingredients). Expired air could allow the real time monitoring of targeted food properties or the synergism of various food-stuffs or even diets enriched with specific groups of compounds (e.g. diet high in protein consumption) [103–106]. Research in this field is still limited; however, these characteristic breath markers could potentially be associated with short- and long-term health effects, beneficial actions or drawbacks of these products. The chemical analysis of

expired air with state-of-the-art analytical instrumentation, novel sampling methodologies and advanced signal processing approaches such as chemometrics, could allow the chemical profiling of breath variations when a particular diet is followed, or a natural or synthetic substance is taken by an individual.

In personalized healthcare, breath analysis has been demonstrated by clinicians to allow determination of the smoking habits of an individual [107–110]. Currently, blood and urine analysis of cotinine (a primary metabolic product of nicotine) was used as a diagnostic tool. However, recent research on breath samples of smokers and non-smokers using SESI-high resolution MS showed that some breath markers (e.g. hydroxy-2,4-hexadienal, a benzene metabolite which is related to tobacco smoke) could provide, with high precision, information on the smoking conditions of a human [107]. Similarly, the early stage metabolites (11-hydroxy- Δ^9 -tetrahydrocannabinol and 11-nor-9-carboxy-tetrahydrocannabinol) of (–)-trans- Δ^9 -tetrahydrocannabinol (THC), was shown that can be detected in human exhaled breath using field asymmetric IMS-MS. The above allows the differentiation of people who use medical and recreational marijuana from non-users (within a few hours after consumption) and provides data for real-time pharmacokinetic measurements [111–116].

In personalized nutrition and healthcare, exhaled air analysis is advantageous compared to conventional blood or urine analysis. This is due to its non-invasive nature, the unlimited sample quantity and requires no sample preparation or pre-treatment. Breath analysis can be supported by demonstrated field analytical chemistry technologies for real-time on-site analysis.

2.4. Safety and security tool

2.4.1. Search and rescue

The most critical task during crisis management operations in any scale of a disaster is the search, early detection and localization of human survivors. Equally important is the localization of dead bodies for delivery to their families. In the recent years, the European Union has funded several search and rescue projects (i.e. SGL for USaR, Darius, ICARUS, TOXI-triage, etc.) [117–120] to investigate state-of-the-art technologies and to develop novel approaches (including artificial sniffing and identification of VOCs emitted from the human body) for the early detection and localization of human victims (alive or dead) under the ruins of collapsed buildings after natural (e.g. earthquakes, tsunami, wildfires, etc.) or manmade (e.g. bombing attacks, terrorist events, industrial accidents, etc.) catastrophes [121,122]. The Second Generation Locator for Urban Search and Rescue Operations (SGL for USaR) project [117] was focused on large scale structural collapses in urban areas. In the framework of this project, an extensive experimentation to identify the chemical profile (metabolites and volatolomics associated with breath, skin and other body secretions) of human volunteers in an entrapment simulation chamber was carried out. The Trapped Human Experiment (THE) [123] aimed to monitor the alterations of the metabolic markers emitted from the human body of 10 healthy participants, enclosed within a confined simulation environment throughout a period of 6h, using gas sensors (CO, CO₂, O₂, NH₃), GC-MS, IMS and health tracking sensors. Human volatile emissions were passed through a column packed with 5 sets of different constructive materials like those that can be found in common buildings to simulate the environment of the debris and were being monitored at different points and standard times [124,125]. Within the same project, optical (visible and thermal cameras) and chemical (MS) sensors were used to study VOCs emitted from the early stage of decay in entrapment situations by using domestic pigs (*Sus scrofa domestica*) as an analogy to the human body both in laboratory and in field conditions. Inorganic gases were periodically monitored using gas sensors and VOCs were collected on standard stainless-steel sorbent tubes filled

with Tenax TA and Carboxen X for bench-top thermal desorption (TD) - time-of-flight (ToF) - MS analysis [126]. In the same context, vital parameters (i.e. cardiac output, blood pressure, electrocardiography, alveolar minute ventilation, etc.) were also investigated and correlated to expired air using an ergometer and PTR-MS. The aim of this work was to study volatile metabolites in the exhaled breath of people under working conditions. Also, interaction of volatile markers (i.e. acetone, propanal, 3-methyl-2-butanone, 2-methylpropanal, 4-heptanone, 2-heptanone and octanal) found in human urine with common building materials (i.e. quartz sand), were also investigated with ion mobility spectrometry (IMS) [127].

As a continuation of the SGL for USaR project, the Deployable SAR Integrated Chain with Unmanned Systems (DARIUS) project [118] aimed to enhance first responders' operational capabilities by integrating chemical sensing systems onto unmanned vehicles. DARIUS combined concepts and multiple agencies to deliver technical solutions. Ground, air, maritime and underwater unmanned robotic platforms equipped with sensing technologies (e.g. cameras, audio, radar, chemical sensors, etc.) were tested in earthquake, forest fire and marine rescue scenarios. Similarly, the "Integrated Components for Assisted Rescue and Unmanned Search operations" - (ICARUS) project [119] focused on the development of optical sensing systems for integration on UAVs for human search and rescue. In the same content, TOXI-triage project [120] aims to develop and deliver novel search and rescue tools and approaches by using non-invasive diagnostic tests based on metabolites of injury (occurred from chemical, biological, radiological and nuclear poisoning - CBRN) found in breath, skin and saliva. The G.A.S. Breath-Spec GC-IMS can be used by first responders to screen human exposure to CBRN agents through rapid analysis and characterization of breath metabolites. The TOXI-triage also develops miniaturized IMS for integration onto unmanned drones for stand-off detection of chemical hazards and toxic industrial compounds (TICs).

To assist USaR teams, researchers developed a low-cost nanostructured metal oxide sensor array (Si-doped WO₃, Si-doped MoO₃, and Ti-doped ZnO) and combined it with commercial CO₂ and relative humidity sensors to detect characteristic breath and skin emitted volatile metabolic tracers (acetone - lipolysis, ammonia - protein metabolism and isoprene - biosynthesis of cholesterol) during the first 2h of entrapment [128]. The developed sensor was tested with nine volunteers placed within a plethysmographic chamber, and its performance was evaluated with selective reagent ionization time-of-flight mass spectrometry (SRI-TOF-MS) [128]. The small size and weight alongside its high sensitivity (low ppb), specificity and response times (<3min) allows integration onto handheld devices of rescuers or on unmanned aerial vehicles (UAV) for remote sensing. Table 3 summarizes representative VOCs emitted from various human body sources.

2.4.2. Forensic aspects

Human body decomposition is a natural complex process integrating continuously evolving physical, chemical and biological changes. Environmental and weather conditions, such as temperature, humidity, environment (soil or aqueous) composition can affect decay process and thus the metabolic processes happening onto the corpse [139,140]. Laboratory-based or on-site detection and characterization of VOCs related to human body decay in crime scenes is interrelated to thanatochemistry (the chemistry of death) and can allow the description of the decomposition process at different stages. Qualitative and quantitative data on specific VOCs can provide information on the exact time of death or can even describe a forensic event or a murder case. Decomposition is a multistage process which evolves from autolysis of individual cells to a more complex tissue breakdown. Briefly it unfolds from the fresh phase to the bloated stage, then to the active decay followed by the advanced decay and eventually to the skeletonization. Large biomolecules breakdown into simple organic matter molecules

and release VOCs with characteristic odours. These VOCs attract specific groups of insects, which can be used by forensic entomologists to estimate the postmortem period [139–145]. Table 4 presents representative volatile compounds in the air produced from animals and humans during the five decomposition stages. Even though the use of VOCs in the forensic science has great potential, there are legal and ethical limitations, which do not allow extensive investigation. Research is mainly based on animals such as pigs as human body simulators. Volatolomics could therefore be a novel non-invasive and precise tool providing evidence for law enforcement. “Body farms” are research facilities that allow in depth comprehension of the decomposition process of the human body using as many analytical techniques as possible in short- and long-term period and at different conditions (different climates, clothing of the corpse, etc.). Experimentation on human death allows forensic anthropologists to obtain a holistic knowledge of the decomposition of the whole body or parts of it, which can then be applied in real-life murder cases. Currently the United States of America hosts 7 body farms, Holland the first forensic body farm in Europe, while there is a big call from the United Kingdom. Australia recently opened a human decomposition facility. Cadaver canines training and performance can be also improved by recoding the chemical “puzzle” of decay. The latest trend towards human decay studies is the wide involvement of advanced separations techniques such as TD-GC×GC-ToF-MS next to chemometrics and the expanding of air volatiles to soil, fabrics, fire debris and cloths forensic VOCs.

Technologies for underwater (e.g. a river or a lake) detection of human corpses need also to be developed. Monitoring of characteristic VOCs emitted from a dead human body hidden under water could be very useful for on-site investigations. There is still a huge gap in knowledge for such environments. Technologies such as membrane inlet MS (MIMS) [146], could be used to screen water sources using membrane sampling probes, which allow the selective detection and screening of VOCs of interest.

3. Analytical instrumentation

3.1. Lab-based systems for volatolomics

GC–MS is the most widely used traditional analytical technique for volatolomics [9,11,100,133]. It is considered to be the gold standard in the chemical analysis of volatile and semi-VOCs, combining characteristics that allow the qualitative identification and quantification of trace-level components evolved from complex sample matrices. A gas chromatograph (GC) is a precise pneumatic and temperature-controlled oven that acts as a pre-separation device, which allows sample molecules to travel through a mobile gas phase over a stationary liquid or solid phase and to be separated according to their retention time prior to the MS introduction and analysis [8]. The MS can have a single, dual or triple quadrupole mass analyser, a time-of-flight (ToF), an ion trap, an orbitrap, etc. [147,148]. Samples can be introduced into the GC injection port by a micro syringe containing sample molecules dissolved in a solvent or with a solid-phase microextraction (SPME) fiber coated with a liquid or a solid extracting phase. Sample VOCs and semi-VOCs collection can also be performed by using stainless steel or glass tubes filled with absorptive materials. The tubes can be then introduced in a thermal desorption unit (TDU) for heating and sample extraction within the GC oven [123,126]. Two-dimensional gas chromatography (GC × GC) combined with ToF-MS [9] provides enhanced chemical separation of molecules (e.g. polar and non-polar), higher selectivity and sensitivity compared to a common GC–MS, improved mass spectral deconvolution and clearer library matches.

The MS may contain either a hard ionization (e.g. electron impact - EI) ion source for fragmentation of the pre-separated sample molecules

or a soft chemical ionization source (e.g. positive or negative) [56,65,66]. The most common detector in GC–MS systems is the electron multiplier (EM) and currently a triple-axis detector was introduced by Agilent [149]. The triple-axis detector is a modified EM which drastically reduces neutral noise and ensures clean signals and very low detection limits. Commercial GC–MS systems contain novel tuning (auto and manual) programs, so that they can perform “self-test” for leak detection and calibration purposes. Data acquisition, interpretation and analysis software (e.g. the “Mass Hunter” and “Chem Station” algorithms by Agilent, the GC/MS solution by Shimadzu [150], the Xcalibur™ by Thermo Scientific [151], the MS Workstation by Bruker [152], etc.) have been developed to provide smart approaches for both qualitative and quantitative analysis. The Wiley 10th and NIST libraries with > 638,000 compounds and 267,376 compounds, respectively are commercially available databases containing EI mass spectra and chemical structures required for the chemical characterization and identification of samples under examination. Novel algorithms based on probability-based matching (PBM), Manhattan distance composite algorithm and identity algorithms have also been developed to support library searches.

SIFT-MS [153–157] is an analytical technique that allows the direct analysis of VOCs in real-time providing quantitative information. In SIFT-MS, reagent ions react with sample VOCs with well-understood and controlled mechanisms. Reagent ions could be H_3O^+ , OH^- , O^- , O_2^- , O_2^+ , NO^+ , NO_2^- , and NO_3^- . SIFT-MS can perform self-calibration by using exhaled breath absolute humidity and has detection limits of ultra-low ppt within a few seconds.

PTR-MS [68,153,158] utilises a soft ionization ion source which generates hydronium ion to react with gaseous sample molecules. In PTR-MS sample molecules receive a proton from the hydronium ion and thus they are ionised. PTR-MS has response times < 1 s and detection limits below 1 ppt. Due to the soft ionization, PTR-MS can provide clear mass spectra originating from complex samples such as exhaled breath or the headspace area above biological fluids.

MIMS [56,65,66] is a simple analytical technique with great potential for metabolomics and volatolomics. Its main advantage is the capability to be integrated onto mobile or portable field-deployable systems. It is based on the pervaporation process, which is a three-stage procedure. Sample molecules originating from the gaseous, aqueous and solid phase absorb onto the surface of a membrane, they diffuse selectively through the membrane inlet and they finally desorb in the vacuum system and the MS for analysis. MIMS is ideal for in-situ applications offering high sensitivity (low limits of detection (LOD) - high pptv), selectivity, fast and accurate analysis (within seconds), with no or minimum sample preparation requirements.

Qualitative metabolomic results can be treated by complete commercial libraries, equipped with hundreds of thousands of different compounds or built-in-house databases of reference compounds for cross-checking. Different novel ionization approaches result to mass spectra, which need to be confirmed by usually lab based spectral libraries of standard compounds. Design of an experiment, e.g. using factorial design, sample classification and chemometric analysis e.g. multivariate statistical data analysis, principal component analysis, etc. can be utilised to extract high value information from complicated data matrices. Quantitative information is also important to understand the chemical message that a compound carry and how this interferes with other factors. The exploratory stage is followed by the validation and the modelling stage, which allows to specific VOCs to become targeted.

These characteristics make MS ideal for implementation in medical centres for on-site diagnostic purposes or on-line monitoring of specific metabolites in human exhaled breath, urine, saliva, etc. [159–162] (Table 5).

3.2. Portable systems

Existing mainstream portable MS-based instruments [165–171] available in the market (Table 6) for volatolomics studies have limitations and improvements are still needed. The disadvantages that they present are mainly connected with their size, weight, power consumption, as well as the mass range that they can detect and the speed of analysis. Even when designed as fieldable instruments, their dimensions render them to be not user friendly, difficult for transportation and for on-site operation. They usually weight between 14.5 and 37 kg with power consumption between 120 and 600 W, slow response times (s to min) and a limited small mass range of compounds that they can detect.

Portable Fourier transform infrared (FTIR) spectroscopy and e-noses have also the potential for on-site analysis of VOCs emitted from biological samples. The **IRSpirit** from SHIMADZU [150] is a compact and lightweight FTIR spectrophotometer able to perform reliable detection and quantification tests. A portable electronic nose called **PEN** from AIRSENSE Analytics [172] is a small and robust system able to analyse gas mixtures up to 10 components. It can provide quantitative analysis and can be used for in-field applications of volatolomics. **Cyranose® 320** [173] is also a handheld chemical sensor (array of nanocomposite sensors and advanced pattern recognition algorithms) that can measure vapours and VOCs in low concentrations. **Cyranose® 320** has already been utilised in medical diagnostics for breath metabolomics for pneumonia, lung cancer, and pulmonary diseases as well as in colorectal cancer and toxic exposures. It has investigated also in micro-organism volatolomics, e.g. bacterial classification or bacteria identification in blood and urine. The portable **zNose** [174] is based on miniaturized gas chromatography that can provide accurate chemical analysis of complex mixtures within 60 s. Due to its technical characteristics **zNose** can perform on-site analysis of pathological samples and VOCs at low ppt concentrations.

4. Conclusions

Metabolomics is a broad area of experimentation targeting the analysis and comprehension of the metabolic processes occurring within an organism. A subset of the metabolomics is volatolomics, which focuses on the chemical investigation (detection and monitoring) of volatile metabolites associated with in-body biological activities. VOCs analysis has wide application in medical diagnostics, safety, forensics, nutrition and healthcare, molecular communication, etc. Advances in detection tools and chemical sensing systems, allow accurate measurements with on-site real-life applications. This review paper gives an overview and examples of volatolomics in humans, plants, insects and microorganisms and explores current application areas. Different analytical techniques for volatolomics have been discussed with extensive consideration of MS-based instruments. Portable systems with field analytical chemistry capabilities are also presented alongside their technical characteristics.

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