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Determination of sevoflurane and isopropyl alcohol in exhaled breath by thermal desorption gas chromatography–mass spectrometry for exposure assessment of hospital staff

Silvia Ghimenti[a], Sara Tabucchi[a], Francesca G. Bellagambi[a], Tommaso Lomonaco[a], Massimo Onor[b], Maria Giovanna Trivella[c], Roger Fuoco[a], Fabio Di Francesco[a,c,*]

[a] Department of Chemistry and Industrial Chemistry, University of Pisa, Via Moruzzi, 3, 56124 Pisa, Italy
[b] Institute of Chemistry of Organometallic Compounds, CNR, Via Moruzzi 1, 56124 Pisa, Italy
[c] Institute of Clinical Physiology, CNR, Via Moruzzi 1, 56124 Pisa, Italy

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ABSTRACT

Volatile anaesthetics and disinfection chemicals pose ubiquitous inhalation and dermal exposure risks in hospital and clinic environments. This work demonstrates specific non-invasive breath biomonitoring methodology for assessing staff exposures to sevoflurane (SEV) anaesthetic, documenting its metabolite hexafluoroisopropanol (HFIP) and measuring exposures to isopropanol (IPA) dermal disinfection fluid. Methods are based on breath sample collection in Nalophan bags, followed by an aliquot transfer to adsorption tube, and subsequent analysis by thermal desorption gas chromatography–mass spectrometry (TD-GC–MS). Ambient levels of IPA were also monitored. These methods could be generalized to other common volatile chemicals found in medical environments. Calibration curves were linear ($r^2 = 0.999$) in the investigated ranges: 0.01–1000 ppbv for SEV, 0.02–1700 ppbv for IPA, and 0.001–0.1 ppbv for HFIP. The instrumental detection limit was 10 pptv for IPA and 5 pptv for SEV, both estimated by extracted ion-TIC chromatograms, whereas the HFIP minimum detectable concentration was 0.5 pptv as estimated in SIM acquisition mode. The methods were applied to hospital staff working in operating rooms and clinics for blood draws. SEV and HFIP were present in all subjects at concentrations in the range of 0.7–18, and 0.002–0.024 ppbv for SEV and HFIP respectively. Correlation between IPA ambient air and breath concentration confirmed the inhalation pathway of exposure ($r = 0.95$, $p < 0.001$) and breath-borne IPA was measured as high as 1500 ppbv. The methodology is easy to implement and valuable for screening exposures to common hospital chemicals. Although the overall exposures documented were generally below levels of health concern in this limited study, outliers were observed that indicate potential for acute exposures.

1. Introduction

Hospital staff may be exposed to many potentially harmful substances [1,2]. Volatile anaesthetics and alcoholic disinfectants are two main classes of harmful volatile substances commonly found in hospital environments [2]. Alcohol-containing hand rubs and gels are widely used in the healthcare environment for hand decontamination. Two representative compounds of these classes of volatile pollutants were selected, namely sevoflurane (SEV), a widely used anaesthetic gas, and isopropyl alcohol (IPA), one of the main components of skin antiseptics. Since there is a real risk of contamination for exposed hospital personnel, a monitoring to these substances is very important for the protection of hospital staff' health.

SEV (fluoromethyl 2,2,2-trifluoro-1-trifluoromethylethyl ether) is used in anaesthesiology for invasive surgery due to its favourable pharmacokinetic properties, i.e. low blood-gas partition coefficient and tissue solubility, fast metabolism and low cardio-depressant effect [3,4]. The low blood solubility leads to the rapid induction of anaesthesia and a rapid recovery afterwards. SEV is directly eliminated via exhaled breath and indirectly metabolized in the liver by the isoenzyme CYP2E1 [5–7], with the formation of inorganic and organic fluorides such as hexafluoroisopropanol (HFIP) and HFIP-glucuronide. Most HFIP is excreted in 12 h, and only very

* Corresponding author at: Department of Chemistry and Industrial Chemistry, University of Pisa, Via G. Moruzzi 3, 56124 Pisa, Italy. Tel.: +39 0502219308; fax: +39 0502219260.
E-mail address: fabio.difrancesco@unipi.it (F. Di Francesco).

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low concentrations are found 2 days after anaesthesia [8]. The unconjugated fraction, which represents less than 15% of total HFIP concentration [5,6], is eliminated via exhaled breath.

Occupational exposure by the inhalation of anaesthetics may produce several collateral effects. Hospital staff working in operating and recovery rooms, and dental clinics, are the most exposed workers. Since the early 1980s, various epidemiological studies have suggested that chronic exposure to low doses of anaesthetic gases is an occupational risk factor for spontaneous abortion and congenital defects [9–15]. Furthermore, long-term occupational exposure to trace levels of anaesthetic mixtures, including halogenated compounds, has been shown to affect lymphatic systems. Acute headaches, asthenia, neurobehavioral changes and effects on performance have also been reported [16,17].

SEV may thus pose a hazard to hospital workers, and the European and United States health authorities recommend exposure limits for volatile anaesthetics. Although an occupational exposure standard for SEV has never been set in Europe, a target level of 20 ppm as an 8-h time-weighted average (TWA) has been recommended [18]. On the other hand, the U.S. National Institute of Occupational Health and Safety (NIOSH) recommends a general exposure limit of 2 ppm for all volatile anaesthetics, which is mostly interpreted as a ceiling value [19].

The second widespread contaminant in hospital environments is IPA. It is very often used as a cleaning agent and as a solvent in mild disinfectants, antiseptic solutions and rubbing alcohols [20,21]. This compound is rapidly absorbed and distributed throughout the body after inhalation, ingestion or absorption through the skin, but most intoxication are related to oral ingestion [22]. The volume of distribution of IPA in the human body is 0.5 L kg^{-1}. A half-life ranging from 2.5 to 6.4 h is estimated, which could be longer in the case of high blood concentrations occurring in intoxication due to the saturation of alcohol dehydrogenase (ADH). Elimination mainly depends on the liver (80–90%) and kidneys [22]. The critical step in the biotransformation of IPA is oxidation to acetone, which is catalyzed by the liver enzyme ADH [23–25]. Unlike alcohols such as methanol or ethylene glycol, the toxic effects of IPA are directly related to the molecule rather than its metabolites [21,23]. IPA has an anaesthetic effect and irritates the respiratory mucosa if inhaled [25–28] as well as the central nervous system (CNS) [20,22].

Different safety and occupational health agencies indicate threshold values for exposure to IPA in ambient air. The European agency for safety and health at work (EU-OSHA) enforces a legal ambient air permissible exposure limit (PEL) of 400 ppmv averaged over an 8-h work shift. The same TWA limit of 400 ppmv and a short-term exposure limit (STEL) of 500 ppmv are reported in the NIOSH guide to chemical hazards and by the American conference of governmental industrial hygienists (ACGIH) [26].

Several analytical methods are suitable for monitoring exposure to potentially dangerous environmental volatile organic compounds (VOCs). The determination of SEV and IPA is mainly implemented in biological matrices such as blood and urine, or in ambient air. Although studies on plasma and urinary biomarkers of low-level occupational exposure to SEV have been carried out in the last few decades [29–32], few studies have been carried out by analysing ambient air and no study to the best of our knowledge has examined the exhaled breath of hospital staff.

In two studies, SEV concentrations, ranging from 0.1 to 12 ppm, were determined by photo acoustic infrared spectrometry in the ambient air of operating rooms [13,14]. Room staff exposure was related to the anaesthetic doses as well as the duration of the intervention, the position of the room staff, and the type and functioning of the ventilation system in an operating room. In another study, a portable ambient air analyser called MIRAN 1B, which used a single beam infrared spectrophotometer was applied to measure SEV background concentrations (4–17 ppm) in working environments during gaseous induction with the anaesthetic [18]. Other studies involved hospital personnel exposed to volatile anaesthetics, using MIRAN 1B to evaluate halogenated anaesthetic concentrations in the gas samples thus leading to the conclusion that exposures for post-operative nurses may exceed NIOSH ceilings [33]. Nurses who are exposed to volatile anaesthetics exhaled by patients were involved in several studies because they are particularly exposed to anaesthetic gases, as well as the staff working in operating theatres [34].

IPA poisoning can be diagnosed by normal acid-base parameters, the evaluation of hyperosmolarity (the most common laboratory abnormality associated with isopropanol poisoning), and positive nitroprusside reactions in urine and/or blood [20,21,23]. At the same time, a non-invasive biological monitoring of IPA-exposed workers can be carried out by ambient air, saliva, or urine analysis [35–38]. Two important institutions for workplace safety, NIOSH and EU-OSHA, have proposed methods to monitor IPA exposure in ambient air.

The analytical method proposed by NIOSH to determine IPA in ambient air was based on sampling air in an adsorption tube (coconut shell charcoal) followed by thermal desorption gas-chromatography analysis with flame ionization detector [39]. Two 8-mm o.d. (6-mm i.d.) Anasorb® 747 tubes in series were proposed in the OSHA method. Analytes were eluted with a 60/40 N,N-dimethylformamide/carbon disulphide solution which was then analyzed by gas-chromatography with flame ionization detector. The detection limit of the overall procedure was 13 ppb [40].

In standard methods, SEV and IPA are routinely monitored in working ambient air, however determination in exhaled breath would be a more meaningful measurement of hospital personnel exposure. Based on this background information, we optimized a previously published analytical methodology [8,41] involving the collection of mixed exhaled breath samples in disposable Nalophan bags and analysis by thermal desorption gas chromatography–mass spectrometry (TD-GC–MS). This methodology was then used to determine SEV and IPA to assess exposure levels in a hospital environment.

VOCs found in human breath are linked to various physiological conditions as they represent the products of metabolism in human bodies, and VOCs detected in human breath can be directly correlated to specific diseases or environmental contaminations. In fact, the determination of exogenous substances, or their metabolites, in the exhaled breath may reveal their possible assumption.

Being able to detect metabolites uniquely correlated with the intake of exogenous substances is an additional advantage of breath analysis compared to ambient air analysis. The determination of contaminants such as SEV and IPA in exhaled breath should help to better assess exposure levels in the workplace. In addition, compared to traditional specimen testing, breath analysis is a non-invasive approach. It is a simple alternative to traditional specimen testing in both clinical diagnosis and therapeutic monitoring, and when quantifying exposure at work, [42–44]. Breath analysis can also easily be expanded to the analysis of other potentially harmful VOCs that require monitoring in the workplace.

2. Materials and methods

2.1. Chemical reagents

Fluoromethyl 2,2,2-trifluoro-1-trifluoromethylethyl ether (with a purity >99.9%) was purchased from Abbott (USA). 1,1,1,3,3,3-Hexafluoro-2-propanol (puriss. p.a. standard for GC grade >99.0%) was purchased from Fluka, Sigma–Aldrich (Italy). Isopropyl alcohol was purchased from AccuStandard, Inc.

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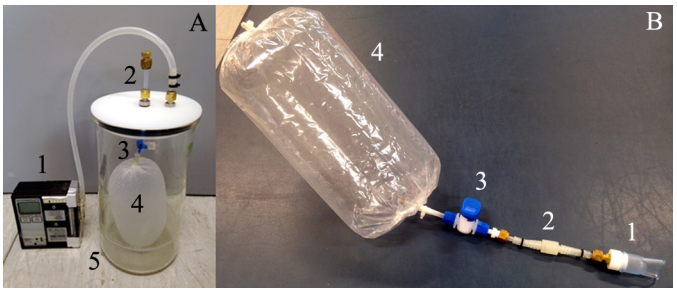

Fig. 1. (A) Air sampling system composed by (1) pump, (2) PTFE tube, (3) three-ways stop valve, (4) Nalophan bag, and (5) vessel; (B) Breath sampling system composed by (1) disposable mouthpiece, (2) non-return valve, (3) stopcock, and (4) Nalophan bag.

Chemical Reference Standard (USA). Labelled isopropanol-D8 and toluene-D8 (both puriss. p.a. standard for GC grade of 99.8%) were purchased from ARMAR Chemicals (Switzerland). Reagents were stored at 4 °C to minimize the risk of evaporation.

2.2. Preparation of standards

A gaseous standard of IPA, SEV and HFIP (MIX3) was prepared by evaporating 5 μL of each liquid standard in a pre-evacuated glass flask (2 L) equipped with a septum and held at 37 °C. The calculated concentrations were 830 ppmv for IPA, 480 ppmv for SEV and 610 ppmv for HFIP. MIX3 was diluted injecting known volumes in the flow of pure air (Hydrocarbon free, purity of 99.5%, Sol, Italy) at 500 mL min^{-1} during Nalophan bags (5 L) filling. The resulted gaseous standard mixture was further diluted in the same way to obtain mixtures at suitable concentrations for the method performances evaluation.

A gaseous mixture of labelled isopropanol-D8 and toluene-D8 (MIX 2D), for use as an internal standard, was prepared by evaporation of 5 μL of both compounds in a 2 L glass flask equipped with a septum, pre-evacuated and held at 37 °C. The corresponding concentrations were 830 ppmv and 600 ppmv, respectively.

2.3. Air and breath sample collection

The ambient air was collected using a gas-tight cylindrical glass vessel containing a Nalophan bag (approximate volume of 1 L) connected to room air by a short PTFE tube (1/4 in. i.d.) and a bulkhead union mounted on the vessel lid (Fig. 1A). A pump, connected to the vessel by a second bulkhead union on the lid, decreased the pressure in the gap between the bag and the vessel wall, thus inflating the bag. After collection, room air samples were analyzed in the same way as the breath samples.

Disposable bags (approximate volume of 3 L) were made from a roll of Nalophan tube (polyethylene terephthalate film, thickness 20 μm) supplied by Kalle (Germany). One end of the Nalophan bag was rolled and tightened by nylon cable ties. The other end was wrapped and tightened around a PTFE tube (1/4 in. i.d.) connected to a stopcock, a one-way valve, and a mouthpiece, as shown in Fig. 1B. All parts of the sampling system were made of inert materials and were freshly sterilized before sample collection. Each subject was asked to calmly fill a bag with multiple deep breaths. All subjects who volunteered to join the study gave written informed consent prior to their participation. The breath sampling was carried out in two different applications.

2.3.1. Application A: monitoring of SEV exposure levels

Mixed breath samples were collected from five anaesthesiologists (2 males, 3 females), aged between 27 and 33 years (average value 29 ± 2 years), working in different operating rooms at the university hospital in Pisa, Italy. Work shifts were organized on a weekly basis with 5 consecutive working days followed by 2 days of rest. Sample collection was designed to assess the effects of both the working day and the working week. Three different samples of exhaled breath were collected from each subject. The first sample was collected when the anaesthesiologist arrived at the hospital at the beginning of the first day of work (t_0), the second sample at the end of the same day (t_1) and the last sample was collected at the end of the anaesthesiologist's working week (t_2).

The sampling of ambient air inside the operating room was not taken for safety reasons and in order not to hamper the surgical operations in progress.

2.3.2. Application B: monitoring of IPA exposure levels

To assess IPA exposure of hospital staff, mixed breath and ambient air samples were simultaneously collected in a room specifically used for blood drawings, before the beginning of the work shift (t_0), and 90 (t_1) and 180 (t_2) min later. For this application, nine nurses (3 males, 6 females), aged between 22 and 43 years (average value 29 ± 9 years), were enrolled at the Institute of Clinical Physiology (National Research Council, Pisa, Italy) in a time span of 2 months.

2.4. Sample analysis

Sampling bags containing air or breath samples were stabilized at 37 (±1) °C in a thermostated box for half an hour to prevent water condensation. An aliquot of the sample (250 mL) was then flowed through a drying tube filled with 9 g of anhydrous sodium sulphate (SKC, Italy) for water removal, and transferred into a glass adsorption tube packed with 250 mg of 60/80 mesh Tenax GR phase (70% Tenax TA, 2,6-diphenyl-p-phenylene oxide and 30% graphite, Supelco, USA). During the sample transfer, the sampling bag and the drying tube were kept at 37 °C, whereas the adsorption tube was kept at ambient temperature. A low flow pocket pump (210-1002TX, SKC, Italy) was used to transfer breath samples into adsorption tubes, using a constant flow of 50 mL min^{-1} for 5 min^{-1}. The adsorption tubes were then thermally desorbed by an automated two-stage thermal desorption unit (STD 1000, DANI Instrument, Italy) equipped with an internal focusing trap packed with 70 mg of Tenax GR. During the first desorption stage, carried out at 250 °C for 5 min under a helium splitless flow of 35 mL min^{-1}, the sample was concentrated in a cold trap at 5 °C. The cold trap was then flashed at 250 °C to inject the analytes into the capillary column (DB-624, 60 m length, 0.25 mm internal diameter, 1.4 μm film thickness, Agilent Technologies, USA) of the gas chromatograph (Trace GC Ultra, Thermo Electron Corporation, USA) coupled to a quadrupole mass spectrometer (Trace DSQ, Thermo Electron Corporation, USA) operated in the positive electron impact (EI) ionization mode (70 eV). Chromatograms were collected in both total ion current (TIC) and selected ion monitoring (SIM) acquisition modes. The ions at m/z 45, 131 and 99 were used for IPA, SEV and HFIP identification and quantification, respectively. The ions at m/z 49 were used for isopropanol-D8 and m/z 98 for toluene-D8. The oven temperature programme was 35 °C for 10 min, 4 °C min^{-1} to 130 °C, 2 min hold, 20 °C min^{-1} to 250 °C, 10 min hold, 25 °C min^{-1} to 260 °C, 15 min hold. The total GC–MS run time was 56 min. The temperature of the injector was set at 200 °C. Helium (constant pressure 210 kPa, split flow of 10 mL min^{-1}) was used as carrier gas. Dedicated software controlled the thermal desorption unit (TD Manager, DANI Instrument, Italy) and the GC–MS (Xcalibur, Thermo Electron Corporation, USA). The GC–MS response factor stability unit was checked daily by injecting 50 μL of labelled MIX2D. The analysis of all the collected samples was carried out in triplicate.

The chemical stability of IPA, SEV and HFIP was evaluated by filling Nalophan bags with standard mixtures and then analyzed soon after filling (t_0) and after 0.5, 2.5, 5 and 24 h. For this

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purpose, 2.5 mL of MIX3 were injected in the aspiration flow during the filling of Nalophan bags (5 L) with pure air at 500 mL min^{-1}. The calculated concentration of SEV, HFIP and IPA in the bag was 240, 305 and 415 ppbv, respectively. 250 mL of gaseous mixture were loaded into the adsorption tube at 50 mL min^{-1} and 50 μL of MIX2D were injected in the aspiration flow during the sample transfer. Adsorption tube was finally analyzed in the same way as the breath samples.

Relative response factors to labelled internal standards were calculated according to the following:

$$K = \frac{A_i \times m_{D8}}{A_{D8} \times m_i} \quad (1)$$

where A_i and m_i are the chromatographic peak areas (a.u.) and the theoretical amounts (ng loaded in the adsorption tube) of the *i*th compound, respectively. A_{D8} and m_{D8} are the chromatographic peak areas (a.u.) and the theoretical amounts (ng loaded in the adsorption tube) of the internal labelled standards, respectively. To determine *K*, 50 μL of each standard (MIX3 and MIX2D) were injected in the aspiration flow during the transfer of 250 mL of pure air into the adsorption tube at 50 mL min^{-1}. Five adsorption tubes were analyzed in the same way as the breath samples.

Isopropanol-D8 was used as internal standard for the quantification of IPA and SEV, whereas toluene-D8 was used for the quantification of HFIP.

3. Results and discussion

3.1. Analytical performance

The analytical method had already been proposed and validated in previous studies [8,41]. In this study, the application to assess workers' exposure to potentially harmful VOCs in a hospital environment was tested. Stability test showed that within 5 h there were no significant variations of IPA (415 ppbv), SEV (240 ppbv) and HFIP (305 ppbv) concentrations in the Nalophan bags and a decrease of about 10% within 24 h was observed. Standard gaseous mixtures prepared according to the method described in 2.2 were analyzed as described in Section 2.4. Seven points calibration curves showed a good linearity (r^2 = 0.999) in the ranges 0.01–1000 ppbv for SEV, 0.001–0.1 ppbv for HFIP, and 0.02–1700 ppbv for IPA.

The instrumental detection limits (IDLs), calculated considering the concentrations producing a signal-to-noise ratio equal to 3, were 10 pptv for IPA, and 5 pptv for SEV. The HFIP minimum detectable concentration was 0.5 pptv as estimated in SIM acquisition mode.

In the experimental conditions, the retention time of IPA, SEV, HFIP, isopropanol-D8 and toluene-D8 was 9.14, 7.35, 23.43, 8.86 and 25.37 min, respectively.

The mean relative response factors (n = 5), with a RSD of about 6%, were 0.87 for IPA, 1.34 for SEV and 0.54 for HFIP.

3.2. Determination of SEV in breath samples

All subjects involved in the study were working 8 h per day, and participated in surgeries of different types and length carried out in different operating rooms for a maximum of 6 h each shift. They were of a similar age but were of different sexes and body weights. Potential exposures were also different, depending on the kinds of surgery and doses of anaesthetic used.

Fig. 2 shows SEV (A) and HFIP (B) concentrations measured in the collected breath samples. A mean SEV/HFIP breath concentration ratio of 170 ± 150 was observed, in good agreement with the pharmacokinetic model previously described [8]. SEV was measured in most samples, but in four out of five t_0 samples, the concentration

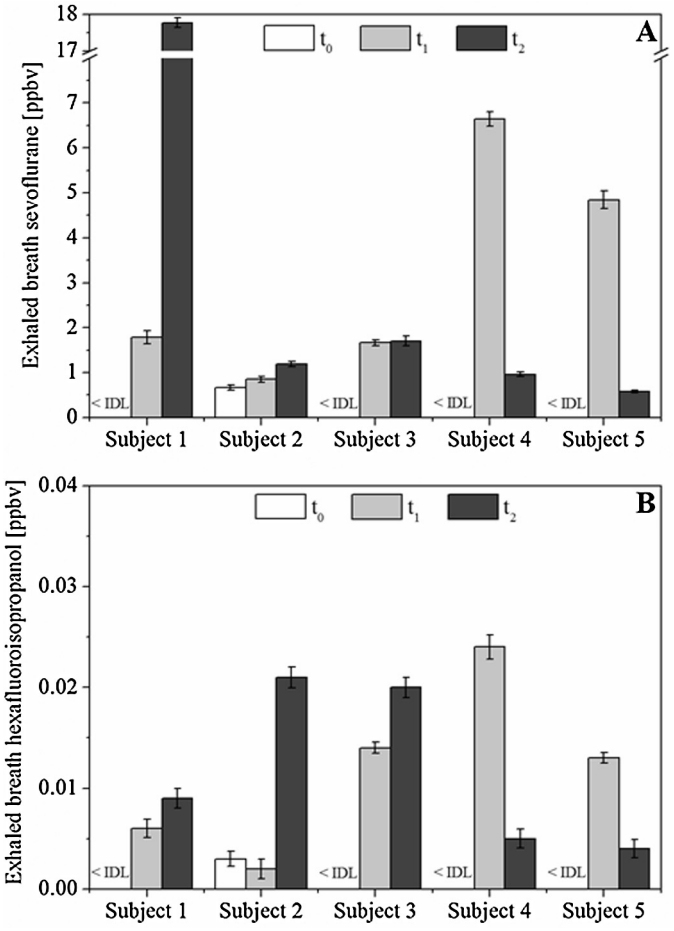

Fig. 2. SEV (A) and HFIP (B) levels (ppbv) in trainees' exhaled breath. Each trainee filled the sampling bags at the beginning of the working week (t_0), at the end of the first day of work (t_1), and at the end of the last working day (t_2).

was below the IDL. This reasonably means that usually concentrations lower than 5 pptv remained in the subject's breath after the weekend rest. Concentration profiles during the week did not seem to follow the same pattern for all the anaesthesiologists. In three cases, SEV concentrations were higher at the end of the first working day (t_1) than at the end of the working week (t_2). If time between two consecutive working days is insufficient to let SEV concentrations drop below the IDL, then a cumulative increase in concentration during the working week would be observed, resulting in higher SEV levels in t_2 samples. Instead, our results appeared more compatible with a highly variable exposure, in which daily variability plays a major role.

Note that SEV concentration in breath was always very low, far below the limit of 2 ppm suggested by NIOSH in ambient air [19].

Our statistics are insufficient to draw ultimate conclusions and we lack data concerning SEV concentrations in ambient air, since we were not allowed to access surgery rooms during surgeries as this was considered to pose risks for patients. However, it seems that the exposure of workers involved in the study was of acceptable levels. This is very important, because the risk of harmful effects from chronic occupational exposure to SEV is so serious that NIOSH declared that a safe level of exposure for waste-anaesthetic gases could not be identified, and recommended that risks should be minimized by "reducing exposures to the greatest extent possible" [19].

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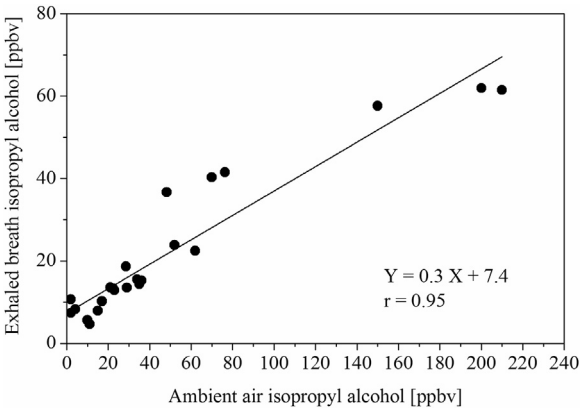

Fig. 3. IPA concentrations in workers' breath samples versus IPA concentrations in ambient air.

3.3. Determination of IPA in air and breath samples

An antiseptic water-alcohol solution containing 70% of IPA was identified as the likely source of isopropyl alcohol in the air of the blood sampling room. Cotton balls were typically soaked with the solution and used to disinfect the skin before blood sampling, then thrown into a basket.

Fig. 3 shows IPA levels in breath versus concentrations measured in the air. The good correlation ($r = 0.95$, $p < 0.001$) between these concentrations suggests that breath levels can be used at the same time to monitor exposure and to have an idea of the level of ambient contamination. In a hospital, where largely variable conditions are found in different rooms depending on use, breath levels will be a weighted average of the concentrations based on the time spent by the subjects in the different areas.

During our study, an accidental exposure to higher than normal IPA concentration levels occurred to a subject who probably remained very close to the basket containing the waste cotton balls. In this case, a concentration of 1500 ± 70 ppbv was measured, compared to a mean value of 20 ± 20 ppbv determined in the other nurses' exhaled breath. This level is in any case far below the TWA limit of 400 ppmv and a STEL of 500 ppmv recommended by NIOSH for ambient air [26], and concentration in breath decreased more than seven times in about half an hour, suggesting that the risks for health remained quite low.

4. Conclusions

In hospitals, anaesthetic gases, antiseptics and disinfectants are a primary source of air contamination. The consequent presence of potentially harmful VOCs in the air poses a risk for hospital staff in terms of acute and chronic exposure.

Our method was successfully used to measure the two representative contaminants – SEV and IPA – in breath, and may also be exploited to determine volatile metabolites of xenobiotics, such as HFIP in the breath samples. HFIP is a biologically damped metabolite of SEV, and so longer-term chronic exposures would eventually appear as the metabolite despite the fact that the on-board original SEV may have already been lost to exhaled volatilization.

Managing cotton balls soaked with IPA undoubtedly requires careful storage pending disposal. In addition there should be a ventilation system in any environment where potentially harmful volatile substances are used, such as anaesthetic gases.

However, appropriate precautions are taken in the workplace environment of the subjects involved in our study, as demonstrated by the fact that the concentrations of the analytes of interest were all below the recommended legal limits.

The main advantages of our method are non-invasiveness and the simple sampling procedure compared to conventional biological fluids (e.g. blood and urine). In addition, the method enables the determination of both SEV and IPA at concentration levels far below the occupational exposure limits in both exhaled breath and ambient air. This indicates that in conjunction with other monitoring programmes our method could be used for sensitive, short-term monitoring of hospital personnel exposed to potentially harmful VOCs as well as for monitoring staff exposure to other potentially harmful VOCs.

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