# Blood and breath levels of selected volatile organic compounds in healthy volunteers

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## Abstract

Gas chromatography with mass spectrometric detection (GC-MS) was used to identify and quantify volatile organic compounds in blood and breath of healthy individuals. Blood and breath volatiles were pre-concentrated using headspace solid phase micro-extraction (HS-SPME) and needle trap devices (NTD), respectively. The study involved a group of 28 healthy test subjects and resulted in the quantification of altogether 74 compounds in both types of sample. The concentrations of species under study varied between 0.01-6700 nmol/L in blood and between 0.02-2500 ppb in exhaled air. Limits of detection (LOD) ranged from 0.01 to 270 nmol/L for blood compounds and from 0.01 to 0.7 ppb for breath species. Relative standard deviations for both measurement regimes varied from 1.5 to 14%. The predominant chemical classes among the compounds quantified were hydrocarbons (24), ketones (10), terpenes (8), heterocyclic compounds (7) and aromatic compounds (7). Twelve analytes were found to be highly present in both blood and exhaled air (with incidence rates higher than 80%) and for 25 species significant differences (Wilcoxon signed-rank test) between room air and exhaled breath were observed. By comparing blood, room air and breath levels in parallel, a tentative classification of volatiles into endogenous and exogenous compounds can be achieved.

**Keywords:**

Breath analysis, blood analysis, biomarkers, volatile organic compounds, SPME, NTD.

## 1. Introduction

Analysis of exhaled air has a great potential for medical diagnosis and therapeutic monitoring [1-4]. It offers a unique and non-invasive method for tracking biomarkers originating from normal biochemical processes as well as from pathological disorders. For instance, alkanes and methylated alkanes proved to be useful in distinguishing lung cancer patients from healthy controls [1, 5-8], for recognizing heart rejection after transplantation [9], breast cancer [10], or for the detection of oxidative stress [11-12]. A major prerequisite for the successful application of breath tests is the assumption that a robust correlation between the blood and breath levels of analytes of interest can be established. Unfortunately, the origin and metabolic fate of numerous breath species have not been elucidated in sufficient depth, thereby limiting the clinical application of breath tests. In this context, the identification of blood-borne breath constituents and species resulting from exogenous sources (e.g., environmental exposure) as well as the understanding of their physiological levels in human tissues and fluids is of fundamental importance.

Recently, volatile organic compounds forming human scent have received a special attention in the field of safety and security, as they are potential markers of human presence during Urban Search and Rescue (USaR) operations organized after natural or man-made disasters (e.g. earthquakes, explosions and terrorist attacks) [13-17]. Breath, next to skin, is a principal source of human scent constituents. Contrary to some temporal sources like blood or urine, it offers long-lasting emission of VOCs. This is due to the fact that an entrapped victim has to breathe and, thereby, breath constituents can help to discriminate between living humans and corpses. Nevertheless, the role of blood, or urine VOCs in the vicinity of victims should not be underestimated. Bearing in mind that earthquake victims are frequently severely injured [18], it becomes clear that blood is an important reservoir of scent VOCs. In this context the knowledge of the human scent profile and the contribution of particular sources in the scent pool is critical.

While the quantitative analysis of breath constituents has received widespread attention [5, 19-22], relatively few studies have investigated the levels of these volatiles in human blood. Moreover, the majority of studies investigating blood VOCs were focused on selected classes of species (e.g. toxic or carcinogenic substances), or dealt with specific groups of individuals (e.g., smokers, mechanically ventilated patients, or subjects exposed to predefined amounts of contaminants). A number of studies investigated the blood levels of halogenated hydrocarbons and aromatics (BTEXS) as biomarkers of environmental exposure [23-27]. In non-occupational exposure settings Perbellini *et al.* [28] reported blood and breath levels of 1,3 butadiene, benzene and 2,5 dimethyl furan. The blood levels of smoking-related species were analyzed, e.g., by Houeto *et al.* [29] and Chambers *et al*. [30]. In the field of breath gas analysis Miekisch *et al.* [31] investigated the blood concentrations of isoprene, dimethylsulfide, n-pentane and isoflurane in mechanically ventilated patients and the blood concentrations of propofol in patients under anesthesia [32]. A particular focus has also been on isoprene. O'Hara *et al.* reported breath and blood levels of isoprene (and acetone) in volunteers during re-breathing [33-34], Cailleux *et al*. [35] provided its blood abundances in spontaneously breathing test subjects and King *et al*. [36] determined the isoprene concentrations in blood and breath of muscle dystrophy patients. Regarding aldehydes, blood hexanal and heptanal were determined by several authors as potential biomarkers of lung cancer [37-38].

Due to the above-mentioned lack of studies measuring breath and blood levels of VOCs in parallel the primary goal of this work was the quantification of the widest possible range of volatile organic compounds in both types of sample. In particular, by this we also intended to provide a comprehensive list of reliable reference concentration values for healthy volunteers as well as to tentatively classify the observed species into systemic/exogenous compounds by comparing their absolute concentrations in blood, breath, and room air. A secondary goal was to create a library of potential blood-borne and breath-borne markers of human presence. Gas chromatography with mass spectrometric detection was employed as the analytical method for the determination of breath and blood constituents.

## 2. Experimental

### 2.1. Materials and calibration mixtures

Gaseous and liquid multi-compound calibration mixtures were prepared from pure liquid or gaseous substances. The reference substances with purities ranging from 90-99% were purchased from Sigma-Aldrich (Austria), Fluka (Switzerland), ChemSampCo (USA), Acros Organic (Belgium) and SAFC (USA).

The preparation of the gaseous calibration mixtures was dependent on the compound's volatility and solubility in water. Mixtures of less volatile and well soluble species were produced by means of a GasLab calibration mixtures generator (Breitfuss Messtechnik, Germany). The GasLab unit consists of an integrated zero air generator, a 2-stage dynamic injection module for evaporating a liquid and diluting it with zero air, and a humidification module enabling the preparation of gas mixtures at well-defined humidity levels (up to 100% relative humidity (RH) at 37°C). When using the pure liquid substances GasLab is able to produce a flow of up to 10 L/min of complex trace gas mixtures diluted in dry or humidified zero air containing from 10 ppb to 100 ppm of each solute. However, for the goals of this study, pure substances were additionally diluted (1:2000-1:3000) with distilled water prior to evaporation in order to reduce the resulting concentration levels. Effectively, humid gas mixtures (80% RH at 37°C) with volume fractions ranging from approximately 0.02 to 1000 ppb were used during calibration and validation.

Multi-compound standards of poorly soluble and very volatile compounds (mainly hydrocarbons) were prepared in a distinct manner. In a first step, primary standards were prepared in 1-L glass bulbs (Supelco, Canada). Before usage, each bulb was thoroughly cleaned with methanol and dried at 70°C for at least 12 h to remove potential contaminants. Then, the bulb was evacuated using a vacuum membrane pump and approximately 1-2 µL of liquid (or 0.5-1 mL of gaseous) analyte was injected through a rubber septum. Next, the bulb was heated to 60°C for 30 min to ensure complete evaporation and subsequently pressure was balanced to ambient levels with high-purity nitrogen (6.0 - 99.9999%). The final calibration mixtures were prepared by transferring appropriate volumes of the primary standard into Tedlar bags filled with predefined amounts of humidified zero air (80% RH at 37°C), the latter again being produced by the GasLab generator.

To mimic the composition of real breath samples all calibration mixtures additionally contained 100 ppb of isoprene and 800 ppb of acetone. For each compound, breath calibration curves were obtained on the basis of 3-fold analyses of 7 distinct and independently prepared concentration levels.

Blood species were calibrated using human plasma samples [31, 34]. The latter were obtained from centrifuged heparinized whole blood (CS-6R Centrifuge, Beckman, USA) transferred into glass vials and frozen at -20°C immediately after centrifugation. Defrosting was performed at room temperature directly before the calibration measurements. For the purpose of reducing background signals all plasma samples were conditioned prior to the standard mixture preparation. This was achieved by stirring the samples at room temperature and under vacuum conditions [34]. Calibration solutions were prepared in two steps. For the majority of species primary solutions were produced by adding 1-200 µL (depending on the analyte solubility and desired blood concentration range) of pure liquid substance into 250-500 mL of distilled water (M00 200 system, Modulab, Austria), followed by intensive stirring for 20 minutes at 24°C. If very low concentration levels (below 1 nmol/L) were targeted the primary solution was additionally diluted with water at a ratio of 1:100. The final calibration solutions were prepared by transferring appropriate aliquots of primary solutions into crimped vials containing 2.7 mL of plasma and 0.3 mL of Dulbecco's PBS (PAA Laboratories, Austria).

The blood calibration solutions of very volatile compounds poorly soluble in blood (mainly hydrocarbons) were prepared with the help of glass bulbs (Supelco, Canada). In a first step, primary gaseous mixtures were prepared in analogy to the calibration of very volatile breath compounds as described before. Next, these primary standards were diluted with nitrogen at a ratio of 1:200 – 1:300 using an additional glass bulb. Finally, crimped vials containing conditioned plasma samples were spiked with appropriate volumes of the diluted gaseous mixture using gas-tight syringes (Hamilton, Switzerland). Finally, blood volatiles were calibrated against plasma calibration solutions covering concentration ranges from 0.01 to 9000 nmol/L, depending on the substance under scrutiny.

### 2.2. Human subjects and sampling

A cohort of 28 healthy volunteers (14 males, 14 females, age range 18-54 years, median 32.5 years, 6 smokers) was recruited. All subjects gave written informed consent to participate. The blood and breath collection was approved by the Ethics Commission of Innsbruck Medical University. No special dietary regimes were applied, however, volunteers were asked to rest for at least 10 min before sampling to avoid temporal breath VOCs concentration changes related to exercise [39-42]. In addition, prior to the sampling step all individuals had been staying in the room atmosphere for at least one hour. During this time, volunteers completed a questionnaire describing their health and smoking status, as well as recent food intake.

For each volunteer venous blood was sampled twice from the median cubital vein using BD Valu-Sets (BD, UK) and Multi-Adapters (Sarstedt, Germany) into 2.7 mL blood monovettes (Sarstedt, Germany), previously rinsed with high-purity air for 4-6 hours at 50°C to remove contaminants emitted by the monovettes material (plastic). Prior to the sampling procedure a small amount of heparin (Ebewe Pharma, Austria) was added to the rinsed monovettes to prevent clotting. In parallel with each blood sampling, one blank sample containing 2.7 mL of distilled water was collected using the same protocol and the same materials as in case of blood sampling. This was done to identify possible contaminants stemming from sources other than blood. Blank samples were analyzed in the

same way as blood samples and the resulting concentration levels were subtracted from the respective values in the associated blood samples.

End-exhaled breath samples were collected into 3-liter Tedlar bags (SKC Inc., USA) in a $CO_2$ controlled manner using an in-house made breath sampler developed at Innsbruck Medical University, Austria [43]. In brief, the device selectively extracts the last segments of each exhalation (i.e., the portion of exhaled breath characterized by carbon dioxide content higher than a predefined chosen threshold of 3% ) and automatically directs them from a mouthpiece into the sampling bag via a heated Teflon transfer line. Additionally, a separate room air sample was taken for determining the background levels of all VOCs detected. Before their use, all bags were thoroughly cleaned to remove potential pollutants. This was achieved by flushing the bags five times with high-purity nitrogen (6.0 - 99.9999%), followed by overnight heating at 55°C (while filled with $N_2$), re-flushing and evacuation.

### 2.3. Blood sample preparation and HS-SPME procedure

Blood VOC analyses followed a slightly modified version of the extraction procedure developed by Miekisch *et al*. [31-32]. Extraction of volatiles from blood samples was performed in 20 mL headspace vials (Gerstel, Germany) crimped with 1.3 mm butyl/PTFE septa (Macherey-Nagel, Germany) and containing stirring bars. Vials were evacuated by means of a membrane pump and 0.3 mL of Dulbecco's PBS (PAA Laboratories, Austria) was added with the help of a glass syringe. Heparinized blood samples were immediately transferred from the monovette into the evacuated vial using an appropriate needle adapter (Sarstedt, Germany). In order to prevent losses of poorly soluble species and contamination an effort was made to transfer blood samples avoiding any contact with laboratory air. Finally, pressure in the vials was balanced with high-purity nitrogen (6.0 – 99.9999%).

Head space solid phase microextraction (HS-SPME) was performed automatically using a multipurpose sampler MPS2 XL (Gerstel, Germany). For extraction purposes the blood sample vials were incubated in a temperature-controlled agitator at 37°C and stirred intensively (1200 rpm). Extraction was achieved by inserting a 75 µm Carboxen-PDMS SPME fiber (Supelco, Canada) into the vials and exposing it to the head-space gas for 50 minutes. This extraction period was found to be a reasonable trade-off between good detection limits and sampling duration. In particular, the latter had to be sufficiently short to avoid unfavorable effects related to blood ageing. Subsequently, the fiber was introduced into the inlet of the gas chromatograph where the compounds of interest were thermally desorbed at 290°C in splitless mode (1 min). The fiber was conditioned at 290 °C for 5 minutes prior to each analysis.

### 2.4. NTD extraction procedure

Three-bed 23-gauge stainless steel needle trap devices (NTD) (PAS Technology, Germany) with side-hole were employed for the pre-concentration of breath samples. Needle trap devices are a relatively novel technique for gaseous sample pre-concentration and have been described in detail elsewhere in the literature [44-46]. In brief, a certain amount/volume of sample is drawn through a micro-needle packed with selected sorbent materials. Due to the small dimensions and low sorbents masses NTDs offer rapid desorption (additional focusing is not required) that

can be accomplished in the standard inlets of gas chromatographs. Consequently, contrary to traditional sorbent trapping, no additional equipment (e.g., thermal desorbers) is required.

To improve inertness all needles were Silcosteel-treated. The NTD multilayer sorbent bed consisted of 1 cm of Tenax TA (80/100 mesh), 1 cm of Carbopack X (60/80 mesh) and 1 cm of Carboxen 1000 (60/80 mesh). Prior to their use all NTDs were pre-conditioned at 290°C by flushing them with a high-purity nitrogen flow (6.0 – 99.9999%) for 4 h. Since NTDs were found to exhibit relatively huge differences with respect to extraction efficiency (deviations of up to 70%, even when originating from the same production lot) the NTDs used within the study were pre-selected according to the requirement that their inter-needle variability should be below 10%. This selection was based on the comparison of NTD-GC-MS analyses of a predefined standard gas mixture containing several breath constituents at physiological levels using the same conditions as for real breath samples (i.e. flow 10 ml/min, 37°C).

NTD trapping of breath constituents was accomplished dynamically by drawing 200 mL of a breath sample directly from the Tedlar bag (the latter being heated to 37°C). This was done with the help of a membrane pump (Vacuubrand, Germany) at a steady flow rate of 10 mL/min, using a mass flow controller (RED-Y, Burde Co. GmbH, Austria). Consequently, no transfer line had to be installed between the breath sample and the needle trap. To minimize the storage time of the breath samples in the Tedlar bags the NTD extraction was performed shortly (approximately 5 min) after breath sampling. Following extraction the NTD was manually introduced into the inlet of the gas chromatograph where the compounds of interest were thermally desorbed at 290°C in a splitless mode (1 min).

### 2.5. Chromatographic analysis

Chromatographic analyses were performed using an Agilent 7890A/5975C GC-MS system (Agilent, USA). During SPME/NTD desorption, the split/splitless inlet operated in the splitless mode (1 min), followed by a split mode at ratio 1:20. The volatiles of interest were separated using a PoraBond Q column (25 m x 0.32 mm, film thickness 5 μm, styrene-divinylbenzene copolymer phase, Varian, USA) working in a constant flow mode (helium at 1.5 mL/min). The column temperature program involved an initial increase from 40°C to 260°C at a rate of 7°C/min followed by a constant temperature of 260°C for 5 min. The mass spectrometer worked in a SCAN mode with an associated m/z range set from 20 to 200 and an acquisition rate of 4.3 scans/s. The applied GC conditions provided more than 20 scans per peak. The quadrupole, ion source, and transfer line temperatures were kept at 150°C, 230°C and 280°C, respectively.

The identification of compounds was performed in two steps. Firstly, the peak spectrum was checked against the NIST mass spectral library. Next, the NIST identification was confirmed by comparing the respective retention times with retention times obtained on the basis of standard mixtures prepared from pure compounds (see Table 1). Peak integration was based on extracted ion chromatograms. The substance-specific m/z ratios selected for this purpose generally allowed for a proper separation of compounds from their neighboring peaks, even when the latter were overlapping in the total ion count chromatogram. The applied quantifier ions are presented in Table 1.

## 3. Results and discussion

### 3.1. Method validation

Limits of detection (LODs) were calculated using extracted ion chromatograms and the standard deviation of 10 consecutive blank signals [47]. In case of blood species conditioned human plasma samples were used as blank, whereas for breath compounds humidified zero air containing 100 ppb of isoprene and 800 ppb of acetone was used for this purpose. The LOD values ranged from 0.01 to 270 nmol/L for blood and from 0.01 to 0.7 ppb for breath. The limit of quantification (LOQ) was defined as 3 × LOD. Relative standard deviations (RSDs) were calculated on the basis of consecutive analyses of five independent standard mixtures (in case of breath), or plasma samples spiked with calibration solutions (in case of blood). The calculated RSDs varied from 1.5-14% for blood measurements and from 2-13% for breath analyses, which is satisfactory for the aims of this study. The system response was found to be linear within the investigated concentration ranges (see Table 1), with coefficients of variation ranging from 0.907 to 0.999. Blood acetone was not calibrated as the blood analysis focused on VOCs exhibiting much lower concentrations. As a matter of fact, acetone signals obtained within this study generally exceeded the dynamic range of the MS detector. An exemplary chromatogram from a blood HS-SPME-GCMS analysis is presented in Figure 1.

### 3.2. Volatile blood constituents

Within the present study a total number of 90 volatile organic compounds was detected in the measured blood samples. The majority of these (62 species) could reliably be identified and quantified using the aforementioned procedures. The associated detection and quantification incidences as well as the observed concentration ranges are given in Table 2. The remaining compounds could not be identified and/or quantified properly, either due to the unavailability of pure substances from commercial vendors, or due to problems related to the preparation of reliable standard mixtures. The predominant chemical classes in blood were hydrocarbons and ketones with nineteen and nine species, respectively. Apart from these, there were seven heterocyclic compounds, six volatile sulphur compounds (VSCs), seven aromatics, seven terpenes and three esters. Only two aldehydes were detected (propanal and 2-propenal), however, it has been reported that the analysis of species from this chemical class requires special sample treatment (e.g., derivatisation) [37-38]. The observed concentrations ranged from 0.01 nmol/L for furan to 6700 nmol/L for 2-propenal. More than half of all quantified species (51%) exhibited mean concentration values below 1 nmol/L. The highest mean levels were noted for 2-propenal (2440 nmol/L), acetonitrile (746 nmol/L) and 3-buten-2-one (156 nmol/L), however, the detection rate of the latter was very low (4 out of 28 cases). Ten compounds (acetone, dimethyl sulphide, methyl acetate, isoprene, 2-butanone, 2-pentanone, 4-heptanone, 2-heptanone, p-cymene, and limonene) were found in all samples and further six exhibited incidence rates higher than 80% (dimethyl selenide, 3-methyl furan, n-hexane, methyl propyl sulphide, n-octane, and p-xylene). A relatively high fraction of all volatiles detected (40%) displayed blood incidence rates below 20%.

### 3.3. Volatile breath constituents

67 compounds were identified and quantified in breath as well as in room air samples (see Table 2). This number does not include species found to be emitted by the employed materials (e.g., Tedlar bags, septa, NTDs), as it was assumed that the breath levels of these compounds would be too distorted for a sound quantitative analysis (e.g., COS, $CS_2$, acetaldehyde, pyrimidine, cyclohexane, acetophenone). Additionally, room air contaminants appearing in potentially high and variable levels during sampling such as 1-propanol, 2-propanol and ethanol were excluded. The highest levels were observed for acetone and isoprene (mean 950 and 130 ppb respectively) which is consistent with literature data [22, 48]. The majority of compounds (65%) exhibited sub-ppb levels (considering means). The mean concentration values of the remaining volatiles spread around 1-10 ppb. Hydrocarbons comprised 34% of all quantified species, ketones 10%, aromatics 10%, volatile sulphur compounds 9%, terpenes 12%, heterocyclic compounds 7%, esters 3%, and aldehydes 6%. The remaining classes (e.g., nitriles, ethers, selenides) were represented only by single species. Twenty compounds exhibited incidence rates of 100% and further 5 were present in all samples but one (see Table 2). Around 16% of all quantified analytes exhibited occurrence rates below 20%.

### 3.4. Comparison of blood, breath and room air levels of quantified VOCs.

Although the blood levels of VOCs obtained within this study refer to peripheral venous blood, comparing these values with breath and room air concentrations can provide valuable information regarding the origin (endogenous/exogenous) of some volatile species. For instance, high occurrence in blood and breath and low room air levels may point towards blood as a main source of an analyte in breath. Conversely, high room air concentrations and low levels in exhaled breath and blood are typical for exogenous contaminants. Several compounds were found to occur exclusively, or at higher concentrations in breath and blood of smokers. However, due to the fact that only six smokers were recruited within his study the classification of these species was additionally confirmed by the qualitative findings from our previous study [49].

For 32 compounds significant differences between breath and room air levels were found (Wilcoxon signed-rank test). Twenty-two of them exhibited higher levels in breath than in room air samples (see Table 2). Among these species 16 showed detection frequencies higher than 80%. The highest breath-to-room-air-ratios (considering means) were noted for methylpropylsulfide (37), isoprene (26), allylmethylsulfide (21), dimethylsulfide (13) and 2,3-butanedione (10). Apart from six species (2,3-butanedione, 3-buten-2-one, 4-heptanone, γ-terpinene and α-pinene and β-pinene) the blood incidence rates of these compounds were similar to the ones in breath, suggesting that a major part of the amount exhaled in breath stems from blood. In case of ten analytes (propanal, decane, 2-butanone, benzaldehyde, hexanal, 3-methyl thiophene, 2-methyl butane, ethylacetate, acetonitrile and 2-methyl hexane) room air levels were significantly higher than breath levels. Thus, these species - despite their presence in blood - are most likely environmental contaminants. Several compounds (n-hexane, n-pentane, toluene, 2-methyl pentane, furan) were found to have comparable levels in breath and room air samples. However, the high blood detection rate of these species implies that at least part of their blood abundance stems from exogenous sources and that the similarity between breath and room air levels probably results from an equilibration between blood and room atmosphere.

Five ketones were detected in all blood samples: acetone, 2-butanone, 2-pentanone, 2-heptanone and 4-heptanone. This finding is not surprising as these analytes are also omnipresent in human urine [15, 50]. Acetone, 2-butanone and 2-pentanone were also omnipresent in breath, however, only acetone and 2-pentanone exhibited higher concentrations in breath than in room air. The abundances of 2-butanone were higher in room air than in breath suggesting a considerable contribution of room air to 2-butanone blood levels. Both 2-butanone and 2-pentanone showed comparable blood levels ranging from 10 – 105 nmol/L. However, in breath 2-pentanone was found at four-fold lower concentrations than 2-butanone. This difference could be explained by a higher blood solubility of 2-pentanone in blood as well as increased room air levels of 2-butanone. Although 2-heptanone and 4-heptanone were present in all blood samples their occurence in breath was markedly lower (60% of all volunteers). This is most probably due to low (close-to-LOD) breath concentrations of heptanone isomers. Interestingly, in blood 2-heptanone showed slightly higher concentrations than 4-heptanone, whereas in urine the levels of 4-heptanone were reported to significantly exceed those of 2-heptanone [51]. Perhaps, the renal removal of 4-heptanone from the blood stream is more effective than for its isomer. 2,3-butanedione was ubiquitous in breath showing on average three times higher levels in exhaled air than in room air. However, the fact that it was never detected in blood suggest an exogenous source of this compound. Since 2,3-butanedione is a common constituent of butter it is conceivable that the oral cavity might act as reservoir for this volatile. The remaining ketones (3-buten-2-one, 3-penten-2-one, 2-hexanone, and 3-hexanone) generally showed much lower detection rates (15-25%) in blood and were never detected in breath samples (with the exception of 3-buten-2-one).

Dimethyl sulphide (DMS) was the only omnipresent volatile sulphur compound and also exhibited the highest abundances in blood and breath samples (mean concentrations of 8.3 nmol/L and 5 ppb, respectively). The blood DMS values obtained within this study were higher than the ones observed by Miekisch *et al* [31] in mechanically ventilated patients. While it is difficult to compare such different groups of individuals, this discrepancy could be explained, e.g., by different diet regimes. Detection frequencies of methylpropylsulfide (MPS) and allylmethylsulfide (AMS) were slightly lower (89% and 71% in blood and 96% and 90% in breath, respectively), however, the observed concentration ranges in blood were comparable with DMS (mean concentrations of 4.4 nmol/L and 2.7 nmol/L, respectively). Interestingly, room air levels of DMS, AMS and MPS were by a factor of 11-21 lower than in breath, thereby rendering these species as potentially blood-borne compounds. The levels of the remaining VSCs were below 0.5 nmol/L in blood and 0.06 ppb in breath.

A total number of 24 hydrocarbons (HCs) were detected in blood and/or breath samples, making this family the predominant chemical class within this study. Isoprene showed an incidence of 100% in both fluids and also was present at the highest concentrations (3.5-34 nmol/L in blood and 31-273 ppb in breath) [52]. Apart from isoprene only four HCs (n-pentane, n-hexane, n-octane, and n-decane) were found in more than 50% of all blood samples. These four HCs also showed high detection frequencies in breath samples. Furthermore, for n-octane and n-decane significant differences between breath and room air levels were noted. Breath levels of n-octane were found to be higher than in room air, while for n-decane the opposite was true. Also, n-pentane and n-hexane exhibited similar levels in breath and room air. This points towards room air as a major source for the appearance of these HCs in

blood. Several hydrocarbons (e.g., isobutane, 2-methyl-1-propene, 2-methyl butane 2-methyl pentane, and 2-methyl hexane) were omnipresent in breath and room air and simultaneously relatively rare in blood. Within this group 2-methyl butane and 2-methyl hexane showed higher concentrations in room atmosphere than in breath. For the remaining ones no statistically significant difference between expired air and room air could be observed. The low blood detection incidence of these HCs might be explained by the low blood solubility of these species [53], implying that the venous blood concentrations were probably close to the analytical limits of the applied method. Very low, close-to-LOD breath levels can also explain low blood occurrence of some other HCs (e.g., 4-methyl-1-pentene, 2,3-dimethyl butane). Several unsaturated hydrocarbons were present exclusively (1,3-pentadiene, 2,4-hexadiene), or predominantly (1,3-butadiene, 2-pentene) in the breath of smokers, this being consistent with previous studies [49]. The detection frequency of the remaining HCs was usually below 30%.

Seven aromatic compounds were quantified in blood and breath samples. The highest incidences were noted for benzene, toluene, and styrene. Benzene, toluene, and o-xylene were found to be smoking-related species. For example, benzene exhibited ten-fold higher levels in blood and breath of smokers (0.14-0.98 (0.56) nmol/L, and 0.57-5.7 (2.7) ppb, respectively) than in non-smokers (0.03-0.1 (0.06) nmol/L and 0.16-0.6 (0.27) ppb, respectively). Similar differences between smokers and non-smokers were also observed for toluene (0.36-3.1 (1.6) nmol/L vs 0.08-0.48 (0.22) nmol/L for blood, and 0.7-8.6 (3.7) ppb vs 0.3-1.3 (0.6) ppb for breath).

Concentration levels of heterocyclic compounds were relatively low, typically falling below 0.5 nmol/L in blood and 0.5 ppb in breath. Only pyrazine showed higher blood concentrations ranging from 15 – 32 nmol/L. Furan, 2-methyl furan and 2,5-dimethyl furan exhibited higher abundances in exhaled air and blood of smokers. Interestingly, 3-methyl furan occurred in more than 80% of breath and blood samples and its breath levels were significantly higher than those in room air. These findings point towards blood as a main origin of this analyte. One possible source of this volatile in human organism could be the degradation of isoprene induced by alkoxy radicals [54]. Two pyrroles were found in blood samples, namely pyrrole and 1-methyl pyrrol. Their incidences were relatively low, particularly when compared to their high occurrence in urine samples [15]. However, it must be remembered in this context that due to the pre-concentration capabilities of kidneys VOC levels in urine are usually much higher than those in blood and thus much easier to detect. Pyrrole was found both in breath and blood samples with similar occurrence rates, however, breath concentrations were comparable to room air levels.

A number of terpenes were detected in this study. However, only two species (p-cymene and limonene) were present in all matrices. They also showed higher levels in breath than in room air (breath-to-room-air-ratios of 3.8 and 4.2, respectively, considering means). All remaining terpenes also exhibited higher concentrations in exhaled air than in room air. α-Pinene and β-pinene were found in 96% and 78% of all breath samples, respectively, but their blood incidence was very low. Other terpenes generally occurred in less than 35% of all samples.

Only two aldehydes (2-propenal and propanal) were found in blood samples showing incidence rates of 50%. The levels of 2-propenal were particularly high and ranged from 880 to 6700 (2440) nmol/L. This compound was omnipresent in breath and room air, however, the difference between these matrices was not significant. Propanal

exhibited lower blood levels (11-29 nmol/L) and its mean breath level was four times lower than the corresponding room air concentration, thus indicating an exogenous origin of this species in blood and breath. A similar conclusion can be drawn for hexanal. The remaining aldehydes were found exclusively in breath and room air samples and not in blood.

Three esters were quantified within this study. Methyl acetate was omnipresent in blood and breath samples and exhibited higher levels in breath than in room atmosphere, this being consistent with the literature [39]. Methylpropionate was detected in 46% of blood samples, however, it was not found in breath. It seems that this poor detection incidence may be due to much lower blood levels of this compound compared to methyl acetate. Dimethyl selenide was ubiquitous in all samples with detection incidences of 90%. Considering its low room air levels it seems that this volatile is a blood-borne compound.

Apart from 2-propenal only acetonitrile exhibited blood concentrations at μmol/L level. Although this substance was also present in blood and exhaled air of non-smokers, its levels in smokers were substantially higher (mean 463 nmol/L vs 1405 nmol/L for blood and 25 ppb vs 52 ppb for breath). These levels of acetonitrile agree well with the values obtained by *Houeto et al*. [29] in blood of smoking individuals (2200 – 10000 nmol/L, mean 4450 nmol/L).

A comparison of the blood VOCs levels obtained within this study with selected data from the literature is presented in Table 3. Although human blood concentration data are relatively sparse and were frequently obtained for specific group of individuals (e.g. smokers, mechanically ventilated patients) a reasonable agreement could be achieved.

## 4. Conclusions

The present study aimed at providing a comprehensive list of concentration reference values for a wide range of volatile organic compounds in blood and breath of healthy volunteers. For this purpose gas chromatography with mass spectrometric detection coupled with two pre-concentration techniques (SPME and NTD) was applied. 74 species were quantified in breath and blood of 28 healthy volunteers. The observed concentrations ranged over several orders of magnitude, from 10 pmol/L to 6.7 μmol/L (without acetone) in blood and from 0.02 ppb to 2500 ppb in breath. The quantified compounds belonged to several chemical classes, however, hydrocarbons were the most numerous chemical family (24 species). Other well-represented classes were ketones (10), terpenes (8), heterocyclic compounds (7) and aromatic compounds (7). Twelve compounds were simultaneously present in both fluids (>80% occurrence). In case of 22 species breath levels were significantly higher than room air levels (Wilcoxon signed-rank test). Within this group 11 volatiles (isoprene, acetone, limonene, dimethyl selenide, p-cymene, 2-pentanone, methyl propyl sulphide, dimethyl sulphide, n-octane, 4-heptanone, and methyl acetate) also showed very high occurrence in blood, which seems to render blood as a main source for their presence in breath. Consequently, these species are the most promising breath-borne markers of human presence. On the other side, ten species (propanal, decane, 2-butanone, benzaldehyde, hexanal, 3-methyl thiophene, 2-methyl butane, ethylacetate,

acetonitrile, and 2-methyl hexane) exhibited higher levels in room air than in breath which suggests an exogenous origin of these compounds. Although a relatively small number of smokers was involved in this study, several blood and breath compounds were found to be smoking related. This group included unsaturated hydrocarbons (1,3-butadiene, 1,3-pentadiene, 2-butene, 2,4-hexadiene), furans (furan, 2-methyl furan, 2,5-dimethylfuran), and acetonitrile. The fact should be stressed that the proposed classification of quantified species into systemic (blood-borne) and exogenous volatiles is certainly tentative as some species may originate from several distinct sources. In particular, the term "blood-borne" does not necessarily mean that the substance is of metabolic origin. It also includes diet-related or drug-related species. The blood and blood-borne breath species exhibiting incidence higher than 80% can be considered as potential markers of human presence to be verified during further field studies.

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*Table 1.* Retention times $R_t$ [min], quantifier ions, LODs [nmol·$L^{-1}$, ppb], RSDs (%), coefficients of variation ($R^2$) and linear ranges [nmol·$L^{-1}$, ppb] of compounds under study for blood and breath measurements. Compounds are ordered with respect to increasing retention time.

| VOC | CAS | $R_t$ [min] | Quantifier ion | Blood | | | | Breath/Room air | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | LOD [nmol/L] | RSD [%] | $R^2$ | linear range [nmol/L] | LOD [ppb] | RSD [%] | $R^2$ | linear range [ppb] |
| Propene | 115-07-1 | 3.99 | 41 | 3.7 | 10 | 0.907 | 11-53 | 0.7 | 10 | 0.999 | 2-60 |
| Propane, 2-methyl- | 75-28-5 | 8.21 | 43 | 0.23 | 4.5 | 0.999 | 0.8-13 | 0.12 | 9 | 0.995 | 0.4-19 |
| 1-Propene, 2-methyl- | 115-11-7 | 8.43 | 56 | 0.11 | 4.5 | 0.989 | 0.3-26 | 0.05 | 7 | 0.997 | 0.15-20 |
| 1,3-Butadiene | 106-99-0 | 8.48 | 54 | 0.07 | 5 | 0.999 | 0.2-26 | 0.06 | 3 | 0.999 | 0.2-10 |
| Acetonitrile | 75-05-8 | 9.04 | 41 | 14.8 | 13 | 0.998 | 44-2800 | 0.24 | 3.5 | 0.990 | 0.7-30 |
| n-Butane | 106-97-8 | 9.08 | 43 | 0.13 | 3.5 | 0.999 | 0.4-26 | 0.12 | 8 | 0.982 | 0.3-19 |
| 2-Propenal | 107-02-8 | 10.29 | 56 | 270 | 6 | 0.998 | 800-9000 | 0.13 | 4 | 0.999 | 0.4-31 |
| Furan | 110-00-9 | 10.65 | 68 | 0.012 | 3 | 0.999 | 0.03-10 | 0.01 | 7 | 0.985 | 0.03-9 |
| Propanal | 123-38-6 | 10.83 | 58 | 1.3 | 4 | 0.997 | 4-66 | 0.17 | 7 | 0.998 | 0.5-32 |
| Acetone | 67-64-1 | 10.98 | 58 | - | - | - | - | 0.1 | 6 | 0.995 | 0.3-1500 |
| Dimethyl sulfide (DMS) | 75-18-3 | 11.52 | 62 | 0.1 | 1.5 | 0.991 | 0.3-100 | 0.05 | 6.6 | 0.998 | 0.15-25 |
| Methyl acetate | 79-20-9 | 12.35 | 43 | 1 | 9 | 0.993 | 3-93 | 0.2 | 9 | 0.999 | 0.5-20 |
| Ether, ethyl vinyl | 109-92-2 | 12.75 | 72 | 0.04 | 7 | 0.999 | 0.12-6 | 0.05 | 7 | 0.998 | 0.15-10.5 |
| Butane, 2-methyl- | 78-78-4 | 13.02 | 57 | 0.07 | 5 | 0.999 | 0.2-15 | 0.05 | 6 | 0.994 | 0.14-12 |
| 1-Butene, 2-methyl- | 563-46-2 | 13.10 | 55 | 0.05 | 4 | 0.996 | 0.15-9 | 0.03 | 10 | 0.998 | 0.08-6.5 |
| Isoprene | 78-79-5 | 13.22 | 67 | 0.04 | 4 | 0.995 | 0.1-53 | 0.01 | 5.5 | 0.995 | 0.04-270 |
| 2-Pentene, (E)- | 646-04-8 | 13.44 | 55 | 0.04 | 3 | 0.999 | 0.12-6 | 0.02 | 4 | 0.999 | 0.06-3.4 |
| 2-Pentene, (Z)- | 627-20-3 | 13.53 | 55 | 0.04 | 6 | 0.998 | 0.1-2.6 | 0.02 | 3.5 | 0.999 | 0.06-2 |
| n-Pentane | 109-66-0 | 13.65 | 43 | 0.1 | 3 | 0.999 | 0.3-17.5 | 0.04 | 8 | 0.995 | 0.12-18 |
| Dimethyl selenide | 593-79-3 | 13.90 | 95 | 0.03 | 4 | 0.997 | 0.08-12 | 0.01 | 10 | 0.997 | 0.05-6 |
| 1,3-Pentadiene, (E)- | 2004-70-8 | 13.92 | 67 | 0.03 | 7 | 0.999 | 0.09-7.6 | 0.01 | 4.5 | 0.998 | 0.03-7 |
| 1,3-Pentadiene, (Z)- | 1574-41-0 | 14.02 | 67 | 0.02 | 10 | 0.999 | 0.06-3.6 | 0.01 | 3.5 | 0.997 | 0.03-3.6 |
| 2-Propenal, 2-methyl- | 78-85-3 | 14.20 | 70 | 0.9 | 7.5 | 0.999 | 2.6-318 | 0.03 | 8 | 0.992 | 0.09-12 |
| 3-Buten-2-one | 78-94-4 | 14.87 | 55 | 40 | 10 | 0.986 | 120-3600 | 0.15 | 7 | 0.993 | 0.45-15 |
| Furan, 2-methyl- | 534-22-5 | 15.25 | 82 | 0.01 | 4 | 0.999 | 0.03-6 | 0.01 | 7 | 0.995 | 0.03-11 |
| 2,3-Butanedione | 431-03-8 | 15.34 | 43 | 4 | 10 | 0.989 | 13-154 | 0.2 | 13 | 0.987 | 0.6-54 |
| 2-Butanone | 78-93-3 | 15.39 | 72 | 0.4 | 5.5 | 0.994 | 1.2-250 | 0.08 | 7.5 | 0.999 | 0.25-25 |
| Furan, 3-methyl- | 930-27-8 | 15.51 | 82 | 0.015 | 4.5 | 0.999 | 0.05-6 | 0.01 | 8.5 | 0.994 | 0.03-6 |
| Sulfide, ethyl methyl | 624-89-5 | 15.87 | 61 | 0.06 | 5 | 0.997 | 0.16-8 | 0.02 | 5.5 | 0.999 | 0.05-5 |
| Ethyl Acetate | 141-78-6 | 16.16 | 43 | 0.1 | 13 | 0.998 | 0.3-11 | 0.05 | 6 | 0.996 | 0.14-10 |
| Methyl propionate | 554-12-1 | 16.44 | 57 | 0.13 | 12 | 0.981 | 0.4-30 | 0.06 | 6.5 | 0.992 | 0.2-8 |
| 1-Pentene, 4-methyl- | 691-37-2 | 16.49 | 56 | 0.03 | 5 | 0.996 | 0.07-8.4 | 0.02 | 8 | 0.994 | 0.07-6.5 |
| Butane, 2,3-dimethyl- | 79-29-8 | 16.90 | 43 | 0.06 | 5.5 | 0.997 | 0.18-7.3 | 0.02 | 8.5 | 0.999 | 0.06-6.5 |
| Thiophene | 110-02-1 | 16.98 | 84 | 0.01 | 3 | 0.999 | 0.03-7 | 0.01 | 4 | 0.999 | 0.03-5 |
| Pentane, 2-methyl- | 107-83-5 | 17.00 | 43 | 0.08 | 4 | 0.999 | 0.25-9 | 0.04 | 11 | 0.995 | 0.12-7 |
| 1-Hexene | 592-41-6 | 17.26 | 56 | 0.02 | 3 | 0.999 | 0.06-8 | 0.01 | 7 | 0.995 | 0.03-7 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Benzene | 71-43-2 | 17.42 | 78 | 0.015 | 2 | 0.999 | 0.04-10 | 0.03 | 7 | 0.994 | 0.1-10.5 |
| n-Hexane | 110-54-3 | 17.69 | 57 | 0.02 | 2.5 | 0.999 | 0.07-5 | 0.01 | 8 | 0.994 | 0.03-6 |
| 2,4-Hexadiene, (E,Z)- | 5194-50-3 | 18.03 | 82 | 0.02 | 7 | 0.999 | 0.06-2.7 | 0.01 | 6 | 0.991 | 0.04-2 |
| Pyrrole | 109-97-7 | 18.15 | 67 | 0.015 | 13 | 0.995 | 0.04-14 | 0.03 | 8 | 0.993 | 0.08-6.6 |
| Pyrazine | 290-37-9 | 18.46 | 80 | 4.5 | 9 | 0.999 | 13-144 | - | - | - | - |
| 2-Pentanone | 107-87-9 | 19.09 | 43 | 0.25 | 8 | 0.999 | 0.8-208 | 0.02 | 3 | 0.999 | 0.05-4.5 |
| Furan, 2,5-dimethyl- | 625-86-5 | 19.13 | 96 | 0.025 | 6 | 0.999 | 0.07-12 | 0.02 | 9 | 0.978 | 0.05-9 |
| Sulfide, allylmethyl | 10152-76-8 | 19.13 | 88 | 0.03 | 3 | 0.994 | 0.09-80 | 0.01 | 5.5 | 0.994 | 0.03-10 |
| Pyrrole, 1-methyl- | 96-54-8 | 19.40 | 81 | 0.1 | 12 | 0.999 | 0.03-166 | 0.05 | 11 | 0.980 | 0.15-10.5 |
| Sulfide, methyl propyl | 3877-15-4 | 19.74 | 61 | 0.04 | 2.5 | 0.991 | 0.12-134 | 0.01 | 6 | 0.996 | 0.03-10 |
| 3-Penten-2-one, (E)- | 3102-33-8 | 20.07 | 69 | 2.5 | 4 | 0.991 | 7.5-122 | 0.02 | 6 | 0.997 | 0.06-7.5 |
| Hexane, 2-methyl- | 591-76-4 | 20.61 | 85 | 0.02 | 7 | 0.999 | 0.05-8 | 0.01 | 8 | 0.996 | 0.02-6 |
| Thiophene, 3-methyl- | 616-44-4 | 21.05 | 97 | 0.02 | 4.5 | 0.998 | 0.03-11 | 0.01 | 8 | 0.995 | 0.02-5.2 |
| Toluene | 108-88-3 | 21.32 | 91 | 0.03 | 6.5 | 0.999 | 0.1-11 | 0.1 | 8 | 0.998 | 0.3-9 |
| 3-Hexanone | 589-38-8 | 22.42 | 57 | 0.15 | 8.5 | 0.996 | 0.5-32 | 0.04 | 7 | 0.996 | 0.12-4 |
| 2-Hexanone | 591-78-6 | 22.62 | 43 | 0.15 | 7 | 0.999 | 0.4-60 | 0.06 | 7 | 0.995 | 0.2-5 |
| Hexanal | 66-25-1 | 22.84 | 56 | - | - | - | - | 0.2 | 9 | 0.993 | 0.6-15 |
| γ-Butyrolactone | 96-48-0 | 23.16 | 42 | - | - | - | - | 0.2 | 2 | 0.999 | 0.5-20 |
| n-Octane | 111-65-9 | 24.51 | 85 | 0.04 | 7 | 0.998 | 0.12-6.5 | 0.01 | 10 | 0.995 | 0.03-6 |
| Ethylbenzene | 100-41-4 | 24.52 | 91 | 0.4 | 6 | 0.999 | 1-9 | 0.07 | 4 | 0.999 | 0.2-7.5 |
| p-Xylene | 106-42-3 | 24.73 | 91 | 0.07 | 4.5 | 0.999 | 0.2-10 | 0.7 | 7 | 0.999 | 2-8 |
| Styrene | 100-42-5 | 24.98 | 104 | 0.1 | 9 | 0.980 | 0.3-10 | 0.1 | 11 | 0.997 | 0.3-9 |
| o-Xylene | 95-47-6 | 25.11 | 91 | 0.08 | 5 | 0.999 | 0.25-10 | 0.3 | 8.2 | 0.996 | 1-9 |
| 4-Heptanone | 123-19-3 | 25.38 | 71 | 0.05 | 9 | 0.998 | 0.12-12 | 0.01 | 2.5 | 0.998 | 0.02-7.5 |
| 2-Heptanone | 110-43-0 | 25.78 | 43 | 0.2 | 10 | 0.999 | 0.6-12 | 0.03 | 2.5 | 0.998 | 0.08-6.5 |
| Benzaldehyde | 100-52-7 | 26.01 | 106 | 2.5 | 12 | 0.978 | 8-145 | 0.3 | 12.5 | 0.998 | 0.9-9 |
| Octane, 4-methyl- | 2216-34-4 | 26.67 | 43 | 0.15 | 8 | 0.999 | 0.45-6.6 | 0.04 | 10 | 0.997 | 0.1-5.5 |
| α-Methylstyrene | 98-83-9 | 27.52 | 118 | 0.1 | 9 | 0.999 | 0.3-10 | 0.01 | 13 | 0.997 | 0.03-8 |
| α-Pinene | 80-56-8 | 27.69 | 93 | 0.06 | 7 | 0.982 | 0.2-12 | 0.02 | 7.5 | 0.981 | 0.06-5.8 |
| β-Pinene | 127-91-3 | 28.68 | 93 | 0.04 | 7 | 0.993 | 0.1-10 | 0.01 | 10 | 0.981 | 0.03-6 |
| 3-Carene | 13466-78-9 | 29.06 | 93 | 0.9 | 8 | 0.991 | 3-12 | 0.02 | 13 | 0.988 | 0.06-8 |
| p-Cymene | 99-87-6 | 29.60 | 119 | 0.1 | 9.5 | 0.986 | 0.3-36 | 0.01 | 5.5 | 0.997 | 0.03-6.5 |
| Limonene | 138-86-3 | 29.80 | 68 | 0.08 | 7 | 0.991 | 0.24-69 | 0.01 | 5 | 0.991 | 0.03-5 |
| n-Decane | 124-18-5 | 30.08 | 57 | 0.3 | 5 | 0.984 | 0.9-12 | 0.03 | 6 | 0.996 | 0.8-5.5 |
| γ -Terpinene | 99-85-4 | 30.08 | 93 | 1 | 12 | 0.992 | 3-51 | 0.02 | 9 | 0.990 | 0.06-10 |
| Eucalyptol | 470-82-6 | 30.35 | 43 | 0.8 | 13 | 0.996 | 2.3-65 | 0.1 | 10 | 0.991 | 0.25-11 |
| n-Undecane | 1120-21-4 | 32.64 | 57 | 0.7 | 8 | 0.924 | 2-11 | 0.03 | 9 | 0.990 | 0.1-4 |
| Menthone | 10458-14-7 | 33.49 | 112 | 0.6 | 14 | 0.980 | 1.7-62 | 0.06 | 12 | 0.977 | 0.18-10 |

*Table 2.* Detection ($n_d$) and quantification ($n_q$) incidences of the compounds under study, together with breath, blood, and room air concentration ranges. n.s. – not significant.

| VOC | Blood | | Breath | | Room air | | p value Wilcoxon test Breath vs room air | Tentative origin |
|---|---|---|---|---|---|---|---|---|
| | Incidence $n_d(n_q)$ | Range (mean) [nmol/L] | Incidence $n_d(n_q)$ | Range (mean) [ppb] | Incidence $n_d(n_q)$ | Range (mean) [ppb] | | |
| Propene | 12(12) | 4-61.5 (14) | 0(0) | - | 0(0) | - | - | |
| Propane, 2-methyl- | 5(2) | 0.8-1.5 (1.2) | 25(20) | 0.4-4.7 (1.4) | 21(18) | 0.4-13 (1.6) | n.s. | |
| 1-Propene, 2-methyl- | 1(1) | 3.4 | 28(28) | 0.6 - 2.8 (1.3) | 28(27) | 0.6-3.9 (1.3) | n.s. | |
| 1,3-Butadiene | 8(8) | 0.05-0.27 (0.17) | 10(7) | 0.2-1.6 (0.8) | 10(5) | 0.2-0.34 (0.27) | n.s. | smoking |
| Acetonitrile | 20(20) | 101-2334 (745) | 26(26) | 13-78.5 (31.5) | 26(26) | 10-117 (43.6) | 1.53E-02 | exogenous |
| n-Butane | 5(5) | 0.13-0.46 (0.34) | 13(13) | 0.75-7.6 (2.4) | 13(13) | 0.8 -2.5 (1.5) | n.s. | |
| 2-Propenal | 13(13) | 880-6700 (2440) | 28(28) | 2.9 - 19 (5.9) | 21(21) | 2-21.5 (7.7) | n.s. | |
| Furan | 14(14) | 0.01-0.36 (0.1) | 21(21) | 0.08-2.3 (0.42) | 21(21) | 0.07-0.77 (0.22) | n.s. | smoking |
| Propanal* | 15(15) | 11-29 (16) | 28(28) | 5-66 (18.3) | 28(28) | 3.7-432 (77.6) | 5.85E-04 | exogenous |
| Acetone | 28(28) | - | 28(28) | 281-2525 (950) | 28(28) | 9-454 (134) | 3.79E-06 | Blood-borne |
| Dimethyl sulfide | 28(28) | 2-32.8 (8.3) | 28(28) | 1.4-28 (5) | 28(16) | 0.13-1.3 (0.38) | 3.79E-06 | Blood-borne |
| Methyl acetate | 28(27) | 3.4-156 (30.5) | 27(26) | 0.64-18.8 (2.6) | 26(17) | 0.55-2.6 (1.1) | 1.32E-04 | Blood-borne |
| Ether, ethyl vinyl | 6(5) | 0.08-0.23 (0.13) | 16(12) | 0.15-0.67 (0.34) | 14(7) | 0.15-2.1 (0.8) | n.s. | |
| Butane, 2-methyl- | 6(5) | 0.14-2.1 (0.74) | 28(28) | 0.6-9.5 (2.3) | 28(28) | 0.64-13.5 (2.8) | 1.04E-03 | exogenous |
| 1-Butene, 2-methyl- | 0(0) | - | 4(4) | 0.08-0.35 (0.15) | 4(3) | 0.1-0.21 (0.17) | - | |
| Isoprene | 28(28) | 3.5-34 (14.6) | 28(28) | 31-273 (131) | 28(28) | 0.9-18 (5) | 3.79E-06 | Blood-borne |
| 2-Pentene, (E)- | 1(1) | 0.13 | 6(4) | 0.1-0.22 (0.16) | 6(3) | 0.07-0.1 (0.086) | - | smoking |
| 2-Pentene, (Z)- | 0(0) | - | 6(6) | 0.08-1.34 (0.56) | 6(5) | 0.06-0.17 (0.12) | 3.13E-02 | smoking |
| n-Pentane | 19(18) | 0.19-0.81 (0.37) | 28(28) | 0.34-22 (1.8) | 28(28) | 0.24-35 (2.4) | n.s. | |
| Dimethyl selenide | 25(25) | 0.13-0.5 (0.26) | 26(26) | 0.16-0.64 (0.35) | 6(4) | 0.08-0.14 (0.1) | 8.30E-06 | Blood-borne |
| 1,3-Pentadiene, (E)- | 2(2) | 0.09-0.1 (0.09) | 3(3) | 0.2-0.66 (0.44) | 3(0) | - | - | smoking |
| 1,3-Pentadiene, (Z)- | 2(0) | - | 3(2) | 0.1-0.2 (0.15) | 2(1) | 0.06 | - | smoking |
| 2-Propenal, 2-methyl- | 0(0) | - | 28(28) | 0.4-2.9 (1.2) | 28(28) | 0.3-3.5 (1.2) | n.s. | |
| 3-Buten-2-one | 4(4) | 126-181 (156) | 28(28) | 0.8-14.4 (3.8) | 28(28) | 0.7-11.3 (2.4) | 3.31E-03 | Blood-borne |
| Furan, 2-methyl- | 2(2) | 0.05-0.26 (0.15) | 28(28) | 0.1-3.7 (0.55) | 28(28) | 0.1-3.0 (0.4) | n.s. | smoking |
| 2,3-Butanedione | 0(0) | - | 28(28) | 1.4-187 (29) | 28(28) | 0.9-7 (3) | 1.86E-05 | |
| 2-Butanone | 28(28) | 8.4-72 (35) | 26(26) | 0.5-5 (2.2) | 26(26) | 0.35-27 (6.2) | 3.77E-04 | exogenous |
| Furan, 3-methyl- | 23(10) | 0.03-0.1 (0.06) | 23(23) | 0.05-0.39 (0.18) | 23(23) | 0.03-0.24 (0.08) | 1.27E-04 | Blood-borne |
| Sulfide, ethyl methyl | 12(5) | 0.2-0.82 (0.39) | 13(2) | 0.05-0.06 (0.06) | 0(0) | - | - | |
| Ethyl Acetate | 2(2) | 0.5-5 (2.7) | 21(16) | 0.16-9.4 (1.2) | 22(22) | 0.23-5.1 (1.3) | 7.79E-04 | exogenous |
| Methyl propionate | 13(13) | 0.3-15 (2.8) | 0(0) | - | 0(0) | - | - | |
| 1-Pentene, 4-methyl- | 0(0) | - | 15(5) | 0.08-0.1 (0.09) | 5(1) | 0.12 | - | |
| Butane, 2,3-dimethyl- | 0(0) | - | 12(8) | 0.07-1 (0.24) | 11(10) | 0.06-0.3 (0.14) | n.s. | |
| Thiophene | 16(16) | 0.03-0.14 (0.05) | 2(2) | 0.05-0.08 (0.06) | 2(1) | 0.03 | - | |
| Pentane, 2-methyl- | 4(3) | 0.26-0.53 (0.35) | 28(27) | 0.1-6.4 (0.54) | 28(26) | 0.14-1 (0.34) | n.s. | |
| 1-Hexene | 10(10) | 0.03-0.21 (0.08) | 12(11) | 0.05-0.44 (0.16) | 11(10) | 0.04-0.2 (0.12) | n.s. | |
| Benzene | 15(15) | 0.03-0.98 (0.26) | 28(28) | 0.16-5.8 (0.8) | 28(28) | 0.2-0.75 (0.4) | n.s. | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| n-Hexane | 24(24) | 0.02-0.57 (0.17) | 28(28) | 0.07-1.8 (0.32) | 28(28) | 0.07-2.84 (0.37) | n.s. | |
| 2,4-Hexadiene, (E,Z)- | 0(0) | - | 4(4) | 0.25-0.94 (0.62) | 3(0) | - | - | smoking |
| Pyrrole | 17(17) | 0.25-1.89 (1.04) | 17(17) | 0.09-0.27 (0.17) | 17(16) | 0.08-0.26 (0.15) | n.s. | |
| Pyrazine | 15(9) | 15-32 (20) | 0(0) | - | 0(0) | - | - | |
| 2-Pentanone | 28(28) | 9.4-105.4 (34.7) | 28(28) | 0.1-2.1 (0.62) | 28(21) | 0.06-0.34 (0.09) | 3.79E-06 | Blood-borne |
| Furan, 2,5-dimethyl- | 6(6) | 0.2-0.66 (0.41) | 5(5) | 0.62-2.78 (1.6) | 3(1) | 0.07 | n.s. | smoking |
| Sulfide, allylmethyl | 20(20) | 0.18-21.7 (2.7) | 25(25) | 0.09-12.7 (1.6) | 16(7) | 0.03-0.2 (0.07) | 1.23E-05 | Blood-borne |
| Pyrrole, 1-methyl- | 5(4) | 0.41-0.6 (0.48) | 0(0) | - | 0(0) | - | - | |
| Sulfide, methyl propyl | 25(25) | 0.18-76.4 (4.4) | 27(27) | 0.05-39 (2.2) | 20(12) | 0.03-0.13 (0.06) | 6.28E-06 | Blood-borne |
| 3-Penten-2-one, (E)- | 5(5) | 6.3-20.3 (10) | 0(0) | - | 0(0) | - | - | |
| Hexane, 2-methyl- | 9(9) | 0.03-0.57(0.13) | 27(27) | 0.04-0.77(0.15) | 27(27) | 0.05-0.37(0.15) | 4.36E-02 | Exogenous |
| Thiophene, 3-methyl- | 11(1) | 0.04 | 20(15) | 0.02-0.08 (0.03) | 7(4) | 0.02-0.035 (0.024) | 1.83E-04 | Exogenous |
| Toluene | 22(22) | 0.08-3.1 (0.6) | 28(23) | 0.3-8.6 (1.42) | 28(28) | 0.38-2.26 (1.1) | n.s. | |
| 3-Hexanone | 6(1) | 0.48 | 0(0) | - | 0(0) | - | - | |
| 2-Hexanone | 7(7) | 0.1-0.5 (0.36) | 0(0) | - | 0(0) | - | - | |
| Hexanal | 0(0) | - | 8(2) | 0.63-0.67 (0.65) | 8(8) | 1.46-3 (2.1) | 7.81E-03 | Exogenous |
| γ-Butyrolactone | 0(0) | - | 20(20) | 0.63-7.96 (2.8) | 20(20) | 0.35-8.48 (2.23) | n.s. | |
| n-Octane | 25(25) | 0.1-3.45 (1.3) | 23(23) | 0.04-0.22 (0.12) | 23(23) | 0.05-0.17 (0.09) | 3.86E-03 | Blood-borne |
| Ethylbenzene | 4(1) | 1.96 | 14(6) | 0.22-1.92 (0.61) | 20(8) | 0.25-0.6 (0.4) | n.s. | |
| p-Xylene | 23(23) | 0.08-11.2 (0.96) | 3(1) | 7.3 | 13(1) | 2.16 | - | |
| Styrene | 10(10) | 0.13-0.73 (0.36) | 27(26) | 0.22-4.5 (0.92) | 27(27) | 0.25-0.73 (0.4) | n.s. | |
| o-Xylene | 3(3) | 0.38-5.2 (2.2) | 1(1) | 2.68 | 1(0) | - | - | |
| 4-Heptanone | 28(27) | 0.2-2.15 (0.83) | 17(9) | 0.02-0.05 (0.03) | 0(0) | - | 3.91E-03 | Blood-borne |
| 2-Heptanone | 28(28) | 0.6-5.7 (2.7) | 17(1) | 0.1 | 17(0) | - | - | |
| Benzaldehyde | 0(0) | - | 28(9) | 1-3.4 (1.8) | 27(23) | 1-19.8 (2.8) | 2.03E-03 | Exogenous |
| Octane, 4-methyl- | 7(7) | 0.44-2.4 (0.97) | 3(1) | 0.27 | 5(1) | 0.44 | - | |
| α-Methylstyrene | 3(2) | 0.19-0.20 (0.2) | 13(7) | 0.04-0.24 (0.13) | 13(4) | 0.04-0.06 (0.05) | n.s. | |
| α-Pinene | 0(0) | - | 27(27) | 0.17-3.7 (0.6) | 27(27) | 0.05-0.72 (0.3) | 1.52E-02 | Blood-borne |
| β-Pinene | 4(4) | 0.43-1.5 (1.08) | 22(22) | 0.14-3 (0.59) | 22(22) | 0.04-0.92 (0.22) | 4.98E-03 | Blood-borne |
| 3-carene | 4(4) | 2-4.4 (3.4) | 9(9) | 0.1-0.52 (0.26) | 9(6) | 0.07-0.13 (0.09) | 1.17E-02 | Blood-borne |
| p-Cymene | 28(27) | 0.3-5.4 (1.1) | 28(28) | 0.02-0.6 (0.14) | 28(23) | 0.015-0.11 (0.04) | 9.98E-06 | Blood-borne |
| Limonene | 28(28) | 0.94-42.6 (9.3) | 28(28) | 0.27-7.42 (1.46) | 28(28) | 0.07-0.93 (0.35) | 7.26E-06 | Blood-borne |
| n-Decane | 24(22) | 0.62-13.2 (3.1) | 25(16) | 0.07-0.31 (0.14) | 24(19) | 0.08-0.6 (0.19) | 2.14E-04 | Exogenous |
| γ -Terpinene | 9(9) | 0.06-1.7 (0.41) | 8(3) | 0.05-0.14 (0.09) | 5(5) | 0.08-1.9 (0.74) | 3.91E-03 | Blood-borne |
| Eucaliptol | 10(7) | 3.9-10 (6.41) | 10(9) | 0.28-2.8 (1.16) | 4(2) | 0.39-0.6 (0.49) | 3.91E-03 | Blood-borne |
| n-Undecane | 3(3) | 1.9-2.6 (2.2) | 14(9) | 0.08-4.5 (0.6) | 13(11) | 0.09-0.53 (0.22) | n.s. | |
| Menthone | 3(3) | 2.4-7.8 (4.9) | 7(7) | 0.36-19.7 (6) | 6(0) | - | 1.56E-02 | Blood-borne |

* in 20% of cases the separation of propanal from acetone was not satisfactory (resolution 60-70%)

Table 3. Comparison of the blood VOCs levels obtained within this study with some literature data.

| VOC | Literature data | | This study |
|---|---|---|---|
| | Range (mean) [nmol/L] | Remarks | Range (mean) [nmol/L] |
| 1,3-Butadiene | 0-0.93 (0.08) [28] | smokers | 0.05-0.27 (0.17) |
| Acetonitrile | 2200-10000 (4450) [29] | smokers | 101-2334 (745) |
| DMS | 0-1.72 (0.41) [31] | Mechanically ventilated patients | 3.5-34 (14.6) |
| Isoprene | 15-70 (37) [35]<br>4.5-38 (14) [34]<br>0.5-24.4 (9) [31] | Healthy volunteers<br>Rebreathing experiment<br>Mechanically ventilated patients | 3.5-34 (14.6) |
| Pentane | 0-58 (11.8) [31] | Mechanically ventilated patients | 0.19-0.81 (0.37) |
| 2-Butanone | (99) [24] | general U.S. population | 8.4-72 (35) |
| Furan, 2,5-dimethyl- | 0-3.9 (0.3) [28]<br>0.14-4.6 (0.77) [30] | smokers<br>smokers | 0.2-0.66 (0.41) |
| Benzene | 0.12-21.2 (4.3) [26]<br>0.4-6.2 (1.2) [28]<br>0.32-14.1 (1.8) [30]<br>(1.67) [24]<br>0.41-9.31 (2.26) [25] | Non-occupational exposure<br>smokers<br>smokers<br>general U.S. population<br>general U.S. population | 0.03-0.98 (0.26) |
| Toluene | 0.25-54.4 (9) [26]<br>0.81-27.2 (3.6) [30]<br>(5.65) [24]<br>0.25-53 (4.8) [25] | Non-occupational exposure<br>Smokers<br>general U.S. population<br>general U.S. population | 0.08-3.1 (0.6) |
| p-Xylene | (3.49) [24]<br>0.34-50 (2.5) [25] | general U.S. population<br>general U.S. population | 0.08-11.2 (0.96) |

**Figure captions**

*Figure 1:* An exemplary chromatogram from a blood HS-SPME-GCMS analysis (smoker).