J Chem Ecol (2013) 39:569–578
DOI 10.1007/s10886-013-0286-z

REVIEW ARTICLE

Human Skin Volatiles: A Review

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Received: 9 January 2013 / Revised: 2 April 2013 / Accepted: 3 April 2013 / Published online: 25 April 2013
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Abstract Odors emitted by human skin are of great interest to biologists in many fields; applications range from forensic studies to diagnostic tools, the design of perfumes and deodorants, and the ecology of blood-sucking insect vectors of human disease. Numerous studies have investigated the chemical composition of skin odors, and various sampling methods have been used for this purpose. The literature shows that the chemical profile of skin volatiles varies greatly among studies, and the use of different sampling procedures is probably responsible for some of these variations. To our knowledge, this is the first review focused on human skin volatile compounds. We detail the different sampling techniques, each with its own set of advantages and disadvantages, which have been used for the collection of skin odors from different parts of the human body. We present the main skin volatile compounds found in these studies, with particular emphasis on the most frequently studied body regions, axillae, hands, and feet. We propose future directions for promising experimental studies on odors from human skin, particularly in relation to the chemical ecology of blood-sucking insects.

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Keywords Blood-sucking insects · Human · Chemical ecology · Sampling method · Skin odor · Volatiles

Introduction

What kinds of volatile compounds are emitted by the human body, and how they are perceived by other animals, are questions that have long intrigued biologists. Numerous studies have investigated the chemical composition of odor of skin (Bernier et al., 2000; Curran et al., 2005; Gallagher et al., 2008) and of exhaled breath (Kusano et al., 2012), as well as volatiles from urine (Kusano et al., 2011, 2012), hair, and scalp (Goetz et al., 1988), and even flatus (Suarez et al., 1998). Objectives of these studies ranged from simply describing the chemical composition of human body "scent", searching for putative human pheromones (Brooksbank et al., 1974; Mostafa et al., 2012), or understanding the skin-mediated chemical transformation of perfumes (Behan et al., 1996; Ostrovskaya et al., 2001), to evaluating the ability of devices that could reduce malodorous emanations (Natsch et al., 2005; Ohge et al., 2005; Ara et al., 2006; Caroprese et al., 2009). Deciphering human body odors also may provide tools for diagnosing human diseases or infections (Prugnolle et al., 2009; Kim et al., 2012; Santonico et al., 2012), and has proved to have various applications in forensic studies (Prada and Furton, 2008, 2012; Curran et al., 2010a; DeGreef and Furton, 2011).

In addition, several studies on human body odors have aimed at understanding how blood-sucking insects locate and choose their vertebrate hosts for blood meals, with particular attention to anthropophilic mosquitoes that transmit pathogens to humans. e.g., *Anopheles* (Takken and Knols, 1999; Meijerink et al., 2000), *Culex* (Syed and Leal, 2009), and *Aedes* (Dekker et al., 2005; Logan et al., 2008). These insects are responsible for transmission of widespread and sometimes deadly infectious diseases, including malaria and dengue. Because host location in these

mosquitoes is known to be mediated by olfactory cues, and because skin emanations contribute to the distinctive olfactory signature of humans (e.g., Verhulst et al., 2010a; Smallegange et al., 2011), the chemical analysis of human skin volatiles represents a crucial step for the identification of olfactory stimulants and the design of innovative methods of vector control (Carlson and Carey, 2011).

In contrast to the situation for plants, for which biosynthetic pathways and the production of volatile compounds have been relatively well analyzed and described in long-standing studies (Dudareva et al., 2004; Knudsen et al., 2006), the analysis of volatile chemicals from mammalian species, particularly humans, is more complex and has encountered technical difficulties (Pandey and Kim, 2011; Charpentier et al., 2012). Methodology for sampling human skin volatiles has even been subject to controversy (Curran et al., 2006; Preti et al., 2006). Human odors are produced in small amounts, and are likely to show high variability, due to many environmental factors such as diet (Havlicek and Lenochova, 2006; Lefèvre et al., 2010) or disease (Pavlou and Turner, 2000). Skin microbial composition, which varies greatly among different human subjects (Fierer et al., 2008; Grice et al., 2009), also strongly affects the production of human body odors (Verhulst et al., 2010a, 2011a, b) (see below). Moreover, the use of various fragranced products by humans typically results in the detection of numerous exogenous compounds in skin odor analyses, although volunteer subjects often are asked to avoid fragrance soap/shampoo, deodorants, and perfumes several days before odor sampling.

In this first review on volatile compounds emitted by human skin, we detail the different sampling methods that have been used for the collection of skin odors as well as their pros and cons; we present the main skin volatile compounds found in these studies and highlight some contaminants misidentified as human volatiles; and we propose future directions for studies on odors from human skin.

Skin Glands, Skin Bacteria and Production of Volatiles

Production of volatile organic compounds by human skin is governed mainly by the secretion of three types of glands: eccrine, sebaceous, and aprocrine glands (Noël et al., 2012). Different human body odors emitted by distinct body parts partly reflect the distribution of these gland types on the skin surface (Smallegange et al., 2011). Eccrine glands (producing odorless sweat) are the most abundant and widely distributed on the skin surface, and are particularly concentrated on the hands and feet. Apocrine glands (which secrete lipids, proteins and steroids) are found particularly in the axillae and genital regions, while sebaceous glands (which secrete sebum and lipids) are distributed all over the body but are concentrated on the head.

Secretions from these glands provide various niches adapted to the development of dense populations of commensal, cutaneous microorganisms, which have long been considered as key contributors to the formation of human body odor (Shelley and Hurley, 1953). For example, many studies have evidenced the relationships between specific odorous components emanating from axillae and the presence of a particular microbial fauna (Taylor et al., 2003; James et al., 2004a, b; Natsch et al., 2005, 2006). Skin-inhabiting bacteria also have been cited often in currently recognized explanations for inter-individual variation in body odor (Penn et al., 2006). Indeed, the composition of skin microbiota differs greatly among human subjects (Fierer et al., 2008; Grice et al., 2009), and several studies have suggested a strong link between particular body odors and skin microbial composition (Marshall et al., 1988; Natsch et al., 2006; Verhulst et al., 2010a; Barzantny et al., 2012a). Recently, some authors reported that skin microbiota may play a major role in human attractiveness to blood-sucking insects. Freshly produced human sweat is typically odorless and unattractive to mosquitoes (Verhulst et al., 2010b), while the presence of microorganisms allows conversion of sweat components into odorous and attractive compounds (Ara et al., 2006; Verhulst et al., 2011b).

Sampling Methods for Analyses of Skin Volatiles

Numerous studies have examined human skin volatiles (Table 1). Different sampling methods, each having its own advantages and drawbacks, have been applied. One method routinely used to sample human skin volatiles is solvent extraction: a sweat sample is extracted by a solvent, or compounds may be first collected with a cotton pad, then extracted with a solvent (hexane, dichloromethane, ether). The main drawback of this rapid method is that it isolates some compounds that are not volatile at naturally occurring body temperature. A second method, dynamic headspace adsorption onto various porous polymers (e.g., Tenax, Porapak Q), often has been preferred for collecting airborne volatile compounds actually emitted by skin. In these methods, skin compounds usually are first absorbed on gauze or cotton pads (or sometimes on clothes that have been worn), then volatiles released by these materials are collected onto adsorbent traps (glass tubes filled with Porapak or Tenax adsorbent) using an airflow process. However, the use of an intermediate medium (sorbent material such as gauze or cotton) poses three problems. First, these media may fail to transfer certain compounds. Second, even if these media are biologically sterile, they may not be analytically clean (Prada et al., 2010), and exogenous contaminants may be

Table 1 Chemical analyses of human body odor: body part, sampling method and procedures used for the collection of human skin volatiles

Human body part	Collection method	Sample size	Compounds identified	References
Axilla	Collection on cotton-wool pads, solvent extraction	12 males	5α-androstenol-3α-ol	Brooksbank et al., 1974
Axilla	Sweat sample, solvent extraction	?	?	Sastry et al., 1980
Axilla	Collection with cotton pads. Solvent extraction (ethanol + chloroform/methanol) (1 hr)	6 females	36 compounds	Zeng et al., 1996
Axilla	Collection with gauze pads. Headspace SPME in vials (15 hr)	4 males, 4 females	54 compounds : 23 "common" compounds, 7 present in all samples[a]	Curran et al., 2005
Axilla	Collection with cotton pads. Solvent extraction (ethanol + hexane)	?	28 carboxylic acids	Natsch et al., 2006
Axilla	Sweat samples collected with PDMS-coated stir bars. Thermal desorption	197 adults	373 peaks	Penn et al., 2006
Axilla	Sweat samples collected by a stir-bar sampling device	196 individuals	?	Xu et al., 2007
Axilla	Collection with gauze pads. Solvent extraction (methanol), headspace SPME in vials	2 males (age 26 and 30)	44 compounds	Mebazaa et al., 2010, 2011
Forearm	Glass sampling device on the skin, headspace SPME (45 min)	50 females (age 18 to 60)	6 major compounds[b]	Ostrovskaya et al., 2001
Forearm	Forearm wrapped in aluminium cylinder, headspace SPME (1 hr)	16 individuals (different countries)	4 major compounds[c]	Syed and Leal, 2009
Forearm and upper back	Glass funnel : headspace SPME (30 min) + solvent extraction (50/50 ethanol/hexane)	25 adults	92 compounds (58 in SPME samples, 49 in solvent extracts)	Gallagher et al., 2008
Arm/hand	Headspace SPME (30 min)	15 individuals	35 compounds	Zhang et al., 2005
Arm/hand	Glass beads handled by subjects (15 min)	4 males	303 compounds	Bernier et al., 2000
Hand	Direct sampling of vapors: one-line detection by SESI (Secondary electrospray ionization)	1 male	19 compounds	Martínez Lozano and De La Mora, 2009
Hand	Collection on cotton gauze, cotton fabric, polyester. Headspace SPME in vials	?	5 main compounds[d]	Prada and Furton, 2008
Hand	Collection with Dukal bran gauze pads (10 min), SPME in vials (12 hr)	5 females, 5 males (age 17 to 28)	37 compounds	Curran et al., 2010b
Hand	Collection with sorbent textiles and STU-100. SPME in vials, (21 hr)	3 females, 3 males (age 24 to 33)	58 compounds	Prada et al., 2011
Hand	Collection with STU-100. Headspace SPME in vials, (21 hr)	?	6 main compounds[e]	DeGreef and Furton, 2011; DeGreef et al., 2011
Hand	Collection with Dukal bran gauze pads (10 min), SPME	15 men, 16 women (age 19 to 36)	36 compounds	Kusano et al., 2012
Foot	Nylon stockings worn 3 days, dynamic headspace (Tenax), elution pentane	15 individuals	23 compounds	Qiu et al., 2004
Foot	Solvent extraction (socks, feet) with ethyl ether	?	Low-molecular-weight fatty acids, isovaleric acid	Kanda et al., 1990
Foot	Sweat sample, solvent extraction (Ether)	30 individuals	9 fatty acids	Ara et al., 2006
Foot	Collection with cotton wool (6 hr) interdigital area, SPME in vials (10 min)	4 males, 2 females (age 38)	9 fatty acids	Caroprese et al., 2009
Foot	Solvent extraction, chromatoprobe dynamic headspace, contact SPME, headspace SPME	14 men, 12 women (age 4 to 45)	44 compounds	Dormont et al., 2013

Table 1 (continued)

Human body part	Collection method	Sample size	Compounds identified	References
Back	T-shirts worn 3 days, Tenax extracts of pieces cut from the T-shirts	13 males, 9 females	2-nonenal detected only in older subjects	Haze et al., 2001
Forehead, trunk	Sweat sample, solvent extraction (dichloromethane)	14 adults	28 carboxylic acids	Cork and Park, 1996
1.5 ml sweat sample	Dynamic headspace (Tenax)	9 males, 5 females (age 21 to 52)	40 compounds	Meijerink et al., 2000
Whole body within aluminumized plastic bags (except head)	Dynamic headspace (Porapak Q) (2 hr), elution diethylether	9 adults (age 21 to 60)	24 compounds[f]	Logan et al., 2008
Whole body (except head)	Dynamic headspace (Tenax GR and Porapak Super Q) (150 min), elution pentane	4 volunteers	6 main compounds[g]	Harraca et al., 2012

[a] Decanal, methyl dodecanoate, nonanal, methyl octanoate, phenol, tetradecane, methyl tetradecanoate

[b] Nonanal, octanal, decanal, tetradecane, pentadecane, hexadecane. In some samples: 6-methyl-5-hepten-2-one

[c] 6-methyl-5-hepten-2-one, nonanal, decanal, geranylacetone

[d] 6-methyl-5-hepten-2-one, nonanal, decanal, lilial, geranylacetone

[e] 6-methyl-5-hepten-2-one, nonanal, decanal, octanoic acid, pentadecane, geranylacetone

[f] Main compounds: 6-methyl-5-hepten-2-one, octanal, nonanal, decanal, geranylacetone

[g] Heptanal, 6-methyl-5-hepten-2-one, octanal, nonanal, decanal, geranylacetone

isolated. Recently, odors from skin have been collected directly onto adsorbent traps, without intermediate absorption onto cotton pads (Logan et al., 2008; Harraca et al., 2012; Dormont et al., 2013). Finally, these methods require the use of a solvent to elute volatiles that have been trapped into the adsorbent solid phase. The resulting diluted solutions need a step of concentration before Gas Chromatography (GC) analysis, with the risk that very low molecular weight volatile compounds may evaporate and be lost. Dynamic headspace with miniaturized trapping tubes, such as ChromatoProbe micro-vials, avoids the use of solvent, the trapping tubes being directly inserted into the GC injector for thermal desorption (Dormont et al., 2013).

A more recent method, solid-phase micro-extraction (SPME), originally developed for the monitoring of air pollutants and later extended to diverse applications including the sampling of volatiles from living organisms (Musteata and Pawliszyn, 2007; Duan et al., 2011), is now widely used for the collection of human odors. SPME is a simple, sensitive, solvent-free technique that enables trapping various volatile semiochemicals on adsorbent-coated fibers, followed by direct thermal desorption into a GC injector. This technique has been used widely for the sampling of volatiles emitted from axillae, forearm, hands, or back (see Table 1). However, SPME has so far most frequently been used following preliminary collection of skin volatiles on various sorbent materials (gauze or cotton pads), leading to the potential isolation of many exogenous compounds (DeGreef et al., 2011; Prada et al., 2011). More recently, contact SPME, in which fibers are directly stroked over the skin, has been applied to collect volatiles from feet, providing results similar to those obtained with classical headspace SPME (Dormont et al., 2013).

Skin treatment procedures before odor collection also vary greatly among studies. During the days before collection of skin volatiles, volunteers often have been asked to follow particular instructions related to diet and the use of fragrance soap/shampoo. In some cases, no specific instruction was given to subjects before the day of odor collection (Bernier et al., 2000; Zhang et al., 2005). In contrast, some protocols require volunteers to avoid spicy food and garlic several days before odor sampling (Ostrovskaya et al., 2001; Logan et al., 2008; Harraca et al., 2012). In most cases, subjects were asked to use no deodorant, no perfume, and to use fragrance-free soaps the days before odor collection. Just before odor sampling, the area of skin from which volatiles were collected was usually washed with tap water, or sometimes with olive-oil based soap (Prada and Furton, 2008; Curran et al., 2010b; Kusano et al., 2012). In some cases, participants were instructed to do some exercise so that the skin became sweaty (Curran et al., 2005; Gallagher et al., 2008).

Finally, both diverse sampling methods and distinct analytical procedures (such as pretreatment procedures) have been used to collect human skin volatiles. The only way to evaluate potential pitfalls specifically related to the sampling method used, and to limit the risk of errors due to sampling procedure, would be to compare different sampling methods used simultaneously on the same sample. In contrast to studies of plant volatiles, where direct and simultaneous comparisons of odor sampling methods have been processed and evaluated (Agelopoulos and Pickett, 1998; Raguso and Pellmyr, 1998; Tholl et al., 2006), volatiles from humans have not been analyzed through similar practical approaches, except in a few cases (Gallagher et al., 2008; Prada et al., 2011; Dormont et al., 2013). Another pitfall associated with chemical analyses of human volatiles is the risk of recording chemical compounds that are clearly of non-natural origin (Charpentier et al., 2012). In the literature, chemical profiles of human volatiles often include some molecules originating from industry, such as (*R*,*S*)-2-ethyl-1-hexanol, naphthalene, and dichlorobenzene (Bernier et al., 2000; Haze et al., 2001; Zhang et al., 2005; Gallagher et al., 2008; Logan et al., 2008). Although such contaminants have been detected in numerous human samples, and even if some of these molecules have been shown to elicit electrophysiological responses in some insect species (Qiu et al., 2004; Logan et al., 2008), their biological and evolutionary relevance in human–vector interactions remains open to question.

Volatile Compounds Emitted by Skin

The literature shows that the chemical profile of skin volatiles varies greatly. The use of different sampling procedures is probably responsible for many inconsistencies in the compounds detected. Comparison of results from the literature requires a number of precautions because of the large differences in both the sampling methods and in the part of the body that was sampled.

More than 400 compounds have already been isolated and identified from human skin extracts. However, studies that have used headspace collection of volatiles, i.e., analyzing the airborne volatiles really emitted by skin surfaces at naturally occurring body temperature, have detected only 20 to 90 compounds from human odors. Table 2 compiles the 25 chemical compounds most often reported in these studies. These studies have shown the chemical composition of human skin volatiles to be highly diversified, but only a few families of compounds are represented, such as carboxylic acids of various chain lengths and derivative esters, aldehydes, alkanes, short chain alcohols, and some ketones. In particular, four compounds often have been reported to be largely predominant in the volatile profile of human skin, 6-methyl-5-hepten-2-one, nonanal, decanal, and (*E*)-6,10-dimethyl-5,9-undecadien-2-one (geranylacetone) (see Table 1). For example, Syed and Leal (2009) found these four molecules to be major components of volatile emissions from human forearms, regardless of the subject's ethnic background. Compounds not known to occur in nature also are often reported, such as the industrial chemical (*R*,*S*)-2-ethyl-1-hexanol, regularly cited in the literature, suggesting inclusion of contaminants. In fact, many exogenous compounds are regularly isolated from analyses of human skin, due to the copious use of diverse fragranced products, even when rigorous protocols are applied before odor sampling to reduce isolation of such compounds (Penn et al., 2006; Gallagher et al., 2008). Some of these compounds, although undoubtedly of non-natural origin, have even been considered as marker compounds of human body odor (Penn et al., 2006). In contrast, other compounds not produced by mammals, but possibly produced through interactions with skin microbiota, appear more relevant. These include compounds such as limonene or lilial (see Table 2), given that bacteria have the ability to transform terpenoid compounds (Parshikov et al., 2012). The presence of limonene in human body odor has been correlated with dietary behavior of human subjects, and particularly the intake of citrus fruit (Friedman et al., 1994). However, terpenoids in human odor samples also may originate from many possible exogenous sources that contain these compounds (fragranced products, cleaning fluids, etc.).

Axillae The axillary region has been proven to be a particularly important source of diverse volatile compounds, which have been suggested to be useful as individual markers (Penn et al., 2006). Indeed, apocrine, eccrine, and sebaceous glands commonly co-occur at high densities in the axillae, together with a large diversity of microbial flora (Taylor et al., 2003; James et al., 2004b), which are likely to be involved in the emanation of many odorous volatile compounds. In particular, lipophilic corynebacteria, which dominate the commensal bacterial community on the axillary region of the skin, are largely responsible for the production of malodorous volatile products (Natsch et al., 2005; Barzantny et al., 2012a, b). Odours from axillae mostly consist of alkanes and C_6–C_{11} carboxylic acids (Zeng et al., 1996; Curran et al., 2005; Natsch et al., 2006; Penn et al., 2006), but the chemical composition of axillary odors found in these studies has been the subject of intense debate (Curran et al., 2006; Preti et al., 2006). In some studies, volatile profiles have been reported to be dominated by two key odoriferous compounds, 3-methyl-2-hexenoic acid and 3-hydroxy-3-methylhexanoic acid (Zeng et al., 1996; Natsch et al., 2006), but other authors did not find these compounds in axilla samples (Curran et al., 2005). However, it should be noted that these last authors

Table 2 Literature review: 25 compounds most frequently isolated from headspace samples of human skin, based on compilation of 31 references (see Table 1)

Retention index[a]	Compound	Biosynthetic origin	Occurrence
606	Acetic acid	Primary metabolism	11
634	Propanoic acid	Primary metabolism	8
718	3-hydroxy-2-butanone	Primary metabolism	6
801	Hexanal	Lipid pathway	12
827	Isovaleric acid[b]	Lipid pathway	7
921	Methyl hexanoate	Lipid pathway	11
987	6-methyl-5-hepten-2-one	Terpene pathway[e]	19
998	Octanal	Lipid pathway	12
1011	(*R*,*S*)-2-ethyl-1-hexanol	None (industrial origin)	6
1024	limonene	Terpene pathway	9
1026	Benzyl alcohol	Shikimic pathway	11
1100	Undecane	Shikimic pathway	10
1104	Nonanal	Lipid pathway	21
1157	(*E*)-2-nonenal[c]	Lipid pathway	14
1201	Decanal	Lipid pathway	21
1290	Indole	Shikimic pathway	8
1305	Undecanal	Lipid pathway	13
1453	Geranylacetone	Terpene pathway[e]	18
1500	Pentadecane	Lipid pathway	10
1524	Methyl dodecanoate	Lipid pathway	9
1527	Lilial	Terpene pathway	6
1600	Hexadecane	Lipid pathway	11
1614	(*E*)-3-methyl-2-hexenoic acid[d]	Lipid pathway	9
1722	Methyl tetradecanoate	Lipid pathway	6
1921	Methyl hexadecanoate	Lipid pathway	8

The column "occurrence" indicates the number of references in which the compound was reported

[a]Retention indices refer to those reported in the Adams database on nonpolar DB-5 stationary phase (Adams, 2007)

[b]Feet with strong odor (Ara et al., 2006)

[c]Hypothesized as a specific ageing compound, found only in individuals >40 years age (Haze et al., 2001; Yamazaki et al., 2010)

[d]Major odor-causing compound (Zeng et al., 1996)

[e]Carotenoid derivative

investigated axilla volatiles with a headspace technique (SPME), whereas Zeng et al. (1996) and Natsch et al. (2006) both sampled axilla odors using solvent extraction.

Hands Odors from hands have been largely investigated in the context of forensic sciences (Prada and Furton, 2008; Curran et al., 2010a; DeGreef and Furton, 2011; Kusano et al., 2012). Indeed, individualized characteristics of human hand odors may serve as volatile individual signatures in forensic investigations, e.g., for scent discrimination by canines (Curran et al., 2010b). Hand volatile profiles are often dominated by aldehydes and ketones, and particularly by 6-methyl-5-hepten-2-one, nonanal, decanal, undecanal, and geranylacetone. The same compounds also have regularly been found as major components of forearm volatiles, together with some alkanes and carboxylic acids (Ostrovskaya et al., 2001; Gallagher et al., 2008; Syed and Leal, 2009). Comparing hand odors from 10 subjects, Curran et al. (2010b) identified 24 main compounds that may constitute the "primary odor" profile of human scent. Six compounds were found to be highly frequent in hand volatiles: 2-furancarboxaldehyde, 2-furanmethanol, phenol, nonanal, decanal, and dimethyl hexanedioate. Among these compounds, only nonanal, decanal, and some carboxylic acid-methyl esters have been isolated regularly from hand odors in other studies (Zhang et al., 2005; Prada and Furton, 2008; DeGreef and Furton, 2011; Prada et al., 2011; Kusano et al., 2012).

Feet The chemical composition of foot odors has received limited attention in comparison to volatile emanations from other parts of the human body (axillae, forearm, hands). As for the axillary region, populations of skin-inhabiting bacteria have been shown to be especially dense on feet, resulting in the production of many malodorous volatiles (Marshall et al., 1988). In the past decade, there have been studies aimed at identifying specifically volatile compounds from feet, with two distinct objectives: (i) evaluating devices that can reduce foot malodor (Ara et al., 2006; Caroprese et al., 2009), and (ii) investigating olfactory cues that mediate host-seeking behavior of blood-sucking insects (Qiu et al., 2004; Dormont et al., 2013). Odours emitted by feet have been proven to influence strongly the behavior of several anthropophilic mosquitoes (Lacey and Cardé, 2011; Hawkes et al., 2012). The feet are the preferred biting sites for the

main human malaria vectors in Africa, *Anopheles gambiae* and *Anopheles arabiensis* (De Jong and Knols, 1995; Dekker et al., 1998), and foot odors have been demonstrated to be highly attractive to *A. gambiae*. Traps baited with nylon socks worn by human subjects have been shown to be very efficient for catching adult mosquitoes (Njiru et al., 2006; Schmied et al., 2008; Jawara et al., 2009).

Carboxylic acids have been cited as main components of foot volatiles. Ara et al. (2006) reported several short-chain fatty acids in solvent extracts of foot sweat, isovaleric acid being most likely responsible for strong foot odor. However, when processing headspace extracts of foot odors (with Tenax adsorbent), Qiu et al. (2004) did not detect such compounds. Tenax might be hypothesized to be less efficient for trapping volatile acids, but other authors have succeeded in isolating carboxylic acids from other human body parts with this adsorbent (Meijerink et al., 2000; Haze et al., 2001). In another study, Caroprese et al. (2009) isolated fatty acids when they exposed SPME fibers to cotton samples that had been applied for six hours in the interdigital area of the foot of human subjects. Isolation of short-chain fatty acids from foot skin emanations is probably dependent on both the sampling method used and the precise area examined. Moreover, the production of such types of compounds may be largely modified through microbial action or inhibited by various fragrance materials (Ara et al., 2006; Caroprese et al., 2009). Consistently, the cutaneous microflora has been reported to vary between feet exhibiting low and high levels of odor (Marshall et al., 1988).

Other Body Parts Volatile compounds from back, forehead, trunk, and even the whole body also have been investigated. When examining the volatile emissions from T-shirts worn by 22 participants, Haze et al. (2001) detected the unsaturated C_9 aldehyde (*E*)-2-nonenal only in odors from men and women aged 40 years and more. This compound has been proposed to be a key component of body odor associated with ageing (Haze et al., 2001; Yamazaki et al., 2010), but recent findings have not supported this suggestion (Gallagher et al., 2008; Curran et al., 2010b). Analyzing emissions from the upper back, Gallagher et al. (2008) suggested three other compounds to be biomarkers of increased age: dimethylsulphone, benzothiazole, and nonanal.

Two studies recently investigated the volatiles emitted by the whole human body, by placing human volunteers within individual aluminumized plastic bags, with only their heads outside (Logan et al., 2008; Harraca et al., 2012). In both cases, the authors attempted to conduct chemical analyses coupled with olfactory detection by anthropophilic insects. Using coupled GC-EAD, Logan et al. (2008) identified 24 volatile compounds from whole human bodies that were proved to be physiologically active for *Aedes* mosquitoes. The "classic" compounds emitted by human skin, 6-methyl-5-hepten-2-one, octanal, nonanal, decanal, and geranylacetone, were found to play a key role in insect attractiveness to human hosts. Harraca et al. (2012) isolated six main compounds from whole body volatiles, mostly C_7–C_{10} aldehydes (heptanal, octanal, nonanal, decanal), together with 6-methyl-5-hepten-2-one and geranylacetone. By coupling gas chromatography and single sensillum recordings from antennae of the common bed bug *Cimex lectularius*, these authors demonstrated that only these volatile compounds (except geranylacetone) were clearly detected by the olfactory receptor neurons of these insect species.

Perspectives

Identification of the molecules produced and released by humans—and potentially attractive to host-seeking insects—remains an important challenge for chemical ecologists.

We have shown in this review that the observed chemical profiles of human skin volatiles vary greatly with the sampling method used. We underline the great interest of further studies that compare and evaluate the efficiency of different sampling methods for the trapping of volatile compounds produced by human skin by applying these different techniques simultaneously on the same sample as has been done for plant volatiles. Because of the great diversity of compounds emitted by human skin, such comparative experiments will probably show that two or more different methods have to be simultaneously applied for the sampling of the whole scent profile from skin. Further comparative tests also should identify optimal conditions of sampling by testing the possible effects of pretreatments applied to the skin before sampling of volatiles (i.e., diet, washing the skin with water). In addition, some objectives, particularly the study of host odors that mediate behavior of blood-sucking insect vectors of human disease, require the use of convenient methods, adapted to field conditions, of sampling human skin volatiles (Dormont et al., 2013). It is thus important to investigate new sampling methods, and to test the feasibility of these methods under real field conditions. Such studies may open new possibilities for examining the olfactory cues that govern the behavior of host-seeking anthropophilic insects. This could allow elucidation of mechanisms underlying human/vector/pathogen interactions.

Whether the volatile profiles obtained with the sampling methods used so far reflect the exact olfactory cues perceived by flying, blood-feeding insects remains under question, given that no method applied alone allows trapping of the whole human scent (some molecules are always missing in the profile). Several EAG and GC-EAD tests have already shown that mosquitoes detect several of the compounds isolated from skin volatiles, in *Anopheles gambiae* (Cork and Park, 1996; Meijerink et al., 2000; Constantini et

al., 2001; Qiu et al., 2004), *Aedes aegypti* (Logan et al., 2008), and *Culex* spp. (Syed and Leal, 2009). Further behavioral and olfactory tests that examine insect responses to each of the compounds of the volatile profile are needed to identify more precisely which compounds of human skin odors are physiologically active and attractive (or repellent, see Logan et al., 2010) for vector insects. In particular, whether minor compounds of the human scent profile may play a role in the attraction of blood-sucking insects has never been explored. In plant–insect relationships, host location and recognition by insects are sometimes governed by particular or specific minor plant volatile compounds, which elicit electroantennographic responses of insect antennae at concentrations below the detection level of the GC analyses (D'Alessandro et al., 2009; Bruce and Pickett, 2011).

Further studies of the olfactory cues that mediate host-seeking by anthropophilic mosquitoes also will have to consider the possible changes in human body odors in people with infectious diseases. People infected with transmissible stages of malaria were reported to be more attractive for anopheline mosquitoes than uninfected people (Lacroix et al., 2005). Similar observations have been demonstrated recently for *Culex* species attracted to malaria-infected birds (Cornet et al., 2012). Whether such modifications of host odor following infection may be of adaptive significance, for either the parasite or the host, is under debate (Lefèvre et al., 2006; Prugnolle et al., 2009). For the moment, whether humans infected and uninfected by malaria show differences in their volatile profiles is not known, and further investigations on skin volatiles emitted by subjects infected by malaria are needed for a better understanding of the chemical ecology of human/vector/pathogen interactions.

Acknowledgments We thank Doyle McKey, Université Montpellier II and CEFE-CNRS, for reviewing the manuscript and for useful discussions.

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