A Pragmatic Approach to Formalin Safety in Anatomical Pathology

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Abstract
Formaldehyde exposure is a safety concern in anatomical pathology, and it is considered a carcinogen by the International Agency for Research on Cancer (IARC). The Occupational Safety and Health Administration (OSHA) determined a set of regulations for formaldehyde industrial and laboratory use. There are no clinical and epidemiological data on increased morbidity or mortality from cancer among workers in the histology laboratory, where a 10% formalin or 4% formaldehyde water solution is used. Nevertheless, a certain set of monitoring and working practices is required to prevent adverse health effects. Based on the literature and personal experience, this article presents recommendations for handling adverse situations of formalin use in anatomical pathology. There is an emphasis on spills, clean up, and splashes. Regular monitoring of formaldehyde exposure, appropriate engineering controls, and the culture of professional laboratory work can help to employ formalin, the ubiquitous fixative in anatomical pathology, without harmful effects.

Formaldehyde Safety Concerns
Safety considerations include 3 unequal groups: carcinogenicity, general medical problems, and acute harmful effect. The formaldehyde carcinogenicity will have a disproportional length of presentation due to its significance as the main safety concern.

Carcinogenicity
In the “Safety in the Laboratory” section of the popular histological techniques manual, Dapson calls the formaldehyde “carcenogen.”6 However, the question of formaldehyde’s carcinogenicity is more complicated.

During the 1980s, there was a politically charged dispute between the US Environmental Protection Agency (EPA), OSHA, College of American Pathologists (CAP), Formaldehyde Institute, DuPont, and labor unions about formaldehyde’s occupational exposure evaluation,7 which ultimately required the involvement of the US Court of Appeals for the District of Columbia in 1987. In 1989, the American Medical Association (AMA) summarized literature data through 1985 on this subject. By mentioning that OSHA regards formaldehyde as a possible human carcinogen, AMA noticed that “this is a controversial opinion in the view of many industry and academic scientists.”7

The main organization that influences the assessment of reagents as carcinogenic is the World Health Organization’s (WHO) International Agency for Research on Cancer (IARC) based in Lyon, France. The IARC summarizes literature data, predominately epidemiological research, as well as some experimental studies. According to IARC, formaldehyde is
Formaldehyde has an apparent deleterious effect that everyone experiences with a different degree of tolerance. Eye irritation, tears, and some sensations of odor are common in most individuals. There can be an adverse reaction of hypersensitivity. Relatively low concentrations have provoked symptoms in some individuals. It has been suggested that long-term inhalation of formaldehyde may trigger classic IgE-mediated nasal allergy in atopic individuals. Clinical data document dermatitis and skin sensitization among histotechnologists after chronic exposure to formalin.

A study of 34 workers in a gross anatomy laboratory with an exposure to formaldehyde ranging from 0.07 to 2.94 ppm during dissection operations revealed decreased forced vital capacity (FVC) and forced expiratory volume in 3 seconds (FEV3).

There are scarce studies of histotechnologists in regards to formaldehyde exposure. One of the studies presented results of chronic workplace exposure to formaldehyde and solvents in 280 non-smoker histology technicians studied during national workshops for 4 years. The study found a small difference in steeper decrement in vital capacity and flows in comparison with the control population.

A group of 15 histology technicians who worked in 3 different pathology departments had a subclinical statistically significant increase in nasal resistance. A chronic cumulative effect of formaldehyde exposure has been excluded in this study.

Although personal experience has only anecdotal value, I am glad to state that for many years of work in anatomical pathology, I have not seen or heard about any coworker with a formaldehyde-related general health problem or neoplasm. Ironically, the anatomical pathology manager I worked with tried to avoid any presence in the histology laboratory for good reason. While entering the laboratory, she immediately developed a face rush with eye, nose, and throat irritation. She has never worked in a histology laboratory before.

**Preventive Measures in the Surgical Pathology Laboratory**

For the most part, the relatively low threshold of response and the disagreeable, irritating pungent suffocating odor of formaldehyde prevent one from breathing intolerable amounts of gas. Although in rare massive acute exposures, victims have suffered pulmonary edema and even death. Such a situation cannot happen in an anatomical pathology practice due to the limited amount of formalin that is used.

The US Department of Labor passed The Formalin Standard in 1987. This standard was revised in 1992 to include lower exposure limits and new monitoring procedures. Besides the regulations that must be obeyed, there are a vast number of actions which require knowledge of the substance a person works with, in this instance formalin.

**Formaldehyde vs Formalin Safety Rationale**

The physical and chemical characteristics of formaldehyde are presented in some detail to provide a background for safety considerations. These data can help a laboratory professional better understand how to prevent its harmful effects.

Formaldehyde (HCHO), a colorless gas, is rarely found in its original state because it has a short half-life in air due to its decomposition in light. Formaldehyde (methanal) is manufactured as a product of catalytic oxidation of methanol (CHOH). The concentrated water solution (37%–40%) of formaldehyde is called Formalin by its German trade name. The anatomical pathology practice uses Neutral Buffered Formalin (NBF) to prevent acidification due to formaldehyde’s...
tendency to be oxidized to formic acid. The buffer solution also enhances formation monomeric formaldehyde (methylene hydrate), as a fixation reagent.

There are 2 aspects of formaldehyde exposure: local at the place of the initial contact (respiratory and digestive tracts, skin, etc.) and general as a result of absorption. More than 90% of inhaled formaldehyde is absorbed in the upper respiratory tract and mixes with the endogenous formaldehyde pool. Endogenously produced, formaldehyde is a metabolic intermediate in all cells. The endogenous concentration of formaldehyde in human blood does not increase (2.77 microgram/gram) after inhalation for 40 minutes of 1.9 ppm formaldehyde. Because of its rapid metabolism in erythrocytes, no increase in tissue concentration of formaldehyde is detectable even moments after exposure. Absorbed formaldehyde can be oxidized to formate and exhaled as carbon dioxide. These data suggest that local exposure has the most significance from the safety approach.

As a small light molecule, formaldehyde evaporates easily from the formalin surface. The kinetic energy of evaporation depends on temperature, humidity, and air flow. The thinner the layer of the liquid where formaldehyde is dissolved, the easier formaldehyde molecules can overcome the intermolecular boundaries, including Van der Waals force, and escape to the gas phase. The kinetic theory also explains the well-known observation that evaporation depends on the temperature (the higher the more intensive). Everyone who had to open a working tissue processor during a formalin phase can remember experiencing irritation of the eyes or throat. Humidity prevents evaporation and thus limits formaldehyde gas escape from the liquid phase. Air flow increases formaldehyde escape from the formalin surface as well. Formaldehyde gas physics should be considered in the organization of the laboratory working space and in emergencies of formalin spills.

As far as safety considerations are concerned, some chemical features of formaldehyde behavior in its formalin water solution are important to discuss. Formaldehyde forms in water methylene glycol (methylene hydrate). The equilibrium between methylene glycol and formaldehyde lies in favor of methylene glycol. Formaldehyde requires conversion from methylene glycol for covalent chemical reaction. This feature has a well-known name, especially to histotechnologists, fixation. Formaldehyde behaves as a fast penetrating, but slow fixative. Fast penetration is due to diffusion of methylene glycol. The slow fixative feature depends on covalent chemical reaction of carbonyl formaldehyde with proteins, glycoproteins, nucleic acids, and polysaccharids for intra-and intermolecular cross-linking of macromolecules. A slow fixation rate is positive from a safety perspective because it buys time for formaldehyde elimination from the upper respiratory and digestive tracts before fixation damage is done.

Some anatomy and physiology data might be useful for understanding formaldehyde damage prevention methods. They should be considered in connection with physical and chemical features of formaldehyde and its formalin water solution.

Formaldehyde’s high solubility in water causes fast absorption in mucus of the upper respiratory tract, predominately in the nose cavity and sinuses. A mucous blanket is the body’s first line of defense in formaldehyde exposure. The nasal mucosa of the lateral, inferior, and medial walls of the nose, paranasal sinuses, and conches is covered with ciliated pseudostratified, columnar epithelium whose cilia form a carpet on which dust settles. The vibration of the cilia in the direction of the conches drives out the settled dust. The mucous membrane contains mucous glands (Goblet cells) whose secretions produce mucus 1 liter per day. It wraps around the dust, makes its expulsion easier, and humidifies the air. The mucous blanket, which is mowed by the cilia, flows to the sinus ostia and then to the nasopharynx where it is excreted or swallowed. Mucus is 97% water. Formaldehyde has absolute solubility in water. Formaldehyde is diluted and absorbed. It does not reach the pharynx under non-extreme exposure. However, formaldehyde can damage the cilia, the most vulnerable structures. All preventive measures should be concentrated on minimizing this damage.

**Monitoring**

The use of formalin has changed substantially since the years when main epidemiological studies were conducted. Now most laboratories use pre-filled containers for biopsies opened for a short time just to remove the specimen. Material of large specimens is received in a fresh state and often processed before fixation. There are different models of laboratory stations equipped with exhaust engineering devices. Of course, monitoring of formaldehyde exposure at the working place changed the game.

The threshold for subjective effects varies considerably from 0.1 to 2.5 ppm; most people feel symptoms in the throat first. According to OSHA, the odor threshold is 0.8–1 ppm. The limit for airborne exposure to formaldehyde, set by OSHA’s Formaldehyde Standard Time-Weighted Average (TWA), is 0.75 ppm in an 8-hour time-weighted average and 2 ppm for a 15-minute Short-Term Exposure Limit (STEL). In 1987, TWA was 3 ppm.

OSHA requires monitoring by the employer if the exposure to formaldehyde exceeds the 0.5 ppm (the Action Level) or the 2.00 ppm STEL. A “representative employee” is asked to wear a sampling passive badge device to collect formaldehyde (industrial monitoring uses a different methodology). Determinating TWA collected from the employee’s breathing zone air during full shift is considered optimal. Depending on exposure levels, OSHA determines rules of employee monitoring as initial and periodic. Usually monitoring is done on an annual basis, although there can be variations in different institutions.

Two personal stories reflect the relative value of this monitoring. Being “soaked” by formalin for many years, my annual monitoring had never revealed any abnormal reading. Accidentally, I left a monitoring badge on my coat near a bucket with formalin overnight, but someone opened the lid. I do not have any explanation why the reading was normal. Recently, during annual monitoring, personal samples at 2 grossing stations collected on the same day near each other came back with different readings. One was 10 ppm while another showed 0.055 ppm. No one on this day reported any odors that would be consistent with high formaldehyde exposures. It was a simple explanation—splashing could contaminate the sample badge—but management became so agitated that a special consulting firm was contracted and spent many days monitoring performances, meetings, and papers. No one wants to take chances when dealing with regulatory governmental institutions. Unfortunately, the right idea of formaldehyde exposure monitoring collides with fear that it is not the best adviser to common sense.
Usually histology laboratories use a passive badge monitor containing bisulfite-impregnated paper with chromotropic acid analysis with TWA validation range from 0.2 to 4.9 ppm and overall error +/- 18.6%.

Annual monitoring is mandatory, but during the year many events might occur with the disruption of the ventilation system and other violations of formalin handling. An established monitoring system, which includes passive monitoring of areas, not only individuals, hood vanecometers, filtering systems, handheld formalin monitors, and even an oximeter, might be beneficial.

Perhaps in addition, it is reasonable to have qualitative monitors on a regular basis, like canaries in the old coal mines for methane and carbon monoxide overconcentration detection. Some reagents, like histology laboratory Schiff reagent (red) or reticulin diamine silver solution (black), in contact with aldehydes can provide a warning that will provide an alert when there are signs of formaldehyde overexposure at different areas of the histology laboratory. The bisulfite indicator that is a reagent in the standard monitor badge might be used for qualitative monitoring. I am using this opportunity to challenge manufacturers in developing such monitors. The market can be sufficient for a commercial return of the development investment for such a device.

Meanwhile, a Schiff reagent would be useful to have handy in every surgical pathology laboratory to prevent sniffing containers with formalin in question. This popular habit is obviously unhealthy.

### Spill Handling

Formalin spills are the real challenge. They are not that rare and require attention, training, and understanding. It makes sense to discuss this unfortunate situation in detail.

Every institution has policies and protocols regarding handling chemical hazard spills which reflect Material Safety Data Sheets (MSDS). OSHA has a Hazard Communication Standard (29 CFR 1910.1200) that includes provisions and emergency actions to take in case of an accident. This article provides the author’s approach to handling formalin spills based on personal experiences and physical and chemical features.

An article about laboratory safety had a section titled, “What to Do if Formaldehyde Is Spilled.” Formalin is spilled in the histology laboratory. This distinction is substantial for cleaning up actions when the goal is to prevent evaporation of formaldehyde from its water solution, namely formalin.

How much formalin constitutes a spill as far as safety is concerned? OSHA has an “informative” definition as an “appreciable quantity.” For example, OSHA recommends “if a spill of appreciable quantity occurs, leave the area quickly unless you have specific emergency duties” and wait for the designated person to stop the leak. This is probably for industrial situations. A histology laboratory rarely manipulates at the same time quantities more than 1 gallon (3.8 liters). Usually spills, which can be a safety concern, range from 50 ml to 2 liters. Of course, there is a difference where the spill occurs: on the grossing station’s table or on the laboratory floor. By the way, a spill of 20–40 ml osmium tetroxide is more dangerous than a spill of a gallon of 10% formalin.

Who is supposed to handle a formalin spill? Should you seek outside help if a large spill occurs? What constitutes a large spill for a histology laboratory? All of these provisions should be included in the safety section of the laboratory’s Standard Operating Procedures (SOP). If the institutional policies definitely determine the amount of the spilled formalin that requires Hazardous Materials Response Department involvement, of course, a phone call is obligatory to be in compliance. However, often it is useless and even contra productive because the deficit of time is a very substantial factor. As a rule, spills are not planned but occur suddenly. Hopefully, a spill kit is stored in every laboratory that uses formalin.

Fortunately for anatomical pathology laboratories, the formalin spill falls into the Manageable Chemical Spill category short of Immediately Dangerous to Life and Health (IDLH) when the exposure can be lethal or cause irreversible damage. In most instances, the spill can be cleaned up by a non-hazmat trained worker.

Formaldehyde gas evaporation depends on the square surface but not on the spilled fluid volume. Formalin in the 50 ml container is relatively harmless, but the same amount that has been spread on the board or floor immediately irritates. The mode of handling the spill is to contain it by minimizing the surface of the spill.

Laboratory rooms, where spills occur, are not empty and floors are not completely flat. Formalin should be contained as much as possible, otherwise it will spread everywhere including under tables and equipment with gradual evaporation. Cleanup of a spill should start immediately with or without a call for outside help.

First and foremost, appropriate personal protective equipment (PPE), such as a disposable gown, gloves, and safety glasses, must be worn. Vented goggles are preferable while cleaning up. I have not seenvented splash-proof goggles in any laboratory. Additionally, a wet mask (preferably a Kimberly-Clark Face Shield type) should be worn. The wet mask is ideal because the evaporating formaldehyde goes through the multi layers of a dry mask, but a wet mask partially absorbs formaldehyde due to its high solubility in water. What about a full-face respirator with formaldehyde-absorbing cartridges, which is usually recommended? Use it if it’s available, fits the face, and the employee is trained to use it. In practice, all 3 conditions are not met.

Both types of laboratory gloves, nitrile and latex, used in anatomical pathology laboratories are eventually formalin permeable. However, the main problem is that tiny, almost invisible round tears occur without any apparent reason and usually go unnoticed. Nitrile gloves seem more resistant to mechanical damage. Every day practice gloves should be changed often for safety reasons, as well as to prevent specimen contamination. In a spill cleanup, this rule is just obligatory. Double gloves are highly recommended.

The spill can be contained by forming a dike-like wall of wet paper towels/cloth around it to absorb formalin as much as possible. This prevents formalin from spreading onto the floor and under the tables. The thin layer of formalin evaporates formaldehyde intensively. The absorbing material is moved from the periphery to the center. The soaked paper or cloth should be collected in sealable plastic waste bags that are placed in a closed container and replaced by dry paper/cloth. While moving the wet paper/cloth towels to the center, the floor can be covered by a neutralizer, such as Spill-X-FP. Absorption and polymerization require time, at least 10–15 minutes.

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Simultaneously, it is necessary to enhance ventilation at grossing stations and other areas, as well as to open running water faucets to increase humidity in the room diminishing formaldehyde evaporation. It is necessary to change the wet face mask many times because it becomes saturated with formalin. In this situation, the wet mask also becomes an obstacle to breathing under conditions of intensive physical labor during the clean up operation.

If an outside cleaning team arrives, let them finish the job according to institutional policies. If an outside help team is not involved, make sure to put neutralizer into containers with clean up materials soaked with formalin. The entire area of the clean up requires moping with generous amounts of soapy water.

Taking care of the individuals involved in the spill cleanup should be a priority. Of course, if somebody feels ill, medical help must be provided. In an acute exposure, when the dose of formaldehyde excites the absorption and dilution by the nose cavity mucus layer, most people first feel irritation of the throat. This is especially true under conditions of emergency intensive work and communications. Milk or alkaline drinks (for individuals who cannot tolerate milk) is optimal for immediate drinking. Keep it in the mouth and gargle.

Some years ago, late in the evening, my coworker dropped a bucket with cassettes collected for processing and 2 liters of formalin on the floor. In a rush to collect the dispersed on the floor cassettes and cleaning up the spilled formalin, we violated every rule of safety. As a result, I had a painful sore throat and lost my voice for almost a week.

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<tr>
<th>Table 1</th>
<th>Formalin Spill Management</th>
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<td><strong>Individual Actions</strong></td>
<td><strong>Engineering Measures</strong></td>
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<tr>
<td>Contain to minimize evaporation</td>
<td>Intensify local and general ventilation</td>
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<tr>
<td>Absorb in wet paper/fabric towels</td>
<td>Humidify the space of the room</td>
</tr>
<tr>
<td>Eliminate absorbed formalin towels in closed bags</td>
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</tr>
<tr>
<td>Neutralize absorbed formalin</td>
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<tr>
<td>Mop the floor with soapy water</td>
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I knew how to handle such an injury. Since then, the first thing I do when entering the histology laboratory is to put on safety glasses.

Splash-proof goggles are unpractical for every day work because they are uncomfortable, limit the vision field, and irritate peri-orbital skin. OSHA is not categorical regarding goggles, ie, wear goggles or some other type of complete protection for the eye. Good safety glasses with above and side shields completely protect from splashes. Some recent models are unreliable because the modern design leaves too much open space for formalin splashes. A shield mask alone, like the Kimberly-Clark type, does not provide reliable protection from splashes. Personal glasses obviously cannot be substituted for safety glasses that require wearing them both.

Eye washing after a formalin splash is obligatory, and every histology laboratory must have an eyewash fountain. Usually it is recommended to rinse the eye for a full 15 minutes. Nevertheless, in my opinion, this is not only practically unsustainable but wrong. It is completely sufficient to wash for only a couple of minutes. Tap water is obviously not sterile; it contains chemical substances which irritate the sclera and conjunctiva. Formaldehyde cannot penetrate deep. Although uncomfortable, water should be cold because warm formaldehyde penetrates faster, but the goal is the opposite. It is more reasonable to allow sterile tears to wash away the remnants of formalin. Though this doesn’t sound seriously sufficient, I wish I had an onion when my accidents occurred, which would emanate bactericidal ethers that can generate healing tears in abundance. Medical help would be highly recommended if the individual was uncomfortable after eye rinsing.

Splashes

Formalin spills are often accompanied by splashes that are another safety concern in the laboratory and require a different set of precautions. Of course, splashes occur without spills also. They are always a result of poor working practices or negligence.

Just as a final confession, many years ago when the pathologists grossed by themselves and the specimens always arrived at the laboratory after surgery in formalin, I had formalin splashes in my eyes twice. While opening ovarian cysts, the formalin fixed content burst out during the cut. Intolerable pain, treatment in the emergency room, and some time of persistent soreness in the eyes were the punishment for working without glasses. Clouded vision lasted for a week. This happened before eye washing stations existed and before
(the flow rate at the front of the hoods) in the 60–100 fpm range. The velocity should be certified and periodically tested. The optimal working place is near the back-vented area with horizontal or angled backward sashes.

Proper work practices can diminish short-term formaldehyde exposure. Every detail counts. Here are some examples.

Everything can make a difference, including how the container with pre-filled formalin is opened, how the specimen is taken out, and how carefully the lid is placed back on. Storage of containers with wet specimens and after biopsy processing should be carefully monitored to prevent formalin evaporation.

After formalin fixation, brain washing (literally) for post autopsy cut up, should be carefully carried out. Preferably, the procedure should be done under the hood. The same applies to the additional cut up of previously fixed surgical pathology specimens such as the colon (often additional search for lymph nodes), breast, etc. In practice, this requirement is often violated.

Fixed in formalin bones require special attention. Bone dust during sawing makes formaldehyde inhalation more traumatic due to injury of the upper respiratory tract by small sharp bone particles loaded with formalin.

Formalin warms up in the bucket with grossed cassettes by the end of the day by chemical reaction during fixation. Placing the bucket with cassettes on a cold plate can decrease formaldehyde evaporation while opening the lid to put in new cassettes and for other manipulations.

While opening a working tissue processor in the formalin phase, a protective mask and safety glasses are obligatory (goggles are preferable). The warm formaldehyde vapor and possible splash can be harmful. Of course, any heating of formalin for fixation in a non-laboratory microwave oven is dangerous. Fortunately, modern microwave processors make this bad working practice more and more obsolete.

Formalin recycling, besides questionable economical benefits, might be a source of saturation of laboratory air with formaldehyde vapor. Areas of formalin neutralization should be provided with effective ventilation that is not easy to achieve if large quantities are collected. The formalin neutralization practice in laboratories is controversial. The limited amount of formalin in use due to pre-filled containers make the large poorly closed capacities with formalin for neutralization out of date. The laboratory must comply with local EPA regulations—determine whether or not formalin can be dumped in the wastewater system in small increments without damaging the biology of waste treatment.

The processing cassettes should be washed off from formalin during the time-consuming count after grossing. It does not harm the material because the already penetrated formaldehyde is bound with the tissue. Only formaldehyde that evaporates from the tissue surface is harmful.

The list of working practice rationalizations that decrease formaldehyde exposure can be endless. For example, smaller stock formalin boxes and absorbing neutralization pads, secure collection of soaked formalin waste, etc.

**Conclusion**

The harmful effects of formaldehyde in anatomical pathology should be kept in perspective without underestimating them but also without overreacting. Monitoring, PPE, and measures for limitation of formaldehyde exposure substantially diminish its harmful effects. While using formalin, appropriate working practices include minimizing formaldehyde evaporation as the safety rationale. Formalin can remain for a long time as the ubiquitous fixative reagent in anatomical pathology.

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4. OSHA. 29 CFR 1910.1048

