REVIEW

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Formaldehyde in pathology services: from molecular toxicity to histopathological change and occupational risk

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Abstract

Background and Objective: Formaldehyde (FA), classified as a Group 1 human carcinogen by the *International Agency for Research on Cancer* (IARC), constitutes a significant occupational hazard within hospital pathology service, where it remains the "gold standard" fixative for tissue preservation. Despite widespread recognition of its toxicological properties, the specific carcinogenic and non-carcinogenic health risks confronting pathology personnel subjected to chronic, low-level, and intermittent exposures remain incompletely characterized. This review synthesizes the current body of evidence regarding the cellular and molecular mechanisms of FA toxicity, histopathological (HP) alterations in target tissues, and associated occupational health risks among pathology staff. *Study selection for review*: A comprehensive literature search was conducted across *PubMed/MEDLINE*, *Web of Science*, and *Scopus* databases, encompassing publications through December 2025. Studies were selected based on relevance to FA toxicity mechanisms, HP effects, and occupational exposure in pathology settings. Given the heterogeneity of study designs and outcomes, a narrative synthesis approach was adopted. *Evidence synthesis*: The synthesized evidence demonstrates that pathology personnel are routinely exposed to FA concentrations exceeding recommended occupational exposure limits (OELs). At the cellular level, FA exerts toxicity through deoxyribonucleic acid (DNA)–protein crosslink formation, oxidative stress induction, and inflammatory pathway activation. HP examination of exposed individuals reveals a characteristic progression from ciliary loss and goblet cell hyperplasia through squamous metaplasia to epithelial dysplasia in the nasal mucosa. Non-carcinogenic health effects, including respiratory symptoms and genotoxicity biomarker elevation, are highly prevalent. However, direct epidemiological evidence substantiating elevated cancer risk within this specific occupational cohort remains limited, mainly due to improper (occupational medicine) reporting. *Conclusions*: This review confirms substantial non-carcinogenic health effects among pathology personnel, with documented HP alterations representing preneoplastic changes at the portal of entry. The mechanistic evidence supports biological plausibility for carcinogenic risk, though epidemiological confirmation specific to this workforce remains lacking, highlighting a critical research gap.

Keywords: formaldehyde, histopathology, DNA–protein crosslinks, oxidative stress, occupational exposure, tissue fixation.

Introduction

Formaldehyde (FA; formalin; methanal) is a ubiquitous, colorless, gaseous organic compound characterized by a pungent odor and considerable toxicity. Paradoxically, it remains an indispensable chemical reagent in pathology services within healthcare institutions, where it serves primarily as the "gold standard" fixative for tissue specimens [1, 2]. The 10% neutral buffered FA routinely used in histopathology laboratories contains approximately 4% FA by weight, and its crosslinking properties are essential for preserving cellular morphology, preventing autolysis, and rendering tissues suitable for paraffin embedding, sectioning, and subsequent histological analysis [3, 4].

Although FA's preservation properties are essential for accurate histological diagnosis, its volatile nature and toxicity constitute a significant occupational health hazard for medical personnel operating within these environments [1, 2]. The same chemical reactivity that makes FA an effective fixative, mainly its ability to form covalent bonds with nucleophilic sites on proteins and nucleic acids, underlies its toxicity to living tissues [5, 6].

The safety profile of FA is complex and remains a subject of ongoing scientific debate. While acute toxicity at low concentrations is limited, prolonged occupational exposure, even at concentrations below established occupational exposure limits (OELs), has been associated with a broad spectrum of adverse health effects [7]. These effects range from acute irritation of mucosal membranes to carcinogenic outcomes, thereby placing laboratory technicians and pathologists at potentially substantial risk [8, 9].

Occupational exposure to FA occurs across numerous industrial sectors; however, healthcare workers, particularly those employed in histopathology laboratories, represent a critical high-risk population owing to their daily manipulation of FA solutions, frequently within inadequately ventilated workspaces [10, 11]. This professional exposure is further compounded by the specific working environment of hospital anatomic pathology laboratories, which may involve concurrent exposure to additional chemical agents including xylene, toluene, and alcohols used in tissue processing. Although non-occupational sources, including certain consumer products and environmental pollution, contribute to the overall body burden in humans, the concentrated and repetitive nature of professional exposure within these

laboratory settings constitutes the primary concern for the etiology of occupation-related diseases [12].

The classification of FA as a human carcinogen (Group 1) by the *International Agency for Research on Cancer* (IARC) has prompted extensive epidemiological investigation into its associations with various malignancies. Subsequent meta-analyses have examined the relationship between occupational FA exposure and specific cancer types, including lung cancer [13], non-Hodgkin's lymphoma [14], and leukemia [15], with varying levels of supporting evidence [16–18]. However, the preponderance of epidemiological data concerning carcinogenic risk originates from studies conducted among industrial workers, for example, in resin production and garment manufacturing, who encounter exposure scenarios that differ both qualitatively and quantitatively from those prevailing in hospital anatomic pathology laboratories [19–21].

Furthermore, although carcinogenic risk predominates in scientific discourse, a holistic assessment must equally consider the substantial burden of non-carcinogenic effects. These include well-documented acute and chronic respiratory disorders, sensory organ irritation, allergic sensitization following exposure, and histopathological (HP) alterations of the nasal mucosa, all of which directly impact the health status and work capacity of laboratory personnel [1, 2, 7, 9].

This narrative review aimed to bring together and critically evaluate the current scientific evidence on the cellular and molecular mechanisms of FA toxicity, HP changes in target tissues, and the health risks, both cancerous and non-cancerous, that are linked to FA exposure, with a focus on pathology staff.

Study selection for review

This narrative review synthesizes the current scientific literature on health risks associated with occupational FA exposure among hospital histopathology laboratory personnel, with particular emphasis on cellular mechanisms and HP alterations. A comprehensive literature search was conducted across three major electronic databases, *PubMed/MEDLINE*, *Web of Science Core Collection*, and *Scopus*, encompassing publications from database inception through December 2025.

The search strategy used controlled vocabulary terms, like medical subject headings, and free-text keywords that were grouped into four main areas: (*i*) the exposure agent (FA); (*ii*) cellular and molecular mechanisms [deoxyribonucleic acid (DNA)–protein crosslinks (DPCs), oxidative stress, genotoxicity, apoptosis, inflammation]; (*iii*) HP effects [nasal mucosa, squamous metaplasia (SM), dysplasia, epithelial changes]; and (*iv*) the occupational setting and population (histopathology laboratory, pathology department, hospital laboratory, laboratory personnel). Reference lists of key articles and relevant reviews were manually screened to identify additional publications.

Studies were selected according to their alignment with the objectives of the review. Original research investigating the cellular mechanisms underlying FA toxicity, HP examinations of affected tissues, and studies concentrating on hospital pathology personnel were prioritized. Since the study designs were so different from each other, a narrative synthesis approach was used. The results are structured thematically, featuring sections that address cellular and molecular mechanisms, observable changes in target tissues under a microscope, biomarkers indicating exposure and effects, the characterization of occupational exposure, and the evidence pertaining to carcinogenic risk.

Evidence synthesis

Cellular and molecular mechanisms of FA toxicity

Chemical reactivity and macromolecular interactions

FA exerts its cytotoxic effects through multiple interconnected mechanisms at the cellular and molecular level. As a highly reactive electrophilic aldehyde (molecular weight 30.03 Da), FA rapidly penetrates cell membranes and forms covalent adducts with nucleophilic sites on cellular macromolecules [5, 6]. The primary targets include the amino groups of proteins, particularly lysine (Lys), cysteine, histidine, and tryptophan residues, and the exocyclic amino groups of DNA bases, predominantly deoxyguanosine (dG) and deoxyadenosine (dA) [6, 22].

The reaction of FA with biological macromolecules occurs in a two-step process. First, FA reacts with a relatively strong nucleophile, most commonly a Lys ε-amino group, to form a hydroxymethyl intermediate (Schiff base). This intermediate can then react with a second nucleophile to form a stable methylene bridge crosslink [5, 6]. Structural characterization studies have demonstrated that crosslinks between amino acids and deoxynucleosides involve FA-derived methylene bridges, with Lys–dG crosslinks being the most abundant product [6].

DNA–protein crosslinks and genotoxicity

DPCs represent the hallmark genotoxic lesion induced by FA exposure. These bulky adducts form when FA creates methylene bridges between DNA and histone or non-histone proteins, creating physical obstacles to DNA replication and transcription that threaten genomic integrity [10, 22, 23]. Shaham *et al.* [10] demonstrated DPC formation both *in vitro* and *in vivo* following FA exposure, establishing the utility of this biomarker as a molecular dosimeter for occupational exposure assessment.

The cellular response to FA-induced DPCs involves multiple DNA repair pathways. Recent studies have demonstrated that DPCs are subject to transcription-coupled nucleotide excision repair (NER) that requires the Cockayne syndrome group B protein and downstream factors [23, 24]. In this process, proteins crosslinked with DNA are degraded to remnant peptides by the valosin-containing protein (VCP/p97) and proteasome axis before removal by NER machinery [24]. The differential pathway response to chronic *vs.* acute FA exposures, with homologous recombination predominating under chronic low-dose conditions and NER under acute high-dose conditions, has important implications for risk assessment [24].

The accumulation of unrepaired DPCs can lead to replication fork stalling, double-strand breaks (DSBs), and chromosomal instability, key initiating events in carcinogenesis [22, 25]. Cytogenetic studies in FA-exposed workers have consistently demonstrated elevated frequencies of micronuclei (MN) in buccal and nasal mucosal epithelial cells, as well as chromosomal aberrations in peripheral blood lymphocytes [8, 26, 27].

Oxidative stress and inflammatory responses

Beyond direct macromolecular damage, FA induces oxidative stress through generation of reactive oxygen species (ROS), leading to lipid peroxidation of membrane phospholipids, protein carbonylation, and mitochondrial (MT) dysfunction [28–30]. Studies in exposed animals have demonstrated increased levels of malondialdehyde (MDA), decreased superoxide dismutase (SOD) activity, and glutathione depletion in target tissues [29–31].

The disruption of cellular redox homeostasis activates stress-responsive signaling pathways, including the nuclear factor-*kappa* B (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, triggering inflammatory cytokine release [29, 32]. FA exposure induces secretion of pro-inflammatory cytokines including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) from exposed epithelial tissues [32]. This inflammatory microenvironment further contributes to tissue injury and creates conditions favorable for carcinogenic transformation.

Apoptotic and proliferative responses

The biological action of FA is dose-dependent, with different cellular outcomes observed across concentration ranges [33]. *In vitro* studies have demonstrated that FA at high concentrations (≥10 mM) causes necrotic cell death, moderate concentrations (~1 mM) result in enhanced apoptosis and reduced mitotic activity, while low concentrations (0.1–0.5 mM) may paradoxically enhance cell proliferation and reduce apoptotic activity [33].

Apoptosis induced by FA involves both intrinsic (MT) and extrinsic (death receptor) pathways, evidenced by decreased MT membrane potential, altered B-cell lymphoma-2 (Bcl-2)/Bcl-2-associated X protein (Bax) ratios, cytochrome *c* release, and caspase activation [29, 30]. The compensatory cellular proliferation observed following chronic low-dose exposure increases the probability of replication errors and fixation of mutations in dividing cells, representing a critical mechanistic link to carcinogenesis [33, 34].

Histopathological alterations in target tissues

Normal histology of the nasal respiratory mucosa

The nasal respiratory mucosa, which constitutes the primary portal of entry for inhaled FA, is normally lined by pseudostratified ciliated columnar epithelium interspersed with mucus-secreting goblet cells [35]. The ciliated cells bear approximately 200–300 motile cilia per cell on their apical surface, which beat in a coordinated metachronal wave to propel the overlying mucus blanket toward the nasopharynx, the mucociliary clearance mechanism that represents the primary defense against inhaled particulates and irritants [35, 36].

The underlying *lamina propria* contains serous and mucous glands, a rich vascular network, and scattered immune cells. This anatomical arrangement is essential for the conditioning of inspired air and the protection of the lower respiratory tract [35].

Spectrum of FA-induced histopathological changes

HP examination of nasal mucosal biopsies from FA-exposed workers reveals a characteristic spectrum of morphological alterations that progress with increasing exposure duration and intensity. Multiple studies employing standardized histological grading systems (typically scored 0–8) have documented these changes [35–38].

Early changes (grade 1–2)

The earliest HP alterations include loss of ciliated epithelial cells and goblet cell hyperplasia [9, 36, 37]. Scanning electron microscopy (SEM) demonstrates shortened, disorganized, or absent cilia on the apical surface of epithelial cells [36]. Goblet cell hyperplasia represents a protective mucus-secreting response to chronic irritation, with an increased proportion of mucus-secreting cells relative to ciliated cells.

Intermediate changes (grade 2–3)

With continued exposure, metaplastic transformation occurs. The normal pseudostratified ciliated columnar epithelium is progressively replaced by cuboidal epithelium and subsequently by stratified squamous epithelium, a process termed 'squamous metaplasia' [9, 36–38]. Histologically, this manifests as flattened, polygonal cells with increased cytoplasmic eosinophilia and loss of the normal columnar architecture. Edling *et al.* [9], in their landmark study of 75 FA-exposed workers, found that 78% exhibited SM, with only three of 75 subjects having normal nasal mucosa.

Advanced changes (grade 4–6)

In cases of more severe or prolonged exposure, keratinization of the metaplastic squamous epithelium may occur, and cellular dysplasia becomes apparent [9, 36, 38]. Nuclear atypia includes nuclear enlargement, hyperchromasia, irregular nuclear contours, and increased nuclear-to-cytoplasmic (N:C) ratio. Edling *et al.* observed mild to moderate dysplasia in 8% of exposed workers [9], while Boysen *et al.* [38] documented epithelial dysplasia in 8% (3/37) of FA-exposed chemical plant workers.

Stromal changes

At the stromal level, chronic inflammatory infiltrates composed predominantly of lymphocytes and plasma cells are observed in the *lamina propria*, accompanied by vascular congestion and edema [36, 37]. Subepithelial fibrosis may develop in cases of prolonged exposure.

Histological grading systems

Several histological grading systems have been developed to standardize the assessment of FA-induced nasal mucosal changes. The system proposed by Torjussen and subsequently modified by Edling assigns scores as shown in Table 1 [9, 36].

Table 1 – ***Torjussen–Edling histological grading system for FA-induced nasal mucosal alterations (scores 0–8)***

Score 0:	Normal respiratory epithelium
Score 1:	Loss of ciliated epithelial cells
Score 2:	Mixed cuboidal/squamous epithelium, metaplasia
Score 3:	Stratified squamous epithelium
Score 4:	Keratosis
Score 5:	Keratosis with budding of epithelium
Score 6:	Mild or moderate dysplasia
Score 7:	Severe dysplasia
Score 8:	Carcinoma

FA: Formaldehyde.

Table 2 summarizes the principal HP findings reported across key studies employing this grading system.

Multiple studies have demonstrated significantly higher mean histological scores in FA-exposed workers compared to unexposed controls (typically 2.5–2.9 *vs.* 1.5–1.8, $p<0.05$) [9, 36–38].

Correlation with exposure parameters

The relationship between HP changes and quantitative exposure metrics has been investigated in several studies. While individual studies have produced somewhat inconsistent findings regarding dose–response relationships, meta-analyses of animal data have established clear concentration-dependent responses [34, 39]. Notably, the severity of FA-induced epithelial damage appears more dependent on concentration than on the product of concentration and duration of exposure, supporting the importance of controlling peak exposures [39].

Table 2 – ***Summary of histopathological findings in nasal mucosa of FA-exposed workers across key studies***

Study	Year	Population	*N* (exposed)	Exposure type	SM [%]	Dysplasia [%]	Mean histological score (exposed)	Mean histological score (controls)
Edling *et al.* [36]	1987	Factory workers (FA-exposed)	70	Chronic occupational	~70%	N/A	2.5	1.5
Edling *et al.* [9]	1988	FA-exposed workers (various industries)	75	Chronic occupational	78%	8% (6/75)	2.9	1.8
Holmström *et al.* [37]	1989	Workers exposed to FA alone or FA + wood dust	Variable	Chronic occupational	>60%	N/A	2.6	~1.6
Boysen *et al.* [38]	1990	Chemical plant workers	37	Chronic occupational	N/A separately	8% (3/37)	N/A	N/A
Ballarin *et al.* [27]	1992	Plywood factory workers	Not specified	Chronic occupational	Present (concurrent with MN elevation)	N/A	N/A	N/A

Histological scoring based on the Torjussen–Edling grading system (scores 0–8). SM corresponds to scores 2–3; dysplasia corresponds to scores 6–7. FA: Formaldehyde; MN: Micronuclei; *N*: No. of cases; N/A: Not reported; SM: Squamous metaplasia.

Animal studies have demonstrated that SM occurs most prominently in the anterior regions of the nasal cavity where FA concentrations are highest following inhalation, supporting the portal-of-entry hypothesis for FA toxicity [39]. Long-term animal studies (104 weeks) have documented progression from SM through dysplasia to squamous cell carcinoma at high exposure concentrations, providing mechanistic support for the carcinogenic potential observed in epidemiological studies [40].

We summarize key FA-induced HP progression in the nasal respiratory mucosa in Figure 1, correlating them with clinical outcomes.

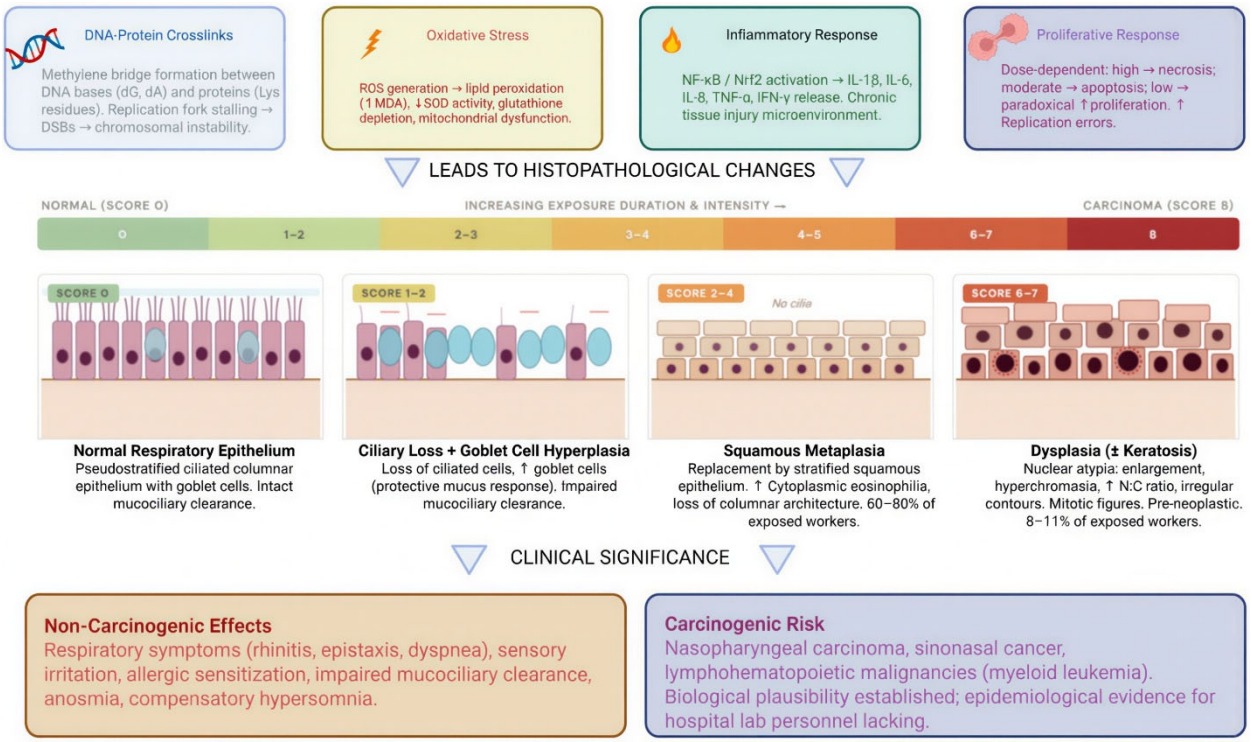

Figure 1 – ***Schematic overview of FA-induced histopathological progression in the nasal respiratory mucosa, from molecular mechanisms to clinical outcomes. dA: Deoxyadenosine; dG: Deoxyguanosine; DNA: Deoxyribonucleic acid; DSBs: Double-strand breaks; FA: Formaldehyde; IFN-γ: Interferon-gamma; IL: Interleukin; Lys: Lysine; MDA: Malondialdehyde; N:C: Nuclear-to-cytoplasmic ratio; NF-κB: Nuclear factor-kappa B; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-alpha.***

Biomarkers of exposure and early biological effect

DPC as molecular dosimeters

The formation of DPCs represents a specific and well-validated biomarker of FA exposure and genotoxicity. Shaham *et al.* [10] demonstrated that DPC levels in peripheral blood leukocytes are elevated in FA-exposed workers compared to unexposed controls and correlate with workplace exposure levels. This biomarker reflects the direct interaction of FA with cellular macromolecules and provides an integrated measure of absorbed dose.

Cytogenetic biomarkers

Elevated frequencies of MN in exfoliated nasal and buccal epithelial cells represent another validated biomarker of FA-induced genotoxicity [8, 27, 41]. Ballarin *et al.* [27] demonstrated significantly higher MN frequencies in nasal mucosal cells of plywood factory workers exposed to FA (0.90±0.47 *vs.* 0.25±0.22 per 1000 cells, $p<0.01$) compared to controls, with concurrent cytological evidence of SM.

Chromosomal aberrations in peripheral blood lymphocytes, including chromatid breaks, chromosome breaks, and structural aberrations, have also been documented in FA-exposed workers [8, 26]. Pala *et al.* [8] demonstrated elevated DNA damage indices in research institute personnel including laboratory staff, underscoring the genotoxic hazard even in ostensibly well-controlled occupational settings.

Genetic susceptibility factors

Individual susceptibility to FA-induced genotoxicity is modulated by genetic polymorphisms in genes encoding metabolic enzymes and DNA repair proteins [26, 42]. Pinto *et al.* [26], in their systematic analysis, investigated the influence of polymorphisms in genes encoding aldehyde dehydrogenase (ALDH2), glutathione S-transferases (GSTM1, GSTT1, GSTP1), and DNA repair proteins on the detection and magnitude of genotoxic damage. These genetic factors add an important dimension of interindividual variability to risk assessment and may identify subpopulations at heightened risk.

Occupational exposure in hospital pathology services

Sources and patterns of exposure

A consistent finding across multiple environmental monitoring investigations is that pathology personnel are routinely exposed to FA concentrations that frequently exceed recommended OELs established by international regulatory bodies, including the *Occupational Safety and Health Administration* (OSHA), the *National Institute for Occupational Safety and Health* (NIOSH), and the *American Conference of Governmental Industrial Hygienists* (ACGIH) [1, 2, 7].

This pattern of overexposure is particularly pronounced during specific high-risk tasks associated with elevated FA release, such as specimen grossing and dissection, tissue processor loading and unloading, cassette preparation, and manipulation of FA-containing receptacles [1, 2]. Notably, short-term "peak" exposures during these discrete activities represent a critical and often underappreciated characteristic of the occupational exposure profile, distinct from the time-weighted average concentrations typically used for regulatory compliance assessment [2, 7].

Yahyaei *et al.* [1] conducted a comprehensive exposure assessment across multiple hospital pathology departments and demonstrated that a substantial proportion of air samples, both personal breathing zone and area measurements, exceeded the threshold limit value–time-weighted average (TLV-TWA) of 0.3 ppm recommended by *ACGIH*. Mucci *et al.* [2] implemented an automated continuous air sampling system within a hospital histopathology laboratory, confirming that specific tasks generate airborne FA concentrations significantly exceeding established OELs.

The paradox of FA as fixative and toxicant

Pathology services present a unique occupational setting in which the same chemical agent that poses health risks to personnel, FA, is simultaneously essential for the diagnostic mission of the laboratory. The 10% neutral buffered FA standard in histopathology contains approximately 4% FA by weight [3, 4]. Understanding the mechanisms of FA fixation provides insight into both its indispensability and its toxicity.

FA fixation occurs through crosslinking of tissue proteins, primarily *via* methylene bridge formation between adjacent amino acid residues, the same mechanism underlying its genotoxicity [3–5]. This crosslinking preserves cellular morphology, prevents autolysis, and renders tissues suitable for paraffin embedding and sectioning. Alternative fixatives, including glyoxal-based fixatives, zinc-based fixatives, and alcohol-based solutions, have been developed to reduce FA exposure; however, these alternatives often compromise immunohistochemical antigenicity, molecular preservation for polymerase chain reaction (PCR)-based applications, or morphological quality, limiting their widespread adoption [3, 5].

Correlation of exposure with biological effects

Motta *et al.* [7] conducted simultaneous environmental air monitoring and biological monitoring among hospital laboratory staff, establishing a direct correlation between ambient FA concentrations and biomarkers of absorbed dose. Their investigation revealed that even within modern hospital facilities equipped with contemporary ventilation systems, histopathology laboratory personnel experience chronic low-to-moderate baseline exposure punctuated by acute concentration peaks during specific procedures.

Carcinogenic risk: evidence and gaps

Evidence from industrial cohorts

Carcinogenic risk among industrial workers has been extensively investigated over several decades. Major cohort studies, including the United States *National Cancer Institute* (NCI) study of industrial workers and embalmers, have reported associations between FA exposure and increased mortality from lymphohematopoietic malignancies, particularly myeloid leukemia. Hauptmann *et al.* demonstrated elevated leukemia mortality among embalmers with high cumulative FA exposure [19]. Major meta-analyses have synthesized these industrial data with heterogeneous conclusions [13–16, 18].

The critical gap: hospital-based epidemiology

The fundamental limitation identified through this review is the near-complete absence of high-quality, direct epidemiological data on cancer risk specific to hospital pathology personnel. The investigation by Kauppinen *et al.* examining Finnish laboratory workers represents one of the few studies that specifically includes this occupational segment, but it did not demonstrate significantly elevated risk of lymphohematopoietic malignancies specifically attributable to FA exposure, though statistical power was limited [12].

The exposure scenario for a histopathology laboratory technician, characterized by lower cumulative lifetime exposure but frequent, short-duration peak exposures within a mixed-exposure environment, is qualitatively and quantitatively distinct from that of an embalmer or resin production facility worker [11, 19–21, 43]. Extrapolating cancer risk estimates derived from long-term, high-dose industrial exposures to the intermittent, lower-dose exposure profile characteristic of hospital laboratory settings introduces substantial uncertainty.

Biological plausibility vs. epidemiological evidence

For hospital laboratory personnel, a notable discrepancy exists between established biological plausibility and available epidemiological evidence. Genotoxicity biomarkers (DPC, MN, chromosomal aberrations) confirm that occupational-level FA exposure induces DNA damage, a critical initiating event in carcinogenesis [8, 10, 26]. HP alterations of the nasal mucosa demonstrate FA's capacity for tissue injury and potentially precancerous epithelial transformation [9, 40]. Collectively, these findings constitute robust biological plausibility supporting carcinogenic risk.

However, direct epidemiological evidence necessary to confirm a measurable increase in cancer incidence or mortality within this specific occupational segment remains absent. This discrepancy may be attributable to several factors: lower cumulative lifetime doses, the healthy worker survivor effect, prolonged latency periods, or risk elevations too modest to detect without very large prospective cohort investigations.

Discussions

The evidence synthesized in this review illustrates a dual reality regarding occupational FA exposure in pathology services. A robust and internally consistent body of data, spanning molecular mechanisms, HP studies, and biomarker investigations, confirms a substantial burden of non-carcinogenic health effects directly attributable to documented overexposure. Simultaneously, a critical disconnect persists between the well-established biological plausibility for carcinogenesis and the absence of conclusive epidemiological evidence specific to this occupational workforce.

HP alterations documented in FA-exposed workers, progressing from ciliary loss through SM to epithelial dysplasia, represent clear morphological evidence of chronic tissue injury at the portal of entry [9, 36–38]. These changes are biologically coherent with FA's chemical reactivity: the electrophilic aldehyde forms covalent adducts with cellular macromolecules, induces oxidative stress, activates inflammatory pathways, and triggers compensatory proliferation [5, 6, 28, 29, 33]. The consistent demonstration of elevated genotoxicity biomarkers provides mechanistic support for potential carcinogenic risk, as DNA damage and chromosomal instability represent critical early events in the multistep process of carcinogenesis [8, 10, 22, 26].

The histological grading systems employed across multiple studies demonstrate remarkable consistency in findings: the majority of FA-exposed workers exhibit some degree of nasal mucosal pathology, with SM present in 60–80% and dysplasia in 8–11% of exposed individuals [8, 36–38]. These prevalence figures underscore the near-universal impact of chronic FA exposure on the respiratory epithelium and highlight the importance of preneoplastic surveillance in this occupational population.

However, extrapolation of cancer risk estimates from industrial cohorts to hospital laboratory personnel remains problematic. The exposure paradigm differs qualitatively and quantitatively: histopathology technicians experience lower cumulative lifetime doses but frequent, intermittent peak exposures during specific tasks, often within a mixed chemical environment [2, 7, 43]. While biological monitoring confirms both exposure and early biological effect, these biomarkers, though validated indicators of genotoxic insult, are not specific predictors of clinically manifest malignancy.

Romanian experience

Although pathology is often assumed to be safe, the Ordinary legislative procedure 2018/0081(COD) [44] sets the limit for FA at 0.37 mg/m^3 or 0.3 ppm, effective 11 July 2024. In practice there is no measurement done (at least in Romanian hospitals) on FA, and no one is accountable. Romanian Governmental Decision 355/2007 [45] establishes the minimum requirements for the health surveillance of workers in relation to occupational risks and specifies that this surveillance is carried out by occupational medicine physicians. In practice, this is implemented through pre-employment medical examinations, periodic medical examinations (depending on the identified risks), and medical assessments upon return to work / for work adaptation / job change, etc. From this we understand that occupational medicine focuses mainly on identifying already recognized occupational diseases and has no effective function in monitoring risk or in discovering and reclassifying emerging occupational disease patterns.

A central issue for pathology is the conversion of apparently non-occupational disease into suspected and then confirmed occupational disease when criteria are met. In practice, this conversion depends on three steps: (*i*) systematic suspicion (occupational history and symptom–task temporal correlation), (*ii*) exposure documentation (measurements, job–task exposure matrices, incident logs, ventilation audits), and (*iii*) administrative/medical pathway activation for reporting and confirmation. In practice, none of this is happening in pathology departments, and thus we come close to what can be defined as "hidden morbidity".

The occupational physician is uniquely positioned to integrate workplace risk assessment with clinical evaluation. However, this requires that the occupational health service has access to meaningful exposure information and that the employer supports systematic monitoring of engineering controls (local exhaust ventilation, sealed systems, container management, and spill response) and work practice controls

(standardized grossing procedures, closed containers, minimized open handling time, and training), which in practice is not ensured.

From the authors' experience, an increased frequency of ectopic pregnancy, different from other reproductive and developmental toxicity reports [46], as well as loss of smell and compensatory sleep (as observed by other studies [47] are present among pathology staff; however, these issues are not formally documented or reported in any surveillance system.

More broadly, the literature on pathology-specific long-term outcomes, including cancer risk, is frequently less definitive than the mechanistic and short-term clinical evidence would suggest. This discrepancy may be cautiously interpreted as a consequence of methodological limitations inherent to the available evidence: small occupational cohorts, heterogeneous exposure conditions across settings, inadequate exposure reconstruction, prolonged latency periods, and, critically, systematic under-reporting or misclassification of occupational disease attribution. The present review identifies biological signals and early biological effects consistent with chronic FA exposure while acknowledging that the robustness of epidemiological evidence may be constrained by incomplete surveillance and reporting practices in real-world clinical settings. At the policy level, anatomical pathology should be explicitly recognized as a high-priority setting for occupational health improvement, given the combined chemical and biological hazards and the short-term exposure peaks that occur during specific tasks. Accordingly, a clear regulatory framework should be established to mandate FA exposure monitoring and ensure consistent implementation across laboratories.

Limitations and implications for practice and research

This narrative review has several limitations. As a narrative rather than systematic review, the study selection process may be subject to selection bias. The heterogeneity of exposure assessment methods and histological grading systems across studies precluded quantitative synthesis. Publication bias may affect the available evidence, and the search was limited to major databases. Finally, the rapidly evolving literature means recent publications may not have been captured.

Pending definitive epidemiological data, occupational health policy for this workforce should be guided by the precautionary principle, emphasizing implementation of stringent engineering controls (enhanced local exhaust ventilation, enclosed tissue processors, FA-free or reduced-FA fixation alternatives), administrative measures (task rotation, exposure time limitations), appropriate personal protective equipment, and comprehensive health surveillance programs incorporating both symptom monitoring and periodic histological and biomarker assessment.

Conclusions

This review has synthesized the current scientific evidence regarding cellular mechanisms, HP alterations, and health risks confronting pathology services personnel consequent to occupational FA exposure. The findings reveal a coherent mechanistic pathway from chemical exposure through cellular and tissue-level damage to potentially irreversible pathological changes.

At the molecular level, FA induces DPC, oxidative stress, and inflammatory responses. At the tissue level, these mechanisms manifest as a characteristic HP progression in the nasal mucosa: from ciliary loss and goblet cell hyperplasia through SM to epithelial dysplasia, changes documented in the majority of chronically exposed workers. These preneoplastic alterations, combined with elevated genotoxicity biomarkers, establish robust biological plausibility for carcinogenic risk.

However, direct epidemiological evidence for elevated cancer incidence in this specific occupational population remains lacking, mainly due to lack of proper monitorization. This represents a critical knowledge gap that precludes evidence-based quantitative risk assessment. The principal conclusions are therefore twofold: first, prevention of non-carcinogenic health effects, including the documented HP alterations, must constitute an unequivocal priority in occupational health management; second, the uncertainty regarding carcinogenic risk should not be interpreted as evidence of safety but rather as a mandate for targeted investigation.

Only through rigorous prospective cohort studies incorporating HP surveillance can the existing ambiguity be resolved and a definitive evidence base be established to inform comprehensive risk assessment and optimal protection of this essential healthcare workforce.

Conflict of interests

The authors declare that they have no conflict of interests.

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