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FORMALIN SAFETY IN ANATOMIC PATHOLOGY WORKFLOW AND INTEGRATED AIR MONITORING SYSTEMS FOR THE FORMALDEHYDE OCCUPATIONAL EXPOSURE ASSESSMENT

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Abstract
The potential carcinogenicity of formaldehyde (FA) has prompted increasing preventive measures in anatomic pathology (AP) laboratories and new strategies aimed at innovating airborne FA monitoring systems. This review provides an updated overview of the most recent improvements in preventive measures, safe practices, and exposure monitoring tools in the FA usage and handling. A computer-based search of scientific and non-scientific sources was performed on PubMed, Web of Science, Google and Google Patents databases, querying the main topics of real-time, in-continuous FA monitoring instruments for sale, and commercially available tools for improving preventive measures in formalin management. In order to simplify the sampling process and to choose a better analytic solution to FA assessment, the main characteristics of each FA monitoring instrument were described. The novel technical tools recently introduced on the global market, aimed at reducing FA emissions in AP laboratories, were summarized. This review is directed at anatomic pathologists to draw their attention to the rapidly growing field of safe formalin practices. A repeated exposure assessment is recommended to evaluate technical changes in air monitoring programs to keep FA emissions low, in compliance with the limit value; thus, evolved monitoring devices are needed. Int J Occup Med Environ Health. 2021;34(3):319–38

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INTRODUCTION

In 1892, Jean Auguste Trillat observed that formaldehyde (FA, CAS Registry No. 50-00-0) hardened soft tissues and triggered coagulation [1]. The following year, Ferdinand Blum, working intensively on the use of an FA solution (later to be called formalin) in antiseptic procedures, reported that the fingertips' skin became visibly thickened after prolonged exposure, thus becoming impregnated [2]. Blum's results were later confirmed by Cohn, Kenyon, and Blum, as reported by Durig [3]. The process of formalin fixation was extensively described in the reviews by Dell'Isola [4] and Blum [5,6]. The purpose of fixation is to preserve tissues permanently in as life-like a state as possible.

To date, there have been 5 groups of fixatives, i.e., aldehydes, mercurials, alcohols, oxidizing agents, and picrates, but formalin is considered the most effective for all uses [7]. While FA is readily available, cheap and easy to store, it also allows a long-term storage, preserves lipids well, and has been recognized as the gold standard fixative, with no clear "all-purpose" alternative found to date [8]. In a water solution, FA allows one to rapidly obtain as much histopathological information as possible from a fixed tissue. Furthermore, macroscopically, none of the alternative fixatives was able to compete with FA in a broad range of tissue samples [9]. The long-term use has made it the fixative of choice for almost all histo-techniques, to the extent that, e.g., all antibody manufacturers have optimized their products for formalin-fixed paraffin-embedded tissues. Thus, FA is the standard fixative for routine work; in fact, it is the choice in 81% of U.S. histology laboratories and in close to two-thirds in the rest of the world [10].

Acute exposure to FA via inhalation produces causes rapid local irritation in mucous membranes, including the eyes, the nose, and the upper respiratory tract. Olfactory and sensory irritations of the upper airways and eyes have been described as acute reversible effects due to airborne FA exposure in >50% of the exposed population, including students, teachers, and laboratory staff [11–13]. Moreover, other acute effects linked to high levels of FA in humans are coughing, wheezing, chest pains, and bronchitis [14]. Concerning the chronic effects related to FA exposure, nasopharyngeal cancer and sensitization are the most relevant diseases. In sensitized persons, FA can cause bronchial asthma [15] and contact dermatitis [16]; in persons who are not sensitized, a prolonged inhalation of FA at low levels, e.g., <1 ppm, is unlikely to result in a chronic pulmonary injury [17]. As a sensitizer, FA can cause an allergic skin reaction and irritant effects on the mucosal surface of the upper airways and eyes [18–20]. However, some adverse effects on the central nervous system, such as an increased prevalence of headache, depression, mood changes, insomnia, irritability, attention deficit, as well as impaired dexterity, memory, and equilibrium, have been reported to result from long-term exposure [21].

Harrington et al. [22], having analyzed the cause of death among pathologists in the United Kingdom from the 1950s until the late 1980s, found excessive death rates due to suicide, and higher rates of brain tumors, hematopoietic and lymphatic malignancies, all of which could be attributable to FA exposure.

The carcinogenicity of FA and the derivation of a safe occupational exposure limit (OEL) have been the matters of documentations by several scientific expert panels, including the German Research Foundation (Deutsche Forschungsgemeinschaft), the Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards, the Nordic Expert Group and the Scientific Committee on Occupational Exposure Limits (SCOEL) [23]. The American Conference of Governmental Industrial Hygienists (ACGIH) and the SCOEL are scientific organizations with expertise in occupational and environmental health. In 2016, the ACGIH proposed a time-weighted average (TWA) threshold limit value for FA of 0.1 ppm at 8-hour, and a short-term exposure limit (STEL) of 0.3 ppm at 15-minute [24]. The National

Institute for Occupational Safety proposed the FA recommended exposure limits as a 10-hour TWA (0.016 ppm) and a 15-minute ceiling (0.1 ppm).

In 2015, the European Union (EU) SCOEL proposed the FA OELs of 0.3 ppm for 8-hour exposure and 0.6 ppm for 15-minute exposure, i.e., well above the ACGIH's recommended levels. Besides, the expert panel endorsed Directive 2019/983 of June 5, 2019, which introduced a transitional period of 5 years for the healthcare sector, during which the FA limit value of 0.5 ppm for 8-hour exposure would apply. At the same time, it encouraged workplaces to meet the 8-hour 0.3 ppm limit values wherever possible. These values are only suggested guidelines, while the Occupational Safety and Health Administration, the U.S. governmental institution aimed to ensure safe and healthful working conditions, established a TWA of 0.75 ppm and a STEL of 2 ppm as the mandatory permissible exposure limit [25]. At the European level, there exist no unified legal limit values, but the policy-agency of each country can establish its limits; however, it is recommended to follow the OEL indications [26]. The People's Republic of China, New Zealand, Finland, Israel, Canada-Quebec, and Canada-Ontario indicate FA OEL in terms of a ceiling (0.3 ppm).

Besides, FA is a ubiquitous pollutant, and the outdoor sources of FA may contribute to the indoor air quality in houses or working environments. For example, general outdoor air pollutants may be regional sources, such as long-range transport, or heavy and light industrial vehicles, but also nearby sources of air pollution, such as road traffic, and including emissions from parking facilities themselves [27,28]. Hence, to better assess the occupational exposure and the consequent health risk, the knowledge of environmental outdoor and indoor background values is essential [28].

The common use of FA in working activities and the related health effects entail the need to assess occupational exposure to evaluate health risks. Recently, Scarselli et al. [29] have conducted a study to estimate the Italian occupational exposure to FA, evaluating 1301 exposure situations (the healthcare sector, wood industry, chemical industry, furniture manufacturing, sewage and refuse disposal, and sanitation activities). They reported that the FA concentration in Italy, observed in these scenarios, ranged 0.01–0.30 mg/m^3; the highest average levels of airborne FA exposure were recorded in the healthcare sector, particularly among medical doctors and laboratory technicians.

To assess FA exposure, air monitoring ensures the highest correlation with occupational exposure given the fact that there are no validated FA biological indicators. For example, Dimenstein [30] indicated that the endogenous concentration of FA in human blood does not increase (2.77 μg/g) after 40-minute inhalation of 1.9 ppm of FA inasmuch oxidized to formate and exhaled as carbon dioxide. Because of its rapid metabolism in erythrocytes, no increase in the tissue concentration of FA is detectable even a few moments after exposure [31]. Thus, no significant improvement can be noticed between the FA deriving from exogenous exposure and its endogenous share. Moreover, the urinary FA has been indicated as a marker for other pathological conditions, such as prostate cancer [32,33]; thus, it cannot be considered a specific marker of occupational exposure to FA.

As regards environmental monitoring, numerous analytical methods for determining the airborne FA values and for assessing occupational exposure have been developed [34–36]. Still, no standardized recommended approach has been issued for measuring real-time formalin levels in exposed employees. Moreover, only a few of the proposed methods of integrated monitoring provide a validated strategy for evaluating the FA risk in healthcare activities [37,38]. The current, validated methods for detecting gaseous FA are based on either active or passive sampling: the former using 2,4-dinitrophenylhydrazine (DNPH) as a reagent on a filter, and the latter using O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine as a reagent

on a solid sorbent [39]. These methods are standardized and robust, but they require skilled personnel to conduct them, and they often face the unwillingness of the monitored operators.

As mentioned before, the healthcare sector, particularly the anatomic pathology (AP), is characterized by the highest average levels of airborne FA exposure. In AP laboratories, formalin is handled many times throughout the workflow:

– in operating theatres, during the immersion of biopsies in formalin pre-filled containers,
– in the secretariat office during samples registration,
– in cutting operations in the grossing room [37].

The solutions widely used to minimize FA exposure in these scenarios are benches with aspiration hoods or conventional AP fume hoods. These, on the one hand, protect the operators during work activities but, on the other hand, they poorly allow ergonomics of the operations and could be scarcely upgraded with technological systems, such as a dictaphone or a digital recording system. Because of these limitations, technicians employed to perform data transcription procedures are needed, which leads to an unnecessary cost for the laboratory and, most importantly, to an unnecessary FA exposure. In addition, specimens are collected in a pre-filled container with FA to reduce the risk related to the emission during specimens collection, handling, and storage. Although it constitutes a better solution than the holding systems (preparing and conserving bulk solutions of 4% FA in the AP laboratories to fill the containers), they can represent an exposure source due to leaks or spilling.

In this scenario, the implementation of safe practices in AP laboratories and the adoption of new, reliable, airborne FA monitoring methods are crucial [29].

This review summarizes the trends of innovative operative solutions to mitigate FA emissions in AP laboratories, together with commercially-available direct-reading instruments for the airborne FA occupational exposure assessment. To adopt the best practices and to lower the airborne FA values, attention is paid to innovative solutions for the safe management of formalin, and to integrating these with continuous and remotely managed monitoring systems. This study aims to provide a useful tool that easily consents a modern approach to the safe handling of formalin and the related FA occupational exposure assessment.

METHODS

In December 2019, research for scientific sources was conducted in bibliographic databases of peer-reviewed journals (PubMed, Web of Science) to provide a broad view of the most recent solutions to mitigate FA exposure and monitoring systems. This first research was subsequently integrated from Google, Google Scholar, and Google Patent with non-scientific sources, such as manufacturer datasheets and application notes, available, e.g., on the manufacturers or suppliers' websites. Due to the vast literature available on FA occupational exposure and related health risks, the research focused on some specific topics, in particular, the latest real-time, in-continuous FA monitoring, and the modern commercially-available tools for improving preventive measures in formalin management. Following this preliminary research, specific products and devices were selected, and each name of the commercially available devices was entered into the previously mentioned databases individually.

RESULTS

The research led the authors to evaluate several sources; most scientific articles were related to monitoring direct-reading systems (notably, electrochemical instruments). This is probably due to the fact that they are the oldest on the market and have a more widespread use than other FA exposure mitigation and monitoring devices.

Monitoring airborne FA
by portable direct-reading instruments

One effective way to assess occupational exposure to FA is by air monitoring because of the lack of any validated occupational exposure biomarkers for FA [32,40]. To simplify the sampling process and analytic operations, portable direct-reading FA monitors are of increased interest, laying the bases for on-site analyses as confirmation-level methods, with high specificity, similar to conventional monitoring methods (e.g., passive or active sampling with dinitrophenylhydrazine cartridges) [37].

In Table 1, the main features that must be considered during monitoring the device choice, which allow evaluating the FA levels below the mandatory occupational limit values, have been described. Target prices, based on the Italian market, have been reported, too.

The experimental and field comparisons showed that direct-reading instruments are consistent [41–44]. Furthermore, they can be easily integrated into an occupational hygiene plan to prevent significant acute toxicity resulting from FA air monitoring in the workflow connected to the AP laboratory [38,42].

Photometry

Photometric instruments are generally based on the chemical reaction between airborne FA and β-diketone that can be on specific supports, such as porous glass, a tape, or a tablet. The reaction produces a yellowing characterized by absorbance at 407–424 nm, which is measured via photoelectric photometry [45].

The NEMo air quality monitoring station and Profil Air are passive or active samplers that differ from the conventional photometric instruments because they are built with a nano-porous sensor, and they use the Hantzsch reaction (the acetyl acetone method) which entails the cyclization of 2,4-pentanedione, ammonium acetate and FA to obtain dihydropyridine 3,5-diacetyl-1,4-dihydrolutidine (DDL). The detection of FA is based on the color variation of these initially transparent materials; the readings are performed in-continuous and stored in a cloud system. The detection range of modern photometric instruments ranges 0.005–5 ppm, with a sampling frequency of 3–120 min.

Fluorimetry

Fluorimetry is based on the Hantzsch reaction. Fluorescence emission of DDL occurs at 510 nm when excited with light at 410 nm. Since the reaction works in an aqueous solution, gaseous FA must be first trapped in the aqueous media. This is achieved in a stripping coil, where air and a stripping solution are brought into contact, continuously, at defined flow rates and contact surfaces. The air and liquid streams are separated afterwards, and the solution is then analyzed for FA. The linear detection range of this technology is 0.001–3 ppm, with a sampling frequency of 2 s–2 min.

Electrochemical devices

Formaldehyde is determined by the electrochemical oxidation of FA at a metal electrocatalyst [46,47], while maintaining the electrode at a fixed potential and measuring the current flowing through the electrode. There are a lot of commercially-available handled electrochemical sensors. The sensitivity of conventional electrochemical instruments can reach a maximum of 10 ppb, and the specificity of these sensors can be affected by other airborne organic compounds [38], especially alcohols often used in AP laboratories. To face these drawbacks, New Cosmos Electric Co., Ltd (Osaka, Japan) produces the XP-308B Formtector, which uses a DNPH-impregnated filter to reduce the influence of volatile organic compounds during FA measurements. Interscan Corporation (Chatsworth, CA, USA), instead, makes a voltammetric sensor (U.S. patent No. 4017373) which is an electrochemical gas detector operating under diffusion-controlled conditions with a guaranteed limit of detection of 5 ppb.

Table 1. Direct-reading instruments for formaldehyde determination currently available on the market, December 2019

Monitoring device	Producer	Portable	Dimensions	Weight	Price [EUR]	Detection mode	Range [ppm]	Sampling frequency
FP-31: photoelectric photometry method with colorimetric tablets for detection (accumulating measurement)	RKI Instruments (Union City, NJ, USA)	+	8×15×4 cm	250 g	1000–2000	photometry	0.005–1	15–30 min
FP-330: photoelectric photometry method using a tape cassette	RKI Instruments (Union City, NJ, USA)	–	16×19.8×26.3 cm	6.5 kg	2500–3500	photometry	0.03–5	3–10–30 min
FM-801: reusable sensor cartridge that employs the chemical reaction with β-diketone	GrayWolf Sensing Solutions (Shelton, CT, USA)	+	16×19×6 cm	300 g	2000–3000	photometry	<0.02–1	30 min
NEMo: air quality monitoring station that employs ultra-sensitive nano-porous materials	Ethera (Crolle, France)	–	19×13.5×7 cm	520 g	5000–6000	photometry	0.001–2	15–120 min
µF-1 analyzer: microfluidic analyzer that traps FA in an aqueous solution with the Hantzsch reaction	In'Air Solutions (Strasbourg, France)	+	32×29×15 cm	5 kg	–	fluorimetry	0.001–2	2–120 s
Monitor AL4021: analyzer based on the Hantzsch reaction	Aerolaser (Garmisch-Partenkirchen, Germany)	–	45×15×56 cm	20 kg	45 000–55 000	fluorimetry	0.001–3	90–300 s
HAL-HFX205: direct real-time reading fast response device	HAL Technology (Fontana, CA, USA)	+	8×4.5×15.7 cm	200 g	500–1500	electrochemical	0.01–5	1 min
Formaldemeter™ htV-M: analyzer based on electro-oxidation of FA at the catalytically active electrodes	PPM Technology (Caernarfon, United Kingdom)	+	15×8×3.5 cm	300 g	500–1500	electrochemical	0.01–10	2 min
FM200: handheld device with a detachable probe	Extech-FLIR Commercial Systems (Nashua, NJ, USA)	+	16×6×4 cm	181.4 g	500–1500	electrochemical	0.01–5	<2 s

Z-300XP: electrochemical cell 4-electrode type; an active filter eliminates potential interference from common chemicals	Environmental Sensor Company (Waterway, CA, USA)	+	19×14.6×7 cm	900 g	1500–2500	electrochemical	0.01–30	<60 s
MultiRAE: up to 6 gas sensors and wireless portability	RAE Inc. (San Jose, CA, USA)	+	19.3×9.6×6.6 cm	880 g	1500–2500	electrochemical	0.01–10	<80 s
4000 Series Portable Analyzer: voltametric sensor operating under diffusion-controlled conditions	Interscan Corporation (Simi Valley, CA, USA)	+	17.8×10.2×2.25 cm	2 kg	5500–6500	electrochemical	<0.005–2000	<40–50 s
PortaSens II: hand-held device that measures different gasses by inserting the appropriate gas sensor module	PortaSense (Collegeville, PN, USA)	+	8.9×22.9×14 cm	2.2 kg	1000–2000	electrochemical	0.020–2000	<60 s
XP-308B: simplified detector; reduced influence of VOCs with a DNPH filter	New Cosmos Electric Company (Tokyo, Japan)	+	17.5×14×8.6 cm	2.5 kg	500–1500	electrochemical	0.01–30	10–30 min
Gasera One Formaldehyde: photoacoustic detection technology with a QCL source	Gasera (Turku, Finland)	–	48×13×44 cm	13 kg	80 000–90 000	IR spectroscopy	0.001–10	60 s
ProCeas®: pre-calibrated laser IR spectrometer that employs a patented low-pressure sampling system	Ap2e (Aix-en-Provence, France)	–	42×23.6×5.5 cm	20 kg	55 000–65 000	IR spectroscopy	0.001–10	<60 s
G2307 Gas Concentration Analyzer: based on CRDS technology	Picarro Inc. (Sunnyvale, CA, USA)	–	43×18×45 cm	21.3 kg	70 000–80 000	CRDS	0–30	2–10 s–5 min
VOICE200ultra: real-time analysis using SIFT-MS	Syft Technologies (Darmstadt, Germany)	–	100×90×80 cm	220 kg	295 000–305 000	MS	0.007–4	<2 s

CRDS – cavity ring-down spectroscopy; DNPH – dinitrophenylhydrazine; FA – formaldehyde; IR – infrared; MS – mass spectrometry; QCL – quantum cascade laser; SIFT-MS – selected-ion flow-tube mass spectrometry; VOCs – volatile organic compounds.

Infrared spectroscopy

Infrared (IR) spectroscopy monitors the interaction of functional groups in chemical molecules with IR light resulting in predictable vibrations that provide a "fingerprint" characteristic of a chemical. Gasera (Turku, Finland) has developed outstanding improvements to Fourier transform-IR photoacoustic spectroscopy (PAS), reaching a sensitivity for FA of 1 ppb. This new direct-reading sampler, called Gasera One Formaldehyde, is based on combining a cantilever enhanced PAS detection technology and a quantum cascade laser operating via a mid-IR fundamental spectral absorption. The Durag Group (Novara, Italy) sells the ProCeas Air, in which the IR-laser technology, implemented with optical feedback cavity-enhanced absorption spectroscopy (WO patent No. 03031949), is used for detection. Both these 2 instruments can reach a sensitivity of 0.001 ppm, and they guarantee a linear response of 0.001–10 ppm.

Cavity ring-down spectroscopy

Cavity ring-down spectroscopy (CRDS) is a highly sensitive optical spectroscopic technique that measures absolute optical extinction in aerosol samples which scatter and absorb light. A highly sensitive detector has been produced by Picarro Inc. (Santa Clara, CA, USA), called the Picarro G2307 analyzer, which enables precise and stable measurements of FA by the CRDS technology (patent No. US7106763B2). In CRDS, the beam from a single-frequency laser diode enters a cavity created by 3 high reflectivity mirrors, enabling gases to be monitored in seconds or less at the ppb level, and some gases even at the ppt level. Moreover, coated SilcoNert and teflon elements are used in the G2307 gas pathway to reduce the FA adsorption onto pathway surfaces, increasing the response time and reducing the measurement bias.

Mass spectrometry

Mass spectrometry (MS) is a sensitive and specific analytical technique, providing qualitative and quantitative analytical data of the trace and ultra-trace of the analyte. Mass spectrometers have become far more accessible, cheaper to purchase and operate, and easier to use, as a consequence of the introduction of compact, bench-top instruments, coupled to gas or liquid chromatographs [48]. Recently, MS has been applied to on-field air monitoring. selected-ion flow-tube (SIFT-MS) analyzes the air directly and within seconds, using soft chemical ionization. This method yields exceedingly precise, real-time, quantitative analyses, thus eliminating the phases of sample preparation, pre-concentration, and chromatography [49]. Such FA monitoring, using this technology, is achieved by combining the Voice 200 ultra SIFT-MS (Syft Technologies, Christchurch, New Zealand) with a GERSTEL (Mülheim an der Ruhr, Germany) multipurpose sampler.

Improvements of preventive measures in formalin management in AP workflow

Applying mitigating measures to ensure the safe handling and use of formalin is essential for managing AP workflow. The following summarized technical mitigations for FA reduce formalin emissions from the operating theatres, the secretariat area and the grossing room in a pathology laboratory:

- ergonomic consoles,
- absorbent materials to collect any residual draining of formalin from the anatomical specimens,
- kits containing an FA-neutralizing agent for formalin spills,
- closed-circuit systems for biopsy storage.

Best practices for maintaining and engineering air handling, and possibly for redesigning processes and systems (such as equipment functions, building operations, and industry procedures), are needed to operate effectively, in line with the new safety regulations. Attention paid to ergonomic design, both in terms of body-friendly adjustments and streamlined workflow, contributes to these best practices [50].

Grossing workstation

Pathologists spend long hours in front of the aspirating chemical fume hood; thus, an ergonomic console is desirable to provide comfort [51]. The fume cupboards/grossing workstations provide a multi-featured ergonomic, safe, and practical work area for specimen grossing: all potential operating features linked to a standard workflow are within easy reach, while an ergonomic posture is maintained and, at the same time, safer management of formalin is guaranteed. Recently, the main fume hood cupboard manufacturers have improved the ductility of these stations, implementing their function and their optional tools in order to obtain multitask workstations [52,53].

The latest generation of grossing workstations is equipped with a laminar and/or back downdraft ventilation system and a working surface without front glass (Table 2). The development of a high-performance and cost-effective digital optical console has been the goal of recent years. Replacing the traditional dictation of anatomical pathology reports by the more recent voice recognition technology (VRT) has been showing improving success [54,55]. Flexible and efficient console systems have recently been produced with several new features such as modular architecture, connectivity using appropriate middleware with the AP laboratory's information system, a digital pathology system that records whole images of process specimens [56], and VRT.

Supplemental air handling options and automated FA neutralization devices

Extra ventilation and optimized design are not always enough to neutralize residual FA fumes or formalin in AP laboratories, especially since peak FA exposure could lead to temporary shutdowns or a reduced operational capacity of the ventilation system. Portable room filters, such as the Room Filtration Module – Pure Path – BF840 (Mopec, Oak Park, IL, USA) or Exhale 3000 (Danaus Srl, Rome, Italy), can be easily positioned in laboratories filtering problematic areas to prevent FA overexposure and to help maintain a safe environment. These devices can be fitted for external exhaust or with recirculating exhaust systems, which safely neutralize the harmful FA fumes by chemisorption with activated carbon, impregnated with potassium permanganate [57] or sodium metabisulfite [58]. Indeed, FA reaction with bisulfite forms an FA sodium bisulfite adduct (sodium hydroxymethanesulfonate, CAS 870-72-4), which is very stable under normal conditions. Recently, Ethera has released a purification system called PureTECH which is an irreversible granular FA entrapment filter with an integrated saturation indicator [59]. Ohmichi et al. [60] specifically demonstrated the effectiveness of the photocatalyst technology in anatomy laboratories, reducing FA concentration by about 80%. A photocatalytic oxidation and manganese oxide air purification system for airborne FA is marketed by Innovative Labs LLC (Petaluma, CA, USA). Finally, Novaerus (Stamford, CT, USA) uses a patented atmospheric plasma discharge of the dielectric barrier discharge type, whereby the plasma discharge comprises electrons and ions, causing FA neutralization [61].

Closed-circuit systems for biopsies

Closed-circuit systems used for small biopsies prevent the user from touching FA. The market offers several brands of pre-filled formalin containers, all consisting of 2 containers with lids (Table 3). Using the containers with the lid has dramatically reduced the use of formalin in the operating theatre, along with providing a safer handling in the secretariat area and the grossing room [37,38]. Another innovation has been the adoption of containers for large biopsies which employ modified atmosphere packaging (MAP) or under vacuum storage (UVS) systems immediately after tissue insertion [62]. While T-Filler (Combifill, Bergamo, Italy) dispenses a 4% FA solution into rigid containers, the Tissue Vacuum Plus and the Tissue Filling System (Kaltek, Padua, Italy) uti-

Table 2. Latest generation grossing workstations currently available on the market, and their main features, December 2019

Workstation	Producer	Ventilation	Springkler washing system	Computer integration	VRT	Dictaphone	Dissection cutting board	FA dispenser
Grossing tables CT1BT	Propath Europe (Ronse, Belgium)	D	–	+	+	–	+	+
Grossing station PMT	PMT Scientific (Redford, MI, USA)	B	–	+	+	–	+	+
Grossing station EMEC G515	Emec Scientific (Selangor, Malaysia)	B/D	–	+	+	+	+	+
Elevating pathology grossing station Model GL100	Mortech (Azusa, CA, USA)	B/D	–	+	+	+	+	+
GrossPath GP-1500 ECO-line	Kugel Medical (Regensburg, Germany)	D	+	+	+	–	+	+
Grossing workstation ZT HS 455	UFSK International (Regensburg, Germany)	D	–	+	+	+	+	+
Grossing workstation Zenon	Zenon Diagnostic (Istanbul, Turkey)	B/D	–	+	+	+	+	+
Grossing station Backdraft Premium (RBi Series)	Apzem Inc. (Chennai, India)	B	–	+	+	–	+	+
Grossing station M-GWS	Medimeas Instruments (Ambala, India)	B	+	+	+	+	+	+
Grossing station Mopec Maestro	Mopec (Madison Heaights, MI, USA)	B	+	+	+	+	+	+
Elevating grossing station Tissue-Tek® Accu-Edge®	Sakura Finetek (Torrance, CA, USA)	B	–	–	–	–	+	+
Grossing station eGROSS	Milestone (Milan, Italy)	B/D	–	+	+	–	+	+

B/D – back and/or down draft; FA – formaldehyde; VRT – voice recognition technology.

Table 3. Closed-circuit system for the safe handling of formalin in the healthcare sector, currently available on the market, December 2019

Closed-circuit system	Producer	Available volume [ml]	Rigid/Non-rigid
SafeCapsule	Diapath (Martinengo, Italy)	31.7×8.3–19	rigid
Bioprotektor	Kaltek (Padua, Italy)	40–90	rigid
Klessidra	Bio-Optica Milano (Milan, Italy)	20–30	rigid
Tecnobilife Biopsy Box	PRAXI Intellectual Property (Civitanova Marche, Italy)	20–30–60–90	rigid
Securbiop	Traces (Carmagnola, Italy)	20–60–120–250–300	rigid
Zero	Meccanica GM (Loreto, Italy)	20–40–60	rigid
Biopker	Kerfilter (Carmagnola, Italy)	10–20–30	rigid
Furma	Aquamana (Carmagnola, Italy)	30–50–100	rigid
BiopSafe	Axlab Inn. (Vedbæk, Denmark)	20–60	rigid
FormSafe	Menarini (Berkshire, United Kingdom)	60	rigid
T-Filler	Combifill (Bergamo, Italy)	600–5700	rigid
TVP/TFS	Kaltek (Padua, Italy)	250–500	rigid
Biopreserve	Patholab (Selargius, Italy)	600–5000	rigid
SealSafe	Milestone (Sorisole, Italy)	customized	non-rigid

lize MAP technology and dispense formalin into rigid containers. The Biopreserve (Patholab, Selargius, Italy) method, instead, adopts a rigid container, filled with formalin in a UVS medium. The latter 2 devices use bags for transporting the fresh biopsy or for storing it, following the initial fixation phase in formalin inside a rigid container. Instead, SealSafe by Milestone [63] uses a non-rigid container – more specifically, bags with a double-barrier layer of polyamide and polyethylene – for fixation with FA 4% and UVS processing. As an added bonus, these bags significantly reduce the space occupied by the specimens so that they can be stored and transported more easily. Furthermore, Zenon Diagnostic (Istanbul, Turkey) offers Formadose, a fully automated formalin preparation and dispensing device.

Formalin spill kits with FA-neutralizing agents

The transport of formalin-fixed specimens and the formalin handling itself are clearly critical phases in AP workflow [30] since they augment the risk of formalin spills and the likelihood of reaching the immediately-dangerous-to-life-and-health level. Both the scientific literature and the design of many industrial products (whether produced or described in patents) suggest that some compounds can transform formalin into non-hazardous waste [64]. In fact, for this purpose, a formalin spill kit with an FA-neutralizing agent, based on sodium metabisulphite, is manufactured by Aldon Corporation (Avona, CT, USA), while a mixture of trisodium phosphate and sodium metabisulphite, called Tissue-Tek® FormaGo, is marketed by Sakura Finetek Europe (Rijn, the Netherlands) [65].

Other similar products are available on the market, but information regarding the composition and the reactivity of Neutralex, patented by Scigen Inc. (Paramount, CA, USA) and certified by the California Environmental Protection Agency and PolyForm-F™ (Newcomer Supply, Middleton, USA), is not available from the manufacturers.

Discussion

The AP market was valued at USD 33 billion in 2019 and was estimated to grow to USD 44.4 billion by 2024, at a compound annual growth rate (CAGR) of 6.1% [66]. The increasing volume of diagnostic tests performed in AP laboratories and the rising needs of personalized oncology are the key factors driving this growth. Contemporaneously, the market for direct-reading FA monitors is growing significantly; the global FA detector production revenue is estimated to reach USD 103.81 million by 2022, with a CAGR of 3.77% in 2017–2022 [67].

New regulatory provisions have been introduced for FA regarding its classification and reference or limit values; thus, companies have introduced new devices on the market for a safer use of formalin. Since 2013, key studies have been published, and key cancer cohorts have been updated confirming that FA is genotoxic, causing DNA adduct formation, with clastogenic effects. However, the exposure-response relationships were non-linear, and the relevant genetic polymorphisms were not identified [18,68]. New updates from the U.S. National Cancer Institute cohort, nevertheless, confirmed that relative risk was not increased if the mean air FA exposures were <1 ppm and the peak exposures were <4 ppm [18]. These possible effects on human health have prompted the reorganization of workflow processes and new FA assessment strategies (Table 4).

For an accurate evaluation of the occupational FA exposure scenario in an AP laboratory, the use of both screening- and confirmation-level airborne FA measurement methods is recommended. The choice of the instruments/methods to be adopted will be based on various factors, such as the financial resources available, the expected concentration and range values, etc. However, portable, real-time monitors already exist, and the market continues to invest in the development of such devices; hence, they are becoming ever-more affordable. These instruments, furthermore, are fully networkable, and instrument operation, data handling, and troubleshooting can be performed remotely, even by a smartphone or a tablet, with very easy-to-use packages.

In agreement with Dimenstein [69], it is reasonable to expect a widespread usage of quantity airborne FA monitors on a regular basis, and this paper represents an opportunity to challenge manufacturers to develop such devices. Notably, FA occupational exposure could be carried out by purchasing many units for various workstations, though with cheaper in-continuous monitors, while the more expensive devices can be equipped with multi-channel monitoring, with sometimes up to 12 sample inlets, enabling a multi-point monitoring strategy.

Indeed, modern healthcare institutions often have multiple clinics, hospitals, operating rooms, and laboratories at separate geographic locations, with consequent logistic problems related to the environmental sampling of airborne FA. Thus, investing in remote-monitoring devices and packages will reduce the number of hours needed by personnel to assess workplace exposure.

Annual monitoring is mandatory, but during the year many significant events might occur, such as the disruption of the ventilation system or violations of formalin handling. The area monitoring approach by remote, in-continuous instruments, placed within the breathing zone of the operators, can eliminate human errors and reduce the personnel costs related to sampling. Moreover, the different systems illustrated in this review can be combined to allow high-throughput remote monitoring, ensuring a complete picture of workplace exposure. Recently, Mucci et al. [38] have described an AP workflow where FA management is confined to fume cupboard workstations located in the operating theatres, secretariat areas and grossing rooms. Subsequently, Dugheri et al. [70] 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 in-continuous measuring instruments

Table 4. Scientific papers about innovations and processes leading to formaldehyde occupational exposure reduction, December 2019

Reference	Year	Theme	Subject matter
Dugheri et al. [70]	2020	monitoring	strategy, devices, comparison
Ogawa et al. [71]	2019	best practices	ventilation system, strategy
Mastracci et al. [63]	2019	best practices	UVS
Mucci et al. [38]	2019	monitoring	strategy, devices, comparison
Dugheri et al. [37]	2018	monitoring	strategy
Xu et al. [72]	2016	mitigation	ventilation system
Zarbo et al [62]	2015	best practices	UVS
Klein et al. [73]	2014	mitigation	ventilation system
Di Novi et al. [74]	2010	best practices	UVS
Bussolati et al. [75]	2008	best practices	UVS
Ohmichi et al. [60]	2007	mitigation	photocatalytic device

UVS – under vacuum storage.

within the breathing zone – placed in front of the fume cupboard workstation. This device combines the in-continuous monitoring units mounted on it with the further advantages of an ergonomic workstation.

A future improvement to FA occupational monitoring could be field-portable gas or liquid chromatography coupled with MS or other detectors for these specific compound classes to evaluate DNPH, or with O-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine samplers [37]. However, the specificity offered by chromatographic analysis systems is also guaranteed by real-time monitors, some of which can be considered instruments for confirmation-level monitoring. Specifically, IR, photometric, fluorimetric, and MS techniques can eliminate the interferences given by other substances, while providing a measurement certainty comparable to the conventional methods [38,76]. Due to the FA electrochemical sensor high cross-sensitivities and long recovery times after their exposure to selected compounds, these sensors are not suitable for AP laboratories, where xylenes and alcohols are used in the same workstation as FA. Nevertheless, the detection limit must be considered, and real-time monitors that can determine airborne FA values of 1 ppb are recommended. The FA air guideline levels proposed by WHO are comparable to the other limits proposed [77]. Nonetheless, all efforts should be made to remain as low as possible below this value, in accordance with the as-low-as-reasonably-achievable (ALARA) principle.

At this point, how to behave when the reference values and the adopted limit values are very close? The airborne FA concentrations and air exchange rates in occupational settings are inversely correlated [78,79]. Adopting ventilation equipment with chemisorption or adsorbent filters is a possible alternative, but they considerably increase energy consumption. This gives rise to the question of whether the technical efforts required to minimize these emissions outweigh the benefits. This would certainly not seem to be the case when these target concentrations are excessively below well-established guidelines.

However, a reduction of FA concentration by means of engineering controls of the general ventilation system is mandatory. A computer-based control system, the Building Management System, must be installed to control and monitor the building's mechanical and electrical equip-

ment, such as its heating, ventilation, and air conditioning parameters, and to interface with the extraction system of the fume hoods, too. The fume cupboards must be maintained in strict accordance with all the indications given in their mandatory technical standards, UNI EN 14175-2:2004/3:2004/4:2005/5:2007/6:2006, UNICHIM M 192/3:2009/2013, AFNOR NF X15-206:2005/211:2009, and UNI/TS 11710:2018, which are the guidelines to guarantee both system function and user safety. In particular, the technical standard UNI/TS 11710:2018 contains the performance specifications required for fume cupboards to be used in the handling of chemicals, with the acceptable limit values for containment and the robustness of containment, face velocity, and air exchange efficiency.

Particular attention to the measurement of these parameters must be paid when applying them to the latest generation of pathology laboratory grossing workstations, equipped with a laminar and/or back downdraft ventilation system. This technology pushes air from the front of the cutting surface through the back area, creating a laminar flow pattern for each operator with their own workspace preferences, and for each laboratory with its own safety and workflow requirements (Mopec Inc., patent No. US20060180057A1). These workstations, in addition to reducing airborne FA as efficiently as conventional fume cupboard grossing workstations, simplify workflow, thus lowering the operator's exposure, by offering an open work surface, nozzles for in-continuous washing with water, and personalized ergonomic modulation. Moreover, the possibility of customization (the image acquisition system, dictaphone-VRT, towel and glove dispensers, waste bins, etc.) allows for the further lowering of FA emissions by reducing the number of workflow actions required, which in the past would have had to be done outside of the fume cupboard area.

The use of the formalin closed-circuit system for pre-loaded containers and UVS systems, furthermore, has been a winning solution, combining safe usage with robustness and practicality [38,74]. These innovations have drastically reduced the use of FA, because closed-circuit systems are pre-filled with it and do not require the manual addition of FA, while UVS systems can often be used in 2 operating modes: without FA or using the minimum amount of FA, depending on the type of the sample. The related reduction of FA use in AP laboratories leads to lower exposure, and thus to an improvement of working conditions. The Higher Health Council of Italy and the Italian Group of Mammary Pathology of the Society of Pathology have called for improvements in all phases of biopsy handling, including transportation, to prevent harm to employees [80,81]. Moreover, adopting the UVS and/or MAP systems has restricted the use of FA to dedicated areas in pathology laboratories since large boxes of the formalin fixative no longer have to be transported throughout the hospital.

The introduction of high-tech tools, such as video and photo acquisition systems or dictaphones, can also minimize errors in the workflow of AP laboratories. After several years of a slow start, recently there has been a rise in the availability of informatics tools.

Nevertheless, a key challenge is the cost of this new technology; initially, setting up a high-tech system requires significant spending. To date, a limited number of institutions have adopted speech recognition and digital pathology equipment because of their high costs and complexity. Prices are, however, becoming more affordable. After an initial capital investment, the running costs are minimal. Moreover, the Internet has simplified communications and overcome the problem of installing specialized lines to communication equipment. The preliminary cost of these systems is also balanced by reducing the cost of sample storage and by eliminating the working hours associated with transcribing and digitizing AP reports and images.

Another challenge that is usually overlooked is the resistance of pathologists towards this change. Generally,

a large percentage of anatomical pathologists are not in favor of transitioning into high-tech practices. This can be attributed to many factors, including the understanding of new technologies, with their strengths and limitations. Moreover, there is generally a lower level of comfort with the new procedures, as for any new process. However, failure to adopt technology will become a handicap and be viewed, in the future, as a shortcoming. After witnessing successful examples in other medical disciplines (such as radiology), pathology will surely be no exception. Thus, training the pathologists is essential to achieve a better understanding of the nature and limitations of these new devices, in addition to benefiting future practice. Legal issues related to the archiving and protection of electronic data must also be thoroughly explored, and then resolved.

CONCLUSIONS

The aim of this review was to focus on the current work practices and possible new implementations to reduce FA vapor emissions in the AP workflow. Specifically, easy-to-use and economical airborne FA monitoring devices were listed along with their main features in order to assist in improving the safety in AP workplaces, in compliance with national mandatory occupational limit values. The authors' goal is to encourage the pinpointing of those technical changes that would mitigate emissions. Repeated exposure assessment will help to evaluate whether technical changes in an air monitoring program do keep FA emissions low. The lack of biological indicators for FA and its low odor threshold suggest that air monitoring ensures the highest degree of safety.

The use of formalin in the AP laboratories' workflow has changed substantially since the years when the main epidemiological studies were conducted; of course, it was the monitoring of FA exposure at the workplace that changed the game. The practice of surgical pathology is under constant pressure to deliver the highest quality of service, to reduce errors, to increase throughput, and to decrease turnaround time, while at the same time dealing with an aging workforce, increasing financial constraints, and economic uncertainty. Although it is not possible to implement total laboratory automation, great progress continues to be made in workstation automation in all areas of the pathology laboratory.

This report highlights the technological challenges of pathology automation, showing middleware and how it facilitates automation, as well as presents the progress made so far in the AP laboratory, introducing such newly-available high-tech IT tools (i.e., speech recognition and image capturing systems).

The grossing activities could be the main target for reducing pollution by formalin vapors; this would, however, require a longer and closer examination. Namely, in-continuous air monitoring to capture the highest levels of exposure during grossing activities is desirable. In contrast, the 8-hour TWA levels are not always appropriate because they are influenced not only by the proportion of large vs. small specimens grossed during the work shift, but also heavily by the intra-day workload variation. For these reasons, the introduction of in-continuous monitoring systems during grossing activities should be adopted to make a fair assessment of FA exposure and, at the same time, to evaluate the goodness of high-tech tools and FA mitigation solutions adopted.

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