Formalin, an aqueous solution of formaldehyde, is widely used in tissue preservation protocols due its favorable fixative properties. However, its routine use in healthcare settings may also expose workers to underappreciated hazards. In studies stretching back several decades, exposure to formaldehyde, the main ingredient in formalin, has been linked to respiratory tract and skin irritation after immediate exposure. Long-term formaldehyde exposure has also been shown to increase the risk for developing nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia. Indeed, basic science research and studies in various animal models have revealed the mutagenic potential of formaldehyde, underscoring the need for safety protocols that help mitigate exposure. The recent introduction of innovative solutions for specimen handling are helping to reduce or eliminate formaldehyde exposure in healthcare settings.
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INTRODUCTION

Formalin, a 37% to 40% aqueous solution of formaldehyde, is widely used in tissue preparation protocols. The fixative properties of formaldehyde were discovered serendipitously in the late 19th century by the German physician Ferdinand Blum, who was studying the chemical as a potential antiseptic. Formaldehyde mechanistically instigates cross-linking of proteins in biologic samples containing cells, tissue, or entire organisms. Although slow acting, formaldehyde is considered a highly efficient fixative due its small size, which allows it to easily permeate cell walls and membranes. Laboratory practice typically employs 10% neutral buffered formalin, which contains around 4% formaldehyde (i.e., a 10% solution of a 37–40% formaldehyde solution). The addition of phosphate-buffered saline in formalin neutralizes pH, while methyl alcohol in the solution prevents polymerization, thereby enhancing its fixative properties.

However, formaldehyde exposure in occupational settings is associated with numerous health hazards, including eye and respiratory stress, as well as potentially elevated risk for cancer locally at the site of exposure and distally after the initiation of carcinogenic pathways. Formaldehyde is listed as a known carcinogen by numerous health and safety regulatory and oversight bodies. The cancer risk associated with exposure to formaldehyde has been studied since at least the early 1980s, with a long list of historical references prior to that time demonstrating associations between formaldehyde exposure (mostly in the context of occupational settings) and various health hazards. Based largely on a 1980 study finding increased cancer risk among rats exposed to formaldehyde, the National Toxicology Program (NTP) listed the chemical as a potential carcinogen in 1981. The Environmental Protection Agency (EPA) designated the link as probable in 1986. The International Agency for Research on Cancer (IARC) later classified formaldehyde as a known human carcinogen. Subsequently, the NTP upgraded the listing of formaldehyde to identify it as a known human carcinogen. In 2011, the National Academy of Sciences reported that formaldehyde exposure is associated with increased risk of developing cancer based on epidemiologic evidence and biologic rationale. Other agencies, such as the Occupational Health and Safety Agency (OSHA) and National Institutes of Health (NIH), have also noted elevated risk for respiratory tract irritation associated with immediate exposure while also noting that formaldehyde is known to be carcinogenic and mutagenic.

In light of these concerns, several regulatory and oversight bodies have established safe handling protocols, as well as a series of rules and regulations that employers must follow to ensure safe working conditions for individuals potentially exposed to formaldehyde as a result of using formalin. Most of these recommendations focus on the idea of ensuring that exposure does not exceed safety standards that have been established in numerous
scientific studies. It is not entirely clear, however, whether such guidelines sufficiently protect all individuals who may come in contact with formalin or formaldehyde while working in health care settings. At the same time, there may be alternative solutions that eliminate the potential for formalin exposure, thereby obviating concerns over what may constitute an “acceptable safety level” of formaldehyde or formalin exposure.

### POTENTIAL HAZARDS ASSOCIATED WITH IMMEDIATE AND LONG-TERM EXPOSURE TO FORMALDEHYDE

Formaldehyde is a highly reactive chemical that has potential to cause tissue irritation and damage on contact. While acute ingestion of formaldehyde is rare, it can lead to severe consequences, and fatalities have been reported after consumption of as little as 30 mL of formaldehyde. More common sources of formaldehyde exposure are inhalation and skin exposure.

Formaldehyde inhalation has been shown to have immediate implications for health, inducing various breathing-related and respiratory tract symptoms, as well as cumulative effects, as continued exposure increases sensitivity to upper and lower respiratory tract discomfort. In a study tracking the effects of formaldehyde exposure in workers in a gross anatomy lab, 94% were exposed during dissection procedures to levels exceeding the ceiling value of 0.3 parts per million (ppm) suggested by the American Conference of Governmental Industrial Hygienists (ACGIH). Roughly a third of workers exceeded 0.5 ppm of inhalation exposure during a typical 8-hour shift, a cut point established by OSHA as requiring initiation of active monitoring protocols. In the latter study, decrements were noted in forced vital capacity (FVC) and forced expiratory volume in 3 seconds (FEV3), and reports of irritation of eye (88%), nose (74%), throat (29%), and airways (21%) were common. In a separate study, Kilburn and colleagues demonstrated a decrease in vital capacity among histotechnologists after long-term exposure. Moreover, evidence of a linear relationship between exposure levels above 0.3 ppm and severity of eye, nose, and throat irritation have been noted in the literature since at least 1966. Other studies have noted significant upper airway and eye irritation at exposure levels as low as 0.1 ppm.

The potential for contact formaldehyde exposure to cause primary skin irritation or allergic dermatitis has been known since at least the 1940s. Historical studies have also shown that skin contact with formaldehyde may cause urticaria. Several studies have established that formaldehyde is a potent experimental allergen in humans. The potential for allergic contact dermatitis, histopathological abnormalities of the nasal mucosa (such as hyperplasia, squamous metaplasia, and mild dysplasia), occupational asthma, reduced lung function, altered immune response, and hemotoxicity have been consistently reported in the literature over the past several decades.

Formaldehyde exposure has also been suggested as a potential source for numerous nonspecific symptoms related to the nervous system. Construction workers exposed to formaldehyde in resins reported thirst, headaches, dizziness, apathy, and inability to concentrate; and others exposed to phenol-formaldehyde resins complained of headaches, dizziness, disturbed sleep, weakness, and apathy. Changes monitored on electroencephalography have been noted among individuals exposed to as little as 0.044 ppm of formaldehyde. Additionally, a probable link between formaldehyde exposure and Reynaud Syndrome has also been reported.
Most research to date on the link between formaldehyde exposure and cancer risk distinguishes between tumors occurring at the “portal of entry” (e.g., nasopharyngeal and sinonasal cancers) and distally (e.g., lymphohematopoietic and hematopoietic cancers and solid tumors). On the whole, these associations are based on such strong and convincing epidemiologic evidence that it is unlikely that either chance or bias would explain such findings. The link between formaldehyde exposure and cancer risk is also supported by biologic rationale, as well as a voluminous library of studies providing evidence of carcinogenicity in laboratory animals.

An increased risk for developing portal of entry cancers among individuals exposed to formaldehyde has been shown in a number of large-scale clinical studies. A multicenter, population-based case control study of patients followed by the National Cancer Institute’s SEER program found a trend toward increasing risk of squamous and unspecified epithelial carcinomas and increasing duration and cumulative exposure, even after controlling for cigarette use, race, and other risk factors. The link with nasopharyngeal cancer was noted in a cohort of workers in formaldehyde industries followed as part of a separate National Cancer Institute study. An association with sinonasal cancers was demonstrated in a pooled analysis of 12 case-control studies finding significantly increased risk of adenocarcinoma and an elevated risk of squamous cell carcinoma among men and women with a high probability of exposure to formaldehyde.

Although the exact mechanism by which distal cancers develop in the context of formaldehyde exposure is unclear, there is nevertheless strong epidemiologic evidence linking formaldehyde exposure with myeloid leukemia among individuals with different occupational exposure risks, including formaldehyde industry workers, garment workers, and funeral industry workers. The most probable explanation for the elevated risk is that long-term exposure, likely occurring at a portal of entry, initiates one or more systemic mechanistic pathways that ultimately result in carcinogenesis. Supporting evidence for the latter is found in studies highlighting increased genotoxicity and mutagenicity, hematologic effects, and effects on gene expression in circulating blood cells of individuals with exposure to formaldehyde. Furthermore, formaldehyde exposure has been shown to incite gene alterations in experimental models, in vitro, in animal models, and in humans. Specific to lymphohematopoietic cancers, several non-mutually exclusive biologic mechanisms have been proposed in the literature, including that formaldehyde may: (1) directly damage stem cells in the bone marrow; (2) cause damage to circulating stem cells; and/or (3) damage pluripotent stem cells present in the nasal turbinate or olfactory mucosa. Notably, while the specific dynamics of tumorigenesis after exposure to formaldehyde have not been fully elucidated, regulatory and oversight agencies have stated that this lack of understanding should not distract from the weight of evidence regarding the carcinogenic potential of formaldehyde. According to the National Toxicology Program of the US Department of Health and Human Services, “while it would be desirable to have an accepted mechanism that fully explains the association between formaldehyde exposure and distal cancers, the lack of such mechanism should not detract from the strength of the epidemiological evidence that formaldehyde causes myeloid leukemia.”

Several professional organizations offer guidance for handling of biopsy samples in which formalin is used as a preservative or fixative agent. In addition, OSHA, acting under the auspices of the Department of Labor, has designated a series of rules and regulations for
safe handling of formalin, including strategies for reducing potential exposure. For example, employers are required to perform monitoring for individuals who have brief but intense exposure to formaldehyde and they must provide safety equipment for any employee who handles formaldehyde or formalin, including respiratory protection, protective gloves, eye protection, and other protective equipment, such as impervious clothing.\textsuperscript{10} The agency also requires employers to enact engineering controls that limit workers’ exposure risk,\textsuperscript{12} which may include use of local exhaust ventilation (such as a fume hood when opening formaldehyde-containing containers) or general mechanical ventilation, whereby fresh air is continually cycled into the workroom to lower the breathing zone concentration of formaldehyde. It is unclear, however, whether all workers in a typical healthcare setting have access to the same degree of protection against formaldehyde exposure. For instance, the worker who opens a biopsy sample in the lab does so using a fume hood, while the individual who collects the sample most often does not use a fume hood.

The Role of Innovation

While engineering controls to reduce exposure to formaldehyde appear to be the most optimal strategy for harm reduction, even OSHA acknowledges that such measures may not always be feasible, in turn shifting the burden to employers to safeguard workers against the dangers of formaldehyde exposure.\textsuperscript{10,12} Indeed, installing general mechanical ventilation across all areas of a hospital or other healthcare setting in which formaldehyde is used may be cost-prohibitive, not physically possible, or else a less than desirable option.

Recent innovations may offer an alternative and decidedly more cost-efficient mechanism for reducing exposure to formaldehyde. The BiopSafe Biopsy Sample System (Merit Medical) is a novel and innovative solution to the need for safe protocols for physicians, technicians, and nurses to use during tissue preparation activities.\textsuperscript{32} The system consists of a vial and a proprietary lid system that contains capsuled formalin. The product is recommended for use as part of a simple three-step process:

1. The sample is placed in the vial
2. The lid is sealed
3. Pressure on the lid releases formalin to the sample

Because all maneuvers are performed inside the sealed vial, use of the system in this manner reduces formalin exposure while still preserving the integrity of the biopsy sample.\textsuperscript{32} Once preserved, the sample is safe for transport with no further risk of vapor release or liquid spill.

BiopSafe was validated in a two-part study. In the first part, interviews were used to assess staff’s attitudes toward BiopSafe relative to existing protocols. The second part consisted of four tests to study four aspects of BiopSafe using Hounisen Laboratoriedstyr A/S’s closed fixation system as a control: (1) the fixability of BiopSafe during worst case scenarios during prolonged transport; (2) the influence of the fixation time on the fixation by BiopSafe; (3) the fixability of BiopSafe for specific immunohistochemical staining; and (4) applicability of BiopSafe in the institution’s existing routine.\textsuperscript{33} The authors reported that the closed fixation system used in comparison contained 1-5% formaldehyde and 1–5% methanol.\textsuperscript{33} The formalin in the BiopSafe fixation system contains ~ 4% w/w formaldehyde and <2.5% w/w methanol. The authors concluded that integration of BiopSafe resulted in a low reported level of issues or complications while using the system, and that BiopSafe provided comparable effectiveness as a fixative as long as standard fixation times were used. In addition, there was less risk of fixation artifacts affecting the quality of the sample with BiopSafe compared to the closed formaldehyde system used as a control.\textsuperscript{33}

CONCLUSION

Throughout healthcare, various safeguards are used to mitigate exposure to potentially dangerous substances. The routine use of gloves and splashguards to protect against blood exposure is one example. As well, lead aprons are used by radiographic technicians and patients to reduce unwanted exposure to radiation. At the current time, however, safeguards that would protect against formaldehyde exposure are not nearly as universally understood or practiced. Although federal mandates require employers to provide for safe conditions for workers in the context of formaldehyde or formalin, there may be several underappreciated exposure risks throughout a typical healthcare setting. The established science regarding the health hazards following formaldehyde exposure suggest there is no true safe level of exposure. For instance, changes on electroencephalography have been noted after exposure to as little as 0.044 ppm of formaldehyde\(^2\) and studies have found significant upper airway and eye irritation occurring after exposure to 0.1 ppm of airborne formaldehyde odor\(^4\)—both of which are far below the 0.5 ppm action level established by OSHA.

Thus, while well intentioned, the current focus on establishing safe and acceptable levels of formaldehyde exposure may provide a false sense of security. On the other hand, innovative solutions currently in the marketplace have potential to reduce exposure to formalin, and thus its main ingredient. Moreover, technology like the BiopSafe Biopsy Sample System protects the individual taking the biopsy sample from formaldehyde without the need for a fume hood in the treatment area. The sealed container further minimizes the potential for leakage or spill, thereby improving safety during transport.

See how the BiopSafe Biopsy Sample System can reduce exposure to formaldehyde by requesting a sample of containers at BiopSafe.us/get-in-touch/
REFERENCES
