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STRATEGY TO MONITOR AND EVALUATE THE IMPACT OF FORMALDEHYDE IN ANATOMICAL PATHOLOGY LABORATORY – PART I: OCCUPATIONAL EXPOSURE AND CANCER RISK ASSESSMENT

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SUMMARY: Formaldehyde (FA) is a chemical compound commonly used in anatomical pathology laboratories as a tissue preservative, and it is common and epidemiologically related to cancer. Therefore, the personnel resident in the anatomical pathology laboratories is among the workers most exposed to FA and its related cancer and non-cancerogenic risk. Thus, risk assessment, cancerogenic and non-cancerogenic, and a careful occupational exposure assessment are recommended. In this study, FA was monitored in an Italian anatomical pathology laboratory to perform an occupational exposure assessment, according to the UNI EN 689:219, and to determine the Hazard Quotient (HQ) and the Lifetime Cancer Hazard Risk (LCHR) for carcinogenic and non-carcinogenic risk assessment, respectively. The exposure observed for pathologists and technicians is lower than the EU Occupational exposure limit mandatory (0.62 mg/m^3), and both group of workers are in Compliance with it. Nevertheless, concerning the risk assessment, both the HQs and the LCHRs resulted in being higher (1.3 and 1.6 HQ and 3.2x10^{-5} and 3.9x10^{-5}, for pathologists and technicians, respectively) than the ones observed in similar scenarios. This study shows how the exposure assessment to FA could face striving situations in terms of workers' health safeguard, due to the differences among occupational limits recommended and the high health risks, especially in the healthcare field.

Key words: *formaldehyde, health risk assessment, occupational exposure*

INTRODUCTION

Formaldehyde (FA) is a ubiquitous environmental chemical classified as a human carcinogen by the International Agency for Research on Cancer (IARC) (Group 1), the American Conference of Governmental Industrial Hygienists (ACGIH) (Category A1), and presumed human carcinogen (Category 1B) from Classification, Labelling and Packaging (CLP) of the European Union (EU) *(Protano et al., 2022)*. The Integrated Risk Information System (IRIS) program of the United States (US) Environmental Protection Agency (EPA) released a review in April 2022 referring to evidence that inhalation of FA causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia in humans. The World Health Organization (WHO) has accepted a limit of 0.08 ppm of FA to prevent nasal cancers and showed that nasopharyngeal cancer in humans had not been observed by FA exposure below 1.02 ppm *(Nielsen et al., 2017)*. In addition, a No-Observed

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Adverse Effect Level (NOAEL) value of 2 ppm was confirmed for respiratory tract carcinogenicity in animal studies *(Nielsen et al., 2017)* FA chronic exposure can also result in the onset of other illnesses, and pathological effects, such as headaches, dizziness, sleep disorders, memory loss, pulmonary function damage, pancytopenia, and possible menstrual disorders of adult females *(Tang et al., 2009)*.

The number of European workers exposed to FA above the ubiquitous level (1.5-16.4 μg/m^3) is 1.7 million *(Scarselli et al., 2017)*. The most exposed workers are in chemical and plastics factories; however, the highest mean levels of airborne FA exposure have been recorded in the healthcare sector *(Vimercati et al., 2010, Dugheri et al., 2018)*. In this field, FA is widely used in pathology or histology departments and autopsy rooms. It is used for sterilizing and as a preservative (formalin) or dehydrating agent during mixture preparation, tissue processing, and staining *(Yahyaei et al., 2020)*. In anatomy laboratories, FA exposure might occur by direct contact with the eyes or skin, and inhalation is the dominant source of exposure. The inhalation exposure is due to the high volatility of FA (Henry's Law = 2.6E-6 atm-m^3/mol); *(United State Environmental Protection Agency, 2022)* and its immediate proximity to the breathing zone of the operator in the working processes *(Adamović et al., 2021)*, leading to several occupational health risk problems in the healthcare sector *(Scarselli et al., 2017)*. Thus, the Risk Assessment (RA) of occupational exposure to FA is an essential step in chemical monitoring *(Yahyaei et al., 2020)*.

RA can be defined as the estimation of adverse effects on human health associated with exposure to environmental chemical agents *(Dugheri et al., 2022)*. Potential health risks, such as cancer and non-cancer risks, can be evaluated using different methods adopted by international Agencies *(Cruz et al., 2020)*.

RA may be done as a relatively rapid 'desktop' study or 'screening' study for simple issues or might be a large and complex process where there are significant health concerns. The ECHA recommends that chemical exposure could also be calculated using exposure models and that parameters used to calculate the Exposure Scenario (ES) should be communicated in extended-Safety Data Sheets (e-SDS) as workplace instructions. Several studies have focused on the validity *(Landberg et al., 2017, Spinazze et al., 2017)* and the reliability of the recommended exposure models *(Landberg et al., 2015, Lamb et al., 2017, Spinazzè et al., 2019)*. Currently, Tier 1 (European Centre for Ecotoxicology and Toxicology of Chemicals'); *(Hutchinson et al., 2000)*, EMKGExpo-Tool *(Lee et al., 2019)* Tier 1.5 *(Koivisto et al., 2022)*, and Tier 2 *(Koivisto et al., 2022)* models have been developed and are widely used to predict occupational exposure for solids, liquids, and dusts to cover the exposure situations in many European countries *(Lee et al., 2018)*. Under REACH, Tier 1 screening models are used to identify the exposure situations and provide rough estimates of occupational inhalation exposures in each situation. Still, some Tier 1 models do not always produce sufficiently conservative assessment outcomes *(Landberg et al., 2017, van Tongeren et al., 2017)*. Between-user variability was high, thus resulting in inconsistencies in the modelling outcomes of multiple users, which differed by several orders of magnitude when either Tier 1 or 2 tools were used for the same exposure scenarios *(Lee et al., 2018)*. Debate continues about the accuracy of these models and when they should be used to assess chemical exposure *(Fransman, 2017)*.

The Globally Harmonised System (GHS) for classification and labeling of chemicals is the United Nations system to identify hazardous chemicals, inform users about these hazards, and support the RA. In September 2020, the Final Scope of the Risk Evaluation for FA published by US EPA *(United State Environmental Protection Agency, 2020)* identified FA as one of 20 high-priority chemicals for Toxic Substances Control Act (TSCA), and its use such as one that requires the definitions of the Conditions of Use (CoU), that will be determined for the human health risk evaluation *(Sherman et al., 2022)*. Among the purposes of the US EPA and its TSCA Risk Evaluations, there is also the managing of the workplace environment, overlapping their recommendations with the responsibilities and the mandatory requirements of the regulatory agency for occupational safety, such as the Occupational Safety and Health Administration (OSHA) in the US.

The same scenario can be observed in Europe, where since 2016, the operations of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and CLP Legislations have promoted and pursued the protection of both worker and consumer health and the environment *(Reach and CLP, 2021)*.

In 2016, the EU started a review phase of its legislation to update the Occupational Exposure Limit Values (OEL) – as Indicative Occupational Exposure Limit Values (IOELVs) and Binding Occupational Exposure Limit Values (BOELVs) – and defined the Derived No Effects Levels (DNEL) to achieve the same level of health protection for the workers in all Member States *(European Agency for Safety and Health Work, 2018, Senior Labour Inspector's Committee- European Commission, 2015)*.

Classifications and DNEL are essential information for generating safety advice; moreover, the registrants of the Member States have determined the safe operating conditions and the risk management for each identified substance use, based on exposure estimates and risk characterisation and using harmonised criteria. DNELs are often, but not always, lower than OELs established by the EU or national level. This is due largely to the difference in aim and methodologies and may be to the updated scientific information available. The method for deriving DNELs differs from the process used by the Scientific Committee on Occupational Exposure Limit Values (SCOEL) establishing the OELs: the first ones are derived by the registrant of the Member States using the tool provided by the European Chemicals Agency (ECHA), whereas the OEL relies on expert judgment. It is worthy of note that these limit values for occupational exposure have been published based on the NOAEL approach using animal studies *(Davis et al., 2011, Ringblom et al., 2014)* and fewer studies reported standards according to human exposure *(Zendehdel et al., 2018)*.

In 2013, FA was included in the Community Rolling Action Plan (CoRAP) under REACH because of its Carcinogenic Mutagenic and Toxic for Reproduction (CMR) properties, and EU has adopted - based on two key studies *(Lang et al., 2008, Mueller et al., 2013)* - 8-hours' Time Weighted Average (TWA)-BOELV (0.3 ppm) and 0.6 ppm as 15-minutes Short-Term Exposure Limit (STEL). However, Directive 2019/983 of 5th June 2019 introduced a transitional period of 5 years for the healthcare sector, during which the FA limit value of 0.5 ppm for 8-hours exposure would apply. For workers, DNEL for long-term inhalation exposure was proposed to be 0.369 mg/m^3 and for short-term DNEL to 0.74 mg/m^3 *(European Chemical Agency, 2019)*. Several Member States of the EU have already set national OELs for FA. These OELs are slightly different across European countries also because of the legal and advisory framework, which affects the way the limit is interpreted and applied.

Thus, there are substantial differences among associations' guidelines concerning FA occupational exposure, not only in terms of concentrations but also regarding which values to assess, resulting in a striving definition of safety workplace with minimized risk of FA exposure (Figure 1).

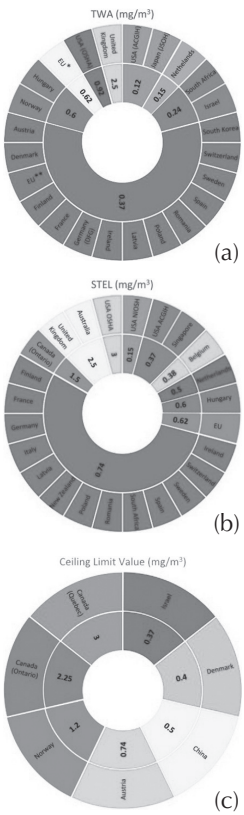

Figure 1. Graphical representation of the heterogeneity of occupational exposure limits (mg/m^3) for formaldehyde: a) Time Weighted Average, b) Short-Time Exposure Limit, c) Ceiling Limit Value

Slika 1. Grafički prikaz heterogenosti granica profesionalne izloženosti (mg/m^3) za formaldehid: a) vremenski ponderirani prosjek, b) granica kratkotrajne izloženosti, c) gornja granična vrijednost

For example, the American National Institute for Occupational Safety and Health (NIOSH) recommends exposure limits as 8-hours TWA (0.016 ppm) and 15-min STEL (0.1 ppm), which are significantly lower than the workplace exposure limits indicated by the OSHA, the U.S. governmental institution (0.75 ppm for the Permissible Exposure Limit-PEL 8-hours TWA and 2 ppm as STEL), and UK's Health and Safety Executive (2 ppm for 15-minutes STEL). In contrast, the People's Republic of China, New Zealand, Israel, Canada-Quebec, and Canada-Ontario indicate FA occupational exposure limits in terms of a Ceiling (C). Similarly, the ACGIH, for many years, adopted a threshold limit value (TLV)-C (0.3 ppm). In 2016, the ACGIH proposed a TWA-TLV (8-hours) for FA of 0.1 ppm, and a STEL (15-min) of 0.3 ppm *(American Chemistry Council (ACC), 2016)*. NIOSH's Immediately Dangerous to Life or Health is 20 ppm for FA. In EU there are not unified legal limit values, but the policy-agency of each country establishes its limits (Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA)-Deutsche Gesetzlich Unfallversicherung (DGUV)). However, it is recommended to follow the OEL indications *(European Chemicals Agency, 2019)* even though these values are only suggested guidelines, while OSHA - the US governmental institution - established the permissible exposure limit as mandatory. In Italy, in some cases, the limits recommended by ACGIH are adopted by the industrial hygiene organization and surveyors when no national limits are adopted by law.

Several strategies have been proposed to assess the results of occupational monitoring relating to the occupational limit values and also, to define how and when acting to control the exposure and linked hazard: the NIOSH proposed a decision scheme, frequently used as Occupational Exposure Sampling Strategy and in several OSHA health standards *(Tuggle, 1981)*; an alternative evolution of these scheme was subsequently proposed, also by NIOSH, based on the one-sided tolerance limits *(Tuggle, 1982)*. In Europe, to harmonize the methods to assess compliance with occupational limit values for exposures to airborne substances in workplaces, the European standard UNI EN 689 was developed in 1995 and updated in 2018 *(European Committee for Standardization, 2019)*. The compliance assessment of workers' exposures is performed for Similarly Exposed Groups (SEGs) by applying several standardized tests. The exposure assessment must be based on quantitative evaluations of employees' potential exposures.

Because of the lack of validated occupational exposure biomarkers for FA, one effective way to assess occupational exposure to FA is by air monitoring *(Chiarella et al., 2016, Motta et al., 2021)*. The current validated methods for detecting gaseous FA are based on sampling it using 2,4-dinitrophenylhydrazine (DNPH) as the derivatizing reagent. The analyses are carried out by liquid chromatography (LC) or gas chromatography (GC) *(Dugheri et al., 2021)*. Portable direct-reading FA monitors are of increased interest, laying the bases for on-site analyses as confirmation-level methods to simplify both the sampling process and the analytic operations. They are characterized by high specificity, like conventional monitoring methods, and can be easily integrated into an occupational hygiene plan, mainly to prevent significant acute toxicity *(Hirst et al., 2011, Dugheri et al., 2020, 2021)*.

Substantially, the monitoring required in occupational hygiene is compliance monitoring to define occupational exposure limit focused on identifying and promptly reducing individual exposures. However, acting in the same scenario, the TSCA Risk Evaluation and ECHA-RAC seeks to characterize all workplace exposures, including workers who do not handle the chemical but are in a workplace where the chemical is present (Figure 2). The potential overlay of the recommendations, evaluations, and relative corrective actions between general risk management agencies, such as US EPA and ECHA, and occupational/industrial hygiene's authority, such as NIOSH, could represent new challenges for industrial hygienists, exposure/risk assessors, and risk managers.

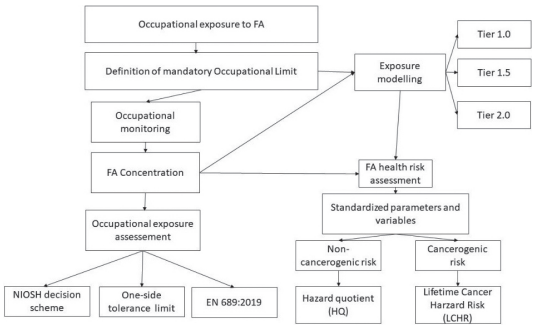

Figure 2. Risk and occupational exposure assessment strategies for FA exposure

Slika 2. Strategije procjene rizika i profesionalne izloženosti FA

In this research, FA occupational exposure monitoring and FA-related RA in the Anatomy Department of an Italian Hospital has been conducted. The occupational exposure evaluation has been carried out by a conventional air sampling campaign according to EN 689:2019, while the evaluation of FA-related cancer and non-cancer risks has been done using different approaches adopted by international Agencies. This study aims to analyse the possible implications and challenges linked to the overlapping between the occupational exposure evaluation and the RA, to prioritize the related recommendations and corrective actions, potentially.

MATERIALS AND METHODS

Sampling site, sample collection, and chemical analysis

This study was conducted in January 2022 at the General Hospital of Macerata (Macerata, Italy). The data were collected in the anatomical pathology laboratory, especially in the gross room, where residents, pathologists, and trained technicians examine and dissect tissue specimens. Data about the working conditions (working time, FA exposure frequency, working period, personal protective equipment use, occupational health training) were collected. The operators were grouped according to their exposure to FA, in two SEG, technicians and pathologists, respectively. All the workers enrolled in the study are women.

Collection of the air samples for FA was conducted based on UNI EN 1540:2022 and UNI EN 689:2019. Personal active air sampling was performed by Sep-Pak XpoSure Aldehyde Sampler Plus Short DNPH-coated cartridges on a silica sorbent attached to GilAir Plus pumps, equipped with Gilian CONNECT software at 0.3 L/min 8-h. The collected samples were then analyzed by a Varian CP-3800 Gas Chromatograph coupled with a Varian Saturn Ion-trap 2200 Mass Spectrometer (MS). The sampling and analytical methods details are reported in our previous study *(Dugheri et al., 2017, 2019, 2021)*.

Occupational exposure assessment: UNI EN 689:2019

The UNI EN 689:2019 gives a strategy for testing compliance with limit values in occupational exposure, measuring exposure to chemical agents by inhalation. It recommends a procedure to perform a small number of exposure measurements to demonstrate with a high degree of confidence that workers are not likely to be exposed to concentrations higher than the limit values, considering the variability of exposures.

According to this recommendation, 5 working shifts in the grossing room were sampled. The 20 samples obtained for pathology technicians and doctors have been used to carry out the statistical analysis, according to the UNI EN 689:2019, to demonstrate whether less than 5% of exposures in the SEG exceed the limit values (compliance); *(European Committee for Standardization, 2019)*. The compliance condition occurs when the parameter UR, calculated as a function of the mean and standard deviation of the data collected and the limit value, is found to be greater than the value of UT, tabulated according to the number of samples. The statistical analysis can be applied if more than six samples have been collected, and a normal or a log-normal regression can approximate the data trend.

The occupational exposure limit used in the study is the one proposed by the ACGIH Panel, supported by the EU Directive 2019/983 of 5th June 2019, which set a limit of 0.620 mg/m^3 for eight hours for healthcare, funeral, and embalming sectors. This five-year transitional limit will be set at 0.370 mg/m^3 the 11th July 2024. In addition, the UNI EN 689:2019 analysis was carried out also with the OSHA limit of 0.925 mg/m^3 and the current mandatory limit of ACGIH of 0.120 mg/m^3.

Hazard Quotient (HQ) and Lifetime Cancer Risk (LCR)

The definition of the chronic non-carcinogenic levels to use in comparison with the respective pollutant concentrations observed in the studied environments is required to perform the non-carcinogenic health RA *(Cruz et al., 2020, Rodricks, 2006, Huang et al., 2013)*. These levels are proposed by several governmental and non-governmental organizations and are reported in Table 1. To carry out the RA in this study, the Reference Concentration (RfC) (7 μg/m^3) of the IRIS (US EPA) was used.

The Hazard Quotient (HQ) for non-carcinogenic risk and the Lifetime Cancer Hazard Risk (LCHR) are used to estimate the health risk of workers exposed to FA, following the standard method of the US Environmental Protection Agency (EPA) *(U.S. Environmental Protection Agency (USEPA), 2011).*

These RA indicators imply many factors related to exposure, such as frequency and duration, inhalation rate, body weight, the average lifetime of the population, and concentration of the pollutants. Some of these parameters are standardized and are shown in Table 2.

Table 1. List of the chronic and acute non-carcinogenic levels for formaldehyde proposed by several international organizations

Tablica 1. Popis kroničnih i akutnih nekancerogenih razina formaldehida koje je predložilo nekoliko međunarodnih organizacija

Parameter	Description	Authority	Value
MRLsFA	Chronic inhalation non-cancer	Agency for Toxic Substance and Disease Register (ATSDR)	10 μg/m^3
$nHBV_{Acute}$	Minimum Risk Levels	Minnesota Department of Health (MDH)	50 μg/m^3
$nHBV_{Chronic}$	Acute Non-cancer		9 μg/m^3
$RELs_{Acute}$	Health Based Value	California Office Environmental Health Hazard Assessment (OEHHA)	55 μg/m^3
$RELs_{Chronic}$	Chronic Non-cancer		9 μg/m^3
$RfCs_{Acute}$	Health Based Value	IRIS of U.S. Environmental Protection Agency (USEPA)	100 μg/m^3
$RfCs_{Acute}$	Acute non-cancerogenic inhalation Reference Concentrations	Chinese National Indoor Air Quality Standard	
$RfC_{Chronic}$	Chronic non-cancerogenic inhalation Reference Concentrations	IRIS of U.S. Environmental Protection Agency (USEPA)	7 μg/m^3
$ESLs_{long}$	Reference Concentrations	Texas Commission on Environmental Quality (TCEQ)	3.3-18.5 μg/m^3
ESL_{short}	Reference Concentrations		4.9-14.8 μg/m^3
EL	Reference Concentrations	European Commission Directorate General Joint Research Centre	1 μg/m^3

Table 2. Standardized parameters for the determination of Hazard Quotient and Lifetime Cancer Hazard Risk

Tablica 2. Standardizirani parametri za određivanje kvocijenta rizika i doživotnog rizika od raka

Description	Parameter	Value	Unit
Exposure Concentration	C	---	mg/m^3
Inhalation Rate Adult	IR	1.02	m^3/h
Exposure Duration Adult	ED	8	h/day
Exposure Frequency	EF	48	week/year
Length Exposure	L	30	year
Average Lifetime	ATL	82.3	year
Body Weight	BW	70 woman - 80 man	kg
Number Of Days Per Year	NY	285	day
Days Of Work Per Week	D	6	day
Slope Factor	SFFA	0.0455	mg/kg·day
Reference Concentrations	RfCsFA	0.007	mg/m^3

For the estimation of the HQ, the doses in the period of exposure, expressed as chronic daily intake (CDI) and chronic daily intake yearly (CDIY), were calculated according to the following Equations:

$$CDI = \frac{C \times IR \times ED}{BW} \quad [1]$$

$$CDI_y = CDI \times \frac{D}{7} \times \frac{EF}{52} \quad [2]$$

where C is the exposure concentration, IR is the inhalation rate (4.8 m^3/h for men and 2.9 m^3/h for women who work under a heavy-duty or, alternatively, 1.02 m^3/h (average inhalation) *(U.S. Environmental Protection Agency (USEPA), 2011)*, ED is the duration of the exposure, BW is the body weight, D the days of works and EF is the exposure frequency.

The ratio between the CDIy and the RfC is used to estimate the HQ by the equation:

$$HQ = \frac{CDI_y}{RfC} \quad [3]$$

where RfC is the concentration below the one the adverse health effects are unlikely to occur.

Values of HQ ≤ 1 indicate a non-relevant risk, while values > 1 potentially correspond to adverse health effects *(Cruz et al., 2020, U. S. Environmental Protection Agency (USEPA), 2016)*.

Concerning the risk estimation with a cancer endpoint, expressed in terms of the probability of developing cancer from a lifetime of continuous exposure to chemical substances, the LCHR indicator is used. It represents the highest probability of cancer incidence by continuous lifetime exposure to a specific chemical, and it is estimated using the Chronic Daily Intake Lifetime (CDIL), obtained by the following equation:

$$CDI = \frac{C \times IR \times ED \times EF \times L}{BW \times ATL \times NY} \quad [4]$$

where L is the exposure length, ATL is the average lifetime, and NY is the days per years of exposure.

The LCHR is obtained by the multiplication between the CDIL and the cancer potency factor in a unit (mg/kg/day) of FA (Slope Factor-SF, equal to 0.0455 mg/kg/day for FA) *(U.S. Environmental Protection Agency, 2022)*:

$$LCHR = CDIL \times SF \quad [5]$$

where LCHR is considered by US EPA below the level of concern when below 1 in a million ($<1 \times 10^{-6}$), while a risk value above 100 in a million ($>1 \times 10^{-4}$) signifies an immediate need to initiate interventions to protect human health *(Adamović et al., 2021, Lee et al., 2006, Ho et al., 2013)*. Generally, US EPA uses the 1 in 10,000 to 1 in 1,000,000 risk range as a target range within which the agency strives to manage risk; the 1 in 10,000 risk level is considered an appropriate cut-off level for decisions on whether risk management action is required at a site.

RESULTS AND DISCUSSION

Air monitoring results and occupational exposure assessment

The results obtained by the air monitoring of the pathologist and technicians are reported in Table 3.

Table 3. Results of occupational monitoring and related occupational exposure assessment, according to the UNI EN 689:2019

Tablica 3. Rezultati nadzora na radu i povezane procjene profesionalne izloženosti, prema UNI EN 689:2019

Operator	N°	FA Average (mg/m^3)	FA Range (mg/m^3)		UNI EN 689:2019 OEL 8-h EU: 0.620 mg/m^3	UNI EN 689:2019 OEL 8-h EU: 0.370 mg/m^3	UNI EN 689:2019 PEL 8-h OSHA: 0.925 mg/m^3	UNI EN 689:2019 ACGIH TWA: 0.120 mg/m^3
			min	max				
Pathologist	20	0.10	0.01	0.28	compliance	compliance	compliance	non compliance
Technician	20	0.12	0.02	0.29	compliance	compliance	compliance	non compliance

Both the monitored populations were exposed to FA during the work shift: the pathologists were exposed to an average concentration of airborne FA equal to 0.10 mg/m^3, while the technicians to an average concentration equal to 0.12 mg/m^3. The values observed are in line with the operational scenario of the gross room: the operators, both pathologist and technicians, are engaged in the sectioning of tissue samples (in a fume hood with a foot pedal for formalin control), and the tissue samples are inserted in pre-filled containers with 4% FA encapsulated in the lid.

The analysis of the data according to UNI EN 689:2019 showed that for both the SEGs, the occupational scenario complies with the chosen limit values of 0.620 mg/m^3 (Figure 3).

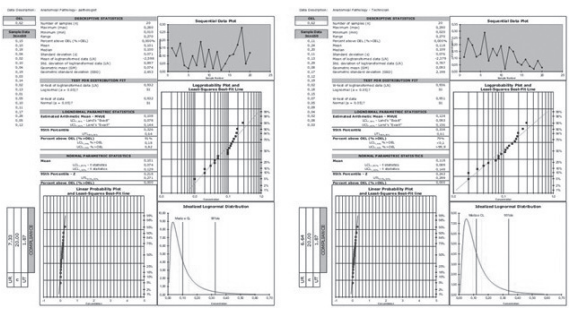

Figure 3. Data analysis according to the UNI EN 689:2019, using the 0.620 mg/m^3 exposure limit

Slika 3. Analiza podataka prema UNI EN 689:2019, koristeći granicu izloženosti od 0,620 mg/m^3

The data were also tested with the TLV-TWA of 0.370 mg/m^3, as the next mandatory limit, and also here, compliance is observed for both the SEGs (Figure 4). However, the scenario with the next mandatory limit is very close to the non-compliance, which could result from a slight deterioration of working procedures or working station (less extraction by the fume hood or less cleaning of the working board). Indeed, using the limit proposed by ACGIH (0.120 mg/m^3), the monitored scenario resulted in non-compliance according to UNI EN 689:2019 (Figure 5). The limit for FA of ACGIH is lower than OEL; however, as mentioned above, in some cases, the ACGIH occupational limit values can be used, lacking mandatory levels; thus, this evaluation seems legitimate considering the worldwide continuous lowering of the limit for FA.

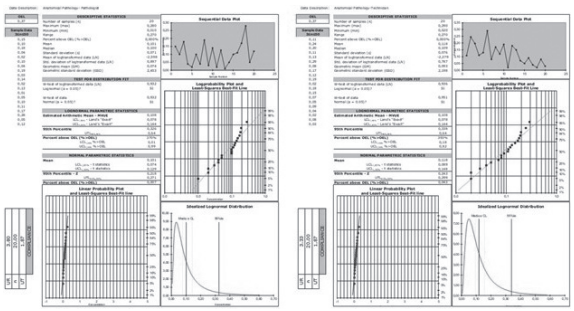

Figure 4. Data analysis according to the UNI EN 689:2019, using the 0.370 mg/m^3 exposure limit

Slika 4. Analiza podataka prema UNI EN 689:2019, koristeći granicu izloženosti od 0,370 mg/m^3

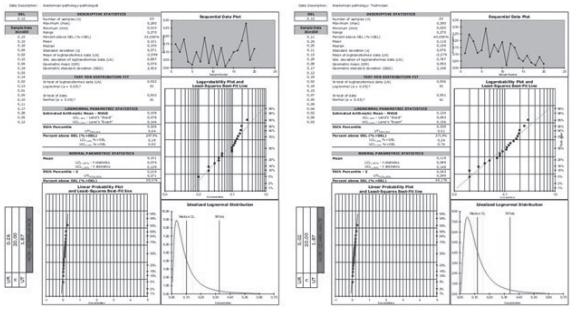

Figure 5. Data analysis according to the UNI EN 689:2019, using the 0.120 mg/m^3 exposure limit

Slika 5. Analiza podataka prema UNI EN 689:2019, koristeći granicu izloženosti od 0,120 mg/m^3

The FA values observed - higher than other recent studies *(Dugheri et al., 2020)* - could be linked to some specific causes, such as the poor sealing of the sample containers before and after they were opened for the insertion of biopsy, the lack of a specific system of containment for wastes (including used gloves and pad tissues), and procedures not performed correctly by operators.

Indeed, the levels of inhalation FA exposure in anatomical pathology laboratories have decreased over the years *(Fustinoni et al., 2021)*: in 2022, a systematic review on occupational exposure to FA *(Cammalleri et al., 2022)*, showed data collected from 2004 until 2019, and it reported FA values greater than 2 mg/m^3 in the anatomical pathology workflow; lower values of FA were observed instead by Motta et al. *(2021)*, that performed on a 4-year timescale (2016-2019) an airborne FA monitoring in 16 exposed healthcare workers of an

Anatomical Pathology Unit, detecting maximum concentrations of FA equal to 0.1957 mg/m^3 ppm. In the same period, Dugheri et al. *(2020)* revealed that until 2007, FA concentrations in an Italian hospital ranged between 0.706 to 0.875 mg/m^3 in 8-hours TWA measurements. Still, by 2016, these FA readings strongly dropped (0.016-0.037 mg/m^3) thanks to new safe practices and the introduction of pre-loaded sample containers, and innovative systems to safely manage the FA.

Thus, these recent updates of the anatomical pathology workflow, such as Under Vacuum Sealing (UVS), the ergonomic grossing workstation *(Dugheri et al., 2021)*, a dedicated ventilation system *(Ogawa et al., 2018)*, a filtered bin for contaminated wastes, coupled with the re-organization of lab spaces, improved work procedures, and training initiatives *(Dugheri et al., 2020, Fustinoni et al., 2021)* could lead in the studied gross room to a minimization of the exposure to FA, to better face the future lowering of the occupational exposure limit.

Health risk assessment for inhalation of FA in the gross room

Concerning the health RA, particularly the non-carcinogenic one, the definition of a chronic non-carcinogenic level of FA concentration is required. As indicated above, these levels are proposed by several organisations, and they are not standardized, both the value and the mechanism to establish them. The REL, MRL, and EL values are based on the same occupational study population reported by Holmstrom et al. *(1989)* and Wilhelmsson and Holmstrom *(1992)*; the numerical differences among the values are due to differences in the methods used to extrapolate from occupational exposure to a continuous one, and the selection of uncertainty factors. The REL of 9 µg/m^3 by the OHAA was supported by a case-control study of 88 asthmatic children and 104 non-asthmatic children, evaluating the association of parent-reported respiratory symptoms (cough, shortness of breath, etc.) and FA concentrations in their homes *(Rumchev et al., 2002)*. EPA derived a REL of 10 µg/m^3 from this study of asthmatic children after dividing the NOAEL of 30 µg/m^3 FA in indoor air by an uncertainty factor of 3 to account for toxicodynamic differences among children. The MRL is based on an occupational exposure study's Lowest Observed Adverse Effect Level (LOAEL) of 298 µg/m^3 *(Holmstrom et al., 1989)*. The critical effects described by ATSDR are mild irritation of the eyes and upper respiratory tract and mild histopathological changes in the nasal epithelium. The MRL of 10 µg/m^3 was derived by dividing the LOAEL of 298 µg/m^3 by a total uncertainty factor of 30. The EU EL, exposure limit for indoor air of 1 µg/m^3 is based on EPA's 1999 REL with adjustments to the uncertainty factors. It has been derived by dividing the adjusted NOAEL of 30 µg/m^3 by a total uncertainty factor of 30: 10 for human population variability and 3 for consideration of evidence that children are more sensitive to formaldehyde than adults.

The EPA methodology to estimate the RfC is based upon a quantitative approach to assess toxicity data to derive a dose-response estimate. The RfC derivation starts with the identification of a NOAEL and a LOAEL. It requires conversion by dosimetric adjustment of the NOAELs and LOAELs observed in laboratory animal experiments or in human epidemiological or occupational studies to human equivalent concentrations (HECs) for ambient exposure conditions. These conditions are currently assumed to be 24 h/day for a lifetime of 70 years. For FA, the overall RfC is within the narrow range between 6 and 9 µg/m^3 and the concentration 7 µg/m^3 is assumed as the RfC one can breathe every day for a lifetime that is not anticipated to cause any harmful non-cancer health effects. The RfC methodology, unlike the previous level proposed by the EPA (such as the Reference Doses - RfDs and Acceptable Daily Intake - ADI), takes into account the dynamics of the respiratory system as the main entrance to the body. It includes dosimetric adjustments to account for the species-specific relationships of exposure concentrations to deposited/delivered doses. Moreover, the physicochemical characteristics of the inhaled agent are considered critical determinants of its interaction with the respiratory tract. As a consequence of this more comprehensive evaluation, the FA RfC values were utilized to assess health risk in this study, considering the application of EPA method and equations to evaluate both the non-carcinogenic and the carcinogenic ones.

The personal occupational monitoring results were used to obtain an average value of FA con-

Table 4. Result of health risk assessment in the anatomical pathology laboratory

Tablica 4. Rezultat procjene zdravstvenog rizika u anatomsko-patološkom laboratoriju

Operator	CDI mg/Kg·day	CDIy mg/Kg·day·year	HQ *HQ<1 non relevant HQ>1 relevant*	CDIL	LCHR *LCHR<1x10⁻⁶ non concern LCHR>1x10⁻⁶ concern*
Pathologist	0.011	0.009	1.3	0.0007	$3.2x0^{-5}$
Technician	0.013	0.011	1.6	0.0008	$3.9x10^{-5}$

CDI: Chronic Daily Intake; CDIy: Chronic Daily Intake yearly; HQ: Hazard quotient; CDL: Chronic Daily Intake lifetime; LCHR: Lifetime Cancer Hazard Risk.

centration for both the monitored population, 0.10 and 0.12 mg/m^3 for pathologists and technicians, respectively. According to the US EPA, these data were used as the exposure concentration values (C) in the equations to determine the health RA. The CDI, HQ and LCHR results are shown in Table 4.

The assessments for the non-cancerogenic and cancerogenic risks for both the studied groups present the relative indexes above the non-relevant risk level: the HQ is 1.3 and 1.6, and the LCHR is $3.25x10^{-5}$ and $3.90x10^{-5}$ for pathologists and technicians, respectively. These data are in line with other studies on residents in a pathology laboratory *(Zain et al., 2019)*, while studies on workers in other typical workplaces exposed to FA showed lower and acceptable risk levels *(Rovira et al., 2016)*. However, recently Dugheri et al. *(2020)* reported that the concentration of airborne FA observed in an Italian anatomical pathology laboratory was lower than in this study. Using the average FA concentration observed by Dugheri et al. (0.018 mg/m^3) for the definition of HQ and LCHR, they are equal to 0.3 and $6.5x10^6$, respectively These data contrast with the ones observed in this study, considering the very similar occupational scenario (modern Italian hospital with a centralized anatomical pathology laboratory). This difference could be due to the lack of FA containment and minimization measures present in the laboratory of this study, compared to the one of the Dugheri et al. study *(2020)*, such as Under Vacuum Storage system for tissues specimen or specific specimen transportation chests. Considering the monitored groups, both the cancerogenic risk and the non-cancerogenic risk in this study results were higher for the technicians than for the pathologists. This outcome was in line with the EPA standard *(U.S. Environmental Protection Agency, 1989)* for CDI assessment and cancer risk *(U.S. Environmental Protection Agency, 2022)* that, in the comparison of the work positions in the laboratory, found that a higher cancer risk seemed to be in the functions with more prolonged working exposure to FA concentrations, particularly among the pathology technicians and the investigative mortuary personnel.

CONCLUSIONS

This study presents the results of a cancer RA and chronic health RA among workers exposed to FA in an anatomical pathology laboratory. Both pathologists and technicians showed increased cancer risk and increased risk of adverse health effects, especially the second one. The occupational exposure assessment in the study showed compliance with the occupational exposure limit for both the SEG monitored. However, the future lowering of the occupational limits for FA and the high health risks observed suggest that measures and actions must be adopted to minimize the exposure and the risk for the workers of anatomical pathology laboratories. Reducing the exposure time and the number of operators to FA and supporting safer working conditions with good laboratory design and practices, as well as engineering controlled ventilation, are recommended to reduce the hazard for the workers.

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STRATEGIJA ZA VREDNOVANJE DJELOVANJA FORMALDEHIDA U LABORATORIJU ZA ANATOMSKU PATOLOGIJU – 1. DIO: IZLOŽENOST NA RADU I RIZIK ZA RAK

SAŽETAK: Formaldehid je kemijski spoj koji se obično koristi u laboratorijima za anatomsku patologiju kao konzervans za čuvanje tkiva, a često ga se povezuje s rakom. Osoblje u takvim laboratorijima najizloženije je formaldehidu i s njim povezanom raku, a i nekancerogenom riziku. Stoga se preporuča procjena rizika, kancerogenih i nekancerogenih, a također i procjena izloženosti na radu. Ova studija pratila je formaldehid u jednom talijanskom laboratoriju za patologiju kako bi se procijenila izloženost na radu prema UNI EN 689:219 i utvrdio kvocijent opasnosti (HQ) kao i doživotnog rizika od raka (LCHR) te kancerogeni i nekancerogeni rizici. Izloženost patologa i tehničara bila je niža od Europske obvezne granice za izloženost na radu (0.62 mg/m^3) i obje skupine bile su ispod te granice. No, ipak, što se tiče procjene rizika, oba parametra HQ i LCHR bila su viša (1.3 i 1.6 HQ, i 3.2x10^{-5} i 3.9x10^{-5} za patologe te tehničare, tj. viša od drugih zamijećenih u sličnim situacijama. Studija prikazuje kako procjena izloženosti formaldehidu može pomoći u očuvanju zdravlja radnika utvrđivanjem odstupanja od preporučenih graničnih vrijednosti i posljedično visokih rizika za zdravlje, posebno u zdravstvu.

Ključne riječi: *formaldehid, procjena rizika za zdravlje, izloženost na radu*

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