Exposure and management of the health risk for the use of formaldehyde and xylene in a large pathology laboratory

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ABSTRACT

Background. Formaldehyde and xylene are two hazardous chemicals widely used in pathology laboratories all over the word. The aim of this work was to survey a large volume pathology lab, measuring exposure of workers and residents to formaldehyde and xylene, and verify the efficacy of the undertaken preventive actions and the accomplishment with occupational limit values.

Methods. Environmental, personal, and biological monitoring of exposure to formaldehyde and xylene in different lab rooms and in 29 lab attendants was repeated yearly from 2017 to 2020. Continuous monitoring of airborne formaldehyde was performed to evaluate the pattern of airborne concentrations while specific tasks were performed. Several risk management and mitigation measures, including setting a new grossing room, reducing the number of samples to be soaked in formaldehyde, and improving the lab practices and equipment, such as the use of chemical hoods, were undertaken after each monitoring campaign, based on the results obtained from the exposure monitoring.

Results. Significant exposures to formaldehyde in pathologists and residents, especially during the grossing of samples, were observed in the first two years, with exposure exceeding the occupational exposure limit value; the following surveys showed that the risk management and mitigation measures were effective in reducing airborne concentrations and personal exposure. Xylene, assessed with both environmental and biological monitoring, was always well below the occupational exposure limit value and biological limit values, respectively.

Conclusion. Critical exposure to air formaldehyde in attendants of a pathology laboratory could be reduced with the re-organization of lab spaces, new and improved work procedures, and awareness and training initiatives.

Keywords: formaldehyde**,** xylenes, pathology laboratory, chemical hazard, prevention

What's important about this paper

Occupational exposure to air formaldehyde and xylene in the attendants of a large pathology laboratory was survey for a 4-year period. Environmental, personal and continuous monitoring, and biomonitoring were used. The exposure to xylene was always well below the occupational limit value, while the exposure to formaldehyde was above the limit value in some lab rooms and job tasks. Following each year survey, suitable preventive measures were undertaken. Critical exposure to formaldehyde was reduced with the re-organization of lab spaces, new and improved working procedures, and awareness and training initiatives.

INTRODUCTION

The examination of tissue and cytological samples in pathology laboratories requires a multistep pre-analytic phase that begins with fixation (Bussolati et al., 2015). Since the mid-1890s, formalin has been recognized as a valuable reagent to preserve the biological samples from autolysis and decay (Musiał et al., 2016). The aqueous solution of formaldehyde (CH_2O; EC 200-001-8; CAS: 50-00-0; 1 ppm = 1.23 mg/m^3 at 1 atm and 25°C) and methanol (CH_3OH) was generally employed as a 10% neutral buffered formalin, containing 4% formaldehyde in phosphate buffered saline (PBS) (Grizzle, 2009; Kiernan, 2008). Several characteristics led the formalin to become the gold standard fixative in pathology laboratories (Musiał et al., 2016; Berrino et al., 2020). First, formalin-fixed specimens show long-lasting preservation of cell morphology and tissue architecture. Second, the acceptable integrity of DNA and RNA obtained with formalin fixation allows for the most advanced molecular investigations. In addition, formalin has antiseptic properties, ease of storage, and, last but not least, very low cost.

Clearing is another important pre-analytic step in tissue processing, aiming to remove alcohol and other dehydrants from tissues prior to permeation of the embedding material, more commonly paraffin wax. This process is carried out using xylene (C_8H_{10}; EC 215-535-7; CAS: 1330-20-7; 1 ppm = 4.34 mg/m^3 at 1 atm and 25°C), an aromatic hydrocarbon referred to as any of the three isomers of dimethylbenzene ($(CH_3)_2C_6H_4$). This mixture shows excellent compatibility with alcohol and paraffin wax and is relatively cheap.

Despite their usefulness and general acceptance, formaldehyde and xylene represent major hazards for human health. Formaldehyde has been recognised as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC, 2006) based primarily on its association with nasopharyngeal cancer. With the Regulation (EU) No 895/2014 amending Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, formaldehyde has been classified as a category 1B carcinogen (substances for which human carcinogenic effects are presumed mainly on the basis of studies on animals). The new classification, into force from 01/01/2016, entailed the need to consider the carcinogenic risk for the purposes of managing the health and safety of workers,

or the applicability, for processes involving the use of formaldehyde, of the standard for the protection from carcinogens and mutagens (Decreto Legislativo 81, 2008). According to the harmonised classification and labelling approved by the European Union, this substance is toxic if swallowed, is toxic in contact with skin, causes severe skin burns and eye damage, is toxic if inhaled, may cause cancer, is suspected of causing genetic defects and may cause an allergic skin reaction (European Chemical Agency, Formaldehyde, 2020). Xylene, according to the European Union harmonised classification and labelling (CLP00), is harmful in contact with skin, is harmful if inhaled and causes skin irritation (European Chemical Agency, Xylene, 2020).

Several studies have attempted to address the applicability of alternative solution to formalin and xylene in the health care sector (Alwahaibi et al., 2019; Benerini Gatta et al., 2012; Belloni et al., 2013; Alwahaibi et al., 2018). Additionally, guidelines of the Italian Public Health Ministry, exhort every formalin user to minimize utilization and, after a 3-year period, to achieve a complete formalin ban (Consiglio Superiore di Sanità, 2015). However, the costs, effectiveness, and safety of potential substitutes are still unsatisfactory. As such, a strategy directed towards the minimization of the airborne concentration by adopting behaviour measures could represent a valid approach (Di Novi et al., 2010).

For formaldehyde, the EU Carcinogens and Mutagens Directive of 2019 has recently introduced binding occupational exposure limit (BOEL) values of 0.37 mg/m^3 (0.3 ppm) for long-term exposure (8-hour time-weighted average) and of 0.74 mg/m^3 (0.6 ppm) for short term exposure (15-min) for all work sectors, and a specific 8-h limit value of 0.62 mg/m^3 (0.5 ppm) for the health care, funeral and embalming sectors, the latter valid until July 2024 (Directive EU 2019/983). These are therefore the legal permissible exposure limits values currently in force in occupational settings. This directive officialised the former recommendation by the Scientific Committee on Occupational Exposure Limits of the European Union (SCOEL/REC/125, 2016), but recognized the difficulties to keep under control the concentration of formaldehyde in some critical sectors, specifically allowing a transitory higher limit value. For xylene, a 8-h indicative occupational limit value (IOEL) of 221 mg/m^3 (50 ppm) and a short term (15-min) IOEL of 442 mg/m^3 (100 ppm) were introduced by Commission Directive

2000/39/EC, for the protection of the health and safety of workers (Commission Directive 2000/39/EC).

Concerning biological monitoring of occupational exposure, no biological limit value is available for formaldehyde; conversely, the determination of methylhippuric acid is indicated for the biological monitoring of occupational exposure to xylene in urine samples collected at the end of the shift. The American Conference of Governmental Industrial Hygienists recommends a biological limit value of 1.5 g/g creatinine (ACGIH, 2019). Table 1 summarizes the occupational exposure limits, and biological limit values for formaldehyde and xylene.

In the present work, we sought to share our experience in a high-volume pathology laboratory of a university hospital implementing formalin and xylene chemical risk management. Specifically, we depict i) the procedures used for monitoring both personnel and residents, ii) the strategies adopted to decrease the personal and environmental exposure, iii) the results obtained in the surveys performed from 2017 to 2020.

METHODS

The surveys were carried out in a large volume pathology lab from 2017 to 2020.The first monitoring campaign was done on 19th October 2017; the following campaigns were performed on 16th April 2018, 6th February 2019, and 19th February 2020. After each campaign, actions aimed at reducing air pollution in critical situations were implemented.

Environmental, personal and biological monitoring for the assessment of exposure to airborne formaldehyde and xylene in the rooms and in the personnel of the laboratory were performed.

Overall, 10 rooms were investigated for airborne pollution: 2 rooms for formaldehyde, 2 rooms for xylenes and 6 rooms for both chemicals. The lab is provided with a mechanical ventilation system integrating fans and air conducts in the ceiling. A map of the laboratory is shown in Figure 1.

Twenty-nine health care workers worked in the laboratory at the time of the first survey; this number remained almost stable in the following years. Personal exposure was measured repeatedly along the years, obtaining 49 and 26 measures of personal exposure to formaldehyde and xylene, respectively. Nineteen individuals were submitted to biological monitoring for the measurement of urinary methylhippuric acid, metabolite of xylene.

During samplings, a time-activity diary was also used to separate the continuous data as a function of the different monitored environments and working tasks, and to allow the collection of information regarding the activities performed, anomalous events, and specific procedures adopted by the workers.

Lab attendant tasks and lab description

Lab attendants belonged to the following groups. (i) Lab technicians; these workers take care of most activities in the lab, including anatomical parts registration and storage, grossed sample fixation and processing for embedding in paraffin wax, sample slicing with microtome, and staining. (ii) Pathologists and residents take care of sampling anatomical parts and making the diagnosis on prepared samples. (iii) The lab cleaner takes care of lab waste, lab housekeeping, and the supply of reagents and small consumables.

A map of the laboratory with the indication of the lab rooms is shown in Figure 1. In the original setting, there were: a registration and grossing room (A), equipped with two hooded suction tables

(Propath) with formalin dispensers, and two large ventilated cabinets for sample storage; a staining room (B), equipped with two chemical hoods; a microtome room (C) with 3 working positions and two chemical hoods; an histochemical room (D) with a chemical hood; a second microtome room (F) with 3 working positions; a meeting room (G); a processing room (I) containing a processing machine (Peloris, Leica); an administrative office (J), and two lavatory rooms (H and E). Additionally, the second floor of the building hosted several medical offices and a cytology room (L).

The laboratory deals with about 20.000 samples/year; after the analysis, samples are stored in the lab for minimum 2 months, according to the law, in aspirated cabinets. In 2017 the reagent stocks included about 150 L of formalin, 80 L of xylene, 80 L of ethanol, 30 L of surgical spirit, and 40 kg of paraffin wax. In the following years, the volume of formalin stock was reduced to 100 L. The overall annual use of formalin decreased form 5000 L to 4200 L from 2017 to 2018.

Personal and biological monitoring

Personal exposure to formaldehyde and xylene was assessed using radial diffusion samplers (Radiello, Sigma-Aldrich, Milano, Italy) worn by personnel and residents in the breathing zone (the hemisphere of 30 cm radius extending in front of the face) (Rodes and Thornburg, 2004) for the whole work shift. The mean (minimum-maximum) sampling duration was 425 (149 - 591) minutes.

Formaldehyde sampling was performed using a stainless steel mesh cartridge filled with Florisil impregnated with 2,4-dinitrophenylhydrazine (DNPH) (Radiello®: diffusive body code 120-1 and cartridge code 165, Sigma-Aldrich Inc., Milano, Italy), where formaldehyde reacts with DNPH to give the formaldehyde-2,4-dinitrophenylhydrazone. Xylene sampling was performed with Carbograph based cartridges (Radiello®: diffusive body code 120-2 and cartridge code 130, Sigma- Aldrich Inc., Milano, Italy). Field blanks were also collected in each campaign. Before and after sampling, the formaldehyde and xylene sampling cartridges were stored in the proper glass tube in refrigerator (4°C) and at room temperature, respectively, and analysed according to their stability.

For those potentially exposed to xylene, a spot urine sample was collected at the end of the work shift to measure methylhippuric acid. Urine samples were kept in the dark at – 20 °C and analysed within three months.

TWA Environmental monitoring

Time weighted average (TWA) environmental monitoring of formaldehyde and xylene was performed using passive radial diffusion samplers (Radiello), as described in the previous paragraph. In this case, the samplers were placed in the centre of each room, not closer than 1 m to the wall. Passive samplers were set at the average height of a worker's respiratory tract (i.e. 150 cm of height for operators in upstanding position and 110 cm of height for the operators in a seated position). Ventilation channels and heating sources were avoided. In practice, the samplers were fixed to a wire attached to the ceiling or placed in a metallic rack. The sampling was performed for the entire working time, typically from 7:30 a.m to 5:30 p.m.

Continuous environmental monitoring

Continuous environmental monitoring of airborne formaldehyde was carried out with a photoacoustic infrared spectrometry analyser (Bruel & Kjaer 1302, Naerum, Denmark). Air samples were taken sequentially using a Bruel & Kjaer 1303 multipoint sampler (Bruel & Kjaer 1303, Naerum, Denmark) equipped with four probes (10-m length polyamide tubes), positioned in different locations in the registration/grossing rooms and in the hallway, taken as reference. This instrument allowed real-time measurement (frequency acquisition of a data every 90 seconds, approximately), thus allowing to observe the presence of peaks. The lower detection limits for formaldehyde was 0.01 mg/m^3. The measurements were automatically corrected for air humidity and carbon dioxide (CO_2) as main confounding factors. Humidity, air pressure, temperature and the influence of one gas on the other were compensated. Reading accuracy was within 2% either way of the measured value. Gas sampling was accomplished under ambient pressure. Sampling was performed for the entire working time, typically from 7:30 a.m to 5:30 p.m.

The photoacoustic infrared spectrometry analyser was calibrated by a dedicated factory service (Airnova s.r.l. - Limena (Padua) Italy) approximately annually. The calibration service consisted in verifying the functionality of the sampling and analysis system, and in particular the linearity of response in a range of concentrations between 0 ppm (ultra-pure nitrogen as standard gas) and a known concentration of the investigated chemical (for formaldehyde 15.3 ppm ± 3%).

Analytical measurements

Formaldehyde was desorbed from the sampling cartridges with 2 mL of acetonitrile at room temperature for 30 minutes. An aliquot of each eluate (5 µL) was analysed by a high performance liquid chromatograp (Thermo Scientific, Rodano, Italy) equipped with a Betasil C18 column (150mm length, 2.1 mm internal diameter and 5 µm particle size; Thermo Scientific,Rodano, Italy), kept at 25°C, using an isocratic mixture of acetonitrile (37%) and water (63%) flowing at 400 µl/min, as eluent. The liquid chromatograph was interfaced with a diode array detector operating at a wavelength of 365 nm. Quantification was performed using a calibration curve. During routine analysis, calibration curves, QC, and duplicate samples were run with each set of unknown samples. The throughput was about 50 samples/day. The intra- and inter-day precision of the method, as CV%, was less < 10%, the accuracy was 94 – 111%, and the limits of quantification (LOQ) was 0.01 mg/m^3. The quantification of unknown samples was performed after subtraction of the signal in the blank.

Xylene was desorbed from the sampling cartridge using benzene-free carbon disulfide (CS_2, Sigma Aldrich, Milan) at room temperature for 30 min, in the presence of xylene-d10 as internal standard. The solution was analyzed via gas chromatography mass spectrometry using a gas chromatograph (Agilent 6890N, Cernusco sul Naviglio, Italy) equipped with a mass spectrometer (Agilent 5975, Cernusco sul Naviglio, Italy) with an inert electron impact (EI) source (70 eV) and an autosampler (CombiPal, Agilent, Cernusco sul Naviglio, Italy). Analyte separation was performed on a DB1 capillary column (60 m, 0.25 mm i.d., 1.0 µm film thickness, J&W Scientific, CPS Analitica, Milan, Italy). The GC analysis was performed at the following conditions: helium carrier gas at a constant flow rate of 1 ml min^{-1}; injector temperature 250 °C, gas chromatograph oven temperature programmed from 35 °C (5 min initial hold) to 90 °C at 5 °C min^{-1}, and then to 200 °C at 10°C/min (final temperature 2 min hold). Signals were acquired in the single ion monitoring mode (SIM) registering the positive ion to charge ratio m/z 106 for xylenes and 116 for xylene-d10. Quantification limit (LOQ) was 100 µg/L. Considering the average sampling time and the uptake rates of xylenes, this concentration was estimated to correspond to airborne levels of xylene of 0.01 mg/m^3.

The determination of urinary methylhippuric acid was performed using a Chromsystems kit (Order no.: 43000) containing the calibrator, two control materials (L1 and L2), the internal standard solution,

the chromatographic column and the mobile phase. Briefly, 10 µL urine sample were added with 1 mL of the internal standard solution; after centrifugation, 20 µL of supernatant ware directly analysed using an isocratic HPLC system (Agilent Technologies) interfaced with a UV detector operating at 208 nm wavelength. During routine analysis, calibrator, quality controls material and duplicate samples were run with each set of unknown samples. The throughput was about 40 samples/day. The quantification limit was 0.02 g/L.

Creatinine measurement was performed using an automated chemical-clinical method based on the Jaffè reaction (Kroll et al., 1986).

The analytical work was performed at the laboratory of Toxicology of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Risk management and mitigation measures

In Table 2, a summary of risk management and mitigation measures undertaken along the years in the lab setting and in the work organization to decrease the chemical air pollution is described. Noteworthy, a new grossing room with two closed chemical hoods (Labosystem hood Typhoon 5001 grossing bench) for large samples was set in the previous second microtome room (F); while the registration and grossing room (A) was dedicated only to small samples. Moreover, the number of samples to be treated with formalin was greatly reduced, following a new protocol that included the freezing of placenta instead of their soaking in formalin. Other actions, such as the setting of a storage room for lab waste, a new protocol for formalin-soaked waste, and the increase in the frequency of hood maintenance, were undertaken. For those entering the processing room, a half facepiece respirator (3M™ 6500 QL) with a suitable filter for chemicals (3M Organic Vapours and Formaldehyde 6075 A1) was provided. Lab attendants were fit tested and received one-to-one training by the hospital's health and safety manager.

Statistical analysis

The statistical analysis was performed with the IBM software SPSS ver 24. Environmental and personal chemical measurements were described using median, 5^{th} and 95^{th} percentile and maximum values. Airborne formaldehyde concentration was decimal log-transformed to achieve a normal distribution. The comparison of occupational exposure values was performed with analysis

of variance (ANOVA) on log-transformed values, considering workers' job tasks and the period (year) of monitoring as categorical independent variables. Post-hoc Bonferroni test was used to perform multiple comparisons. The exposure trend along the years was investigated using a linear regression model. Statistical results were considered significant when $p < 0.05$.

RESULTS

Environmental, personal and biological monitoring

Table 3 reports a summary of personal and environmental measurements of formaldehyde and xylene in the years from 2017 to 2020.

As regards formaldehyde, median TWA environmental levels decreased along the years (median 0.21 vs. 0.12 mg/m^3 in 2017 and 2020, respectively, even if no significant trend was detected); the maximum level was observed in 2019, with 1.45 mg/m^3 registered in the processing room (see also Figure 2A). The concentrations of formaldehyde measured by continuous monitoring show decreasing median levels along the years (0.47 vs. 0.22 mg/m^3 in 2017 and 2020, respectively). In Figure 3, the profiles of continuous environmental monitoring of formaldehyde, in 2017 and in 2019, are shown. In 2017, median level was 0.47 mg/m^3, with repeated exposure peaks (up to 4.97 mg/m^3), in correspondence of the grossing of large samples, refill of the formalin reservoirs, and the incorrect use of the hood sash of the suction table. In 2019, the median level was 0.11 mg/m^3, with the absence of significant exposure peaks and a maximum value of 0.51 mg/m^3. Considering personal exposure, median levels of formaldehyde were roughly constant, while a notable decrease of maximum levels was observed (2.30 vs. 0.49 in 2017 and 2020, respectively) (see also Figure 2C); however the decreasing trend was not significant (p value = 0.121).

As regards xylene, median and maximum TWA environmental levels were constant along the years (2017-2019); while for personal monitoring maximum levels decreased (10.4 vs. 3.7 in 2017 and 2019, respectively) and median levels increased along the years (1.4 vs. 3.6 in 2017 and 2019, respectively). As personal exposure is influenced by the number of monitored workers and by their job task, it is useful to note that in the first survey of 2017, almost all lab workers were monitored (n = 21), while in 2018 and 2019 only workers specifically dealing with xylene were monitored (n = 2 and 3, respectively). As regards the biological monitoring of xylene, urinary methylhippuric acid was always lower than or equal to the detection limit (0.02 g/L).

Lab rooms

Table 4 reports the results of the environmental monitoring of formaldehyde and xylene in the different laboratory rooms.

For formaldehyde, in 2017 the highest TWA value (0.74 mg/m^3) was found in the registration/grossing room. After the new grossing room was opened (2018), environmental formaldehyde in the registration/grossing room decreased (0.17 mg/m^3 in 2018) and remained constant in the following campaigns. In the new grossing room, a value of 0.45 mg/m^3 was measured in 2018, but in the following years lower values were registered (0.32 mg/m^3 in 2020). A high formaldehyde concentration was measured in 2019 in the processing room (1.45 mg/m^3), due to the temporary allocation of lab waste there, but the levels decreased in 2020 (0.53 mg/m^3), when the waste was moved to a dedicated location. Comparing the concentrations of formaldehyde in the different rooms, a significant difference was found (ANOVA p value = 0.033), with lower levels in the administrative office and in the hallway (see also Figure 2B). In Table 4 continuous measurements of environmental formaldehyde in the different monitoring positions is also reported. In the registration and grossing room, higher concentrations were measured at the grossing workstation then at the registration workstation. In general, median levels were comparable to those measured with passive monitoring.

As regards xylene, the maximum level was measured in the processing room, with a concentration of 10.8 mg/m^3 in 2018, similar in the different years; this is consistent with the use of xylene in this room and the presence of a xylene reservoir in the processing machine. Lower levels of xylene were found in the office and in the staining room; in these rooms a decrement along the years was observed (i.e. 1.0 vs. 0.3 and 8.1 vs. 3.7 mg/m^3 in 2017 vs. 2019, respectively).

Job Tasks

Table 5 reports the results of the personal exposure to formaldehyde and xylene in the lab workers, divided according to the year and the different job tasks. The comparison among job tasks shows a marginally significant difference (ANOVA p value = 0.072); post-hoc Bonferroni test shows no significant difference between group pairs; marginally higher formaldehyde concentration was found in residents than in technicians (p = 0.086). Formaldehyde exposure of pathologists and residents decreased passing from median levels of 2.30 to 0.35 and from 1.08 to 0.32 mg/m^3 in 2017 and 2020, respectively. For technicians, median personal formaldehyde levels were constant (0.21 vs. 0.19 in 2017 and 2020, respectively), while a decrease in maximum levels was observed (1.61 vs.

0.49 in 2017 and 2020, respectively). Also for the lab cleaner, personal exposure to formaldehyde decreased along the years (0.49 vs. 0.17 mg/m^3 in 2017 and 2020, respectively) (see also Figure 2D).

For xylene, median exposure was higher (3.6 vs. 1.6 mg/m^3) while maximum level was lower (3.6 vs. 10.4 mg/m^3) in 2019 than 2017.

DISCUSSION

This work describes the periodical surveys carried out from 2017 to 2020 in a large laboratory of pathology to evaluate the exposure to formaldehyde and xylene in lab attendants and the efficacy of preventive actions implemented to improve the air quality. At the time of the first survey, 2017, formaldehyde had been recently classified in the EU as carcinogen of category 1B (Regulation (EU) No 895/2014). This new classification enforced a stricter adoption of preventive measures to reduce the occupational exposure.

Given the existence of a recommendation by SCOEL for an 8h OEL of 0.37 mg/m^3 and a STEL of 0.74 mg/m^3 (SCOEL/REC/125, 2016), these limit values were taken as reference values for the exposure and risk assessment (Table 1). During the first survey, exposure to formaldehyde highlighted criticisms mostly in the registration and grossing room, especially focused on the pathologist and residents (Table 4 and 5) for which both the 8-h OEL and the STEL were largely exceeded. Analysing the continuous monitoring pattern (Figure 3), we could attribute these criticisms to the number of large samples grossed by the pathologist and the poor protection offered by the hooded suction table, often operated with the sash in the improper position. During the following months, a new grossing room was set in which two new closed chemical hoods were positioned (Table 2); these were devoted to deal with large size samples. Moreover, new general standard operative procedures for a safe working with formaldehyde and new pathologist procedures, to reduce the number of samples to be treated with formaldehyde, were adopted (Table 2). In particular, the large number of placenta samples from the maternity department of the hospital, the major of the city with about 6.000 deliveries per year, were no more treated with formalin, but were deep-frozen: therefore, a drastic reduction of the use of formalin in the laboratory was obtained. Finally, a training on the correct use of the suction table was offered. No critical issue was observed for xylene, based both on environmental and biological monitoring results and their comparison with the EU OEL of 221 mg/m^3 (Commission Directive 2000/39/EC) and the biological limit value (Table 1) (ACGIH, 2019).

In the following survey, in 2018, the exposure to formaldehyde in pathologists and residents, especially those operating in the new grossing room and dealing with a large number of samples,

was decreased, but still above the recommended OEL, with a maximum concentration up to 1.82 mg/m^3. On the contrary, the exposure of lab technicians and the lab cleaner was lower in comparison with the previous year, and none exceeding the OEL (Table 5). A close observation of the procedures adopted during grossing highlighted the presence of open disposal bins placed outside the hoods, in close proximity of the pathologists and residents, used to dispose formaldehyde-wet tissues used to dab samples during grossing operations. The high personal exposure to formaldehyde in pathologists and residents was therefore attributed to the evaporation of formaldehyde from these bins. Consequently, small disposal bins for formaldehyde-wet waste to be placed under the hoods were adopted to reduce formaldehyde pollution (Table 2). Moreover, as a general preventive action to reduce air pollution, laboratory waste to be sent to the incinerator, i.e. vessels with processed samples soaked in formalin, temporary positioned in the laboratory hallway, were moved to the processing room. This room was identified as storage room as no workstation was present here, even if it was attended from selected technicians and the lab cleaner during short periods for instrumentation maintenance and/or sample loading. For those entering the processing room, a half facepiece respirator with a suitable filter for chemicals was provided. As for xylene, the number of controls for exposure assessment was reduced to involve only those individuals directly handling xylene; again, no criticism was found in both environmental and biological monitoring.

In the February 2019 survey, the personal exposure to formaldehyde was within the 8h-TLW recommended OEL of 0.37 mg/m^3 for all workers of the lab, testifying the efficacy of the preventive actions undertaken to reduce chemical risk. However, a concentration of formaldehyde as high as 1.45 mg/m^3 was found in the processing room, pointing to an excessive pollution probably due to the presence of several bins with laboratory waste. Following this finding, and to reduce formaldehyde pollution in the processing room, it was decided to reallocate the laboratory waste again. A new dedicated storage room, in the place of a unused lavatory, was therefore set and laboratory waste was moved here. As for xylene, no criticism was confirmed.

While the survey was on going, in June 2019 the EU directive 983 defined the binding occupational exposure limits (BOEL) for formaldehyde (Directive (EU) 2019/983) to 0.62 mg/m^3 for the health care setting, until July 2024, in recognition of the difficulties to accomplish the limit value in this particular

work sector. The EU position supports the present experience that highlights the criticisms in accomplishing the stricter limit value for formaldehyde. Finally, the 2020 survey showed median personal exposures within the stricter OEL of 0.37 mg/m^3 for all job tasks, including pathologists and residents; for these workers maximum exposures were exceeding this limit, but were within the 2019 BOEL of 0.62 mg/m^3. Similarly, environmental pollution was always below BOEL, with the highest concentration in the processing room.

Comparing different job tasks, the highest personal exposures was found for pathologists and residents, both performing the grossing of samples soaked in formalin. This finding was expected due to the direct handling of formalin and the short distance between the worker and the chemical. At the same time, we think that a role in determining the high exposures was played by the over-familiarity with formaldehyde, used for years by the experienced pathologists and tutors of residents, without particular precautions. Indeed, it was officially recognised as a carcinogen by EU only in 2016 (Regulation (EU) No.895/2014). However, we noted a significantly decrease of maximum exposures along the years, probably associated with both the improvement actions undertaken, and with the increased awareness of risks for health associated with the recognition of formaldehyde as a carcinogenic chemical. As a part of this process, the sharing and discussion of results with workers after each monitoring campaign and specific trainings may have contributed to increase the awareness, allowing to beyond habit.

In conclusion, formaldehyde is a hazardous chemical needed for fixing tissues in the health care sector, for which no effective alternative chemical is available yet. The protection of health care workers in the pathology lab calls for *ad hoc* risk management and mitigation measures. It is globally recognized that a general hierarchical approach in risk management must be implemented to eliminate the hazard when possible, substitute it with a less hazardous material or, if not feasible, control the hazard at or as close to the source as possible. A typical hierarchical risk management approach (Table 2) was implemented in the study work setting, coherently with a precautionary approach (Mirer and Stellman, 2008), to control exposure to formaldehyde associated with the lab's activity. In particular, although the elimination or replacement of dangerous chemical agents was not possible, the following measures were undertaken:

i. isolation of activities at greater emissions: new grossing room and new storage room for waste disposal, to contain the level of exposure of lab attendants;

ii. engineering control: improvement, implementation, and optimization of collection systems at the source (suction tables, chemical hoods, cabinets' air flow, etc.);

iii. administrative controls: adoption of new general standard operative procedures for the work with formalin and a new pathologist procedure to reduce the number of sample to be soaked in formalin;

iv. use of PPE: identification and purchase of PPE, to be worn only in the processing room;

v. check the efficacy of interventions: campaigns of environmental and biomonitoring of exposure.

These initiatives, together with the involvement of workers in the discussion of monitoring campaign results, to increase their awareness and find together the best technical solutions and the periodical training to refresh/update knowledge on chemical risks, can be recommended as useful actions to control the chemical risk in any pathology laboratory.

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