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Quantification of acetonitrile in exhaled breath and urinary headspace using selected ion flow tube mass spectrometry

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Abstract

A study has been carried out of acetonitrile in exhaled breath and in the headspace of urine from several cigarette smokers and several non-smokers using selected ion flow tube mass spectrometry (SIFT-MS). The ion chemistry involved in the detection and quantification of acetonitrile in the gas phase by SIFT-MS using H_3O^+ ions is outlined. Further to this, experiments have been carried out to determine the Henry's Law partition coefficients for dilute aqueous solutions of acetonitrile, which allow the determination of liquid phase urinary acetonitrile concentrations from headspace concentrations. The results of this study show that acetonitrile is readily detected by SIFT-MS in the breath and urinary headspace of smokers at levels dependent on the cigarette consumption, but is practically absent from the breath and urine headspace of non-smokers. Exploiting the measured values of the Henry's Law partition coefficients, the urinary phase concentrations have been deduced. The results of this study show that typical breath concentrations of acetonitrile are within the range 17–124 ppb (mean value 69 ppb), which are in close agreement with previous studies. The urinary acetonitrile concentrations are within the range 0–150 μg/L (mean value 57 μg/L), which are close to the concentrations determined previously in blood. These collected data imply that the acetonitrile is equilibrated amongst the body fluids (blood, total body water and urine) and that excretion occurs via both exhaled breath and urine.

Keywords: SIFT-MS; Acetonitrile; Smoking; Breath; Urine

1. Introduction

In celebration of his 60th birthday, we are proud and privileged to dedicate this paper to Professor Helmut Schwarz, a good friend and colleague, an outstanding scientist, a stimulating speaker and a good man of broad interests and high culture.

Identification of volatile markers of smoking has been of considerable interest in breath analysis for many years. Earlier attempts using GC-MS were restricted to higher molecular weight compounds, and notably, 2,5-dimethyl furane was identified as a

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significant breath marker of smoking [1]. In 1995, Lindinger and colleagues [2] described the use of proton transfer reaction mass spectrometry (PTR-MS) to detect acetonitrile in exhaled breath, finding acetonitrile levels of typically 30–100 ppb in smokers breath and 5–10 ppb in non-smokers breath. Subsequently, Smith and Španěl [3] using selected ion flow tube mass spectrometry (SIFT-MS) detected acetonitrile in the smoke from a lit cigarette (with and without a filter) as well as in breath samples from smokers. Later, headspace gas–liquid chromatography was used to detect acetonitrile in the blood of smokers [4]. For those smoking more than 10 cigarettes a day, the mean blood levels were 148 μg/L and for those smoking 1–10 cigarettes a day the mean level was 43 μg/L. They did not detect acetonitrile in the blood of non-smokers, and concluded that this compound is a specific and sensitive marker of cigarette smoking, with a dose–effect relationship. Further studies by Lindinger's group [5,6] indicated that acetonitrile accumulates in the body to a level where equilibrium is reached between the rate of excretion via exhaled breath and intake by smoking. This contrasts with other volatile organic compounds associated with cigarette smoking that are excreted unchanged within a few hours, e.g., benzene, or those that undergo fast metabolism, e.g., toluene [7]. They calculated that the body of a smoker of weight 71 kg with a breath acetonitrile level of 100 ppb contains a total of 4.1 mg of acetonitrile, which is equivalent to 82 ug/L of body fluid. They describe a passive smoking experiment and conclude that spending 8 h in a smoke-laden environment is equivalent to smoking one to two cigarettes. However, it is important to appreciate when making these estimates that it has been reported that acetonitrile is slowly metabolised to hydrogen cyanide in the body [8].

During our SIFT-MS analyses of exhaled breath and the headspace of urine from cancer patients in search of volatile molecular biomarkers of tumours, we observed that acetonitrile appeared in the exhaled breath of smokers and also in the headspace of their urine (the latter, to our knowledge, not previously reported). These observations have prompted us to carry out a SIFT-MS study of the breath and urine acetonitrile concentrations of several smokers and non-smokers. In this paper, we outline the ion chemistry involved in SIFT-MS analyses of acetonitrile using H_3O^+ precursor ions and indicate how breath analysis and urine headspace analyses are performed. We have also investigated the partition of acetonitrile between the liquid and vapour phases (Henry's Law; [9]) as is required to derive urine liquid phase acetonitrile concentrations from the headspace analyses. The results of this study are presented and compared with those from the previous studies of breath and blood acetonitrile concentrations referred to above.

2. Outline of selected ion flow tube mass spectrometry (SIFT-MS)

The physics and chemistry involved in SIFT-MS are given in detail in previous publications [3,10]. In brief, precursor ions are extracted from a discharge ion source, mass selected using a quadrupole mass filter and injected into helium carrier gas in a flow tube. The commonly used precursor ions are H_3O^+, NO^+ and $O_2{}^+$ because these do not react rapidly with the major components of air. A sample of the air/breath/liquid headspace is added to the carrier gas/precursor ion swarm and the trace gases in the sample react with the precursor ions generating characteristic product ions. A downstream mass spectrometer is used to measure the count rates of the precursor and product ions and from these, together with measurements of the carrier gas and air sample flow rates, quantification of particular trace gases in the air sample is achieved. The most commonly used precursor ion is H_3O^+ because this reacts with a wide range of organic species, M, by non-dissociative proton transfer producing MH^+ ions, although it must be appreciated that for some organic species, notably alcohols, partial dissociation of the nascent MH^+ ions often occurs [11]. Therefore, a large kinetics database is required if SIFT-MS analyses of complex mixtures are to be achieved [3].

We used H_3O^+ precursor ions only in the present study of acetonitrile. The primary reaction involved in its analysis is the simple proton transfer reaction:

$$H_3O^+ + CH_3CN \rightarrow CH_3CNH^+ + H_2O \quad (1)$$

However, the ion chemistry involved is not so simple, because the introduction of humid air samples, such as breath and urine headspace, into the carrier gas results in the production of hydrated hydronium ions, $H_3O^+(H_2O)_{1–3}$, by sequences of well-known three-body association reactions [12]. These cluster ions react rapidly with acetonitrile molecules via ligand switching [3], e.g.:

$$H_3O^+(H_2O) + CH_3CN \rightarrow CH_3CNH^+H_2O + H_2O \quad (2)$$

In this way, hydrates of CH_3CNH^+ are formed, the higher order hydrated hydronium ions producing higher order cluster ions like $CH_3CNH^+(H_2O)_{2,3}$. There have been several previous studies of these ligand switching reactions in both flow tube experiments [13–15] and ion beam experiments [16]. They proceed at their collisional rates. The rate coefficients for these reactions, which are used in these SIFT-MS studies to quantify the acetonitrile in breath and urine headspace (see later), are given in ref. [13]. The $CH_3CNH^+(H_2O)_{1–3}$ hydrates can also be partially formed in three-body reactions of CH_3CNH^+ ions with water molecules, e.g.:

$$CH_3CNH^+ + H_2O + He \rightarrow CH_3CNH^+H_2O + He \quad (3)$$

Regardless of their origin, all the CH_3CNH^+ hydrated ions must be included as product ions and all the $H_3O^+(H_2O)_{1–3}$ ions must be included as precursor ions in absolute quantitative SIFT-MS analyses. Details of the SIFT-MS analytical procedure have been given in previous publications [12,17,18].

The downstream analytical quadrupole can be operated in two distinct modes, the full scan mode (FSM) and the multi-ion mode (MIM) [10,17]. In FSM, the quadrupole is scanned over a desired *m*/*z* range for a predetermined number of scans. In this way, the volatile compounds in the breath/headspace sample can be identified and quantified. In MIM, the analytical quadrupole is rapidly switched and dwells on predetermined *m*/*z* values of the precursor and the product ions. This mode is inherently more accurate for quantification, especially for species present in low concentrations, and thus, it has been used almost exclusively for the present studies. By targeting particular trace gas molecules in this way, more time is available to determine accurate ion count rates. This is especially important when the sample time is restricted, as it is for individual breath exhalations (typically only 5 s).

A FSM spectrum obtained using H_3O^+ precursor ions when a sample of the headspace of an aqueous solution of acetonitrile in a sealed glass bottle is introduced into the helium carrier gas is shown in Fig. 1a. Note the presence of the precursor hydronium ions and their hydrates at *m*/*z* values of 19, 37, 55 and 73 (and even a trace of 91) and the CH_3CNH^+ ions and their hydrates at 42, 60, 78 and 96. At these relatively high concentrations of acetonitrile, even the $(CH_3CN)_2H^+$ dimer ion is present at an *m*/*z* value of 83, although this is absent in the analysis of the breath and urine of smokers, which have much lower concentrations of acetonitrile (see Fig. 1b). Determination of the acetonitrile concentration can be achieved as described above from the precursor and product ion count rates. However, a serious complication arises when analysing breath and urinary headspace because of the inevitable presence of acetone (molecular weight 58 Da), which is one of the most abundant volatiles in breath and urine [3,19]. When acetone reacts with H_3O^+ ions, the protonated parent ion at an *m*/*z* value of 59 and its hydrates at *m*/*z* values of 77 and 95 are formed. At the relatively high concentrations of acetone compared to acetonitrile, the ^{13}C isotopomers of the acetone ions at *m*/*z* values of 60, 78 and 96 overlap the $CH_3CNH^+(H_2O)_{1–3}$ hydrated ions. It is therefore impractical to use the $CH_3CNH^+(H_2O)_{1–3}$ hydrated ions for the analysis of acetonitrile in breath and urine headspace. Hence, only the CH_3CNH^+ ions at *m*/*z* value of 42 are used for the analysis, scaling up the derived acetonitrile by an appropriate factor to account for the omission of the $CH_3CNH^+(H_2O)_{1–3}$ hydrated ions. This factor was

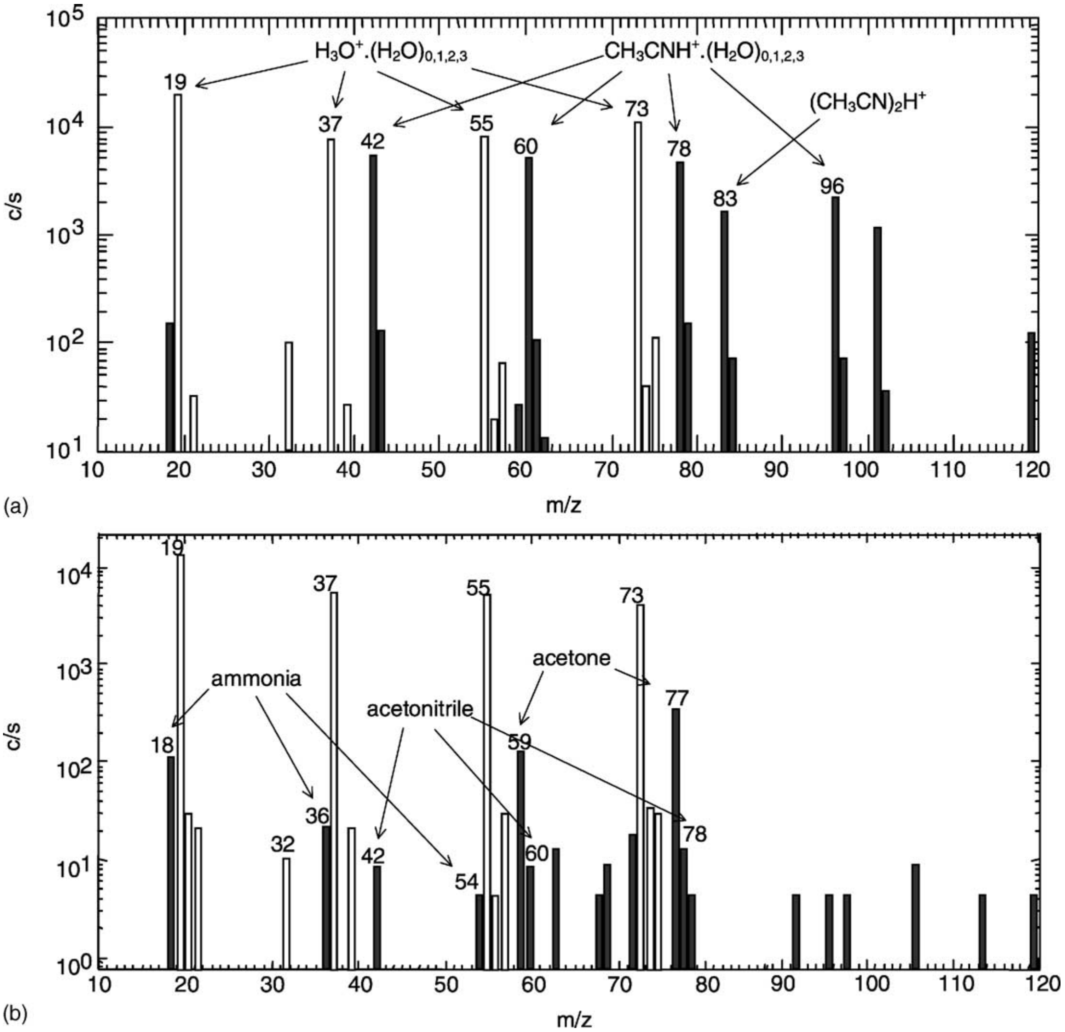

Fig. 1. Sample SIFT-MS full scan (FS) spectra obtained using H_3O^+ ions over an *m/z* range from 10 to 120 for the analysis of acetonitrile. The open bars are the precursor ions and the filled bars are the product ions. (a) Obtained when the headspace from an aqueous solution of acetonitrile is introduced into the helium carrier gas. Note the appearance of the CH_3CNH^+ hydrates and even the acetonitrile dimer ion $(CH_3CN)_2H^+$ at *m/z* of 83. (b) Obtained when the headspace of a urine sample from a smoker is introduced. In addition to acetonitrile, ammonia and acetone are seen at the characteristic ions indicated.

determined experimentally by analysing the acetonitrile in the headspace of an aqueous solution at the same temperature and sample flow rate using data such as those in Fig. 2.

A corresponding MIM data sample is shown in Fig. 2a. Here, we have only targeted the H_3O^+ and the CH_3CNH^+ ions and their hydrates. The analysis of these data for acetonitrile concentration is shown in Fig. 2b. These data demonstrate an important point that we address later, which is that the pressure in a sealed glass vessel reduces as the headspace is sampled into the SIFT-MS instrument and this needs to be accounted for in accurate analyses of urine headspace. We have dealt with this phenomenon in detail in a recent paper [20]. Of course, when breath is sampled either as direct exhalations or from bag

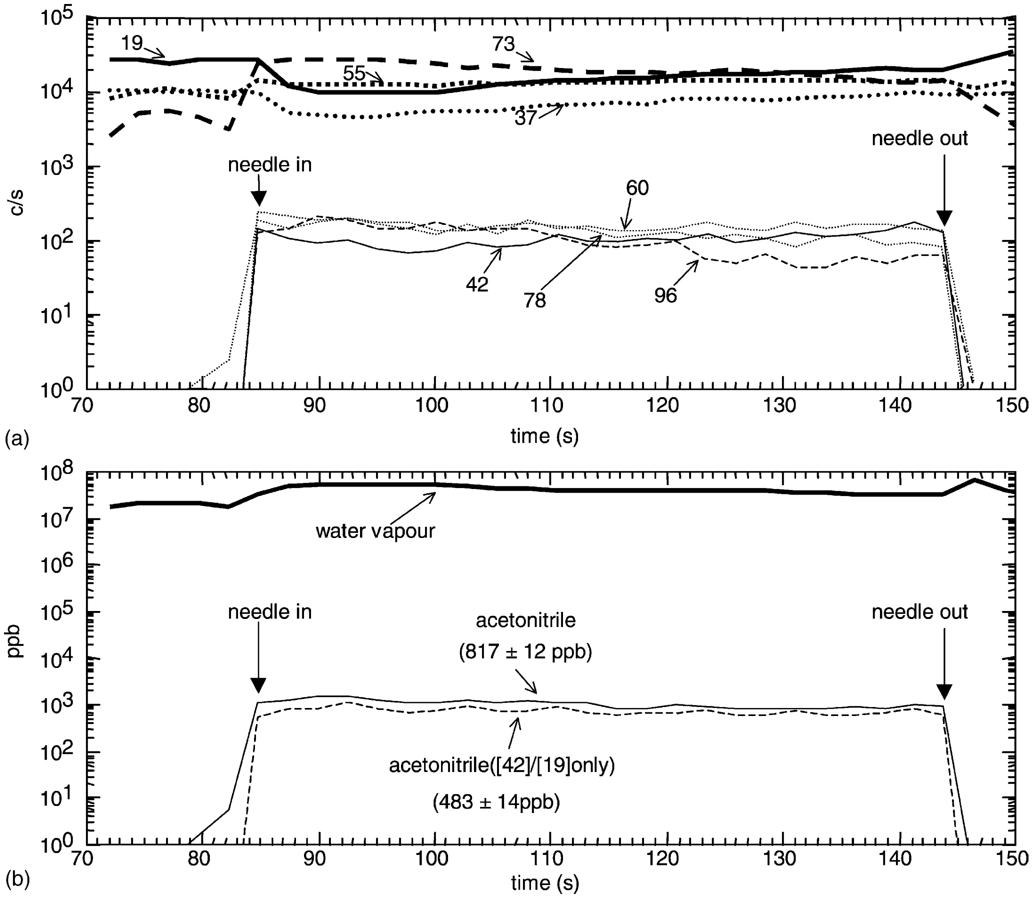

Fig. 2. (a) A MIM analysis of the headspace of an aqueous solution of acetonitrile contained in a glass bottle sealed with a septum, which is punctured with a hypodermic needle connected directly to the SIFT-MS instrument. The ion count rates are given in counts per second, c/s (note the logarithmic scale). As can be seen, the data were accumulated over about 60 s. The large count rates in the upper part relate to the precursor ions, $H_3O^+(H_2O)_{0-3}$ and those at lower count rates relate to the product ions, $CH_3CNH^+(H_2O)_{0-3}$. (b) The concentration of acetonitrile in ppb derived from the data in panel (a) considering only the CH_3CNH^+ product ions (dotted line) and the higher values that include the $CH_3CNH^+(H_2O)_{1-3}$ hydrated ions (see the text for further explanation). The water vapour partial pressure above the aqueous solution (in ppb) is derived from the signal levels of the $H_3O^+(H_2O)_{0-3}$ ions.

samples, the pressure does not reduce below atmospheric pressure.

3. Experimental protocol

In this section, we discuss the methods of sample collection and analysis, these being distinctly different for breath and urine. Informed consent was obtained from all subjects before the collection of breath and urine samples.

3.1. Sample collection and analysis

3.1.1. Breath

SIFT-MS can be used in two ways to analyse exhaled breath. The most desirable way is to allow direct exhaled breath to displace the laboratory air from the entrance to the SIFT-MS sample inlet port. The short time response (20 ms) of the SIFT-MS and the use of the MIM allow changes in the trace gas concentrations through a single exhalation to be observed in real time. This also allows the analysis to focus on the end-tidal (alveolar) portion of breath. Obviously, this requires the subject providing the breath sample to be adjacent to the instrument!

Alternatively, breath samples can be collected into bags, which can then be brought to the instrument and sampled at a steady, measured rate. This method collects total breath, including dead-space air as well as the alveolar portion. For the present studies 3 L Tedlar® bags (SKC Inc., PA, USA), each fitted with a closure valve, were used. According to the manufacturers, Tedlar resists gas permeation both into and out of the bag, assuring sample integrity and is inert to a wide range of chemicals, retaining its tensile strength and allowing for re-use. Before use, the bags were purged with dry cylinder air that was exhausted immediately before the breath sample was taken. Using disposable mouthpieces in order to eliminate cross infection, breath samples were collected by asking each subject to take a deep breath, pause and then exhale into the bag. This "vital capacity" air is thought to contain volatile organic compounds in close proportion to their amounts in alveolar air [21]. The inlet port of the SIFT-MS instrument has a fitting to allow the bag to be quickly attached but does not inhibit the operation of the valve, which can then be quickly opened and closed as desired. The bag (and valve) was placed in an enclosure to heat it to body temperature in order to return any condensates (especially water and soluble metabolites, such as ammonia) to the gas phase. We have carried out parallel studies involving direct breath measurements and breath collected into bags from the same subjects. We obtained good agreement between the two methods for acetonitrile in the breath of smokers, but there are problems with ammonia collection into bags [22]. The bag samples, in common with the direct breath sampling, were analysed using MIM. To repeat, the breath sample in the bag remains at atmospheric pressure during the sampling period as the bag volume decreases. The determination of the partial pressures of the trace gas compounds in the breath samples is achieved in the usual way for SIFT-MS, as described in several previous papers [3,17,18].

3.1.2. Urine

Urine samples were collected into sterile 100 mL plastic containers (Sarstedt Ltd.) following standard guidelines for mid-stream urine collection. None of the subjects included in this study had known urinary tract problems. Dipstick urinalysis tests (Multistix® Bayer plc) were routinely performed and those samples that were positive for nitrites and/or leucocytes were excluded on the grounds that they may be infected [23]. The samples were immediately frozen and stored at −70 °C for later analysis. Our previous experiments have shown that no deterioration in the urine samples or changes in emitted trace gases occurs following long-time storage at −70 °C [19].

To prepare for the SIFT-MS analysis of the urine headspace, clean glass bottles (volume 150 mL) were flushed with dry cylinder air and sealed with septa. This allows the introduction of the urine via syringe injection, thus avoiding contamination by atmospheric air. The frozen urine samples were thawed, pH measurements taken and 10 mL aliquots were introduced into each bottle, which were then placed in a water bath at 40 °C for 10 min. The headspace mixture comprising cylinder air, water vapour and volatile compounds was sampled by puncturing the septum with a hypodermic needle connected directly to the input port of the SIFT-MS instrument. This results in a slow reduction in the headspace pressure in the sealed bottle and a subsequent reduction in the flow of headspace compounds into the helium carrier gas, as is illustrated in Fig. 2. Details of the analytical procedure used to determine headspace partial pressures of the various trace compounds and how the reducing pressure is accounted for are given in previous publications [19,20].

3.2. Derivation of urine acetonitrile concentrations from the headspace partial pressure

To obtain liquid phase concentrations of acetonitrile and other compounds from headspace analyses, it is necessary to know the respective liquid phase/gas phase partition coefficients (Henry's Law coefficients) at the appropriate temperature. These have been determined for many compounds, including acetonitrile, in

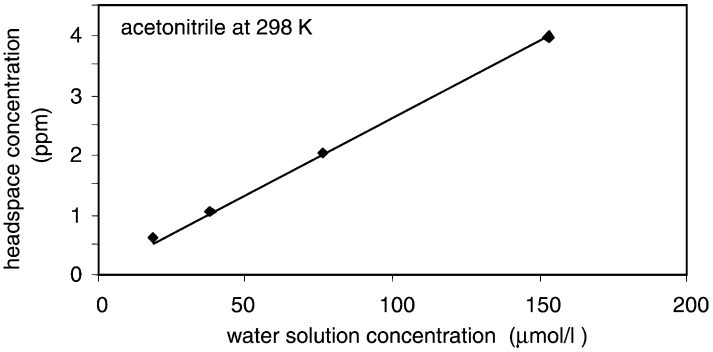

Fig. 3. The acetonitrile concentration in the headspace (ppm) of a dilute aqueous solutions of acetonitrile (concentrations in µmol/L) at a liquid temperature of 298 K. The slope of the line is 2.6×10^4 ppm/(mol/L). The inverse of this value gives the Henry's Law constant for acetonitrile at 298 K as 38 mol/L/ppm (equivalent to 38 mol/kg/bar). From these data and those obtained at 313 K, a value for $\Delta H/R$ of 3400 K is obtained, which is close to the value of 3500 K obtained previously [28].

dilute aqueous solution [24]. Nevertheless, we considered it necessary to determine the Henry's Law coefficient for aqueous solutions in order to investigate any influence there might be of the pH of the solution. It is well known, and our many studies confirm, that the pH of human urine can range from 4.5 to about 8 [25], but is generally within the range 6–7. Urine headspace concentrations of ammonia are known to vary greatly with pH [19] and, like ammonia, acetonitrile is a very polar molecule. However, acetonitrile is neither an acid nor a base, and thus, its headspace concentration does not vary significantly with the pH of the liquid.

Dilute aqueous solutions of acetonitrile at four known concentrations were made up and headspace analyses were then carried out at 298 and 313 K (i.e., close to body temperature), using the sealed bottle method described above, in order to obtain Henry's Law partition coefficients. The standard temperature of 298 °C was chosen to allow comparison with the published values [24,26]. A plot of the measured headspace concentration (in ppm) against the liquid phase concentration (in µmol/L) is shown in Fig. 3. Henry's Law simply relates the molar concentration of a compound in the liquid, M_{m}, to its vapour pressure above the liquid surface, p_{t}, as $M_{\mathrm{m}} = k_{\mathrm{H}} p_{\mathrm{t}}$ [27]. Hence, the Henry's Law coefficient, k_{H}, is simply obtained from the inverse slope of the plot shown, in units of µmol/L/ppm, which are equivalent to the conventional units mol/kg/bar (see the compilations in the NIST database [26]). Measurements were then carried out for a fixed aqueous concentration of acetonitrile at six different pH values (4, 5, 6, 7, 8 and 9). No significant difference was seen in the headspace acetonitrile concentration over this pH range. Therefore, in the present study all the urine samples were analysed only at their natural pH. The value obtained for the Henry's Law coefficient at 298 K was measured to be 38 µmol/L/ppm, which compares favourably with the published values (20% lower than the value of 48 mol/kg/bar given in ref. [28]). The value of this coefficient at 313 K is measured to be 22 µmol/L/ppm. Using this coefficient, the urine (liquid phase) concentrations of acetonitrile were determined from the SIFT-MS headspace analyses. Although urine is a complex mixture of soluble salts and organic species, it is unlikely that the partitioning of acetonitrile between the liquid and gas phases will be greatly different than that for the aqueous acetonitrile solution. However, we intend to investigate this point during the course of our further research in urinary analysis.

4. Results

We first present the results of the breath analyses and then the results of the urine analyses. We then

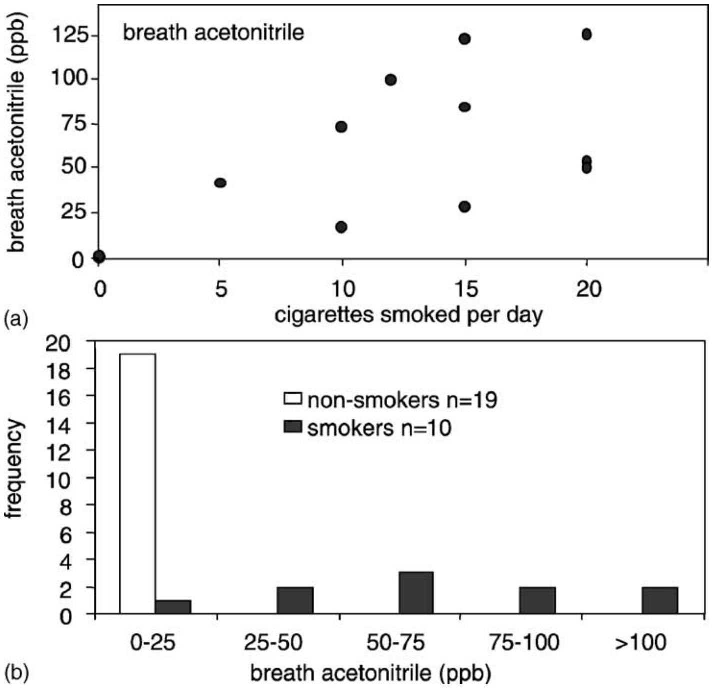

Fig. 4. (a) Correlation of breath acetonitrile concentration (in ppb) with the approximate number of cigarettes smoked per day. (b) Distributions for the breath acetonitrile concentration (in ppb) for non-smokers and smokers (*n* is the number of subjects in each category).

compare our breath and urine analyses with previous data obtained for the acetonitrile composition of blood from smokers.

4.1. Breath

The breath of 29 subjects has been analysed, 10 being smokers taking about 5–20 cigarettes per day. There is a positive correlation of the breath acetonitrile concentration with the number of cigarettes taken per day, as can be seen in Fig. 4a. No control was exercised on the time of breath sampling in relation to the time that the last cigarette was taken. The mean acetonitrile concentration in the breath of the non-smokers (2 ppb) is essentially at the instrument's lower sensitivity (noise) level, whilst that in the smokers breath is clearly elevated. The mean values and their spreads are given in Table 1 and represented as a frequency plot in Fig. 4b. These acetonitrile levels are quite consistent with the previously determined exhaled breath values [2,5]. The slight elevation in the breath of one of the non-smokers is probably just statistical variation, but passive smoking cannot be ruled out entirely (see the discussion in refs. [4,5]).

4.2. Urine

The headspace of urine from 57 subjects has been analysed, 14 being smokers again taking about 5–20 cigarettes per day. There is a clear correlation of the urine headspace acetonitrile concentration with the number of cigarettes taken per day, as can be seen in Fig. 5a. Again, no control was exercised on the time of urine sampling in relation to the time that the last cigarette was taken. The mean values and the spreads are given in Table 1 and represented as a frequency plot in Fig. 5b. Note that the acetonitrile concentrations in the headspace of the urine from 5 of the 43 non-smokers are significantly greater than the mean value for this group, but well below the mean value

Table 1
Mean breath and urinary headspace concentrations of acetonitrile in ppb and the ranges of these parameters for the number of smokers and non-smokers, *n*, as determined in the present SIFT-MS study

Acetonitrile	Group	*n*	Mean	Range	P[a]
Breath	Smokers	10	69 ppb	17–124 ppb	<0.001
	Non-smokers	19	2 ppb	0–17 ppb	
Urine headspace (urine liquid)	Smokers	14	63 ppb (56.8 μg/L)	0–166 ppb (0–150 μg/L)	<0.001
Urine headspace (urine liquid)	Non-smokers	43	3 ppb (2.7 μg/L)	0–29 ppb (0–26 μg/L)	
Blood liquid[b]	Smokers 1–10 per day		43 μg/L		
	Smokers >10 per day		148 μg/L		
	Non-smokers		Not detected		

Also given are the derived liquid urinary concentrations in μg/L.

[a] The very small P value indicates the significance of the difference between smokers and non-smokers.

[b] Mean blood acetonitrile levels determined using GC-MS obtained from ref. [4].

for the smoking group. We cannot positively explain these higher levels, but again passive smoking may be the cause [5]. As far as we are aware, there are no previous data on urinary acetonitrile levels with which to compare the data obtained in this study. Using our experimentally derived Henry's Law coefficient for acetonitrile at 313 K, the liquid phase urinary concentrations have been calculated from the headspace concentrations. These urinary concentrations are given in Table 1.

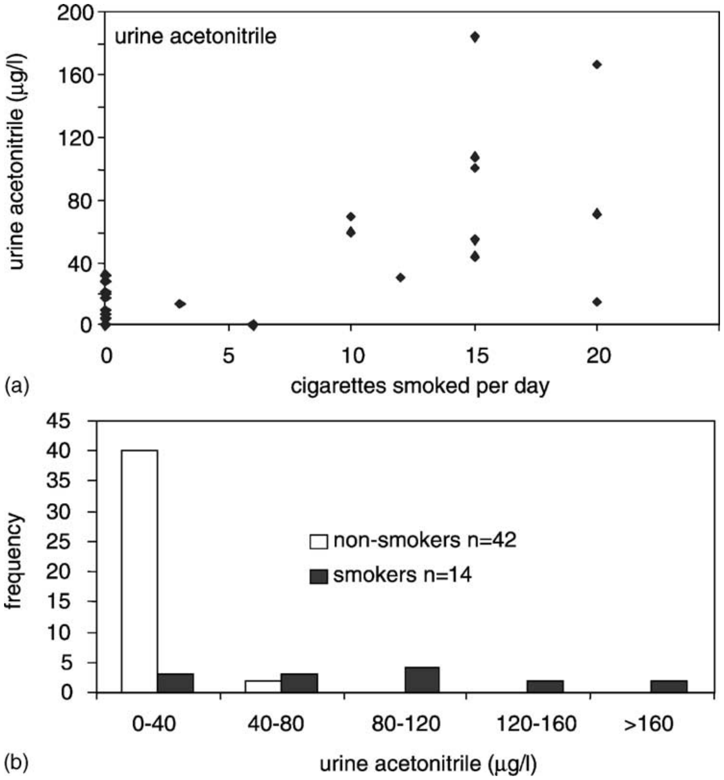

Fig. 5. (a) Correlation of urine acetonitrile concentration (in μg/L) derived from SIFT-MS headspace concentrations, with the approximate number of cigarettes smoked per day. (b) Distribution of the urine acetonitrile concentrations (in μg/L) for non-smokers and smokers (*n* is the number of subjects in each category).

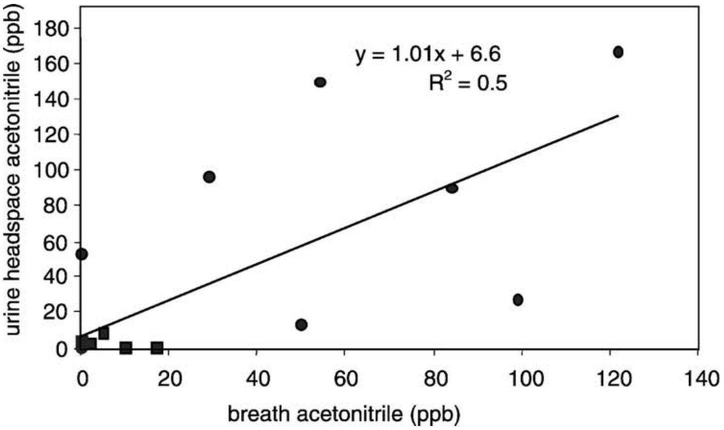

Fig. 6. Correlation of urine headspace (at 40 °C) and breath acetonitrile concentrations (in ppb) for smokers (filled circles) and non-smokers (filled squares). The regression equation and the correlation coefficient R^2 are also given.

4.3. Comparison of breath and urinary headspace acetonitrile concentrations

A glance at Table 1 shows that the mean breath and urinary headspace acetonitrile concentrations are very similar. Further to this, there is a rough correlation ($R^2 = 0.5$) between these parameters for the few subjects from which both breath and urine samples were obtained, as can be seen in Fig. 6. Clearly, more data are needed to establish this correlation without question, but as far as it goes these data suggest that the acetonitrile is systemic, i.e., distributed throughout the body fluids. Some of the variation is surely due to the fact that a finite time is required for the acetonitrile entering the blood stream to be distributed throughout the body fluids and for the passage of urine into the bladder. Thus, there will be some difference in the breath/urinary headspace concentration if breath sampling is taken shortly after smoking.

The previously determined blood concentrations of acetonitrile for smokers taking 1–10 cigarettes per day and >10 per day [4] are included in Table 1. Note that the mean of these values is close to the mean urinary values obtained in the present study. Although these data were obtained from different cohorts, they do suggest that the acetonitrile is equilibrated amongst the body fluids, i.e., blood, total body water and urine. This allows the total body burden of acetonitrile to be estimated. This is typically several milligrams, agreeing with the estimate previously indicated by Lindinger and colleagues [5].

5. Concluding remarks

This SIFT-MS study has confirmed that acetonitrile can be detected and quantified in the exhaled breath of smokers with sufficient sensitivity to distinguish between heavy and light smokers. The absolute concentrations detected in breath are in good agreement with those found previously [2,5]. Additionally, this study has shown how urinary concentrations can be obtained from SIFT-MS analyses of urinary headspace measurements. This provides another non-invasive method for differentiating between smokers and non-smokers. The combined data obtained from the previous and present breath analyses, the present urinary analyses and previous blood analyses [4] indicate that the acetonitrile is distributed and equilibrated amongst the various body fluids. It has been suggested previously that the major loss of acetonitrile from the body, excluding metabolism, is via exhaled breath [6]. However, it is readily shown from the data presented here, and using estimates of urine production, that loss via urinary excretion is comparable to the loss via exhaled breath.

Acknowledgements

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