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Breath gas concentrations mirror exposure to sevoflurane and isopropyl alcohol in hospital environments in non-occupational conditions

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Abstract

Anaesthetic gases and disinfectants are a primary source of air contamination in hospitals. A highly sensitive sorbent-trap methodology has been used to analyse exhaled breath samples with detection limits in the pptv range, which allows volatile organic compounds (VOCs) to be detected at significantly lower levels (5-6 orders of magnitude below) than the recommended exposure limits by different organizations. Two common VOCs used in hospital environments, isopropyl alcohol (IPA) and sevoflurane, have been evaluated. Forced-expiratory breath samples were obtained from 100 volunteers (24 hospital staff, 45 hospital visitors and 31 external controls). Significant differences for IPA were found between samples from volunteers who had not been in contact with hospital ~~these~~ environments (mean value of 8.032 ppbv) and people staying (20.981 ppbv, p=0.0002) or working (19.457 ppbv, p=0.00009) in such an environment. Sevoflurane, an anaesthetic gas routinely used as an inhaled anaesthetic, was detected in all samples from volunteers in the hospital environment but not in volunteers who had not been in recent contact with a hospital environment. The levels of sevoflurane were significantly higher (p=0.00024) among staff members (0.522 ppbv) than among visitors to the hospital (0.196 ppbv). We conclude that highly sensitive methods are required to detect anaesthetic gas contamination in hospital environments.

Keywords: breath, sevoflurane, isopropyl alcohol, exposure

Introduction

Volatile organic compounds (VOCs) are ubiquitous contaminants in ambient and indoor air from many and varied anthropogenic and biogenic sources. There is great interest in determining the levels of VOCs in air samples in order to assess exposure to contaminants. However, all existing regulations and recommendations are focused on ambient air or workplace exposure and there are no exposure limits for contaminants in indoor air, even though people in developed countries spend more than 70% of their time indoors [1].

In clinical practice, workplace exposure to anaesthetic gases has become a significant issue since the introduction of “newer” inhaled anaesthetics since the 1970s (e.g., enflurane, isoflurane, desflurane, and sevoflurane) [2,3]. These compounds have improved safety and provide better induction and emergence transitions for patients than older halogenated gases such as chloroform and trichloroethylene. Sevoflurane (1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane; CAS number 28523-86-6) is the newest anaesthetic agent – it was first introduced into clinical practice in Japan in 1990 – but is now one of the most widely used inhaled anaesthetics [4,5]. The exclusion of all halogen atoms except fluorine makes sevoflurane (and also desflurane) more resistant to metabolism, and only around 3% of the absorbed dose is metabolized [2]. Therefore the vast majority of this compound is routinely vented to the atmosphere through the operating room scavenging system. Although it is recommended that excess gases be collected through local exhaust systems, some contamination of the operating rooms by these compounds is unavoidable through different contamination pathways [4].

Waste anaesthetic gases (WAGs) are defined by the US National Institute for Occupational Safety and Health (NIOSH) as “small amounts of volatile anesthetic gases that leak from the patient’s anesthetic breathing circuit into the air of operating rooms during delivery of anesthesia” [3]. Moreover, these gases may also be exhaled by patients recovering from anaesthesia. Other sources of pollution include the liberation of anaesthetics through leaks in connection tubes and accidental spillage of liquid anaesthetics when filling vaporizers [4,6,7]. Environmental contamination with sevoflurane can also be rapid because it has to be used at higher concentrations than other halogenated anaesthetics such as isoflurane of halothane [8].

Although an occupational exposure standard for sevoflurane has not been established by regulatory agencies, NIOSH has a recommended exposure limit (REL) of 2 ppmv for an isolated WAG or 0.5 ppmv if the halide is used in combination with N_2O and these

are the values that are widely used in clinical practice. It is important to note that these REL values are based on the minimum concentration that can be detected using the recommended procedures (i.e., portable infrared spectroscopy gas analysers for the direct measurement of anaesthetic agent concentrations in air, with detection limits in the range 0.3-0.7 ppmv). The recommended 8-hour TWA limits in Western countries range from 2 to 20 ppmv [9-11].

Other than health considerations, these compounds also have significant environmental implications as they are greenhouse gases (anaesthetic halogenated ethers) and smog precursors (nitrous oxide, a common carrier gas in the anaesthetic process) [4,12-15]. Although they can be present at an atmospheric concentration approximately one million times lower than CO_2, their global-warming potential (GWP, defined as the CO_2 equivalence) ranges from 210 for N_2O to 5090 for desflurane [12].

All studies related to the toxicological effects of sevoflurane have been undertaken either in experimental animals or patients receiving anaesthesia. Occupational studies have been devoted to the analysis of the air in operating rooms or post-anaesthetic care units (PACUs) [10,16,17] in order to assess the level of exposure of medical staff and nurses who are in direct contact with the agent. Few studies have been devoted to the analysis of exhaled breath of people exposed to these substances [16-19] even though this matrix has shown itself to be a promising alternative to air analysis in exposure assessment as it permits the determination of levels that can in fact reach the blood stream [20]. One of the limitations of the analysis of breath samples is that highly sensitive methods are required with detection limits in the range of pptv when non-occupational exposures are being evaluated. Such limits cannot be reached with conventional infrared spectroscopy gas analysers for the direct measurement of anaesthetic agent concentrations in air.

Another VOC of interest in hospital environments is isopropyl alcohol (IPA) as it is an intermediate level disinfectant extensively used as a topical antiseptic and to disinfect the surface of medical equipment [21]. The use of alcohol-based hand rubs has increased significantly in hospitals as these solutions have proved to be significantly more efficient in reducing hand contamination than hand washing with antiseptic soap [22,23].

IPA is a relatively ubiquitous air contaminant as it can be present in many industrial environments and consumer products. Although this compound can produce symptoms that primarily affect the gastrointestinal tract and the central nervous system [24-26], it presents lower toxicity than WAGs, and NIOSH suggests an 8-hour TWA value of 400

ppmv and a STEL value for short exposure of 500 ppmv [27]. Even though these high levels would not be expected in hospital environments, it might be interesting to check whether the increased use of alcohol-based hand rubs leads to any significant difference between the breath levels detected between people staying in a hospital environment and controls.

In the present study, breath samples obtained from clinical staff who have not been inside any operating room or PACU, visitors of a university hospital, and people that have not been in contact with any hospital or clinical atmosphere for more than 48 hours have been evaluated in order to assess whether there is exposure to IPA and WAGs in areas of hospitals that are unaffected by the exhaust systems of operating rooms and which are not part of PACU environments.

Materials and methods

Chemicals

All reagents were reagent grade with ≥99.0% purity (Sigma-Aldrich, Steinheim, Germany). Sample stocks were prepared by injecting 1-2 μL of single components into cleaned 10 L Tedlar gas-sampling bags (SKC, Eighty Four, PA, USA) filled with nitrogen (99.9990% purity) purified for hydrocarbons, oxygen and water vapour. To ensure complete vaporization, the mixture was equilibrated for 60 min at room temperature before the preparation of working standards, which were made by taking a fixed volume of the stock gas mixture with a gas-tight syringe and diluting to 10 L with purified nitrogen in a clean Tedlar bag. Stock and working standards were freshly prepared for each calibration. For quantification, a minimum of six calibration points were used for each compound.

~~Breath collection~~ Volunteers

Breath analyses were conducted in 100 adult volunteers (24 hospital staff, 45 hospital visitors and 31 external controls), who were randomly asked to participate in the study. The study was approved by the ethics committee of the hospital. The criteria chosen to select the participants in the study were as follows: (i) staff members were all chosen from those that had not been inside any operating room or PACU on the day of the sampling but who had been working inside the Dr Josep Trueta University Hospital for at least one hour before sampling, (ii) visitors attending the same hospital were required to have spent at least 30 minutes inside the hospital building before giving a

sample, and (iii) external controls were required not to have visited any hospital, medical, dental or veterinary building for at least 48 hours before sampling. All participants were asked about their smoking habits and the information obtained was confirmed by the analysis of the specific breath biomarker 2,5-dimethylfuran [28]. Given that the main objective of this study was to assess possible contamination by anaesthetic compounds and IPA from different areas of a hospital building, no other specific requirements were taken into account prior to breath sampling.

Breath collection

Forced-expiratory breath samples were collected for each individual as follows: the first 2-3 seconds of the expiration were not collected in order to minimize the sampling of dead-space air, and the remaining fraction was collected until about 900 mL of breath had been introduced into the 1 L Tedlar gas-sampling bags (SKC Inc.). Each sample was analysed no more than two hours after being collected to avoid the loss of analytes from the bags [29]. Specific evaluation of the storage stability of the three target compounds confirmed that effusion losses were <5% after 3 hours of storage in the Tedlar bags used.

Each bag was cleaned with purified nitrogen several times before new samples were collected. In order to confirm the validity of the cleaning process, the last portion of nitrogen collected in the cleaning process was analysed in the same conditions as breath samples to confirm that no detectable levels of any compound were found. Each bag was used for a maximum of 10 breath samples.

Breath analysis

For each sample, 750 cm^3 of breath was required for the chromatographic analysis. Breath was passed through an in-house sorbent microtrap device at a fixed and controlled flow rate until the predetermined volume of sample was passed through the sorbent trap. Specific details about the instrumentation are described in previous publications [30,31]. Briefly, it consists of a three-bed microtrap filled with 2.5 mg of Carboxen 1000 and Carbopack X and 5.5 mg of Carbopack B (Supelco, Bellefonte, PA, USA), which were sequentially introduced in an 80 mm long, 1.35 mm i.d. Ni/Co alloy tube (Accu-Tube Corp., Englewood, CO, USA). Adsorption of VOCs from samples contained in Tedlar bags was done at 30 $mL \cdot min^{-1}$ over 25 min with a vacuum pump (Air Cadet Vacuum Station, Barnat Co. Barrington, IL, USA) and a mass flow controller

(Alicat Scientific, Tucson, AZ, USA). A fast heating pulse (1 s) at 280-290ºC was applied for the quantitative thermal desorption of all retained compounds.

Gas chromatography-mass spectrometry (GC-MS) analyses were performed with a Focus GC chromatograph (Thermo Scientific, Waltham, MA, USA) with a DSQ II quadrupole mass spectrometer (Thermo Scientific). The in-house microtrap-GC-MS system used was specifically developed for the analysis of VOCs in breath samples [28]. Component separation was achieved by the use of a 30 m long TR-Meta.VOC column with an 0.25 mm i.d. and 1.5 μm film thickness (Teknokroma, Barcelona, Spain). The oven temperature was as follows: 35 ºC held for 3 min and then ramped at 5 ºC/min to 210 ºC and held for 1 min. MS analyses were carried out in full-scan mode with a scan rate of 40-200 amu. Qualifier and quantifier ions used for the detection and quantification of the target analytes are shown in Table 1. Electron impact ionisation was applied at 70 eV. Helium carrier gas was used, with a constant inlet pressure of 31 kPa, after purification for water vapour, hydrocarbons, and oxygen. The acquisition of chromatographic data was performed by means of Xcalibur software (v. 1.4, Thermo Scientific).

Table 1. Quality parameters of the micro-trap-GC-MS method used in the present study. MDL = method detection limit.

Analyte	Quantifier ion	Qualifier ions	MDL[(a)] (pptv, n=5)	Trueness (%, n=3)	Repeatability (RSD, n=5)
Sevoflurane	131	181, 69, 79	5	97	1
IPA	45	43,59	10	92	11
2,5-dimethylfuran	96	95, 81, 53	5	109	7

[(a)] Values corresponding to a sample volume of 750 cm^3.

Validation and quality control

The proposed method was validated by analysing breath and synthetic air samples (n≥5 for each group) with the developed microtrap and a conventional thermal desorption method. Statistical comparison of the results obtained confirmed that no significant differences were found between the proposed and the standard method (p>0.25). Table 1 sets out the results obtained in the assessment of different quality parameters. Trueness of the method, measured as recovery obtained from three

breath samples fortified with 10 ppbv of each of the target compounds, yielded values in the 92-109% range. Inter-day precision (repeatability) was measured in terms of relative standard deviation and values between 1-11% were obtained, which are considered satisfactory. The method detection limit (MDL) was calculated by analysing a standard at 10-15 pptv (n=5) with the standard deviation obtained being taken as the SD of the blank (SD_{blank}) [32,33]. The $3 \cdot SD_{blank}$ criterion was applied to calculate the MDLs.

All traps were analysed without sample collection before the analysis of a sample to verify the absence of memory effects.

Data analysis

Statistical analyses were performed using SPSS for Windows version 15.0. For calculations of significance, two-sided testing was used and $p<0.05$ was considered as significant. The Shapiro-Wilk (S-W) and Kolmogorov-Smirnov (K-S) tests were used to determine whether the samples came from normally distributed populations. Non-normal distributions were found for all the target compounds in the three groups evaluated ($p<0.0006$ for K-S test and $p<0.0001$ for S-W test), therefore non-parametric statistics was used in subsequent analyses to compare the values obtained in the different groups. The Mann-Whitney *U* test was used to compare the values between the groups.

Results

Figure 1 shows the extracted chromatograms obtained in the analysis of breath samples from a physician working in the hospital and an external control. IPA – an endogenous compound – was detected in all samples (Table 2). However, sevoflurane and 2,5-dimethylfuran, which are exogenous contaminants, were only detected in samples of people that had been exposed to the contaminant. In the example given in Figure 1, sevoflurane is only detected in the medical staff sample and 2,5-dimethylfuran is detected in an external control who was a smoker.

As suggested in a previous study [28], 2,5-dimethylfuran is a highly selective biomarker of smoking status. In the present study, this compound was only detected in all samples corresponding to smokers (n=43, 100%), independently of the group

evaluated (Table 2). In two cases, the people involved did not indicate that they were smokers in the preliminary questionnaire but recognised that they were after being confronted with the results.

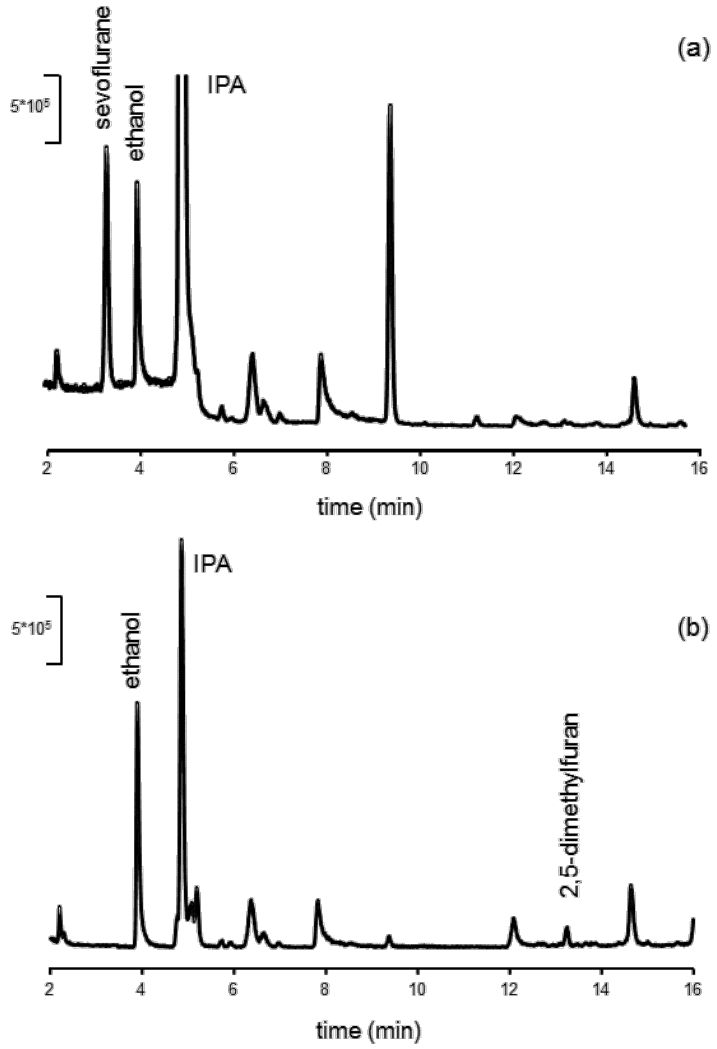

Figure 1. Extracted chromatograms (m/z = 45, 96, 131) of breath samples from (a) a physician working in the hospital and (b) an external control.

No differences between sex were found for any of the target compounds evaluated (p>0.145). In the case of smoking status, the only compound that gave significant differences was 2,5-dimethylfuran (p<0.0002) in the three groups. In the case of sevoflurane and IPA, the significance was p>0.08 and p>0.180, respectively.

From the samples obtained amongst the staff and people visiting the hospital, 67 samples (97.1%) were positive for sevoflurane (Table 2). In only two samples (2.9%) was this compound not detected. These two samples were obtained from people who, whilst attending the hospital area, were visiting an annex building that was not directly

connected to the main hospital building. No external control samples (31 samples, 100%) gave positive detection for sevoflurane.

Table 2. Concentrations of compounds analysed and demographic data of test participants.

		Staff (n=24)	Visitors (n=45)	External controls (n=31)
Male/Female		4 / 20	23 / 22	22 / 9
Ages (years±sd)		40.7±12.5	43.9±9.0	35.4±8.5
Smokers/Non-smokers		10 / 14	25 / 20	8 / 23
Sevoflurane (ppbv)	Mean	0.522	0.196	nd
	Median	0.368	0.109	nd
	Max	2.346	0.864	nd
	Min[a]	0.055	nd (2)	nd (31)
	sd	0.554	0.524	---
IPA (ppbv)	Mean	19.457	20.981	8.032
	Median	16.193	13.236	5.631
	Max	111.058	161.344	27.733
	Min	3.634	2.404	2.353
	sd	20.632	25.421	6.961
2,5-dimethylfuran (ppbv)	Mean	0.234	0.282	0.015
	Median	nd	0.015	nd
	Max	2.504	2.250	0.229
	Min[a]	nd (14)	nd (20)	nd (23)
	sd	0.677	0.524	0.047

[a] in brackets the number of samples where the compound was not detected

As has been stated above, IPA is an endogenous compound in breath samples [34,35]. This compound was detected in all the samples evaluated (Table 2).

Discussion

Assessment of sevoflurane in breath samples

Sevoflurane is the most interesting of the target compounds evaluated due to its anaesthetic characteristics and the potential impact that it has on the environment. Different occupational studies that evaluated air quality in PACUs [10,17] found that the levels of sevoflurane were very low during the night and in the early hours of the morning on work days when there were hardly any patients in the PACUs. However, there was a fast increase, within 15 minutes, when the first patient entered the PACU and, in some cases, peak levels of around 1,000 ppbv were detected, depending on the occupancy of the PACU [17]. Rieder et al. [10] evaluated the mean exposure to sevoflurane at a urological PACU over three days and found a mean value of 15.9 ppbv, well below the maximum REL.

When the breath of personnel exposed to sevoflurane, in operating or PACU rooms, was evaluated [16,17,18], the levels detected before a shift in which they were exposed to these compounds were always significantly lower than after a shift. Moreover, a significant increase in the breath levels for controls was observed between samples obtained before and after shifts [17]. One study indicated that non-detectable levels of sevoflurane were found for hospital staff the first day back at work after a two-day rest period [18].

From the studies cited above, those that evaluated control breath samples [16,17] found the presence of sevoflurane in all controls tested. The exogenous characteristics of this compound suggest that some type of contamination or exposure took place in these controls. An evaluation of the characteristics of the control subjects shows that control samples were obtained from people without direct occupational exposure but who attended or worked in a hospital. Taking into account the high volatility of sevoflurane, these results suggest that this compound diffuses into the atmosphere of a hospital building to spaces adjacent to the operating or PACU rooms. Therefore, the detection of sevoflurane in controls might be due to a mild contamination of the hospital environment.

In a preliminary evaluation of the analysis device used in the present study, we were unable to detect the presence of sevoflurane in any breath sample obtained from volunteers working in chemistry laboratories but without any contact with hospital environments. This confirms that sevoflurane is not an endogenous compound and

suggest the hypothesis that different hospital areas are contaminated with small amounts of sevoflurane and other VOCs commonly used in these environments.

It should be noted that the different experimental groups that we evaluate in the present study consisted of people that were not working in operating and PACU rooms, who in earlier studies would have been considered as controls [16,17]. However, we decided to separate the subjects into three sub-groups depending on the different level of exposure that would be expected if any contamination of the hospital environment occurred.

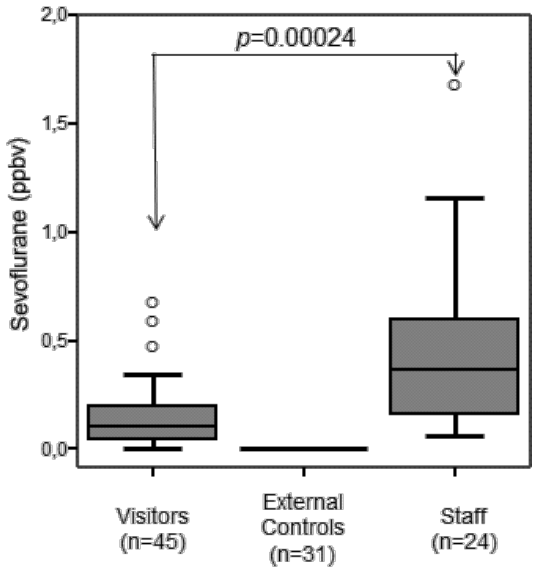

Figure 2. Box-plots for data obtained for sevoflurane. The bottom and top of the box are 25th and 75th percentiles; the line inside the box is the median (50th percentile) and the whiskers indicate the lowest and highest data within 1.5 interquartile range. Circles indicate individual outliers

Figure 2 shows the box-plot obtained for sevoflurane in the three groups. As indicated in the results section, all external controls gave non-detectable levels of sevoflurane, which confirms that this compound is an exogenous compound and that some exposure is required in order for its presence to be detected in exhaled breath samples.

All samples obtained from people being inside the hospital environment gave detectable levels of this compound, confirming the hypothesis of mild contamination of the hospital environments. There were only two samples that gave non-detectable levels of sevoflurane but these were obtained from an annexe for outpatients' visits that

was not in contact with the environment of the main hospital building where the operating and PACU rooms are located.

The evaluation of the results show a significant difference (p=0.00024) between hospital staff and visitor samples with larger levels of exposure in the hospital staff samples. This can be attributed to the fact that all staff member samples were obtained after being in contact with the hospital environment for at least one working day and having been inside the hospital for at least one hour before a sample was taken. In the case of visitors, they were only in contact with the hospital environment on the day of the sampling and many of the samples were obtained between 30 and 60 minutes after arriving at the hospital.

For visitors, samples were obtained on different floors of the main building both above and below the level of operating and PACU rooms. No significant differences (p=0.400) were obtained from the different floors evaluated, suggesting that the level of contamination in the hospital environments, other than operating rooms and PACUs, is small but distributed throughout the building.

Levels of sevoflurane detected in all samples were well below recommended RELs (2-20 ppmv), with a maximum amount for staff members of 2.3 ppbv and 0.9 ppbv for visitors, which are three to five orders of magnitude below RELs.

Assessment of isopropyl alcohol (IPA)

IPA is routinely used in many sections of the hospital evaluated as alcohol-based hand rub. It has been demonstrated that the extensive use of this disinfectant increases its ambient air levels in hospital environments, and that these levels correlate with the exhaled breath levels of people in these environments [18]. Results obtained (Table 2) indicate that mean values for exhaled IPA are 30 to 100 times larger than those obtained for sevoflurane. The presence of alcohol-based hand rubs in all the corridors of the hospital leads to higher level of this contaminant in the air, which results in higher exposure values being obtained.

As IPA is an endogenous compound, it was detected in all samples evaluated (Figure 3). Nonetheless, there is a significant difference between the levels of exhaled IPA found in the staff samples and the external controls (p=0.00009) and between the visitors and external controls (p=0.0002). When the values between staff and visitors are compared, exhaled breath levels are not significantly different (p=0.734). The values obtained for samples given inside the hospital environment do not differ from

those obtained by Ghimenti et al. [18], who found a mean value of 20 ppbv for exhaled IPA.

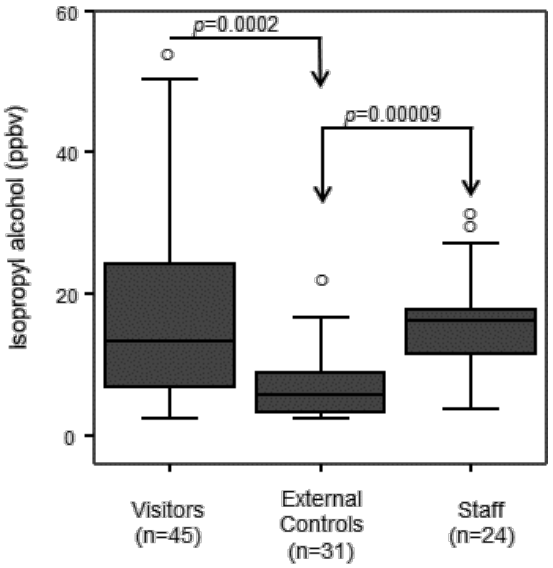

Figure 3. Box-plots for data corresponding to isopropyl alcohol (IPA).

As in the case of sevoflurane, there is clear contamination by IPA in the hospital environments. However, the greater presence of IPA and the fact that this compound is distributed all along the different sections of the hospital results in no differences between the exposure of staff and visitors of the hospital if staff members are not specifically exposed to this compound. As for sevoflurane, the increase in exposure to IPA still remains far below the TWA (400 ppmv) and STEL (500 ppmv, for short exposure) limits recommended by NIOSH [27].

Conclusions

The evaluation of breath samples from people being in contact with a hospital atmosphere, although in conditions that cannot be considered as occupational exposure, confirms a significant increase in the exhaled breath levels of sevoflurane and IPA, two common volatile compounds that are present in different substances routinely used in clinical environments.

The extensive use of IPA in hospital environments results in a significant increase in the exhaled levels of hospital staff and visitors when compared with people who are not exposed to a hospital environment. The presence of alcohol-based hand rubs on all

floors of the hospital has resulted in similar exposure of the two groups present inside the hospital environment and to there being no differences between the staff and the visitors to the hospital.

In the case of the anaesthetic sevoflurane, which is a more controlled and regulated contaminant, lower levels of contamination are detected, leading to significantly higher exhaled breath levels in staff members as they may spend more time in contact with the contaminant.

The results obtained indicate that although specific scavenging systems are used in the hospital environments to prevent contamination by anaesthetic gases, a part of these gases can diffuse throughout the different hospital environments. Small amounts of sevoflurane can be detected in the exhaled breath of any person that has stayed for at least 30 minutes inside the hospital environment. This study has confirmed the existence of VOC contamination in hospitals although exposure levels are well below the recommended exposure limits. Although some dependency might be expected between hospital exposure and breath concentrations over time, the present study was not able to evaluate this as the participating hospital visitors were not asked how long they had been in the hospital, given that the detection of sevoflurane among short-term visitors and staff working at considerable distance from operating rooms was a surprise result that did not form part of our preliminary hypothesis.

The main interest of the present study is that is shows that the current instrumentation used in evaluating WAG contamination in hospital environments is not sufficiently sensitive as to be able to screen faithfully the true exposure that people in these environments face.

References

1. H.K. Lai, M. Kendall, H. Ferrier, I. Lindup, S. Alm, O. Hänninen, M. Jantunen, P. Mathys, R. Colvile, M.R. Ashmore, P. Cullinan, M.J. Nieuwenhuijsen, “Personal exposure and microenvironment concentrations of $PM_{2.5}$, VOC, NO_2 and CO in Oxford, UK”, Atmos. Environ. 38 (2004) 6399-6410
2. E.I. Eger, “New inhaled anesthetics”, Anesthesiology 80 (1994) 906-922
3. CDC Workplace Safety and Health, “Waste anesthetic gases: Occupational hazards in hospitals”, NIOSH (2007), http://www.cdc.gov/niosh/docs/2007-151/
4. J.S. Yasny, J. White, “Environmental implications of anesthetic gases”, Anesth. Prog. 59 (2012), 154-158
5. D. Benhamou, I. Constant, D. Longrois, S. Molliex, K. Nouette-Gaulain, A. Bull, “Use of volatile anaesthetic agents in anesthesia: a survey of practice in France in 2012”, Anasth. Crit. Care Pain Med 34 (2015), 205-209
6. H. Heijbel, R. Bjurstön, J.G. Jakobsson, “Personnel breathing zone sevoflurane concentration adherence to occupational exposure limits in conjuction with filling vaporisers”, Acta Anaestheol. Scand. 54 (2010), 1117-1120
7. K.H. Hoerauf, T. Wallner, A. Akça, R. Taslimi, D.I. Sessler, “Exposure to sevoflurane and nitrous oxide during four different methods of anesthetic induction”, Anesth. Analg. 88 (1999), 925-929
8. C. Byhahn, K. Heller, V. Lischke, K. Westphal, “Surgeons’ occupational exposure to nitrous oxide and sevoflurane during pediatric surgery”, World J. Surg. 25 (2001), 1109-1112
9. A.T. Saber, K.S. Hougaard, “141. Isoflurane, sevoflurane and desflurane”, The Nordic expert group for criteria documentation of health risks from chemicals, University of Gothenburg (2009), https://gupea.ub.gu.se/handle/2077/21413
10. J. Rieder, P. Prazeller, M. Boehler, P. Lirk, W. Lindinger, A. Amann, “Outline monitoring of air quality at the postanesthetic care unit by proton-transfer-reaction mass spectrometry”, Anesth. Anal. 92 (2001), 389-392
11. C. Byhahn, H.J. Wike, K. Westphal, “Occupational exposure to volatile anaesthetics: epidemiology and approche to reducing the problem”, CNS Drugs 15 (2001), 197-215
12. K.P. Shine, “Climate effects of inhaled anesthetics”, Br. J. Anaesth. 105 (2010), 731-733

13. M.P. Sulbaek Andersen, S.P. Sander, O.J. Nielsen, D.S. Wagner, T.J. Sanford, T.J. Wallington, “Inhalation anaesthetics and climate change”, Br. J. Anaesth. 105 (2010), 760-766
14. S.M. Ryan, C.J. Nielsen, “Global warming potential of inhaled anesthetics: application of clinical use”, Anesth. Analg. 111 (2010). 92-98
15. Y. Ishizawa, “General anesthetic gases and the global environment”, Anesth. Analg. 112 (2011), 213-217
16. G. Summer, P. Lirk, K. Horeauf, U. Riccabona, F. Bodrogi, H. Raifer, M. Deibl, J. Rieder, W. Schobersberger, “Sevoflurane in exhaled air of operating room personnel”, Anesth Analg 97 (2003), 1070-1073
17. P. Trefz, M. Schmidt, P. Oertel, J. Obermeier, B. Brock, S. Kamysek, J. Dunkl, R. Zimmermann, J.K. Schubert, W. Miekisch, “Continuous real time breath gas monitoring in the clinical environment by proton-transfer-reaction-time-of-flight-mass spectrometry”, Anal. Chem. 85 (2013), 10321-10329
18. S. Ghimenti, S. Tabucchi, F.G. Bellagambi, T. Lomonaco, M. Onor, M.G. Trivella, R. Fuoco, F. Di Francesco, “Determination of sevoflurane and isopropyl alcohol in exhaled breath by thermal desorption gas chromatography-mass spectrometry for exposure assessment of hospital staff”, J. Pharm. Biomed. Anal. 106 (2015), 218-223
19. S. Ghimenti, F. Di Francisco, M. Onor, M.A. Stiegel, M.G. Trivella, C. Comite, N. Catania, R. Fuoco, J.D. Pliel, “Post-operative elimination of sevoflurane anesthetic and hexafluoroixopropanol metabolite in exhaled breath: pharmacokinetic models for assessing liver function”, J. Breath Res. 7 (2013), 036001
20. M. Alonso, J.M. Sanchez, “Analytical challenges in breath analysis and its application to exposure monitoring”, TRAC Trends Anal Chem 44 (2013), 78-89
21. W.A. Rutala, D.J. Weber and the Healthcare Infection Control Practices Advisory Committee (HICPAC), “Guideline for disinfection and sterilization in healthcare facilities, 2008”, CDC (2008)
22. Center for Disease Control and Prevention, “Guideline for hand hygiene in health-care settings: recommendations of the healthcare infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA hand hygiene task force”, MMWR 2005; 51(No. RR-16): 1-45
23. E. Girou, S. Loyeau, P. Legrand, F. Oppein, C. Brun-Buisson, “Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: randomised clinical trial”, BMJ 325 (2002), 362

24. M.A.M. Smeets, C. Mauté, P.H. Dalton, “Acute sensory irritation from exposure to isopropanol (2-propanol) at TLV in workers and controls: objective versus subjective effects”, Ann. Occup. Hyg. 46 (2002), 359-373
25. I.T. Yu, N.L. Lee, X.H. Zhang, W.Q. Chen, Y.T. Lam, T.W. Wong, “Occupational exposure to mixtures of organic solvents increases the risk of neurological symptoms among printing workers in Hong Kong”, J. Occup. Environ. Med. 46 (2004), 323-330
26. J.D. Clark, “Isopropyl alcohol intoxication”, J. Emerg. Nurs. 36 (2010), 81-82
27. CDC, “NIOSH pocket guide to chemical hazards”, http://www.cdc.gov/niosh/npg
28. M. Alonso, M. Castellanos, J.M. Sanchez, “Evaluation of potential breath biomarkers for active smoking: assessment of smoking habits”, Anal. Bional. Chem., 396 (2010), 2987-2995
29. M. Alonso, A. Godayol, E. Antico, J.M. Sanchez, “Assessment of environmental tobacco smoke contamination in public premises: significance of 2,5-dimethylfuran as an effective marker”, Environ. Sci. Technol. 44 (2010), 8289-8294
30. J.M. Sanchez, R.D. Sacks, “On-line multibed sorption trap and injector for the GC analysis of organic vapors in large-volume air samples”, Anal. Chem. 75 (2003), 978-985
31. M. Alonso, M. Castellanos, J. Martin, J.M. Sanchez, “Capillary thermal desorption unit for near real-time analysis of VOCs at sub-trace levels. Application to the analysis of environmental air contamination and breath samples”, J. Chromatogr. B, 877 (2009), 1742-1478
32. ICH Q2A Guideline, “Validation of analytical methods: definitions and terminology”, Geneva, 1995
33. ICH Q2B Guideline, “Validation of analytical procedures: methodology”, Geneva, 1996
34. P.L. Davis, L.A. Dal Cortivo, J. Maturo, “Endogenous Isopropanol: forensic and biochemical implications”, J. Anal. Toxicol., 8 (1984), 209-212
35. J.M. Sanchez, R.D. Sacks, “Development of a multibed soption trap, comprehensive two-dimensional gas chromatography, and time-of-flight mass spectrometry system for the analysis of volatile organic compounds in human breath”, Anal. Chem. 78 (2006), 3046-3054