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Environmental Carcinogens and Tissue Pathology: Chemical Mechanisms Linking Environmental Exposure to Human Cancer Development

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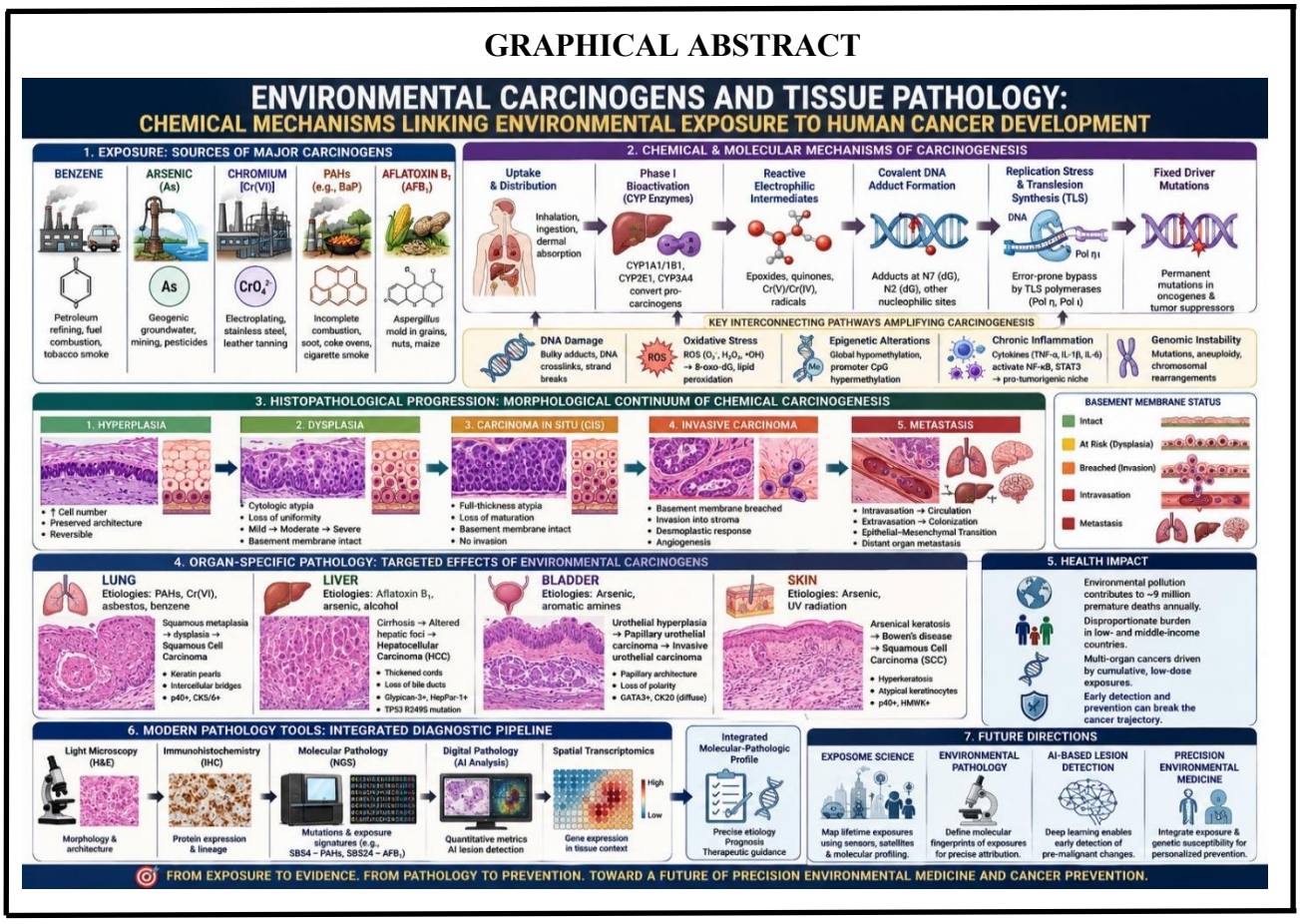
GRAPHICAL ABSTRACT



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Abstract: Environmental contamination by synthetic and naturally occurring xenobiotics represents a critical driver of the global cancer burden. This review synthesizes the cross-disciplinary paradigms of environmental chemistry, toxicology, and anatomic pathology to map the journey of major environmental carcinogens, specifically benzene, inorganic arsenic, hexavalent chromium [Cr(VI)], polycyclic aromatic hydrocarbons (PAHs), and aflatoxins, from anthropogenic and natural sources to specific histopathological endpoints. We examine the molecular mechanisms driving this toxicity, including metabolic activation to highly reactive electrophiles, covalent DNA adduct formation, oxidative stress-mediated biomolecular damage, epigenetic reprogramming, and persistent chronic inflammation. Furthermore, we trace the morphological evolution of chemical carcinogenesis through sequentially distinct pathological stages from adaptive hyperplasia and atypical dysplasia to carcinoma *in situ*, invasive malignancy, and subsequent distant

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metastasis. By integrating classic tissue-based diagnostic pathology with advanced modern tools, such as immunohistochemistry, molecular pathology, digital image analysis, and spatial transcriptomics, this work demonstrates how specific chemical exposures dictate characteristic organ-specific lesions. Finally, we discuss how the integration of exposome science and artificial intelligence (AI) is shifting public health paradigms toward precision environmental medicine and proactive oncology intervention

1. Introduction

1.1 Global Burden of Environmentally Induced Cancers

Maladaptive interactions between human populations and chemical components within the ambient, occupational, and domestic exposome represent a primary driver of global oncological morbidity and mortality (Guillien *et al.,* 2023). According to macro-epidemiological assessments by the Lancet Commission on Pollution and Health, environmental pollution is responsible for an estimated 9 million premature deaths annually worldwide, with chemical carcinogens in air, water, soil, and food systems contributing significantly to this total (Fuller *et al.,* 2022). Unlike hereditary cancer syndromes, which are governed by high-penetrance germline mutations, environmentally induced malignancies are driven by cumulative, multi-decade somatic changes. These changes result from sustained exposure to low-to-moderate doses of environmental xenobiotics (Mafe & Büsselberg, 2026). The structural distribution of these cancers reveals profound socioeconomic disparities, with low- and middle-income countries (LMICs) bearing a disproportionate share of the toxicological burden due to rapid industrialization, permissive occupational frameworks, and inadequate waste management infrastructure (Dlamini *et al.,* 2025).

1.2 Environmental Chemistry and Carcinogenesis

The transformation of a benign, homeostatically regulated cell into an autonomously replicating neoplastic entity is fundamentally a chemical process. Carcinogenesis depends on the environmental persistence, physical state, and specific chemical properties of the xenobiotic in question (Wogan *et al.,* 2004). Environmental chemistry dictates whether a toxicant remains adsorbed to airborne particulate matter (PM), dissolves within aquifers, or bioaccumulates within trophic webs. Once a xenobiotic enters a human host via inhalation, ingestion, or dermal absorption, its molecular structure determines its metabolic fate. While some compounds act as direct-acting carcinogens that possess sufficient inherent electrophilicity to modify cellular macromolecules without prior chemical transformation, most environmental agents are pro-carcinogens. These require extensive bioactivation by Phase I biotransformation enzymes (predominantly the cytochrome P450 mono-oxygenase superfamily) to yield highly unstable, electron-deficient reactive intermediates (Miller & Banbury Exposomics Consortium, 2025). These reactive intermediates ultimately drive genetic and cellular damage.

1.3 Role of Anatomic Pathology

Anatomic pathology serves as the definitive structural validator of chemical carcinogenesis, bridging molecular toxicological mechanisms with clinical manifestation. By assessing tissue architecture and cytomorphological variations under light microscopy, the surgical pathologist documents the somatic consequences of toxic injury. Historically restricted to describing late-stage tumor specimens, modern environmental pathology utilizes a highly integrated diagnostic framework. This approach combines classical histomorphology with high-sensitivity molecular,

immunophenotypic, and digital tools to trace the continuous evolution of tissue from initial chemical injury through predictable pre-malignant phases to frank, invasive carcinoma (Beier *et al.,* 2025). Understanding these tissue-specific responses is essential not only for identifying specific environmental etiologies but also for predicting tumor behavior and tailoring targeted therapeutic strategies.

2. Major Environmental Carcinogens

2.1 Benzene

Benzene (C_6H_6) is a volatile, monocyclic aromatic hydrocarbon derived principally from crude petroleum refining, chemical synthesis, vehicular emissions, and tobacco smoke (Snyder, 2002). Because of its high volatility, inhalation serves as the predominant route of human exposure. Once absorbed via the pulmonary epithelium, benzene distributes into lipid-rich tissues, including the adipose architecture and the gelatinous matrix of the bone marrow. In the bone marrow, its metabolic derivatives exert potent myelotoxic and genotoxic pressures, directly targeting multipotent hematopoietic stem cells and restricted myeloid progenitor lineages (Smith, 2010). Chronic low-dose or acute high-dose exposures are strongly linked to hematopoietic malignancies, particularly acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) (McHale *et al.,* 2012).

2.2 Arsenic

Inorganic arsenic (As) represents a widespread metalloid contaminant distributed globally through geochemical leaching into groundwater reservoirs and industrial mining effluents (Hughes *et al.,* 2011). Millions of individuals globally consume drinking water that exceeds the World Health Organization's maximum permissible limit of 10g/L (Naujokas *et al.*, 2013). Inorganic trivalent arsenite [As(III)] and pentavalent arsenate [As(V)] enter cells through aquaglyceroporins and phosphate transporters, respectively. Once inside, they disrupt cellular physiology by binding to sulfhydryl groups on proteins and competing with inorganic phosphate during ATP synthesis. Chronic ingestion manifests as systemic multi-organ carcinogenicity, targeting the cutaneous epithelium, the pulmonary parenchyma, and the transitional urothelium of the urinary bladder (Kuo *et al.,* 2017).

2.3 Chromium (VI)

Hexavalent chromium, Cr(VI), is a highly reactive transition metal oxyanion generated through a range of industrial activities, including chromate pigment production, stainless steel welding, electroplating, and leather tanning (Holmes *et al.,* 2008). In contrast to the biologically essential and relatively inert trivalent chromium, Cr(III), Cr(VI) exhibits strong carcinogenic potential due to its ability to enter cells and induce intracellular oxidative stress. Structurally, Cr(VI) mimics endogenous sulfate (SO_4^{2-}) and phosphate (PO_4^{3-}) ions, enabling its uptake through non-specific anion transport systems, particularly sulfate transporters. This molecular mimicry allows Cr(VI) to bypass the lipid barrier of the plasma membrane and accumulate intracellularly. Once inside the cell, Cr(VI) undergoes sequential reduction by intracellular reducing agents such as glutathione and ascorbate. This redox process generates unstable intermediate species, including Cr(V) and Cr(IV), and produces significant amounts of reactive oxygen species (ROS). The resulting oxidative burden leads to DNA strand breaks, protein modification, and genomic instability, which are strongly implicated in the development of occupational lung cancers in exposed populations (Nickens *et al.,* 2010; Baszuk *et al.,* 2021).

2.4 Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a class of fused-ring aromatic compounds formed primarily through the incomplete combustion of organic matter. Major environmental sources include fossil fuel combustion, industrial coke ovens, municipal waste incineration, charbroiled or smoked foods, and tobacco smoke (Ewa & Danuta, 2017). Among them, benzo[a]pyrene (BaP) is widely used as a prototypical model compound for studying PAH-induced toxicity and carcinogenesis. **Table 1** lists major environmental carcinogens and their associations with cancer.

Table 1: Major Environmental Carcinogens and Cancer Associations

Carcinogen	Major Exposure Source	Target Organs & Systems	Confirmed Histopathological Cancer Types	Key Diagnostic & Exposure Biomarkers
Benzene	Petroleum refining, fuel combustion, vehicular emissions, tobacco smoke	Bone marrow, hematopoietic system	Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS)	Urinary *S*-phenylmercaptouric acid (*S*-PMA), *trans,trans*-muconic acid (*t,t*-MA)
Arsenic	Geogenic groundwater leaching, mining smelting, pesticides	Skin, lungs, urinary bladder mucosa	Cutaneous Squamous Cell Carcinoma, Basal Cell Carcinoma, Urothelial Carcinoma	Total urinary arsenic speciation via ICP-MS, hair/nail arsenic concentrations
Chromium VI	Chromate pigment synthesis, electroplating, leather tanning	Respiratory tract epithelium, pulmonary parenchyma	Bronchogenic Squamous Cell Carcinoma, Small Cell Lung Carcinoma	Intracellular erythrocyte chromium loading, urinary total chromium excretion
PAHs (e.g., BaP)	Incomplete organic combustion, soot, coke ovens, cigarette smoke	Lungs, skin, gastrointestinal tract	Pulmonary Adenocarcinoma, Cutaneous Squamous Cell Carcinoma	Urinary 1-hydroxypyrene (1-OHP), anti-BPDE-N2-dG adducts in white blood cells
Aflatoxin B_1	Agricultural mold contamination (*Aspergillus* spp.) in grains/nuts	Hepatic parenchyma	Hepatocellular Carcinoma (HCC)	Serum Aflatoxin B_1-albumin adducts, urinary AFB_1-N7-guanine excretory products

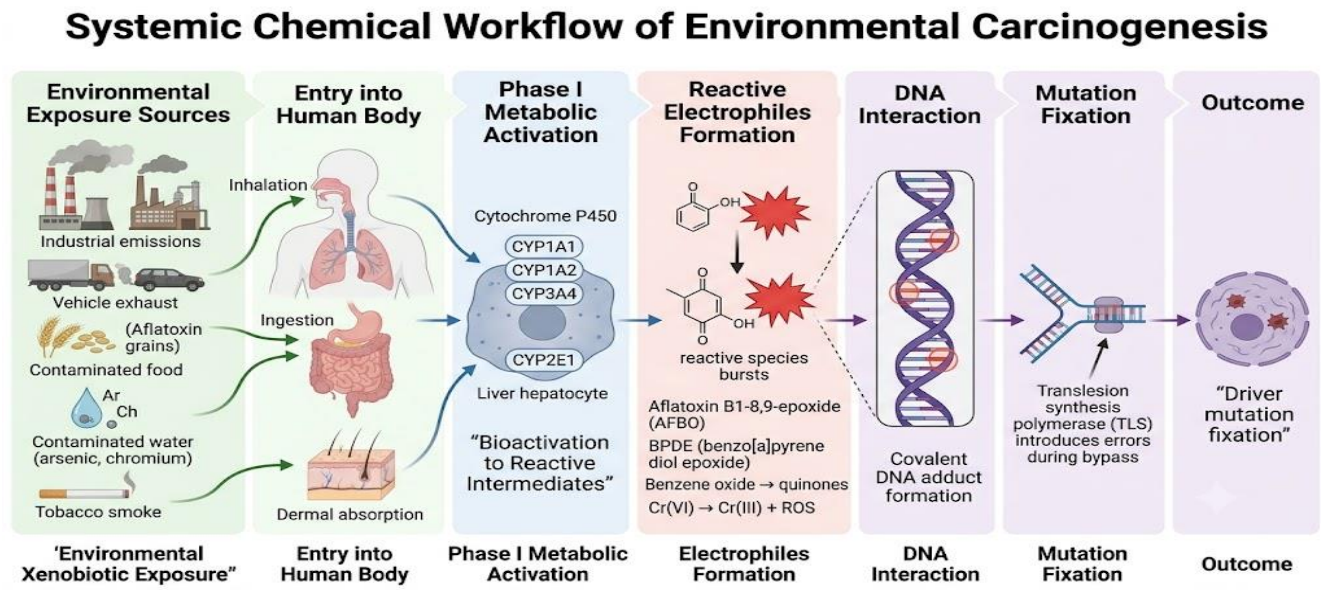

Figure 1: Systemic chemical workflow illustrating the progression of environmental pro-carcinogens from initial exposure through Phase I enzymatic bioactivation, generation of reactive electrophilic intermediates, covalent DNA adduct formation, and error-prone translesion synthesis leading to fixed driver mutations.

Owing to their high lipophilicity, PAHs readily traverse cellular membranes and bind to the cytosolic aryl hydrocarbon receptor (AhR). Ligand binding activates AhR-mediated transcriptional signaling, leading to the upregulation of Phase I xenobiotic-metabolizing enzymes, particularly cytochrome P450 isoforms CYP1A1 and CYP1B1. Paradoxically, this metabolic induction facilitates the conversion of relatively inert PAHs into highly reactive diol-epoxide intermediates. These electrophilic species form covalent DNA adducts, thereby initiating mutagenic events in target tissues such as the lung, skin, and gastrointestinal epithelium (Ross & Nesnow, 1999; Pratt *et al.,* 2011). The systemic environmental workflow of carcinogens is illustrated in **Figure 1.**

2.5 Aflatoxins

Aflatoxins are structurally complex, highly oxygenated difuranocoumarin secondary metabolites synthesized by the saprophytic molds *Aspergillus flavus* and *Aspergillus parasiticus*. These fungi commonly contaminate agricultural staples such as maize, peanuts, and tree nuts under conditions of high temperature and humidity, particularly during improper post-harvest storage (Wild & Gong, 2010). Among the various aflatoxin analogs, aflatoxin B_1 (AFB_1) is recognized as the most potent naturally occurring chemical carcinogen. Following ingestion, AFB_1 undergoes extensive hepatic bioactivation primarily via cytochrome P450 enzymes CYP3A4 and CYP1A2, forming a highly unstable and electrophilic epoxide intermediate, aflatoxin B_1-8,9-epoxide (AFBO). This reactive metabolite exhibits strong specificity for hepatocellular DNA, forming covalent adducts that disrupt genomic integrity. Consequently, dietary exposure to aflatoxin B_1 is a major risk factor for hepatocellular carcinoma (HCC), particularly in individuals with concurrent chronic hepatitis B virus (HBV) infection, where synergistic interactions markedly increase carcinogenic risk (Groopman *et al.,* 2008).

3. Environmental Chemistry and Toxicological Fate

The capacity of an environmental chemical to induce tissue-specific pathology depends on its journey through the environment and the host. This pathway is defined by four core chemical

properties: environmental persistence, bioavailability, metabolic activation, and the formation of reactive intermediates.

3.1 Environmental Persistence

Environmental persistence is governed by a compound's structural resistance to photolytic, chemical, and microbial degradation. Halogenated compounds, such as per- and polyfluoroalkyl substances (PFAS), owe their exceptional persistence to the high thermodynamic strength of the carbon-fluorine bond (~485kJ/mol), preventing natural decomposition and leading to accumulation across environmental compartments (Fenton *et al.,* 2021; Alsadik *et al.,* 2025). For PAHs, persistence increases with molecular weight and the number of fused benzene rings. This lipophilic character ensures these compounds stick tightly to organic fractions in soil and airborne particulate matter, resisting aqueous dissolution and volatilization (Baan *et al.,* 1994).

3.2 Bioavailability

Bioavailability defines the fraction of an environmental dose that enters systemic circulation. This profile is governed by a compound's octanol–water partition coefficient (log K_ow), water solubility, and physical state. Lipophilic xenobiotics with a high log K_ow (e.g., PAHs and aflatoxins) readily partition across the phospholipid bilayers of the gastrointestinal tract or pulmonary alveoli via passive diffusion. In contrast, hydrophilic metallic species such as Cr(VI) rely on active transport mechanisms. Soluble chromate anions (CrO_4^{2-}) possess a structural geometry similar to endogenous sulfate (SO_4^{2-}) and phosphate (PO_4^{3-}) ions, allowing them to exploit specialized anion transport channels (SLC26 and SLC4 transporter families) to bypass the hydrophobic cellular membrane (Nickens *et al.,* 2010).

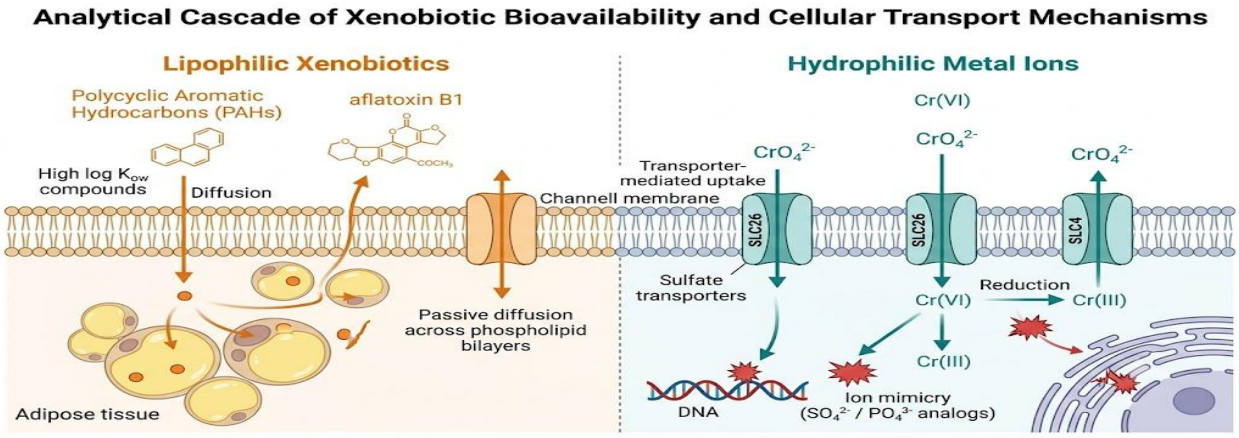

Figure 2: Analytical cascade demonstrating the toxicological fate of a lipophilic xenobiotic, emphasizing its intracellular transit, cytochrome-mediated bioactivation, and eventual nucleophilic attack on genomic structures.

3.3 Metabolic Activation

Once inside the cell, lipophilic pro-carcinogens must undergo biotransformation to become mutagenic. This paradoxical bioactivation is primarily mediated by microsomal cytochrome P450 (CYP) monooxygenases. For example, benzo[a]pyrene is metabolized sequentially by CYP1A1/CYP1B1 and epoxide hydrolase, converting the relatively inert parent hydrocarbon into the highly reactive (+)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE) (Phillips, 2005). Similarly, aflatoxin B_1 is activated in the liver by CYP3A4 to form aflatoxin B_1-8,9-epoxide (AFBO). This metabolite exists as two stereoisomeric forms- the endo-epoxide and the highly reactive exo-epoxide, with the exo-isomer being primarily responsible for its potent carcinogenic activity (Smela *et*

al. 2001). The analytical cascade demonstrating the toxicological fate of a lipophilic xenobiotic, emphasizing its intracellular transit, cytochrome-mediated bioactivation, and eventual nucleophilic attack on genomic structures is shown in **Figure 2.**

3.4 Reactive Intermediates

The products of metabolic bioactivation are typically highly reactive, electron-deficient electrophiles that preferentially target electron-rich nucleophilic sites within cellular macromolecules. Within DNA, these reactions occur predominantly at nucleophilic centers on deoxyribonucleosides, particularly the exocyclic amino groups and ring nitrogens of purine bases, such as the N7 and N2 positions of guanine (Hernandez-Castillo *et al.* 2023). These sites are especially susceptible to covalent modification due to their high electron density and accessibility within the DNA double helix. For instance, the exo-epoxide form of aflatoxin B_1-8,9-epoxide (AFBO) undergoes stereospecific nucleophilic attack by the N7 position of guanine residues. This reaction yields the pro-mutagenic DNA adduct trans-8,9-dihydro-8-(deoxyguanosin-7-yl)-9-hydroxyaflatoxin B_1 (dG-N7-AFB_1), which can destabilize the glycosidic bond and promote depurination, thereby generating apurinic sites that contribute to mutagenesis if not accurately repaired (Poirier, 2016). Similarly, benzene-induced toxicity arises from its metabolic activation pathway. Benzene is initially oxidized by CYP2E1 to form benzene oxide, which exists in equilibrium with its oxepin tautomer and subsequently rearranges into phenolic metabolites such as phenol, hydroquinone, and catechol. These intermediates undergo further oxidation in the bone marrow microenvironment, particularly via myeloperoxidase (MPO), generating reactive quinones including p-benzoquinone and o-benzoquinone. These electrophilic species form covalent DNA adducts and can also disrupt essential cellular proteins, including topoisomerases and components of the mitotic spindle apparatus, thereby contributing to chromosomal instability and leukemogenesis (Snyder, 2002; McHale *et al.,* 2012).

4. Molecular Mechanisms of Environmental Carcinogenesis

The transition from a chemically modified genome to an autonomous, malignant tissue phenotype depends on several distinct, interacting molecular mechanisms.

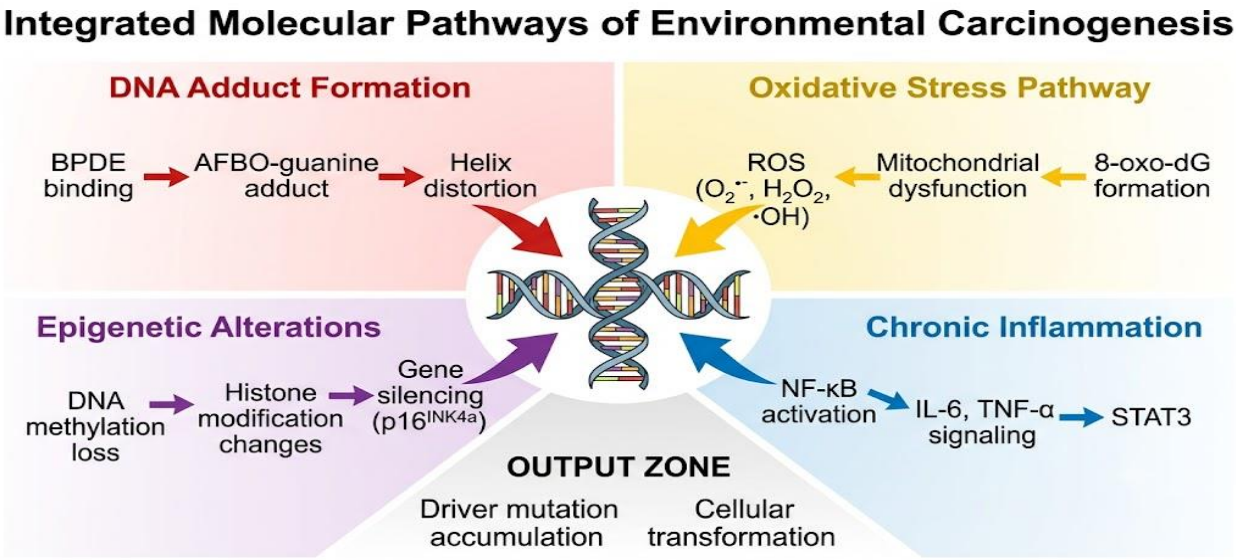

Figure 3: Integrated molecular schematic showcasing the parallel pathways of environmental carcinogenesis, illustrating how direct covalent modifications and indirect oxidative stress converge to induce driver mutations, epigenetic alterations, and chronic inflammatory signaling.

4.1 DNA Damage

Covalent modification of genomic DNA represents a critical initiating event in chemical carcinogenesis. Bulky DNA adducts, such as those formed by benzo[a]pyrene diol epoxide (BPDE) and aflatoxin B_1-8,9-epoxide (AFBO), induce significant steric distortion of the DNA double helix, altering its canonical B-form geometry (Poirier, 2016). These structural perturbations impede the progression of the high-fidelity replisome during S-phase, increasing the likelihood of replication errors, fork stalling, and misincorporation events.

In contrast to organic electrophilic adducts, metal-induced genotoxicity often involves complex coordination chemistry. Following intracellular reduction of Cr(VI) to Cr(III), the trivalent chromium ions form stable ternary complexes that bridge DNA with intracellular ligands such as glutathione, cysteine, or histone-associated proteins. These Cr(III)–DNA crosslinks generate bulky, highly stable lesions that significantly distort chromatin architecture and present a substantial challenge to nucleotide excision repair (NER) pathways. The persistence of these lesions contributes to replication stress, chromosomal instability, and the fixation of mutations that promote carcinogenic transformation (Nickens *et al.* 2010). **Figure 3** illustrates an integrated molecular schematic of the parallel pathways of environmental carcinogenesis, illustrating how direct covalent modifications and indirect oxidative stress converge to induce driver mutations, epigenetic alterations, and chronic inflammatory signaling.

4.2 Mutagenesis

If structural DNA lesions escape repair prior to cell division, replicative DNA polymerases δ and ε stall upon encountering the damaged templates. To maintain replication fork progression and prevent fork collapse, cells activate specialized translesion synthesis (TLS) polymerases, including DNA polymerase η and DNA polymerase ι. Although these enzymes can bypass bulky DNA lesions, their enlarged active sites lack intrinsic proofreading activity, rendering DNA synthesis across damaged templates inherently error-prone (Cohen & Arnold, 2011). This error-prone bypass process leads to permanent fixation of mutations within the genome. For example, the dG–N7–AFB_1 adduct frequently induces G:C → T:A transversion mutations during replication. In hepatocellular carcinoma, this mutational event is characteristically enriched at codon 249 of the TP53 tumor suppressor gene (AGG → ATG), resulting in the substitution of arginine with tryptophan (R249S). This hotspot mutation serves as a well-established molecular fingerprint of dietary aflatoxin exposure and is widely used as an epidemiological biomarker linking environmental exposure to liver cancer risk (Smela *et al.* 2001; Wild & Gong, 2010).

4.3 Oxidative Stress

Many environmental carcinogens promote cellular transformation indirectly through the sustained generation of reactive oxygen species (ROS), including superoxide anions ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH). This oxidative stress arises when xenobiotic exposure depletes intracellular antioxidant defenses, particularly glutathione, or inhibits key detoxifying enzymes such as superoxide dismutase and catalase (Jomova *et al.* 2026). During intracellular redox cycling, as observed in Cr(VI) reduction or benzene-derived hydroquinone/semquinone interconversions, repeated single-electron transfer reactions establish a self-propagating cycle of ROS production (Snyder, 2002). These reactive species oxidize nucleic acid bases, with guanine being particularly susceptible due to its low redox potential, thereby forming 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) (Klaunig *et al.* 2010). If not efficiently repaired by base excision repair pathways, 8-oxo-dG mispairs with adenine during DNA replication, resulting in characteristic G:C →

T:A transversion mutations across the genome. Beyond nuclear DNA damage, ROS also disrupt mitochondrial integrity by inducing lipid peroxidation of mitochondrial membranes and impairing electron transport chain function. This dysfunction promotes further ROS amplification and facilitates the release of cytochrome c into the cytosol, thereby activating downstream apoptotic or dysregulated survival signaling pathways that contribute to malignant progression (Zuo *et al.* 2024).

4.4 Epigenetic Alterations

Chemical carcinogens can also alter the presentation of genetic information without changing the underlying DNA sequence. This epigenetic reprogramming involves altering DNA methylation patterns, modifying histones, and changing non-coding RNA expression profiles (Klibaner-Schiff *et al.,* 2024). Arsenic exposure disrupts these pathways by competing for the cell's methyl group supply. The detoxification of inorganic arsenic requires methyl group donation from *S*-adenosylmethionine (SAM) via arsenic methyltransferase (AS3MT). Chronic arsenic exposure depletes SAM reservoirs, leaving insufficient methyl donor levels for DNA methyltransferases (DNMTs) (Kuo *et al.,* 2017). This leads to global genomic hypomethylation, which can undesirably reactivate oncogenes and transposable elements. At the same time, it can induce regional hypermethylation within the CpG islands of tumor suppressor gene promoters (such as *p16INK4a* and *RUNX3*), effectively silencing genes that regulate cell cycle checkpoints (Zhang *et al.,* 2024).

4.5 Chronic Inflammation

Sustained exposure to environmental carcinogens frequently initiates a persistent and unresolved inflammatory response within affected tissues. Damaged or stressed cells release damage-associated molecular patterns (DAMPs) into the extracellular microenvironment, thereby recruiting and activating resident immune cells, including macrophages, neutrophils, and mast cells (Mao *et al.,* 2025). These infiltrating and tissue-resident inflammatory cells perpetuate the response through continuous secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). This chronic inflammatory milieu activates key transcriptional regulators in adjacent epithelial and stromal cells, most notably nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) (Krajka-Kuźniak *et al.,* 2024). NF-κB activation promotes transcription of multiple pro-survival and proliferative genes, including BCL-2 and cyclin D1, while simultaneously suppressing apoptotic pathways. It also induces expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), further amplifying oxidative and inflammatory signaling within the tissue microenvironment. Collectively, this sustained inflammatory feedback loop creates a pro-tumorigenic niche that supports the survival and clonal expansion of genetically damaged, pre-neoplastic cells. Over time, this environment facilitates malignant progression by coupling ongoing mutational burden with persistent proliferative signaling (Sule *et al.,* 2025).

5. Histopathological Progression of Cancer Development

The molecular mechanisms of chemical carcinogenesis manifest structurally as a series of distinct, sequential histopathological transformations. This morphological evolution marks a tissue's transition from a homeostatic state to an invasive malignancy.

5.1 Hyperplasia

Hyperplasia represents the earliest structural response of a tissue to chronic toxic or chemical injury. It is characterized by an absolute increase in the number of morphologically normal cells within an organ or tissue framework. In this stage, cell division remains regulated, tissue architecture is preserved, and the change is completely reversible if the toxic stimulus is removed. For example, when the cutaneous epithelium is chronically exposed to low concentrations of inorganic arsenic via contaminated water, the basal keratinocytes undergo hyperplastic expansion. This manifests clinically and histologically as arsenical keratosis, a state of increased cell production driven by the chemical activation of epidermal growth factor receptor (EGFR) signaling pathways, long before any fixed genetic mutations appear (Naujokas *et al.,* 2013).

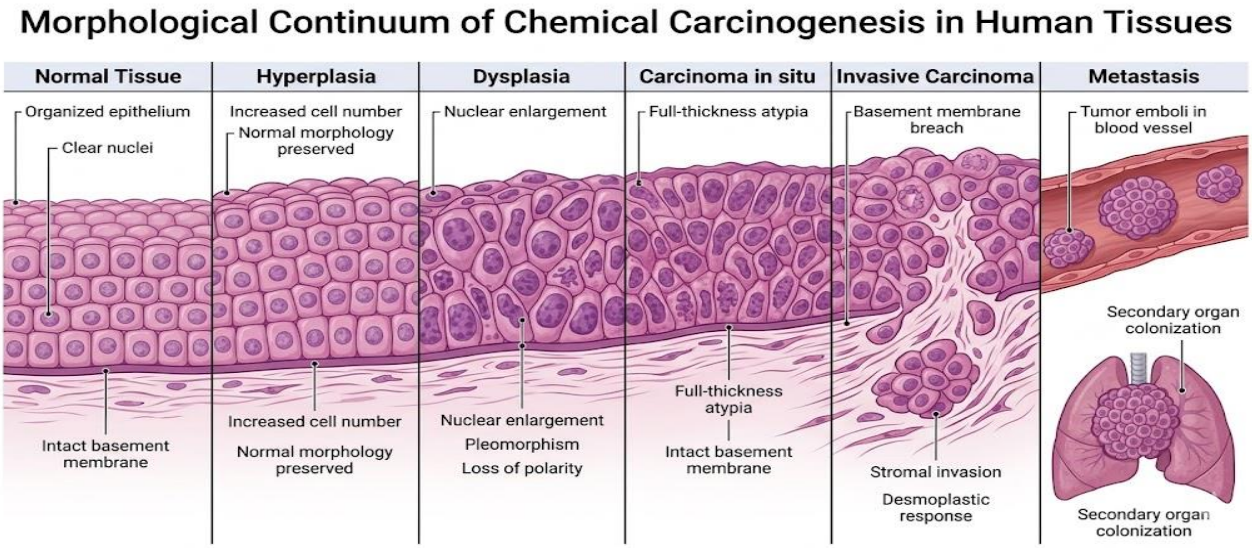

Figure 4: Morphological continuum of environmental carcinogenesis, tracing the step-by-step structural changes from healthy tissue through hyperplasia, dysplasia, carcinoma in situ, basement membrane invasion, and distant metastasis.

5.2 Dysplasia

If chemical exposure persists, the tissue progresses from simple hyperplasia to dysplasia. This stage represents an abnormal pattern of development characterized by a loss of cellular uniformity and architectural orientation. Under the microscope, dysplastic tissue displays cytologic pleomorphism, marked variation in cell size and shape. Cells exhibit hyperchromatic, enlarged nuclei with irregular nuclear membranes and an elevated nuclear-to-cytoplasmic (N:C) ratio. Mitotic figures become more frequent and appear in atypical locations above the basal tissue layers. Importantly, dysplasia is graded semi-quantitatively as mild, moderate, or severe depending on how much of the epithelium is affected. While severe dysplasia represents a advanced pre-malignant state, the cells still respect structural boundaries and have not breached the underlying basement membrane (Weinstein *et al.,* 1985). A diagrammatic continuum of environmental carcinogenesis, tracing the step-by-step structural changes from healthy tissue through hyperplasia, dysplasia, carcinoma in situ, basement membrane invasion, and distant metastasis is shown in **Figure 4.**

5.3 Carcinoma in situ

Carcinoma *in situ* (CIS) represents the advanced stage of localized neoplasia. At this step, the cytologic features of malignancy affect the entire thickness of the epithelium. The tissue displays a complete loss of cellular maturation and architectural orientation from the basal layer to the surface.

Under microscopic examination, CIS exhibits frequent, abnormal mitotic figures and prominent nucleoli. However, despite these malignant features, the lesion remains strictly non-invasive. The dense extracellular matrix of the basement membrane remains completely intact, preventing the neoplastic cells from accessing the lymphatic channels or blood vessels in the underlying stroma (Wogan *et al.,* 2004).

5.4 Invasive Carcinoma

The transition from carcinoma *in situ* to invasive carcinoma is defined by the physical destruction and breach of the basement membrane. Neoplastic cells achieve this by downregulating cell-cell adhesion molecules like E-cadherin and secreting zinc-dependent matrix metalloproteinases (such as MMP-2 and MMP-9) that degrade the type IV collagen and laminin framework of the basement membrane. Once this barrier is breached, malignant cells invade the surrounding interstitial stroma. This stromal invasion triggers a localized desmoplastic response, the proliferation of activated, alpha-smooth muscle actin-positive myofibroblasts and the deposition of dense, disorganized type I collagen. This altered stroma provides a supportive microenvironment that promotes tumor growth and angiogenesis (Cohen & Arnold, 2011).

5.5 Metastasis

Metastasis represents the final phase of malignant progression, during which neoplastic clones spread from the primary tumor site to distant organs. This complex process requires tumor cells to enter blood or lymphatic vessels (intravasation), survive the mechanical stresses and immune surveillance within circulation, exit the vasculature at distant sites (extravasation), and adapt to a foreign tissue microenvironment (colonization). The initial step is often driven by an epithelial-to-mesenchymal transition (EMT). During EMT, chemical signaling pathways induce carcinoma cells to shed their epithelial characteristics and adopt a mobile, mesenchymal phenotype. This phenotypic switch allows them to migrate along stromal collagen tracks toward new vascular channels, leading to widespread systemic dissemination (Zuo *et al.,* 2024).

6. Organ-Specific Pathology

The interaction between an environmental carcinogen's chemical properties and a tissue's local physiological features dictates where tumors develop. This target-organ specificity reflects where compounds are preferentially absorbed, metabolized, or excreted.

6.1 Lung

The pulmonary architecture is directly exposed to airborne environmental carcinogens, making it a primary site for chemically induced malignancies. Inhalation of particulate matter coated with PAHs (such as Benzo[a]pyrene) or occupational exposure to Cr(VI) aerosols causes targeted damage to the bronchial mucosa. Histologically, this chronic irritation causes the normal pseudostratified ciliated columnar epithelium to undergo a protective but maladaptive transformation into a stratified squamous epithelium, a process known as squamous metaplasia. If exposure continues, this metaplastic tissue accumulates genetic hits, progressing through moderate and severe dysplasia to squamous cell carcinoma. This malignancy is characterized under light microscopy by nests of polygonal cells showing varying degrees of squamous differentiation, marked by extracellular keratin pearls and prominent intercellular bridges (desmosomes) (Baszuk *et al.,* 2021; Zhang *et al.,* 2024).

6.2 Liver

The hepatic parenchyma is the body's primary site for xenobiotic metabolism, exposing it to high levels of reactive intermediates. Ingestion of Aflatoxin B_1 targets hepatocytes in Zone 3 of the hepatic acinus, where CYP3A4 concentration is highest. The generation of reactive epoxides causes acute hepatocellular injury, characterized by lipid accumulation (steatosis) and single-cell necrosis.

Over decades of chronic low-dose exposure, the liver undergoes repeated cycles of necrosis and compensatory regeneration, developing dense fibrous septa that distort hepatic architecture, a state of cirrhosis. Within this regenerative environment, mutated hepatocytes form pre-neoplastic altered hepatic foci. These progress into Hepatocellular Carcinoma (HCC), which appears histologically as thickened cords of atypical hepatocytes (greater than 3 cells wide) that disrupt normal sinusoidal layouts and lack bile ducts (Wild & Gong, 2010; Beier *et al.,* 2025).

6.3 Bladder

The transitional urothelium of the urinary bladder acts as a storage reservoir for concentrated water-soluble toxins and their metabolites, making it vulnerable to chemical injury. Ingested inorganic arsenic and inhaled industrial aromatic amines undergo hepatic biotransformation to form water-soluble glucuronide conjugates, which are excreted into the urine. Once in the bladder, the slightly acidic environment of urine can hydrolyze these conjugates, releasing free, highly reactive electrophiles directly against the urothelial lining.

This chronic exposure triggers urothelium proliferation, progressing from low-grade papillary changes to invasive Urothelial Carcinoma. Microscopic examination of these tumors reveals complex, branching papillary stalks lined by atypical transitional cells that exhibit a loss of normal polarity, enlarged hyperchromatic nuclei, and frequent mitotic figures (Kuo *et al.,* 2017).

6.4 Skin

The cutaneous epithelium is exposed to environmental carcinogens through both direct physical contact and systemic circulation. Chronic ingestion of inorganic arsenic leads to accumulation in keratin-rich tissues like the skin, fingernails, and hair. In the epidermis, arsenic disrupts mitotic signaling and alters DNA methylation profiles, manifesting as widespread arsenical keratoses. Histologically, these lesions display hyperkeratosis (thickening of the stratum corneum), parakeratosis (retention of nuclei in the stratum corneum), and marked acanthosis (hyperplasia of the stratum spinosum), alongside irregular down-growths of the rete ridges. These pre-malignant lesions can progress into invasive cutaneous Squamous Cell Carcinoma (SCC) or Basal Cell Carcinoma (BCC), characterized by nests of atypical basaloid cells with a distinct peripheral palisading architecture (Naujokas *et al.,* 2013; Mahraz *et al.,* 2024). The histopathological features of environmentally induced cancers and specific organs are shown in **Table 2** above.

7. Modern Pathology Tools in Environmental Carcinogenesis

Evaluating environmentally induced malignancies has advanced beyond basic light microscopy. Modern pathology utilizes an integrated framework that combines immunophenotyping, molecular sequencing, and computer-assisted image analysis to link structural tissue changes with their specific chemical causes.

Table 2: Histopathological Features of Environmentally Induced Cancers

Organ System	Characteristic Pre-Malignant Lesions	Common Environmental Etiologies	Defining Histopathological Features under Light Microscopy	Immunohistochemical (IHC) & Molecular Profiles
Lung	Squamous metaplasia, severe bronchial epithelial dysplasia	PAHs, Hexavalent Chromium [Cr(VI)], Asbestos fibers	Nests of atypical polygonal cells, keratin pearl formation, intercellular bridging, dyskeratotic cells	P40(+), CK5/6(+), p63(+), TTF-1(-); frequently harbors *TP53* and *KRAS* mutations
Liver	Altered hepatic foci (clear cell/basophilic), bridging cirrhosis	Aflatoxin B_1(AFB_1), chronic alcohol, arsenic ingestion	Thickened hepatocyte cords (>3 cells thick), pseudoglandular patterns, loss of portal tracts, bile canaliculi dilation	HepPar-1(+), Glypican-3(+), Arginase-1(+); *TP53* codon 249 transversions (R249S)
Bladder	Non-invasive papillary urothelial hyperplasia	Inorganic arsenic, industrial aromatic amines (e.g., benzidine)	Branching papillary structures lined by multilayered atypical transitional epithelium, nested infiltrative growth	GATA3(+), CK20(aberrant full-thickness expression), p53(diffuse strong positivity)
Skin	Arsenical keratosis, Bowen's disease (carcinoma *in situ*)	Inorganic arsenic, combined solar Ultraviolet (UV) radiation	Hyperkeratosis, parakeratosis, irregular acanthosis, atypical keratinocytes with nested dermal invasion	High molecular weight cytoperatins (+), p40(+); exhibits global genomic CpG hypermethylation

7.1 Immunohistochemistry

Immunohistochemistry (IHC) allows investigators to visualize specific protein expression patterns directly within preserved tissue architecture. In environmental pathology, IHC helps determine a tumor's tissue of origin and evaluate the activation of downstream oncogenic pathways. For example, when evaluating suspected chemically induced lung malignancies, pathognomonic antibody panels can differentiate between squamous cell carcinomas (p40+, p63+, CK5/6+) and adenocarcinomas (TTF-1+, Napsin-A+) (Zhang *et al.,* 2024). Additionally, IHC can detect direct signs of chemical injury. Antibodies specific for 8-oxo-dG or anti-BPDE-DNA adducts can map exactly where oxidative and chemical damage is distributed across different cellular compartments within a tissue biopsy (Pratt *et al.,* 2011).

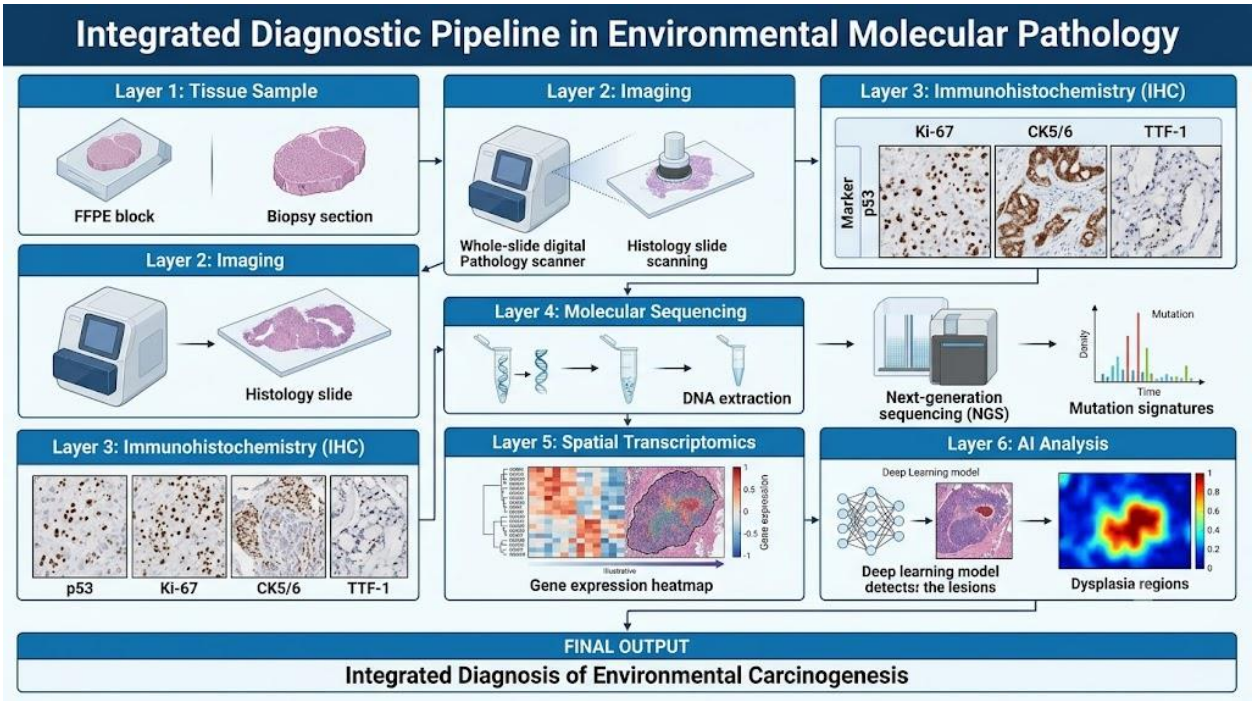

Figure 5: Multi-disciplinary diagnostic pipeline illustrating how modern pathology tools integrate morphological, immunophenotypic, and molecular data to generate a comprehensive profile for precision oncology.

7.2 Digital Pathology

Digital pathology replaces conventional glass slides with high-resolution whole-slide images (WSIs), allowing for automated, quantitative tissue analysis. Computer-assisted image analysis can precisely measure features that are difficult to standardize by eye, such as absolute mitotic counts, the total surface area of dysplastic epithelium, and the specific distribution of tumor-infiltrating lymphocytes (TILs) within the stroma. Furthermore, deep learning models can analyze digital slides to identify subtle morphological variations that correspond to specific environmental exposures. For example, these algorithms can distinguish the unique structural patterns of aflatoxin-driven hepatocellular carcinomas from those caused by metabolic dysfunction or viral hepatitis alone (Beier *et al.*, 2025).

7.3 Molecular Pathology

Molecular pathology investigates the specific genetic alterations that underpin chemical carcinogenesis by linking environmental exposure to distinct, reproducible mutational patterns in human tissue. Using nucleic acids extracted from formalin-fixed paraffin-embedded (FFPE) specimens, researchers apply next-generation sequencing (NGS) to identify exposure-associated mutation signatures across the genome. This approach enables high-resolution mapping of how individual chemical agents generate characteristic mutational landscapes in a trinucleotide sequence context. Mutation signatures are typically analyzed within their immediate sequence environment, represented as:

5′–[Nucleotide]–X–[Nucleotide]–3′
3′–[Nucleotide]–Y–[Nucleotide]–5′

where X:Y denotes the affected base pair and adjacent nucleotides define the trinucleotide context that influences mutational susceptibility. A common analytical framework quantifies mutation frequency within a specific context as:

$$\textit{Relative Frequency} = \frac{\textit{Observed Count of } N[T \rightarrow A]N \textit{ Mutations}}{\textit{Total Somatic Mutation Burden}}$$

This metric captures the proportion of specific base substitutions occurring within defined trinucleotide sequences relative to the overall mutational load, enabling comparison across exposure types and tumor samples.

In environmental carcinogenesis, distinct mutational signatures correspond to specific exposures. For example, COSMIC Signature 4 is dominated by C:G → A:T transversions and is strongly associated with tobacco smoke and PAH exposure. In contrast, COSMIC Signature 24 exhibits a high frequency of T:A → A:T transversions and serves as a molecular fingerprint of aflatoxin B_1 exposure, particularly in hepatocellular carcinoma (Groopman *et al.,* 2008); National Toxicology Program, 2023). These exposure-specific patterns provide robust molecular evidence linking environmental carcinogens to defined cancer etiologies.

7.4 Spatial Transcriptomics

Spatial transcriptomics represents a major advance in tissue analysis, allowing researchers to measure global gene expression profiles while fully preserving the visual layout of the tissue section. This technology uses barcoded capture probes on specialized slides to link RNA sequencing data directly to specific histological features, such as areas of necrosis, regions of dysplasia, or the invasive tumor front. In environmental toxicology, spatial transcriptomics can map out how cells vary their gene expression in response to a localized toxic gradient. Researchers can trace exactly how inflammatory pathways, oxidative stress responses, and extracellular matrix-degrading enzymes are upregulated in the cells immediately surrounding a chemical insult, providing insight into how the tissue microenvironment drives tumor progression (Cheng *et al.,* 2025). A multi-disciplinary diagnostic pipeline illustrating how modern pathology tools integrate morphological, immunophenotypic, and molecular data to generate a comprehensive profile for precision oncology is shown in **Figure 5.**

8. Future Directions

8.1 Exposome Science

The traditional toxicological approach of studying single chemical compounds in isolation is giving way to exposome science, which seeks to map the totality of environmental exposures an individual encounters over their lifetime (Miller & Banbury Exposomics Consortium, 2025). Future research must focus on how complex real-world mixtures of low-dose xenobiotics interact to drive carcinogenesis. This approach requires combining high-resolution environmental sensors and satellite exposure mapping with deep molecular profiling of blood and tissue samples (Zhu *et al.,* 2024). By integrating these large-scale exposomic datasets with clinical health records, researchers can better understand how simultaneous exposures to different classes of pollutants interact to accelerate neoplastic transformation.

8.2 Environmental Pathology

Environmental pathology is expanding from a purely descriptive discipline into a functional, predictive science. Future diagnostic work will increasingly rely on identifying specific molecular fingerprints, such as characteristic DNA adduct profiles, distinct histone modification patterns, and specialized multi-gene expression scores, to determine the environmental causes of individual tumors. Establishing these definitive diagnostic criteria for chemical exposures will help identify hidden environmental hazards, trace specific malignancies back to occupational or industrial sources, and provide objective data to help guide environmental policy and regulation.

8.3 AI-Based Lesion Detection

The integration of artificial intelligence (AI) and deep learning into digital pathology frameworks is set to improve the identification of pre-malignant tissue changes. Convolutional Neural Networks (CNNs) and transformer-based vision models can be trained on vast collections of multi-institutional slides to recognize the earliest structural signs of chemically induced dysplasia. These AI tools can screen large volumes of biopsy samples with high reproducibility, highlighting subtle areas of nuclear atypia or architectural distortion that might be missed by human observers. This automated screening can assist pathologists by ensuring early, reliable detection of pre-cancerous lesions when they are most responsive to intervention.

8.4 Precision Environmental Medicine

The long-term goal of integrating environmental chemistry and molecular pathology is to realize precision environmental medicine. Rather than applying uniform public health recommendations, this approach aims to tailor disease prevention and clinical screening strategies to an individual's unique exposure profile and genetic susceptibility (Smith, 2010). By identifying specific genetic variants in biotransformation or DNA repair genes (such as polymorphisms in *CYP2E1*, *GSTM1*, or *XRCC1*) that make an individual more vulnerable to specific chemical exposures, clinicians can design targeted screening schedules and proactive antioxidant or chemopreventive strategies. This shift from reactive treatment to personalized, proactive risk management represents the future of environmental oncology.

8.5 Natural Plant-Derived Chemopreventive Agents

In addition to synthetic detoxification strategies and regulatory interventions, increasing attention is being directed toward the role of natural plant-derived compounds in mitigating environmentally induced carcinogenesis. A wide range of medicinal plants and dietary phytochemicals exhibit chemopreventive properties through their ability to modulate xenobiotic metabolism, suppress oxidative stress, and inhibit inflammatory and proliferative signaling pathways. Bioactive compounds such as curcumin (from *Curcuma longa*), resveratrol (from *Vitis vinifera*), epigallocatechin-3-gallate (EGCG) (from *Camellia sinensis*), and sulforaphane (from cruciferous vegetables such as *Brassica oleracea*) have been extensively documented to enhance Phase II detoxification enzymes, including glutathione S-transferases, while concurrently downregulating Phase I cytochrome P450-mediated activation of pro-carcinogens (Gao *et al.* (2015); Meeran *et al.* (2010). These phytochemicals also exert potent antioxidant effects by scavenging reactive oxygen species and restoring intracellular redox

balance, thereby reducing oxidative DNA damage such as 8-oxo-deoxyguanosine formation (Naujokat & McKee (2021). Furthermore, several plant-derived compounds demonstrate epigenetic modulatory activity, including the reversal of aberrant DNA methylation patterns and histone modifications associated with carcinogen exposure (Meeran *et al.* (2010); Gao *et al.* (2015). Collectively, these natural agents provide a complementary preventive framework within environmental oncology, supporting the development of dietary-based and plant-derived interventions as part of integrated precision environmental medicine strategies (Tortorella *et al*. (2015).

9. Conclusions

Understanding environmental carcinogenesis requires a comprehensive look at how chemical pollutants traverse our environment and alter human tissue architecture. As detailed in this review, the journey from an industrial or natural xenobiotic to an invasive malignancy is a complex, multi-stage process governed by fixed chemical and biological principles. The environmental persistence and bioavailability of a compound dictate its entry into the human host, where metabolic biotransformation can inadvertently generate highly reactive, electrophilic intermediates. These intermediates drive a cascade of cellular damage, including structural DNA adducts, fixed driver mutations, oxidative stress, epigenetic silencing, and chronic inflammatory signaling, that systematically undermines cellular homeostasis.

For the pathologist and clinician, these molecular alterations manifest visually as a predictable morphological continuum, leading tissues through adaptive hyperplasia and atypical dysplasia to carcinoma *in situ* and invasive, metastatic cancer. This structural evolution demonstrates clear organ- and tissue-specificity, reflecting where specific chemical agents are naturally metabolized or excreted by the body.

By upgrading our diagnostic toolkit from classical light microscopy to advanced multi-parametric methods, such as immunohistochemistry, molecular sequencing, digital pathology, and spatial transcriptomics, we can better identify the chemical signatures behind individual malignancies. Ultimately, combining these modern tissue-based tools with exposome science and artificial intelligence will drive the development of precision environmental medicine, providing the insights needed to mitigate environmental risks and improve global cancer prevention strategies.

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Author Contributions

KSO conceptualized the study, developed the manuscript draft, provided overall supervision, literature review, chemical interpretation, and critical editing of the manuscript. OTA contributed specifically to histopathological components of the framework, clinical and anatomical pathology insights and the critical interpretation of disease–pathology relationships. All authors reviewed, revised, and approved the final version of the manuscript.

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Declaration of Generative AI and AI-Assisted Technologies

The authors declare that artificial intelligence tools (ChatGPT, OpenAI) were used only for language polishing and readability enhancement. No AI tools were used in the generation, analysis, or interpretation of scientific data. The authors retain full responsibility for the content of this manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

This study is a critical review and did not generate new experimental data. All information used in the manuscript was obtained from previously published studies, which are appropriately cited throughout the text.

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