Scientific Research Publishing

Journal of Environmental Protection, 2024, 15, 827-841
https://www.scirp.org/journal/jep
ISSN Online: 2152-2219
ISSN Print: 2152-2197

A Comparison of Airborne Formaldehyde Field Measurements Collected in an Anatomic Pathology Laboratory

Maria Teresa Piccardo[1*], Massimo Cipolla[1], Alberto Izzotti[1,2], Paola Canepa[1], Vincenzo Fontana[3]

[1]Mutagenesis& Cancer Prevention Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[2]Department of Experimental Medicine (DIMES), University of Genova, Genova, Italy
[3]Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy
Email: *mariateresa.piccardo@hsanmartino.it

How to cite this paper: Piccardo, M.T., Cipolla, M., Izzotti, A., Canepa, P. and Fontana, V. (2024) A Comparison of Airborne Formaldehyde Field Measurements Collected in an Anatomic Pathology Laboratory. *Journal of Environmental Protection*, **15**, 827-841.
https://doi.org/10.4236/jep.2024.158047

Received: March 14, 2024
Accepted: July 30, 2024
Published: August 2, 2024

Abstract

Environmental monitoring of airborne formaldehyde (FA) using sensitive methodologies is fundamental to prevent health risks. The objective of this study was to compare three different FA monitoring methods during the daily activities of an anatomic pathology laboratory. Daily eight-hour measurements deriving from Radiello® passive diffusive samplers (PDS), NEMo XT continuous optical sensor (COS), and multi-gas 1512 photoacoustic monitor (MPM) were simultaneously compared over a period of 14 working days. Given the different daily distributions of the measurements performed by the three devices, all measurements were time-aligned for comparison purposes. The 95% limit of agreement (LOA) method was applied to estimate the degree of concordance of each device with respect to the others. Formaldehyde arithmetic mean measured using PDS was 32.6 ± 10.4 ppb (range: 19.8 - 62.7). The simultaneous measures performed by COS and MPM were respectively 42.4 ± 44.8 ppb (range: 7.0 - 175.0) and 189.0 ± 163.7 ppb (range: 40.0 - 2895.4). The MPM geometric mean (171.3 ppb) was approximately five times higher than those derived from COS (32.3 ppb) and PDS (31.4 ppb). The results of the LOA method applied to log-transformed FA data showed the same systematic discrepancies between MPM and the other two devices. A good agreement between PDS and COS could lead to a tailored approach according to the individual specificity of these techniques. This tool may be useful for accurately assessing the risk of FA exposure among healthcare workers. However, the limited specificity of the MPM does not support its use as a monitoring method for FA in the workplace.

Keywords

Occupational Exposure, Occupational Health, Formaldehyde Monitoring

Devices, Indoor Air Quality

1. Introduction

Formaldehyde (FA) is a ubiquitous pollutant naturally present in the atmosphere and is derived from the oxidative metabolism of hydrocarbons in mammals and some foods [1]. It is used in the industrial production of buildings, furniture, and textile materials [2] and is a by-product of combustion processes, tobacco smoking, and cooking [1] [3].

FA is widely used in medical applications worldwide, notably as an aqueous solution or as formalin. It is used for the collection and transportation of tissue derived from biopsies or surgical interventions and as a tissue fixative in histopathology and anatomy laboratories [4] [5]. All national and international guidelines recommend buffered formalin for histological, immunohistochemical, and molecular examination. In addition, all validated standardized protocols used formalin-fixed tissue [4].

Anatomic pathology professionals may be exposed to higher daily levels of FA than the general population [6]. Epidemiological research has pointed out several adverse health effects in healthcare workers attributable to short-term exposure to FA, including nausea, headaches, contact dermatitis, and irritation of the eyes, nose, and throat [7] [8]. In addition, the same subject has also been found to be at a higher risk of carcinogenic effects derived from long-term exposure, including nasopharyngeal cancer [9], myeloid leukaemia [10] and Hodgkin lymphoma [11].

Prolonged FA exposure has long been known to cause adverse health effects. In 1987, the United States Environmental Protection Agency classified FA as a probable human carcinogen [12]. In 2004, the International Agency for Research on Cancer reclassified FA as a human carcinogen (Group 1), based on epidemiological evidence that this molecule can cause nasopharyngeal cancer in humans [13]. In 2014, EU Regulation no.605/2014 imposed a further reclassification of FA in category 1B (*i.e.*, it can cause cancer) based on clear evidence of carcinogenicity in humans and experimental animals.

The carcinogenic and non-carcinogenic effects of FA exposure have motivated the development of national and international air quality guidelines from which occupational exposure limits were derived. In 2010, the World Health Organization established indoor air quality guidelines for short- and long-term exposures to FA of 0.1 mg/m^3 (0.08 ppm) for all 30-minute periods at lifelong exposure [14]. Presently, there is no agreement on safe limit values for FA occupational exposure. In 2016, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted the following threshold limit values (TLV): 124 μg/m^3 (0.1 ppm) as a time-weighted-average of 8 hours (TLV-TWA), and 369 μg/m^3 (0.3 ppm) as a short-term-exposure-limit of 15 minutes (TLV-STEL) [15]. Recently, the European Directive EU 2019/983 [16], introduced Occupational Ex-

posure Limit (OEL) values of 0.37 mg/m^3 (0.3 ppm) for long-term exposure (8-hour time-weighted average) and 0.74 mg/m^3 (0.6 ppm) for short-term exposure (15 min) for all work sectors, and a specific 8-h limit value of 0.62 mg/m^3 (0.5 ppm) for the healthcare, funeral and embalming sectors until July 2024 for the latter. Safety limits should attenuate the potential for sensory irritation, mainly in the respiratory tract and eyes, and protect against both increased cell proliferation and cancer risk in the upper respiratory tract [17].

Environmental monitoring of airborne FA using sensitive methodologies is fundamental to preventing health risks. Many techniques have been developed to measure FA. These are time-integrating methods based on FA's indirect reaction with a derivatization agent, combined with HPLC-UV detection and direct-reading continuous online methods. The former methods are utilized for both environmental and personal monitoring programs, whereas the latter methods are used to evaluate source emissions and concentration variations. There are two international time-integrating methods for active sampling (ISO 16000 - 3:2001, 2001) [18] and passive sampling (ISO 16000 - 4:2001, 2004) [19]. These methods involve the reaction of the carbonyl function with 2,4-dinitrophenylhydrazine (DNPH) to form a UV absorption chromophore, 2,4-dinitrophenylhydrazone.

Over the years, various derivatization agents have been proposed and tested. However, DNPH is the most commonly used compound for both active and passive sampling methods [20]. Several studies have compared the performances of active and passive sampling methods and reported good agreement [21] [22] [23].

Different DNPH-passive samplers such as Radiello®, Analyst®, and UMEx 100 have been evaluated for the measurement of airborne aldehydes [24] [25]. Among these, Radiello® passive samplers have been the most extensively described in the literature [8] [21] [24] [26] [27] [28].

Direct and continuous online methods are commonly used to evaluate FA emissions because they simplify the sampling process. Currently, different FA monitoring instruments based on photometry, fluorimetry, and infrared technology are commercially available. However, cross-sensitivity between FA and various organic compounds has been described, thereby making some of them unsuitable for monitoring all types of workplaces [29].

This study aimed to compare three different FA monitoring methods used during the daily activities of an anatomic pathology laboratory. Daily eight-hour measurements deriving from Radiello® passive diffusive samplers (PDS) (RestekSrl, Milano, Italy), NEMo XT continuous optical sensor (COS) (Ethera Technology, Rolles, France), and multi-gas 1512 photoacoustic monitor (MPM) (Lumasense Technology, Airnova, Limena, PD, Italy) were compared over a period of 14 working days. The purpose was to find a continuous FA measurement system that could record all daily variations in FA levels, thereby providing better health protection for operators.

2. Methods

2.1. Study Design

This study was conducted from 25 May to 14 June 2022 at the Anatomic Pathology Unit of the San Martino Polyclinic Hospital, Genoa, Italy. The unit is located in dedicated rooms on the second floor of a clinical building. The rooms are equipped with a ventilation system assuring eight air changes per hour and maintaining a controlled temperature of 20˚C ± 2˚C in winter and 26˚C in summer, as well as a relative humidity of 35% - 45% and 50% - 60%, in accordance with the Italian regulation on the subject of the hospital microclimate (UNI EN ISO 7730 2006; Dlgs n. 81 2008) [30] [31].

FA is mainly used in an 80 m^2 laboratory to dissect and examine biopsy and surgical samples. Two chemical hoods are utilized to minimize surgical pieces. To compare the data with occupational exposure limits, eight-hour daily measurements of indoor FA levels were taken using MPM, COS, and PDS. The MPM is a useful instrument for measuring anaesthetic gases in surgical operating rooms, and because it is also equipped with a filter for FA detection, we decided to use it along with the other two devices.

The three monitoring devices were positioned close together near the most frequently used chemical hood at a height of 1.6 meters from the floor. Once positioned, COS remained continuously active for the entire 14-day sampling period, providing one FA data point every two hours. Every morning, at the beginning of the work shift, a new PDS was positioned for an eight-hour daily sampling; simultaneously, MPM was activated for the same sampling time: the former with a single daily response for FA and the latter providing a data point every two minutes. Simultaneously, another PSD was placed in the secretariat for an eight-hour sampling period as a control. Figure 1 depicts the different FA monitoring devices installed in the workplace.

In this study, the threshold limit values recommended by ACGIH were selected as the reference because they are considered to offer greater protection for workers.

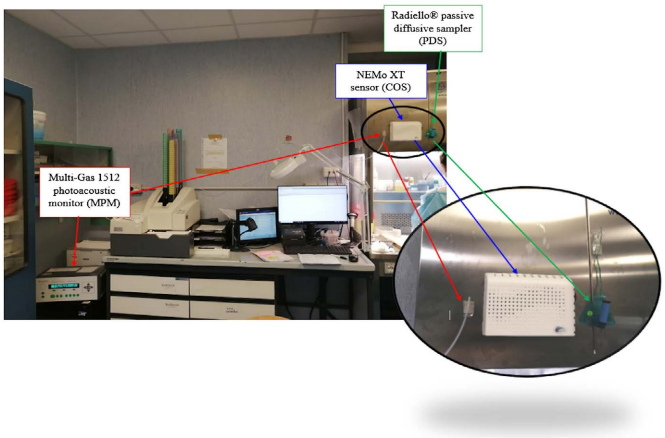


Figure 1. Formaldehyde monitoring devices.

2.2. FA Monitoring Devices: Description and Methods

2.2.1. Passive Sampler

The Radiello® passive sampler is a radial symmetry passive diffusive sampler (PDS), conceived, certified (EN 13528-1; EN 13528-2, 2002), and patented by Maugeri S.P.A. Clinical Scientific Institutes (Padoa, Italy) [32] [33]. This PDS has been validated with reference to the UNI EN 838 standard (2010) [34]. The chemo-adsorbent cartridge consists of a cylindrical stainless-steel mesh filled with Florisil and coated with 2,4-dinitrophenylhydrazine (2,4-DNPH); FA reacts with 2,4-DNPH to yield the corresponding 2-4 dinitrophenylhydrazone, which is extracted with acetonitrile and analysed by reverse-phase HPLC and a UV detector.

During sampling, the cartridge was placed inside a cylindrical blue diffusive body made of microporous polyethylene, which is suitable for sampling light-sensitive compounds. At the end of sampling, the cartridge was removed from the diffusive body and placed in its test tube, which was then sealed and kept in the dark and refrigerated during transport and storage until desorption and analysis.

Each cartridge was extracted by introducing 2 ml of acetonitrile (Lichrosolv Merck) directly into the tube and stirring periodically for 30 min. The resulting solution was filtered (PTFE 0.45 μm) and 10 μl was analysed using the HPLC system 1260 Infinity II (Agilent Technologies Italia SpA, Cernuscosulnaviglio, MI, Italy), equipped with a variable wavelength UV detector, and Agilent OpenLAB CDS ChemStation software. Separation of FA hydrazone was performed at the wavelength λ: 365 nm; column Raptor C18 150 mm × 4.6 mm ID and particle size 2.7 μm, equipped with a Raptor C18 guard column cartridge, 5 mm × 4.6 mm ID, and a particle size 2.7 μm. Elution was conducted at a flow rate of 0.8 ml min-1, using a linear gradient of acetonitrile: water, starting from 58:42 v/v to 100% in 4 min, then maintaining a 100% acetonitrile concentration for 5 min. Quantification in μg was performed using an external standard calibration based on a four-point curve derived from the RAD 302 standard solution with a concentration of 50 μg ml-1 (Restek). The average concentration (C), calculated over the entire sampling time according to the Radiello® manufacturer's instructions (2019) [35], was (1)

$$C\left(\mu g \cdot m^{-3}\right) = \frac{M}{Q \cdot T} \cdot 1,000,000 \quad (1)$$

where,

M = mass of FA (μg)

T = exposure time in minutes

Q = sampling rate (99 ml·min^{-1} at 25˚C and 1013 hPa)

Quality control was performed by analysing two unexposed cartridges (blanks) for each of the two packs of utilised adsorbent cartridges, and the analytical data were corrected by subtracting the value of the corresponding blanks. Moreover, the limits of detection (LOD) and reproducibility were assessed.

Four blank samples ranged from 0.02 to 0.20 μg, corresponding to an average air concentration of 0.7 μg m^{-3}, corresponding to 0.6 ppb.

The LOD value calculated as three times the standard deviation of the blanks, as reported in EN 13528-2 (2002), was 0.04 μg, which corresponded to an estimated air concentration of 1.0 μg m^{-3} (0.8 ppb). The coefficient of variation for the reproducibility test (n = 6) is 1%.

2.2.2. Optical Sensor

The optical sensor NEMo XT (Ethera Technology, Rolles, France) is a continuous (24-hour) optical reading sensor (COS) without filters, consisting of nanoporous materials that allow trapping of large quantities of targeted gases. Designed to be permanently wall-mounted, it can operate either electrically or on a battery. FA measurements are based on the colour variation of initially transparent materials that react to specific colorimetric reagents.

An optical reader performs this reading. The LOD of Ethera Technology is approximately 7 ppb, and the measurement ranges are 7 - 200 ppb and 200 - 2800 ppb for indoor air quality and safety, respectively.

2.2.3. Multi-Gas Photoacoustic Monitor

The multi-gas photoacoustic monitor (MPM), (Lumasense Technology, Airnova, Limena, PD, Italy) is based on photoacoustic infrared spectroscopy (PAS) and its selectivity is guaranteed through special optical filters. FA selectivity is achieved by using a UA 986 filter. The instrument includes the following two software packages: BZ7002 Calibration Program and BZ7003 Offline Program to download the data stored in the internal memories of the gas detector. Calibration is performed by Airnova, using the BZ7002 Calibration Software. The final calibration was performed on 5 May 2022. LOD is 40 ppb. The linearity range of the response is five orders of magnitude (e.g., maximum limit = 100,000 times the minimum detectable level) without scale switching. The reproducibility of the measurement is equal to 1% of the measured values, while the accuracy is ensured by the ability of the MPM to compensate for both temperature and pressure fluctuations and for water vapour and other known gas interferences present in the sample air. The sampling cycle is activated by the start button or by programming the start time. The pump draws air through the sample tube, which then passes through two filters and enters the analysis cell. The light from an infrared source is reflected by a mirror, passed through a mechanical modulator, and transmitted to pulses through an optical filter. Subsequently, the light is selectively absorbed by the monitored gas, resulting in an increase in the gas temperature, which in turn causes an acoustic signal in the closed cell. Two microphones are mounted on the cell wall to measure the pressure wave, which is directly proportional to the concentration of the monitored gas present in the cell.

2.3. Statistical Analysis

Given the different daily distributions of measurements carried out by the three

devices, particularly 240 measurements of two-minute means for MPM, four measurements of two-hour means for COS, and only one measurement of eight-hour mean for PDS, all measurements were time-aligned for comparison purposes. In practice, using COS daily measurement timing as a reference, MPM two-minute means were averaged over each two-hour period, while only the PDS daily mean was repeated four times, thereby obtaining four measurements of two-hour synchronized values per day.

Arithmetic/geometric means (AM/GM), standard deviations (ASD/GSD), median (Me), inter-quartile range (IQR), and range of variation (ROV) were used to describe the main statistical features of eight-hour FA measurements over a fourteen-day study period.

Furthermore, to estimate the degree of concordance of each device with respect to the others, the method of 95% limits of agreement (LOA) was applied [36]. LOA is essentially based on two statistical components: the first is the mean of differences between FA levels identified by two different devices simultaneously and represents a structural and consistent tendency (bias) of one device to exceed the other; the second is the standard deviation of the differences (s_d) which measures the random fluctuations around bias and is used to derive the lower and upper values of LOA according to the following Equations (2):

$$\text{Low (LOA)} = \text{bias} - 1.96 \cdot s_d \quad \text{Upp (LOA)} = \text{bias} + 1.96 \cdot s_d \tag{2}$$

Most of the differences are expected to fall within the LOA, particularly 95%, if they are normally distributed. Moreover, 95% confidence intervals (95%-CI) were also calculated for bias and LOA estimates. The LOA method was applied to log-transformed FA data because a preliminary graphical analysis indicated skewed distributional forms of FA differences when derived from the original data. All statistical analyses were performed using Stata software (StataCorp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC).

3. Results

The results of simultaneous FA monitoring using PDS, COS, and MPM over 14 working days are presented in Table 1.

Table 1. Formaldehyde concentrations (ppb) detected by the four different measuring devices over a 14-day study period.

Device	N	AM	ASD	ROV
Control PDS	14	7.0	3.9	2.4 - 15.3
PDS	14	32.6	10.7	19.8 - 62.7
COS	56	40.4	29.3	7.0 - 175.0
MPM	2880	189.0	163.7	40.0 - 2895.4

PDS: Radiello® passive diffusive sampler (Restek, S.r.l. Milano, Italia); COS: NEMo XT continuous optical sensor (Ethera Technology, Rolles, France); MPM: Multi-Gas 1512 photoacoustic monitor (Lumasense Technology, Airnova, Limena, PD, Italy); N: number of original measurements; AM: arithmetic mean; ASD: standard deviation; ROV: range of variation.

As already stated, PDS reported only one daily mean (14 measurements), COS provided a mean FA concentration every 2 hours (56 measurements), and MPM should ideally have produced a response every 2 minutes (3,360 measurements). Unfortunately, a technical glitch prevented MPM from recording for two days; thus, the final number of responses obtained was 2,880.

FA arithmetic mean measured using PDS and PDS control were 32.6 ± 10.4 ppb (ROV: 19.8 - 62.7) and 7.0 ± 3.8 ppb (ROV: 2.4 - 15.3), respectively. The simultaneous measures performed in the laboratory were 42.4 ± 44.8 ppb (ROV: 7.0 - 175.0) for COS and 189.0 ± 163.7 ppb (ROV: 40.0 - 2895.4) for MPM.

As PDS provides the time-weighted average concentration of the pollutant, the maximum measured value (62.7 ppb) indicates that the daily FA concentration was always below the TLV-TWA. During the same period, although the average daily concentration of FA measured by COS was largely below the TLV-TWA and comparable to the mean FA concentration reported by PDS, the maximum two-hour mean value was 175.0 ppb. In addition, MPM's daily measurements consistently exceeded the TLV-TWA, with maximum values surpassing the recommended threshold limit value of 0.3 ppm, which serves as a short-term exposure limit of 15 minutes (TLV-STEL).

The mean temperature and relative humidity during the 14-day sampling period were 24.2˚C ± 1.5˚C and 57.0% ± 11.6%, respectively, in compliance with Italian regulations. Table 2 presents a few statistical indexes estimated from FA concentrations when expressed as two-hour mean values. MPM GM (171.3 ppb) was approximately five times higher than those derived from COS (32.3 ppb) and PDS (31.4 ppb), whereas no appreciable GM difference was identified between the COS and PDS measurements.

The 14-day time trends of log-transformed FA levels measured using the four different devices (Figure 2) appear to be consistent with the abovementioned results. In particular, while the measurements obtained by COS and PDS, apart from random variability, were superimposable, the FA levels from MPM monitoring were consistently much higher over the entire period.

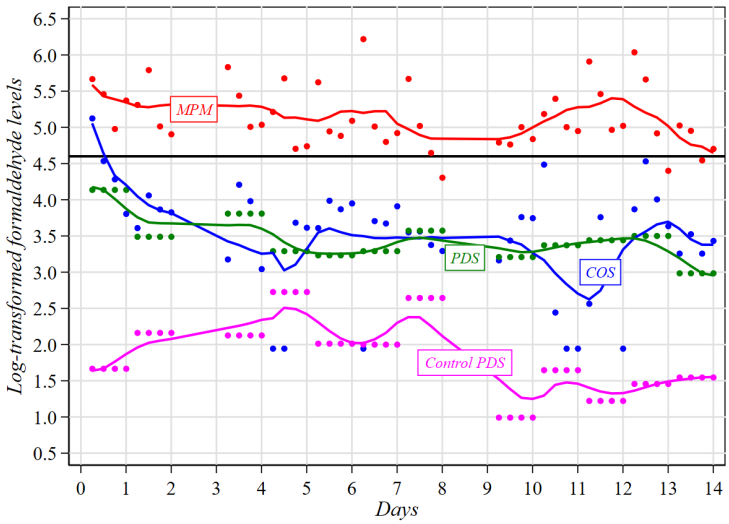
Table 2. Formaldehyde concentrations (ppb) detected by the four different measuring devices over a 14-day study period.

Device	N	AM	ASD	GM	GSD	Me	IQR	ROV
Control PDS	56	7.0	3.8	6.4	1.7	6.4	4.3 - 8.5	2.4 - 15.3
PDS	56	32.6	10.4	31.4	1.3	30.3	25.4 - 35.7	19.8 - 62.7
COS	56	41.4	26.7	32.3	2.1	38.7	26.5 - 49.0	7.0 - 168.3
MPM[a]	48	188.7	91.9	171.3	1.5	150.6	133.7 - 232.7	74.2 - 503.1

PDS: Radiello® passive diffusive sampler (Restek, S.r.l. Milano, Italia); COS: NEMo XT continuous optical sensor (Ethera Technology, Rolles, France); MPM: Multi-Gas 1512 photoacoustic monitor (Lumasense Technology, Airnova, Limena, PD, Italy); N: number of measurements (four two-hour means per day over a 14-day monitoring period); AM/ASD: arithmetic mean/standard deviation; GM/GSD: geometric mean/standard deviation; Me: median; IQR: inter-quartile range; ROV: range of variation. MPM[a] device failed to record measurements of two days due to a technical glitch.

Table 3 presents the results of the LOA method applied to the log-transformed FA data. As expected, the systematic discrepancies between the MPM and the other two devices were the same (approximately 1.70), amounting to an MPM GM which was approximately five times higher (5.46). Consequently, the COS-vs-PDS comparison produced an AM difference and a GM ratio (antilog-transformation of AM) of approximately zero (0.03) and one (1.03), respectively (Figure 3).

Regarding the random component, the LOA method indicated ample variability when MPM measurements were used. For example, on a ratio scale, the lower and upper 95% LOA were 0.94 and 30.0, respectively, when the MPM was compared to COS. In practice, this implies that the GM value of FA concentrations detected by MPM is expected to be up to approximately seven times higher or lower by chance. Similar variability was also observed for the MPS vs. PDS comparison (2.29-13.0), whereas a remarkable reduction (0.26 - 4.12) was found when the COS and PDS devices were considered (Table 3 and Figure 3).



Solid lines: lowess smoother; red: MPM; blue: COS; green: PDS; magenta: control PDS. Each point represents a 2-hour arithmetic mean.

Figure 2. Fourteen-day time trend of log-transformed levels of formaldehyde measured by the different devices.

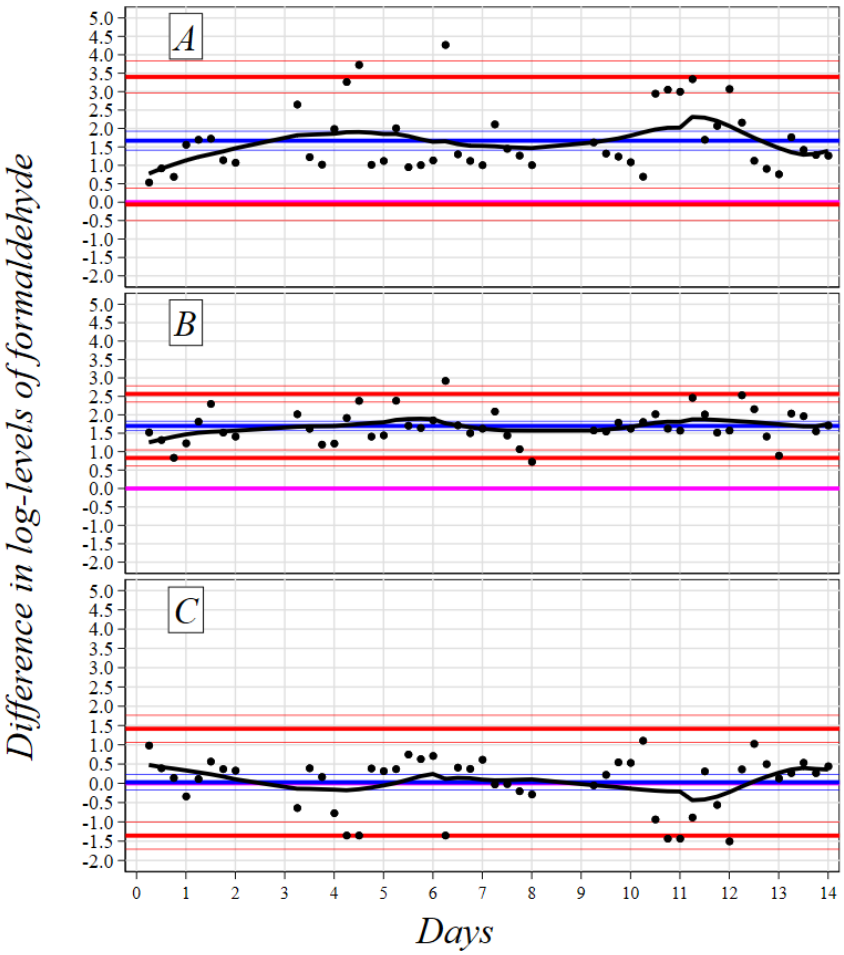
Table 3. Comparisons among formaldehyde levels detected using the three device sexpressed in terms of bias and limits of agreement.

	Statistical parameters	Comparison		
		MPM vs COS	MPM vs PDS	COS vs PDS
		(N = 48)	(N = 48)	(N = 48)
Difference	Bias	1.67	1.70	0.03
	(95%-CI)	(1.41/1.92)	(1.57/1.83)	(−0.18/0.23)
	Low(LOA)	−0.06	0.83	−1.36
	(95%-CI)	(−0.50/0.38)	(0.61/1.05)	(−1.71/−1.01)
	Upp(LOA)	3.40	2.57	1.42
	(95%-CI)	(2.96/3.84)	(2.35/2.79)	(1.06/1.77)

Continued

Ratio	Bias	5.30	5.46	1.03
	(95%-CI)	(4.10/6.85)	(4.80/6.21)	(0.84/1.26)
	Low(LOA)	0.94	2.29	0.26
	(95%-CI)	(0.61/1.46)	(1.84/2.85)	(0.18/0.37)
	Upp(LOA)	30.0	13.0	4.12
	(95%-CI)	(19.3/46.4)	(10.5/16.2)	(2.90/5.85)

PDS: Radiello® passive diffusive sampler (Restek, S.r.l. Milano, Italia); COS: NEMo XT continuous optical sensor (Ethera Technology, Rolles, France); MPM: Multi-Gas 1512 photoacoustic monitor (Lumasense Technology, Airnova, Limena, PD, Italy); Bias: mean difference; N: number of measurements; LOA: limits of agreement; Low (LOA): lower value of LOA; Upp (LOA): upper value of LOA; 95%-CI: 95% confidence interval for bias and Low/Upp(LOA).



Black line/points: lowess smoother/observed differences; blue lines: mean difference (bias) and 95%-CI: red lines: LOA and 95%-CI; magenta line: null bias (zero differences).

Figure 3. Time trend of differences in log-transformed levels of formaldehyde measured by the three devices.

4. Discussion

FA concentrations measured using PDS and COS were comparable. This result

is consistent with a previous study, in which FA measurements by COS NEMo were compared to FA concentrations obtained by active and passive sampling methods [20]. The authors obtained comparable results for all three methods in both experimental tests performed by a dynamic calibration system and in field tests conducted in the operating room and anatomic pathology laboratory.

The FA concentrations measured using the MPM were much higher. Although FA selectivity was guaranteed by the UA 986 filter and the instrument was set to compensate for any interference from water vapor and isopropanol, it is likely that the overestimation of MPM measurements was due to cross-sensitivity with alcohols, which are usually present in an anatomic pathology laboratory. Cross-sensitivity is a phenomenon that has already been identified using photoacoustic systems. The MPM is the instrument of choice for the measurement of anaesthetic gases. Herzog-Niescery *et al*. (2019) [37] used MPM in a German university hospital operating theatre for isoflurane, sevoflurane, and desflurane monitoring. The authors found false-high values for anaesthetic gases, which were attributable to cross-sensitivity with alcohols that are widely used in hospital operating rooms. Liu *et al*. (2020) [38] observed a significant overestimation of ammonia, their target compound measured by MPM, due to non-targeted volatile organic compounds interferences. Previously, Wu *et al*. (2004) [39] monitored FA using MPM in representative office buildings in Taiwan Region. The authors found high FA eight-hour average concentrations, from 0.1 ppm to 0.89 ppm, during the working time, and concluded that these results were at odds with previous reports in non-industrial environments. In this case, there may have been an overestimation of FA due to the measurement system. The specificity of the optical filters is limited by their bandwidth. The overlay of infrared spectra with non-targeted gases can cause significant errors in the final results due to the absorption at similar wavelengths.

FA eight-hour average concentrations measured by PDS and COS were always below the adopted TLV-TWA, thereby demonstrating the effectiveness of FA containment measures adopted by our institute: separate management ventilation of the anatomic pathology rooms from the remainder of the building, which allows the maintenance of thermo-hygrometric conditions and ensures adequate air changes for hours; fume hoods with external canalization and filters for FA containment; adoption of vacuum sealing technologies for packing and transporting specimens; presence of aspirated cabinets for storing all the materials in formalin; training of operators on the safety working procedures to minimise FA exposure risk, in accordance with Italian Legislative Decree 81/08 [31]. As revealed by other recent studies, the effectiveness of multilevel interventions can lower FA concentrations in the workplace and minimize workers' exposure [40] [41].

The good agreement between the PDS and COS could lead to the combined use of the two techniques. The Radiello® sampler, which is easy to wear, remains the most valuable tool for assessing personal FA exposure. Furthermore, it can be used for 15-minute measurements, allowing the assessment of the TLV-STEL. The opt-

ical sensor that provides continuous measurements performs real-time environmental assessment of FA and immediately detects technical glitches and/or human errors. The risk during a specific task can be analysed immediately.

In addition, the presence of sensitive nanoporous materials makes COS a versatile tool that is able to trap large quantities of the target gases. Consequently, apart from the FA concentrations, it is possible to determine the total levels of volatile organic compounds, carbon dioxide, humidity, and temperature.

Undoubtedly, our study has a few limitations, the majority of which are probably due to a rather low degree of compliance of the observed FA measurements with the statistical assumptions underlying the LOA methods (*i.e.*, normally distributed differences and independence between differences and means), even after log-transforming the data, particularly when COS measurements were used in the analyses (Figure S1). The reason for this drawback is, at least partially, due to the synchronization process applied to make the three-time distributions comparable. However, we believe that it is unlikely that this problem can largely invalidate the statistical results of our study given the significant differences observed between FA levels detected by the MPM and COS/PDS devices.

5. Conclusion

Despite the carcinogenic effect of FA, formalin—that is, its aqueous solution—cannot be replaced in anatomic pathology laboratories because no effective alternative chemical for fixing tissues is available. Therefore, it is extremely important to implement all necessary measures to minimise FA exposure in the workplace while maintaining the effectiveness of the control systems at the highest level.

In this study, three monitoring devices were tested. The results obtained using PDS, COS, and MPM were not uniformly comparable. Although the FA concentrations measured using PDS and COS were similar, those obtained using MPM were much higher.

The good agreement between the PDS and COS indicates the feasibility of a tailored approach that considers the distinctive features of each technique. This might be a valid tool for performing an accurate risk assessment in healthcare workers exposed to FA. Moreover, continuous environmental monitoring of FA contamination may enable immediate targeted interventions aimed at preventing FA dispersion, thereby achieving the goal of creating healthier workplaces.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

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