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Review

Advances in the Mechanisms and Mutational Signatures of Gene Mutations Induced by Typical Environmental Chemical Carcinogens

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Abstract: Somatic mutations driven by DNA damage, repair imbalance, and replication errors upon exposure to environmental chemical carcinogens represent a fundamental molecular basis for tumor initiation and progression. With advances in high-throughput sequencing technologies, exposure-associated mutational signatures have gradually emerged as crucial molecular markers for identifying exogenous carcinogens, tracing exposure origins, and assessing genotoxicity risks. Given the wide variety and mechanistic complexity of environmental chemical carcinogens, this review focuses on International Agency for Research on Cancer (IARC) Group 1 carcinogens with clear environmental exposure relevance and distinct mechanisms, while incorporating selected well-characterized derivatives or model compounds as mechanistic exemplars where they illuminate pathway-specific signatures. Drawing on dimensions commonly used in carcinogen mechanism studies, such as metabolic activation or electrophilicity, oxidative stress, genotoxicity, DNA repair alterations, genomic instability, and epigenetic alterations, we systematically review the major mechanisms and their differences underlying gene mutations induced by typical environmental chemical carcinogens along the pathway from exposure through metabolic activation, oxidative stress, DNA damage and repair, and replication responses, to mutation fixation and mutational signatures. This review aims to elucidate how different mutagenic steps influence mutation types and the formation of mutational signatures, thereby providing a reference for genotoxicity evaluation and exposure-related health risk research.

Keywords: environmental chemical carcinogens; gene mutations; mutational signatures; DNA damage; DNA repair

1. Introduction

Gene mutations are stable alterations in the base composition or sequence order of genomic DNA, the defining feature of which is that the sequence changes can be retained and transmitted through cell division [1]. Accordingly, gene mutations are fundamentally distinct from DNA damage. DNA damage refers to a state in which the DNA molecular structure is disrupted by physical or chemical factors, which is usually reversible and repairable; mutations arise only when the damage is not promptly eliminated and becomes a permanent sequence alteration during replication or repair [2]. In tumorigenesis, somatic mutations have been established as critical molecular events driving malignant transformation. Activation of proto-oncogenes, inactivating mutations of tumor suppressor genes, and disruption of genomic stability collectively promote the acquisition of abnormal proliferation, invasion, and metastasis capabilities [3–5].

Among the sources of somatic mutations, environmental factors are important drivers of acquired mutations. Physical, chemical, and biological factors can all induce genomic alterations, among which exposure to environmental chemicals is characterized by complex sources, long duration, and partial intervenability. Reports indicate that various modifiable risk factors accounted for approximately 37.8% of new cancer cases worldwide in 2022, with environmental and occupational factors related to exposure to chemical carcinogens accounting for a significant proportion of those cases [6]. The International Agency for Research on Cancer (IARC) of the World Health Organization classifies carcinogens into four groups based on the sufficiency of carcinogenic evidence, with Group 1 consisting of agents for which there is sufficient evidence of carcinogenicity in humans [7,8]. Existing mechanistic studies indicate that these chemical carcinogens do not act through a single pathway but concurrently exhibit key characteristics such as metabolic activation to electrophiles, induction of DNA damage, alteration of DNA repair or induction of genomic instability, induction of oxidative stress, and epigenetic alterations [9]. These mechanisms do not all equate directly to mutations, but collectively they increase the probability that DNA damage evades repair and becomes fixed as a mutation.

Given the significant role of genetic mutations in chemical carcinogenesis, this article focuses on representative typical environmental chemical carcinogens, comparing their exposure sources, damage types, repair responses, and mutation results. It systematically outlines a multidimensional classification framework for the induction of mutations by these substances, constructs a common temporal mutagenic pathway from metabolic activation to mutation fixation, and, through horizontal comparison of the metabolic pathways, damage sites, and repair target differences of different chemical carcinogens, interprets the characteristic mutation signatures of different chemicals. Through systematic integration, it provides a reference for the evaluation of genetic toxicity and health risk assessment of environmental chemicals.

2. Types and Functional Classification of Gene Mutations

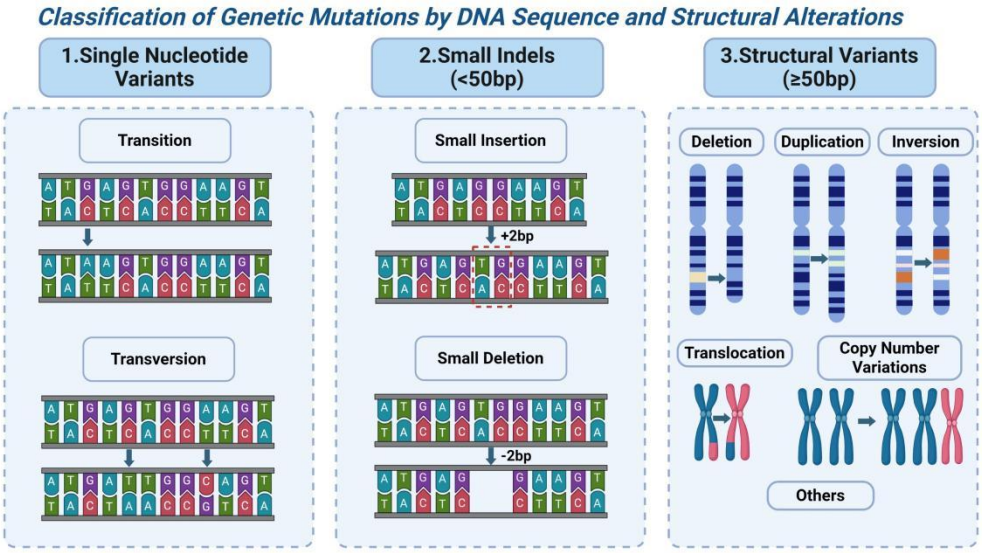
Based on modern genetic theory, the multidimensional classification framework for gene mutations, ranging from molecular structure to functional effects, has become increasingly mature, laying a theoretical foundation for systematically dissecting the mutagenic mechanisms of environmental chemical carcinogens. Current research primarily defines gene mutation types along two major dimensions: DNA sequence structural alterations and abnormalities in protein-coding function [10,11].

From the perspective of DNA sequence structure, gene mutations can be classified into three categories based on the length of genomic base sequences and the form of rearrangement: single nucleotide variants (SNVs), small insertions and deletions (Indels), and structural variants (SVs) (**Figure 1a**). SNVs generally refer to single-base substitutions in the DNA sequence, comprising transitions and transversions, and represent the most commonly used basic unit in somatic mutation spectrum analysis. As the major type of mutation induced by environmental chemical carcinogens, different chemicals not only exhibit a high degree of preference for specific base substitution types, but their mutagenic processes are also markedly influenced by the adjacent sequence context of the mutation site [12,13]. This base substitution preference, combined with sequence context, constitutes the molecular

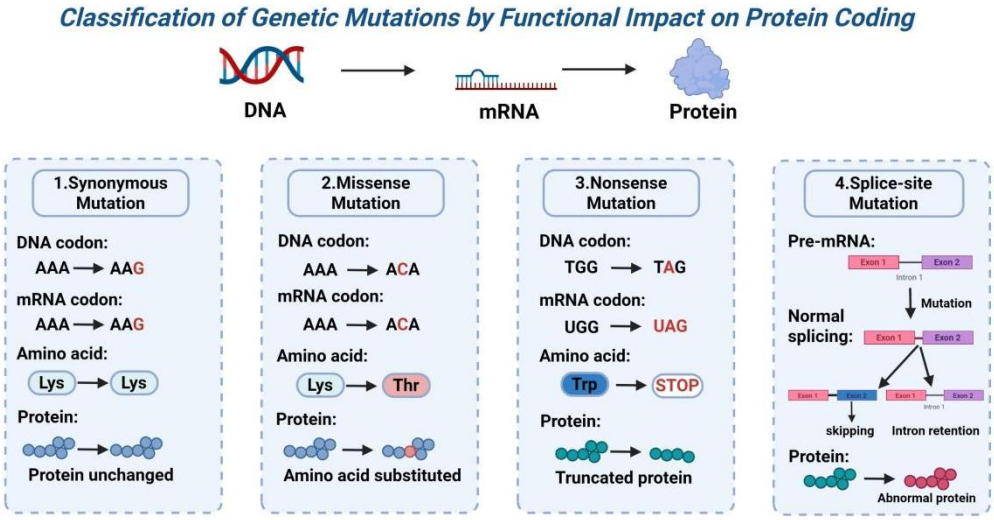
basis for extracting and recognizing characteristic mutational signatures [14]. Indels typically refer to sequence alterations of < 50 bp in length. When such mutations occur in the coding region of a gene and the length is not a multiple of three, they give rise to frameshift mutations, altering the downstream amino acid coding sequence and usually resulting in truncated or functionally aberrant protein products, with a significant impact on gene function. SVs refer to sequence rearrangements or copy number changes of ≥ 50 bp in the genome, involving larger-scale deletions, inversions, translocations, insertions, copy number variations, and the like. Such large-scale variants are mostly caused by DNA double-strand breaks, DNA crosslink damage induced by complex environmental exposures, and the subsequent error-prone repair pathways. The above three categories of variation encompass genomic alterations at different scales, from single bases to large chromosomal segments, and collectively drive clonal evolution in tumor initiation and progression [4,5,15].

From the perspective of protein-coding function, mutations occurring in the gene coding region or canonical splice sites can generally be classified into four categories based on their effects on transcripts and protein products: synonymous mutations, missense mutations, nonsense mutations, and splice site mutations [16,17]. This classification does not merely describe the form of DNA sequence alterations but emphasizes the impact of mutations on protein structure, expression levels, and functional status, serving as an important criterion for evaluating the biological significance, pathogenicity, and carcinogenic effects of mutations (**Figure 1b**). Synonymous mutations, which do not alter the encoded amino acid, have traditionally been considered to have minimal functional impact or to be nearly neutral; however, recent studies have shown that some synonymous mutations can affect protein expression levels and even folding processes by altering mRNA secondary structure, stability, splicing regulatory elements, or translation rate [18,19]. Missense mutations lead to single amino acid substitutions in the polypeptide chain. Their functional effects are highly dependent on the evolutionary conservation of the mutation site, the importance of the affected domain, and the physicochemical differences between the original and substituted amino acids. Missense mutations occurring in critical domains, catalytic sites, or highly conserved regions are highly likely to disrupt protein conformation, stability, or enzymatic activity, whereas those in non-conserved regions may have only limited impact [20–22]. Nonsense mutations convert a sense codon into a premature termination codon (PTC), leading to premature translation termination and loss of the C-terminal portion of the protein. mRNAs carrying a PTC are frequently recognized and degraded by nonsense-mediated mRNA decay (NMD), thereby limiting the production of truncated proteins [23]. PTCs located in NMD-sensitive positions typically result in loss-of-function (LOF), because NMD degrades the PTC-containing mRNA and prevents the production of both full-length and truncated proteins. In contrast, PTCs near the 3’ end or within the last exon can escape NMD and produce truncated proteins that may accumulate and exert dominant-negative (DN) or gain-of-function (GOF) effects. Splice site mutations frequently occur at the conserved sequences of the junctions between exons and introns or adjacent splicing regulatory elements and can disrupt normal RNA splicing, generating aberrant transcripts. Such alterations can further cause reading frame shifts, deletion of critical protein domains, or aberrant protein expression, representing

important mechanisms that affect gene function and contribute to tumorigenesis and various genetic diseases [24,25].



(a)



(b)

Figure 1. Schematic overview of gene mutation classification. **(a)** Mutation classification at the DNA sequence structural level. **(b)** Mutation classification at the protein-coding functional level. Created in BioRender.

In recent years, with advances in functional genomics and large-scale functional assessment of variants, the classification of mutations has extended beyond the form of sequence alterations or consequences on protein coding to encompass their effects on gene function and cellular phenotypes. Based on their biological consequences, mutations can be primarily classified into three categories: LOF mutations, DN mutations, and GOF mutations, which differ markedly in their pathogenic mechanisms [26]. LOF mutations lead to reduced or abolished normal activity of the gene product and are typically caused by nonsense mutations, frameshift mutations, aberrant splicing, or missense mutations that disrupt key functional domains [27–29]. DN mutations refer to the scenario in which the mutant protein, in the presence of the wild-

type protein, inhibits the function of the wild-type protein through mechanisms such as competitive binding, formation of abnormal complexes, or interference with multimer function, thereby producing a dominant phenotype [30–32]. GOF mutations confer new biological functions, abnormal activity, or enhanced native function on the gene product [33]. There is no one-to-one correspondence between mutation types at the sequence level and their functional outcomes, and the same gene or even the same class of mutation can produce different functional effects under different cellular contexts. For example, certain missense mutations in the tumor suppressor gene *TP53* can not only lead to loss of the native transcriptional regulatory function of the p53 protein but also promote tumor cell survival, invasion, and therapeutic resistance through dominant-negative effects or gain-of-function mechanisms, and these effects jointly drive the evolution of malignant phenotypes [34–36].

The types of gene mutations serve as the basic vocabulary for deciphering the mutational signatures of chemical carcinogens. A mutational signature is not equivalent to a single mutation type but rather a statistical mutation pattern shaped in the genome by a specific mutagenic process [37]. For single-base substitutions, mutation signatures are conventionally recorded with reference to the pyrimidine base, so that C > A and G:C→T:A describe the same substitution direction. In the case of chemical carcinogens, the formation of mutation signatures depends on the type of primary DNA damage induced by the chemical, cellular repair pathways, replication bypass processes, and the biological context of the exposed tissue [38].

3. Molecular Mechanisms and Mutational Signatures of Typical Environmental Chemical Carcinogens

Mutagenesis caused by exogenous factors typically generates a large number and diversity of mutation events across the entire genome. By integrating information such as their compositional types, base substitution directions, trinucleotide sequence contexts, Indels features, structural variant patterns, transcriptional strand bias, and replication timing, an overall distribution pattern can be derived as the mutational signature [37,39,40]. In environmental exposure attribution studies, mutation signatures with etiological indicative value are often referred to as exposure-associated mutation signatures, emphasizing their traceability value in identifying potential mutagenic sources [41,42]. For the broader field, the COSMIC database provides a standardized reference framework for cataloguing single base substitutions (SBS), doublet base substitutions (DBS), small insertions and deletions (ID), copy numbers (CN), and structural variants (SV) signatures [43]. However, for most chemical carcinogens, validated COSMIC mutation signatures specific to those carcinogens and applicable to humans have not yet been established. Therefore, we describe the observed patterns as exposure-associated mutation signatures and indicate their relationship to established COSMIC signatures only when supporting evidence is available.

In chemical carcinogen research, mutational signatures elucidate the molecular mechanisms linking carcinogen exposure to tumorigenesis. Due to differences in carcinogen-DNA binding preferences, adduct conformations, dependence on distinct DNA repair pathways, and tissue-specific metabolic activation, individual chemicals often exhibit characteristic exposure-specific mutational signatures [44]. For example,

DNA adducts associated with polycyclic aromatic hydrocarbons (PAHs) are more likely to result in substitution patterns characterized by G:C→T:A transversions [45,46], whereas adducts of certain aromatic amines are more frequently associated with frameshift mutations or specific base transversions [47–49]. Therefore, mutational signatures can provide important evidence for attributing exposure to chemical carcinogens, but they are essentially probabilistic and biological context-dependent molecular markers and cannot yet serve as an independent criterion for causal judgment. In practical applications, mutational signatures should be interpreted in conjunction with evidence on exposure dose and duration, tissue type, metabolic enzyme activity, DNA repair status, and other factors [43,50,51]. From a mechanistic perspective, mutation induction by environmental chemical carcinogens is not a single event but rather a temporal process involving multiple steps and synergistic mechanisms [52–54]. This process begins with the chemical entering the organism and undergoing metabolic activation, subsequently causing DNA damage and triggering a response from the repair system; if the damage is not promptly corrected, it is fixed as a mutation, ultimately leading to the disruption of genomic stability [55,56] (**Figure 2**). This common mutagenic pathway constitutes the shared underlying logic by which different chemicals generate specific mutational signatures, while the biological heterogeneity at each step collectively determines the characteristics of the final mutational signature. Based on this understanding, this review first constructs the common mutagenic pathway of environmental chemical carcinogens, and then, building on that, horizontally compares the distinct mutational signatures of four classes of carcinogens (heavy metals, PAHs, aromatic amines, and mycotoxins), focusing on the dominant links that induce DNA damage, interfere with the repair and recombination processes, and ultimately shape the mutation signature (**Table 1**).

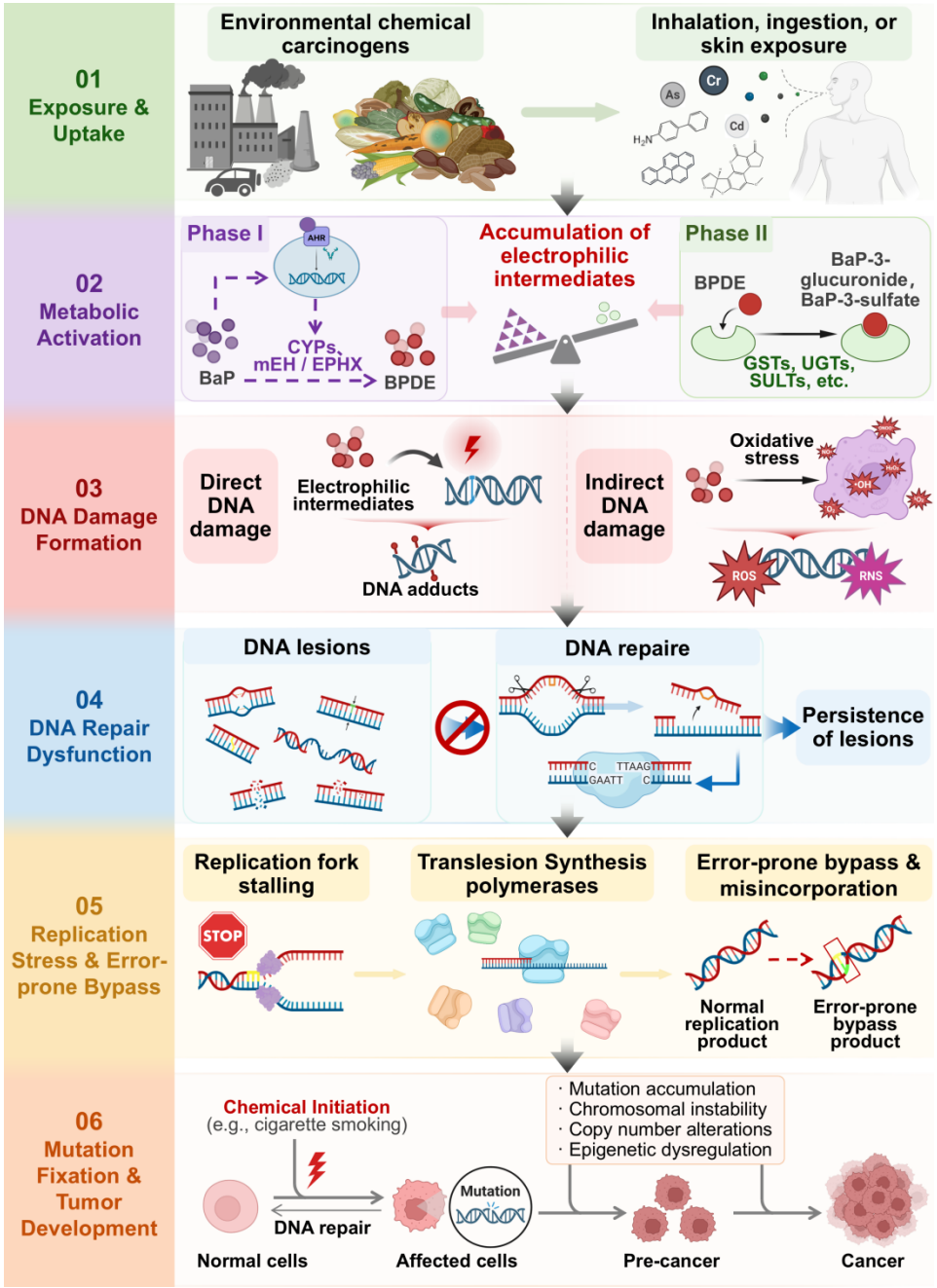


Figure 2. Schematic overview of the sequential molecular mechanisms of gene mutation induction by environmental chemical carcinogens. Created in BioRender.

Table 1. Comparison of Mutational Characteristics of Typical Environmental Chemical Carcinogens.

Chemical Carcinogens	IARC Group [a]	Metabolic Activation	DNA Damage Mechanism	Adduct(s)	Characteristic Base Substitution	Mutation Hotspot/Sequence Preference	Dominant Mutation Type	References
Heavy Metals								
As	1	No metabolic activation required	Indirect: oxidative stress, repair inhibition	No typical covalent adducts	Candidate: T:A→G:C; G:C→C:G	No clear consensus sequence	Predominantly SNVs	[7,79,110–117]
Cd	1	No metabolic activation required	Indirect: oxidative stress, repair inhibition	No classical covalent adducts	No validated SBS	No clear preference	Predominantly SVs(multilocus deletions)	[7,80,86,118,119,121–125,128]
Cr(VI)	1	Intracellular reduction to Cr(III)	Direct: Cr(III)-DNA adducts; Indirect: ROS-induced oxidative damage	Cr(III)-DNA adducts	In vitro: T:A→A:T, T:A→G:C; Human *TP53*: G:C→T:A, etc.	A/T-rich sequences, NGG sequences	SNVs and SVs co-exist	[7,108,130–138]
PAHs								
BaP	1	CYP enzymes →BPDE	Direct: BPDE-dG adducts	BPDE-dG adducts	G:C→T:A	Methylated CpG dinucleotides (5’-MeCG)	Predominantly SNVs	[7,45–47,142–147]
Nitro-PAHs	2A / 2B / 3	Nitroreductase	Direct: guanine adducts; Indirect: lipid peroxidation	dA/dG etheno adducts	G:C→T:A; G:C→A:T; G:C→G:C	Not well defined	Predominantly SNVs	[7,13,150]
Aromatic Amines								
4-ABP	1	CYP/NAT→ nitrenium ion	Direct: dG-C8-ABP adducts	dG-C8-4-ABP adducts	G:C→T:A	NarI site (GGCGCC), G-rich regions	Predominantly SNVs	[7,49,152,155,157,160]
AAF	None	CYP/NAT→ nitrenium ion	Direct: dG-C8-AAF adducts	dG-C8-AAF adducts	G:C→T:A; G:C→A:T	NarI site (GGCGCC), G-rich regions	Predominantly frameshifts	[7,47–49,157,158,160]
2-NA	1	CYP/NAT→ nitrenium ion	Direct: dG-C8-2-NA adducts	dG-C8-2-NA adducts	G:C→T:A	Not well defined	Predominantly SNVs	[7,49,155]
Mycotoxins								
AFB1	1	CYP3A4/CYP1A2→AFBO	Direct: AFB1-N7-dG and AFB1-Fapy-dG adducts; Indirect: repair inhibition	AFB1-N7-dG; AFB1-Fapy-dG	G:C→T:A	*TP53* codon 249; CGC/CGG contexts	Predominantly SNVs	[7,163–171]

[a] IARC group classifications are based on the IARC Monographs, Volumes 1–142 (updated on July 3, 2026).

Abbreviations: IARC denotes International Agency for Research on Cancer; SNV: single nucleotide variant; SV: structural variant; SBS: single-base substitution; dG: deoxyguanosine; dA: deoxyadenosine; NAT: N-acetyltransferase; AFBO: AFB1-exo-8,9-epoxide; Fapy: formamidopyrimidine; ROS: reactive oxygen species; CYP: cytochrome P450.

3.1. Common Mutagenic Pathways of Environmental Chemical Carcinogens

After environmental chemical carcinogens enter the body, their metabolic transformation is a critical determinant of genotoxic potency. Most organic chemical

carcinogens are procarcinogens that lack direct mutagenic activity and require biotransformation by metabolic enzyme systems to exert genotoxic effects. This metabolic transformation primarily involves two interconnected phases, Phase I and Phase II [57,58]. Phase I metabolism mainly comprises functionalization reactions such as oxidation, reduction, and hydrolysis, with the cytochrome P450 enzyme superfamily (CYPs) serving as the core catalytic enzymes [59]. For procarcinogens such as PAHs, aromatic amines, and nitrosamines, Phase I metabolism does not merely reduce toxicity; rather, it can convert parent compounds of low reactivity into electrophilic reactive intermediates, thereby endowing them with the ability to covalently bind to DNA bases, which is a process known as metabolic activation [60,61]. Phase II metabolism primarily proceeds via conjugation reactions such as glucuronidation, glutathione conjugation, sulfation, or acetylation to increase the water solubility of metabolites and promote their excretion. Glutathione S-transferases (GSTs) and UDP-glucuronosyltransferases (UGTs) are typical detoxification-related enzymes [62]. However, Phase II metabolism does not always result in detoxification; some sulfation or acetylation reactions may also lead to the formation of highly reactive intermediates from compounds such as aromatic amines [63–65]. The expression levels and catalytic activities of Phase I and Phase II metabolic enzymes largely determine the ultimate fate of the chemical: when the rate at which Phase I metabolism generates reactive intermediates exceeds the clearance capacity of Phase II conjugation, or when the chemical itself inhibits detoxification enzymes, leading to intracellular accumulation of reactive intermediates, the risk of DNA damage increases significantly [66]. Furthermore, some chemicals can themselves upregulate the expression of Phase I enzymes such as CYP1A1 by activating nuclear receptors like the aryl hydrocarbon receptor (AHR), further amplifying the production rate of activated metabolites and accelerating the shift in metabolic balance toward a pro-mutagenic state [67,68]. It is precisely the differences in this metabolic transformation step that provide the important material basis and initial conditions for the variation in mutational signatures among different chemicals, and even for the same chemical across different tissues or individuals.

DNA damage induced by chemical carcinogens can be divided into two categories: direct damage and indirect damage [69]. Direct damage refers to the covalent binding of electrophilic intermediates to DNA bases, forming stable DNA adducts [70]; this represents an important genotoxic mechanism of organic chemicals such as PAHs and aromatic amines [71]. Such adducts can interfere with normal base pairing or block replicative polymerases, thereby causing base substitutions or frameshift mutations during replication [72,73]. Indirect damage primarily involves the attack on DNA by reactive intermediates such as reactive oxygen species (ROS) or reactive nitrogen species (RNS) generated by the chemical, resulting in oxidative damage, base modifications, and strand breaks [74]. Heavy metals such as arsenic, cadmium, and chromium can all cause oxidative damage through this pathway. Among the resulting lesions, 8-oxoguanine (8-oxoG) is a typical oxidative DNA damage product that can mispair with adenine during replication, leading to G:C→T:A transversions [75]. Persistent oxidative stress can also attack the DNA replication fork, causing fork stalling or even collapse, thereby predisposing the genome to chromosomal structural variants [76,77].

Upon the occurrence of damage, cells initiate DNA damage repair processes, including pathways such as base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ), in an attempt to eliminate the damage [78]. Environmental chemical carcinogens can induce mutations by inhibiting repair functions through various mechanisms: directly targeting the functional domains of repair proteins to inactivate them [79,80]; damaging key residues of repair proteins via oxidative stress or direct chemical modification, thereby affecting their DNA-binding or catalytic activity or even triggering proteasomal degradation [81–83]; they can also influence the transcriptional levels of repair genes through epigenetic regulation, reducing the synthesis of repair proteins at the source [84–86]. Furthermore, some chemicals can weaken the overall function of the repair system through indirect pathways, such as interfering with cell cycle checkpoints or depleting key repair cofactors [87,88]. Inhibition of distinct repair pathways leads to distinct mutational outcomes; for example, suppression of BER primarily causes oxidative base substitutions [89,90]; loss of NER function increases characteristic transversions induced by bulky adducts [91]; and deficiency in HR and NHEJ not only fails to correctly repair double-strand breaks resulting from replication fork collapse but also promotes structural variants such as deletions, translocations, and copy number alterations through error-prone end-joining pathways like microhomology-mediated end joining (MMEJ) [92,93]. Thus, the impairment of repair functions allows DNA damage to persist, establishing the conditions for subsequent mutation fixation, which is a key step for environmental chemical carcinogens to amplify mutation frequency.

When unrepaired lesions enter S phase, replication forks stall and activate the low-fidelity translesion synthesis (TLS) pathway, in which specialized Y-family polymerases bypass the lesions to continue replication; however, this process substantially increases the probability of misincorporation [94,95]. The persistent fixation of damage-induced mismatches and error-prone translesion synthesis ultimately leads to genomic instability, manifested as mutation accumulation, chromosomal structural rearrangements, and an increase in copy number variations [96,97]. If cell cycle checkpoints, telomere homeostasis, or apoptotic clearance mechanisms are simultaneously compromised, cells carrying mutations may evade immune surveillance or apoptosis and continue to proliferate [98–101]. Under conditions of sustained exposure, the accumulation of mutations, structural rearrangements, copy number variations, and epigenetic dysregulation mutually amplify one another, ultimately driving genomic instability and tumor clonal selection [53,102].

In summary, mutation induction by environmental chemical carcinogens is a dynamic, multi-step process involving the coordination of multiple mechanisms. The mutagenic pathway from damage formation, through repair imbalance and replication bypass/error-prone repair, to mutation fixation constitutes a common mechanistic framework underlying somatic mutations induced by most environmental chemical carcinogens. It is important to note that different chemicals exhibit marked differences in their target sites and effect intensities at various steps of this pathway, thereby generating highly specific mutational signatures. These characteristic mutational

signatures can not only be used to trace exposure sources but also reflect the intrinsic mechanistic differences in the carcinogenic processes of different chemicals.

3.2. Mutation Signatures and Differential Mechanisms Associated with Exposure to Typical Environmental Chemical Carcinogens

3.2.1. Heavy Metals

Heavy metal-based environmental carcinogens are widely present in the natural environment and occupational exposure settings. Human exposure primarily occurs through drinking contaminated water, consuming contaminated food, inhaling metal particulates or industrial fumes, and occupational exposure in related industries [103]. Unlike organic carcinogens, the genotoxicity of heavy metals is highly dependent on the element type, valence state, and intracellular reduction state [104]. Arsenic (As), cadmium (Cd), and hexavalent chromium [Cr(VI)] are all classified as IARC Group 1 carcinogens [105], yet their modes of action differ considerably. As and Cd exert their toxicity mainly through indirect mechanisms, including the induction of oxidative stress, inhibition of DNA repair, and triggering of epigenetic reprogramming [106,107]. Cr(VI) not only acts through these indirect pathways but is also progressively reduced by intracellular ascorbic acid and glutathione to Cr(V)/Cr(IV), ultimately forming Cr(III). The intermediate products themselves do not react with DNA, but they can react with H_2O_2 to generate hydroxyl radicals, causing oxidative DNA damage; the final product, Cr(III), can form Cr-DNA adducts by directly coordinating with the N7 position of guanine in DNA. Consequently, Cr(VI) exhibits both direct and indirect mutagenic characteristics [108,109].

As occurs mainly as trivalent arsenite [As(III)] or pentavalent arsenate [As(V)], with As(III) exhibiting markedly greater toxicity [110]. As itself is a weak mutagen; it causes DNA damage (e.g., 8-oxoG) primarily through the induction of oxidative stress and inhibits DNA repair by binding to zinc finger motifs, thereby indirectly increasing the mutation frequency [79,111–112]. As generally does not typically form stable, classical covalent DNA adducts, which is an important distinction from direct genotoxicants such as PAHs and aromatic amines [113]. Furthermore, As can induce replication stress by inhibiting RAD18-mediated translesion synthesis, manifested as increased single strand DNA gaps and double strand breaks at replication forks, with dose-dependent chromatid breaks and gaps *in vivo* [114,115]. Evidence for a distinctive arsenic-associated mutational signature in human tumors remains limited. A whole-genome sequencing analysis of a single arsenic-related lung tumor from a never-smoker identified a low overall single-base substitution burden with a high fraction of T > G/A > C mutations and a low fraction of C > A/G > T transversions, as well as a rare *TP53* G > C mutation [116]. Experimental evidence provides partial mechanistic support: *in vivo* gpt-delta transgenic mice assays have reported that arsenic induces G:C→T:A transversions through the formation of 8-OHdG induced by oxidative stress [117]. However, no validated human-specific COSMIC mutational signatures for As have yet been established; the T > A/G > C and G:C→C:G mutations are candidate signatures that require validation in larger tumor cohorts before they can be considered a defined COSMIC signature.

Cd, similar to As, is an indirect mutagen with very weak direct interaction with DNA; the adducts formed are highly unstable, resulting in low activity in standard

mutagenicity assays [118]. In assay systems capable of detecting both intragenic and multilocus mutations, Cd(II) primarily induces multilocus deletions [119]. Studies in humans and animals have consistently demonstrated that Cd(II) exposure can cause chromosomal aberrations such as chromatid breaks, dicentric chromosomes, and ring chromosomes [120–122]. The mechanisms primarily involve inducing ROS production and inhibiting DNA repair [123], such that Cd(II) can displace Zn(II) in the zinc-hook domain of RAD50, disrupting the assembly of the MRE11-RAD50-NBS1 (MRN) complex and inhibiting homologous recombination repair [124]; it can also displace Zn(II) in the zinc fingers of repair proteins such as Fpg and XPA, inhibiting the enzymatic activity of OGG1 and the DNA damage recognition function of XPA, thereby impairing BER and NER [80,125,126]; additionally, Cd(II) can competitively displace Mn(II) in protein phosphatase 5 (PP5), leading to hyperphosphorylation and premature dissociation of DNA-dependent protein kinase catalytic subunit (DNA-PKcs) from DSB sites, thereby suppressing NHEJ and increasing the risk of aberrant double-strand break (DSB) repair [127]. Furthermore, Cd(II) can induce overexpression of DNMT1 and DNMT3a, leading to hypermethylation of promoter regions of DNA repair genes and their transcriptional silencing, thereby weakening DNA repair capacity at the epigenetic level [86]. At the SNV level, experiments in mammalian cells have shown that Cd-induced base substitutions are predominantly transversions, with mutation frequencies roughly comparable at T·A and G·C base pairs [128]; however, this pattern derives from select cell systems rather than human tumors. Human tumor sequencing data link integrated heavy-metal exposure, with Cd among the strongest contributors, to increased Indels burden in lung adenocarcinoma and colorectal cancer, rather than to a single dominant SBS signature [129]. No validated agent-specific COSMIC signature for Cd currently exists. The Cd-associated mutational signature is therefore best described as an exposure-associated signature dominated by structural variants and multilocus deletions, with a heterogeneous and non-signature-level SNV component whose specific base-substitution features require validation in larger human somatic mutation datasets.

Cr(VI) differs from As and Cd by acting through both direct and indirect DNA damage. After entering cells via anion channels, it is reduced intracellularly to Cr(III) [108,130], generating ROS and forming Cr(III)-DNA adducts at N7-guanine with NGG preference [131]. It is worth noting that differences in reducing agent levels, TLS polymerase expression profiles, and regulatory mechanisms among different cell lines result in variations in the mutagenic signatures of Cr(VI) across different cells or populations [94,97]. A defining feature of Cr(VI) is its ability to induce chromosome instability (CIN). Chronic Cr(VI) exposure affects DNA repair and centrosome homeostasis, leading to both structural and numerical CIN [132]. Mechanistically, Cr(VI) induces DSBs and inhibits their high-fidelity repair, specifically targeting the RAD51 step of homologous recombination; repair-compromised cells resort to error-prone pathways such as NHEJ or MMEJ, thereby introducing deletions, translocations, and copy-number changes [130]. Cr(III) can also trap proteins to form DNA-protein crosslinks (DPCs) or bridge double-stranded DNA to generate interstrand crosslinks (ICLs), further impeding replication and transcription [130,133,134]. Furthermore, Cr(VI) can induce hypermethylation and silencing of the promoters of

DNA repair genes, further amplifying the mutagenic effects [85,135]. This type of genomic instability, driven by repair failure, is considered a key driver of the carcinogenic effects of chromium(VI). At the SNV level, *in vitro* data show strong sequence specificity, whereas the available human data are sparse and internally inconsistent. In CHO-K1 cells, over 90% of the base substitutions induced by Cr(VI) occur at A·T base pairs and are predominantly T:A→A:T and T:A→G:C transversions [136]; however, these findings derive from a single rodent cell line and cannot be directly extrapolated to human tumors. Human data are limited to p53-targeted sequencing of small occupational cohorts and are discordant. Harty et al. associated coding-strand G:C→T:A transversions with chromate exposure in 88 smokers, but the exposed subgroup comprised only three large-cell carcinomas [137], whereas Kondo et al. found no increase in G→T transversions among 20 chromate-exposed lung cancers, with half of mutations at A·T pairs [138]. These differences may reflect variations in exposure type, tumor histology, and sample size; however, to date, there have been no reports of whole-genome or whole-exome analyses of somatic mutations in tumors from populations exposed to chromium(VI). In summary, the Cr(VI)-associated mutational signature is best described as an exposure-associated signature dominated by structural and numerical CIN, with a sequence-specific but heterogeneous SBS component that does not meet validated agent-specific criteria; no validated Cr(VI)-specific COSMIC SBS, ID, or SV signature currently exists.

3.2.2. Polycyclic Aromatic Hydrocarbons

PAHs are a class of organic compounds composed of multiple fused aromatic rings, originating mainly from the incomplete combustion of organic matter and widely present in tobacco smoke, vehicle exhaust, and industrial emissions [139]. Current research on the mutagenic mechanisms of PAHs is relatively well characterized: after entering the body, PAHs undergo metabolic activation to form highly electrophilic intermediates, which subsequently bind to DNA to form adducts and induce specific base substitutions during replication [140,141].

Benzo[a]pyrene (BaP) is an important representative of PAHs and a major carcinogenic component of tobacco smoke. BaP is recognized to be metabolized by the CYP enzyme system, and to be activated into the “bay region” benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE), which can subsequently form adducts with DNA bases [142]. In this process, BPDE preferentially attacks the N^2 position of guanine, forming BPDE-dG adducts. During replication, the TLS polymerases preferentially incorporate adenine opposite the adduct, primarily inducing G:C→T:A transversions [143]. Studies have shown that BPDE adducts form selectively at the guanine positions 157, 248, and 273 of the *TP53* gene, which are precisely the major mutation hotspots in smoking-associated human lung cancer [144]. Furthermore, in the COSMIC database, BPDE-induced G:C→T:A transversions share partial similarity with SBS4, a signature consistently associated with tobacco smoking in large cancer genomics studies [145,146]. This evidence supports a plausible mechanistic contribution of BaP/BPDE to tobacco-related mutagenesis. The site specificity of BPDE adducts stems from the fact that methylated CpG dinucleotides are highly reactive targets for BPDE-induced mutagenesis, because cytosine methylation enhances the reactivity of the adjacent guanine towards BPDE, contributing to *TP53* mutation hotspots in smoking-associated lung cancer [45].

However, it is necessary to be cautious that tobacco-related mutagenesis is not specific to BPDE, which may also reflect other mutagens such as the tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), as well as the aldehydes acrolein, formaldehyde, and acetaldehyde [147,148]. Accordingly, the BPDE findings should be interpreted as evidence for one mechanistic contribution to tobacco-related mutagenesis, rather than a complete explanation of SBS4 or the smoking-associated *TP53* mutation spectrum. Moreover, the mutagenic mechanisms of PAHs are not entirely uniform. Differences in ring number, substituent type, and spatial conformation can influence metabolic activation pathways, DNA adduct formation sites, and replication error patterns, thereby giving rise to distinct mutational spectrum biases [143,149]. For example, nitro-PAHs, although not classified as IARC Group 1, are discussed here as diesel-derived PAH derivatives that can be metabolically activated by nitroreductase and trigger lipid peroxidation via the Fenton reaction to generate reactive aldehyde intermediates. These intermediates form etheno adducts with dA/dG and often induce G:C→T:A transversions [150]. Methyl-substituted PAHs such as 7,12-dimethylbenz[a]anthracene (DMBA) exhibit a preference for adenine, predominantly inducing A:T→T:A transversions with pronounced strand specificity [151].

3.2.3. Aromatic Amines

Aromatic amines primarily originate from chemical manufacturing, tobacco smoke, and high-temperature cooking [152]. Their mutagenic mechanisms are similar to those of PAHs in that they require metabolic activation to form DNA adducts; however, they differ markedly in adduct binding sites, DNA conformational changes, and mutation types. Aromatic amines typically undergo N-hydroxylation catalyzed by CYPs, followed by further activation by N-acetyltransferases (NATs) or sulfotransferases to generate highly electrophilic arylnitrenium ions [153,154]. Unlike PAHs, which predominantly form N^2-dG adducts, the reactive metabolites of aromatic amines preferentially attack the C8 position of guanine, forming C8-aryl-dG adducts [155].

The mutagenic effects of C8-aryl-dG adducts are not uniform; the acetylation status and planarity of the aryl group significantly influence the conformation of the adducts, which in turn affects the type of mutation. The bulky adducts at the C8 position exhibit pronounced conformational heterogeneity and can shift the glycosidic bond preference from the normal anti to the syn conformation [156,157]. This conformational rearrangement stabilizes mismatches and promotes two-base slippage rearrangement at the replication fork, thereby sterically interfering with high-fidelity replicative polymerases and favoring error-prone bypass by TLS polymerases [48,158,159]. Specifically, highly planar aromatic amines such as 2-acetylaminofluorene (AAF) are more likely to induce frameshift mutations, particularly in sequences with a high G content, such as the NarI site (GGCGCC). In contrast, non-planar or weakly planar aromatic amines, such as 4-aminobiphenyl (4-ABP) and 2-naphthylamine (2-NA), have more flexible conformations and are more frequently bypassed by TLS polymerases via base substitution, primarily resulting in G:C→T:A transversions [49,155]. In addition, the sequence context can further alter the results produced by specific adducts. As exemplified by the NarI hotspot (5'-GGCGCC-3'), Koffel-Schwartz and Fuchs demonstrated that the frequency of -2

frameshift mutations induced by the AAF-C8-dG adduct is highly dependent on the 3' flanking bases of the adduct, suggesting that local sequence can determine the outcome of mutation by stabilizing the slipped mutagenic intermediate [160].

In summary, the mutational signatures of aromatic amines depend on the specific compound and sequence context: AAF is predominantly associated with frameshift mutations at the NarI site and repetitive G sequences; 4-ABP mainly exhibits G→T and G→C transversions, with low-frequency frameshifts; 2-NA induces almost exclusively base substitutions. All of these aromatic amines have reproducible mutational signatures in experimental systems, but these signatures have not yet become validated reference signatures in human tumors.

3.2.4. Mycotoxins

Mycotoxins are toxic secondary metabolites produced by filamentous fungi that contaminate food and feed crops under warm and humid storage conditions [161]. Among them, aflatoxins are the most extensively characterized with respect to both carcinogenicity and mutagenic mechanisms. Aflatoxin B_1 (AFB_1), produced mainly by Aspergillus flavus and A. parasiticus, primarily contaminates maize, peanuts, rice, and other staple crops. IARC classifies naturally occurring aflatoxins collectively as Group 1 carcinogens, with AFB_1 being the most potent and serving as a representative environmental and food-borne chemical carcinogen [162]. Other mycotoxins (e.g., ochratoxin A, fumonisin B_1, and citrinin) differ markedly in genotoxic mode and do not share the adduct chemistry or characteristic spectrum of AFB_1; they are therefore not treated as equivalent representatives of this class.

Like PAHs and aromatic amines, AFB_1 cannot react directly with DNA and requires metabolic activation by cytochrome P450 enzymes, primarily CYP3A4 and CYP1A2, to the highly electrophilic AFB_1-exo-8,9-epoxide (AFBO) [163]. The exo-AFBO isomer is the major mutagenic form and covalently binds the N7 position of guanine to form the AFB_1-N7-dG adduct, which can undergo ring-opening rearrangement to the more stable AFB1-Fapy-dG adduct [164]. AFB_1 adducts are removed mainly through nucleotide excision repair and base excision repair. If the adduct is not removed before replication, translesion synthesis polymerases tend to insert adenine opposite the lesion, fixing the damage as a G:C→T:A transversion [165,166]. The most iconic manifestation of the AFB_1 mutational signature is the hotspot mutation at *TP53* codon 249, which substitutes arginine with serine; this mutation accounts for approximately 50% of hepatocellular carcinomas (HCCs) in AFB_1-high-exposure regions [167]. At the genome-wide level, experimental AFB_1 signatures from human cell lines and mouse liver tumors are remarkably similar across systems; AFB_1-associated HCC mutational spectra are dominated by G→T transversions, enriched in GpG/CpG and GGC sequence contexts, and closely match COSMIC SBS24 [168,169]. SBS24 has been experimentally confirmed and is annotated with "aflatoxin exposure" as its proposed aetiology [170]. It should be emphasized that AFB_1 is primarily a base-substitution mutagen; frameshifts and small Indels are not its dominant features. Nevertheless, frameshifts, small deletions, and chromosomal deletions/rearrangements have been observed as accompanying events in some experimental systems, indicating that low-proportion Indels or SVs signals

can arise under high-dose or repair-deficient conditions [171].

4. Summary and Prospects

This review systematically outlines the molecular mechanisms by which typical environmental chemical carcinogens induce somatic mutations and constructs an integrative theoretical framework spanning from basic classification to cascade networks and characteristic mutational signatures. Studies have demonstrated that gene mutations, as the core molecular events in chemical carcinogenesis, are no longer classified solely by sequence alterations; their classification has evolved into a multi-level description integrating DNA structure, protein function, and biological consequences. For many carcinogens requiring metabolic activation, a common mechanistic sequence involves activation, DNA damage, lesion repair or persistence, mutation fixation during replication, and, in some cases, subsequent genomic instability. However, this framework does not imply that each chemical class produces a single characteristic mutation type. The resulting spectrum varies with the individual compound, its metabolic products, the identity and genomic context of DNA lesions, and the repair and translesion synthesis pathways engaged. For example, some PAHs, including BaP-derived BPDE, form guanine adducts that can promote G:C→T:A transversions, whereas other PAHs may yield different substitution patterns, including mutations at A:T base pairs. Likewise, certain aromatic amine adducts, such as C8-guanine adducts derived from 2-acetylaminofluorene, can induce frameshifts in susceptible sequence contexts, but aromatic amines can also induce base substitutions. Heavy metals may contribute to mutagenesis through mechanisms including oxidative damage, interference with DNA repair, and chromosomal instability; their effects are not limited to structural variants. Thus, the mutation types discussed here should be interpreted as compound- and context-dependent outcomes, rather than fixed properties of broad chemical categories.

An in-depth analysis of the aforementioned mechanisms not only helps reveal the molecular basis of tumorigenesis but also provides a key entry point for exposure risk assessment and precision prevention and control [172]. The precise identification of characteristic mutation fingerprints and the elucidation of key early-stage nodes can be translated into biomarkers for exposure source and early screening, while also providing a solid theoretical basis for targeted interventions in high-risk populations [37,41,173]. With the continuous iteration of detection technologies, research approaches have evolved from early karyotyping, which could only detect large-fragment aberrations, to the current era of next-generation sequencing (NGS). Short-read NGS has become a standard tool for deciphering chemical-specific mutational signatures and identifying COSMIC mutational signatures [37,174]; long-read NGS, with its amplification-free advantage, offers unique benefits in resolving structural variants induced by heavy metals [175,176]; and emerging technologies such as digital PCR (dPCR), CRISPR-Cas-mediated detection, and circulating tumor DNA (ctDNA) liquid biopsy collectively advance the absolute quantification and non-invasive dynamic monitoring of low-frequency mutations [177–183]. This deep integration of technological innovation and mechanistic research serves as the core driving force for overcoming current knowledge bottlenecks.

However, current research still faces several bottlenecks that urgently require resolution. At the exposure level, human populations are often simultaneously exposed to multiple chemical carcinogens in real-world environments. The interactive mutational effects under combined exposure and the relationship between dose and mutation response have yet to be systematically investigated, and the kinetics of mutation accumulation under long term exposure at low doses remain unclear [184–186]. At the model translation level, species and microenvironmental biases exist between the mutational spectra of commonly used cell lines and animal models and the mutational signatures of real human tissues. Establishing more reliable humanised models represents a core challenge in this field [173]. At the technical level, sequencing platforms and data analysis pipelines vary across laboratories and are not yet standardized. The lack of a standardized database of chemical-induced mutational signatures hinders cross-comparison and integration of results [187,188]. At present, validated agent-specific COSMIC signatures exist for only a minority of environmental chemical carcinogens, which further limits the attribution of observed mutation patterns to specific agents. At the mechanistic level, the temporal dynamics of mutation accumulation mediated by epigenetic regulation remain poorly understood. In particular, how early events such as changes in DNA methylation and histone modifications following chemical exposure coupled with mutation fixation still need to be elucidated through time-series multi-omics studies [187,189].

Furthermore, given the large number of chemicals and the severe resource constraints associated with case by case assessment, grouping environmental carcinogens has become an important direction for improving regulatory efficiency. Classifying environmental carcinogens according to exposure related mutational signatures may provide a reference for regulatory science. In the European Union, the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation and the European Chemicals Agency (ECHA) Read-Across Assessment Framework (RAAF) use structural similarity as a prerequisite for grouping and require mechanistic explanation to support the read across hypothesis, thereby filling data gaps between substances. The revised Classification, Labelling and Packaging (CLP) Regulation (EU 2024/2865) further clarifies and strengthens weight of evidence reasoning in classification decisions, specifying that when data are insufficient for direct classification, grouping and read across can form part of the weight of evidence. In this context, over the medium to long term, mutational signatures may serve as a supplementary reference for grouping carcinogens with convergent mechanistic features. However, this approach requires caution, because most substances currently lack validated human mutational profiles specific to individual carcinogens, and heterogeneity also exists within the same substance class. Experimentally induced mutational signatures are also not clearly identifiable for all carcinogens; in controlled systems, only 41 of 79 known or suspected environmental carcinogens produced characteristic substitution signatures [44]. Therefore, classification based on mutational signatures must be comprehensively judged together with structural, metabolic, and toxicological evidence, rather than replacing traditional hazard assessment. Establishing a standardized and experimentally validated database of chemical induced mutational signatures will be an important step in translating this concept into a regulatory decision support tool.

Future research can be advanced in three directions. First, conducting exposomics and large-scale prospective population cohort studies, combined with high-resolution exposure monitoring, *in vivo* biomarkers, and gene mutation detection, establishes a traceable evidence chain linking chemical exposure, mutational signatures, and disease outcomes, thereby providing robust population-based evidence for environmental health risk assessment and precision prevention [190–192]. Second, integrating genomic, epigenomic, transcriptomic, single-cell, and spatial omics data to dissect the formation and evolution of mutant clones within cellular heterogeneity and tissue microenvironments and to elucidate the molecular mechanisms by which typical environmental chemical carcinogens induce gene mutations and drive tumor initiation and progression, providing a theoretical basis for the discovery of early biomarkers and potential intervention targets [193–196]. Third, leveraging artificial intelligence and machine learning technologies and integrating toxicological, multi-omics, and exposomics data to construct predictive models for the mutagenic potential and health risk evaluation of typical environmental chemical carcinogens, thereby providing technical support and enhancing capabilities for risk assessment of emerging contaminants and combined exposures [197–201]. Through the above research, exposure-associated mutational signatures are expected to evolve from mechanistic explanatory tools into auxiliary molecular evidence for environmental exposure source tracing, early warning, and precision prevention and control.

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