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FORMALIN SAFETY IN PATHOLOGY LABORATORY AND INNOVATIVE MONITORING FOR AIRBORNE FORMALDEHYDE EXPOSURE

UDK 661.727.1:331.45
RECEIVED: 2020-09-28
ACCEPTED: 2021-03-01

SUMMARY: This review is directed at preventive health professionals, anatomic pathologists and technicians to focus their attention on the rapidly growing field of safe formalin practices. An updated overview of the most recent improvements in preventive measures versus formaldehyde (FA) in the anatomic pathology laboratories (APL) is provided. The occupational hygienist role and the required knowledge for a modern and clear occupational exposure assessment are described. Real-time, in-continuous, commercial analyzers for repeated FA exposure assessment are considered to evaluate technical changes in air monitoring programs, introduced to mitigate FA emissions, in compliance with the adopted limit values. To better choose the adequate instrumentation, the main features of each FA monitoring instrument recently introduced on the market are listed. Moreover, the main features of the modern workflow setting in APL are summarized. A computer-based scientific and non-scientific reports search by key-words was performed on PubMed, Web of Science, Google Scholar and Google Patents databases, querying the following topics: i) grossing workstation for ergonomic layout, ii) commercially available direct reading tools to measure formalin, iii) real-time, in-continuous FA monitoring instruments for sale. This review represents a useful tool to summarize the technical requirements and expert know-how necessary to minimize FA emissions and produce an exhaustive FA assessment in the APL.

Key words: *formaldehyde, exposure assessment, occupational monitoring, anatomic pathology, formalin*

INTRODUCTION

In 1991, Hall and Harrington analyzed the causes of pathologists' death in the United Kingdom from the 1950s until the late 1980s. They found excess death rates due to suicide and higher rates of brain tumors and hematopoietic and lymphatic malignancies. Among the possible causes of these findings, formaldehyde (FA) exposure had been noticed *(Hall, Harrington, Aw, 1991, Harrington, Oakes, 1984, Harrington, Shannon, 1975, Scheepers et al., 2018)*. Students, teachers, and laboratory personnel reported acute health effects due to FA exposure; it principally involves FA smell and sensory irritation of the nose, nasal cavity, pharynx, larynx, and eyes *(Nielsen, Larsen, Wolkoff, 2017)*, approximately in half of the exposed population *(Onyije, Avwioro, 2012, Vimercati et al., 2010, Flyholm, Menne, 1992)*. Furthermore, FA results to be a sensitizer, which can cause an allergic skin reaction *(Friis et al., 2014)*. In addition to these short-term health effects, there is concern about long-term effects, including an increased risk of carcinogenicity *(Reingruber, Pontel, 2018)*. Since 2013, new key studies have been published, and key cancer co-

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horts have been updated, confirming that FA is genotoxic, causing DNA adduct formation. The exposure-response relationships are nonlinear, and relevant genetic polymorphisms are not yet identified *(Nielsen, Larsen, Wolkoff, 2017)*. Concerning FA exposure risk, new updates of the US National Cancer Institute (NCI) cohort confirmed that the relative risk was not increased with mean FA exposures below 1 ppm and peak exposures below 4 ppm *(Beane Freeman et al., 2013)*. In order to prevent workers' injuries and illness, anticipating, recognizing, evaluating, and controlling workplace conditions is necessary: occupational hygienists use environmental monitoring and analytical methods to detect the extent of worker exposure and employ engineering, work practice controls, and other methods to control potential health hazards. Effective management of worker safety and health protection is a decisive factor in reducing the extent and severity of work-related injuries and illnesses and their related costs *(US Department of Labor OSHA, 2006)*.

In the European Union, the number of workers exposed to formaldehyde (FA) above the ubiquitous level (1.5-16.4 μg/m^3) *(World Health Organization, 2010)* is calculated to be 1.7 million (Scarselli et al., 2017). Although most exposed workers are foreseeably engaged in chemical and plastics factories, the highest mean levels of airborne FA exposure were recorded in the healthcare sector *(Vimercati et al., 2010, Dugheri et al., 2018)*. Generally, three typical scenarios using FA were investigated: i) operating theatres where small biopsies are soaked into closed-circuit system 4% FA containers, ii) secretariat of anatomic pathology laboratories (APLs) during the registration of biopsies and iii) APLs during the slicing of biopsies *(Dugheri et al., 2018)*. Especially in the latter, high air FA concentration levels have been found *(Vimercati et al., 2010, Dugheri et al., 2017, Dugheri et al., Unpublished manuscript)* in APLs where correct, safe practices were not adopted *(Ochs et al., 2012)* or where there were not adequate structural containing measures for formalin emission.

APL's safety is an ever-growing concern, particularly regarding exposure to airborne FA *(Cipolla et al., 2017)*. In this regard, it is useful to mention the Technical Note issued by SIAPEC-IAP (Italian Society of Pathological Anatomy and Cytopathology diagnostics - Italian Division of IAP) concerning the possible measures aimed at minimizing the duration and the exposure level of formaldehyde operators in the APLs *(Cavallo, Cattaneo, Spinazzè, 2017)*. One crucial aspect is the ideal layout of APL spaces: a matter of debate, varying between different laboratories and pathologists' needs. Multiple design solutions exist around the general principles of an APL *(Suvarna, Layton, Bancroft, 2013)*. However, the dissection area must have good lighting, proper ventilation, washable non-absorbent surfaces, appropriate protective clothing for the laboratory personnel, gloves, and other equipment (photography, tissue macerators, disposal containers). The dissection room should be a comfortable environment that allows undisturbed work by the pathologist and technical support personnel. Since the range of specimens received in most laboratories is wide, the technical staff has to be familiar with the various requirements of the different samples. Pathologists spend long hours for the biopsies cut up, increasing their risk of FA occupational exposure *(Gürbüz et al., 2016, Fritzsche et al., 2012)*. Moreover, in daily practice, there are multiple possibilities of errors in the APL, with several impacts on patient care and prognosis *(Santana, de Lima Ferreira, 2018)*.

This review is directed to anatomic pathologists and occupational safety employees to minimize the FA occupational exposure, through an ergonomic and functional layout for the grossing pathology operations and the adoption of the safe practice supported by real-time, in-continuous FA monitoring.

MATERIAL AND METHODS

In May 2020, a computer-based scientific and non-scientific source research was performed on the following databases: PubMed, Web of Science, Google Scholar, and Google Patent. This research has been integrated with non-scientific sources, such as manufacturer datasheets and application notes. Concerning monitoring devices and APL workflow optimization tools, specific products and devices were selected, and each name of the commercially-available devices was entered into the previously-mentioned databases individually. The literature related to monitoring

direct-reading systems has resulted in being the amplest, probably due to the regulatory pressure of the past few years, which triggered the need to know the concentration values of airborne FA, before intervening with workflow optimization device.

RESULTS AND DISCUSSION

Occupational monitoring and occupational hygienist

The decision of the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Committee of reclassifying FA as a Category 1B carcinogen has relevant implications in terms of workplace health and safety management in European countries. Mainly, to better focusing protective measures and public health policies, the pinpoint of workers' groups at risk is crucial (REACH, 2016, available at http://echa.europa.eu/substance-information/-/substanceinfo/100.000.002) *(Scarselli et al., 2017, ECHA - European Chemicals Agency)*. Just a competent figure – someone with the "know-how", and practical experience necessary to assess the risks from work activities with hazardous compounds – can conduct air sampling *(Ahamad, Garreit, 1977)*. To this end, experts mus be present, having a definite grade of competence to carry out general supervision and to go on with judgment as appropriate. Such professionals are known as occupational/industrial hygienists *(Senn, 1991)*. For an accurate assessment of the occupational risk to support occupational hygienists, analysis laboratories, which can provide accurate and repeatable results, are necessary. These facilities can guarantee these benefits by participating in quality control programs.

Occupational/industrial hygienists accreditation

For years, there was a need to define requirements that could guarantee high and standardized professional figures operating in the sector, especially considering the importance of occupational hygienists for the health of workers in particular and of the population in general. Fifteen organizations have had their certification schemes recognized by the International Occupational Hygiene Association (IOHA) according to the requirements of the National occupational hygiene Accreditation Recognition (NAR) for stipulated the professional ethics required for occupational hygienists (https://www.ioha.net/ioha-activities/national-accreditation-recognition-nar/). More recently, the UNI EN 689:2018 standard also calls for the need to have an "appraiser", that is a person who is sufficiently trained and experienced about principles of occupational hygiene, work techniques, and measurement, to carry out the part of the assessment that they are leading according to state of the art. In Italy - in conformity with UNI CEI EN ISO/IEC 17024:2012 - the standard UNI 11711:2018 was published: here, the figure of the industrial hygienist is in no way superimposable even on the regulated professions, to whom the activities of exclusive competence remain in charge.

International organizations for research and development of air monitoring methods

Air monitoring is the quantitative or qualitative assessment of the extent of pollutants in or around the workplace, and it can be either periodic or continuous. When a risk assessment reveals that monitoring is required, workplace air sampling is mandatory. The primary purposes for air sampling are to guarantee compliance with legislation, determine exposure levels, and prove the efficiency of control actions; consequently, sampling should be part of a planned strategy founded on risk assessment *(Ramachandran, 2005)*. Air monitoring strategy should be done considering the most suitable approach in terms of costs and practicality. Monitoring strategies, commonly used to workplace exposure assessment, are often based on guidelines that are not harmonized: this creates ambiguities and inconsistencies. To overcome this shortcoming, the international standards are in development: they ensure that commonly used air monitoring have agreed-upon procedures in all their steps (sampling and analysis) *(Desauziers, 2004)*. To ensure suitability and harmonization between sampling strategy and analytical method is crucial to guarantee the reliability of the measurements. Measurement methods are available from many international organizations summarised in Table 1.

Table 1. List of international organizations for sampling and analytical standard method development

Tablica 1. Popis međunarodnih organizacija za uzorkovanje i razvoj standardnih analitičkih metoda

ASSOCIATION	STATE	OBJECTIVE
International Organization for Standardization (ISO)	Switzerland	International Standards (ISO standards) is an international nongovernmental organization made up of national standards bodies; it develops and publishes a wide range of standards.
European Committee for Standardization (CEN)	Belgium	European Standards (EN standards) are developed by the European Standardization Organizations. European Committee for Standardization (CEN) provides a platform for the development of European Standards (EN standards) and other technical documents in relation to various kinds of products, materials, services and processes.
German Research Foundation (DFG)	Germany	The Deutsche Forschungsgemeinschaft (DFG) is the central, independent research funding organization in Germany. It serves all branches of science and the humanities by funding research projects at universities and other research institutions.
Health and Safety Executive (HSE)	UK	Methods for the Determination of Hazardous Substances (MDHS) is a series published by HSE Books that describes procedures for the measurement of personal exposure to contaminants in air.
National Research and Safety Institute (INRS)	France	The French National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS) aims to contribute to the prevention of occupational diseases through a set of complementary actions. It conducts research in a variety of areas, offers training activities, develops information on occupational safety and health, and provides technical, legal, medical and documentary expertise.
National Institute for Occupational Safety And Health (NIOSH)	US	National Institute for Occupational Safety And Health (NIOSH) is a research agency focused on the study of worker safety and health, and empowering employers and workers to create safe and healthy workplaces. It develops or adapts methods for sampling and analysis of contaminants in workplace air, surfaces, and in the blood and urine of workers who are occupationally exposed.
Occupational Safety and Health Administration (OSHA)	US	Occupational Safety and Health Administration (OSHA) aims to ensure safe and healthful working conditions for working men and women by setting and enforcing standards and by providing training, outreach, education and assistance.
Environmental Protection Agency (EPA)	US	Environmental Protection Agency (EPA) offices and laboratories, and outside organizations, have developed approved methods for measuring the concentration of a substance or pollutant.
American Society for Testing and Materials (ASTM)	US	American Society for Testing and Materials (ASTM) is an international standards organization that develops and publishes voluntary consensus technical standards for a wide range of materials, products, systems, and services.
CSIR-National Environmental Engineering Research Institute (CSIR-NEERI)	India	The CSIR-National Environmental Engineering Research Institute (CSIR-NEERI) is a research institute that focuses on water supply, sewage disposal, communicable diseases and to some extent on industrial pollution and occupational diseases.
Japan Association for Working Environment Measurement (JAWE)	Japan	The Japan Association for Working Environment Measurement is a nonprofit organization that has the purpose of contributing to the improvement of measurement taking by experts work environment measuring, working environment measurement agencies and employers who perform working environment measurement using their own experts, and maintaining the dignity of working environment measurement experts.
Associazione per l'unificazione nel Settore dell'Industria Chimica (UNICHIM)	Italy	Associazione per l'unificazione nel Settore dell'Industria Chimica (UNICHIM) develops and provides interlaboratory proficiency tests and in the field of occupational hygiene and environmental monitoring.

Industrial Hygiene Proficiency Analytical Testing programs

Quality control entails two complementary processes: internal quality control (IQC) and external quality control (EQC), identified as proficiency testing (PT). IQC is composed by some procedures carried out by a laboratory to guarantee results consistency. It ensures that no significant variations of the factors influencing the result degree of uncertainty occurs over a defined period. Using independent standards and analyzing reference materials are examples of IQC. IQC processes are restricted to data obtained inside a laboratory and they may be characterized by a severe bias that could be not detected and, for this reason, must be performed in conjunction with EQC. This is mostly done by participating in an accredited PT scheme.

To monitor the quality of the services provided by a laboratory, taking part to an inter-laboratory comparison program is recommended. The goal of external-laboratory PT is then twofold: analytical method validation and laboratory performance assessment. PT's aim is to offer interested parties with objective evidence of a laboratory's ability to generate data that is both accurate and repeatable for the activities listed in its scope of accreditation. The laboratory's competence can be confirmed by favourable PT data. The standard ISO/IEC 17043/2010 imposed the necessity of test organizers accreditation in EU; it describes the criteria regarding the quality that need to be respected developing proficiency tests and the possible use of these tests by the accreditation bodies (ILAC-G13 (2007), and the ISO 13528 (2005)). In this respect, FA PT schemes are contained in the European Proficiency Testing Information System (www.eptis.bam.de) database, too.

Specifically to the important associations, the AIHA program with the Industrial Hygiene Proficiency Analytical Testing (IHPAT), the Health and Safety Laboratories of LGC Standards, the Institut national de recherche et de sécurité (INRS) with ALASCA (French acronym of Ability of Laboratories to Analyse Airborne Chemical Products) *(Langlois, Boulet, Kauffer, 2008)*, propose PT schemes for FA. Other research groups created frameworks by carrying out FA inter-laboratory exercises *(Huynh, Vu-Duc, 2002, Hafkenscheid, van Oosten, 2002)*.

Personal v/s area sampling

In Europe and the USA, to detect the sources of hazardous chemicals and to test the protection equipment's effectiveness, area monitoring is recommended. Consequently, it is programmed on rather fewer cases than personal exposure monitoring. This also happens because area monitoring is a less informative alternative to personal exposure monitoring.

Because personal exposure monitoring permits for continuous monitoring of workers' breathing area, it is more simple to follow worker movement and job variety. Depending on the risk and the situation, a reasonable risk evaluation and management can be conducted with flexibility, to establish whether or not to monitor, which monitoring method is required, and the time interval needed before re-monitoring *(Hashimoto et al., 2017)*. The procedure and the concept are very different for area sampling.

Some studies have been carried out so far on the correlation between the data of personal exposure monitoring and those of area sampling (personal v/s area sampling). It is usually reported that personal monitoring reveals higher concentrations respect to area sampling *(Ochs et al., 2012)*.

The accepted explanation is that, in personal exposure monitoring, the sampling provides air with a relatively chemicals high concentration due to the movement of workers. EN 689:2018 encourages the use of personal sampling devices within the breathing zone of the worker. EN 1540:2011 and ISO 18158:2016 specify that the breathing zone corresponds to a hemisphere (circa 30 cm in radius) extending out in front of the face, centered on the midpoint of a line running from ear to ear, with a plane connecting this line, the top of the head and the larynx.

However, some Authors *(Vimercati et al., 2010, Lee et al., 2017, Dugheri et al., Unpublished manuscript)* revealed similar FA median concentrations of the personal and area exposures, indicating that they were comparable - with an approximate ratio of 1.0 - when work processing no-requires continuous movement around the work area. Subsequently, Dugheri et al. *(Dugheri et al., Unpublished manuscript)* 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 within the breathing zone - placed in front of the fume cupboards-workstation; this device couples the in-continuous monitoring devices mounted on it with the advantages of an ergonomic workstation.

Real-time, in-continuous, commercial analyzers for FA air monitoring

The instantaneous measurement method refers to a simplified measuring of the airborne concentration of target substances on the spot, characterized by its capacity to obtain results within a short time. The experimental and field comparisons showed that direct-reading instruments performance are similar to reference methods *(Larsen, Jentoft, Greibrokk, 1992, Dugheri et al., 2018, Soo et al., 2018, Scherer et al., 2019, Dugheri et al., Unpublished manuscript)* and they can be easily integrated into an occupational hygiene plan to prevent significant acute and chronic toxicity. Handheld electrochemical sensor commercially available lack of specificity due to the high cross-sensitivities. However, to overcome this problem in airborne FA measurements, Formaldemeter (PPM Technology, UK) and Z-300 XP (Environmental Sensor Co, US), use an active filter to remove interferences (e.g., phenol and resorcinol), while New Cosmos Electric Co., Ltd (Japan) proposes XP-308B Formtector with DNPH impregnated filter to reduce the influence of other volatile organic compounds.

However, the specificity is also guaranteed by other real-time commercial analyzers, some of which can be considered instruments for confirmation level monitoring: infrared, photometric, differential optical absorption spectroscopy, cavity ring-down spectroscopy, fluorimetric, mass spectrometry techniques, and gas chromatographic separation coupled with methanisation oven and flame ionization detector show measurement uncertainty comparable to the official methods *(Dugheri et al., 2018) (Table 2)*.

The sampling rate and duration should enable to monitor airborne concentrations of FA up to approximately 1/10 of the occupational exposure limit. There are substantial differences among associations' guidelines concerning FA occupational exposure, not only in terms of the concentration value but also on which limit to assess *(Dugheri et al., In Press)*; however, due to its carcinogenicity, the modern approach to FA emissions management in occupational settings is to follow the ALARA (as low as reasonably achievable) principle *(Adamović, 2020)*, staying close to the ubiquitous value. In this context, the relationship between indoor and outdoor pollutants is important: specifically, the indoor FA concentrations reported in the literature are considerably higher than the outdoor ones *(Salthammer, 2013)*. So, for healthcare structures where FA values are quite low, outdoor sources of airborne FA pollution may be a potential threat to indoor air quality, and having an accurate reading of the background pollution is essential *(Dugheri et al., 2019)*.

In this new scenario, the new direct-reading FA monitoring system has been introduced to provide real-time sampling with sensitivity, allowing us to observe slight variations of FA concentration (0.001 ppm), also below ubiquitous value. Moreover, the introduction of remote control can further simplify and upgrade monitoring operations.

Table 2. List of commercially available direct reading instruments for formaldehyde determination

Tablica 2. Popis komercijalno dostupnih instrumenata za izravno očitavanje formaldehida

Monitoring Device Producer	Portable	Dimensions – Weight Price	Detection Mode Range [ppm] / Sampling Frequency
FP-330 RKI Instruments	✕	16x19.8x26.3 cm – 6.5 kg 2500-3500 €	Photometry 0.03-5 / 3-10-30 min
FM-801 GrayWolf Sensing Sol.	✓	16x19x6 cm – 300 g 2000-3000 €	Photometry <0.02-1 / 30 min
NEMo XT Ethera (France)	✕	19x13.5x7 cm – 520 g 5000-6000€	Photometry 0.001-2 / 60 min
Monitor AL4021 Aerolaser	✕	45x15x56 cm – 20 kg 45000-55000 €	Fluorimetry 0.001 / 90 sec
Formaldemeter™ htV-M PPM Technology	✓	15x8x3.5 cm – 300 g 500-1500 €	Electrochemical 0.01-10 / 2 min
FM200 Extech-FLIR Commercial sys.	✓	16x6x4 cm – 181.4 g 500-1500€	Electrochemical 0.01-5 / <2 sec
Z-300 XP Environmental Sensor Co.	✓	19x14.6x7 cm – 900 g 1500-2500 €	Electrochemical 0.01-30 / <60 sec
4000 Series Portable Analyzer Interscan Corporation	✓	17.8x10.2x25 cm – 2 kg 5500-6500 €	Electrochemical <0.005-2000 / <40-50 sec
XP-308B New Cosmos Electric Co.	✓	17.5x14x8.6 cm – 2.5 kg 500-1500 €	Electrochemical 0.01-30 / 10-30 min
GASERA ONE FORMALDEHYDE Gasera	✕	48x13x44 cm – 13 kg 80000-90000 €	Infrared Spectroscopy 0.001-10 / 60 sec
ProCeas ap2e	✕	42x23.6x5.5 cm – 20 kg 55000-65000 €	Infrared Spectroscopy 0.001-10 / <60 sec
G2307 Gas Concentration Analyzer Picarro Inc.	✕	43x18x45 cm – 21.3 kg 70000-80000 €	Cavity Ring-Down Spectroscopym 0-30 / 2-10 sec-5 min
VOICE200ultra - SIFT-MS Syft Technologies	✕	100x90x80 cm – 220 kg 295000-305000 €	Mass Spectrometry 0.007-4 / <2 sec
Airmo HCHO Chromatotec	✓	48.2x22.2x66 cm – 20 kg 30000-40000	Flame Ionization Detector 0.008-10 / 15-20-30 min
AtmosFIR: FTIR Protea	✕	44x45x22.2 cm – 18-20 kg -	Fourier Transform Infrared Spectroscopy 0-80 / 120 sec
MIRA (Middle-Infrared Laser Absorption) Ultra VOC Aeris Technologies Inc.	✓	36.8x30.5x17.8 cm – 6 kg -	MIRA Spectroscopy 0.001-500 / 1 sec
MIRA Pico VOC Aeris Technologies Inc.	✓	29.2x20.3x9.5 cm – 2.75 kg -	MIRA Spectroscopy 0.001-500 / 1 sec
PTR-TOF (Proton Transfer Reaction) 300 Ionicon Analytik	✓	56x61x53 cm – 80 kg 230000-250000 €	Quadrupole Mass Spectrometry <0.00005-10 / <1 sec
HALO 3 Tiger Optics, LLC	✕	22.2x21.8x59.9 cm – 15.4 kg -	Cavity Ring-Down Spectroscopy 0-40 / <3 min

Video Exposure Monitoring (VEM) in Occupational Hygiene

The conventional mode of monitoring, both by the direct and the indirect reading methods, presents issuess for the occupational hygienist because he/she is generally not capable to identify the work activity that has caused the high exposure reading. He/She may not be able to go back to what the worker was performing, during the surveys *(Cocca, Marciano, Alberti, 2016)*. Besides, the notes written during the whole monitoring may not be comprehensive and understandable, not enabling to identify the risky work task. Moreover, monitoring 2 or more workers at the same time can complicate the identification of high risk working activities: the occupational hygienist can't follow and monitor all workers at the same time *(Gray et al., 1992)*. The video exposure monitoring (VEM) consists of recording a video during working activities, while personal/area monitoring is performed by a direct-reading instrument. The video and the exposure data are then merged, synchronized, and analysed together. The occupational hygienist thanks to the VEM can detect any high level of exposure and notice when the excessive level occurred *(Beurskens-Comuth, Verbist, Brouwer, 2011)*.

In literature, VEM has been cited in the various forms and versions that are commercially available: Centrale d'Acquisition au Poste de Travail Informé par Vidéo (CAPTIV) *(Martin, Brand, Servais, 1999)*, Picture Mix Exposure Method (PIMEX) with different technical solutions (PIMEX-PC from the NIWL, Sweden, FINN-PIMEX from VTT, Finland and Exposure Video Visualisation-PIMEX from the Health and Safety Laboratory (HSL) in England) *(Hjortsberg, Karlsson, 1995)*, and Exposure Level Visualisation (ELVis) *(Walsh et al., 2009)*. One application of this technology was reported by Ryan et al. *(2003)*, who demonstrated the excessive laboratory FA exposure by VEM connected to a PID.

Workflow optimization

The adoption of new, reliable, airborne-FA monitoring methods and the implementation of safe practices in APL turned out to be a crucial aspect of increasing interest *(Mucci et al., 2019, Ogawa et al., 2019)*. Applying optimization measures to ensure safe formalin handling and use is essential for managing APL workflow. Specific, improved work practices, from an occupational hygiene point of view, significantly impact air pollution. Best practices for maintaining and engineering air handling and possibly redesigning processes and systems are needed to operate effectively, in line with the new safety regulations. In terms of body-friendly adjustments and streamlined workflow, attention to ergonomic design contributes to these best practices. Within this context, the adoption of ergonomic workstations represents technical mitigation for FA, reducing the emissions from the APL grossing room *(Suvarna, Layton, Bancroft, 2013)*. They have recently been introduced to the market and their effectiveness in mitigating FA emission is under investigation: its mitigation power can be related to their possible customization with digital imaging and dictaphone recording systems, the new generation of cassette printer, as well as safety devices to collect and to neutralize any residual draining and waste of formalin during the biopsies slicing. Moreover, introducing these kinds of technologies could lead to a standardization of anatomy pathology (AP) practices and workflows. Here below, the main features of the mitigation-optimization systems and monitor devices for FA are listed.

Grossing workstation for ergonomic layout and main ventilation system

The leading fume-hood cupboard manufacturers have recently improved their ductility, implementing their optional tools to obtain multitask-working stations, as done by Diapath (Italy) with the conventional, but customizable, fume-hood cupboard Zefiro. All potential operating features linked to standard workflow are within easy reach, while an ergonomic posture is maintained and, at the same time, safer management of formalin is guaranteed. However, the latest generation of grossing rooms present ergonomic workstations, which are different from those of conventional fume-hood cupboard: they are equipped with a laminar and/or back downdraft ventilation system and a working surface without front-glass, allowing wider freedom of movement and easier ergonomic stance. Recently, one of the most important innovations pursued and introduced in the development of modern grossing workstation

are high performance, cost-effective, digital optical console, capable of recording a high-quality image of the tissue specimens *(Chow et al., 2017)* (Figure 1).

Flexible and efficient modern workstation has recently been produced with several new features: modular architecture, connectivity by middleware with the APL's information systems, a digital pathology system (DPS) that records whole images of process specimens, and voice recognition technology (VRT) – dictaphone (Table 3).

These non-conventional workstations, simplify pathologists slicing of biopsies, offering an open work surface, nozzles for in-continuous washing with water, and personalized ergonomic modulation. Moreover, the possibility of customization allows for further lowering of FA emission by reducing the number of workflow actions required, that formerly have to be done outside of the workstation's area. The adoption of Formalin GL Elite Neutraliser Pad (CellPath Ltd, UK) on the slicing plane, as well as a patented FA neutralizer proposed by Zenon (Turkey), capable of converting the excess of formalin into non-hazardous polymers, could lead to the attenuation of the emission of harmful vapours.

Another fundamental aspect of mitigating FA exposure and protecting the operators' health in grossing rooms concerns the general ventilation system. Its engineering controls are mandatory: computer-based control system, the Building Management System (BMS), must be installed to control and monitor the building's mechanical and electrical equipment, such as its Heating, Ventilation, and Air Conditioning (HVAC), and to interface with the extraction system of the workstation. This centralized system allows the rapid identification and repair of technical failures. In Italy, the fume-hood 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 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 handling chemicals, with the acceptable limit values for containment and robustness of containment, face velocity, and air exchange efficiency.

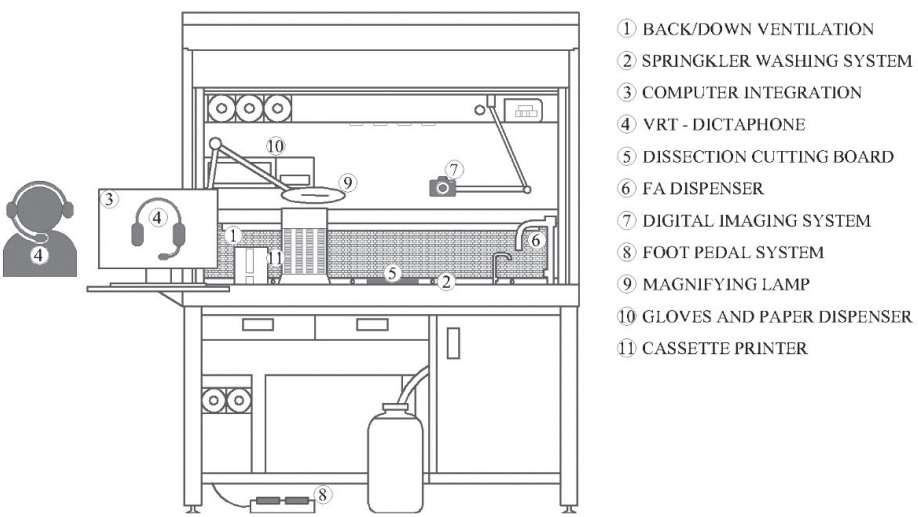

Figure 1. Schematic representation of new ergonomic grossing workstations and possible customization solutions
Slika 1. Shema novih ergonomskih radnih mjesta i mogućnost standardiziranih rješenja

Table 3. List of modern grossing workstations and their main features

Tablica 3. Popis modernih radnih mjesta i njihovih glavnih obilježja

Workstation – Producer	Ventilation B/D/V*	Springkler washing syst.	Computer integration	VRT** – Dictaphone	Dissection cutting board	FA dispenser	Digital Imaging system
AFOS – Afos Group (Kingston Upon Hull, UK)	D	✓	✓	×	✓	✓	×
Backdraft Premium (RBi Series) – Apzem Inc. (Chennai, India)	B	×	✓	×	✓	✓	✓
CT1BT – Propath Europe (Ronse, Belgium)	D	×	✓	×	✓	✓	✓
eGROSS – Milestone (Milan, Italy)	B/D	×	✓	×	✓	✓	✓
EMEC G515 – Emec Scientific (Selangor, Malaysia)	B/D	×	✓	✓	✓	✓	✓
GL100 – Mortech (Azusa, US)	B/D	×	✓	✓	✓	✓	✓
GP-1500 | ECO-line – Kugel Medical (Regensburg, Germany)	D	✓	✓	×	✓	✓	✓
MFPW-1800 – Medfuture Biotech Co., Ltd. (Jinan, China)	B	×	✓	✓	✓	✓	✓
M-GWS – Medimeas Instruments (Ambala, India)	B	✓	✓	✓	✓	✓	✓
Mopec Maestro – Mopec (Madison Heights, US)	B	✓	✓	✓	✓	✓	✓
PMT – PMT Scientific (Redford, US)	B	×	✓	×	✓	✓	✓
Shandon Gross-Star™ – Thermo Fisher Scientific (Waltham, US)	D	×	✓	✓	✓	✓	✓
Tissue-Tek® Accu-Edge® – Sakura Finetek (Torrance, US)	B	×	×	×	✓	✓	×
Zefiro – Diapath S.p.A. (Bergamo, Italy)	V	×	✓	✓	✓	✓	✓
Zenon – Zenon Diagnostic (Istanbul, Turkey)	B/D	×	✓	✓	✓	✓	✓
ZT HS 455 – UFSK International (Regensburg, Germany)	D	×	✓	✓	✓	✓	✓

Dictaphone recording systems

Since the 1980s, Voice Recognition Technology (VRT) for medical transcription has been available, although it was not tailored for broad use by doctors, until more recently. VRT has been successfully applied in many disciplines, particularly in radiology. There are some studies that compares it with transcriptionists in various medical activities and specialties, with different results concerning turnaround time *(Singh, Pal, 2011)*. This technology has several benefits in the grossing room of APL: they lead to marked time reduction for specimen slicing and drastic lowering transcription errors *(Kang et al., 2010)*. Moreover, the introduction of VRT could avoid the technician's dictation, removing his/her undue FA exposure.

The overall VRT market is estimated to reach USD 21.5 billion by 2024 from USD 7.5 billion in 2018, at a Compound Annual Growth Rate (CAGR) of 19.18% and is ascribed to the growth potential in healthcare field. Microsoft (US), Alphabet (US), IBM (US), Amazon (US), Sensory (US), Cantab Research (UK), iflytek (China), Baidu (China), Raytheon BBN Technologies (US), and Nuance (US), are some of the major companies in the VRT market. In the healthcare sector, the focus of these companies is to provide solutions to manage clinical documentations, investing in cloud-based products and operations, entering new markets such as ambulatory care, and expanding global capabilities. In May 2018, Nuance released the cloud-based speech recognition platform, Dragon Medical One *(Kang et al., 2010)*. Moreover, Nuance and IBM, to improve and increase innovative speech solutions aimed to better serve customers, have subscribed a licensing and technical services agreement *(Markets and Markets, 2019)*. However, healthcare companies recently increase their offer of VRT. These new systems can be dedicated for specific workstation or can also be universal: VoiceOver PRO by Voicebrook (US), Fusion Narrate by Digital Voice Systems (US), and HistoCyto by Technidata (France) are software application, that incorporates speech recognition, digital dictation, and several input devices, providing direct integration with the AP system.

Digital pathology system

The use of information technology as a diagnostic tool, and specifically digital pathology system (DPS), is on the rise in APLs *(Park et al., 2013)*. Digital imaging in pathology is defined as the storage of visual information of anatomical pathology in an electronic format and is one of the most commonly used computer tools *(Gabril, Yousef, 2010)*. The first integration of gross pathology digital images into picture archive and communications system (PACS) was achieved by Amin et al. *(Amin et al., 2012)*. They were able to automatically stream nearly 27,000 gross images from APL information systems to their PACS corporate image server in 2012, with a low failure rate (0.5%), those of which had to be manually entered into PACS *(Amin et al., 2012)*.

Cloud-based DPSs help organizations to reduce capital expense (CAPEX) and operating expense (OPEX), enabling the achievement of a considerable level of efficiency at a minimum cost *(Guo et al., 2016)*.

DPS that are commercially-available, like PATHpix™ (Virtus Imaging, US), PathStation hood (SPOT Imaging, US), PAXcamHD (MIS Worldwide Headquarters, US), could be installed inside the grossing station or over a grossing bench and are composed by a high-resolution scientific cameras, motorized zoom lens, autofocus/exposure system, automatic and manually compensation of exposure, gain, white balance system, and user-friendly software interface, and enable laboratory information system (LIS) integration. These devices can be controlled through a foot pedal system, allowing hands-free operation, like capturing images/videos, and the switching between pre-set configurations (e.g., zoom, exposure, fields of view). The modern software, coupled with these DPS, enables capturing images into a database archive, with touch mark-up tools, reporting tools. The operator can draw lines, boxes, and circles on the image manually or with pre-sets, add pre-formatted text phrases, and a calibrated scale bar or multiple scale bars.

As a result, pathologists and technicians can easily capture and share remote consultation videos and snapshots, annotate, and measure gross specimens. These systems provide savings for the organization and the physician by eliminating unreimbursed secondary procedures and increasing patient satisfaction. The consistent documentation of the work activities represents an enhancement for quality assurance.

Cassette printer

To minimize the operation out of the protective area created by fume-hood cupboards/working-station aspiration systems, APLs are asking for smaller, faster, robotic cassette printers that can fit into the grossing station for high throughput and optimized workflow (batch job printing, approximately 10-15 cassettes/minute). Furthermore, printing at the point of use has been proven to reduce the number of labeling errors within the laboratory. The on-demand cassette printer has been optimized and validated for black or colour printing, creating a turn-key system for the best printing results. The introduction of these printers could lead to a reduction of FA emissions due to the lowering of the operators' movements, which could break the protective flow of fume hood cupboards/working-station. The modern printers and their features are showed in Table 4.

Table 4. Modern benchtop printers and their main characteristics

Tablica 4. Moderni 'benchtop' štampači i njihova glavna obilježja

PRODUCT NAME (PRODUCER)	DIMENSIONS SPEED MAX RESOLUTION	COLOR PRINT	IN SERIES	AUTOLOADER
APCP02 AP Itineris Cassette Printer (Diapath S.p.A.) 	31x66x49 cm 12 cassettes/min 300 dpi	✓	✓	×*
LaserTrack AB1 Laser Cassette Printer (General Data) 	25.4x45.72x63.5 cm 12 cassettes/min 200 lpi	×	✓	✓
Leica LP C Cassette Printer (Leica Biosystems) 	25.4x45.7x63.5 cm 12 cassettes/min 200 lpi	×	✓	✓
Signature Cassette Printer (Primera Technology, Inc.) 	30.5x49x65.8 cm 8 casettes/min 300 dpi	✓	✓	✓
Tissue-Tek SmartWrite Cassette Printer (Sakura Finetek) 	35.5x49x65.8 cm 8 cassettes/min 300 dpi	✓	✓	✓
PrintMate AS 900 Cassette Printer (Thermo Fisher Scientific) 	38x43.5x81 cm 8 cassettes/min -	×	✓	✓
VCPA 5001 Automatic cassette printer (Vogel) 	54x35x53 cm 15 cassettes/min 72 dpi	×	✓	✓

CONCLUSIONS

This review aims to focus on current APL work practice optimization and show new implementations to monitor and reduce airborne FA. Specifically, easy-to-use approaches were shown to improve formalin safety compliance with adopted limit values. These technologies and tools, summarized in the text, could help the preventive health professionals in the occupational risk assessment. The occupational hygienist role, thanks to his/her education, experience, and knowledge, results in the crucial figure to pursue an accurate assessment of the job-related exposure, especially in APL, where the wide use of FA represents a high risk for the workers. A skilled occupational hygienist can provide information about the latest technologies to mitigate risk and coordinate environmental/personal monitoring. To evaluate occupational exposure and the goodness of newly implemented technical changes, the approach, foreseen by the modern occupational hygienist, requires repeated exposure assessment, carried out with suitable modern devices, and following standardized methods.

The future perspective is to increase the knowledge and the implementation of the FA emission mitigating tools between preventive health professionals and employers; at the same time, these innovations must be understood and embraced by workers. Thus, with these innovations, aspiring to a safer workplace and improved work conditions are possible.

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SIGURNOST RADA U ANATOMSKOM LABORATORIJU S FORMALINOM I INOVATIVNO PRAĆENJE PROCJENE PROFESIONALNE IZLOŽENOSTI FORMALDEHIDU

SAŽETAK: Ovaj pregled usmjeren je na preventivne zdravstvene radnike, anatomske patologe i tehničare kako bi svoju pozornost usredotočili na brzo rastuće područje sigurnih formalinskih praksi. Ažurirani pregled nudi najnovija poboljšanja preventivnih mjera u odnosu na formaldehid (FA) u laboratorijima za anatomsku patologiju (APL). Opisana je uloga higijeničara na radu i potrebna znanja za modernu i jasnu procjenu izloženosti na radu. Komercijalni analizatori u stvarnom vremenu za kontinuiranu procjenu izloženosti FA razmatraju se za procjenu tehničkih promjena u programima praćenja zraka, uvedenim radi ublažavanja emisija FA, u skladu s prihvaćenim graničnim vrijednostima. Kako bi se bolje odabrala odgovarajuća instrumentacija, navedene su glavne značajke svakog instrumenta za praćenje FA koji je nedavno predstavljen na tržištu. Štoviše, sažete su glavne značajke suvremenih postavki tijeka rada u APL-u. Računalno zasnovano pretraživanje znanstvenih i neznanstvenih izvješća po ključnim riječima provedeno je u bazama podataka PubMed, Web of Science, Google Scholar i Google Patents, s težištem na sljedeće teme: i) prikupljanje radnih stanica za ergonomski raspored, ii) komercijalno dostupni alati za izravno očitanje mjerenja formalina, iii) instrumenti za kontinuirano praćenje FA u stvarnom vremenu u prodaji. Ovaj pregled predstavlja koristan alat za sažimanje tehničkih zahtjeva i stručnog znanja potrebnog za minimiziranje emisija FA i izradu iscrpne procjene FA u APL-u.

Ključne riječi: *formaldehid, procjena izloženosti, profesionalno praćenje, anatomska patologija, formalin*

Pregledni rad
Primljeno: 28.9.2020.
Prihvaćeno: 1.3.2021.