1 # A literature survey of all volatiles from healthy human breath and

2 # bodily fluids: the human volatilome

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Abstract

This paper comprises an updated version of the 2014 review which reported 1846 volatile organic compounds (VOCs) identified from healthy humans. In total over 900 additional VOCs have been reported since the 2014 review and the VOCs from Semen have been added. The numbers of VOCs found in breath and the other bodily fluids are: blood 379, breath 1488, faeces 443, milk 290 , saliva 549, semen 196, skin 623 and urine 444. Compounds were assigned CAS registry numbers and named according to a common convention where possible. The compounds have been included in a single table with the source reference(s) for each VOC, an update on our 2014 paper. VOCs have also been grouped into tables according to their chemical class or functionality to permit easy comparison.

Careful use of the database is needed especially as a number of the identified VOCs only have level 2 - putative assignment and only a small fraction of the reported VOCs have been validated by standards. Some clear differences are observed, for instance, a lack of esters in urine with a high number in faeces and breath. However, the lack of compounds from matrices such a semen and milk compared to the breath for example could be due to the techniques used or reflect the intensity of effort e.g. there are few publications on VOCs from milk and semen compared to a large number for breath. The large number of volatiles reported from skin is partly due to the methodologies used, e.g. by collecting skin sebum (with dissolved VOCs and semi VOCs) onto glass beads or cotton pads and then heating to a high temperature 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 work will not only be a useful database of VOCs listed in the literature but will stimulate further study of VOCs from healthy individuals. For example although this work lists VOCs reported in the literature more work is required to confirm the identification of these VOCs adhering to the principles outlined in the metabolomics standards initiative. 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.

Keywords

62   Volatile organic compounds; breath; urine; saliva; blood; milk; skin; faeces; semen.

63

1. Introduction

Until 2014 there had been no central compendium of volatile organic compounds (VOCs) reported from the human body, this was addressed with a review by de Lacy Costello et al [1]. This review thoroughly updates that compendium and encompasses VOCs from breath, saliva, blood, milk, skin secretions (sweat and follicle fluids), urine, faeces and is extended by the addition of VOCs from semen. In total 906 additional compounds are reported and this opens the question how many more VOCs are yet to be identified? This is very different from other *in vivo* biomolecules e.g. amino acids where it is likely there are no more amino acids to be found. Improving on the 2014 review we include the references that identify each VOC within the table. Therefore, it can now be observed if a particular compound is reported multiple times, which gives more credence to its presence. There is also greater range of sub-tables, based upon the chemical class of the identified VOCs

Only 14 VOCs were found to be reported from all matrices with a further 28 VOCs being common to 7 of the 8 matrices, this is perhaps fewer than anticipated given the large number of total VOCs identified.

The total number of compounds reported has risen since the 2014 review for several reasons. There has been a tendency for larger sample numbers and consequently larger numbers of controls highlighting differences between healthy individuals. There have also been further advances in high throughput devices, automation and pre-concentration methods. This coupled with more sensitive instruments and larger mass spectral databases has further increased the number of "new" VOCs being identified.

To prevent this review from becoming too large and unmanageable general comments will be made about the sources of some compounds, without going into significant detail. The purpose of this review remains to bring together all the reported VOCs from the healthy human body and provide the interested reader with references to the original studies.

2. Compound naming and identification

There is a huge variation in naming conventions used within the source publications. We have kept the compound names as they appear in the original references, so ethanoate and acetate etc. are both used. Frequently, this will be the name as it appears

97 in the NIST spectral library, but this is not always the case and both common and

98 systematic names appear in the tables. Where different nomenclature has been used

99 between references, the alternatives have been listed. Sometimes structural and

100 positional isomers are not specified in a particular paper, but they are still included as a

101 separate entry, with a comment to this effect. Stereoisomers have generally been

102 grouped together under a single entry, particularly as it is unclear how the specified

103 stereoisomers were identified.

104 Chemical nomenclature can be challenging to the non-chemist, hence the utility of using

105 CAS numbers, which are intended to aid identification where different naming

106 conventions are used in the original publications. CAS numbers are not infallible though

107 e.g. the mixed (+/-) camphor has a different CAS number from (-) camphor, when they

108 refer to almost identical compounds.

109 To further aid comparisons subtables have been created based on chemical class. Where

110 a compound contains two different functional groups, it will appear in both of the

111 relevant subtables.

112 Most of the VOCs reported here were identified using gas chromatography mass

113 spectrometry (GC-MS), with library matching to aid tentative identification of the VOCs.

114 In some earlier studies gas chromatography flame ionisation detection (GC-FID) was

115 undertaken with standards, for measuring breath volatiles of ethanol, methanol [2],

116 isoprene [3], and acetone.

117 The identification of compounds by GC-MS is often a difficult task. The VOCs reported

118 within this manuscript have often been assigned an identity by spectral library match

119 only, which can sometimes be misleading, particularly for isomers, especially

120 hydrocarbon isomers. More recent work though often incorporates the use of retention

121 indices to increase confidence in the library identification. However, the use of standards

122 to confirm identification remains the gold standard for validating the identity of VOC

123 metabolites.

124 Improved equipment, for instance two-dimensional gas chromatography combined with

125 high resolution time of flight mass spectrometry (GCxGC-TOF-MS) is able to detect an

126 impressive number of compounds compared to a standard quadrupole GC-MS. It brings

127 in to question the likelihood of co-elution and the possibility of misidentification. Some

128 compounds may not be in the NIST library or other libraries and this can be another

129 reason for misidentification. Other compounds might be from artefacts, such as

130 contamination, degradation/oxidation, which can result from collection, storage, sample
131 treatment, or measurement.

132

133 **3. A comparison of the VOC compounds found in breath, saliva, blood, milk,**
134 **skin secretions, urine, faeces and semen**

135 Table 1 describes 2746 VOCs which have been identified from the healthy human body.
136 This compares to 1840 VOCs identified in a previous 2014 review (de Lacy Costello et al.
137 2014). The numbers of VOCs found in each bodily fluid and breath are: blood 379
138 (additional 225 compounds vs 2014), breath 1488 (additional 616 compounds vs 2014),
139 faeces 443 (additional 61 compounds vs 2014), milk 290 (additional 34 compounds vs
140 2014), saliva 549 (additional 190 compounds vs 2014), semen 196 (not previously
141 included in 2014), skin 623 (additional 91 compounds Vs 2014) and urine 444
142 (additional 165 compounds vs 2014). Therefore, there have been increased numbers of
143 VOCS reported for all the sources of VOCs included in the original 2014 review, with
144 marked increases in breath, blood, saliva and urine. We should re-emphasise that these
145 increases probably just reflect the recent research effort in these areas. Likewise, the
146 small number of compounds in semen is likely because, their source is just one
147 publication. The data in Table 1 has been sub-categorised into 12 classes, which were
148 then further sub-divided to help the observation of inter relationships between
149 compounds.

150 There must be transfer of VOCs throughout the body, from the original source(s) to the
151 final bodily fluid destination. As to whether sufficient chemical transfer occurs for
152 detection, or whether the VOC survives the journey, through the human body is the
153 question. Almost certainly the gut microbiome is the source for many chemicals, and
154 sometimes there is a change of chemistry on route from the gut to e.g. the bladder.
155 Benzoic acid for instance (which naturally occurs in most berries) found in the gut, is
156 derivatised in the liver and excreted as the less volatile hippuric acid
157 (benzoylaminoethanoic acid), the liver can oxidise many compounds e.g. hydrocarbons.
158 Furthermore, esters can be biosynthesised by fatty acid ethyl ester synthases in the liver
159 and pancreas, [4] and there are esterases in the lung etc.

160 Analysis of the 2014 review table showed there were only 12 compounds found in all the
161 matrices. Three of these benzene, toluene and styrene [5] are common pollutants in the
162 environment and are in cigarette smoke [6]. It should be mentioned that 25-40% of

163 absorbed toluene is exhaled and the remaining amount is metabolised and excreted, by
164 oxidation to benzyl alcohol, which is then metabolised to benzaldehyde [7]. With the
165 increase in numbers of compounds, for this review (and the addition of semen), there
166 are still only 14 chemicals in common: ethyl ethanoate, ethanol, 1-butanol, acetone, 2-
167 butanone, 2-pentanone, 2-heptanone, benzaldehyde, ethanal, hexanal, 3-methylbutanal,
168 ethanoic acid, hexanoic acid and limonene. Ethyl ethanoate and ethanal are the two
169 compounds that were not reported in the previous review. Limonene is likely to originate
170 from the environment, it is a commonly used product in household materials, and is in
171 food stuffs, e.g. potatoes. Benzaldehyde can originate from oxidation of toluene in the
172 human body, toluene, is a common atmospheric pollutant. Ethanol may come from
173 drinking alcohol; however, the gut is also capable of ethanol production, and given the
174 significant amount of ethanoic acid in the gut, this can explain the origins of ethyl
175 ethanoate. Hexanoic acid is likely to have its origins in the gut, although it's not clear why
176 this particular short-chain fatty acid (SCFA) is so prevalent. 2-Ketones are certainly found
177 in the gut [8] e.g. 2-butanone was shown to be in all the faecal samples in one study [9].
178 Short chain aldehydes such as hexanal can arise from peroxidation of unsaturated fatty
179 acids [10](potentially in many parts of the body including adipose tissue), and also from
180 oxidation of the respective alcohol.
181

182 **4. Listing of all compounds, with CAS numbers, formulae and origins (Table 1)**
183 Table 1 is an exhaustive table containing every VOC found in the healthy human body to
184 date, across all the different bodily samples (breath, blood, faeces, urine, milk, skin, saliva
185 and semen). Compounds are listed in alphabetical order, and appear with their CAS
186 number assigned by the original authors, where appropriate, and chemical formula. The
187 table rows indicate which particular sample(s) each compound has been found in, and
188 the paper(s) which identified each volatile in each fluid are also noted using reference
189 numbers.
190 While Table 1 lists all the compounds, Tables 2-12 describe VOCs according to their
191 chemical classes, and they are further split into sub-tables where appropriate. Within the
192 tables, the compounds are described in increasing carbon number. A brief discussion is
193 given for the compounds included in these tables.
194

195 *4.1. Nitrogen containing VOCs found in the human body (Table 2a-2c)*

196   There are significantly more nitrogen compounds here than in the 2014 review, these
197   compounds have been split into three sub tables: nitrogen-containing (non-heterocyclics,
198   Table 2a), nitrogen-heterocycles (Table 2b) and nitrogen and sulfur containing
199   compounds Table 2c). These 3 sub tables were then further divided into subgroups as
200   follows:

201   *Nitrogen-containing (non-heterocyclics)*: sundry nitrogen compounds (ammonia, nitric
202   oxide, hydroxylamine, nitric acid), aliphatic monoamine (non-cyclic nitrogen), aliphatic
203   di-, tri, or tetra-amines (non-cyclic nitrogen), anilines, amino acids, amines with
204   carboxylic or sulfonic acids, amines plus other functional groups, hydrazines, azides, azo,
205   nitriles, isonitriles, imines, isocyanates, amides, amide with other functional group,
206   carbamates & carboxamide, ureas, carbamimidate, hydroxylamines, nitroso, oximes and
207   amine oxides.

208   *Nitrogen-heterocycles*: azirine/ aziridine [C_2N ring] azete / azetidine [C_3N ring],
209   pyrrolidines, pyrroline/dihydropyrroles [C_4N ring, pyrrole [C_4N ring], pyrazoles and
210   imadazoles and other diazoles [C_3N_2 ring], pyrazoles and imadazoles and other diazoles
211   [C_3N_2 ring], triazoles [C_2N_3 rings], tetraazoles [C_1N_4 rings]**,** piperidines [C_5N ring],
212   pyridines [C_5N ring], piperazines [C_4N_2 ring]**,** diazines (pyrazines and pyrimidenes) [C_4N_2
213   rings aromatic], indoles, quinolene and hydroquinolines, other multicyclic CN
214   heterocyclics, cyclic amide / lactam, oxazoles, (& oxaline, oxazolidine, isoxazole,
215   isoxazline, isoxazolidine) [C_3NO], other CNO heterocyclics.

216   *Nitrogen and sulfur containing compounds*: At least 8 compound groupings containing
217   both sulfur and nitrogen in the functional group were split into thiocyanate and
218   isothiocyanate, thiazole [C_3NS ring], benzothiazoles, thiazolidines [C_3NS ring], thioamide,
219   thiocarbamate & thiourea and others.

220   Nitrogen-containing (non-heterocyclic) compounds like ammonia, the simplest amine is
221   well known to be linked to breath particularly with high protein intake. Nitric oxide has
222   been found in breath and blood. Human paranasal sinuses and diet can affect production
223   [11]. Hydroxylamine can be synthesised by oxidation of ammonia enzymatically e.g. by
224   ammonia monooxygenase [12]. Interestingly nitric acid has now been reported in breath,
225   it might be considered curious that this strong mineral acid, along with hydrochloric and
226   sulphuric acids can be made by the human body. It is likely that the nitric acid could arise
227   from inhalation of nitrogen dioxide atmospheric pollution, or the oxidation of nitric oxide
228   which can lead to nitric acid synthesis.

229 The largest molecular weight (MW) nitrogen VOC compound detected so far is N, N-
230 dimethyl-1-octadecanamine/ N, N-dimethyl-1-octadecylamine (20 carbons).

231 Many amino acids, particularly in breath have now been reported, e.g. glycine, proline,
232 ornithine, arginine, leucine and valine.

233 Seven hydrazine based compounds have been reported. Hydrazine is a known rocket fuel,
234 however there are rare pointers in the literature for hydrazine synthase enzymes,
235 suggesting conversion from ammonia to hydrazine by bacteria can happen [13]. There
236 are 39 nitrile (cyanide) compounds, the origin of these for instance, alkyl nitrile
237 compounds could arise from diet by ingesting cyanogenic glycosides albeit in small
238 quantities [14]. It has been stated that certain bacteria can make hydrogen cyanide, again
239 confirming that bacteria may be a biosynthetic route.

240 There are a range of primary, secondary and tertiary amines, presumably at some stage
241 they have been synthesised by alkylation of ammonia, it is beyond the scope of this
242 review to attempt to assess the origins of so many diverse compounds.

243 There are rarely 3 and 4 membered ring cyclic nitrogen compounds, in contrast to the 21
244 pyrrole (5-membered) and 18 pyrazines (6-membered di-nitrogen compounds and
245 pyridine), many of which are alkylated. Volatile pyrazines and pyridines can contribute
246 to food flavours [15] and diet is therefore a potential source.

247 There are 37 nitrogen sulfur compounds, mainly found in breath. Many are thiocyanates
248 being the hydrolysis products of glucosinolates, secondary metabolites characteristic for
249 the family *Brassicaceae* e.g. broccoli. For instance, allyl isothiocyanate is responsible for
250 a significant smell of cooked cauliflower. Moreover, methyl thiocyanate, butyl
251 isothiocyanate, 2-methylbutyl isothiocyanate and other sulphides have been found
252 in Brassica vegetables [16,17].

253

254 ### 4.2. Sulfur containing VOCs found in the human body (Table 3)

255 There were 113 sulfur compounds reported (Table 3), further divided into 13 sub
256 sections: elemental sulfur, thiols, sulphides, sulfoxides, sulfonic acid esters, sulfate esters,
257 thioesters, thietane[C_3S], thiophene, thiolane [C_4S], thiane [C_5S], dithiane [C_4S_2], oxathole
258 [C_3OS] and oxadithiane [C_3OS_2].

259 For thiocyanates, thiocarbamates, thioureas, sulfonamides and amino thio acids see
260 Nitrogen Table 2c, also for sulfur containing heterocyclics possessing nitrogen atoms.

261   Many of these compounds probably arise from food and metabolic changes occurring in

262   the body, such as de novo synthesis of glutathione and antioxidative processes in the liver.

263

264   *4.3.   Alcohol containing VOCs found in the human body (Table 4)*

265   The alcohol compounds were divided into 12 sub-groups: straight chain alcohols,

266   branched alcohols, unsaturated alcohols, cycloalkyl alkanols, phenyl alkanols,

267   cyclohexanols, other cycloalkanols, multi-cyclic alkanols, diols, triols, pentols and

268   phenols.

269   The straight chain primary alcohols were present as a homologous series (present with

270   some gaps). From methanol to 1-eicosanol (20 carbons), there were only 2 gaps, 1-

271   heptadecanol and 1-nonadecanol, comparing all the bodily fluids and breath. It is likely

272   that many of the gaps would be filled by undertaking future studies, for instance 1-

273   heptanol and 1-octanol has not yet been found in breath, but they have been identified in

274   other bodily fluids such as faeces.

275   Certainly, alcohols can be made in the gut e.g. via the reduction of the respective acid [9],

276   or by carbohydrate fermentation or fermentation of nitrogenous compounds [18].

277   Moreover, the liver is capable of alcohol synthesis.

278   Alcohols, from methanol to octanol were derived by oxidation of unsaturated fatty acids,

279   $CH_3(CH_2)_nOH$ from n=0-7 except for propanol (n=2) omitted in the homologous series

280   [10]. This is a likely source of saturated alcohols in all bodily fluids and breath.

281

282   *4.4.   Acid containing VOCs found in the human body (Table 5)*

283   The acids (175 compounds) were divided into 8 sub-groups: aliphatic acids-saturated

284   straight chain, aliphatic acids-branched /cyclic, aliphatic acids-unsaturated, aromatic

285   acids, aliphatic dioc/trioic, acids which also contain an alcohol group, hydroxybenzoic

286   acids, acids containing an aldehyde or ketone group and, acids contacting another

287   unspecified group. Amino acids are given in the nitrogen compound table. Phenols,

288   although very weak acids, have not been included in this group and are tabulated with

289   alcohols.

290   Of the straight chain carboxylic acids, all the acids from methanoic acid to docosanoic acid

291   have now been detected in one or more of the fluids and breath from the human body.

292   The complete homologous series of acids from ethanoic to docosanoic acid have been

293   found in saliva, apart from decanoic and undecanoic acid and from methanoic to

294   docosanoic acid in skin secretions, apart from pentanoic acid. The highest MW acid,
295   docosanoic acid possesses 22 carbons. In all the studies, there is a threshold of around
296   16-22 carbon length for the VOCs reported. As to whether there are real biochemical
297   reasons or it is a limitation of the analytical method, is an open question
298   As a general comment, SCFAs from methanoic to hexanoic acids have been reported as
299   the most abundant and significant end products of fermentation in the gut. The ratio of
300   compounds found may be dependent on individuals, which have different
301   gastrointestinal transit times (GITT). For instance, a long GITT can have a significant
302   effect on bacteria metabolism, more protein is broken down into amino acids which are
303   in turn broken down into small fatty acids. Branched SCFAs arise from breakdown of
304   branched amino acids, as opposed to straight chain SCFAs which can arise from
305   carbohydrate metabolism (as well as other routes) [19]. A study has also shown that
306   blood in faeces will also affect the ratio of short chain fatty acids due to the breakdown of
307   haemoglobin [20]. Also, carbohydrate availability can affect acid type production in the
308   gut and therefore VOCs in the faeces. Carbon limited fermentation produces more formic
309   acid [21]. Acetic acid the main SCFA produced in the gut is readily absorbed through the
310   colon wall and is transferred to the liver, where it is used to e.g. synthesise cholesterol
311   [22]. It does not appear to have been detected in blood, although it must be present. Other
312   SCFAs are rapidly absorbed into the blood stream, it is considered that only 5-10 % are
313   excreted [22]. It must be noted that butanoic acid and to a lesser extent other SCFAs are
314   used as an important energy source by the gut wall and the amount of these acids
315   reaching the blood stream maybe low.
316   Acids can also be biosynthesised in the human body from aldehydes. Aldehyde oxidase
317   (AO) is very concentrated in the liver, where it oxidizes multiple aldehydes [23]. AO
318   activity has been indicated as occurring in the epithelial and alveolar cells of the lungs.
319   There have also been indications of AO activity occurring in the kidneys and
320   gastrointestinal tract (both small and large intestine). It should be pointed out that
321   catalysts are not essential, air oxidation can oxidise aliphatic aldehydes into carboxylic
322   acids [24]. A recent report, showed significant, almost 9-fold difference in nonanoic acid
323   abundance between a lung cancer group and control group [25]. Its origins may be due
324   to oxidative stress due to oxidation of unsaturated aldehydes [10].
325   Of the 32 branched acids found in total, more were found in skin secretions [18]. A
326   commonly found acid in faeces, urine, breath, and skin secretions was 2-ethylhexanoic

327 acid, a common contaminant derived from plasticisers e.g. plastic tubing, containers for
328 bodily fluids etc.

329 More unsaturated fatty acids were found in skin than other bodily fluids and breath. The
330 largest chain size was for docosahexaenoic acid (20 carbons), found in breath. Oxidation
331 of unsaturated fatty acids can produce smaller chain unsaturated fatty acids, a list of
332 predicted mono alkene acids expected to be enhanced by oxidative stress is reported in
333 a recent review. The origin of compounds such as 9-decenoic and 10-undecenoic acids
334 (which have been reported from skin) can be satisfactorily explained by such a route [10].
335 The number of very long chain fatty acids (C-20 plus) found will undoubtedly increase in
336 the future with increased sensitivity of analytical methods. They are present in the human
337 body and have been linked to Refsum's disease and maybe adrenoleukodystrophy.
338 Nervonic acid (C-24) is found in brain tissues, and higher amounts have been correlated
339 to schizophrenia. A note of caution however, as identifying long chain fatty acids
340 accurately can be problematic due their susceptibility to breakdown (particularly in the
341 heat of a GC inlet port). Thus, derivatization or alternate analytical methods might be
342 required for absolute compound identification.

343

344 ### *4.5.   Ether containing VOCs found in the human body (Table 6a and 6b)*

345 The ethers were split into two sub-tables: non-cyclic ethers (Table 6a) and cyclic ethers
346 (6b).

347 The non-cyclic ethers were further divided into five sub-classes as follows: (for ethers
348 that contain additional non-hydrocarbon or hydroxyl functional groups see the specific
349 table for that functional group), mono- (34) di- (11), tri- (2) and tetra-ethers (1), non-
350 cyclic hydroxy ethers (27) and peroxides (2).

351 The cyclic ethers were divided into oxiranes (16), furans (21), benzofurans (3),
352 hydrofurans (13), hydrobenzofurans (1), furanones (see listing under lactones in ester
353 table), furans with other functional groups (22), dioxolanes [C_3O_2] (8), dioxolane with
354 other functional groups (1), pyrans, hydropyrans (4), benzopyrans with other functional
355 groups (for pyranones, see the ester table) (10), dioxanes (1), oxepines and oxepanes (4),
356 cyclooxaoctane/enes (11), crown ethers (1) and multicyclic cyclic ethers (13).

357 Some ethers are used in cosmetics (212), and some food additives (16). Peroxidation of
358 certain polyunsaturated fatty acids, enhanced with oxidative stress, can lead to furan
359 generation [10]. However the confirmation of the ether origins requires more studies.

4.6.   *Aldehyde containing VOCs found in the human body (Table 7)*

The total number of volatile aldehydes found in all bodily fluids and breath was 159, (Table 7), an increase of 56 compounds since 2014 [1]. Aldehydes were further divided into: aliphatic (16), branched aliphatics (13), 2-unsaturated (23), other unsaturated linear compounds (17), unsaturated branched (16), aliphatic cyclic (7), benzaldehyde, phenylalkyl aldehydes (23), aliphatic dialdehydes (2), hydroxyl aldehydes (22), ketone aldehydes (2), ether aldehydes (7), carboxylic acid aldehydes (9) and aldehydes with other various functional groups (7).

A complete homologous series of aliphatic aldehydes was observed, particularly for faeces, from methanal to octadecanal, with the omission of heptadecanal. Perhaps future work will report heptadecanal, or there is no biochemical route to this compound. A recent review of products of oxidative stress (oxidation of unsaturated fatty acids) summarises the origins of straight chain aldehydes from ethanal to decanal, $CH_3(CH_2)_nCHO$ from n=0-8, although there are other potential origins [10].

Of the branched aliphatic aldehydes, five 2-methyl aldehydes were reported, from 2-methylpropanal to 2-methylpentanal, then a gap until 2-methylundecanal and then 2-methylhexadecanal.

A complete homologous series of 2-unsaturated aldehydes was found between 2-propenal and 2-hexadecenal, from one or more of the bodily fluids. This is in contrast to the 2014 review, where the series only reached 2-decenal [1]. As is the case for some of the other chemical classes, more recent papers have filled in some of the previous gaps identified in the homologous series. For example, recently, 2-dodecenal has been reported in breath condensate [26].

The reported aldehydes have a cut off in molecular size around 16-18 carbons: octadecanal (18 carbons), 2-methylhexadecanal (17carbons), 2-hexadecenal (16 carbons), 4-hydroxy-2,6- hexadecadienal (16 carbons) and 4-hydroxy-2-hexadecenal (16 carbons). There are two main reasons for a lack of detection of aldehydes with higher carbon numbers namely a lack of biochemical routes, or the low vapour pressure of these compounds.

Lipid oxidation of monounsaturated and polyunsaturated fatty acids are known to produce 2-alkenals, as well as dienals, such as 2,4-heptadienal, which has been found e.g.

392   in milk [27]. It has been reported that 23 different aldehydes in milk can be produced by

393   oxidative degradation of oleic, linoleic and linolenic acids [27].

394   With regard to branched chain saturated aldehydes, a 2020 study of Ratcliffe, *et al* [10]

395   predicted six compounds originating from the oxidation of unsaturated fatty acids: 3-

396   methylbutanal,   3-methylpentanal,   4-methylhexanal,   4-methylpentanal,   5-

397   methylheptanal and 5-methylhexanal, but none were reported in the 2014 review [1].

398   However, 3-methylbutanal and 3-methylpentanal, have now been reported in the current

399   manuscript. It does suggest that other hypothesised compounds will be found in future

400   studies [10] and does highlight the importance of identifying plausible metabolic routes.

401   for VOCs. It should be observed that 5-methylheptanal is not in the NIST library, so its

402   identification is currently unlikely. This does highlight a potential issue with the

403   identification of compounds which heavily relies on putative identification via current

404   mass spectral library entries. Modern mass spectral libraries contain many thousands of

405   compounds and are constantly updated but still contain only a fraction of the possible

406   organic molecules which could be potential metabolites.

407   For mono-unsaturated hydroxyl aldehydes, a homologous series of nine 4 hydroxy-2-

408   enals have been detected, whereas conversely in 2014 none had been reported. The

409   lowest MW compound is 4-hydroxy-2-hexenal, then the 4-hydroxy-2-heptenal is

410   "missing", with the last compound being 4-hydroxy-2-hexadecenal. This again provides a

411   potential target for future analytical studies as do all the "gaps" in the homologous series

412   within these tables. Alternatively it might highlight the need for better mechanistic

413   metabolic studies to understand why certain VOCs may be missing. 4-hydroxynonenal in

414   particular has been extensively reported in association with oxidative stress and lipid

415   oxidative breakdown, especially from *n*-6 PUFAs, mainly arachidonic and linoleic acids

416   [26,28]. To further add to the series, 4-hydroxy-2-pentenal has been found in smoker's

417   breath using secondary electrospray ionisation- mass spectrometry (SESI-MS) [29]**.**

418   The origins of a series of volatile hydroxyl, alkene aldehydes have been listed [10]**.**

419   A whole series of nine 4 hydroxy-2,6-dienals has now been shown starting from 4-

420   hydroxy-2,6-octadienal to 4-hydroxy-2,6- hexadecadienal.

421   With regard to aldehyde oxo-acids, a series of 6-oxohexanoic acid, 7-oxo-heptanoic acid,

422   8-oxooctanoic acid, 9-oxononanoic acid, 10-oxocaproic acid / 10-oxodecanoic acid, 11-

423   oxoundecanoic acid and 12-oxododecanoic acid have been reported herein, four of which

424   have been linked to smoking [29].

425 As a general comment, aldehydes are capable of oxidation to acids, by oxygen, even

426 without the mediation of a catalyst and these aldehydes could contribute to an increase

427 of concentration of carboxylic acids, and a concomitant decrease in aldehyde

428 concentration.

429

430 ***4.7.*** ***Hydrocarbon containing VOCs found in the human body (Table 8a- 8e)***

431 The hydrocarbons were split into five major classes: cyclic hydrocarbons (Table 8a),

432 aromatic compounds (Table 8b), branched chain alkanes (Table 8c), alkenes (Table 8d),

433 and n-alkanes (Table 8e).

434 The alkenes were split into mono alkenes and non- cyclic, branched alkenes, dienes, tri-

435 enes, tetra-enes, penta-enes and hexa-enes and alkynes.

436 The cyclic hydrocarbons were split into cyclopropanes, cyclobutane and cyclobutenes,

437 cyclopentane, cyclopentenes, cyclopentadienes, cyclohexanes and cyclohexenes,

438 cyclohexadienes, cyclo- heptane/ heptane/ heptadiene/ heptatriene, cyclo-octane/

439 octadienes/ octateraenes, cyclic C10, C11, C12, C14, C16, hydronaphthalenes,

440 hydroazulenes, other bicyclo, and other tricycle compounds.

441 The aromatic compounds were split into several sections: benzyl, phenyl, biphenyl,

442 indane/indene, 1,2,3,4-tetrahydronaphthalenes/ dihydronaphthalenes, 1,2,3,4-

443 tetrahydronaphthalenes, naphthalenes, azulenes, anthracene, and acenaphthalenes.

444 There is an impressive complete homologous series from methane to tetratriacontane

445 (34 carbons) when taking into account all the bodily fluids and breath. Breath contains

446 the majority of these compounds with the exception of docosane, tricosane, pentacosane,

447 hexacosane and nonacosane.

448 Alkanes, from methane to octane (at least) can be considered to arise from oxidation of

449 unsaturated fatty acids [10]. It is interesting that many researchers consider that the

450 source of methane in breath is from the gut as 1 in 3 subjects possess gut methanogens

451 [30]. However, lipid oxidation is clearly another potential source. The authors are

452 unaware of any studies undertaken to assess methane lipid origins, in breath, although

453 methane, ethane, propane, butane and pentane have been well described as autoxidation

454 products e.g. from linoleic acid [31]. Straight chain aliphatic hydrocarbons have been

455 considered as non-invasive markers of free-radical induced lipid peroxidation in liver

456 damage, especially breath ethane and pentane, which appear to be better correlated with

457 alcohol induced hepatic injury than to other aetiologies [25].

458   There were more hydrocarbons reported than any other class of VOCs, 853 in total. The

459   origins have not been extensively considered. As a general consideration, GC-MS spectra

460   of diesel and to a lesser extent petrol, shows the huge numbers of potential compounds

461   present. It is possible that we are observing the human volatilome being significantly

462   affected by the industrial world we live in (the exposome).

463   The human body in combination with its bacterial hosts are likely to be capable of

464   biotransformations of hydrocarbons to a lesser or greater extent thus producing more

465   VOCs to potentially confuse VOC biomarker discovery. There are also naturally occurring

466   hydrocarbons in food which add to the impressive list here.

467   Alkenes, from ethene, and propene to decene in a homologous series and their 2-isomers,

468   2-pentene, 2-hexene, and 2-octene would be expected to occur by oxidation of

469   unsaturated fatty acids [10]. As examples in the literature, ethene has been shown in the

470   volatilome of humans and can be formulated from oxidation of omega-3 acids e.g.

471   linolenic acid, by disproportion of ethyl radicals [32] and 1-pentene has been reported to

472   be generated by decomposition of omega-6 unsaturated fatty acid hydroperoxides e.g.

473   from linoleic and arachidonic acid [33].

474

475   *4.8.   Ester-containing VOCs found in the human body (Table 9)*

476   In total 305 esters have been reported. The esters were arranged into sub groups:

477   methanoates,   ethanoates,   propanoates,   butanoates   and   pentanoates,   2-

478   methylbutanoates, 3-methylbutanoates, hexanoates, heptanoates, hexanoates, nonoates,

479   decanoates,   undecanoates,   dodecanoates,   tridecanoates,   tetradecanoates,

480   pentadecanoates, hexadecanoate/heptadecanoate/octadecanoate / docosanoates and

481   tetracosanoates, ene-oates, other-oates, cyclic HC oates and benzoates, salicylates (inc.

482   substituted benzoic acid esters), hydroxy acid esters (except hydroxybenzoic), other

483   mono esters, lactones, delta, pyranones (benzopyranone and dioxanedione), others /

484   uncertain cyclic esters, diesters and triesters (phthalates listed separately) and finally

485   phthalates, carbonates and anhydrides.

486   Acetate (ethanoate) esters were by far the most abundant esters. This is probably

487   reflected by the fact that acetic acid is the most common gut acid. Acetates found in

488   breath were the major contributor to the overall total. There were many esters reported

489   in breath which were not present in other bodily fluids. Therefore, it is not easy to say

490   that breath ester VOCs arose from other bodily fluids.

491 Esters are represented from the whole homologous series from methanoate to
492 octadecanoate, when all the bodily fluids and breath are considered. Then there is a big
493 gap in the series to tetracosanoic acid, methyl ester. The largest ester reported, is behenyl
494 behenate (44 carbons), which is likely to originate from its uses in cosmetics.

495 Bacteria present in faeces have been shown to be capable of ester synthesis [34], and it is
496 very likely that the reaction of alcohols with the respective acid produces many esters in
497 the gut which can then enter the blood stream and circulate throughout the body.
498 Unfortunately for this theory, very few esters have been found in blood, but this is most
499 likely due to the paucity of studies undertaken on VOCs in blood. There are also a variety
500 of esters found in breath which are not found in the gut, this again could be because these
501 esters have not yet been detected in faeces due to analytical imitations or a relative lack
502 of studies. However, it could be that lung based esterases aid ester synthesis and explain
503 in part why more esters have been identified in breath.

504 The phthalates (phthalate esters) are exclusively endogenous and probably arose from
505 plasticiser exposure, and subsequent metabolism. There is a whole range of long chain
506 fatty acid esters and aromatic esters found in skin, which are mainly missing from other
507 bodily fluids and breath. This could be due to the analytical methodologies used.

508 If one considers that all the acids and alcohols reported here can undergo esterification
509 it is possible to rationalise the origins of many of the esters described here. One of many
510 interesting observations, is the lack of esters in urine, apart from lactones. Esters have
511 low solubility in water which could explain the lack of esters in urine.

512

4.9.   Ketone containing VOCs found in the human body (Table 10a, 10b)

514 The ketone table (Table 10a) was divided into a range of sub groups: aliphatic, straight
515 chain ketones, straight chain alkene ketones, aliphatic diones, branched aliphatic ketones,
516 alkyl phenyl ketones, alkyl cyclohexyl ketones, other aliphatic and aromatic ketones,
517 hydroxy ketones, phenol ketones, acid ketones, and ketones with other functional groups.
518 Table 10b presents cycloketones.

519 A homologous series of 2-ketones from acetone (propan-2-one) to 2-nonadecyl ketone
520 (19 carbons) was reported herein. In contrast, the 2014 review described a homologous
521 series which went from acetone to nona-2-one [1].

522 Acetone was found to be one of the most reported volatiles from the human body and is
523 well known to be produced by fatty acid breakdown whereas 2-butanone derives from

524 carbohydrate metabolism. Methyl ketones are produced by many species of bacteria and
525 can also be produced by fungi.

526 The carbonyl group in ketones was found in different positions, in 2, 3, 4, 6 and 8. This is
527 quite selective when compared with the options available. Substitution in the 2 position
528 was by far the most common class of ketone.

529

4.10. Halogenated containing VOCs found in the human body (Table 11)

531 All the halogenated compounds were separated into 6 sub-sections: fluorinated
532 compounds (16), chlorinated compounds (35), alkenyl & benzyl chloro-compounds (19),
533 bromo-compounds (8), iodinated compounds (6), mixed halogen and halogen plus other
534 hetero compounds (17), chlorinated biphenyls and chlorinated and brominated phenol
535 compounds (43).

536 Most of the fluorinated compounds were discovered in breath. Sevoflurane was listed:
537 this is a sweet-smelling, non-flammable, highly-fluorinated methyl isopropyl ether is
538 used as an inhalational anaesthetic, and its occurrence in breath of healthy humans is
539 presumably because of the clinical environment where the breath was collected. 1,1,2-
540 trichloro-1,2,2-trifluoroethane / Freon 113 is used as an electrical cleaning agent and is
541 likely to have come from the environment.

542 With regard to chlorinated compounds, some are solvents. Vinyl chloride originates from
543 PVC and some can arise from chlorinating water.

544 Dibromomethane occurs naturally in small amounts in the ocean where it is formed, most
545 likely by algae and kelp. This and similar brominated compounds can enter the food chain
546 and hence reach humans via the diet. It may also still be used for the fumigation of stored
547 grains, fruits, and vegetables [35].

548 Volatile iodine compounds, such as methyl iodide, ethyl iodide, chloroiodomethane,
549 diiodomethane (CH_2I_2) and bromoiodomethane are widely detected over oceans, where
550 the biogenic activity of phytoplankton and macroalgae are likely to be an important
551 source of these VOCs. Presumably, these types of compounds can also enter the human
552 food chain [36].

553 Many chlorinated fluorinated compounds (CFCs) have been used, especially in the past
554 as refrigerants, propellants in aerosols and solvents. As these are being phased out in
555 consumer products, they and their degradation products must be originating from the

556 environment. Dibromochloromethane and bromodichloromethane also have
557 environmental origins [37].

558 A large number of chlorinated biphenyls and chlorinated and brominated phenol
559 compounds were found such as 4-hydroxy-2,2',3,4',5'-pentachlorobiphenyl which was
560 found in blood and no other bodily fluid.

561

562 ### *4.11. VOCs found in the human body not categorised previously (Table 12)*

563 Table 12 shows compounds not categorised in Tables 2 to 11, encompassing carbon
564 dioxide, carbon monoxide, hydrogen, hydrogen peroxide dimethylselenide and
565 tetramethyl-germane all reported in breath.

566

567 ## 5. DISCUSSION

568 Discussion of the VOCs reported in breath, saliva, blood, milk, skin secretions (sweat and
569 follicle fluids), urine, faeces and semen.

570

571 ### *5.1.   Volatile organic compounds in breath*

572 Exhaled breath contains many different volatile compounds. It has been stated
573 previously that a total of more than 1000 VOCs can be observed, even though they are not
574 present in each person studied [38]. Our literature search revealed 1488 named volatile
575 compounds as being related to exhaled breath. More than half of the screened papers
576 used gas chromatography mass spectrometry (GC-MS) to quantify VOCs in breath,
577 confirming this instrument as the gold standard technique for the analysis of this
578 biological matrix. In most of the papers, GC-MS is typically used in combination with
579 thermal desorption (TD) sorbent tubes to collect and analyse breath.

580 The most used direct sampling techniques are proton transfer reaction mass
581 spectrometry (PTR-MS) and selected ion flow tube mass spectrometry (SIFT-MS) used in
582 25 % of the screened papers. The absence of chromatographic separation in direct
583 sampling techniques however can only tentatively identify the VOC molecular structure,
584 and generally those assignments are confirmed with GC-MS [39] or in the case of breath
585 condensate, with UPLC-MS [40–43].

586 However, in the last five years, a new direct sampling technology, named secondary
587 electrospray ionization (SESI) has been increasingly applied in breath research and is
588 opening new avenues in the field. Since it is based on electrospray ionization of the VOCs,

589 it is able to ionise previously difficult to detect compounds, by covering higher molecular
590 weight, less volatile and more polar species which are not easily analysed with GC
591 approaches [29,41,42,44–47]. While it lacks chromatographic separation and often forms
592 ion adducts (e.g. M+Na$^+$) due to the electrospray ionization, the use of high resolution
593 mass spectrometers with multi-stage (MS^n) capabilities partially counterbalances the
594 aforementioned limitations [48].

595 Many of the volatile compounds related to exhaled breath are not endogenously
596 produced, and some compounds appeared only in a few individuals. The list reported in
597 our table of VOCs is considered as a list for discussion, and we do not consider it
598 comprehensive.

599 Water, oxygen, nitrogen, argon and other rare gases are not listed in this table. For many
600 of these compounds it is unknown if they are produced endogenously. Among the
601 compounds which are listed as appearing in exhaled breath (Table 1), many are related
602 to smoking e.g. 29 dienes, 27 alkenes and 3 alkynes are mentioned as smoking-related
603 [1]. If you smoke it has been stated that your breath contains 2,5-dimethylfuran. A team
604 of Catalan researchers have proved that the presence of this chemical compound
605 indicates that a person has smoked in the last three days and they state that this
606 substance does not appear in the breath of non-smokers, unless they have been in direct
607 contact with tobacco smoke for a long time [49].

608 More recent work of exhaled breath from healthy volunteers, divided into three groups
609 (non-smokers, ex-smokers and smokers) showed that nonanal concentration was
610 dependent on smoking, but was independent of the amount of tobacco consumed, age
611 and gender [50]. A targeted analyses studying healthy smokers showed that acetonitrile
612 is readily detected by SIFT-MS in the breath and urinary headspace of smokers at levels
613 dependent on the cigarette consumption, but is practically absent from the breath and
614 urine headspace of non-smokers, see some further references re breath and smoking
615 [51–57], which also describe various furans. This is not to say that these compounds arise
616 only in smokers, but that they show higher concentrations in them.

617 Quite a number of volatile compounds may be related to food consumption, medication
618 (or effects of) or professional exposure [58–61]. Some of the compounds in breath are
619 produced by bacteria in the mouth [62] and by bacteria in the gut, such as hydrogen [63]
620 and methane [64] and undoubtedly many more. It could very well be the case that

volatiles from oral anaerobes in the mouth confound breath biomarker discovery and this has been studied [9].

The most prominent volatile compounds in breath are isoprene [65–68] and acetone [68–70]. Isoprene, identified and quantified in more than half of the papers analysed for this review, is a by-product of the mevalonate pathway, but also produced (or at least stored) in the periphery of the human body [71,72]. Acetone can be formed from acetoacetate by acetoacetate-decarboxylase. Isoprene is 'the' paradigmatic example for a compound whose concentration in exhaled breath changes enormously during exertion of an effort [71,73–75]. 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 [76]. But the pioneering work of King *et al* [71–73,75] demonstrated that the increase in cardiac output alone would not be able to lead to the observed pronounced increase in isoprene. 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 [71–75]. Apart from isoprene, also other compounds increase during exertion. Among these compounds are methyl acetate, dimethylsulfide and 2-pentanone [74]. This is in contrast to the prediction of Farhi's equation [77], which would predict a decrease in concentration during effort. An example of a compound which follows Farhi's equation is butane [74].

The big advantage of exhaled breath, in comparison to blood, is the fact that it can be sampled as often as 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 [78]. In measurements during sleep, isoprene and acetone display very different concentration characteristics. Both show (often) increasing concentrations during the 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.

In contrast to GC-MS and SESI-MS, a more limited number of volatile compounds in exhaled breath have been investigated with PTR-MS [79-83] and SIFT-MS [84-86]. These techniques are inherently quantitative, without the need of external calibration which greatly expands their real-time measurement capabilities. More recently they have been coupled with thermal desorption units, to enable sample collection and later analysis for

654 large-scale studies [87]. In the future, real-time measurements should be performed for
655 all VOCs, giving rise to the possibility of modelling their production and metabolism
656 within the human body. Also their connection to food consumption, smoking habits or
657 medication would be very interesting. A particular interest is in therapeutic monitoring
658 of drugs and their metabolites. As an example, consider valproate which is administered
659 to avoid seizures in epileptic patients or in persons suffering from propionic acidemia
660 [58] and is metabolized to 3-heptanone which can be observed in exhaled breath [58].
661 Since the concentration of 3-heptanone in normal healthy volunteers is <1 ppb, virtually
662 all the 3-heptanone in exhaled breath can be attributed to metabolized valproate. Such
663 metabolic changes inducing the release of specific VOCs may allow therapeutic
664 monitoring of different drugs in the future.

665 Many of VOCs in breath may have exogeneous sources [88–92], be produced through
666 medication [58,93] or be released by bacteria in the airways [94,95], the oral cavity
667 [93,96–101] or in the gut [30,63]. The concentrations of volatile compounds in exhaled
668 breath may depend on the sampling method [102–105] and on the specific Henry's
669 constant between blood and breath [106–108] which depends on haematocrit (blood cell
670 volume) and other parameters.

671

672 ### *5.2. Volatile organic compounds found in saliva*
673 The profile of VOCs in saliva can give information about the oral health and oral
674 microbiome. Saliva has many advantages over breath in terms of sampling, shipping and
675 storage of samples. Moreover, saliva is considered as an equivalent of blood which does
676 not require invasive collection, because there is an equilibrium of the dissolved
677 metabolites between the blood capillaries and the membranes of the salivary glands
678 [109]. On the other hand, the problem with saliva is the possibility of contamination
679 during sampling and the problem with optimal sampling time, with some people being
680 less capable of saliva production.

681 The most comprehensive profile of VOCs is saliva was provided by al Kateb *et al.* in 2013
682 [110] and this has not changed since the previously published review [1]. After 2014, the
683 biggest contribution to the saliva volatilome was made by Monedeiro *et al.* [111] who
684 reported the presence of 162 VOCs in healthy subjects using headspace solid phase
685 microextraction (HS-SPME)-GC-MS methodology. The total number of VOCs reported in
686 saliva in this review is 549, which represents an increase of 96 compounds since 2014.

687 These additional VOCs were sourced from papers studying differences between diseased
688 subjects and controls (which were hopefully healthy [111–118]). All of these compounds
689 had previously been identified in other body fluids [1]. Most of the studies used SPME
690 fibres with different modifications as a sampling technique. As SPME is based on
691 absorption, the number of compounds detected is limited by the sorption properties of
692 the coating material. Improvements to the SPME method, using materials with larger
693 surface of absorption like coupons, blades and thin-films can significantly improve the
694 absorption capabilities, resulting in the detection of less abundant compounds,
695 impossible to detect with conventional SPME fibres.

696 The application of other, non-absorptive techniques, such as solvent extraction [119] may
697 allow for the extraction of a wider range of metabolites, and the detection of a higher
698 number of salivary metabolites in the future.

699 According to the recent database (Table1), the dominant chemical class in saliva is
700 alcohols, comprising approx. 16 % of all VOCs, followed by ketones (14 %) and cyclic
701 hydrocarbons (12 %). Taking into account all the types of hydrocarbons, they make up
702 34 % of all VOCs in saliva. The difference between the percentage composition of saliva
703 reported previously [1] is mainly due to the work of Monedeiro *et al.* [111] who reported
704 that alcohols and ketones are the dominant groups in saliva.

705 Aside from the studies aimed at profiling bodily fluids, some articles reported attempts
706 to apply saliva characterization for diagnostic purposes. The VOCs in subjects with oral
707 diseases of a possible bacterial origin, such as submandibular abscesses and halitosis
708 were compared to the saliva profiles of healthy individuals [111]. The authors reported
709 the presence of 23 and 41 VOCs specific for halitosis and submandibular abscess,
710 respectively. Halitosis resulted in a larger number of sulfur compounds, while
711 submandibular abscesses, which is an inflammatory disease, was characterized by a
712 greater abundance of inflammation-associated alcohols, aldehydes, and hydrocarbons.
713 The comparison of saliva VOCs between healthy children and children with celiac disease
714 showed that the abundance of some VOCs, such as ethyl acetate, nonanal, and 2-hexanone
715 is different in children with celiac disease treated with a gluten-free diet, compared to
716 healthy children [113].

717 Moreover, saliva analysis has raised interest in the forensic science area. The SPME-GC-
718 MS analysis of different bodily fluids showed that despite the similarities within a fluid,
719 there is a large number of quantitative differences in each specimen, characteristic for

720 the individual person, with a low occurrence of matching errors [112]. It was found that
721 saliva and hand odour were the most efficient for differentiation of subjects, providing
722 sufficient stability and variability for differentiation.

723 SPME in thin-film geometry (TF-SPME) was used for the retrospective analysis of the
724 intake of 49 prohibited substances and steroids by measuring their metabolites in saliva
725 [114]. As the authors underlined, saliva is a good specimen for doping control as it
726 contains mostly non-conjugated, biologically active forms of drugs. GC-MS analysis
727 allowed for the detection of 26 VOCs in saliva, without derivatisation.

728

5.3. Volatile organic compounds in blood

730 Blood directly reflects the internal environment of the body, including nutritional,
731 metabolic, and immune status [120]. Thus, the analysis of plasma-derived VOCs in blood
732 has been an active area of research. However, obtaining blood samples is not trivial
733 requiring trained phlebotomists. It is not well tolerated by patients in comparison to
734 producing a breath or urine sample, and blood samples usually require pre-treatment
735 which is costly and time consuming.

736 379 VOCs have been identified from blood, which is relatively few compared to the
737 number found in breath [106]. However, this is a large increase compared to the previous
738 review in 2014 where only 154 VOCS were reported. There certainly is not a lack of
739 studies reporting the analysis of volatile compounds in blood. However, these studies
740 tend to be focused on the monitoring of exposure to environmental pollutants [121], the
741 quantification of blood alcohol [122] and other inhalants derived from solvents [123],
742 and storage and aging of blood for forensic applications [124–127].

743 However, there have been relatively few studies which compared the volatile profiles
744 above blood in healthy volunteers versus a diseased group. Zlatkis *et al* [128] studied the
745 sera of seemingly healthy individuals versus virus infected patients using capillary GC.
746 Although example chromatograms were presented showing a large number of peaks for
747 both groups, the identification of compounds was limited. It was found that virally
748 infected patients had a wider range of VOCs associated with their samples [129]. Recently
749 there have been two studies which measured the blood volatiles of patients with liver
750 [130] and lung cancer [131] versus healthy individuals. Horvath *et al* [132] described the
751 results of a study where trained dogs could discriminate between blood samples from
752 ovarian cancer patients and blood samples taken from patients with other gynaecological

cancers or from healthy control subjects. A paper by Wang *et al* [133] used SPME-GC-MS to differentiate blood samples of 20 healthy volunteers from colorectal cancer patients. Only the few compounds which were significantly higher in the healthy group were reported.

A few papers exist looking solely at the VOC profiles of healthy volunteer blood without a disease group for comparison [106,118,134]. Mochalski *et al* [106] and Ross *et al* [134] compared the volatiles appearing in blood to those found in breath, and Kusano *et* al used hand odour, oral fluid, breath, blood, and urine to differentiate between individuals.

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 [135]. 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 [136–139]. The studies tended to use purge and trap analysis combined with GC-MS [137] but more recently they have adopted SPME based methods coupled to GC-MS [136]. 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 [135]. 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 [140]. There are commercial tests available which give a measure of the volatile solvent profile in blood versus the NHANES data [135].

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 GC 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 [141]. 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 [123]. Volatiles such as diethyl ether,

786 butane, ethyl acetate, hexane, toluene, xylene, and some halogenated hydrocarbons are
787 common VOCs with the potential for abuse via sniffing [142]. It may be particularly
788 important to measure these compounds in blood samples taken at autopsy, if the death
789 is suspicious [143]. These additional VOCs also have the potential to interfere with the
790 blood alcohol analysis, so their separation and measurement is important [141].
791 The measurement of ammonia in blood is also an established clinical test [144]. Many of
792 the procedures for ammonia determination involve two general steps: the release of
793 ammonia gas or capture of ammonium ions from the sample and the quantitation of the
794 liberated gas or captured ions [145]. Detection is typically via colourimetric/fluorimetric
795 methods [146], gas sensitive electrode [147] or enzymatic methods [148,149]. Elevated
796 levels of ammonia in blood is considered a strong indicator of an abnormality in nitrogen
797 homeostasis, the most common reason is related to liver dysfunction. Hyperammonemia
798 arises from excessive production by colonic bacteria and the small intestine. At high
799 levels ammonia is a potent toxin of the central nervous system and has been linked to
800 hepatic encephalopathy (HE). However, breath ammonia determination is not currently
801 accepted as a reliable marker of HE, although a large amount of data supports the role of
802 hyperammonaemia in the direct and indirect alterations of brain function underlying HE.
803 A relatively recent paper [150] describes the measurement of capillary blood (an
804 equivalent to arterial blood) following an oral glutamine challenge. This method was
805 more successful at identifying minimal HE than the use of capillary blood measurements
806 alone.
807 Since our previous 2014 review [1], there have been a handful of forensic science papers
808 on how storage and aging of blood impacts its VOC profile [124–127], as this has
809 implications for sniffer dog training. Dubois *et al.* used variable energy electron impact
810 ionization TD-GC-GC-TOF-MS and found it was able to monitor subtle changes in blood
811 VOCs within the first week of aging. Whilst these publications have yielded a great of deal
812 of data, and found new compounds previously unidentified in blood, only the data from
813 fresh blood which hasn't aged or decomposed could be included in this review.
814
815 ### 5.4. *Volatile organic compounds in milk*
816 This review has identified 290 compounds in human milk. This represents only a small
817 increase vs the 2014 review where 256 compounds had been identified. There are many
818 papers on the nutritional composition of human milk (as an example see the review by

819   Jenness [151] and also on the presence of environmental chemicals (as an example see
820   the review by LaKind [152]), but there is relatively little specifically relating to the
821   volatile components. Most GC-MS analytical studies appear to be directed at identifying
822   the presence of a specific pollutant, medicinal substance, or group of environmental
823   compounds, to support research on chemical exposure to the nursing infant or using milk
824   as a geographical pollutant indicator. A literature search revealed numerous papers on
825   organochlorine pesticides, brominated diphenyl ethers, dioxins, polychlorinated
826   biphenyls, parabens, triclosan, polycyclic musk fragrances, flavonoids, and many others.
827   However, not all these compounds can be considered as volatiles at body temperatures.
828   Others studies looked for compounds transferring to breast milk from mothers taking
829   specific dietary supplements, such as the search for odorous components from fish oil
830   [153] or 1,8-cineole metabolites after taking 1,8-cineole capsules [154]. Studies looking
831   for specific compounds after exposure to environmental contamination, medication, or
832   dietary supplementation have not been included in the tables. The most extensive list of
833   likely volatiles was given by Pellazari *et al* [155] who identified 156 'purgeable'
834   compounds from maternal milk, in a study to evaluate the utility of using milk in pollutant
835   studies. A wide range of classes of compounds was identified by GC-MS from passing
836   helium gas through warm milk and trapping vapours on a Tenax cartridge. Similar classes
837   of compounds were reported by Shimoda *et al* [156] using a diethyl ether distillation-
838   extraction. Other studies have looked for specific organic compounds in the headspace
839   above milk using SPME with GC-MS (four VOCs [157], monocyclic aromatic amines [158],
840   phthalate esters [159], benzene and alkylbenzenes [5,160]. A broader study, also using
841   the SPME method, attempted to quantify 36 different VOCs [161] and identified 10
842   compounds whose median concentration across 12 samples was above the 'lowest
843   recordable level'. Buettner *et al* has analysed the volatiles from milk and in one study
844   identified 45 odour-active constituents, using olfactory GC in combination with GC-MS
845   [162].
846   A study from 2009 [163] made a comparison between mother milk and formulas,
847   underling in these, the presence of different volatiles related to the heat treatment of milk,
848   such as methional, 2-furfural, and sulphides. On the other hand, the GC-MS analyses
849   revealed a higher variation in the volatiles from milk compositions for the mother's milk,
850   exposing the infant to more diverse flavour, including a higher variety of terpenes
851   probably originating from the maternal diet. Another study regarding the quality of

852   breast milk has been published in 2010 [164], using high-resolution gas
853   chromatography–olfactometry (HRGC-O) to investigate the reasons behind the formation
854   of the typical fish-like and metallic off odour during the storage of human milk, not to be
855   found in the cow milk under the same conditions. In this case, the studies underlined the
856   presence of oxidation products from long-chain (poly)unsaturated fatty acids such as (Z)-
857   1,5-octadien-3-one, trans-4,5-epoxy-(E)-2-decenal, 1-octen-3-one and (Z)-3-hexenal.
858   Fatty acid degradation products have also been found to be responsible for changes in
859   milk flavour [165,166] using two-dimensional high-resolution gas chromatography-mass
860   spectrometry (TD-HRGC-MS) and GC-MS analyses. These studies investigated the
861   modifications occurring in the metabolite profile when breast milk is subjected to
862   different treatments. Analogously, Garrido *et al* [167], showed how high-pressure
863   thermal (HPT) treatments can modify the volatile profile, increasing the abundance of
864   different chemical groups (aldehydes, ketones, furan, pyrans, alcohols), and decreasing,
865   on the other hand, the content of aliphatic hydrocarbons present in the non-treated
866   human milk samples. Also in these cases, the changes in the VOC profile can be attributed
867   to the negative odours sometimes attributed to human milk. As much as the storage and
868   ambient conditions, also the mother's diet, both in the phases of pregnancy and nursing,
869   was found to have a direct connection with the breast milk volatiles profile [168]. On the
870   same issue, Ramsons (a plant with garlic like odour) consumption was found to affect
871   milk aroma, as pointed out by Scheffler *et al* [169], who identified volatile ramson-
872   derived metabolites in human milk, applying gas chromatography-mass
873   spectrometry/olfactometry (GC-MS/O). An analogous study was also conducted
874   regarding garlic consumption [170].
875   Hartmann *et al* [171] employed GC-MS to investigate the presence of 5-α-androst-16-en-
876   3-one in human breast milk, underling the issues and the procedures needed when it is
877   necessary to underline a specific compound in the milk matrix. Another research group
878   also focused on a specific compound [154,172], 1,8-cineole, again investigated by GC-MS.
879   These studies also point out how the analysis of the volatiles in human milk are promising
880   for health monitoring since metabolite profiles in milk might be substantially different
881   from those in the commonly analysed body fluids of blood and urine, due to the high lipid
882   content.
883
884   *5.5.   Volatile organic compounds from skin secretions*

885   The number of different compounds identified from human skin secretions is very large.
886   Our literature search revealed 623 named VOCs analysed from skin secretions (an
887   increase compared to the 532 found in the previous version in 2014 [1]. Odour can be
888   particular to an individual and distinguishable both by people and by canines [173]. Also
889   skin is not homogeneous and the distribution of the different types of glands and
890   microbiota across the body can be expected to lead to different VOC profiles. Even the
891   odours of a single individual varies; with diet, emotional state, menstrual cycle, age, and
892   many others factors [174,175]. Studies of the secretions from the skin are particularly
893   susceptible to interference from personal care products. Although experimental
894   procedures attempt to minimize the presence of exogeneous compounds by asking
895   subjects to refrain from use of such products apart from a designated soap for a time
896   period before testing, some identified compounds are highly likely to come from
897   exogeneous sources [176,177]. Bernier *et al* [178] reported hundreds of compounds
898   spanning a wide range of classes, in a study attempting to identify candidate mosquito
899   attracting compounds. Samples were collected from the hands using glass beads and
900   analysed by GC-MS. Many of the compounds were relatively high MW species and it could
901   be argued that some would be expected to have limited volatility at body temperature.
902   The papers of Zeng *et al* [179,180] list a number of C-6 to C-11 acids and in particular E-
903   3-methylhex-2-enoic acid, as responsible for characteristic axillary (armpit) odours along
904   with a large n-dodecanoic acid peak, lactones and alcohols found in solvent extraction of
905   worn absorbant pads. Other studies also look specifically for odiferous axillary
906   compounds. Kuhn and Natsch found a genetic contribution to odorant carboxylic acids
907   [177] and Hasegawa *et al* [181] found a difference between 'spicy' and 'sour' axillary
908   odour and identified sulfanyl alcohols. Another study analysed compounds on the
909   forearm [176] by using ethanol and hexane extraction. However, relatively few
910   compounds are common to these or other papers.
911   The difficulty of identifying a set of VOCs characteristic of human sweat is exemplified in
912   the paper of Penn *et al* [182] looking at 'fingerprints' in human odour. They used
913   polydimethylsiloxane coated stirrer bars to collect axillary samples from 194 individuals
914   over 10 weeks; 4941 separate GC-MS peaks were found of which only 373 were
915   consistent over time within an individual (118 were chemically identified). They report
916   very few of the peaks as common to all samples. Only 38 compounds were found to be
917   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* [176] lists a set of volatile compounds from the forearm, when collected using SPME fibres held above the arm compared with solvent extraction. Haze *et al* [183] 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. Zhang *et al* [184] 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-GC-MS has also been used to study axillary odour [185] para-axillary and areola volatile compounds for possible mother–infant recognition chemicals [186,187] 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, there are very few named compounds that are common between studies. As an example, nonanal occurs in twelve of the publications under examination, decanal (11 times), octanal and 6-methyl-5-epten-2-one (10 times each) and finally octanoic acid and acetic acid (7 times each). This was also observed by Prada e*t al* [188], using SPME-GC-MS. Dormont *et al* [189] pointed out the great importance of sampling when the sample collection occurs outdoors. The authors compared four methods for sampling skin odours: solvent extraction, headspace SPME, and two new techniques not previously used for the study of mammal volatiles, contact SPME and dynamic headspace with a chromatoprobe design (miniaturized trapping tubes that are directly inserted into the GC injector for thermal desorption). The same study underlined the prevalensce of aldehydes in the volatile profile, in particular nonanal and decanal. The same research group in 2013 [190] pointed out the complexity, in terms of the number of compounds, featuring in the chemical profile of skin volatiles. This work underlined, that the compounds found in human skin vary widely depending on the part of the body where the samples are collected and the sampling methods employed. For example, the axillae region is characterised by apocrine, eccrine and sebaceous glands, which in addition to the microbiota bring about a specific volatile profile. This profile features mostly alkane and C_6-C_{11} carboxylic acids. Different VOCs were found in the hand, primarily aldehydes and ketones (nonanal, decanal, undecanal, 6-methyl-5-hepten-2-on and geranylacetone). This was also confirmed by Mochalski in 2018 [191], where the use of ion mobility spectrometer coupled with gas chromatography (GC-IMS) was found to present considerable potential for the detection

951 of VOCs. At the same time it presented some drawbacks, like the fact that some interesting
952 classes of VOCs such as alkanes cannot be measured using that IMS instrument. The
953 ionisation source determines the range of compounds that may be detected, e.g. a beta
954 emitter such as nickel 63 does not detect alkanes, while a photo ionisation source in
955 conjunction with an IMS detects alkanes sensitively.

956 An IMS coupled with a short multi-capillary column (MCC) was instead employed by
957 Ruzsanyi et al [187] for near real-time monitoring of human skin emissions, who pointed
958 out that octanal, nonanal and decanal may originate from the skin. Curran *et al* [192]
959 presented 24 different compounds employing SPME-GC-MS to measure human scent, and
960 utilize it to identify and distinguish between individuals.

961 Another interesting avenue for VOCs from the skin is finding a correlation between them
962 and the compounds found in blood. From the study of the literature, families of VOCs have
963 been found to be present in both blood and skin. Namely: aromatic compounds (16
964 compounds in common), aldehydes (15), acyclic alkanes, alcohols (14), ketones (13),
965 nitrogen-containing compounds (8), esters (7), acyclic alkenes, acids (6) non-aromatic
966 cyclic hydrocarbon, sulfur-containing compounds and ethers (3 each) and halogenated
967 compounds.

968

969 ### *5.6.   Volatile organic compounds from urine*

970 The recent review revealed 444 VOCs associated with urine [196–198] compared to 279
971 reported in the previous version. The largest number of compounds identified in urine
972 belong to the ketone group. Ketones in urine are likely to at least partially arise from
973 bacterial action in the gut, maybe by decarboxylation from the corresponding oxo-acids,
974 since ketones were found at much lower concentrations in the urine of 'germ free' rats
975 [193]. Levels of the key ketone bodies, propanone (acetone) and acetoacetate have been
976 found to vary between 1.16–14 mol L^{-1} and 1.3–15 mmol L^{-1} respectively in urine [199].
977 The ketone bodies (acetoacetate, hydroxybutyrate and propanone) are produced in the
978 liver during periods of rapid fat oxidation, when the rate of fat breakdown exceeds the
979 capacity of the Krebs cycle to process the resulting acetyl CoA [200,201].

980 Several significant studies of VOCs in urine have been undertaken e.g. [193] **,**[194]. Nine
981 compounds were present in all studies: propanone, 2-butanone, 2-pentanone, 2-
982 heptanone, 3-hexanone, 4-heptanone, 2, 5-dimethylfuran, 2-ethyl-5-methylfuran and
983 toluene, so can be present with a very high degree of certainty. A study [195] of 4-

984   heptanone in urine strongly suggest its presence originates at least in part from *in vivo*
985   oxidation of the plasticizer component, 2-ethylhexanoic acid.

986   Propanone, 2-butanone, 2-pentanone and 2-heptanone were also found ubiquitously in
987   the headspace of faecal samples from healthy individuals [9]. Propanone can be produced
988   by the non-enzymatic decarboxylation of acetoacetate and may sometimes be smelt on
989   the urine and breath in acute diabetes.

990   In summary, the VOCs in urine cover a range of chemical classes: e.g. acids, alcohols,
991   ketones, aldehydes, amines, N-heterocycles, O-heterocycles, sulfur compounds and
992   hydrocarbons (Table 1). When comparing the VOCS from urine and faeces a notable
993   difference is the number of esters. The relative levels have not altered since 2014 with
994   additional esters idemntified in faeces (10) and urine (7). However, there were no new
995   straight chain hydrocarbons identified in urine thus a notable difference remains, making
996   alkanes the smallest group for urine volatiles. Although previously identified, Cozzolino
997   *et al* [202] again detected hexane in their study of healthy children using SPME-GC-MS.
998   Cozzolino *et al* [196] pre-treated samples under both acidic and alkaline conditions,
999   followed by analysis with SPME GC-MS, identifying a total of 162 urine compounds, 42 of
1000   which were previously undetected. The combination of salting, pH change and solvent
1001   extraction by Cozzolino *et al* has shown many hundreds of compounds can be readily
1002   detected by a typical benchtop quadruple GC-MS..

1003   A large number of terpenes are described and are considered to be derived from food
1004   [193]. Little data exists on quantitative measurements of VOCs in urine. Concentrations
1005   of phenol (typically 10 mg day^{-1} excreted in urine) and p-cresol (typically 52 mg day^{-1}
1006   excreted in urine) have been reported to increase in urine with increasing protein intake.
1007   Their formation is considered to be due to gut microbiota acting on tyrosine; anaerobic
1008   bacteria in the left colon producing phenol and aerobic bacteria in the ileum/cecum
1009   producing p-cresol. The relationship is complicated by fibre intake. High fibre intake with
1010   high protein resulted in a smaller increase in concentration due to decreased transit time
1011   [203]. This study was motivated by phenols being implicated in bladder and colon cancer,
1012   which no longer is considered to be the case.

1013   Normal alcohol emission ranges reported are 0-46 mg/24 h for ethanol, 0–300 µg/24 h
1014   for n-propanol and 0–18 µg/24 h for n-butanol; these levels approximately mirror blood
1015   serum levels [183]. Trimethylamine and 4- heptanone, were quantified as 0.5 -20 µg ml^{-1}
1016   and 40–800 ng ml^{-1} respectively in urine [204].

It has been suggested that methylamine and other short chain aliphatic amines may play a significant role in central nervous system disturbances observed during hepatic and renal disease [205]. 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 [205]. 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 [206]. 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 [207].

New, alternative, and combined approaches have been employed to enhance how urine volatiles are detected. The volatiles in urine have recently been evaluated by combined odour and GC-MS chemical analysis. For the first time a comprehensive description of the smell of the individual components has been described [208]. This work also involved enzymatic (glucuronidase) pre-treatment followed by solvent extraction. Recently, Zou *et al* [197] developed a novel ultrasonic nebulization extraction proton transfer reaction mass spectrometry (UNE-PTR-MS) technique to rapidly detect selected compounds within a urine sample. Encouragingly, only 0.66 mL of urine is required for a full scan, which delivers a response in 34 s. The authors state this method overcomes lengthy pre-concentration processes, extended sampling procedures, and prevents alteration to the urine whilst in storage. Although no new urine compounds were detected, the technique showed promising results for common urine VOCs: methanol, acetaldehyde, and acetone, yielding relative recoveries of between 88.39 % and 94.54 %. However, the results stem from just one urine sample, therefore, further analysis would be needed to determine whether this new method is sufficient in detecting larger numbers and more specific VOCs in urine, perhaps identifying new compounds that may aid in disease diagnosis as suggested by the authors.

Benign prostatic hypertrophy (BPH), the medical term for an enlarged prostate, is so common in older men, it could be considered normal. About half of all men between ages

1049 51 and 60 have BPH and up to 90% of men over age 80 have it. This could affect urine
1050 volatiles but has not been investigated in any detail.

1051

5.7.   Volatile organic compounds from faeces

1053 The first report of gas analysis from faeces was in 1861 when Rüge reported that human
1054 rectal gas contained hydrogen, carbon dioxide, and methane, in addition to other
1055 unidentified gases [209]. Flatus is considered to be a mixture of hydrogen (0–50 %),
1056 nitrogen (5–90 %), oxygen (0–10 %), carbon dioxide (10–30 %), and methane (0–10 %).
1057 Methane production occurs in about 50 % of the healthy population, some members
1058 producing higher levels than others; methane production is correlated with
1059 methanogenic bacteria. Similarly, sulfate-reducing bacteria are responsible for the
1060 generation of pungent sulfides [210]. In the original compendium 381 compounds were
1061 reported in faeces, since then a further 62 compounds not stated in the original
1062 compendium have been found. Of these, 24 compounds had been reported from other
1063 fluids and have now been identified in faecal samples (Table 1). This now means that in
1064 total 443 compounds have been assigned an identity from faecal samples. These
1065 additional 62 compounds came from just 5 papers; this is indicative that while
1066 compounds have been added to the compendium it is very likely that there are more to
1067 be found. The 443 compound value still falls far short of the number of compounds found
1068 in breath, which is likely to be a function of a smaller number of studies carrying out
1069 qualitative analysis on faecal samples when compared to breath.
1070 Significant concentrations of a range of volatile fatty acids [211], indoles [212] and
1071 phenols [213] have been observed in faeces. Fermentation of carbohydrates in the gut
1072 produces ethanoic, propionic, butanoic, pentanoic, and hexanoic acids, particularly
1073 by *Bacteroides* [214]. *In vitro* studies [215] have provided evidence that proteinacious
1074 foods also produce SCFAs via the action of bacteria such as *Clostridia spp.*; BCFAs, such as
1075 2-methylbutanoic acid and methylpropionic acids, are principally produced by gut
1076 microbial action on proteins via the respective branched amino acid.
1077 Gould *et al* [216], conducted a study in which ^{13}C labelled compounds were used as
1078 internal standards in faecal samples to quantify 15 compounds. This study is unique as it
1079 is the only work, we have identified in which many compounds were quantified based on
1080 what is in the faeces and not just the headspace. This work also turned the faeces alkaline
1081 by the addition of sodium hydroxide to quantify trimethylamine, which is the first-time

1082   this has been reported from faeces [216]. This paper contributed 12 new compounds to
1083   the previous compendium [1], including 4-isopropyl benzaldehyde (cuminaldehyde), and
1084   2,4-dithiapentane which are associated with cumin and truffle fungus, respectively. Long
1085   chain fatty acids (LCFAs) were quantified in work by Song *et al* [217]. Nine of these
1086   compounds were previously reported as being found in skin and/or saliva (Table 11).

1087   Both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are compounds that
1088   were not found in the original compendium. EPA and DHA are omega 3 fatty acids found
1089   in cold water fish, these compounds are also used as dietary supplements as they are the
1090   fatty acids that form cellular walls in the brain and eyes [218]. A recent mechanistic study
1091   in how unsaturated long chain fatty acids are oxidized in the body to form many smaller
1092   metabolites is described [10].

1093   Volatiles such as methanethiol and ammonia are considered to be derivable from
1094   methionine by the action of bacteria such as *Clostridium sporogenes* [219]. Hydrogen
1095   sulfide and methanethiol can be damaging to the large intestinal epithelium and are also
1096   generated from sulfur-containing substances in the diet [220]. Similarly, fermentation of
1097   tyrosine and tryptophan in faeces has been shown to produce the VOCs phenol and
1098   indole, respectively [219]. Phenol and *p*-cresol are considered to be produced by aerobic
1099   intestinal microbiota acting on tyrosine and the latter by anaerobic organisms [211].

1100   Of the 58 compounds new to faecal samples 13 of those were previously found in saliva.
1101   There is newly emerging evidence that the oral microbiome might have an impact on the
1102   gut microbiome [221]. Olsen and Yamazaki present work in which patients with chronic
1103   periodontitis the bacteria *Prophyromonas gingivalis* creates dysbiosis which in turn cause
1104   dysregulation of the gut microbiota [221].

1105   Two earlier studies stated that a total of 297 and 135 different VOCs have been identified
1106   respectively by Garner *et al* [9] and De Preter *et al* [222] in the headspace of faeces from
1107   healthy individuals on an *ad libitum* diet. These two studies showed that typically, for
1108   each donor the number of VOCs ranged from 78 to 125 (median = 101). Interestingly, 44
1109   compounds were stated to be common to 80 % of the cohort samples [9].
1110   Dixon *et al* [223] hypothesized that the varied functionality of the metabolites in the
1111   headspace of faeces, dictated the use of several diverse SPME fibre coatings for more
1112   comprehensive metabolomic coverage. They evaluated eight different commercially
1113   available SPME fibres in combination with GC-FID and GC-MS. This approach appears
1114   very promising; 267 peaks were found with GC-FID though the authors have yet to

1115 identify all the compounds. SPME can suffer from competitive absorption, the length of
1116 equilibration time of the sample, and length of time the SPME fibre is exposed can all
1117 effect what compounds are absorbed onto the fibre. This means that not all the
1118 compounds from a matrix, particularly one as complex as faeces, are absorbed.

1119 Alcohols were thought uncommon in adult faeces [224]. However, the studies reported
1120 in this review reported 52 different alcohols to be present. Ethanol is very commonly
1121 observed. It is likely that gut bacteria can reduce acids to alcohols. Esters were found to
1122 represent the largest group of compounds identified. An interesting readily observed
1123 feature of the esters in stool is the similarity of the higher MW compounds, they either
1124 possess a long-chain acid and short-chain alcohol or a short-chain acid and long-chain
1125 alcohol. This suggests that the number of esters identified is not a true picture of what is
1126 present in the faeces but a limit on the method i.e. the volatility of the esters. It is very
1127 likely that a more sensitive method or better pre-concentration will significantly increase
1128 the compounds observed.

1129 A diverse range of aromatic compounds (Table 1) including mono-, di-, tri- and tetra-
1130 substituted benzenoids, mono- and di-substituted furans, and nitrogen containing
1131 derivatives of pyridine, pyrrole, and indole have been reported. Most of these have only
1132 been recently reported in faeces, although it has been established that phenolic and
1133 indole compounds arise from the metabolism of aromatic amino acids by gut bacteria
1134 [215]. There are many publications which have observed that alkyl furans are produced
1135 by fungi. In contrast there is a paucity of publications relating to furan biosynthesis by
1136 bacteria. Fungi are well known to be commensal organisms in the gut, which could
1137 explain the origins of furans, possibly from the metabolism of fructose. Furans are now
1138 considered to be also synthesisable from the oxidation of polyunsaturated fatty acids *in*
1139 *vivo* [10]**.** Some benzenoid compounds such as dimethylbenzenes, ethylbenzene, and
1140 toluene (constituents of petrol) probably arise from air pollution.

1141 A range of aldehydes have been reported [9] in the faeces of individuals. A complete
1142 homologous series has been reported from ethanal to octadecanal. Ethanal is of particular
1143 interest due to its abundance and is considered to promote mutagenesis [225–227] and
1144 be associated with bowel cancer. The toxic effects of higher aldehydes have received
1145 much less attention. The origins of some aldehydes may be dietary. For instance, 2-
1146 methylpropanal, 3-methylpropanal, hexanal, nonanal, decanal, and benzaldehyde are
1147 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 [9], which probably arise from fatty acid and carbohydrate metabolism [228]. 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 [9] since it may have health implications by impacting on the growth of some bacteria and yeasts [229]. 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 reduction of carbon dioxide, or from acetic acid, and potentially from oxidation of some unsaturated fatty acids *in vivo*.

Numerous hydrocarbons have now been discovered in faeces although the longer chain species have been found in small numbers [9]. Isoprene has been extracted from faeces [230]. Isoprene in the gut may be the result of cholesterol biosynthesis [231] 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 [232]. 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 [9] 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 [233]. Copaene is found in potato extracts [234].

Many ether compounds have been reported in the headspace of faeces. Commonly, 2-ethoxyethanol occurs in manufactured products like soaps and cosmetics [235] and 1,3-dimethoxybenzene is a registered food additive in Europe [9]. 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 [236]. Chlorination for disinfection of drinking water is another source resulting in the production of chloroform and halogenated methanes [237].

1181   Many nitrogen compounds have been reported (Tables 2a-2c) and are likely to arise from

1182   the diet; for instance, methylpyrazine, pyridine, and pyrrole are constituents of coffee.

1183   However, pyrrole readily polymerizes with acid and, therefore, its presence is unlikely to

1184   be dietary, as it would be unlikely to survive transit through the stomach. Ammonia

1185   results from microorganism activity. In addition, increasing the amount of protein in the

1186   diet from 63 g to 136 g/day was found to increase the amount of faecal ammonia from 15

1187   to 30 mmol l^{-1}. Interestingly, increasing the amount of fibre to the high protein diet was

1188   reported to not alter the ammonia concentration [203]. In a study of nitrogen containing

1189   compounds in the faeces of 30 healthy individuals indole was the only compound found

1190   ubiquitously [9], followed by 3-methylindole, in 73 % of individuals, these compounds

1191   are well known to be produced by microbial degradation of l-tryptophan in the gut. Many

1192   compounds are present in a minority of volunteers. Allyl isothiocyanate was found to be

1193   present in 23 % of cases; this compound is of particular interest due to its suspected anti-

1194   cancer properties. Its occurrence would be expected to be determined by a number of

1195   factors such as diet (cruciferous vegetables e.g. broccoli, cauliflower, and cabbage), the

1196   cooking of these vegetables, and the ability of the host's bacteria to break down sinigrin,

1197   the main glucosinolate of Brussel sprouts.

1198   A diverse range of sulfur compounds has been reported. For instance, methanethiol and

1199   dimethylsulfide have been commonly observed; the former is, at least in part, considered

1200   to be produced from methionine by *Clostridia* in the gut [219]. Methanethiol has a toxicity

1201   approaching cyanide and the factors controlling its concentration and biosynthesis might

1202   warrant further investigation. Methanethiol and dimethylsulfide may also be produced

1203   by methylation of hydrogen sulfide as a detoxification mechanism by mucosal thiol *S*-

1204   methyltransferase [238]. Dimethyldisulfide and dimethyltrisulfide have both been

1205   commonly reported in faeces [9,239,240]. Hydrogen sulphide is probably most likely to

1206   occur due to the metabolism of sulphate by sulphate-reducing bacteria [239]. Sulphate,

1207   which is poorly absorbed in the small bowel, is naturally present in cruciferous

1208   vegetables and nuts and as an additive in bread and beer [239]. The main sulfur-

1209   containing flatus components in healthy individuals have been quantified: hydrogen

1210   sulphide (1.06 µmol l^{-1}), followed by methanethiol (0.21 µmol l^{-1}) and dimethyl sulphide

1211   (0.08 µmol l^{-1} [239]. The authors were concerned about the social aspect of pungent

1212   flatus and found in their study that hydrogen sulphide and methanethiol appeared to be

1213   principally responsible and not indole-based compounds as previously thought.

5.8.   *Volatile organic compounds from semen*

1215

1216 In semen, 196 compounds have been reported. To date, it appears only one research
1217 group has published on VOC profiles in semen, using an investigation of healthy subjects,
1218 using SPME in the headspace above the semen combined with GC-MS detection [241].
1219 Semen assessment is the key test for infertility problems with a seminogram being the
1220 gold standard. Recently, metabolomics research was proposed as a method supporting
1221 male fecundity. Changes in the pattern of metabolites in semen may reflect the metabolic
1222 status of the sperm cells and the composition of the seminal fluid, which could affect the
1223 reproduction capacity. Most of the metabolomic studies on semen have been conducted
1224 using NMR and LC-MS, focusing on the secondary metabolites [242–244]. On the other
1225 hand, the volatile pattern of semen which could contribute to the fast detection of fertility
1226 problems remains hardly explored [241]. The authors detected the presence of 196 VOCs
1227 in semen samples collected from 69 men. The number of VOCs in semen, from each man,
1228 ranged from 3-28 VOCs. Curiously, no compound was present in all samples and 126
1229 compounds was observed only once. Also, interestingly, 98 of the reported compounds
1230 were detected for the first time in biological fluids. The dominant group of compounds in
1231 semen were nitrogen-containing volatiles, comprising more than 30 % of all the
1232 compounds identified. The tetramine, spermine, a compound found in semen at about 3.3
1233 mg/g and responsible for the characteristic odour of semen [245] was not reported in the
1234 study of Longo *et al* [241].

1235 It is worthwhile to underline that the majority of the compounds were detected only in
1236 one of the analysed samples, and only 70 VOCs were detected at least twice. The most
1237 frequently observed compounds were pyrrole, ethanol and 2-methylbutanal. The
1238 majority of the compounds had an exogenous origin according to the Human Metabolome
1239 Database [246], with 57 compounds that could have both exogenous and endogenous
1240 origin. The authors found there was an association between the VOCs profile and the
1241 sperm motility. There surely are more volatile compounds to be discovered in semen,
1242 considering the number of VOCs reported from other bodily fluids. It is suggested that
1243 further research in this area to establish a better base of VOC composition in semen from
1244 healthy men, could be beneficial to aid diagnoses of certain urological diseases.

1245

6. Conclusion

1246

A study of VOCs from healthy humans is presented for a variety of reasons. There are many more papers than ever before now comparing ill patients with controls, These publications more often than not, have a favourable conclusion, that there are promising differences in the VOC profiles between the diseased patients and the non-diseased volunteers. Furthermore, there are many published studies where presence and absence of VOCs is considered for correlations with disease and controls (some researchers, now avoid the term VOC biomarkers). The present review now shows many of these "absences" are being found in healthy subjects, which neutralizes to a degree, their use in disease diagnoses. Presence and absence is no longer good enough, concentration is key. Absence could be that the compound really is not there, such as in the case of detecting a microbial toxin, where a bacterium does or does not produce a toxin. It is appreciated there may still be a case for comparison if exactly the same conditions and equipment sensitivity is applied. Diet from weeks, months ago could affect breath volatiles. It is simply very hopeful to design methods for clean air breathing with the belief that this will permit standardised results. An important reason for justifying this, is expanded on. Diet from weeks/months ago affects the lipid composition of the body, our MUFAs and PUFAs are determined by genetics and diet. These lipids are continuously being oxidized, producing a wide range of VOCs. such as alcohols, alkenes, alcohols and carboxylic acids [10], which can then be further metabolized into daughter compounds, e.g. by further oxidation in the liver etc., also concomitantly there are many new compounds being reported. There is a huge difference, almost 1000 compounds, between the numbers reported in 2014 and in 2020. There is then more scope, considering the huge variety of compounds, for finding correlations for disease diagnoses.

Limited studies have been undertaken on exercise/movement and VOCs in breath etc. One such study has shown isoprene for instance does fluctuate with exercise in healthy humans. This might simply be considered as a simple, interesting observation, however if this phenomenon occurs for isoprene, what about the thousands of VOCs now listed in this review, which have not been studied, maybe the same phenomenon occurs for many of these. It could very well be the case that ill people may be less active, they may even be horizontal in a hospital. If a range of VOCs are being used for disease diagnoses it may be somewhat compromised by this situation.

When the 2014 review was published the tables showed there were many gaps in the sub tables i.e. there would be a homologous series with compounds missing here and there

1280 i.e. "gaps"), such as in the first years of the periodic table being constructed. The absence

1281 of a certain compound could be considered to be due to a lack of a metabolic route, or due

1282 to the inability of the detection equipment, or some other reason. Many of these "gaps"

1283 have been filled in this current review compared to 2014 highlighting that further studies

1284 are required to identify the extent of the human volatilome. Another important

1285 consideration is the lack of validation of the current reported compounds from the human

1286 volatilome with a small % validated by standards. Therefore, effort should also focus on

1287 proper validation of the already reported compounds adhering to the principles of

1288 identification outlined in the metabolomic standards initiative.

1289 This review, unlike the earlier 2014 review shows within the tables the publications

1290 where each compound was originally reported, this can add confidence to the data

1291 especially where several research groups have identified the same compounds.

1292 For discussion, one might think the healthy controls would have many similarities,

1293 although this review shows only 14 compounds were common to all the bodily fluids and

1294 breath. One might not have expected this, and it would be preferable for disease

1295 diagnoses if there was a greater core number of compounds that differ in concentration

1296 between disease states. As an example, a recent study, described herein, found 4941 GC-

1297 MS peaks in the sweat of a group of healthy humans and found very few peaks common

1298 to all samples.

1299 In an attempt to have more control over the jungle of compounds, one might consider

1300 controlling diet, between patients and volunteers however then there is the difficulty that

1301 there are different type and concentrations of bacteria, in our bodies. Gut transit time in

1302 healthy humans, varies between individuals. and this is known to affect gut chemistry.

1303 Then there are the VOCs in the environment – "the human exposome" which is highly

1304 individual, and furthermore these compounds can often be converted to other

1305 compounds in our bodies. The control group and patients are unlikely to individually be

1306 exposed to the same compound types at the same concentration levels.

1307 We are therefore assured that there will be a wide range of differences in the human

1308 volatilome, each of us could very well be unique, hopefully though with enough similarity

1309 so that quality correlations between control and disease states, will occur.

1310 This review now summarises many classes and sub-classes of compounds and hopefully

1311 now that they are easily visible will assist in deciding whether to target particular classes

1312 or sub-classes or combinations thereof, to aid disease diagnoses, and also to decide which

is the appropriate bodily fluid or breath, which is the goal for many researchers in the VOC field.

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