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Occupational exposure to airborne formaldehyde in hospital: setting an automatic sampling system, comparing different monitoring methods and applying them to assess exposure

Nicola Mucci[1], Stefano Dugheri[2], Venerando Rapisarda[3], Marcello Campagna[4], Giacomo Garzaro[5], Andrea Farioli[6], Giovanni Cappelli[1], Giulio Arcangeli[1]

[1] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[2] Industrial Hygiene and Toxicology Laboratory, Occupational Medicine Unit, Careggi University Hospital, Florence, Italy
[3] Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[4] Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[5] Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy
[6] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

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Summary

Background: *In recent years, under-vacuum sealing (UVS) and containers with formalin encapsulated in the lid have been proposed for the reduction of occupational exposure to airborne formaldehyde (FA) in healthcare environments.* **Objectives:** *We are presenting a study focused on the assessment of FA in hospitals: an automatic sampling system was set, different sampling devices were compared, and the concentration of FA was assessed, following its use in different scenarios.* **Methods:** *Three different devices for sampling/measuring FA were compared. They are based on: 1. silica gel cartridges impregnated with 2,4-dinitrophenylhydrazine (2,4-DNPH); 2. SPME® fiber using O-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine; 3. direct reading commercial instrumentation. Three typical scenarios using FA were investigated: operating theatres where small biopsies are soaked into closed-circuit system 4% FA containers, secretariat of pathology laboratories during the registration of biopsies and pathology laboratories during the filling procedure by UVS and the slicing of biopsies.* **Results:** *The automatic sampling system allowed short-, long-, and in continuous-sampling time to measure airborne FA. Different sampling devices provided comparable results when tested to assess FA concentration ranging from 0.020-0.320 ppm in a test chamber, although the devices based on 2,4-DNPH were the best in terms of sensitivity and accuracy. The results of 246 samples showed that the FA concentration was less than 0.04 ppm in 91% of the measurements.* **Conclusions:** *The automatic methods efficiently allow sampling and measurement of FA in hospital settings. When using safe practices, the concentration of FA is well below occupational limit values.*

Riassunto

«Esposizione professionale a formaldeide aerodispersa in ambito ospedaliero: predisposizione di un sistema di campionamento automatico, confronto tra diversi metodi di monitoraggio e applicazione nella valutazione del rischio». **Introduzione:** *In ambito sanitario, per il contenimento dell'esposizione occupazionale a formaldeide (FA)*

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Corrispondenza: Nicola Mucci, Department of Experimental and Clinical Medicine, University of Florence, 1 Largo Piero Palagi, I-50139 Florence, Italy - Tel. +39 055 417 769 - E-mail nicola.mucci@unifi.it

aerodispersa, esistono sistemi automatici sottovuoto per il riempimento con formalina e contenitori di sicurezza con FA al 4% in capsula sigillata. **Obiettivi:** *Questo studio è stato finalizzato alla valutazione dell'esposizione a FA utilizzando un sistema di monitoraggio integrato in diversi scenari di esposizione.* **Metodi:** *Sono stati confrontati tre dispositivi per il monitoraggio: gel di silice con 2,4-dinitrofenilidrazina (2,4-DNPH); fibra SPME® con O-(2,3,4,5,6-pentafluorobenzil)idrossilammina; strumentazione a lettura diretta. Sono stati valutati tre scenari tipici in cui la FA viene impiegata in ambito ospedaliero: in sala operatoria durante l'immersione di campioni bioptici di piccole dimensioni in contenitori con capsula sigillata; nella segreteria dei laboratori di anatomia patologica durante l'accettazione di biopsie; in laboratori di anatomia patologica durante il riempimento sottovuoto e la riduzione dei campioni bioptici.* **Risultati:** *Il sistema di campionamento automatico ha consentito tempi di valutazione brevi, lunghi e continui. I diversi dispositivi di campionamento hanno fornito risultati comparabili per la valutazione di concentrazioni di FA compresa tra 0,020 e 0,320 ppm in una camera di prova; tuttavia, i dispositivi basati su 2,4-DNPH sono risultati i migliori in termini di sensibilità e accuratezza. I risultati di 246 campionamenti hanno mostrato che la concentrazione di FA era inferiore a 0,04 ppm nel 91% delle misurazioni.* **Conclusioni:** *I metodi automatici hanno consentito di effettuare efficacemente il campionamento e la misurazione della FA in ambito ospedaliero. Con l'impiego di procedure operative adeguate, la concentrazione di FA è risultata nettamente inferiore ai valori limite.*

Introduction

Formaldehyde (FA) is one of the most common industrial chemicals worldwide. Discovered by European chemists in the mid-19th century, FA was first used commercially in leather tanning and dye production. Because of its disinfectant properties, morticians have quickly adopted it as embalming fluid. Economical and easy to produce, the chemical was soon adapted for many other applications. In the 1920s and 1930s, inventors filed numerous patents for FA-based textile coatings to make clothing crease-resistant. Non-iron shirts coated in FA and urea-FA were sold on a commercial scale by the 1940s (60). In the 1960s, as FA's health dangers were recognized, the United States Department of Agriculture, eager to make cotton competitive with synthetic fibers, developed wrinkle-resistant coatings that trapped the FA molecules in order to reduce the inhalation of fumes. To date, the revenue from world consumption of FA at the industrial level is forecast to grow 3.77% annually over the period 2017-2022 (34), with world production expected to exceed 52 million tons in 2017. The European production capacity of FA represents 22% (40). Formacare (52), the FA sector group of the European Chemical Industry Council (11), collects 31 memberships.

The major concerns of repeated FA exposure are sensitization and cancer. In sensitized people, FA can cause asthma and contact dermatitis. In people who are not sensitized, prolonged inhalation of FA at low levels is unlikely to result in chronic pulmonary injury. Adverse effects on the central nervous system such as increased prevalence of headache, depression, mood changes, insomnia, irritability, attention deficit, and impairment of dexterity, memory, and equilibrium have been reported as a result of long-term exposure. In humans, FA exposure has been associated with increased risk of nasopharyngeal cancer (5, 7, 29).

Currently, there are substantial differences among associations' guidelines concerning FA occupational exposure, not only in terms of parts per million (ppm) limits but also regarding which values to be assessed (33). The American Conference of Governmental Industrial Hygienists for many years adopted a threshold limit value ceiling (TLV-C) (0.3 ppm). In 2016, however, they began to require additional information: TLV-TWA (0.1 ppm) and TLV-STEL (0.3 ppm) (1). Likewise, the European Scientific Committee on Occupational Exposure Limits recently proposed an FA-related TWA of 0.3 ppm, but a STEL of 0.6 ppm (50). NIOSH's Immediately Dangerous to Life or Health is 20 ppm for FA.

A huge number of analytical methods have been developed to determine airborne FA values. The current validated methods for the detection of gaseous FA are based on either active or passive sampling: the former uses 2,4-dinitrophenylhydrazine (2,4-DNPH) as reagent on a filter and the latter uses O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine (PFBHA) as reagent on solid sorbent. The samples are subsequently analyzed by liquid chromatography (LC) or gas chromatography (GC) (9, 21-24, 55, 58-60). The smart FA detector are convenient, real time, and portable instruments that may be useful as screening tools (17, 56).

Nowadays, FA is extensively used for histopathological preservation, and therefore it is currently not possible to foresee its replacement with alternative fixatives. Alternatives to FA, specifically alcohol-based fixatives, glyoxal-based fixatives, zinc-based fixatives and honey have been suggested without success as chemical substitutes for FA in histology, cytology and autopsy practice (14, 15, 30, 43, 62). In the European Union the number of workers exposed to FA above the background level is calculated to be 1.7 million, of which 175,380 in Italy (28, 49, 53). Although most exposed workers are foreseeably engaged in chemical and plastics factories, the highest average levels of exposure were recorded in the health-care sector (2, 6, 13, 16, 20, 22, 28, 31, 37, 38, 44, 45, 48, 49, 55, 61). Scarselli et al. (49) reported FA exposure levels in the healthcare sector; in detail, 58% of the occupational exposure resulted between 0.01 and 0.25 ppm and 16% was over 0.5 ppm. The results of personal samplings carried out in 12 Italian hospitals (22), showed that 54% of the total measurements were between 0.1 and 0.3 ppm and that 19% ranged from 0.31 to 2.00 ppm, while 4% were greater than 2.01 ppm.

Beyond the conventional local exhaust ventilation to minimize contact with FA, there have been few proposals to eliminate FA's vapours in health-care environments. Ohmichi et al. (45) demonstrated the effectiveness of photocatalyst technology to mitigate air pollution in anatomy laboratories; in this pilot study, FA levels were successfully decreased by using a dissection table equipped with a photocatalyst device that reduced FA concentrations by about 80%. Angelone et al. (3) proposed a rapid method to neutralize FA vapour during the tissue sampling using hydrogen peroxide which transforms FA into carbon dioxide and water. Hu et al. examined the effect of potassium permanganate-modified activated carbon for FA removal (32). Recently, Ethera proposed a commercially available purification system called PureTECH, an irreversible FA entrapment from a granular filter with saturation indicator integrated (25).

We found a lack of evidence-based improvement interventions in the health sector. Almost all of the manuscripts concerning FA exposure controls evaluated the effectiveness of the suggested interventions by monitoring exposure to aldehyde in gross anatomy laboratories (2, 6, 20, 37, 38, 48, 61). Regarding the few studies conducted in hospitals' anatomy pathology laboratories, Ogawa et al. (44) proposed a strategy for the reduction of FA concentration by means of engineering controls of the ventilation system and waste fluid, while Di Novi et al. (19), Bussolati et al. (10) and Zarbo et al. (63) highlighted the effectiveness of under-vacuum sealing (UVS) technologies. The Higher Health Council of Italy has drafted a procedure for collecting and preserving tissue samples where UVS or Modified Atmosphere Packaging (MAP) are recommended for large biopsies (>2 cm in size) (42). Some companies proposed UVS and/or MAP systems: T-Filler (Combifill, Bergamo) (12) dispense 4% FA solution (formalin) into rigid containers from 600 to 5700 mL applying UVS or MAP, Tissue Vacuum Plus and Tissue Filling System (Kaltek, Padua) (36) utilize MAP technology and dispense formalin into rigid containers from 250 to 5000 mL, Biopreserve (Patholab, Selargius) (46) system adopts rigid containers from 600 to 5000 mL filled with formalin in UVS medium, while SealSafe by Milestone (Bergamo) (41) uses no-rigid container – specifically a double barrier layer, polyamide and polyethylene bags – for fixation with FA 4% and UVS process. Moreover, for small biopsies (<2 cm in size) the guidelines invite the use of pre-filled formalin containers; it has been reported that during the soak phase in a pre-filled container there is the possibility of dispersion of airborne FA into the environment, therefore such activities have to be carried out under a fume hood and using all the necessary precautions. Therefore, the closed-circuit system

for pre-loaded containers that prevents the contact between FA and the user are proposed by the market to meet these requirements (8, 18, 35, 39, 47, 57).

Nowadays the results in terms of FA exposure reduction using these new devices has not yet been investigated as well as the proposal of an integrated, automated and remote FA monitoring system for short- (1 minute) and long- (8 hours) sampling periods. Therefore, the aim of this work was the assessment of occupational exposure to airborne FA in three typical health-care scenarios: in operating theatres when small biopsies are soaked into closed-circuit system 4% FA containers, in secretariat of pathology laboratories during biopsies recording, and in pathology laboratories during the filling procedure by UVS and the slicing of biopsies. In addition, our study outlines the validation of a new integrated monitoring approach used to assess FA monitoring in hospital environments. Two laboratory-based methods implemented with automated sampling were then compared with the results from commercially available direct-reading instrument, specifically the NEMo IAQ_Monitor.

Methods

Direct reading instrumentation

NEMo IAQ_Monitor (Cat. No. NE-KIT440, Ethera) is a passive sampler (exposure sensor) built with a nanoporous sensor produced using the sol-gel process. Thanks to specific colorimetric reagents, the detection of the FA is based on the colour variation of these initially transparent materials and the reading is performed continuously with an optical reader every two hours. A remote application to manage FA Monitor for storing, downloading and sharing data in real time is available together with a mobile app. The validation of the method was performed in the dynamic calibration system through exposure sensors and a subsequent spectrophotometric analysis by the optical reading module.

Short- and long-term active sampling

Active air sampling was performed by Sep-Pak XpoSure Aldehyde Sampler Plus Short 2,4-DNPH-coated cartridges on a silica sorbent (Cat. No. WAT047205, Waters) attached to a new 12-position Gascheck Basic automatic collector box (AMS Analitica) with GSM module. It was set to 0.3 and 1.2 L/min for long- (8-h) and short-time (15-min) sampling, respectively.

Short- and long-term passive sampling

Passive air sampling by solid phase microextraction (SPME) was chosen (9, 59). A 65-mm SPME fiber Fast Fit Assembly (FFA) polydimethylsiloxane/divinylbenzene (Cat. No. FFA57293-U, Supelco) was doped with 1 mL PFBHA water solution (17 mg/mL water) for 60 s in the headspace of a 20 mL vial previously equilibrated for 5 min at 60°C. Samplings were performed both by rapid FFA-SPME (59) (for 1 min: experimental sampling rate=18.3±0.8 mL/min) using an SPME Automatic Fiber Sampler (Chromline) with a Wi-Fi module and by TWA-FFA-SPME (45) [for 8 h; experimental sampling rate for Z distance (the retraction of the SPME fiber into the needle) = 3 mm was 0.03±0.0025 mL/min] with a Diffusive Sampling Fiber Holder for FFA-SPME (Cat. No. 57584-U, Supelco).

Active and passive samples analysis

All active and diffusive samples were then analysed by a Varian CP-3800 GC with two injection ports set in splitless mode and equipped with Merlin Microseal Septa (Merlin Instrument Co.). To analyse the FA-2,4-dinitrophenylhydrazone, the method by Dugheri et al. (21-24) was adopted with modifications; in this case, we use a nitrogen-phosphorus thermionic specific detector (TSD), a diphenylamine (Cat. No. 24,258-6, Sigma Aldrich) as internal standard, and a MEGA-35 column (30 m X 0.25 mm X 0.25 mm film thickness) (Mega). Large volume injection of ethyl acetate containing the FA-2,4-dinitrophenylhydrazone was performed into the 1078/1079 programmable temperature vaporizing inlet, in order to immediately cut off most of the solvent while retaining all the target analytes in the liner. Instead, FA-pentafluorobenzyl-oxime was measured by a flame ionization detector (FID)

fitted with an Agilent J&W VF-5 ms column (60 m X 0.25 mm X 1.00 mm film thickness). The initial column temperature was set at 45°C (1 min) and then increased by 7°C/min to 300°C. Helium, flowing at rates of 2.0 and 1.0 mL/min, served as the carrier for both TSD and FID, respectively. Full automation of these GC procedures was achieved using a Flex GC autosampler (EST Analytical) equipped with a 45-position Multi Cartridge/Multi Fiber eXchange (Chromline) that allowed the desorption of the Plus Short cartridge and the FFA-SPME fiber in automated mode. For the two chromatographic techniques, the limit of detection (LOD) and limit of quantification (LOQ) were estimated by injection of the FA-2,4-dinitrophenylhydrazone solution (Cat. No. 56677, Fluka) and FA-pentafluorobenzyloxime (Cat. No. 41558, Sigma-Aldrich).

Sampling site and management of data

All three monitoring devices were installed on a tripod, positioned near the operation area at 40 cm from the operator's breathing zone. Fifteen minutes short-term (n. 141) and eight hours long-term (n. 105) samplings were performed in operating theatres during the immersion of the small biopsy in prefilled containers with 4% FA encapsulated in the lid (SecurBiop S60-Trace, Zero 60A-Meccanica G.M, BiopSafe 20mL-Axlab Innovation, Tecnobilife 30 mL-Tecnobilife), in secretariats during the registration and labelling of the 4% FA container coming from the operating theatre, and in pathology laboratories during: *i)* the cut up of previously fixed small biopsies in pre-filled 4% FA encapsulated in the lid: *ii)* the filling procedure by Tissue-SAFE UVS (Milestone), for large biopsies of surgical specimens from the operating theatre - in this case, inside the premises of the surgical theatre, the samples were vacuum sealed in plastic bags and labelled immediately after air removal and refrigerated at 4 °C until they were transferred to pathology laboratories where the tissue was fixed in 4% FA -; *iii)* the cut up of previously fixed large biopsies from UVS bags; *iv)* sealed by UVS of the labelled bags after the reduction. These methods were introduced in 2017.

They were employed remotely by FA Data Storing System (Chromline) as much as possible to avoid operator variability or mistakes. This novel software was developed for the purpose of this study to allow sampling data and their analytical results to be remotely reliable and controlled, and thus integrated into a laboratory information management system (LIMS, Bika Lab System) generating reports and showing historical data (figure 1).

Before the monitoring campaign, hospital personnel was trained and re-trained in safety equipment and maintenance, research updates and emergency care in order to maximize the preparation and skills on the use of the device The methods and the data collection were in line with the European and Italian privacy laws: EU Regulation no. 2016/679 (GDPR), Italian Legislative Decree no. 196/2003 and subsequent amendments.

Dynamic calibration system

The FA dynamic calibration atmospheres were generated by a Harvard Plus 11 syringe-pump, set to 2 µL/min connected to an Adsorbent Tube Injector System (Supelco). The sampling methods were trialed using FA sets as follow (0.020, 0.040, 0.080, 0.160, and 0.320 ppm). All three samplers were exposed simultaneously for each FA air concentration, and five determinations were performed for each one; the exposure time was 8 hours for each concentration of FA. The FA air concentration ($C_{FA\ air}$) was calculated according to the following formula:

$$C_{FA\ air} = C_{Sol}F_{syringe}/F_{air}$$

where, $C_{FA\ air}$ is the concentration of the analyte in the air (µg/L), C_{Sol} is the concentration of the solution (µg/µL), $F_{syringe}$ is the syringe pump flow (µL/min), and F_{air} is the air flow (L/min). The concentration of water vapor produced by the impinger was determined by measuring the dew point temperature with a photoacoustic infrared Innova type 1312 Multigas Monitor (LumaSense Technologies). Atmospheric pressure was determined with a GE Druck DPI 705 digital pressure indicator (General Electric).

Statistical analysis

The slopes (m) and intercepts (b) for calibration of 2,4-DNPH-coated cartridge sampling, and the

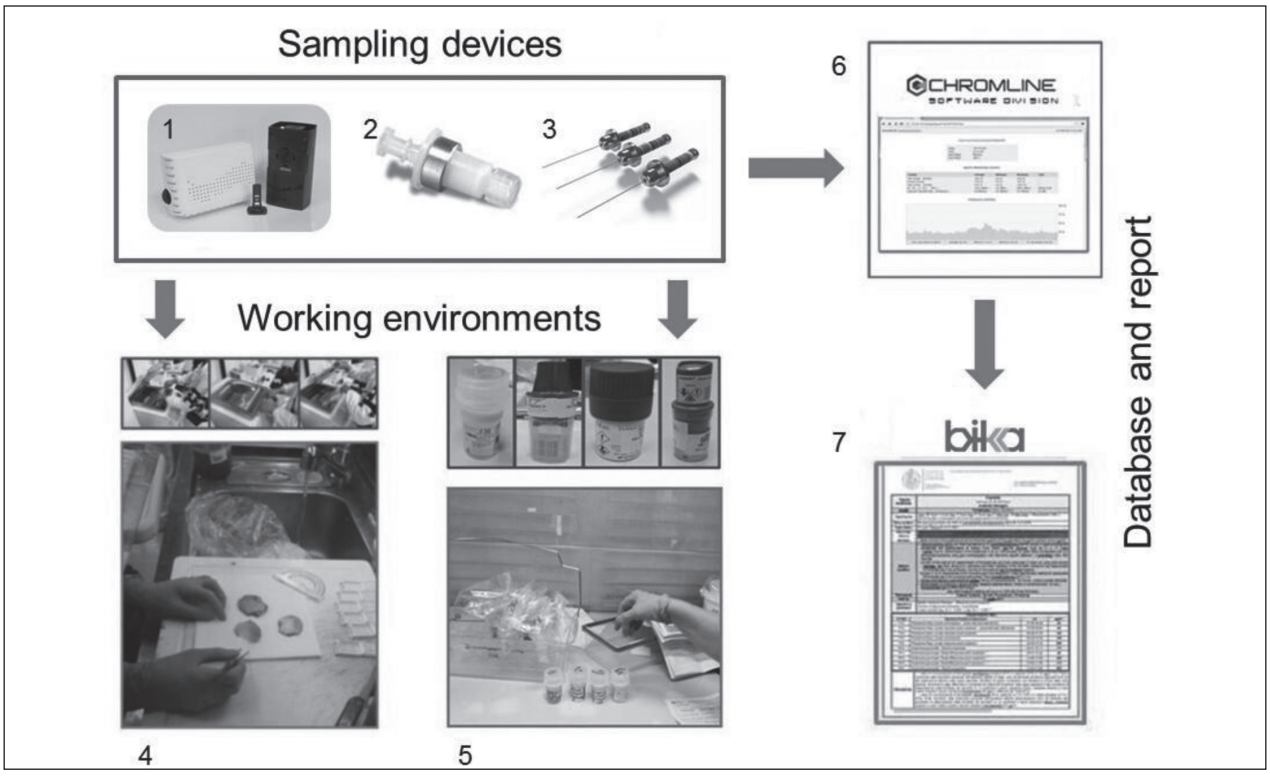

Figure 1 - Sampling devices, working environments, database and report of the automatic monitoring system.
1. NEMo IAQ Monitor; 2. Sep-Pak XpoSure Aldehyde Sampler Plus Short 2,4-DNPH; 3. SPME fiber; 4. Tissue-SAFE under-vacuum sealing; 5. Immersion of small biopsies into containers pre-filled with 4% FA capsuled in the lid; 6. FA Data Storing System; 7. Bika LIMS activity report

PFBHA-SPME sampling methods were calculated with the least-square linear regression analysis, using the following formula:

$$y = mx + b$$

where y is the ratio between the chromatographic area of the analyte and its internal standard, and x is the concentration of the analyte. The LOD was calculated according to the formula:

$$LOD = (3\ SE_b + b) / m$$

where SE_b is the standard error of the intercept. The LOQ was then estimated in the same way using 10*SEb*, which corresponds to 3.3 LOD. The precision of the assay was estimated as a repeatability coefficient of variation (CV%) both within session and as inter-session assay. Within session accuracy was evaluated by recoveries (reported as the percentage ratio between the measured and the nominal concentrations of the dynamic calibration system) at all concentrations used for the calibration plot.

For the performance comparison of the three methods using the dynamic calibration system, mean and standard deviation (SD) of the collected values are reported for each method. Moreover, we report the mean squared error (MSE) computed between observed and theoretical values. Pearson correlation analysis was performed by SPSS version 25.00 for Windows (IBM) to estimate the relationships between direct reading NEMo IAQ Monitor, the 2,4-DNPH-coated cartridge sampling, and the PFBHA-SPME sampling methods with theoretical FA concentration values. Significance was set at p values less than 0.05.

Results

Performance of the three methods

First of all, we had to develop two indirect methods of remote chemisorption monitoring, which are

able to sample at differing time intervals and are highly sensitive, simple to use and economical. We observed that removing the excess of 2,4-DNPH reagent using a polymeric MCX Plus Oasis mixed-mode cation-exchange sorbent, not only decreased the LOQ by one order of magnitude but also LC and GC analyses could be coupled with single- and triple-quadrupole MS. We suggest a GC apparatus with a 35% phenyl, 65% methyl polysiloxane stationary phase column, since it allowed the chromatographic separation both of the 2,4-DNPH degradation product (2,4-dinitroaniline) from the FA-2,4-dinitrophenylhydrazone and of all 2,4-dinitrophenylhydrazones including isomers by the cheaper and easier GC-TSD, rather than the MS one.

Unlike the passive PFBHA method which involves thermal desorption, DNPH active sampling requires chemical extraction before injection into the chromatographic unit. This problem can be easily solved by using SPME, a solvent-free technique that incorporates sampling, isolation, and enrichment in one step. The derivatization kinetics showed that the reaction of PFBHA with FA was instantaneous during the sampling and also the SPME's fiber retraction inside the needle allowed an excellent evaluation of TWA-occupational exposure limits.

The statistical analysis applied on the experimental data obtained from the dynamic calibration system demonstrated that all three methods are suitable for FA vapor monitoring (table 1). Notably, the 2,4-DNPH technique showed the lowest LOQ value compared to the SPME technique (0.004 ppm for TWA) and the lowest imprecision in terms of MSE (0.0001) which is the standard deviation estimator for quantitative analysis (27).

Table 1 - Performance comparison of the three methods performed by dynamic calibration system

Theoretical FA atmospheres (ppm)	Active sampling DNPH- cartridge TWA Mean ± DS (ppm)	Active sampling DNPH- cartridge STEL Mean ± SD (ppm)	Passive sampling PFBHA-SPME TWA Mean ± SD (ppm)	Passive sampling Rapid-PFBHA-SPME Mean ± SD (ppm)	Direct-reading NEMO IAQ Monitor Mean ± SD (ppm)
0.020	0.019±0.003	0.020±0.006	0.024±0.005	0.014±0.009	0.009±0.009
0.040	0.038±0.004	0.040±0.009	0.047±0.010	0.034±0.013	0.034±0.019
0.080	0.077±0.003	0.077±0.012	0.089±0.011	0.067±0.016	0.059±0.036
0.160	0.154±0.011	0.160±0.015	0.162±0.014	0.143±0.024	≥0.100
0.320	0.319±0.016	0.319±0.019	0.327±0.015	0.314±0.056	≥0.100
MSE	0.0001	0.0008	0.0001	0.0006	0.002
R^2	0.999	0.999	0.999	0.998	0.999
LOD	0.002	0.008	0.004	0.014	-
LOQ	0.004	0.025	0.021	0.036	-
Within session accuracy (%)	7	5	6	5	6
Within session repeatability (%)	5	5	8	9	4
Inter session repeatability (%)	5	7	9	11	4
Pearson correlation factor (p.value)	1.000 (p<0.001)	1.000 (p<0.001)	1.000 (p<0.001)	0.999 (p<0.001)	0.989 (p=0.001)

SD: Standard Deviation; MSE: mean standard error; R2 least square correlation coefficient of the calibration curve. LOD: Limit of detection; LOQ: limit of quantification)

Monitoring campaigns

The results of the samplings showed that all the total long-time measurements were between 0.006 and 0.048 ppm. In particular, the highest 2,4-DNPH active-sampling 8-h TWA values (0.039 ppm) were measured in operating theatres for urological endoscopy during the immersion of small biopsies and in the pathology laboratories during the filling of the bag with 4% FA by Tissue-SAFE UVS (0.048 ppm) (table 2). In the operating theatre, the rapid PFBHA-SPME 1-min sampling allowed to evaluate a FA spill between a prostate biopsy and another (0.21 ppm), whereas in the pathology laboratories the highest instantaneous value found was 0.27 ppm when the fume hood of the Tissue-SAFE UVS was malfunctioning.

In pathology laboratories, during the slicing of pathology specimens previously removed by surgery, FA sampling values were lower than 0.03 ppm.

Data management

The two Machine to Machine (M2M) solutions - NEMo IAQ_Monitor by Sigfox and 2,4-DNPH-active sampling via conventional GSM - together with Wi-Fi for PFBHA-passive sampling have successfully allowed remote monitoring systems. A Database Management System (DBMS) has provided a central data repository that be accessed by multiple users in a controlled manner. The centralized storage and management of data within the DBMS has provided: data abstraction and independence, data security and uniform data administration procedures. Its interface with Bika LIMS has allowed to implement instrument interfaces, quality control and ISO 17025 accreditation, eliminating human errors and reducing administration costs.

Discussion

The purpose of this study was the assessment of occupational exposure to airborne FA during the management of small and large biopsies in hospital environments: from the operating room to the pathological anatomy laboratory, passing through the secretariat for registration and labelling. Moreover, we are proposing an airborne FA measuring strategy that includes first and second level detecting systems.

The first requirement for a new approach to air monitoring was to improve data management from the indirect and direct reading methods. The rapid FFA-SPME's 1-min allowed us to identify when peaks in emissions occurred even though it requires a large number of SPME fibers for sampling. TWA limit values could be easily evaluated in terms of feasibility for operators by 2,4-DNPH active sampling and TWA-FFA-SPME, as these analytical methods are both validated. Although active sampling is more sensible and useful to compare with indoor/outdoor in the living environment, passive sampling avoids the difficulties of pumps and wet chemistry. The specificity for FA of NEMo IAQ_Monitor is to be attributed to ultra-sensitive nanoporous materials produced using an established sol-gel process; their porosity results in a very important surface area, allowing them to trap large quantities of the targeted gases. In addition, it is possible to know its concentration of volatile organic compounds, carbon dioxide, humidity and temperature. The lower versatility of NEMo IAQ_Monitor in terms of response times (2 hours) is overcome by the greater specificity (26). Another limit could be represented by 0.1 ppm as the maximum measurable value, but this aspect results negligible when operating in environments where safe practices are carried out. Another commercial FA measuring kit (Profil'Air®, Ethera) allows to perform both active and passive sampling for short- and long-term exposures, as well as a subsequent manual spectrophotometric analysis.

The results of personal sampling of our previous campaign (22) concerned 12 Italian hospitals. In this study we considered data from 3 hospitals which showed that 61% of the total measurements were between 0.1 and 0.3 ppm, 12% ranged from 0.31 to 2.00 ppm, while 4% were greater than 2.01 ppm. In the same hospitals, the present scientific contribute revealed that 91% of the total measurements were lower than 0.04 ppm and that 9% ranged from 0.041 to 0.27 ppm after the adoption of UVS and containers with FA encapsulated in the lid. In the previous campaign (22) it was also noteworthy that the FA concentrations before working

Table 2 - Summary of FA sampling results determined in three hospitals by the three evaluated methods

Hospital wards	Operations	Number of operations/8h (mean)	15-min STEL/8-h TWA (number of samplings)	Active-sampling 2,4-DNPH-cartridge method		Passive-sampling PFBHA-SPME method		Direct Reading NEMo IAQ Monitor	
				15-min exposure* sampling 15 min- mean (min-max) (*ppm*)	**8-h exposure** sampling 8 h- mean (min-max) (*ppm*)	**15 min- exposure*** sampling 1 min- rapid-FFA-SPME mean (min-max) (*ppm*)	**8 h- exposure** sampling 8 h- TWA-FFA-SPME mean (min-max) (*ppm*)	**15-min exposure*** mean (*ppm*)	**8-h exposure** sampling 120 min- mean (min-max) (*ppm*)
Operating theatre**	Immersion of the small biopsy								
	Background****	-	13/9	<0.025 (<0.025)	0.011 (0.009-0.013)	<0.036 (<0.036)	<0.021 (<0.021-0.024)	-	0.009 (0.003-0.019)
	Immersion of biopsies in container pre-filled with 4% FA capsuled in the lid	34	23/12	<0.025 (<0.025-0.21)	0.014 (0.011-0.039)	<0.036 (<0.036-0.29)	0.023 (<0.021-0.037)	-	0.016 (0.014-0.048)
Secretariat***	Registration and labelling of the 4% FA container coming from operating theatre								
	Background****	-	13/9	<0.025 (<0.025)	0.012 (0.011-0.025)	<0.036 (<0.036)	0.023 (<0.021-0.025)	-	0.016 (0.012-0.021)
	Registration and labelling of biopsies in pre-filled 4% FA containers[1,2,3,4]	119	10/12	<0.025 (<0.025)	0.014 (0.006-0.016)	<0.036 (<0.036)	<0.021 (<0.021)	-	0.010 (0.005-0.012)
Pathology laboratory***	Cut up of previously fixed surgical pathology specimens								
	Background****	-	13/9	<0.025 (<0.025)	0.013 (0.009-0.018)	<0.036 (<0.036)	<0.021 (<0.021)	-	0.011 (0.006-0.015)
	Cut up of previously fixed small biopsies in pre-filled 4% FA capsuled in the lid	26	28/19	<0.025 (<0.025)	0.017 (0.015-0.035)	<0.036 (<0.036-0.049)	0.025 (0.023-0.031)	-	0.018 (0.012-0.029)
	Filling procedure by UVS of surgical specimens from operating theatre	24	26/18	<0.025 (<0.025-0.27)	0.020 (0.009-0.048)	0.068 (<0.036-0.29)	0.013 (<0.021-0.033)	-	0.017 (0.009-0.045)
	Cut up of previously fixed large biopsies from UVS bags	28	31/26	<0.025 (<0.025 -0.26)	0.016 (0.011-0.019)	0.037 (<0.036-0.39)	0.026 (0.025-0.029)	-	0.018 (0.009-0.021)
	Sealed by UVS of the labeled bags after the reduction	22	23/18	<0.025 (<0.025 -0.024)	0.016 (0.012-0.021)	<0.036 (<0.036-0.041)	0.019 (<0.021-0.025)	-	0.014 (0.009-0.016)

*The 15 min- measurements were performed during the most critical activity for the occupational exposure. **Surgery department with a mean of eight operating theatres. ***Secretariats and Pathology laboratories receive specimens also from several ambulatories and regional peripheral hospitals. ****Area sampling before starting work.

hours tended to increase with the volume of the container storing FA and FA-treated materials. The finding suggests that contamination of medical workplaces with FA during working hours is attributed not only to the handling of FA and FA-treated materials but also to an inappropriate method for their storage. With the introduction of UVS, the use of FA is restricted to dedicate areas in the pathology laboratory, transfer of large boxes filled with fixative throughout the hospital is cancelled, and the specimens in vacuum-sealed bag drastically reduces volume. The bags - heat-sealed under pressure to reduce the volume - are gas tight and the space occupied by the specimens is reduced so they can be stored and transported easily. The UVS can be used for immediate dispatch of the sample for extemporaneous intra-operative examination or for any other histological examination of a size equal to or greater than about 2 cm. The preservation of fresh surgical samples under vacuum is based on the principle of oxygen removal which limits the growth of the aerobic flora and allows the conservation for a period 6 times greater than that of the non-vacuum conservation (4). The procedure includes that the removed surgical sample is immediately subjected to the UVS procedure in dedicated apparatus, stored and preserved at 4 °C even during transport; the specimen can be preserved in an optimal way up to 48 hours (4).

The collection and transport of small biopsies is performed by the immersion in formalin. However, in the previous study (22) we revealed some limitations regarding the pre-loaded containers without lid to confine 4% FA: i) the non-perfect sealing of the containers both before and after the opening for the insertion of the biopsy, ii) the possibility of dispersion of formalin fumes into the environment during the container filling phase. Therefore, such activities had to be carried out under a fume hood and with all the necessary precautions to avoid dispersion of the fumes in the environment. The introduction of the closed-circuit system for pre-loaded containers was a winning solution in terms of robustness of use and practicality.

Monitoring airborne FA is particularly important due to FA's lack of biological indicators and its low odour threshold. We propose a FA air monitoring protocol that provides remote integration of three monitoring systems in order to simplify sampling and analysis operations, setting the groundwork for on-field analysis regarding second level methods. In fact, since the number of different types of portable GC instruments with different complexity and capacity has continued to grow (51), the two proposed chromatographic methods can be accepted by this technology. In particular, the SPME which has revolutionized many aspects of sample preparation and the introduction of the sample for GC analysis without the use of solvents, but also the Sep-Pak XpoSure Aldehyde Sampler Plus Short 2,4-DNPH-coated cartridges that thanks to their geometry can be managed in the field.

Our experimental and field comparisons demonstrate that these three FA measuring methods agree and are all easily sustainable, either individually or combined, in an industrial hygiene plan to prevent significant exposure to this chemical. The complete elimination of FA is still out of reach, but its substantial reduction from hospital premises is attainable and meets environmental safety requirements.

Conclusion

Due to the potential cancerogenic effect of FA, it is mandatory to monitor its airborne levels in order to keep exposure in the workplace as low as possible. Therefore, we are proposing improvements to the interventions that aim to control exposure to FA.

According to this finding and pending a valid chemical substitute for FA, we suggest the need for more in-depth studies of environmental monitoring programmes to assess the efficacy of any preventive measure adopted.

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