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How improvements in monitoring and safety practices lowered airborne formaldehyde concentrations at an Italian university hospital: a summary of 20 years of experience

Stefano Dugheri[1], Daniela Massi[2,3], Nicola Mucci[4], Nicola Berti[5], Giovanni Cappelli[4], and Giulio Arcangeli[4]

[1] *Careggi University Hospital, Industrial Hygiene and Toxicology Laboratory, Florence, Italy*
[2] *University of Florence, Department of Health Sciences, Section of Pathology, Florence, Italy*
[3] *Careggi University Hospital, Histopathology and Molecular Diagnostics, Florence, Italy*
[4] *University of Florence, Department of Experimental and Clinical Medicine, Florence, Italy*
[5] *Careggi University Hospital, Health and Safety Service, Florence, Italy*

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The last two decades have been crucial for the assessment of airborne formaldehyde (FA) exposure in healthcare environments due to changes in limits and reference values, definition of carcinogenicity, and new monitoring methods. The aim of this study was to analyse twenty years (1999–2019) of experience in automatic, continuous airborne FA monitoring in the Pathology Laboratory and operating rooms at the Careggi University Hospital, Florence, Italy. These 20 years saw gradual improvements in FA monitoring of exposed employees considered at maximum risk, including improvements in analytical methods of detection and sampling strategies, which came with changes in procedures and workflow operations. In 2019, after the adoption of safe practices, including a closed-circuit system using pre-loaded containers and a vacuum sealing, 94 % of the total measurements (FA concentrations) were lower than 16 μg/m^3, and only 6 % ranged from 21 to 75 μg/m^3. In the studied work units, the ratio between area and personal readings ranged from 0.9 to 1.0, both for long and short-term sampling. Personal sampling was simplified with a new workstation, which integrated different monitoring systems into an innovative ergonomic armchair equipped with personal sampling devices. Area monitoring was also improved with a real-time, continuous photoacoustic instrument. Over these 20 years, FA exposure significantly dropped, which coincided with optimised histology workflow and implementation of safety practices. For high-throughput screening and cost savings we propose an innovative ergonomic armchair station which allows remote continuous monitoring.

KEY WORDS: air monitoring; formaldehyde; personal sampling; remote control; safe practices

The fixative features of the disinfectant formaldehyde (FA, CAS Registry Number 50-00-0) were serendipitously identified by Ferdinand Blum at the end of the 19th century (1). Since then, formalin, FA's water solution, has been adopted as the prevalent fixative in pathology (2). With it, however, came acute health effects, primarily involving FA's strong smell and an irritation of the upper airways and eyes, sometimes affecting more than half the exposed population (3–6). FA can also cause an allergic skin reaction (7). In addition to these short-term health effects, there is concern about long-term effects, including an increased risk of carcinogenicity (8–13). In 2004, the International Agency for Research on Cancer (IARC) placed FA in Group I – carcinogenic to humans (14). Two years later, the IARC Monograph Program (15) presented cohort and case-controlled epidemiological studies with "sufficient epidemiological evidence that FA causes nasopharyngeal cancer in humans". Initially, IARC indicated that there was a "strong but not sufficient evidence for a causal association between leukemia and occupational exposure to FA", but in 2012, they recognised causality and also reported a positive association with sinonasal cancer (16).

Monitoring airborne FA is the most appropriate safety approach, as there are no other specific occupational exposure biomarkers (2, 17–19). Being highly soluble in water, FA is quickly absorbed in the mucus of the upper respiratory tract. More importantly, FA can damage the cilia, the most vulnerable structures in the lungs. Here FA behaves as a fast penetrator but a slow fixative (2). How slow fixation will be depends on covalent chemical reactions of carbonyl with proteins, glycoproteins, nucleic acids, and polysaccharides for intra-and intermolecular cross-linking of macromolecules. This slow fixation rate is positive from

Corresponding author: Stefano Dugheri, Careggi University Hospital, Industrial Hygiene and Toxicology Laboratory, Viale G. Pieraccini, 15, 50139 Florence, Italy, E-mail: *stefano.dugheri@unifi.it*

a safety perspective, because it buys time for FA elimination from the upper respiratory and digestive tracts before damage is done.

Environmental monitoring of airborne FA is essential to minimising contact with FA, as it helps to evaluate the safety of practices adopted in different scenarios. In recent years, the highest average levels of airborne FA exposure were recorded in the healthcare sector (20). Scarselli et al. (21) reported exposure to 14-310 μg/m^3 in 58 % of healthcare workers in Italy and exposure to over 620 μg/m^3 in 16 %. Personal monitoring in 12 Italian hospitals (20) further showed that 54 % of measurements varied between 120 and 370 μg/m^3, while 23 % ranged from 371 to 2,470 μg/m^3 .

At present, there is no agreement on FA occupational exposure in terms of safe limit values. Since 1992, the American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a ceiling threshold limit value (TLV-C) of 370 μg/m^3. In 2016, it further specified a TLV-time-weighted average (TWA) of 120 μg/m^3 for eight hours and a TLV-short-term exposure limit (STEL) of 370 μg/m^3 for 15 minutes, which were strongly opposed by the American Chemistry Council's (ACC) FA Panel as too restrictive (22). In 2015, the European Union (EU) Scientific Committee for Occupational Exposure Limits (SC OEL) proposed FA OEL well above ACGIH's TLVs: 370 μg/m^3 for eight hours and 740 μg/m^3 for 15 minutes. The ACGIH Panel, in turn, supported the EU Directive 2019/983 of 5 June 2019 (23) setting a five-year transitional limit to 510 μg/m^3 for eight hours for the healthcare sector, during which time the eight-hour limit should be reduced to 370 μg/m^3 where possible.

In the meantime, a huge number of analytical methods have been developed to determine airborne FA exposure (24, 25), but none of them have become a standard for measuring personal real-time formalin exposure. Only a few of the proposed methods of integrated monitoring provide a validated strategy for evaluating FA risk in healthcare activities (20, 26). Since formalin is used in all diagnostic procedures in anatomic pathology, the priority should be given to monitoring and safety procedures at workplaces where formalin-fixed containers are handled.

In this study, we analysed twenty years of experience with automatic, continuous airborne FA monitoring in the operating theatres and Pathology Laboratory of the Careggi University Hospital, Florence, Italy. In the operating theatres exposure to FA is most likely to occur during the immersion of biopsies, in the Pathology Lab specimen reception during registration and labelling of FA containers coming from the operating theatres, and in the Pathology Lab gross room during slicing of specimens removed in surgery. Here we compare the analytical detecting methods, sampling strategies, and the innovative solutions as they changed with procedures and workflow from 1999 to 2019. We also investigate the benefits of an innovative ergonomic armchair and headrest equipped with remotely controlled instruments for continuous (real-time) monitoring of the breathing zone, as a possible alternative to conventional personal sampling.

MATERIALS AND METHODS

Air monitoring strategies and locations

This study was carried out at the Careggi University Hospital, one of Europe's largest polyclinics. For over 50 years, the Careggi laboratory of Anatomic Pathology had been located in a four-storey historical building, that is, until 2019, when it moved to a new building under a new name: Pathology Laboratory.

Air indoor and personal FA exposure was investigated at three locations: i) operating theatres, where freshly removed surgical samples are put into containers, ii) the Pathology Lab specimen reception, where all pathology samples are received, identified, and prioritised, and iii) the Pathology Lab gross room, where residents, pathologists, and trained technicians examine and dissect tissue specimens. Indoor exposure was measured in vapour and particulate matter samples taken monthly by positioning measuring instruments on the floor at four points, with an inlet at a height of 1.5 meters (27, 28).

Workflows

Between 1999 and 2007, the gross room received disposable containers from the operating theatres at two benches with aspiration hoods. Fume hoods were not installed in the operating theatres, where small (≤2 cm) and large biopsies (≥2 cm) were immersed in containers with 4 % formalin from a 40 % FA solution prepared in-house by lab staff.

Between 2008 and 2016, the Pathology Laboratory and the operating theatres had fume hoods with a foot pedal for formalin control, which served for anatomic pathology (Diapath, Martinengo and Aquaria, Lacchiarella, Italy, respectively). Pre-filled formalin containers (Diapath) were also introduced into the process.

Between 2017 and 2019, small biopsies were immersed in pre-filled containers with 4 % FA encapsulated in the lid [Securbiop® (Traces, Carmagnola, Italy), Zero (Meccanica GM, Loreto, Italy), and BiopSafe (Axlab Innovation, BiopSafe ApS, Vedbæk, Denmark)]. The operating theatres used Tissue-SAFE vacuum sealing (VS) of surgical specimens (Milestone, Sorisole, Italy). Fresh specimens were stored in vacuum-sealed plastic bags and refrigerated at 4° C until transfer to the Pathology Laboratory for fixation under controlled conditions. In the Pathology Laboratory, automated and closed operations ensured that the right amount of formalin was dispensed to obtain standard formalin/specimen ratios. When the lab was relocated to the new building, it got new Trimming Tech 130 fume hoods (Bio-Optica, Milan, Italy) and a computer-based system to

monitor and control heating, ventilation, air conditioning, and extraction from fume hoods. All fume hoods were used and maintained in strict accordance with operating and safety technical standards.

Air monitoring devices

Figure 1 shows the timeline of deployment of various devices to monitor FA at workplace. Between 1999 and 2012, the hospital used personal active air samplers with Lp-2,4-dinitrophenylhydrazine (DNPH)-S10 coated cartridges on a silica sorbent (Cat. No. 21024-U, Supelco, Bellefonte, PA, USA) (29) attached to a GilAir-3 pump (Gilian, San Diego, CA, USA) at 500 mL/min (for 8 h) and 1300 mL/min (for 15 min) and an eight-position automatic manifold pump area sampler (SkyPost Gas/Bravo M Plus, TCR Tecora, Cogliate, Italy). Excess DNPH reagent from the LpDNPH-S10 cartridge after elution with 3 mL of acetonitrile was removed with Dowex 5OW-X8 (Cat. No. 217492, Merck, Darmstadt, Germany) resin (30). The resin was then washed three times with water and twice activated with 2 mol/L of sulphuric acid for 5 min, before being washed another three times with water and twice with ethanol. A 2-mL volume of diethyl ether was eluted through a freshly activated cation-exchange cartridge before sample elution. The eluate was then evaporated to dryness and the residue was dissolved in 1 mL of toluene containing the isobutyl chloroformate derivative of di-*n*-butylamine (Giotto Biotech, Sesto Fiorentino, Italy), as internal standard (IS).

Solid phase microextraction (SPME) was used for on-fibre derivatisation before air sampling (31, 32). A Fast-Fit Assembly (FFA, Chromline, Prato, Italy) with 65-µm polydimethylsiloxane/divinylbenzene SPME fibres (PDMS/DVB, Cat. No. FFA-57293-U, Supelco) was doped for 30 s in the headspace of a 4 mL vial, previously equilibrated by magnetic stirring at room temperature for 20 min with O-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride (PFBHA) purchased from Merck (Cat. No. 76735), Fisher Scientific (Cat. No. NC0674130, Waltham, MA, USA), and Alfa Aesar (Cat. No. ALFAA18368.06, Haverhill, MA, USA), solubilised in 1 mL of water (17 mg/mL). For both personal and area samplings we used rapid-SPME (1 min, at the sampling rate of 18.3±0.8 mL/min) and eight-hour TWA-SPME [at the sampling rate for 3-mm Z distance (distance from the needle opening to the sorbent surface) of 0.03±0.0025 mL/min].

For FA-2,4-dinitrophenyl (DNP)-hydrazone and FA-2,3,4,5,6-pentafluorobenzyl (PFB)-oxime analysis we used two 5 % phenyl-95 % PDMS stationary phase columns of 30 m (Cat. No. CP9013, 0.25 mm × 0.25 µm film thickness, Agilent J&W GC Columns, Santa Clara, CA, USA) and 60 m (Cat. No. CP8949, 0.25x 1.0 film thickness, Agilent J&W GC Columns), respectively, installed in a Varian CP-3800 gas chromatograph (GC) connected to a Varian Saturn 2200 electron ionisation mass spectrometer (MS) with a Varian switching valve (Valco, Vici, Houston, TX, USA). The GC automation of the analytical process was done with a Gerstel Multi Purpose Sampler MPS 2 XL dual head (Gerstel GmbH & Co.KG, Mülheim an der Ruhr, Germany) equipped with an Anatune 300 Automated DNPH unit (Anatune, Cambridge, UK) and a Multi Fiber eXchange (MFX) 25-position tray for FFA-SPME fiber injection (Chromline) (33).

A direct reading instrument, Formaldemeter™ htV-M (PPM Technology, Norfolk, UK), was used. It is an active sampler (a 10-mL snatch-sample of air is taken in by an internal

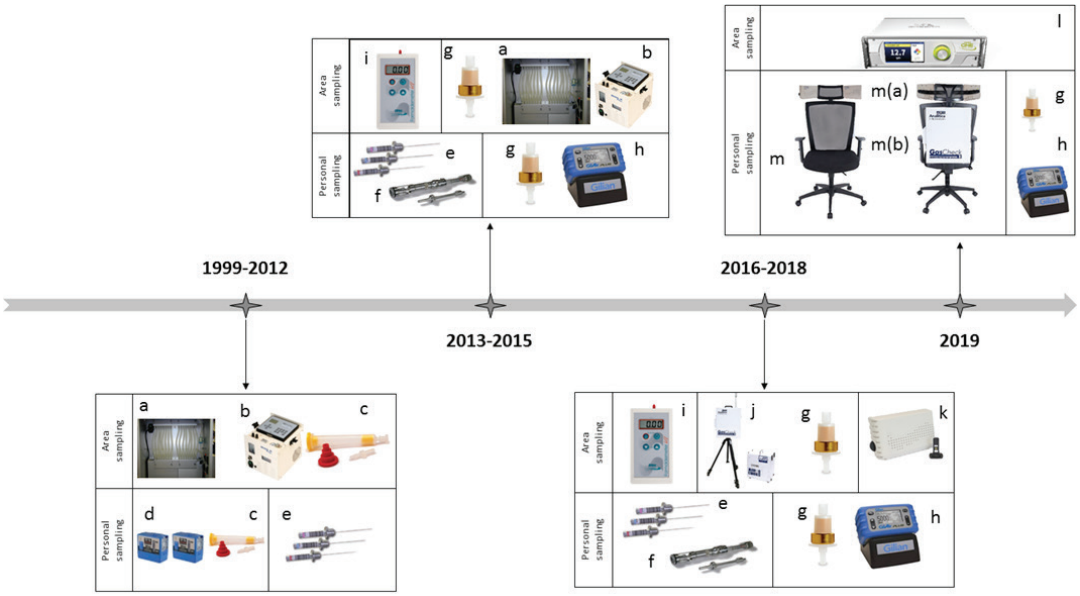

Figure 1 Sampling strategies from 1999 to 2019. a – SkyPost Gas; b – Bravo M Plus pump; c – Lp-2,4-DNPH-S10 coated cartridge; d – GilAir-3 pump; e – FFA-PDMS/DVB SPME fibre; f – diffusive sampling fibre holder; g – Sep-Pak XpoSure sampler plus short DNPH-coated cartridge; h – GilAir Plus; i – Formaldemeter™ htV-M; j – GasCheck Basic; k – NEMo XT; l – Gasera One; m – ergonomic armchair (a) headrest with two NEMo XT and a Gascheck (b)

pump) with an electrochemical sensor with a resolution of 10 μg/m^3 and a mean response time of 60 s. All devices for area sampling were used on a tripod set at the breathing height.

In 2013–2015, FFA-Sep-Pak XpoSure Sampler Plus Short DNPH-coated cartridges on a silica sorbent (Cat. No. WAT047205, Waters, Milford, MA, USA) with magnetic adaptors were introduced together with GilAir Plus pumps (Sensidyne, St. Petersburg, FL, USA) for personal sampling and SkyPost Gas (TCR Tecora) with the GSM module for area sampling.

FA concentrations higher than 370 μg/m^3 measured by Formaldemeter™ htV-M were confirmed with a Chromline automatic fibre sampler with Wi-Fi connection. All devices for area sampling were used on a tripod at the breathing height. For personal SPME air sampling we used a Supelco diffusive sampling fibre holder (Cat. No. 57584-U).

To fully automate gas chromatography, we introduced Flex GC xyz autosampler (EST Analytical, Fairfield, CT, USA) assemblies with: i) Multi Tool Exchanges (MTX) to desorb FA-2,4-DNP-hydrazone from the FFA-Sep-Pak XpoSure Sampler Plus Short DNPH-coated cartridges, remove the excess DNPH derivatizing agent with an FFA-polymeric Oasis Plus mixed-mode cation-exchange sorbent (MCX, Cat. No. 186003516, Waters), dispense the diphenylamine solution as IS, and inject the liquid sample, and ii) an MFX 45-position tray for FFA-SPME fibre injection (Chromline) (25).

In 2016–2018, we used FFA-Sep-Pak XpoSure cartridges for a six-position GasCheck Basic automatic collector box (AMS Analitica, Pesaro, Italy) equipped with a GSM module set to 0.3 and 1.2 L/min flow rate for eight-hour and 15-minute sampling, respectively. The GC analysis of FA-2,4-DNP-hydrazone was performed as described above, save for the following changes: large-volume injection (LVI) used a programmed temperature vaporisation (PTV) injector (34), a 35 % phenyl-65 % PDMS stationary phase column (Cat. No. 122-3832UI, DB-35MS UI, Agilent J&W GC Column,), and a nitrogen-phosphorus thermionic specific detector (TSD). We also introduced a Next Environmental Monitoring (NEMo) XT (Ethera, Crolles, France) passive sampler with a nanoporous FA sensor (Cat. No. NE-FOR01x), which uses a sol-gel process based on colour variation with readings taken with an optical reader every two hours. All devices for area sampling (GasCheck Basic automatic collector box, NEMo XT, Formaldemeter™ htV-M, and FFA-SPME Fiber Automatic Sampler) were placed on a tripod at the breathing height and connected wirelessly to the Chromline FA Data Storing System. Personal air sampling continued to use SPME equipped with a diffusive sampling fibre holder and FFA-Sep-Pak XpoSure Sampler Plus Short DNPH-coated cartridges connected to GilAir Plus pumps.

In 2019, the tripod was replaced with an innovative ergonomic armchair with a headrest housing remotely controlled instruments for continuous measurement: a six-position GasCheck Basic automatic collector box with Sep-Pak XpoSure Sampler Plus Short DNPH-coated cartridges and a new, battery powered, NEMo XT with a larger measuring range (up to 2,450 μg/m^3). For short-term sampling we used a Gasera Multipoint Sampler with multi-channel monitoring via 12 sample inlets, connected with a new direct reading sampler (Gasera One Formaldehyde, Gasera, Turku, Finland). It combines cantilever enhanced photoacoustic detection technology and a quantum cascade laser source operating at mid-infrared fundamental absorption spectra (detection limit of 1.2 μg/m^3, user configurable response time starting from 10 s, and a dynamic range over five orders of magnitude beyond the detection limit) and replaced the Formaldemeter™ htV-M and SPME passive sampling. Personal air sampling still relied on FFA-Sep-Pak XpoSure Sampler Plus Short DNPH-coated cartridges connected to GilAir Plus pumps and on GasCheck and NEMO XT on the ergonomic chair's headrest. This allowed us to compare the methods.

Calibration verification and comparison of the new methods

Calibration was verified with a dynamic calibration system with exposure sensors and then with spectrophotometric analysis using an optical reading module. FA dynamic pressures were calibrated with a Harvard Plus 11 syringe-pump (Harvard Apparatus, Holliston, MA, USA) set to 2 μL/min and connected to an adsorbent tube injector system (Supelco). The active-sampling DNPH cartridge, considered to be the gold standard, and the direct reading Gasera One were tested using the following FA concentrations: 20, 40, 80, 160, and 320 μg/μL. For each FA air concentration, five determinations were performed. FA air concentration ($C_{FA\,air}$) was calculated according to the following formula:

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

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

Statistical analysis

We used the Wilcoxon signed-rank sum test to compare DNPH cartridge active sampling (considered the reference method), DNPH cartridge measurements from the GasCheck Basic automatic collector box set in the back of the armchair, and direct readings taken by the NEMo XT in the headrest. We also compared Gasera One direct

Table 1 Trends in FA concentrations (μg/m^3) at the Careggi Hospital operating theatres and pathology lab over three periods that saw improvements in handling and measuring FA exposure. Decreases are relative to the previous time interval

	Time interval		
	1999–2007	**2008–2015**	**2016–2019**
Operating theatre			
Short-term exposure (15 min)			
Median range (μg/m^3) (no. of monitoring campaigns)	158–200 (9)	61–108 (8)	20–28 (4)
Mean decrease (%)	182 (-)	99 (46)	24 (76)
Pathology laboratory – gross room			
Short-term exposure (15 min)			
Median range (μg/m^3) (no. of monitoring campaigns)	269–613 (9)	71–161 (8)	15–44 (4)
Mean decrease (%)	410 (-)	121 (71)	29 (76)
TWA			
Median range (μg/m^3) (no. of FA campaigns)	706–875 (9)	115–180 (8)	16–37 (4)
Mean decrease (%)	301 (-)	145 (52)	32 (78)
Pathology laboratory – specimen reception			
Short-term exposure (15 min)			
Median range (μg/m^3) (no. of monitoring campaigns)	180–300 (9)	85–90(8)	15–37 (4)
Mean decrease (%)	211 (-)	89 (58)	28 (69)
TWA			
Median range (μg/m^3) (no. of monitoring campaigns)	127–200 (9)	44–73 (8)	10–33 (4)
Mean decrease (%)	160 (-)	59 (63)	25 (58)

FA – formaldehyde; TWA – time-weighted average

readings and DNPH cartridge measurements from the GasCheck Basic automatic collector. All outliers were included in the analysis due to our limited sample size.

To assess calibration, that is to compare the theoretical and measured values, we used simple regression models and evaluated the significance of regression coefficients α and β by testing the hypothesis of perfect calibration (H0: β=1, α=0) using F statistics and coefficient restriction. We also calculated the R-squared value to verify goodness of fit for the estimated regression model for each method.

All statistical analyses were run on Stata Statistical Software, release 11 (StataCorp LP, College Station, TX, USA).

RESULTS AND DISCUSSION

Between 1999 and 2019, our group introduced new airborne FA monitoring strategies that improved measurements in terms of specificity, sensitivity, robustness, and cost reduction. All the analytical methods described are still in use and available on the market. Our decision to renew them over time had an important goal: to fully automate analytical and sampling procedures to improve sample traceability, sustainable chemistry, and data management.

Data distribution

Until 2007, FA concentrations would soar up to 1,286 μg/m^3 in short-term exposure measurements during the most critical activities and up to 813 μg/m^3 in TWA measurements. The likely reasons were on site preparation of containers filled with a 4 % formalin solution (prepared by dissolving 40 % FA) and the lack of fume cupboards with an exhaust air system.

By 2016, these FA readings dropped thanks to the introduction of pre-loaded containers, but continued to be high, with peaks in the gross room reaching 824 μg/m^3 and 399 μg/m^3 for short-term and TWA measurements, respectively. One of the concerns was poor sealing of the containers before and after they were opened for the insertion of biopsy. Another was dispersion of formalin fumes during container filling.

Since 2017, readings dropped even further, thanks to the use of the closed-circuit system for pre-loaded containers and vacuum sealing, which proved robust and practical. Moreover, the adoption of regulation UNI/TS 11710:2018 (35) (specifying the acceptance limits and robustness of containment, face velocity, and air exchange efficiency required for fume cupboards, as well as the methods and procedures for testing them) led to a more careful planning and arrangement of fume cupboard ventilation. This drop in airborne FA observed in 2017–2019 can also be attributed to extensive training of the staff (e.g.,

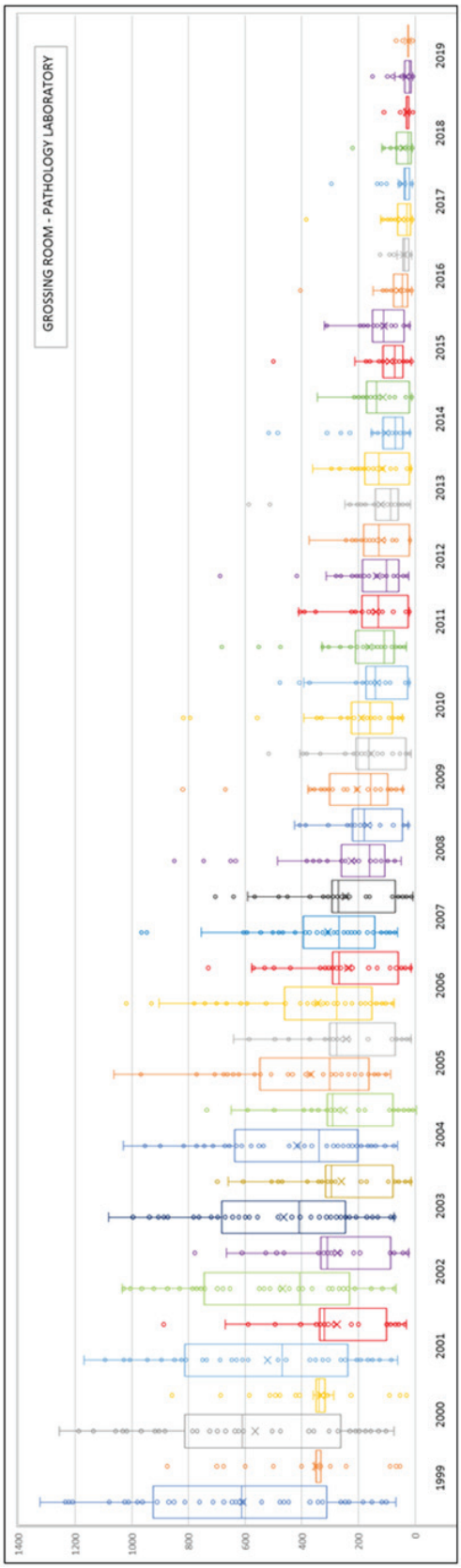

Figure 2 Box plot of the gross room FA monitoring results from 1999 to 2019. Mean, median, and quartile distribution of TWA and short-term concentrations (µg/m^3)

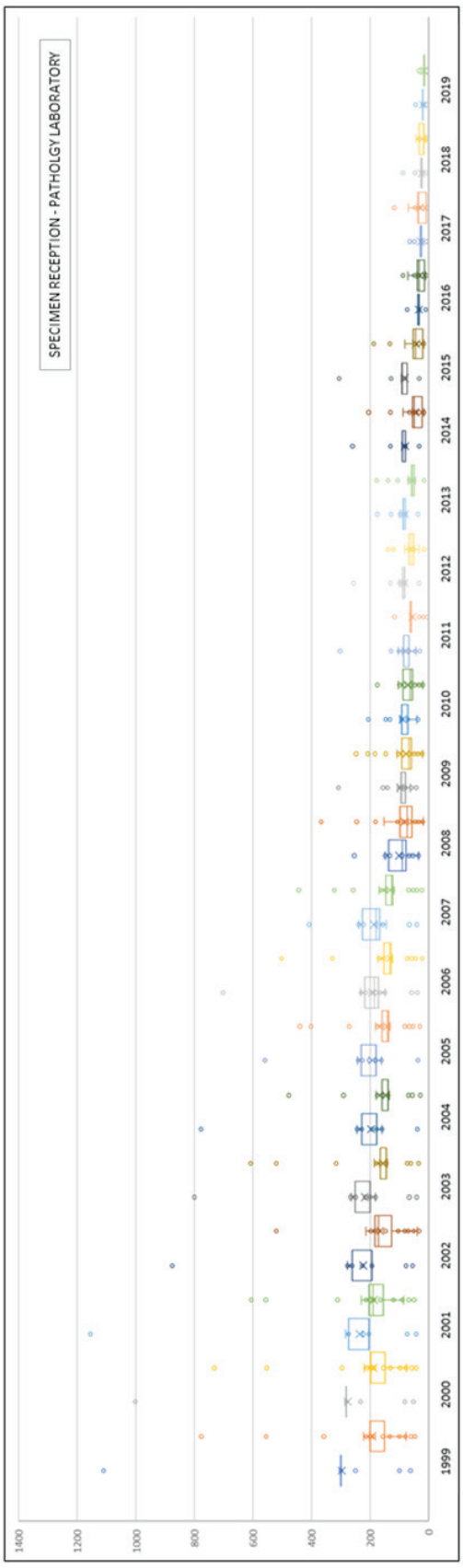

Figure 3 Box plot of the specimen reception FA monitoring results from 1999 to 2019. Mean, median, and quartile distribution of TWA and short-term concentrations (µg/m^3)

regarding safety equipment and maintenance, scientific updates, devices for safe handling, use of personal protective equipment, and emergency care) and the development of functional waste-container management and disposal.

The decrease in FA exposure is shown in Table 1. From 1999 to 2019, the gross room saw a 93 % decrease in TWA and short-term exposure (Figure 2). In the specimen reception this decrease was 87 % (Figure 3). In the operating theatres only short-term exposure was measured during immersion of biopsies, and it dropped 87 % (Figure 4).

Having an accurate reading of background pollution is important for correct estimation of FA exposure, so we simultaneously monitored FA concentrations in nearby outdoor sites. Indoor FA concentrations before working hours were higher than outdoor concentrations. From 1999 to 2018, outdoor concentrations dropped from 8.3 to 2.1 μg/m^3. The decrease recorded in 2019 (average 0.7±0.3 μg/m^3) coincided with the end of two major construction projects in the immediate vicinity – municipal tramway and renovation of the Careggi buildings – both of which involved heavy (diesel-fuelled) vehicle operation and traffic. Moreover, in 2019, the Pathology Laboratory moved to a new building located in a less polluted area on a hill near the hospital campus.

Improvements in FA healthcare management: lowering FA airborne values

The most important improvements in anatomic pathology laboratory workflow were the introduction of closed-circuit systems for small biopsies and of modified

Table 2 2019 FA monitoring campaign overall measurements for all three work units (operating theatres, Pathology Lab gross room, and Pathology Lab specimen reception). The Wilcoxon rank-sum test was using whole data from the three work units. Probability (p) and z score values are reported for each comparison of methods. There is no evidence to reject the null hypothesis (p<0.05) for any of the tests

2019 FA monitoring campaign overall measurements for operating theatres and Pathology Lab specimen reception and gross room (μg/m^3)						
	Active-sampling DNPH cartridge GilAir Plus	**Active-sampling DNPH cartridge GilAir Plus**	**Active-sampling DNPH cartridge GasCheck**	**Active-sampling DNPH cartridge GasCheck**	**Direct-reading NEMO Monitor**	**Direct-reading GASERA Monitor**
	Personal sampling		**Ergonomic armchair**			**Area sampling**
	Short-term	TWA	Short-term	TWA	TWA	TWA
No. of samplings	103	76	103	76	76	76
Mean (μg/m^3)	33	18	29	17	18	14
Median (μg/m^3)	27	14	27	13	14	11
Range (μg/m^3)	5–192	6–61	5–192	5–65	7–55	5–47
Wilcoxon rank-sum test						
Method comparison					p value (*z*)	
Active DNPH-cartridge personal short-term sampling *vs* Active DNPH-cartridge GasCheck Basic automatic collector sampling					0.595 (0.532)	
Active DNPH-cartridge personal TWA sampling *vs* Active DNPH-cartridge GasCheck Basic automatic collector sampling					0.252 (1.144)	
Active DNPH-cartridge personal sampling *vs* Direct-reading NEMO monitor sampling					0.816 (-0.233)	
Active DNPH-cartridge GasCheck Basic automatic collector sampling *vs* Direct-reading Gasera monitor sampling					0.195 (1.296)	

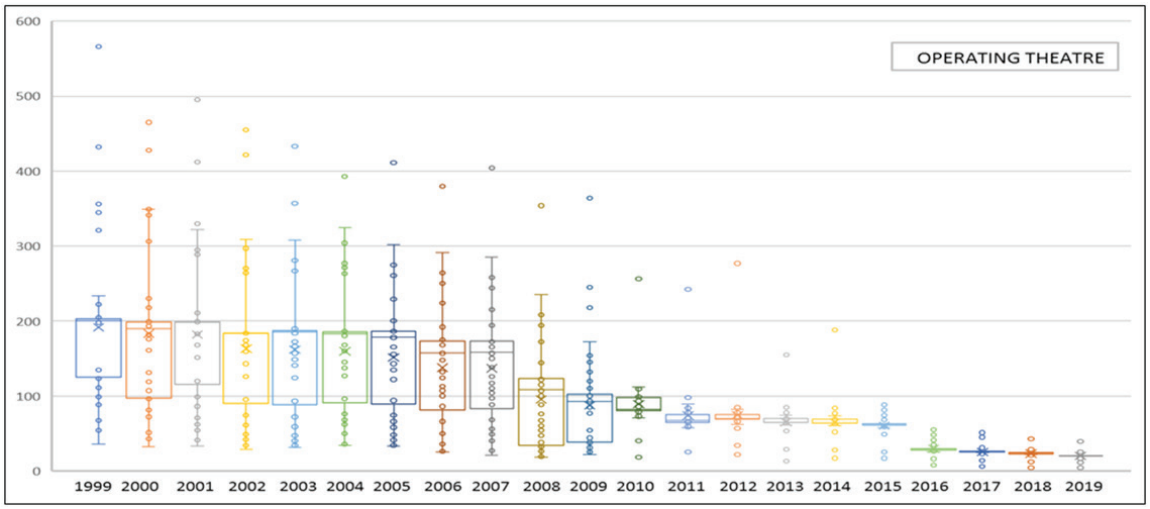

Figure 4 Box plot of the operating theatre FA monitoring results from 1999 to 2019. Mean, median, and quartile distribution of short-term concentrations (μg/m^3)

atmosphere packaging (MAP) and under-vacuum storage (UVS) for large ones. Closed-circuit systems prevent contact with FA. We have been using several brands of pre-filled formalin containers with lids as well as a container with a floating shield of fluid to confine the FA vapours. This dramatically reduced the use of formalin in the operating theatres at our hospital and provided safer handling in the specimen reception and gross room. A word of caution, though: we noticed that formalin is agitated during transport and that FA vapours can pass into the container's headspace. It is therefore necessary to let these containers settle after samples were delivered to the specimen reception.

Another innovation came with containers for large biopsies that employ MAP or UVS systems immediately after tissue insertion. T-Filler (Combifill, Bergamo, Italy) dispenses 4 % FA solution into rigid 600 to 5700 mL containers. Tissue Vacuum Plus and Tissue Filling System (Kaltek) utilise MAP technology and dispense formalin into rigid containers of between 250 and 5,000 mL. The Biopreserve (Patholab, Selargius, Italy) system offers 600 to 5,000 mL containers filled with formalin in UVS. The latter two systems use bags only for transporting fresh biopsy or for storing it after fixation in formalin inside a rigid container. The Careggi hospital opted for SealSafe by Milestone, which uses a non-rigid, double polyamide layer polyethylene bags. As an added bonus, these bags greatly reduced storage room occupied by the specimens.

Transporting formalin, with or without specimen, is clearly a critical phase in the workflow, as it increases the risk of spills and exposure to Immediately Dangerous to Life and Health (IDLH) levels. In fact, the Higher Health Council of Italy (36) and the Italian Group of Mammary Pathology (GIPaM) of the Society of Pathology (SIAPEC) (37) have called for improvements in all phases of biopsy handling, including transportation, in order to prevent harm to employees. We therefore adopted specimen transportation chests, which were well sealed and resistant to shocks and vibration. Moreover, the use of UVS and/or MAP systems restricted the use of FA to dedicated areas in the pathology laboratories, since large boxes of formalin fixative no longer had to be transported throughout the hospital. Last but not least, twenty years of continuous staff training in safe handling and management of formalin also minimised errors in the workflow and accidental formalin spills.

The observed drop in airborne FA at our hospital is owed to new best practices adopted. These were identified and implemented expressly thanks to continuous monitoring of workplace activities.

Improvements in monitoring airborne FA

Since FA occupational exposure limit values (OEL) have yet to be universally accepted, in Italy we recommend the following reference guides, given in order of priority: i) the OELs published in the EU Directives not yet implemented by Italian legislation and ii) the TLVs published by ACGIH.

All measuring procedures and sampling strategies aim to compare occupational exposure measurements against the OELs in order to keep workers safe. Italian laws regulate these procedures and strategies to some degree. EN 689:2018 (38) encourages personal sampling devices to be used within the breathing zone, which corresponds to a 30-cm radius around the face.

Only a few studies have compared FA concentrations in personal and area devices in the healthcare sector. Most involve personal and area monitoring in autopsy rooms, where the operations require continuous movement around the dissection table. These found that personal readings were higher than area readings, as they ranged from 0.04 to 8.91 mg/m^3 compared to 0.05 to 3.01 mg/m^3 (ratio 1–3) (39–41). However, in one of the few studies conducted in a hospital pathology lab, Vimercati et al. (4) observed that personal and area concentrations were comparable, with an

approximate ratio of 1. Our 2019 data (Table 2) are in line with these results.

In 2019, since detected FA concentration values had plummeted by one order of magnitude, we decided to no longer use the SPME technique for eight-hour TWA. The device's 4 μg/m^3 limit of quantification (LOQ) was not always distinguishable from FA in blank PFBHA samples. Instead, combining FFA-SPME's one-minute sampling and Formaldemeter's htV-M IH monitoring enabled us to identify peaks in emissions. Unfortunately, the Formaldemeter htV-M has low specificity in certain conditions, especially in open space settings, as is the case in our new Pathology Lab. In these environments, alcohols and alkanes interfere with device readings. At the same time, possible exposure to FA is no longer limited to gross rooms and vacuum-sealing rooms but includes all of the pathology lab. Luckily, rapid FFA-SPME makes up for Formaldemeter's shortcomings, even though it requires a large number of fibres for sampling. Gasera One Formaldehyde, with a dynamic range 100,000 times above FA detection limit, is a valid alternative. Besides, it is highly selective against carbonyl compounds and other volatile organic compounds (VOCs), while its response time and detection limits are lower by one order of magnitude compared to Formaldemeter htV-M. The same is true for the NEMo IAQ monitor, which employs nanoporous materials, as it separately measures VOCs, carbon dioxide, humidity, and temperature.

Table 3 shows the results of our tests of theoretical FA atmospheric concentrations and corresponding measurements for DNPH-cartridge monitoring method and Gasera One. Given our *p* level of significance of 0.05, we can infer that our direct-reading Gasera One complies with "perfect calibration" in the lab settings.

We introduced an innovative ergonomic armchair, with a piezoresistive pressure sensor to detect the presence of the operator, a barcode reader for personnel identification, and a headrest equipped with remotely-managed continuous measuring instruments within the breathing zone. It could replace conventional personal sampling in order to eliminate human error but also to reduce personal monitoring cost. The NEMo XT's small size (175x95x75 mm), and its low weight (450 grams), allow it to be inserted into the headrest, while the shape of the GasCheck Basic automatic collector box allows it to be applied on the back of the armchair. Thanks to remote control and cloud storage of data, this new chair/workstation allows to monitor various locations simultaneously from a central control location and makes monitoring simpler and cheaper at the same time. In addition, continuous monitoring allows to identify the most error-prone steps in the workflow and to overcome them

Table 3 Calibration data for the analytical method and direct readings in lab setting

Expected FA concentrations of gaseous standards (atmospheres)	**Active-sampling DNPH cartridge**	**Direct-reading GASERA monitor**
(μg/m^3)	Mean ± SD (μg/m^3)	Mean ± SD (μg/m^3)
20	24±7	17±8
40	44±8	63±6
80	83±7	98±12
160	166±15	144±23
320	323±13	337±25
Simple linear regression estimation $y=\alpha+\beta x$		
R^2	0.992	0.964
β (SE)	0.993 (0.017)	0.960 (0.038)
α (SE)	-3.151 (3.008)	-2.675 (6.600)
p value of F test H0: α=0 β=1	0.149	0.131
Method parameters		
LOD (μg/m^3)	1	-
LOQ (μg/m^3)	3	1*
Within session accuracy (%)	4	6
Within session repeatability (%)	7	9
Inter session repeatability (%)	8	9

SD – standard deviation; R^2 – regression estimation parameters (α, β); SE – standard error of simple linear regression; LOD – limit of detection; LOQ – limit of quantification; * LOQ defined by the manufacturer

by training staff better or by introducing technical or system refinements.

Our remotely controlled area monitoring approach combined with the ergonomic armchair with continuous measuring instruments provide a complete picture of workplace exposure, eliminating at the same time human error and reducing personnel costs for sampling. A future improvement to this approach would be to use portable GC instruments to evaluate DNPH cartridge samples in the field. In addition to its many advantages, this would provide immediate, real-time results, allowing us to pinpoint which specific task involves the greatest risk, make and in-depth analysis, and suggest a solution.

Conflicts of interests

The authors declare no conflicts of interest regarding their research, authorship, and/or publication of this article.

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Kako smo poboljšanim mjerama praćenja izloženosti i zaštite na radu snizili razine formaldehida u zraku u sveučilišnoj bolnici u Italiji: sažetak 20 godina iskustava

Posljednja dva desetljeća bila su iznimno važna za procjenu izloženosti formaldehidu (FA) u zraku u zdravstvenim ustanovama zahvaljujući promjenama u preporučenim maksimalnim i referentnim vrijednostima, definiciji njegove kancerogenosti i novim metodama mjerenja/praćenja. Cilj je ovog istraživanja bio analizirati dvadeset godina (1999. – 2000.) iskustva u automatskom, kontinuiranom mjerenju razina FA-a u laboratoriju za patologiju i operacijskim dvoranama talijanske sveučilišne bolnice Careggi u Firenzi. Tijekom tih dvadeset godina bolnica je postupno poboljšavala metode praćenja razina FA-a i osoblja izloženoga najvećem riziku, analitičke metode detekcije i strategije uzorkovanja koje su bile popraćene promjenama u odgovarajućim postupcima i organizaciji rada. Nakon usvajanja novih postupaka zaštite na radu 2019., uključujući i zatvoreni sustav rukovanja spremnicima i sustav vakuumskoga zatvaranja, razine FA-a u 94 % izmjera bile su niže od 16 µg/m^3, a samo 6 % izmjera kretalo se u rasponu od 21 do 75 µg/m^3. Omjer izmjerenih razina prostornih i osobnih skupljača uzoraka u ispitanim scenarijima kretao se od 0,9 do 1,0, bez obzira na to je li posrijedi kratkoročno ili dugoročno mjerenje. Mjerenje osobnim mjeračima dodatno je pojednostavljeno novom radnom stanicom u obliku ergonomskoga radnog stolca, koji u sebi objedinjuje različite sustave praćenja i osobne mjerače. Nisu zaostala ni poboljšanja u prostornom mjerenju, budući da je uveden novi fotoakustični uređaj za kontinuirano mjerenje u stvarnom vremenu. U tih 20 godina izloženost FA-u drastično se smanjila, što je popraćeno poboljšanom organizacijom obrade histoloških uzoraka i zaštite na radu. Radnu stanicu u obliku ergonomskoga stolca svakako preporučujemo zbog velikog kapaciteta protoka za probirno mjerenje, značajnih ušteda i mogućnosti daljinskog upravljanja.

KLJUČNE RIJEČI: daljinsko upravljanje; formaldehid; osobni skupljači uzoraka; praćenje kakvoće zraka; zaštita na radu