IOP Publishing Journal of Breath Research
J. Breath Res. **8** (2014) 014001 (29pp) doi:10.1088/1752-7155/8/1/014001

Topical Review

A review of the volatiles from the healthy human body

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Received 3 June 2013
Accepted for publication 3 September 2013
Published 13 January 2014

Abstract

A compendium of all the volatile organic compounds (VOCs) emanating from the human body (the volatolome) is for the first time reported. 1840 VOCs have been assigned from breath (872), saliva (359), blood (154), milk (256), skin secretions (532) urine (279), and faeces (381) in apparently healthy individuals. Compounds were assigned CAS registry numbers and named according to a common convention where possible. The compounds have been grouped into tables according to their chemical class or functionality to permit easy comparison. Some clear differences are observed, for instance, a lack of esters in urine with a high number in faeces. Careful use of the database is needed. The numbers may not be a true reflection of the actual VOCs present from each bodily excretion. The lack of a compound could be due to the techniques used or reflect the intensity of effort e.g. there are few publications on VOCs from blood compared to a large number on VOCs in breath. The large number of volatiles reported from skin is partly due to the methodologies used, e.g. collecting excretions on glass beads and then heating to desorb VOCs. All compounds have been included as reported (unless there was a clear discrepancy between name and chemical structure), but there may be some mistaken assignations arising from the original publications, particularly for isomers. It is the authors' intention that this database will not only be a useful database of VOCs listed in the literature, but will stimulate further study of VOCs from healthy individuals. Establishing a list of volatiles emanating from healthy individuals and increased understanding of VOC metabolic pathways is an important step for differentiating between diseases using VOCs.

S Online supplementary data available from stacks.iop.org/JBR/8/014001/mmedia

(Some figures may appear in colour only in the online journal)

Introduction

Until now there has been no central compendium of volatile organic compounds (VOCs) reported from the healthy human body. This work attempts to produce tables that encompass all reported volatiles from healthy humans from breath, saliva, blood, milk, skin secretions (sweat and follicle fluids), urine, and faeces. Knowledge of what is normal will help to assess what is abnormal. Analyses of volatiles from patients offers the possibility of rapid diagnoses and also potentially permits the long term monitoring of the population, for early detection of organ impairment or other illness. Breath collection is very patient friendly and analysis potentially offers a non-invasive method for assessing organic compounds in the blood

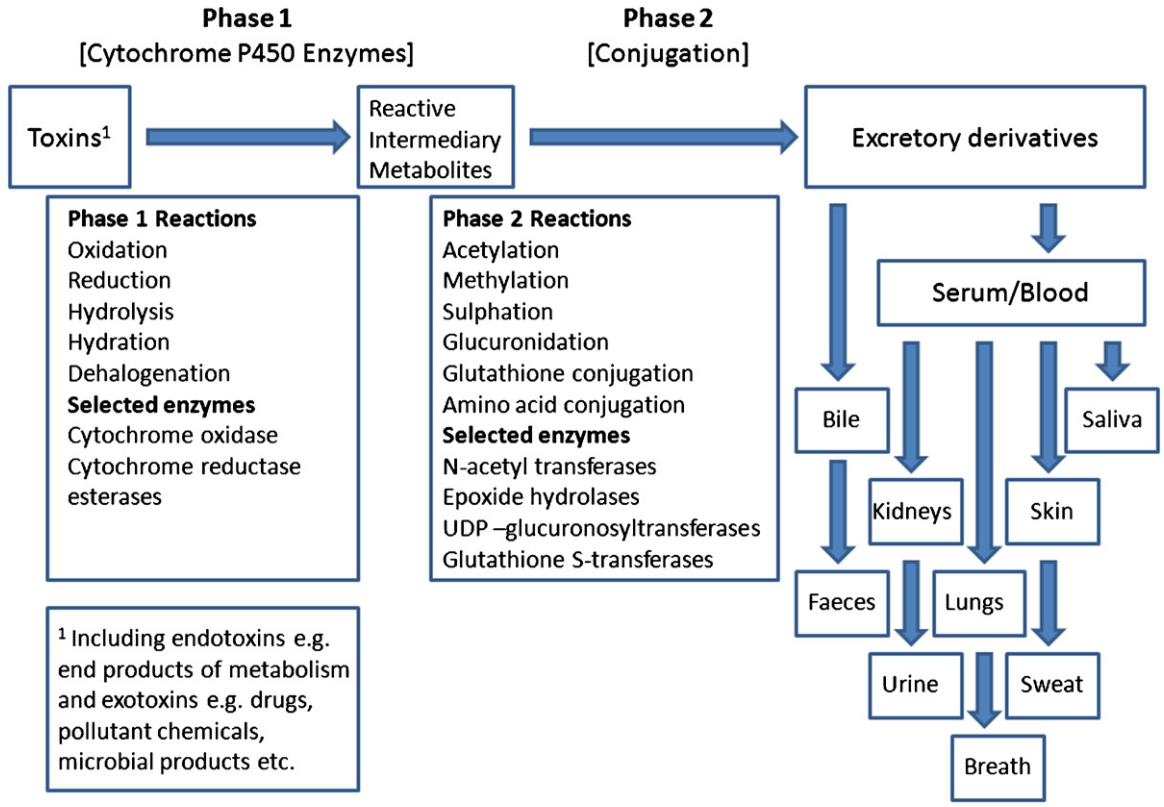

Figure 1. Chemical conversions undertaken by the liver.

(arising from the blood itself e. g. infections and from organs transferring VOCs into the blood), as well as the state of the lung (e.g. lung infection, lung cancer). VOC analysis of small molecules/metabolites is also a facile method for assessing faeces, urine, milk and saliva, and in the former two cases to the state of the gastro-intestinal tract and urinary tract respectively. Much remains to be understood of the chemical origin of the numerous chemicals reported here. It would be a gargantuan task to undertake this, with a huge amount of practical work. There appear to be unfilled gaps, particularly in homologous series, in the tables listed here of volatiles from breath, saliva, blood, milk, skin secretions, urine, and faeces, rather like in the early days of the periodic table. However there are also VOCs present where it is not clearly obvious why, for instance when compounds are found to be present in breath and not in blood, saliva, or faeces. The liver is most likely to be involved in conversion of some VOCs in the blood stream (figure 1), and this may result in some compounds then dropping in concentration below the detectable level whilst new VOCs are produced or existing VOCs increase in concentration. Thus compounds present in faeces in the gastro-intestinal tract might be expected to transfer to the blood and eventually reach the lungs and appear in breath. However, they may not be detected in the breath due to conversion in the liver. The liver has broad substrate specificity enzymes which are capable of oxidizing large numbers of non-polar compounds e.g. hydrocarbons, to more polar compounds, e.g. alcohols, for example the bioconversion of toluene to benzyl alcohol. The liver also possesses aldehyde dehydrogenases which convert aldehydes to acids (which can then be metabolized, e.g. by muscle), amines to the less volatile N-oxides and ammonia to non-polar urea. Furthermore the liver is capable of converting compounds into conjugates, by e.g. reaction with charged species like glutathione, which makes the compound water soluble and easily excretable and converts what was a VOC into a non-volatile compound. Apart from the liver, other organs are capable of substantial biotransformation activity. For instance it is likely that a compound detected in blood but not urine, has been chemically transformed by the kidneys, or even the bladder. For many years the bladder has been considered to be simply a storage facility for urine, however it is capable of biotransformations, as bladder epithelial tissue has, for instance been found to have even higher arylamine acetyltransferase enzyme levels than the liver [1]. Biotransformations can also occur in the lungs or via enzymes in the nose [2].

No one analytical method is suitable for measuring all the bodily fluids and breath described herein. It is also inevitable that researchers would utilize the equipment and methodology available to them. Gas chromatography mass spectrometry (GCMS) has been the main method used, however other methods such as selected ion flow tube mass spectrometry (SIFT-MS) and proton transfer reaction mass spectrometry (PTR-MS) have also been used. Normally, pre-concentration of sample components has been adopted in the studies reported. Also solvent extraction to obtain VOCs has been utilized e.g. in milk studies, and changing the pH of the matrix to alter the VOC profile has been used e.g. for urine and clearly these methods are not compatible with breath analysis. Likewise some skin studies involved using glass beads rolled on to the skin followed by heat to desorb the VOCs [3, 4].

Table 1. Table showing all the 1840 volatile organic compounds reported in the literature from healthy humans. The table lists and compares the number of VOCs identified in faeces (381), urine (279), breath (872), skin secretions (532), milk (256), blood (154) and saliva (359). Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia[a].

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	A							
75-07-0	Acetaldehyde	F	U	Br	Sk	M	Bl	Sa
60-35-5	Acetamide	F		Br				
64-19-7	Acetic acid	F	U	Br	Sk	M		Sa
140-11-4	Acetic acid, benzyl ester/benzyl acetate/acetic acid, phenylmethyl ester				Sk			Sa
123-86-4	Acetic acid, butyl ester	F		Br				
110-19-0	Acetic acid, isobutyl ester/isobutyl acetate			Br				
20298-69-5	Acetic acid, cis-2-tert-butylcyclohexyl ester/cis-2-tert-butylcyclohexyl acetate				Sk			
32210-23-4	Acetic acid, 4-*t*-butylcyclohexyl ester/vertenex/4-*t*-butylcyclohexyl acetate				Sk			
21040-45-9	Acetic acid, cinnamyl ester/*E*-cinnamyl acetate				Sk			
53767-93-4	Acetic acid, dihydromyrcenyl ester/dihydromyrcenol acetate				Sk			
141-12-8	Acetic acid, (*Z*)-3,7-dimethyl-2,6-octadien-1-ol ester/neryl acetate				Sk			
105-87-3	Acetic acid, (*E*)-3,7-dimethyl-2,6-octadien-1-ol ester/geranyl acetate				Sk			Sa

[a] Tables 1–12 were compiled from the references: faeces [16, 219]; urine [178, 189, 220]; breath. [12, 43, 45–50, 221]. Skin secretions [4, 149–155, 157, 158, 222, 223]; milk [17, 24, 168, 170–173, 175, 176]; blood [122–127, 130, 134, 136, 145, 183, 224–230]; saliva [154, 160, 161, 163, 165, 231–233].
Notes. ui: unidentifed isomer; na: no CAS-number available; A: very unlikely reacts with water; B: seen in illness; C: unpublished data; D: in flatus.

This work has produced a master table in alphabetical order for easy access to a particular named chemical, and a series of sub tables with common functionality. The latter tables are very useful for determining any trends which are not obvious in a very large, alphabetical table.

Compound identification

Most of the work reported here has used quadrupole GCMS with library matching to aid identification of the VOCs, in some earlier work GC-FID (gas chromatograph equipped with flame ionization detector) detection with standards was undertaken e.g. for the measurement of the four major endogenous breath volatiles, methanol, ethanol, acetone, and isoprene [5] and e.g. for alcohols [6].

The identification of compounds in GCMS-investigations is no easy task. Often, peaks are identified by spectral library match only. This can sometimes be misleading, particularly for isomers. Some of the later work has used retention time matching to supplement library matching [7–14]. Such a comparison of the retention times of certain peaks with reference material of the respective suspected compound is recommended. This 'double check' gives relatively accurate results. GCxGC TOF MS although not yet widely used has shown the huge number of volatile compounds that exist from bodily fluids. Therefore, it is quite possible that some misidentification has occurred using quadrupole GCMS due to co-elution of peaks. Other potential sources of misidentification include the compound analysed not being in the MS libraries e.g. NIST (this is also a problem with higher dimensionality techniques and direct MS techniques), or due to mass spectral similarities, particularly with isomers of hydrocarbons. Additionally, since there is no separation of sample components prior to ionization in the direct mass spectrometric techniques, such as PTR-MS or SIFT-MS, the recorded spectrum reflects the total sample composition, where ions of particular m/z need to be carefully attributed to certain substance by consideration of its fragmentation pattern [15].

Some quite high molecular weight (MW) compounds have been reported, the volatility of which is suspect; this is often due to the methodology used such as rolling glass beads over the skin and then heating them to a high temperature to desorb VOCs. Not all reported compounds may be endogenous. Also, some of the compounds might result from artefacts such as contamination, degradation or oxidation, which can occur during collection, storage or measurement.

A big advantage of our presentation is the inclusion of the CAS-numbers in table 1. By using the CAS-number, all the compounds are unambiguously defined. But even with CAS-numbers, one should be careful. For example, though the CAS-number 76-22-2 for mixed isomer (±)-camphor is different to the CAS-number 464-48-2 representing (–)-camphor, they both refer to almost identical compounds. The two 'different' compounds can easily slip attention, when one just works with spectral libraries. One should, in particular, be attentive when the identification by spectral library results in an optically active compound (such as (–)-camphor). For proper identification of an optically active compound one would have to use a chiral GC-column, which has rarely been used in human VOC analysis up to now.

The table columns in this review represent the summation of what has been reported in the available literature. If the differences between studies are to be observed, the original source publications can be used. However, the focus on this work is to collate all the compounds reported.

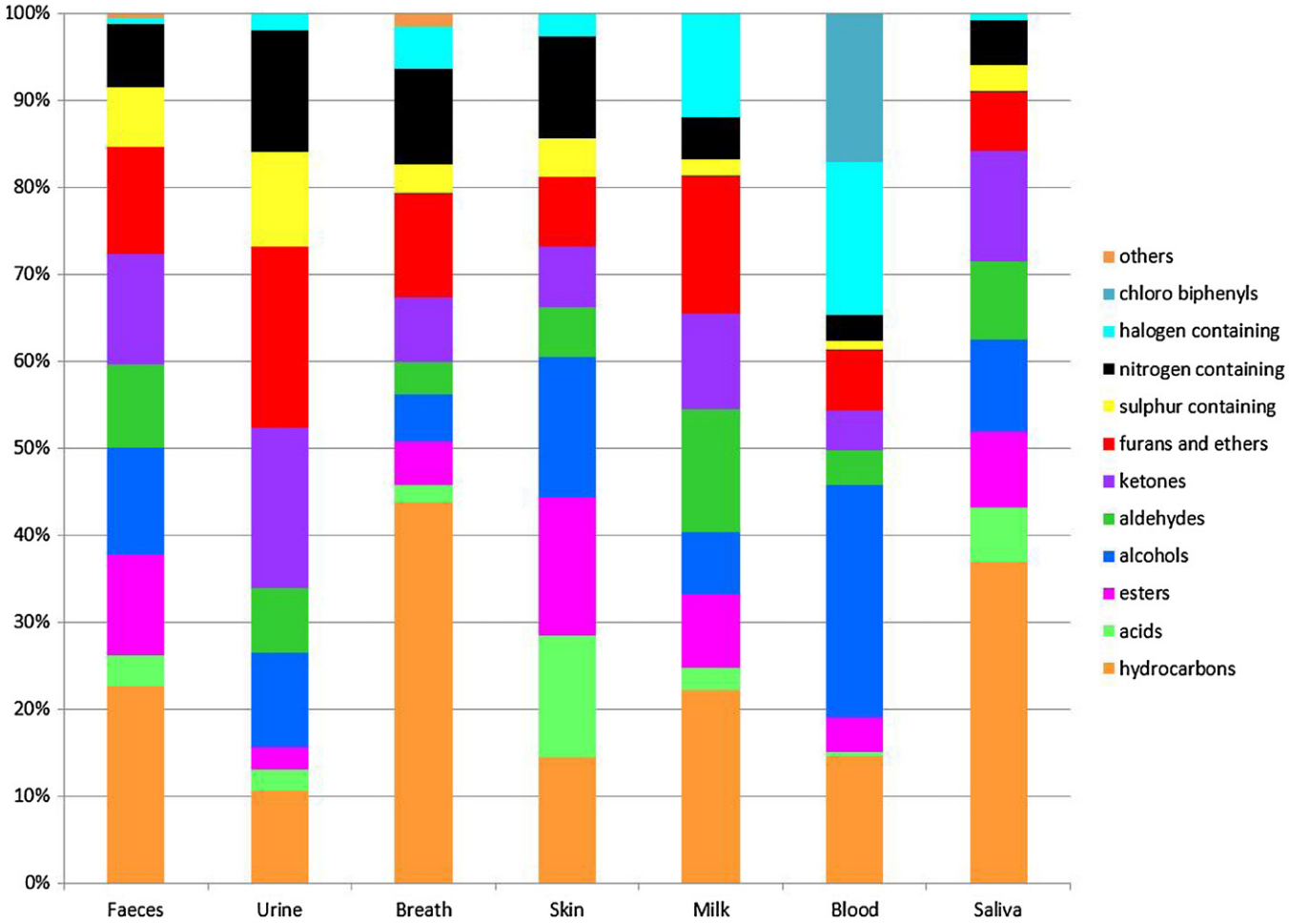

Figure 2. The relative numbers of compounds in each class that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva. (Based on number of different compounds identified, not upon their relative concentrations.)

A comparison of the VOC compounds found in breath, saliva, blood, milk, skin secretions, urine and faeces

In total 1840 compounds have been identified as volatiles from apparently healthy humans and the number for each of the bodily fluids is breath (872), saliva (359), blood (154), milk (256), skin secretions (532), urine (279), and faeces (381); table 1 lists these compounds in alphabetical order.

Inspection of this table shows there are unexpectedly few compounds ubiquitous to all the bodily fluids and breath, just 12 (0.7%): acetaldehyde, 2-propanone (acetone), benzaldehyde, 1-butanol, 2-butanone, hexanal, heptanal, octanal, pentanol, benzene, styrene and toluene. Seven of these possess a carbonyl group and interestingly the first six of these have been reported in either 100% or high abundance in a large cohort/longitudinal study of faeces, and then with heptanal and octanal at 33 and 30% respectively [16]. The latter three compounds are smoking-derived substances [12] and, additionally, they are common pollutants in the environment, with benzene and alkyl benzenes, including toluene found to be at substantially high levels in urban areas in particular [17]. While a significant amount of toluene, 25–40%, is exhaled unchanged via the lungs, a greater proportion is metabolized and excreted via other pathways. The primary route of toluene metabolism is by hydroxylation to benzyl alcohol by members of the cytochrome P450 (CYP) family. It is believed that in humans, benzyl alcohol is metabolized to benzaldehyde by CYP [18].

Figure 2 describes the total classes of compounds and the relative numbers of compounds within a class found in each bodily fluid. Tables 2–12 are sub-tables of table 1 that list VOCs identified in bodily fluids according to their chemical class.

Table 2 describes all the nitrogen containing compounds (totalling 223, as the sum from all bodily fluids), of which there are a very diverse range of aliphatic, aromatic and heterocyclic compounds e.g. amines, amides, cyanides, thiocyanates, anilines and cyclic compounds such as pyrroles, imidazoles, indoles, pyrazines as well as mixed heterocyclic compounds. The order in terms of the abundance of nitrogen containing compounds was breath > skin secretions > urine > faeces > saliva > milk > blood, with 106 compounds found in breath and only 7 reported in blood. A comparison of breath with faeces, urine, skin secretions, blood and saliva showed there were 16, 8, 16 and 7 compounds respectively in common. These five sources would be the most likely source for breath volatiles, therefore there is a substantial shortfall in compounds

Table 2. Table showing all the nitrogen containing volatiles reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans (alphabetical listing). Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
60-35-5	Acetamide	F		Br				
75-05-8	Acetonitrile	F		Br			Bl	Sa
36357-38-7	5-Acetyl-2-methylpyridine	F						
85213-22-5	2-Acetyl-1-pyrroline		U					
ui	Aliphatic amine ui				Sk			
3167-49-5	6-Amino-3-pyridine carboxylic acid				Sk			
7664-41-7	Ammonia	F[B]	U[C]	Br			Bl	
613-89-8	2-Aminoacetophenone					M		
62-53-3	Aniline					M		
105-60-2	1-Aza-2-cycloheptanone			Br				
4025-37-0	2-(Aziridin-1-yl)-ethanamine	F						
7782-79-8	Azoimide			Br				

Table 3. Table showing all the sulphur-containing volatiles reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans (alphabetical listing). Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
34277-65-1	Acetylthiocarbamic acid, methyl ester				Sk			
870-23-5	Allyl mercaptan		U					Sa
2179-58-0	Allyl methyldisulfide		U					
10152-76-8	Allyl methylsulfide		U	Br				Sa
5925-74-6	Benzene ethanethioic acid, *S*-methyl ester	F						
95-16-9	1,3-Benzothiazole			Br	Sk			
2432-51-1	Butane thioic acid, S-methyl ester	F						
56484-52-7	o-2-(Butenylthio)phenol				Sk			
3622-84-2	*N*-Butyl-benzenesulfonamide	F						
592-82-5	Butylisothiocyanate		U					
75-15-0	Carbon disulphide	F	U	Br	Sk	M		
463-58-1	Carbonyl sulphide			Br		M		

Notes. ui: unidentifed isomer; na no CAS-number available; A: very unlikely reacts with water.

Table 4. Table showing all the ether volatiles (including furans) reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Alkyl /alkenyl ethers							
115-10-6	Dimethyl ether	F		Br		M		
540-67-0	1-Methoxyethane			Br				
1634-04-4	Methyl tert-butyl ether			Br		M	Bl	
626-91-5	1-Methoxy-3-methylbutane			Br				
4747-07-3	1-Methoxyhexane				Sk			
2161-90-2	1,3-Cyclohexadien-1-yl methyl ether			Br				
60-29-7	Diethyl ether	F		Br			Bl	
625-54-7	2-Ethoxypropane			Br				
108-20-3	Diisopropylether		U				Bl	
3424-89-3	Propenyl propyl ether			Br				
637-92-3	Ethyl tert-butyl ether			Br				
142-96-1	Di-n-butyl ether	F						

Notes. ui: unidentifed isomer.

and there has to be another source of nitrogen containing volatiles in breath e.g. the lungs themselves, nasal cavity etc or there are a substantial number of compounds awaiting discovery in bodily fluids which contribute to breath nitrogen volatiles. The detection methods in breath analyses may also be implicated in these differences.

Table 3 describes all the sulphur containing compounds (totalling 86, as the sum from all bodily fluids) and includes alkyl sulphides, including thiols, hydrogen sulphide, thioesters, and cyclic compounds such as thiazoles and thiophenes. The order of abundance was urine > breath > faeces > skin secretions > saliva > milk > blood. The first four are in a different order to the nitrogen containing compounds and also all the bodily fluids were reported to have lower numbers of sulphur compounds relative to nitrogen compounds. Although it might be considered that many compounds in breath arise from faeces, only 11 sulphur compounds were found in both breath and faeces. Another ten

Table 5a. Table showing the straight chain alkanes reported in the literature that have been detected in the healthy human body. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
74-82-8	Methane	F[D]		Br				
74-84-0	Ethane			Br				
74-98-6	Propane			Br		M	Bl	Sa
106-97-8	Butane			Br		M[1]	Bl	
109-66-0	Pentane	F		Br		M[1]	Bl	
110-54-3	Hexane	F	U	Br	Sk	M[1]	Bl	Sa
142-82-5	Heptane			Br	Sk	M[1]	Bl	Sa
111-65-9	Octane	F		Br	Sk	M[1]		Sa
111-84-2	Nonane			Br	Sk	M[1]		Sa
124-18-5	Decane	F		Br	Sk	M[1]		Sa
1120-21-4	Undecane	F		Br	Sk	M[1]		Sa
112-40-3	Dodecane	F		Br	Sk	M		Sa

D: in flatus; 1: isomer not actually specified in paper.

Table 5b. Table showing the branched chain alkanes reported in the literature that have been detected in the healthy human body. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
75-28-5	2-Methylpropane			Br				
78-78-4	2-Methylbutane			Br				
75-83-2	2,2-Dimethylbutane			Br				
79-29-8	2,3-Dimethylbutane			Br				
464-06-2	2,2,3-Trimethylbutane	F						
594-82-1	2,2,3,3-Tetramethylbutane			Br				
107-83-5	2-Methylpentane	F		Br			Bl	Sa
96-14-0	3-Methylpentane	F		Br			Bl	Sa
590-35-2	2,2-Dimethylpentane			Br				
565-59-3	2,3-Dimethylpentane			Br				
108-08-7	2,4-Dimethylpentane			Br				
562-49-2	3,3-Dimethylpentane			Br				

Table 5c. Table showing the non-cyclic alkenes (single double bond) reported in the literature that have been detected in the healthy human body. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
74-85-1	Ethene			Br				
115-07-1	Propene	F		Br		M	Bl	
25167-67-3	Butene ui					M		
106-98-9	1-Butene	F		Br				
107-01-7	2-Butene			Br[2]				
25377-72-4	Pentene ui				Sk	M		
109-67-1	1-Pentene			Br				
109-68-2	2-Pentene			Br[2]				
25264-93-1	Hexene ui					M		
592-41-6	1-Hexene			Br				
592-43-8	2-Hexene			Br[2]				
592-47-2	3-Hexene			Br				

ui: unspecified isomer; 2: for more information on stereoisomer(s) see entry in table 1.

sulphur compounds were found in breath which have not been reported in any other bodily fluids.

Table 4 describes the large number of ether compounds (totalling 144, as the sum from all bodily fluids). The ether compounds include both aliphatic, aromatic and cyclic ethers and furans were also included in this section. There were a large number of simple furans, alkyl subsituted furans and other derivatives, (totalling 47, as the sum from all bodily fluids), with more found in breath than the other bodily fluids, although they were well represented in these other fluids. Many of them, especially mono-, di- and trimethylated furans are strongly related to smoking [12], while the source of the remaining furans is not clear to the authors. Furans were the largest group, followed by methoxy ethers with 43 identified in the bodily fluids. The origin of many methoxy esters is not certain, however the liver is capable of methylation to biosynthesize

Table 5d. Table showing the non-cyclic alkenes (multiple double bonds) reported in the literature that have been detected in the healthy human body. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Dienes							
463-49-0	1,2-Propadiene			Br				
78-79-5	Isoprene			Br		M	Bl	
590-19-2	1,2-Butadiene			Br				
106-99-0	1,3-Butadiene			Br				
591-95-7	1,2-Pentadiene			Br				
504-60-9	1,3-Pentadiene	F		Br[2]				
591-93-5	1,4-Pentadiene	F		Br				
592-48-3	1,3-Hexadiene			Br[2]				
592-45-0	1,4-Hexadiene			Br[2]				
592-46-1	2,4-Hexadiene			Br[2]				
1541-23-7	1,5-Heptadiene			Br				
39491-65-1 and/or 3710-30-3	1,3-Octadiene							Sa[2]

ui: unspecified isomer; 2: for more information on stereoisomer(s) see entry in table 1.

Table 5e. Table showing the alkynes reported in the literature that have been detected in the healthy human body. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
74-99-7	1-Propyne			Br				
107-00-6	1-Butyne			Br				
503-17-3	2-Butyne			Br				
689-97-4	1-Buten-3-yne			Br				
26856-36-0	Pentyne ui					M		
627-21-4	Pent-2-yne/1-ethyl-2-methylacetylene			Br				
1574-40-9	3-Penten-1-yne, (*Z*)-			Br				
2004-69-5	3-Penten-1-yne, (*E*)-			Br				
2206-23-7	2-Penten-4-yne			Br				
26856-30-4	Hexyne ui					M		
26856-31-5	Heptyne ui					M		
628-71-7	1-Heptyne			Br				

Table 5f. Table showing the benzyl and phenyl hydrocarbons reported in the literature that have been detected in the healthy human body. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
71-43-2	Benzene	F	U	Br	Sk	M	Bl	Sa
108-88-3	Toluene	F	U	Br	Sk	M	Bl	Sa
106-42-3	*p*-Xylene	F		Br	Sk	M	Bl	Sa
108-38-3	*m*-Xylene	F		Br		M	Bl	
95-47-6	o-Xylene	F		Br		M	Bl	Sa
1330-20-7	Xylene ui		U			M	Bl	
108-67-8	1,3,5-Trimethylbenzene			Br				
526-73-8	1,2,3-Trimethylbenzene	F		Br		M		
95-63-6	1,2,4-Trimethylbenzene			Br		M		
488-23-3	1,2,3,4-Tetramethylbenzene			Br				
527-53-7	1,2,3,5-Tetramethylbenzene			Br				
95-93-2	1,2,4,5-Tetramethylbenzene		U	Br				

ethers, for instance the synthesis of methoxyphenol from phenol. There were 36 ether compounds in breath which were not present in any of the other bodily fluids, how these arose in breath will not be speculated on here. That said, perhaps it is not widely known, the lungs themselves are capable of significant chemical transformations and are more capable of O-methylation than the liver. For example the relative conversion ratios for phenol are quoted as: liver 100, kidney 48, small intestine 3, testis 6, spleen 22, lung 110, heart 0, adrenal 13, brain 3, and muscle 3 [19].

Hydrocarbons represented the largest number of VOCs from bodily fluids (totalling over 600, as the sum from all bodily fluids). Although this review focuses on presence/absence of compounds, it is interesting to observe that isoprene has been reported to be present in the highest concentration in the human body [20]. The hydrocarbons have

Table 5g. Table showing the non-aromatic cyclic hydrocarbons reported in the literature that have been detected in the healthy human body. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
75-19-4	Cyclopropane	F		Br				
18631-83-9	Ethylidenecyclopropane	F						
74685-56-6	2-(Methylenebutyl)-cyclopropane							Sa
287-23-0	Cyclobutane	F		Br				
52097-85-5	2-Propenylidene-cyclobutene	F						
	Cyclopentanes							
287-92-3	Cyclopentane	F		Br		M		
96-37-7	Methylcyclopentane			Br		M	Bl	Sa
1528-30-9	Methylenecyclopentane			Br				
41158-41-2	1-Methyl-2-methylenecyclopentane			Br				
1638-26-2	1,1-Dimethylcyclopentane			Br				
822-50-4 and 1192-18-3	1,2-Dimethylcyclopentane			Br[2]				

Table 5h. Table showing the hydrocarbons (including polycyclics) reported in the literature that have been detected in the healthy human body and not included in tables 5a–5g. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
ui	Sesquiterpene ui				Sk			
ui	Methyl decalin					M		
5208-58-2	Alpha-bourbonene							Sa
5208-59-3	(–)-Beta-bourbonene							Sa
79-92-5	Camphene	F		Br		M		Sa
18968-24-6	Cis-carane							Sa
18968-23-5	Trans-carane							Sa
29050-33-7	(+)-4-Carene		U					
6753-98-6	Alpha-caryophyllene	F						
87-44-5	Caryophyllene/beta-caryophyllene	F			Sk	M		Sa
118-65-0	Isocaryophyllene							Sa
3856-25-5	Alpha-copaene	F						Sa

Table 6. Table showing all the alcohol volatiles (including hydroxy compounds) reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
67-56-1	Methanol	F		Br		M	Bl	
64-17-5	Ethanol	F	U	Br			Bl	Sa
71-23-8	1-Propanol	F	U	Br		M	Bl	Sa
67-63-0	2-Propanol	F	U	Br		M	Bl	Sa
71-36-3	1-Butanol	F	U	Br	Sk	M	Bl	Sa
78-92-2	2-Butanol	F		Br	Sk		Bl	Sa
71-41-0	Pentanol	F	U	Br	Sk	M	Bl	Sa
6032-29-7	2-Pentanol	F						
584-02-1	3-Pentanol	F						
111-27-3	1-Hexanol	F	U		Sk			Sa
626-93-7	2-Hexanol				Sk			
623-37-0	3-Hexanol				Sk			Sa

Notes. ui: unidentifed isomer; na: no CAS-number available.

been grouped in table 5 into the following eight sub-divisions: table 5a (alkanes), table 5b (branched alkanes), table 5c (alkenes and branched alkenes), table 5d (dienes, branched dienes, trienes, tetraenes etc.) table 5e (alkynes), table 5f (benzenoid), table 5g (cyclic non-aromatic) and table 5h (others e.g. polycyclic).

Table 5a clearly shows a whole homologous series of straight chain compounds from methane to dodecane has been observed in breath, and to a significant degree with other bodily fluids with the notable exception of urine, with only two compounds reported. In fact, if the numbers of branched chain alkanes and straight chain compounds are considered, then urine contains only 3 compounds compared to 106 in breath and 28 in faeces. This paucity of compounds in urine versus the other fluids is curious and we can offer no plausible explanation. The gaps in the homologous series of the other fluids may just represent the lack of research in hydrocarbon detection. This must be the case for the lack of reports of

Table 7. Table showing all the aldehyde volatiles reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Aliphatic							
50-00-0	Formaldehyde			Br	Sk			
75-07-0	Acetaldehyde	F	U	Br	Sk	M	Bl	Sa
123-38-6	Propanal	F	U	Br	Sk			Sa
123-72-8	Butanal	F		Br	Sk	M		
110-62-3	Pentanal	F	U	Br	Sk	M		Sa
66-25-1	Hexanal	F	U	Br	Sk	M	Bl	Sa
111-71-7	Heptanal	F	U	Br	Sk	M	Bl	Sa
124-13-0	Octanal	F	U	Br	Sk	M	Bl	Sa
124-19-6	Nonanal	F	U	Br	Sk	M		Sa
112-31-2	Decanal	F		Br	Sk	M		Sa
112-44-7	Undecanal	F		Br	Sk	M		Sa
112-54-9	Dodecanal	F			Sk	M		Sa

Table 8a. Table showing all the primary aliphatic acid volatiles reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
64-18-6	Methanoic acid	F	U		Sk		Bl	
64-19-7	Acetic acid	F	U	Br	Sk	M		Sa
79-09-4	Propanoic acid/propionic acid	F		Br	Sk			Sa
107-92-6	Butanoic acid/butyric acid	F	U	Br	Sk	M[ui]		Sa
109-52-4	Pentanoic acid	F		Br	Sk[ui]	M		Sa
142-62-1	Hexanoic acid/capric acid	F		Br	Sk			
111-14-8	Heptanoic acid	F		Br	Sk			
124-07-2	Octanoic acid	F		Br	Sk	M		
112-05-0	Nonanoic acid		U	Br	Sk	M		Sa
334-48-5	Decanoic acid				Sk	M		
112-37-8	Undecanoic acid				Sk	M		
143-07-7	Dodecanoic acid				Sk	M		Sa

Table 8b. Table showing all the branched aliphatic acid volatiles reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
79-31-2	2-Methylpropanoic acid	F		Br				Sa
116-53-0	2-Methylbutanoic acid	F	U					
503-74-2	3-Methylbutanoic acid	F		Br	Sk			
35915-22-1	Methylbutanoic acid ui					M		
105-43-1	3-Methylpentanoic acid				Sk			
646-07-1	4-Methylpentanoic acid	F		Br				
4536-23-6	2-Methylhexanoic acid				Sk			
3780-58-3	3-Methylhexanoic acid				Sk			
1188-02-9	2-Methylheptanoic acid				Sk			
3004-93-1	2-Methyloctanoic acid				Sk			
54947-74-9	4-Methyloctanoic acid				Sk			
24323-21-5	2-Methylnonanoic acid				Sk			
24323-23-7	2-Methyldecanoic acid				Sk			

methane in blood, as there are unambiguous reports of its detection in breath and faeces, so it must be present in blood presumably to get from the intestines to the lungs. It is not considered that the human body can produce methane while it has been long known that many micro-organisms, such as in the gut, can readily undertake this [21].

Branched hydrocarbons have been mainly reported in breath (table 5b), this may reflect the extensive research that has been undertaken into breath hydrocarbon analyses, likewise for the large number of unsaturated hydrocarbons (tables 5b–5e). Table 5c shows there are fifteen 1,3 dienes and seven 1,4 dienes across breath and the other bodily fluids, their origins (see breath section) probably arises from smoking either by the individual or by secondary (passive) smoking, although this is a review of healthy individuals, it should be recognized that smoking remains a common activity. A

Table 8c. Table showing all the unsaturated acid volatiles reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
79-10-7	2-Propenoic acid				Sk			
107-93-7	2-Butenoic acid				Sk			
626-98-2	2-Pentenoic acid			Br				
13201-46-2	2-Methyl-2-butenoic acid			Br	Sk			
3675-21-6	3-Methyl-2-pentenoic acid				Sk			
10321-71-8	4-Methyl-2-pentenoic acid			Br				
27960-21-0	(*E*)-3-Methyl-2-hexenoic acid				Sk			
54068-86-9	(*Z*)-3-Methyl-2-hexenoic acid				Sk			
18719-24-9	7-Octenoic acid			Br	Sk			
30801-91-3	(*E*)-3-Methyl-2-octenoic acid				Sk			
903503-35-5	(*E*)-4-Methyloct-3-enoic acid				Sk			
903503-34-4	(*Z*)-4-Methyloct-3-enoic acid				Sk			

Table 8d. Table showing all the carboxylic acid volatiles not included in tables 8a to 8c, reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
463-79-6	Carbonic acid							Sa
65-85-0	Benzoic acid	F	U	Br	Sk			
103-82-2	Phenylacetic acid				Sk	M		Sa
50-21-5	Lactic acid ui			Br	Sk			
300-85-6	3-Hydroxybutanoic acid/3-hydroxybutyric acid			Br				
10191-24-9	3-Hydroxyhexanoic acid				Sk			
58888-76-9	3-Hydroxy-3-methylhexanoic acid				Sk			
59866-91-0	3-Hydroxy-4-methylhexanoic acid				Sk			
17587-29-0	3-Hydroxyheptanoic acid				Sk			
160595-71-1	3-Hydroxy-3-methylheptanoic acid				Sk			
903503-32-2	3-Hydroxy-4-methylheptanoic acid				Sk			
14292-27-4	3-Hydroxyoctanoic acid				Sk			

Notes.ui: unidentifed isomer; na: no CAS-number available.

Table 9a. Table showing all the acetic acid esters reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
79-20-9	Acetic acid, methyl ester	F		Br				
141-78-6	Acetic acid, ethyl ester/ethyl acetate	F	U	Br		M	Bl	Sa
109-60-4	Acetic acid, propyl ester	F		Br				Sa
108-21-4	Acetic acid, isopropyl ester/isopropyl acetate			Br				Sa
123-86-4	Acetic acid, butyl ester	F		Br				
110-19-0	Acetic acid, isobutyl ester/isobutyl acetate			Br				
628-63-7	Acetic acid, pentyl ester	F						
626-38-0	Acetic acid, 1-methylbutyl ester/1-methylbutyl acetate			Br				
624-41-9	Acetic acid, 2-methylbutyl ester/2-methyl butyl acetate			Br				
123-92-2	Acetic acid, isopentyl ester/isopentyl acetate			Br				
142-92-7	Acetic acid, hexyl ester	F						
5921-82-4	Acetic acid, 1-methylhexyl ester/1-methylhexyl acetate				Sk			

comprehensive discussion of smoking-related compounds is given in Filipiak *et al* [12]. Certainly butadiene has been detected in tobacco smoke and oxidative stress due to smoking could cause increased lipid peroxidation resulting in diene formation. The alkynes are only represented in breath and milk, apart from one in urine, with no compounds in common. A large number of unsaturated fatty acids are eaten in the diet, which can be expected to produce many hydrocarbons via peroxidation and chain cleavage, such as pentane, heptane, octane and alkenes [22]. A range of mono-, di-, tri- and tetra-substituted aromatic hydrocarbons have been found, with large numbers (between 15 and 22 compounds) in the non-breath samples and 50 in breath. Table 5f represents the polycyclic compounds which were mostly present in faeces and saliva.

The total number of volatile alcohols found in all bodily fluids and breath was 225. The alcohols have been sub divided into straight chain, unsaturated (not cyclic or aromatic), diols and triols, alkoxy alcohols and others (table 6). The order of

Table 9b. Table showing all the other straight chain aliphatic acid esters reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Methanoic acid esters							
110-45-2	Methanoic acid, isopentyl ester					M		
112-23-2	Methanoic acid, heptyl ester	F						
107-31-3	Methanoic acid, methyl ester/methyl formate			Br				
109-94-4	Methanoic acid, ethyl ester/ethyl formate			Br			Bl	
110-74-7	Methanoic acid, 1-propyl ester/*n*-propyl formate			Br				
592-84-7	Methanoic acid, butyl ester	F						
638-49-3	Methanoic acid, isopentyl ester	F				M		
107-31-3	Methanoic acid, methyl ester/methyl formate			Br				
109-94-4	Methanoic acid, ethyl ester/ethyl formate			Br			Bl	
	Propanoic acid esters							
554-12-1	Propanoic acid, methyl ester	F		Br				
105-37-3	Propanoic acid, ethyl ester	F		Br				Sa
106-36-5	Propanoic acid, propyl ester	F		Br				
590-01-2	Propanoic acid, butyl ester	F						

Table 9c. Table showing branched and cyclic aliphatic acetic acid esters reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Branched aliphatic acid esters							
547-63-7	2-Methyl-propanoic acid, methyl ester	F						
97-62-1	2-Methylpropanoic acid, ethyl ester	F						
644-49-5	2-Methylpropanoic acid, propyl ester/*n*-propyl isobutyrate	F						Sa
2445-69-4	2-Methylpropanoic acid, 2-methylbutyl ester/2-methylbutyl 2-methylpropanoate			Br				
868-57-5	2-Methylbutanoic acid, methyl ester	F						
7452-79-1	2-Methylbutanoic acid, ethyl ester/2-methylbutyric acid, ethyl ester ui	F		Br				
37064-20-3	2-Methylbutanoic acid, propyl ester	F						
108-64-5	3-Methylbutanoic acid, ethyl ester/ethylisovalerate			Br				
109-19-3	3-Methylbutanoic acid, butyl ester	F						
7425-14-1	2-Ethylhexanoic acid, 2-ethylhexyl ester/2-ethylhexyl 2-ethylhexanoate				Sk			
5129-65-7	10-Methyldodecanoic acid, methyl ester				Sk			
213617-69-7	9-Methyltetradecanoic acid, methyl ester				Sk			

Table 9d. Table showing all the unsaturated and aromatic carboxylic acid esters reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Benzoic acid esters							
120-51-4	Benzoic acid benzyl alcohol ester/benzyl benzoate				Sk			
2915-72-2	Benzoic acid, dodecyl ester				Sk			
ui	Benzoic acid, dodecyl ester, branched				Sk			
29376-83-8	Benzoic acid, tridecyl ester				Sk			
70682-72-3	Benzoic acid, tetradecyl ester				Sk			
	Phthalic acid esters							
84-66-2	Phthalic acid, diethyl ester/diethyl phthalate/ 1,2-benzenedicarboxylic acid, diethyl ester			Br		M	Bl	
84-74-2	Phthalic acid, dibutyl ester/dibutyl phthalate					M		
117-81-7	Phthalic acid, di(2-ethylhexyl) ester/di(2-ethylhexyl) phthalate					M		
	Salicylic acid esters							
119-36-8	Salicylic acid, methyl ester/methylsalicylate	F	U					
118-56-9	Salicylic acid, homomethyl ester/homomethyl salicylate				Sk			

Table 9e. Table showing all the cyclic esters (including 2-furanones and lactones) reported in the literature that have been detected faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	2-Furanones and gamma lactones							
497-23-4	2(5H)-Furanone			Br				
96-48-0	Dihydro-2(3H)-furanone	F		Br				
22122-36-7	3-Methyl-2(5H)-furanone			Br	Sk			
591-11-7	4-Methyl-2(5H)-furanone			Br				
7475-92-5	3,4-Dimethyldihydrofuran-2,5-dione	F						
108-29-2	Dihydro-5-methyl-2(3H)-furanone/gamma valerolactone	F	U	Br		M		
695-06-7	Gamma-hexalactone	F	U					
105-21-5	Gamma-heptalactone				Sk			Sa
104-50-7	g-Octalactone/g-c8-lactone				Sk			
104-61-0	Gamma nonalactone/g-nonanolactone/gamma-c9-lactone		U		Sk	M		Sa
706-14-9	Gamma-decalactone/gamma-c10-lactone		U		Sk	M		
57084-17-0	Gamma-undecalactone		U		Sk			Sa

Table 9f. Table showing all the other esters and anhydrides not in tables 9a to 9e reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
616-38-6	Dimethylcarbonate			Br			Bl	
623-53-0	Ethylmethylcarbonate			Br				
108-24-7	Acetic anhydride	F		Br				
85-44-9	Phthalic anhydride/phthalolactone/2-benzofuran-1(3H)-one					M	Bl	
547-64-8	Lactic acid, methyl ester/methyl lactate				Sk			
687-47-8	Lactic acid, ethyl ester/ethyl (–)lactate				Sk			
300-85-6	3-Hydroxybutanoic acid/3-hydroxybutyric acid			Br				
6290-49-9	Methoxyacetic acid, methyl ester			Br				
959247-28-0	Methoxyacetic acid, dodecyl ester				Sk			
959263-00-4	Methoxyacetic acid, tetradecyl ester				Sk			
141-97-9	Acetoacetic acid, ethyl ester/ethyl acetotacetate/ ethyl-3-oxobutanoate						Bl	
763-69-9	3-Ethoxypropionic acid, ethyl ester			Br				

Notes. ui: unidentifed isomer; na: no CAS-number available.

Table 10a. Table showing all the straight chain aliphatic ketones reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
67-64-1	Acetone	F	U	Br	Sk	M	Bl	Sa
78-93-3	2-Butanone	F	U	Br	Sk	M	Bl	Sa
107-87-9	2-Pentanone	F	U	Br	Sk	M		Sa
591-78-6	2-Hexanone	F	U	Br	Sk			
110-43-0	2-Heptanone	F	U	Br		M		Sa
111-13-7	2-Octanone	F	U	Br				Sa
821-55-6	2-Nonanone	F	U	Br	Sk	M		Sa
693-54-9	2-Decanone	F			Sk	M		Sa
112-12-9	2-Undecanone	F			Sk	M		Sa
6175-49-1	2-Dodecanone	F			Sk			Sa
593-08-8	2-Tridecanone				Sk	M		Sa
2345-28-0	2-Pentadecanone				Sk			Sa

abundance for all the alcohols was skin secretions > breath > blood > faeces > saliva > urine > milk. The straight chain primary alcohols showed clear trends with homologous series present although with some gaps. Faeces for instance shows alcohols from methanol to tridecanol with only one gap for undecanol. Certainly alcohols can be made in the gastro-intestinal tract e.g. via the reduction of the respective acid [16], and other sources of alcohols could be via pyruvate and citrate metabolism and glycolysis [23]. The liver is also capable of alcohol synthesis and these routes would be likely sources for alcohols in the other fluids and breath, therefore it is likely that in the future the additional alcohols to fill the gaps in the homologous series will be identified. For all fluids and

Table 10b. Table showing all the branched chain and cyclic aliphatic ketones reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Branched aliphatic							
563-80-4	3-Methyl-2-butanone		U	Br				
75-97-8	3,3-Dimethyl-2-butanone		U					
63072-44-6	Methyl pentanone ui					M		
108-10-1	4-Methyl-2-pentanone	F	U	Br	Sk		Bl	Sa
565-61-7	3-Methyl-2-pentanone	F	U	Br				
565-69-5	2-Methyl-3-pentanone	F	U					
564-04-5	2,2-Dimethyl-3-pentanone		U					
565-80-0	2,4-Dimethyl-3-pentanone	F						Sa
2550-21-2	3-Methyl-2-hexanone		U	Br				
105-42-0	4-Methyl-2-hexanone			Br				
110-12-3	5-Methyl-2-hexanone	F						Sa
7379-12-6	2-Methyl-3-hexanone					M		Sa

Table 10c. Table showing all the di-ketones reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
78-98-8	1,2-Propanedione			Br				
431-03-8	2,3-Butanedione	F	U	Br		M		Sa
600-14-6	2,3-Pentanedione	F	U			M		Sa
3848-24-6	2,3-Hexanedione	F						Sa
110-13-4	2,5-Hexandione			Br	Sk			
4437-51-8	3,4-Hexanedione	F						
96-04-8	2,3-Heptanedione	F						Sa
585-25-1	2,3-Octanedione							Sa
3214-41-3	2,5-Octanedione						Bl	
13757-90-9	6,7-Dodecanedione						Bl	
3002-23-1	6-Methyl-2,4-heptanedione	F						
1670-46-8	2-Acetylcyclopentanone			Br				

Table 10d. Table showing all the unsaturated ketones reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
78-94-4	3-Buten-2-one /methyl vinyl ketone			Br		M		Sa
814-78-8	3-Methyl-3-buten-2-one		U	Br				Sa
625-33-2	3-Penten-2-one	F	U	Br		M		Sa
1629-58-9	1-Penten-3-one			Br				Sa
141-79-7	4-Methyl-3-penten-2-one	F	U	Br				
25044-01-3	2-Methyl-1-penten-3-one	F						
565-62-8	3-Methyl-2-penten-4-one			Br				
109-49-9	1-Hexen-5-one			Br				
1629-60-3	1-Hexene-3-one					M		
2497-21-4	4-Hexen-3-one	F		Br				
763-93-9	3-Hexen-2-one			Br				
10575-41-4	4-Hexyn-3-one			Br				

breath, short chain alcohols were very common up to pentanol. Secondary alcohols were considerably less common.

The total number of volatile aldehydes found in all bodily fluids and breath was 103. The aldehydes have been divided into straight chain aliphatic, branched, unsaturated and others (table 7). The order of abundance was skin secretions>faeces>milk>breath>saliva >urine>blood. The straight chain aldehydes showed clear trends of homologous series, particularly for faeces where all the aldehydes from ethanal (acetaldehyde) to hexadecanal were found. As with the alcohols, the short chain aldehydes were very common for all the bodily fluids, except for methanal (formaldehyde), which was only reported in breath. Inspection of table 7 was undertaken which showed that 26 compounds were in breath and also in either faeces, urine, skin secretions or saliva. However, ten aldehydes were only observed in breath, which either means their origin is from some other source or they simply have not yet been observed in bodily fluids. The series of eight alkenals from 2-propenal to 2-decenal are found in one or more of the bodily fluids and breath. Lipid

Table 10e. Table showing other ketones not included in tables 10a to 10d, reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
89975-71-3	4-Propoxy-2-butanone			Br				
33330-50-6	4-Ethoxy-2-pentanone		U					
116-09-6	1-Hydroxy-2-propanone	F		Br				
1075-06-5	2,2-Dihydroxy-1-phenylethanone	F						
513-86-0	3-Hydroxy-2-butanone	F		Br				Sa
21856-89-3	6-Hydroxy-hexan-2-one				Sk			
99-93-4	1-(4-Hydroxyphenyl)ethanone			Br				
3188-00-9	2-Methyltetrahydrofuran-3-one		U					
4225-42-7	2-Methoxy-6-methyl-(4H)-pyran-4-one				Sk			
28564-83-2	2,3-Dihydro-3,5-dihydroxy-6-methyl-(4H)-pyran-4-one				Sk			
36357-38-7	5-Acetyl-2-methylpyridine	F						
4620-54-6	1-Phenyl-3-(1-piperidinyl)-2-buten-1-one				Sk			

Notes. ui: unidentifed isomer; na: no CAS-number available.

Table 11a. Table showing all the halogen containing volatiles reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. The chlorinated biphenyls analysed in blood samples have been listed separately in table 11b. Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
	Chloro							
74-87-3	Chloromethane			Br		M		
75-09-2	Methylene chloride/dichloromethane	F	U	Br		M	Bl	Sa
67-66-3	Chloroform	F	U	Br		M	Bl	
56-23-5	Carbon tetrachloride			Br		M	Bl	
75-00-3	Chloroethane					M		
75-34-3	1,1-Dichloroethane						Bl	
107-06-2	1,2-Dichloroethane			Br			Bl	
71-55-6	1,1,1-Trichloroethane					M	Bl	
79-00-5	1,1,2-Trichlorethane						Bl	
79-34-5	Tetrachloroethane/1,1,2,2-tetrachloroethane		U				Bl	
127-18-4	Tetrachloroethylene		U	Br		M	Bl	Sa
79-01-6	1,1,2-Trichloroethene/Algylen			Br		M	Bl	

Notes. ui: unidentifed isomer; na: no CAS-number available.

Table 11b. List of chlorinated biphenyls that have been reported in blood (none of list reported in breath, faeces, milk, skin secretions, saliva and urine). Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

4,4′-Dihydroxy-2,2′,3,3′,5,5′,6-heptachlorobiphenyl
4,3′-Dihydroxy-2,2′,3,4′,5,5′,6-heptachlorobiphenyl
4,4′-Dihydroxy-2,2′,3,3′,5,5′,6,6′-octachlorobiphenyl
3′4-Dihydroxy-2,2′,3,4′,5-pentachlorobiphenyl
2′,4-Dihydroxy-2,3,3′,4′,5-pentachlorobiphenyl
3-Hydroxy-2,2′,3′,4,4′,6,6′-heptachlorobiphenyl
3-Hydroxy-2,2′,3′,4,4′,5′,6-heptachlorobiphenyl
3-Hydroxy-2,2′,3′,4,4′,5,6′-heptachlorobiphenyl
3-Hydroxy-2,2′,3′,4,4′,5,5′-heptachlorobiphenyl
4-Hydroxy-2,3,3′,4′,5,5′,6-heptachlorobiphenyl
4-Hydroxy-2,2′,3,3′,4′,5,5′-heptachlorobiphenyl
4-Hydroxy-2,2′,3,3′,4′,5,6′-heptachlorobiphenyl

oxidation of unsaturated and polyunsaturated acids is known to produce 2-alkenals as well as dienals, such as 2,4-heptadienal, which has also been found in volatiles from milk. Many of the alkenals have been reported solely in milk. Given that milk might be expected to include unsaturated fatty acids, a lipid mediated oxidation of the double bond(s) route to their synthesis would seem likely [24]. To support this statement, it has been reported that 23 different aldehydes in milk can be produced by oxidative degradation of oleic, linoleic and linolenic acid [25] with heptenal from 11,15-octadecadienoic acid.

The total number of volatile acids found in all bodily fluids and breath was 102. The acids have been divided into primary acids, branched aliphatics, unsaturated and others (tables 8a, 8b, 8c and 8d respectively). Phenols, although very weak acids, have not been included in this group (see alcohols). The complete homologous series of acids from methanoic to octanoic acid have been found in faeces and from methanoic to octadecanoic acid in skin secretions, with gaps in the series for the other bodily fluids (table 8a). For reasons shown below, it would be expected that the gaps between urine and faeces will be filled with future investigations. Skin secretions and saliva have been shown to have acids up as far as octadecanoic acid. Skin secretions had the most straight chain acids, followed by saliva > breath > faeces > milk > urine > blood. The gastrointestinal tract is a major source of short chain fatty acids.

Of the 27 branched acids found in total (table 8b) 23 were identified in skin secretions with a complete homologous

Table 12. Table showing all other compounds not listed in tables 2 to 11 reported in the literature that have been detected in faeces, urine, breath, skin secretions, milk, blood and saliva from healthy humans. The compounds hydrogen [54], hydrogen peroxide, carbon monoxide and carbon dioxide are of great importance. Dimethylselenide is an interesting selenium-containing compound observed in breath (cf. refs. [234, 235]). Only a portion of this table is presented here; for the full version, see the online supplementary material available at stacks.iop.org/JBR/8/014001/mmedia.

CAS-number	Compound name	Faeces	Urine	Breath	Skin	Milk	Blood	Saliva
1333-74-0	Hydrogen	F^D		Br				
7722-84-1	Hydrogen peroxide			Br				
630-8-0	Carbon monoxide			Br				
124-38-9	Carbon dioxide	F^D		Br				
593-79-3	Dimethylselenide			Br				
865-52-1	Tetramethylgermane			Br				

Notes. D: seen in flatus.

series from methylbutanoic to methylheptadecanoic acid. The acid which occurred most commonly in faeces, urine, breath and skin secretions was 2-ethylhexanoic acid, a common contaminant derived from plasticizers (e.g. tubing or monovettes used for urine storage) [26, 27].

There may be as many as 32 volatile unsaturated acids (table 8c), mostly from skin secretions. Of the group, 'other carboxylic acids' (table 8d) of which there were 24 in total, 14 were interestingly 3-hydroxy acids. 3-hydroxybutyric acid can be produced in large amounts by the liver when metabolizing fatty acids [28]. however this and all the other 3-hydroxy acids were absent from all bodily fluids and breath except for skin secretions. Most of these 'other acids' were found solely from skin secretions, although benzoic acid was common to faeces, urine, breath and skin secretions.

Short-chain fatty acids (SCFAs) from methanoic to hexanoic acid have been reported as the chief end products of fermentation in the gut, principally from carbohydrates and amino acids. Separate studies of acid volatiles have produced different ratios of small chain fatty acids. This could be due to differing transit times; for instance long transit times can have a significant effect on bacterial metabolism, leading to more protein breakdown to amino acids [29] which in turn breakdown and affect the ratio of branched to straight chain acids. It is well known [29] that branched chain fatty acids such as 2-methylbutyric acid are formed during the catabolism of branched chain amino acids particularly valine, leucine and isoleucine. A study has also shown that blood in faeces will also affect this ratio due to breakdown of haemoglobin [30].

Carbohydrate availability can also affect the acids, carbon limited fermentation produces more formate [31]. Acetic acid, the main SCFA produced in the colon is readily absorbed through the colonic wall and transported to the liver, and acts as the primary substrate for cholesterol [32], it does not appear to have been detected as a VOC in blood, although it must be present. Other SCFAs are also rapidly absorbed into the bloodstream, it is considered that only 5–10% are excreted [32] and therefore these should also be found as VOCs in blood at some time. It has to be noted that butanoic acid and to a lesser extent propanoic acid are used as an important energy source by the gut wall and the amount of these acids reaching the blood stream may be very small.

The total number of volatile esters found in all bodily fluids and breath was 213. The esters have been divided into acetic acid esters (table 9a), other aliphatic acid esters, (table 9b), aromatic esters (table 9c), unsaturated acid esters (table 9d), cyclic esters (table 9e), and 'other esters' (table 9f). Acetate esters were by far the most abundant ester, 45 in total from all body fluids combined. Although acetic acid is the most commonly occuring gut acid, the gut only contributed to 13 of these esters, with breath as the major contributor. The 'other aliphatic acid ester section' table 9b, has esters from all acids from methanoic to octadecanoic acid as a complete homologous series, with faeces the major contributor of the lower MW esters and skin secretions for the higher MW esters. Table 9c showed that skin secretions had by far the majority of aromatic esters (17), with just two in faeces and one in blood and urine. Although table 9d shows that there were five unsaturated esters in breath, these were not reported in faeces or urine and the four unsaturated esters found in skin secretions were also not reported in urine, faeces and breath, so it is not possible to say that the breath esters arose from the other fluids.

The most notable feature of a comparison of VOCs found in urine and faeces is that many more compounds have been reported in faeces compared to urine. More compounds may exist in urine, but may simply be at too low a level to be measured, when compared to the concentrations found in faeces (table 1). The most prominent difference were the esters, which represent the largest class in faeces, with 55 compounds found compared to 18 compounds in urine. The extraction and sample treatment method has to be considered in the data analysis, hydrolysis of esters would certainly be expected as alkaline treatment of the sample was undertaken in one methodology. Almost certainly, the source of many urinary compounds is from the gut however in most cases there is no definitive published evidence. Some compounds are undoubtedly decreased in concentration from their journey from the gut to the bladder e.g. benzoic acid (which occurs naturally in most berries) is derivitized (in the liver) and excreted in urine as the less volatile hippuric acid (benzoylaminoethanoic acid). Although representatives of many chemical classes were found in the headspace of urine, in general shorter chain species were found in the headspace compared to faeces. Again this is likely to be due to their presence in lower concentrations. One of the most notable differences was for straight chain hydrocarbons, (table 5a), 15 compounds in faeces were reported, with only 2 compounds in urine. It could be the case that hydrocarbons were ingested and remained unchanged through the digestion

process, their low water solubility preventing their detection in urine. Hydrocarbons could also be produced as by-products of reactions involving reactive oxygen species.

Faeces have been shown to be capable of ester synthesis and the origin of the methyl through to hexyl esters of both acetic acid and propionic acid and methyl through to butyl esters of butanoic acids in faeces must be most likely due to the reaction of the respective alcohols with the respective carboxylic acid. Although there were a very large number of esters in faeces and a considerable number in breath, there were surprisingly few reported in blood and urine. The origin of breath esters is unlikely to be due to faecal matter producing esters which then reach the lungs through the blood stream as many esters reported in breath have not been reported in faeces, assuming comparable detection methods.

166 ketones were found in the sum of all the bodily fluids and breath. 15 straight chain methyl ketones (2-ketones) were found, with a complete homologous series from propanone (acetone) to nonan-2-one for faeces, urine and breath (table 10). These compounds were also well represented in skin secretions, milk and saliva. Acetone is well known to be produced from fatty acid breakdown and butan-2-one from carbohydrates. Methyl ketones are produced by many species of bacteria and can also be produced by fungi from carboxylic acids. Table 10b shows all the branched chain and cyclic aliphatic ketones reported in the literature, table 10c all the di-ketones, table 10d all the unsaturated ketones and table 10e shows the additional ketones not included in tables 10a to 10d.

Table 11a shows all the halogen containing volatiles reported in the literature that have been detected in blood, breath, faeces, milk, skin secretions, saliva and urine from healthy humans. The halides have been divided into single halide and mixed halide compounds, of the former, 58 chloride, 7 bromo and 3 iodo compounds were reported as well as 10 mixed halides. Many chlorinated fluorocarbons have been widely used as refrigerants, propellants (in aerosol applications), and solvents. Although many have been phased out, the presence of these and degradation products must be from the environment. Dibromochloromethane and bromodichloromethane also have environmental origins [33]. Methyl sulphonylchloride has been reported, this would seem very unlikely due to its reactivity with water. Table 11b additionally lists a large number of chlorinated biphenyls reported in blood. These would have low vapour pressure, but nevertheless efforts to detect these have been made due to their toxicity; they are man-made and their origins are as environmental pollutants.

Table 12 shows all other compounds not listed in tables 2 to 11a reported in the literature that have been detected in blood, breath, faeces, milk, skin secretions, saliva and urine from healthy humans.

It should be noted that a compound may appear in more than one of the tables 2 to 11a, as there are numerous examples of multifunctional compounds.

Volatile organic compounds in breath

Exhaled breath contains many different volatile compounds. Even though no definite list of such compounds has been published up to now, it has been stated that more than 1000 such compounds can be observed, even though not in each person [34]. Lists of compounds which have been observed in breath were published, e.g., by Manolis [35], Phillips *et al* [34, 36–41], by Ligor *et al* [42, 43], by Kischkel *et al* [44], by Rudnicka *et al* [45], by Bajtarevic *et al* [7] and by Filipiak *et al* [12]. Our literature search [12, 43, 45–48] and additional compounds communicated by Wojciech Filipiak [49] and by Jan Dallinga and Frederik-Jan van Schooten [50] revealed 872 named volatile compounds as being related to exhaled breath. From these compounds, 199 have been identified by spectral library match *and* by retention time. Hence these compounds can be considered to be identified with reasonable certainty. Many of the 872 named volatile compounds related to exhaled breath are *not* endogenously produced, and some compounds appeared only in a few individuals. The list given in table 1 is considered as a list for future discussion, and is certainly not comprehensive. Water, oxygen, nitrogen, argon and other rare gases are not listed in table 1.

For many of these compounds it is unknown if they are produced endogenously. Among the compounds which are listed as appearing in exhaled breath (see table 1), many are related to smoking. 29 dienes, 27 alkenes and 3 alkynes are mentioned as smoking-related [12]. Other examples are acetonitrile [7, 51, 52], and various furans and many specific dienes, such as 1,3-cyclohexadiene, 1,3-pentadiene, 1,4-pentadiene or 1,4-hexadiene [12]. This is not to say that these compounds arise only in smokers, but that they show higher concentrations in them.

Quite a number of volatile compounds may be related to food consumption or medication [53]. Some of the compounds are produced by bacteria in the gut, such as hydrogen H_2 [54] or methane CH_4 [55].

The most prominent volatile compounds are isoprene [56–59] and acetone [60–62]. Isoprene is a by-product of the mevalonate pathway, but also produced (or at least stored) in the periphery of the human body [63, 64]. Acetone can be formed from acetoacetate by acetoacetate-decarboxylase. In humans this conversion is the final step in the ketone-body pathway which supplies the body with a secondary source of energy.

Isoprene is ‘the’ paradigmatic example for a compound whose concentration in exhaled breath changes enormously during exertion of an effort [65–68]. If, for example, a volunteer starts to pedal on a stationary bicycle with 75W, the isoprene concentration increases by a factor 3–4 in end-tidal breath. Originally, it was thought that this increase is just due to an increase of cardiac output [69]. But the pioneering work of King *et al* [64–68] demonstrated, that the increase in cardiac output alone would not be able to lead to the observed pronounced increase in isoprene. This is particularly the case, since during moderate to vigorous exertion the alveolar ventilation also increases, generating a dilution effect and therefore a *decrease* of isoprene concentration in end-tidal breath. For the isoprene concentration in exhaled breath to increase, it is not even necessary to exert an effort. A few leg contractions or arm contractions suffice to increase the isoprene concentration in exhaled breath [63, 64, 66–68].

Apart from isoprene, also other compounds increase during exertion of an effort. Among these compounds are methylacetate, dimethylsulfide and 2-pentanone [67]. This is in contrast to the prediction of Farhi's equation [70], which would predict a decrease in concentration during effort. An example of a compound which follows Farhi's equation is butane [67].

The big advantage of exhaled breath, in comparison to blood, is the fact that it can be sampled as often as it is desirable. Breath can even be sampled and analysed in *real time*, down to breath-to-breath resolution. Breath analysis during sleep illustrates this most convincingly [65]. In measurements during sleep, isoprene and acetone display very different concentration characteristics. Both show (often) increasing concentrations during night. The isoprene concentration displays a very pronounced *peak structure*, which is due to movements of the body or changes in sleep stage. Acetone does not show such a peak structure but just a smooth increase.

Only a few volatile compounds in exhaled breath have been investigated in *real-time* measurements by PTR-MS [71–73], PTR-TOF-MS [74, 75], SIFT-MS [76–79], laser spectrometry or sensors [80–84]: among them are isoprene, acetone, 2-pentanone, dimethylsulfide, methyl acetate [67], eucalyptol [85], hydrogen, methane [21, 86], ethane [87, 88], carbon monoxide [89–93], carbon dioxide ($^{12}CO_2$ and $^{13}CO_2$ [94, 95]), nitric oxide (NO) [96–100] and water (H_2O and HDO [101, 102]). In the future, *real-time* measurements should be performed for all volatile compounds, giving rise to the possibility of modelling the flow of these compounds within the human body as well as their production and rate of metabolism. Also their connection to food consumption, smoking habits or medication would be very interesting.

A particular interest is on therapeutic monitoring of drugs. As an example, consider medication with valproate which is administered to avoid seizures in epileptic patients or in persons suffering from propionic acidemia [53]). Valproate is metabolized to 3-heptanone which can be observed in exhaled breath [53]. Since the concentration of 3-heptanone in normal healthy volunteers is <1 ppb, virtually all the 3-heptanone in exhaled breath can be attributed to metabolized valproate. Such metabolizations with release of volatile compounds may allow therapeutic monitoring in the future.

Compounds listed in table 1 as appearing in exhaled breath are not claimed to be endogenously produced. These compounds may have exogeneous sources [103–107], be produced through medication [53, 108] or be released by bacteria in the airways [13, 14], the oral cavity [109–114] or in the gut [21, 54]. The concentrations of volatile compounds in exhaled breath may depend on the sampling method [115–118] and on the specific Henry constant between blood and breath [48, 119, 120] which depends on haematocrit and other parameters. Here these methodological points are not discussed.

In the tables, compounds in exhaled breath have been considered from Statheropoulos *et al* [46] (15 persons), Ligor *et al* [43] (39 persons), Kischkel *et al* [47] (93 persons), Rudnicka *et al* [45] (23 persons), Mochalski *et al* [48] (28 persons) and from an extension of the list of compounds published in Filipiak *et al* [12] (115 persons). The available concentration ranges are not presented here. For a set of 67 compounds, the concentration ranges in exhaled breath (and in blood) are given in [48].

Volatile organic compounds in blood

Blood directly reflects the internal environment of the body, including nutritional, metabolic, and immune status [121]. Thus, the analysis of plasma-derived VOCs in blood has been an active area of research. However, obtaining blood samples is not trivial requiring trained phlebotomists, it is not well tolerated by patients in comparison to producing a breath or urine sample, and blood samples usually require pre-treatment which is costly and time consuming.

The numbers of volatiles identified in blood are relatively few compared to those identified in breath [48]. There certainly is not a lack of studies reporting the analysis of volatile compounds in blood. However, these studies tend to be focused on the monitoring of exposure to environmental pollutants [122] and the quantification of blood alcohol [123] and other inhalants derived from solvents [124]. There have been relatively few studies which compared the volatile profiles above blood in healthy volunteers versus a diseased group. Zlatkis *et al* [125] studied the sera of seemingly healthy individuals versus virus infected patients using capillary GC. Although example chromatograms were presented showing a large number of peaks for both groups, the identification of compounds was limited. It was found that virus infected patients had a wider range of VOCs associated with their samples. Recently there have been two studies which measured the blood volatiles of patients with liver [126] and lung cancer [127] versus healthy individuals. Horvath *et al* [128] described the results of a study where trained dogs could discriminate between blood samples from ovarian cancer patients and blood samples taken from patients with other gynaecological cancers or from healthy control subjects.

Much of the work relating to environmental exposure to pollutants centres around the National Health and Nutrition examination surveys (NHANES) which have been undertaken in the US [129]. These studies have aimed to quantify a range of common environmental pollutants in the blood of over 1000 volunteers. There have been a number of publications relating to the methods used and the results of these studies [130–133]. The studies tended to use purge and trap analysis combined with GCMS [131] but more recently they have adopted solid phase micro-extraction (SPME) based methods coupled to GCMS [130]. The data from NHANES is used to set expected limits for a range of VOCs in blood (usually in the ppb/ppt range) for non occupationally exposed individuals [129]. Most recently this data has been used comparatively in measuring the blood VOC levels of people living on the gulf coastline of the US who have been exposed to VOCs derived from the Deepwater Horizon oil spill [134]. There are commercial tests available [135] which give a measure of the volatile solvent profile in blood versus the NHANES data [129].

The high level of alcohol consumption in the US and Europe means that blood alcohol analysis is one of the

most common clinical analyses performed. Headspace gas chromatography is commonly used to determine blood alcohol levels. This method is convenient as it can be automated and biological products that can cause interference are not directly injected into the GC. A dedicated range of columns have been developed specifically for blood alcohol analysis and the analysis can be completed in 2 min [136]. Blood gas analysis usually involves the measurement of methanol, ethanol, isopropyl alcohol, 1-propanol, acetaldehyde and acetone. The analysis usually includes the use of an internal standard for example *t*-butyl alcohol (internal standard for the European blood alcohol analysis). However, many forensic laboratories are also interested in the measurement and quantification of an extended number of VOCs which may be derived from inhaling and ingesting dangerous and controlled substances [124]. Volatiles such as diethyl ether, butane, ethyl acetate, hexane, toluene, xylene, and some halogenated hydrocarbons are common VOCs with the potential for abuse via sniffing [137]. It may be particularly important to measure these compounds in blood samples taken at autopsy, if the death is suspicious [138]. These additional VOCs also have the potential to interfere with the blood alcohol analysis so their separation and measurement is important [136].

The measurement of ammonia in blood is also an established clinical test [139]. Many of the procedures for ammonia determination involve two general steps: the release of ammonia gas or capture of ammonium ions from the sample and the quantitation of the liberated gas or captured ions [140]. Detection is typically via colourimetric/fluorimetric methods [141], gas sensitive electrode [142] or enzymatic methods [143, 144]. Elevated levels of ammonia in blood is considered a strong indicator of an abnormality in nitrogen homeostasis, the most common reason is related to liver dysfunction. Hyperammonemia arises from excessive production by colonic bacteria and the small intestine. At high levels ammonia is a potent toxin of the central nervous system, and has been linked to hepatic encephalopathy (HE). However, ammonia determination is not currently accepted as a reliable marker of HE, although a large amount of data supports the role of hyperammonemia in the direct and indirect alterations of brain function underlying HE. A recent paper [145] describes the measurement of capillary blood (an equivalent to arterial blood) following an oral glutamine challenge. This method was more successful at identifying minimal HE than the use of capillary blood measurements alone.

Volatile organic compounds from skin secretions

The number of different compounds identified from human skin secretions is very large. Our literature search revealed 532 named volatile compounds analysed from skin secretions. Odour can be particular to an individual and distinguishable both by people and by canines [146]. Also skin is not homogeneous and the distribution of the different types of glands and bacterial flora across the body can be expected to lead to different VOC profiles. Even the odours of a single individual varies; with diet, emotional state, menstrual cycle, age, and many others factors [147, 148]. Studies of the secretions from the skin are particularly susceptible to interference from personal care products. Although experimental procedures attempt to minimize the presence of exogeneous compounds by asking subjects to refrain from use of such products apart from a designated soap for a time period before testing, some identified compounds are highly likely to come from exogeneous sources (as noted in [149, 150]).

Bernier *et al* reported hundreds of compounds spanning a wide range of classes, in a study attempting to identify candidate mosquito attracting compounds [4]. Samples were collected from the hands using glass beads and analysed by GCMS. Many of the compounds were relatively high MW species and it could be argued that some would be expected to have limited volatility at body temperature. The papers of Zeng *et al* list a number of C-6 to C-11 acids and in particular *E*-3-methylhex-2-enoic acid, as responsible for characteristic axillary (armpit) odours along with a large *n*-dodecanoic acid peak, lactones and alcohols found in solvent extraction of worn absorbant pads [151, 152]. Other studies also look specifically for odiferous axillary compounds. Natsch and Kuhn found a genetic contribution to odorant carboxylic acids [150] and Hasegawa *et al* found a difference between 'spicy' and 'sour' axillary odour and identified sulfanyl alcohols [153]. Another study analysed compounds on the forearm [149] by using ethanol and hexane extraction. However, relatively few compounds are common to these or other papers. The difficulty of identifying a set of volatile compounds characteristic of human sweat is exemplified in the paper of Penn *et al* looking at 'fingerprints' in human odour [154]. They used polydimethylsiloxane coated stirrer bars to collect axillary samples from 194 individuals over 10 weeks; 4941 separate GCMS peaks were found of which only 373 were consistent over time within an individual (118 were chemically identified). They report very few of the peaks as common to all samples. Only 38 compounds were found to be present in at least half the samples.

There are a few studies that attempt to collect the compounds that are volatile at body temperatures rather than by volatilization of collected skin secretions. Gallagher *et al* list a set of volatile compounds from the forearm, when collected using SPME fibres held above the arm compared with solvent extraction [149]. Haze *et al* identified straight chain hydrocarbons, alcohols, acids and aldehydes from headspace analysis of cloth worn on the back and found a link with 2-nonenal and ageing [155]. Zhang *et al* [156] identified 35 compounds predominantly alcohols, alkanes and aldehydes using SPME fibres to collect volatiles from the hand and forearm and found differences between the hot humid spring and cold dry winter. SPME-GCMS has also been used to study axillary odour [157] para-axillary and areola volatile compounds for possible mother–infant recognition chemicals [158]. Ruzsanyi *et al* [159] report aldehydes (e.g. 3-methyl-2-butenal, benzaldehyde, octanal, nonanal, decanal) and ketones (e.g. 6-methyl-5-en-2-one) In these papers, as well, there are very few named compounds that are common between studies.

Volatile organic compounds from saliva

The most comprehensive investigation on the analysis of VOCs in saliva was carried out recently by al Kateb *et al* [160]. They addressed the limited information about saliva organic compounds and reported a database of volatiles they identified by the HS-Trap GC/MS method and also included a review of the current literature. This was a longitudinal investigation in which the headspace volatiles of ten people were assessed over the period of ten days. They reported the presence of 317 compounds in their study and 166 identified from the literature.

The percentage composition of the volatiles detected were 41% for hydrocarbons, 13% for ketones and lactones, 10% aldehydes whereas aromatics and alcohols both represent 8%. The rest of the classes were <5% of all the volatiles detected. They found that the average number of compounds per subject over a ten day period was found to be relatively consistent although the actual composition of these volatiles was subject to a degree of daily variation. The article discussed many intrinsic and extrinsic factors that could give rise to a change in the salivary compositions. More emphasis was on how the salivary volatile composition can be influenced and affected by physiological and pathological factors and by the method of analysis.

There are limited studies on the analysis of VOCs in saliva. Larsson investigated headspace VOCs which were directly sampled with no enrichment from human breath and fresh saliva [161]. The volatiles were directly injected into a GC-FID. They reported the tentative presence of acetaldehyde, acetone, methanol and ethanol. Kostelc *et al* used dynamic headspace extraction using a Tenax trap combined with GCMS to study volatiles in saliva and reported the presence of 29 compounds which were attributed to diverse sources, e.g. air, drinking water, diet and cosmetic preparations [162]. Solvent extraction/derivitisation combined with GCMS was used by Lochner *et al* for the metabolic profiling of saliva [163]. This procedure was designed for the trace analysis of extracted and derivatized components in saliva. Twenty six compounds were reported in the saliva samples, mainly fatty acids and hydrocarbons. Solvent extraction/derivatisation combined with GCMS was also used by Alagendran *et al* to study salivary VOC's during the menstrual cycle [164]. They found 15 compounds to be associated with ovulation and menstrual cycles; these volatiles include acids, aldehydes, amines and alcohols. Penn *et al* and Soini *et al* used stir-bar extraction followed by GCMS to study VOCs in sweat, skin secretions and saliva and found 88 volatile compounds associated with saliva, including alcohols, aldehydes, ketones, carboxylic acids, esters, amines, amides, lactones and hydrocarbons [154, 165]. They associated the volatiles present to dietary, environmental and genetic factors.

Volatile organic compounds in milk

There are many papers on the nutritional composition of human milk (as an example see the review by Jenness 1979 [166]) and also on the presence of environmental chemicals (as an example see the review by LaKind [167]), but there is relatively little specifically relating to the volatile components. Most GCMS analytical studies appear to be directed at identifying the presence of a specific pollutant, medicinal substance or group of environmental compounds, in order to support research on chemical exposure to the nursing infant or using milk as a geographical pollutant indicator. A websearch revealed numerous potential papers on organochlorine pesticides, brominated diphenyl ethers, dioxins, polychlorinated biphenyls, parabens, triclosan, polycyclic musk fragrances, flavanoids and many others. However, not all these compounds can be considered as volatiles at body temperatures. Others studies look for compounds transferring to breast milk from mothers taking specific dietrary supplements, such as the search for odourous components from fish oil [168] or 1,8-cinneole metabolites after taking 1,8-cinneole capsules [169]. Studies looking for specific compounds after exposure to environmental contamination, medication, or dietrary supplementation have not been included in the tables.

The most extensive list of likely volatiles was given by Pellazari *et al* who identified 156 'purgable' compounds from maternal milk, in a study to evaluate the utility of using milk in pollutant studies [170]. A wide range of classes of compounds were identified by GCMS from passing helium gas through warm milk and trapping vapours on a Tenax cartridge. Similar classes of compounds were reported by Shimoda *et al* [24] using a diethyl ether distillation-extraction. Other studies have looked for specific organic compounds in the headspace above milk using SPME with GCMS (four VOCs [171], monocyclic aromatic amines [172], phthalate esters [173], and benzene and alkylbenzenes [17, 174]). A broader study, also using the SPME method, attempted to quantify 36 different VOCs [175] and identified 10 compounds whose median concentration across 12 samples was above the 'lowest recordable level'. Buettner has analysed the volatiles from milk and in one study identified 45 odour-active consituents, using olfactory GC in combination with GC-MS [176].

Volatile organic compounds in urine

The first major study of VOCs in urine was undertaken by Mills and Walker [177] using SPME in conjunction with GC–MS to investigate the VOCs identified in the headspace above urine. They reported 103 volatile compounds associated with urine and analysed urine from five patients with metabolic conditions.

A more recent review of volatiles from urine expanded on the numbers of compounds and also included data of volatiles from elderly, apparently healthy individuals [178]. The results of a review of six studies of the volatiles found in urine from apparently healthy individuals are described by Smith *et al* and updated herein (table 1). Nine compounds were present in all studies: propanone, 2-butanone, 2-pentanone, 2-heptanone, 3-hexanone, 4-heptanone, 2,5-dimethylfuran, 2-ethyl-5-methylfuran, toluene and so must be considered to be present with a very high degree of certainty. The source of some or all of these compounds may be the gut. A study [26] of 4-heptanone in urine strongly suggest its presence

originates at least in part from *in vivo* oxidation of the plasticizer component, 2-ethylhexanoic acid. For comparison, propanone, 2-butanone, 2-pentanone and 2-heptanone were also found ubiquitously in the headspace of faeces from a large number of samples donated from apparently healthy individuals, while a significant number of individuals were found to have 2,5-dimethylfuran, 2-ethyl-5-methylfuran, 3-hexanone and 4-heptanone [16].

The large number of ketones in urine probably at least partially arise from bacterial action in the gut, maybe by decarboxylation from the corresponding oxo-acids, since ketones were found at much lower concentrations in the urine of 'germ free' rats [177]. Levels of the key ketone bodies, propanone (acetone) and acetoacetate have been found to vary between 1.16–14 mol L^{-1} and 1.3–15 mmol L^{-1} respectively in urine [179]. The ketone bodies (acetoacetate, hydroxybutyrate, propanone) are produced in the liver during periods of rapid fat oxidation, when the rate of fat breakdown exceeds the capacity of the Krebs cycle to process the resulting acetyl CoA [180, 181]. Propanone can be produced by the non-enzymic decarboxylation of acetoacetate and may sometimes be smelt on the urine and breath in acute diabetics. In summary, (table 1) the volatiles in urine cover a range of chemical classes: acids, alcohols, ketones, aldehydes, amines, N-heterocycles, O-heterocycles, sulphur compounds and hydrocarbons. An insignificant number of esters have been reported. A large number of terpenes are described, and have been considered to be derived from foods [177]. Little data exist on quantitative measurements of VOCs in urine. Concentrations of phenol (typically 10 mg day^{-1} excreted in urine) and p-cresol (typically 52 mg day^{-1} excreted in urine) have been reported to increase in urine with increasing protein intake. Their formation is considered to be due to gut microflora acting on tyrosine; anaerobic bacteria in the left colon producing phenol and aerobic bacteria in the ileum/cecum producing p-cresol. The relationship is complicated by fibre intake. High fibre intake with high protein resulted in a smaller increase in concentration due to decreased transit time [182]. This study was motivated by phenols being implicated in bladder and colon cancer, which no longer is considered to be the case. Normal alcohol ranges emission rates reported are 0—46 mg/24 h for ethanol, 0–300 μg/24 h for n-propanol and 0–18 μg/24 h for *n*-butanol, these levels approximately mirror blood serum levels [183]. Trimethylamine and 4-heptanone, were quantified as 0.5 -20 μg ml^{-1} and 40–800 ng ml^{-1} respectively in urine [184].

The highest concentrations in a range of urinary volatile short chain fatty acids (and semi-volatile acids) were hippuric > glycolic > benzoic > ethanoic > 2-ketoglutaric > 2-hydroxyisovaleric > lactic, 2-hydroxyisobutyric > oxaloacetic > pyruvic acids, with propionic, isobutyric, butyric and 2-methylbutyric acids as minor components [185]. Interestingly there was poor correlation between urine and serum levels, with lactic > oleic > acetic > palmitic > 3-hydroxybutyric acids as the five most abundant acids in blood serum.

It has been suggested that methylamine and other short chain aliphatic amines may play a significant role in the central nervous system disturbances observed during hepatic and renal disease [186]. To this end a quantitative method was developed for methylamine determination in the gas phase from urine. The average output was 11 mg day^{-1} with a range of 1.7–62 mg day^{-1}, with diet having a small effect, the source was considered to be mainly endogenous. Gut bacteria are likely to be implicated in the production of methylamine (probably from creatinine) as rats with no gut bacteria produced less than half the output [186]. The average daily output for dimethylamine was about 17 mg with values for the majority of the population lying within the 0.68–35.72 mg range [187]. Healthy young adults excrete about 1 mg of trimethylamine and 40 mg of trimethylamine *N*-oxide daily, although these levels are markedly influenced by diet, particularly when it contains marine fish. When marine fish is a dietary component, several hundred mg of trimethylamine N-oxide may be excreted [188].

The volatiles in urine have recently been evaluated by combined odour and GCMS chemical analysis. For the first time a comprehensive description of the smell of the individual components has been described [189]. This work also involved enzymatic (glucuronidase) pretreatment followed by solvent extraction.

There are a very large number of compounds found in low concentrations in urine (table 1). The concentrations of most of these compounds are unknown; often the source is also not known and the effects on health are not well understood.

Volatile organic compounds from faeces

Very little is known about VOCs found in the gut and the diagnostic and health implications of most of these compounds remain to be explored. The first report of gas analysis from faeces was in 1861 when Ruge reported that human rectal gas contained hydrogen, carbon dioxide, and methane, in addition to other unidentified gases [190]. Flatus is considered to be a mixture of hydrogen (0–50%), nitrogen (5–90%), oxygen (0–10%), carbon dioxide (10–30%), and methane (0–10%). Methane production occurs in about 50% of the healthy population, some members producing higher levels than others; methane production is correlated with methanogenic bacteria. Similarly, sulfate-reducing bacteria are responsible for the generation of pungent sulfides [191].

Significant concentrations of a range of SCFAs [192], branched-chain fatty acids (BCFAs), indoles [193] and phenols [194] have been observed in faeces. Fermentation of carbohydrates in the gut produces ethanoic, propionic, butanoic, pentanoic, and hexanoic acids, particularly by *Bacteroides* [195]. *In vitro* studies [196] have provided evidence that proteinacious foods also produce SCFAs via the action of bacteria such as *Clostridia spp.*; BCFAs, such as 2-methylbutanoic acid and methylpropionic acids, are principally produced by gut microbial action on proteins via the respective branched amino acid. Volatiles such as methanethiol and ammonia are considered [197] to be derivable from methionine by the action of bacteria such as *Clostridium sporogenes*. Hydrogen sulfide and methanethiol can be damaging to the large intestinal epithelium and are also generated from sulphur-containing substances in the diet [198]. Similarly, fermentation of tyrosine and tryptophan in

faeces has been shown to produce the VOCs phenol and indole, respectively [197]. Phenol and *p*-cresol are considered to be produced by aerobic intestinal micro flora acting on tyrosine and the latter by anaerobic organisms [192].

The two most up to date studies stated that a total of 297 and 135 different VOCs have been identified respectively by Garner *et al* [16] and De Preter *et al* [199] in the headspace of faeces from apparently healthy individuals on an *ad lib* diet. These two studies show many similarities and also some differences. Typically, for each donor the number of VOCs ranged from 78 to 125 (median = 101). Interestingly, 44 compounds were stated to be common to 80% of the cohort samples [16]. Couch *et al* [200] hypothesized that the varied functionality of the metabolites in the headspace of faeces, dictated the use of several diverse SPME fibre coatings for more comprehensive metabolomic coverage. They evaluated eight different commercially available SPME fibres in combination with GC-FID and GCMS. This approach appears very promising; 267 peaks were found with GC-FID; the authors have yet to identify all the compounds.

Alcohols were thought uncommon in adult faeces [201]. However, it is now known that at least 52 different alcohols can be present. Ethanol is very commonly observed. It is likely that gut bacteria can reduce acids to alcohols. Esters were found to represent the largest group of compounds identified. An interesting readily observed feature of table 9 is the similarity of the higher MW compounds, they either possess a long chain acid and short chain alcohol or a short chain acid and long chain alcohol. This suggests that the number of esters identified is not a true picture of what is present in the faeces but a limit on the method i.e. the volatility of the esters. It is very likely that a more sensitive method or better pre-concentration will significantly increase the compounds observed.

A diverse range of aromatic compounds has been reported for many of the chemical classes (table 1) which include mono-, di-, tri- and tetra-substituted benzenoids, mono- and di-substituted furans, and nitrogen containing derivatives of pyridine, pyrrole, and indole. Most of these have only been recently reported in faeces, although it has been established that phenolic and indole compounds arise from the metabolism of aromatic amino acids by gut bacteria [196]. There are many publications which have observed that alkyl furans are produced by fungi. In contrast there is a paucity of publications relating to furan biosynthesis by bacteria. Fungi are well known to be commensal organisms in the gut, which could explain the origins of furans, possibly from the metabolism of fructose. Some benzenoid compounds such as dimethylbenzenes, ethylbenzene, and toluene (constituents of petrol) probably arise from air pollution.

The aldehydes ethanal, propanal, butanal, and hexanal, have been reported [16] in the faeces of significant numbers of individuals and table 7 shows that a complete homologous series have been reported from ethanal to octadecanal. Ethanal is of particular interest due to its abundance and is considered to promote mutagenesis [202–204] and is associated with bowel cancer. The toxic effects of higher aldehydes have received much less attention. The origins of some aldehydes may be dietary. For instance, 2-methylpropanal, 3-methylpropanal, hexanal, nonanal, decanal, and benzaldehyde are found in potato tubers and hexanal in carrots. However, it is doubtful that these compounds would remain unchanged through the digestive system and biosynthesis by microorganisms in the gut and oxidation of unsaturated fatty acids appears more likely. Acetone and butan-2-one were reported in 100% of faecal samples from a longitudinal cohort study [16], which probably arise from fatty acid and carbohydrate metabolism [205]. Methylketones can be produced by many species of bacteria and can also be produced by fungi from the respective alkanoic acid and undoubtedly other ketonic compounds can also be synthesized by bacteria. The universal presence of 2,3-butanedione is interesting in faeces [16] since it may have health implications by impacting on the growth of some bacteria and yeasts [206]. This group of compounds, and indeed other groups, are not normally the end products of metabolism by microorganisms therefore their concentrations would be expected to be continually changing in the gut.

Methane is a product of bacterial fermentation of monosaccharides, reduction of carbon dioxide, or from acetic acid. Numerous hydrocarbons have now been discovered in faeces although the longer chain species have been found in small numbers [16]. Isoprene has been extracted from faeces [207]. Isoprene in the gut may be the result of cholesterol biosynthesis [208] and it is considered to be the most common hydrocarbon in the human body and therefore would be expected to be found in faeces. Many alkenes/terpenoid compounds found are well documented as naturally occurring plant products [209]. Limonene has been reported as the most abundant of the terpenoid compounds and occurs in high concentration in citrus fruits. Most of the terpenes identified [16] are found in vegetable food stuffs and do not originate from animal products. For instance the following volatiles are present in carrots: pinene, limonene, terpinene (1-methyl-4-(1-methylethyl)-1,4-cyclohexadiene), p-cymene, terpinolene caryophyllene, and humulene [210]. Copaene is found in potato extracts [211].

Many ether compounds have been isolated from the headspace of faeces. 2-ethoxyethanol commonly occurs in manufactured products like soaps and cosmetics [212] and 1,3-dimethoxybenzene is a registered food additive in Europe [16]. Similarly, it is very unlikely that chlorinated compounds found are of biological origin. Consumption of contaminated food or water is the likely source of these compounds. Chloroform may arise as a faeces VOC component from several sources, it is an air contaminant and has been detected in foodstuffs [213]. Chlorination for disinfection of drinking water is another source resulting in the production of chloroform and halogenated methanes [214].

Many nitrogen compounds have been reported (tables 1, 2) and are likely to arise from the diet; for instance, methylpyrazine, pyridine, and pyrrole are constituents of coffee. However, pyrrole readily polymerizes with acid and, therefore, its presence is unlikely to be dietary, as it would be unlikely to survive transit through the stomach. Ammonia results from microorganism activity. In addition increasing the amount of protein in the diet from 63 g to 136 g/day was found to increase the amount of faecal ammonia from

15 to 30 mmol l^{-1}. Interestingly, increasing the amount of fibre to the high protein diet was reported to not alter the ammonia concentration [182]. In a study of nitrogen containing compounds in the faeces of 30 healthy individuals indole was the only compound found ubiquitously [16], followed by 3-methylindole, in 73% of individuals, these compounds are well known to be produced by microbial degradation of L-tryptophan in the gut. Many compounds are present in a minority of volunteers. Allyl isothiocyanate was found to be present in 23% of cases; this compound is of particular interest due to its suspected anti-cancer properties. Its occurrence would be expected to be determined by a number of factors such as diet (cruciferous vegetables), the cooking of these vegetables, and the ability of the host's bacteria to break down sinigrin, the glucosinolate precursor.

A diverse range of sulfur compounds has been identified. For instance, methanethiol and dimethylsulfide have been commonly observed; the former is, at least in part, considered to be produced from methionine by *Clostridia* in the gut [197]. Methanethiol has a toxicity approaching cyanide and the factors controlling its concentration and biosynthesis might warrant further investigation. Methanethiol and dimethylsulfide may also be produced by methylation of hydrogen sulfide as a detoxification mechanism by mucosal thiol *S*-methyltransferase [215]. Dimethyldisulfide and dimethyltrisulfide have both been commonly reported in faeces [16, 216, 217]. Hydrogen sulphide is probably most likeley to occur due to the metabolism of sulphate by sulphate-reducing bacteria [218]. Sulphate, which is poorly absorbed in the small bowel, is naturally present in cruciferous vegetables (cabbage, broccoli) and nuts and as an additive in bread and beer [218]. The main sulphur-containing flatus components in healthy individuals have been quantified: hydrogen sulphide (1.06 μmol l^{-1}), followed by methanethiol (0.21 μmol l^{-1}) and dimethyl sulphide (0.08 μmol l^{-1} [218]. The authors were concerned about the social aspect of pungent flatus and found in their study that hydrogen sulphide and methanethiol appeared to be principally responsible and not indole based compounds as previously thought.

Conclusion

The compilation of the total VOCs from healthy humans enables the observation of trends and suspected gaps in our knowledge of the total volatolome of the healthy human body. Reported studies of each bodily fluid have shown similarities and differences, this is probably a reflection of the study sizes, which are invariably small. Age, diet, sex, height, body fat, differences in the gut flora, behavioural/life style differences and differences in the metabolism of individuals etc will all play a part in shaping the VOCs from blood, breath, milk, urine, saliva, skin and faeces of apparently healthy individuals.

The data described here is only partially censored (providing CAS registry numbers helped to identify incorrectly named compounds in some studies). It may be that some compounds have been mistakingly assigned in the original studies, particularly where there is scope for many isomer possibilities. One of the uses of this study would be to help decide which bodily fluid to collect to assess a particular compound or compounds. It may also be used to aid in the identification of the origin of a VOC which could be of medical value etc.

In summary this is the first compilation of the published literature of all the VOCs from the human body. More work is required to define the range of normality in VOCs from humans in terms of compound assignations and also concentration ranges in bodily fluids and breath. This data could then be used to compare with bodily fluids and breath from patients, and to monitor the continued health or otherwise in mass screening of populations.

Acknowledgments

AA and WF appreciate support from Oncotyrol-project 2.1.1. The Competence Center Oncotyrol is funded within the scope of the COMET—Competence Centers for Excellent Technologies through BMVIT, BMWFJ, through the province of Salzburg and the Tiroler Zukunftsstiftung/Standortagentur Tirol. The COMET Program is conducted by the Austrian Research Promotion Agency (FFG). AA and WF appreciate support by the Sparkling Science Project 'SPA 04/158—FEM_PERS' by the Austrian Agency for International Cooperation in Education and Research (OeAD). AA thanks Jan Dallinga and Frederik-Jan van Schooten for indicating that 15 compounds in table 1 are appearing in exhaled breath, and for supplying 14 additional new compounds to table 1. AA thanks the government of Vorarlberg (Austria) for its generous support.

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