



Review

Toxicoepigenomics: Epigenetic disruption by environmental exposures and implications for biomarker development

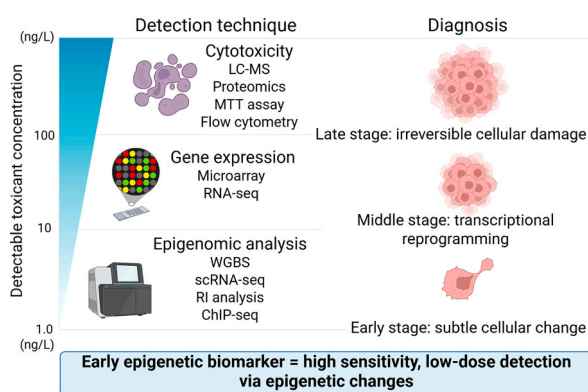
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HIGHLIGHTS

- Environmental toxicants induce multi-layered epigenetic alterations.
- DNA methylation, histone marks, and ncRNAs are affected by real-world exposures.
- Retained introns emerge as novel epigenetic signatures of toxicant response.
- Epigenetic dysregulation links exposures to long-term health risks.
- Epigenomic markers show promise for hazard assessment and biomonitoring.

GRAPHICAL ABSTRACT



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ABSTRACT

Environmental exposures are increasingly recognized as key modulators of the epigenome, contributing to both immediate and long-term disease risk. The field of toxicoepigenomics, which investigates how environmental toxicants alter epigenetic regulation, has demonstrated that exposures to endocrine-disrupting chemicals, heavy metals, polycyclic aromatic hydrocarbons (PAHs), and air pollutants can disrupt gene expression through changes in DNA methylation, histone modifications, non-coding RNA expression, and higher-order chromatin structure. Additionally, lifestyle factors—including diet, physical activity, stress, and sleep—interact with these exposures to shape individual epigenetic profiles and influence health trajectories across the lifespan. This review synthesizes current evidence across major pollutant classes and molecular pathways, emphasizing both well-characterized and emerging mechanisms. Retained introns represent post-transcriptional consequences of chromatin-based epigenetic regulation and serve as sensitive indicators of environmentally induced disruptions in transcriptional elongation and splicing fidelity. We also highlight recent advances in high-throughput

Abbreviations: PAHs, Polycyclic Aromatic Hydrocarbons; BaP, Benzo[a]pyrene; ROS, Reactive Oxygen Species; DNMT, DNA Methyltransferase; HAT, Histone Acetyltransferase; HDAC, Histone Deacetylase; miRNA, MicroRNA; lncRNA, Long Non-Coding RNA; NMD, Nonsense-Mediated Decay; RI, Retained Intron; PM2.5, Particulate Matter ≤ 2.5 micrometers; NO₂, Nitrogen Dioxide; SO₂, Sulfur Dioxide; O₃, Ozone; BPA, Bisphenol A; WGBS, Whole-Genome Bisulfite Sequencing; ChIP-seq, Chromatin Immunoprecipitation Sequencing; ATAC-seq, Assay for Transposase-Accessible Chromatin Using Sequencing; CUT&RUN, Cleavage Under Targets and Release Using Nuclease; EWAS, Epigenome-Wide Association Study; WHO, World Health Organization; NTP, National Toxicology Program.

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technologies, including whole-genome bisulfite sequencing, single-cell epigenomics, and epigenetic clock models, which are rapidly enhancing biomarker discovery and mechanistic understanding. By integrating multilayered epigenetic insights across diverse exposure contexts, this review advances the field of toxicoepigenomics and lays the groundwork for developing robust, exposure-responsive biomarkers of environmental disease. These insights offer significant promise for guiding mechanistic research, improving exposure surveillance, and informing the design of precision strategies in environmental health.

1. Introduction

Environmental exposures are major determinants of human health, contributing to an estimated 13.7 million deaths annually—approximately 24 % of the global disease burden according to the World Health Organization (WHO) [1]. Air pollution alone is responsible for over 7 million premature deaths each year, while exposure to toxic chemicals has been implicated in rising rates of cancer, metabolic syndrome, reproductive disorders, and neurodevelopmental delays [2]. These statistics highlight the urgent need to understand the biological mechanisms through which environmental insults exert long-lasting and sometimes heritable effects on human health.

Epigenetics—the study of heritable gene expression changes that occur without altering the underlying DNA sequence—has emerged as a vital framework for understanding how environmental exposures modulate biological systems and influence disease susceptibility [3]. Unlike genetic mutations, epigenetic alterations such as DNA methylation, histone modifications, and non-coding RNA expression are reversible and environmentally responsive, making them promising candidates for mechanistic toxicology, early detection, and prevention (Fig. 2) [4].

A growing body of research has demonstrated that various classes of environmental toxicants—including endocrine-disrupting chemicals (EDCs), heavy metals (e.g., arsenic, cadmium, lead), air pollutants (e.g., PM_{2.5}, ozone), and polycyclic aromatic hydrocarbons (PAHs)—can induce widespread epigenetic changes. These include promoter hypermethylation of tumor suppressor genes, global hypomethylation contributing to genomic instability, dysregulated microRNA profiles,

and altered histone acetylation states [5–8]. Importantly, several of these epigenetic alterations have been shown to persist across generations, even in the absence of continued exposure, through transgenerational epigenetic inheritance mechanisms [9,10].

To provide a structured foundation for the remainder of this review, we distinguish environmentally induced epigenetic changes along three complementary axes, exposure, effect, and susceptibility, and position them within the Adverse Outcome Pathway (AOP) framework [5,6,11]. Exposure markers capture how toxicants leave measurable epigenetic imprints such as locus-specific DNA methylation or ncRNA signatures that integrate dose, timing, and mixture history in accessible tissues. Effect markers correspond to epigenetic perturbations that function as early key events in AOPs, including chromatin remodeling, histone-mark redistribution, and induction of regulatory ncRNAs that reprogram transcription, splicing, and cell signaling. Susceptibility markers represent pre-existing or developmentally established epigenetic states, shaped by genetics, early-life environments, or lifestyle, that modify individual reactivity to subsequent exposures. Within the AOP continuum, these domains are temporally interconnected: susceptibility markers condition biological responses, exposure-linked epigenetic alterations initiate pathway perturbation, and effect markers propagate molecular cascades toward organ-level toxicity and disease. Fig. 1 summarizes this conceptual framework, mapping DNA methylation, histone modifications, and non-coding RNAs onto the exposure–outcome sequence and illustrating where epigenetic readouts can be leveraged for exposure assessment, early-effect detection, and risk stratification.

The field of *toxicoepigenomics* seeks to elucidate how environmental

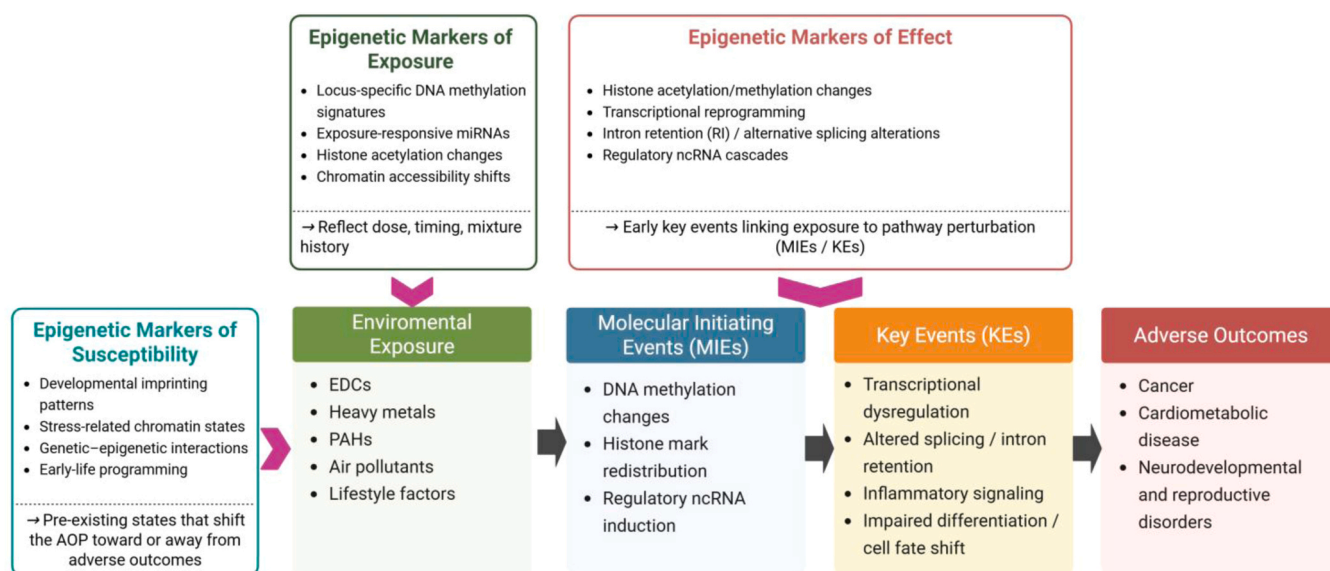


Fig. 1. Conceptual framework linking epigenetic markers of susceptibility, exposure, and effect to the Adverse Outcome Pathway (AOP). Epigenetic susceptibility markers (left) represent pre-existing or developmentally programmed states that modulate an individual's vulnerability to environmental perturbation. Environmental exposures induce epigenetic exposure markers, including locus-specific DNA methylation changes, miRNA shifts, histone acetylation, and chromatin accessibility alterations. These early perturbations function as MIEs, which propagate downstream to key events, such as transcriptional dysregulation, inflammatory signaling, and intron retention, ultimately leading to adverse health outcomes. Epigenetic markers of effect capture these early pathway perturbations and help bridge external exposures with phenotypic outcomes. This framework integrates epigenetic mechanisms across the exposure–disease continuum and contextualizes them within AOP-based toxicoepigenomics. Created with BioRender.com.

exposures reshape the epigenome and mediate adverse health outcomes. However, despite significant advances, regulatory toxicology has yet to fully incorporate epigenetic endpoints into chemical risk assessment frameworks, which continue to rely heavily on mutagenicity and acute toxicity. This gap may lead to underestimation of the long-term and multigenerational health risks posed by environmental contaminants.

In this review, we provide a comprehensive synthesis of current findings on epigenetic mechanisms disrupted by key environmental toxicants. We highlight DNA methylation, histone modification, and non-coding RNA regulation as principal epigenetic pathways influenced by exposures to EDCs, heavy metals, PAHs, and air pollution. We also discuss emerging biomarkers and high-throughput technologies—including epigenetic clocks, whole-genome bisulfite sequencing (WGBS), and single-cell multi-omics—that may enhance exposure monitoring, disease prediction, and regulatory decision-making.

2. Molecular epigenetic mechanisms

2.1. DNA methylation

The core molecular mechanisms of epigenetic regulation encompass DNA methylation, histone modifications, RNA-mediated regulation, and three-dimensional (3D) genome organization. These mechanisms respond dynamically to environmental stimuli and act as critical mediators of toxicoepigenomic effects. DNA methylation is one of the most extensively studied epigenetic modifications and represents a central mechanism by which environmental exposures can influence gene expression [12]. It involves the covalent addition of a methyl group to the 5-carbon position of cytosine residues, predominantly within CpG dinucleotides, and is catalyzed by DNA methyltransferases (DNMTs) [13]. Among these enzymes, DNMT1 maintains existing methylation patterns during cell division, whereas DNMT3A and DNMT3B are responsible for *de novo* methylation during development and in response to environmental stimuli [13,14]. Methylation of gene promoter regions typically leads to transcriptional repression by preventing transcription factor binding or by recruiting repressive chromatin-remodeling complexes. Aberrant DNA methylation patterns—such as global hypomethylation, which contributes to genomic instability, or site-specific hypermethylation of tumor suppressor genes—have been implicated in various diseases, including cancer.

In addition to canonical CpG methylation, non-CpG methylation and N6-methyladenine (m6A) have emerged as important alternative methylation marks. While m6A was once thought to be restricted to prokaryotes, recent high-throughput mapping has confirmed its presence in mammalian embryonic stem cells and suggested its involvement in transcriptional regulation, stress responses, and transposable element silencing [15–17].

DNA demethylation can occur passively through DNA replication or actively through the Ten-Eleven Translocation (TET) enzyme family. TET proteins catalyze the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and subsequent intermediates, contributing to dynamic epigenomic remodeling in response to environmental stimuli [18]. Together, these processes illustrate the intricate balance of DNA methylation and demethylation and underscore their importance in maintaining genomic integrity under environmental stress.

2.2. Histone modifications

Histone proteins, which package DNA into chromatin, are subject to various post-translational modifications (PTMs) that influence chromatin architecture and gene expression [19]. These PTMs include acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, and citrullination, primarily occurring on the amino-terminal tails of histones and are dynamically modulated by cellular signals [20].

Histone acetylation is generally associated with transcriptional activation and is catalyzed by histone acetyltransferases (HATs), while histone deacetylases (HDACs) remove acetyl groups to induce chromatin condensation. Histone methylation, in contrast, can either activate or repress transcription depending on the specific residue and context. For example, H3K4me3 marks active promoters, while H3K27me3 and H3K9me3 are repressive.

Environmental toxicants can perturb the expression or activity of histone-modifying enzymes, leading to altered histone modification landscapes. For example, cadmium and BPA have been reported to increase H3K4me3 and reduce H3K9me2, disrupting normal developmental gene expression patterns [21,22]. These chemically induced histone modifications often result in dysregulated transcriptional profiles and may contribute to epigenetic memory if retained during cell division. Importantly, histone modifications interact with other epigenetic layers. Methylated histones can recruit DNA methyltransferase and chromatin remodeling complexes, while histone acetylation may facilitate binding of bromodomain-containing proteins that enhance transcriptional activation. These interactions highlight the intricate crosstalk between histone marks and other epigenetic regulators, underscoring their integrated role in responding to environmental exposures. Altogether, histone modifications serve as a central hub of epigenetic regulation, dynamically integrating external signals into chromatin states that shape transcriptional outcomes and toxicological responses.

2.3. DNA adducts and epigenetic perturbation

DNA adducts are covalent chemical modifications of DNA that result from the interaction between reactive electrophilic species and nucleophilic sites on DNA bases [23]. These lesions are typically formed following exposure to environmental genotoxins such as PAHs (e.g., benzo[a]pyrene), aflatoxins, and certain heavy metals [24–26]. Although DNA adducts are classically associated with mutagenesis and carcinogenesis through replication errors, emerging evidence suggests that they may also exert long-term transcriptional effects by perturbing the epigenetic landscape.

Although not reversible like canonical epigenetic marks, DNA adducts can impair the accessibility and activity of chromatin-regulatory proteins (see Sections 2.1 and 2.2), thereby indirectly reshaping the epigenomic landscape. For instance, bulky adducts formed by benzo[a]pyrene diol epoxide (BPDE) have been shown to interfere with CpG methylation pattern and chromatin accessibility [27]. In addition, DNA damage response pathways triggered by persistent adducts often lead to the deposition of repressive histone marks, such as H3K9me3 and H2A ubiquitination, around lesion sites, creating a localized transcriptionally silenced chromatin environment [28,29]. Genotoxic DNA adducts can also disrupt the function of chromatin-regulatory proteins by altering histone post-translational modifications and impeding the recruitment of chromatin remodelers and DNA repair factors. For example, specific histone acetylation and methylation marks are required for the proper localization of nucleotide excision repair (NER) complexes at sites of bulky adducts, and disruption of these epigenetic marks can delay chromatin relaxation and impair repair efficiency [30,31]. Repair of DNA adducts through nucleotide excision repair or base excision repair pathways may further contribute to epigenetic memory by altering chromatin states during repair synthesis [32]. In some cases, chromatin remodeling factors recruited to damage foci are not fully removed, resulting in stable changes to histone post-translational modifications and nucleosome positioning. Thus, although DNA adducts are not epigenetic modifications *per se*, their ability to induce long-lasting changes in chromatin architecture and gene expression places them within the broader spectrum of toxicoepigenomic regulators. Taken together, DNA adducts represent a unique class of environmentally induced DNA lesions that can mimic or interact with epigenetic pathways, leading to persistent transcriptional dysregulation. Their dual role

as both genotoxic and epigenetic-like disruptors underscores their importance in understanding the long-term biological impact of environmental exposures.

2.4. Three-dimensional (3D) genome organization

The spatial configuration of chromatin within the nucleus adds an additional layer of epigenetic regulation by influencing DNA accessibility and enhancer-promoter communication [33]. Chromatin is hierarchically organized into nucleosome arrays, chromatin loops, topologically associating domains (TAD), and higher-order compartments (A/B compartments), which together establish a dynamic yet functionally constrained nuclear architecture [34]. These 3D structures enable cell type-specific gene expression programs and are tightly regulated during development and differentiation.

Environmental insults have the potential to disrupt this higher-order chromatin organization, resulting in aberrant transcriptional profiles. For instance, exposure to EDCs, heavy metals, or ionizing radiation can alter the expression or binding affinity of architectural proteins such as CTCF, cohesion, and lamins which play essential roles in maintaining TAD boundaries and chromatin loop stability [35,36]. Perturbation in these structures can lead to aberrant enhancer-promoter interactions, enhancer hijacking, or insulator loss, resulting in the misregulation of genes involved in cell proliferation, differentiation, and stress responses. Furthermore, environmental toxicants may induce oxidative DNA damage and DNA double-strand breaks (DSBs), which are repaired in a chromatin context and can lead to local or global 3D rearrangements. These changes have been implicated in developmental abnormalities, immune dysfunction, and carcinogenesis [37]. Chromatin information capture technologies such as Hi-C and ChIA-PET have revealed that environmental exposures can induce reproducible alterations in 3D genome topology, including domain boundary weakening and compartment switching.

Collectively, 3D genome organization represents a crucial yet underexplored axis of epigenetic regulation in environmental health. Its susceptibility to chemical perturbation and its ability to mediate long-range gene regulatory effects position it as a promising target for future toxicoepigenomic investigations.

2.5. RNA-based epigenetic regulation

Non-coding RNAs (ncRNAs) have emerged as central players in epigenetic regulation, modulating gene expression at the transcriptional and post-transcriptional levels. These include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), PIWI-interacting RNAs (piRNAs), and small nucleolar RNAs (snoRNAs), each of which exerts distinct yet overlapping regulatory effects on the epigenome [38]. miRNAs typically bind to the 3' untranslated regions of target mRNAs, leading to mRNA degradation or translational repression, whereas lncRNAs can act as scaffolds, guides, decoys, or enhancers in the regulation of chromatin states and transcriptional activity [39]. Importantly, ncRNAs also modulate the expression of epigenetic regulators such as DNMTs and HDACs, forming intricate feedback loops within the epigenetic regulatory network. Some lncRNAs, such as HOTAIR and XIST, are well-known for recruiting polycomb repressive complexes (PRCs) to specific genomic loci, leading to histone methylation and transcriptional silencing.

Environmental toxicants can dysregulate the biogenesis and expression of ncRNAs, thereby altering downstream gene expression networks. For instance, exposure to air pollutants and endocrine disruptors has been associated with aberrant expression of miRNAs, which in turn affect inflammatory pathways, cell cycle regulation, and apoptosis [40]. Taken together, RNA-based epigenetic regulators represent a versatile and environmentally responsive layer of the epigenome. Their dynamic expression patterns and regulatory breadth make them key mediators of toxicoepigenomic effects, as well as

promising targets for diagnostic and therapeutic innovation.

2.6. Epigenetic crosstalk as a molecular initiating event: A coordinated framework for environmental toxicity

Although DNA methylation, histone modifications, and non-coding RNAs are often treated as discrete layers, mounting evidence shows that environmental toxicants elicit tightly coordinated responses across these regulatory domains. For example, histone acetylation, driven chromatin opening can gate locus-specific methylation or demethylation, while ncRNAs modulate the abundance or activity of DNMTs, HDACs, and histone methyltransferases, creating feedback circuits that stabilize environmentally induced transcriptional states [19,41].

Within the AOP framework, these early epigenetic perturbations can function as molecular initiating events (MIEs), the first measurable shifts that trigger downstream biological cascades. For several pollutant classes, promoter/enhancer CpG reprogramming, histone-mark redistribution (e.g., H3 acetylation loss), and rapid induction of regulatory miRNAs are detectable at low doses and early time points, preceding overt cytotoxicity [42,43]. From this initiating position, they propagate key events—including transcriptional dysregulation, inflammatory signaling, impaired differentiation, and alternative splicing—that ultimately contribute to adverse phenotypes [44]. Framing these chromatin-mediated shifts as MIEs clarifies their functional position within toxicity pathways and enhances their value for biomarker discovery by highlighting (i) exceptional sensitivity to subtle exposures, (ii) temporal primacy relative to cellular injury, and (iii) utility across exposure, effect, and susceptibility assessment.

2.7. Cross-class regularities and substance-specific resolution

Many environmental toxicants, including heavy metals, PAHs, EDCs, and air pollutants, consistently elicit similar epigenetic responses, such as global DNA hypomethylation, enhancer deacetylation, and stress-related ncRNA activation. These recurring patterns likely reflect conserved molecular programs for managing oxidative stress, inflammation, and metabolic burden [4,39]. In contrast, substance-specific epigenetic effects are much harder to define, largely due to the limited resolution of traditional bulk-level assays. Emerging sequencing technologies now offer the potential to uncover such specificity by examining transcript-level regulatory changes. Intron retention (RI), exon skipping, and alternative splice-site usage respond rapidly to changes in chromatin context, elongation speed, and epigenetic remodeling, and can capture subtle, compound-specific transcriptional shifts. Integrating splicing-aware RNA-seq, long-read transcriptomics, and chromatin accessibility mapping with dose- and time-resolved experimental designs will allow the field to move beyond generalized epigenetic patterns toward defining distinctive regulatory fingerprints for specific toxicants.

3. Environmental toxicants and epigenetic modifications

Environmental exposures can lead to long-lasting epigenetic alterations that affect gene expression and contribute to disease pathogenesis. Although the molecular links between toxicants and specific epigenetic changes are still under active investigation, growing evidence suggests that epigenetic mechanisms form a dynamic regulatory interface integrating genetic and environmental signals. Because of their reversible and context-dependent nature, understanding how epigenetic pathways respond to environmental insults is central to the field of toxicoepigenomics and may inform disease mechanisms and therapeutic strategies.

3.1. Endocrine-disrupting chemicals (EDCs)

Endocrine-disrupting chemicals (EDCs) are exogenous agents that perturb hormonal systems by affecting hormone biosynthesis,

metabolism, transport, receptor expression, and signal transduction [45]. In addition to modulating hormonal pathways, EDCs exert epigenetic effects, including global and locus-specific changes in DNA methylation and histone modifications, which can persistently alter gene expression and cellular function (Table 1) [84,85].

3.1.1. Bisphenol

Bisphenol compounds—including bisphenol A (BPA) and its analogs bisphenol S (BPS) and bisphenol F (BPF)—are ubiquitous in plastics, food containers, and thermal receipts. These compounds were initially introduced with the assumption of improved safety, yet recent findings indicate that all three exert significant epigenetic toxicity.

BPA is the most extensively studied and has been shown to induce widespread epigenetic changes that contribute to developmental abnormalities, metabolic disorders, and reproductive dysfunction [86–89].

Prenatal and perinatal BPA exposure disrupts DNA methylation patterns in genes regulating neurodevelopment, metabolism, and reproduction. A classic example is BPA-induced hypomethylation of the *Agouti* gene in mice, which results in altered coat color and obesity phenotypes [46]. Similarly, genome-wide methylation profiling in human and rodent studies has revealed differential methylation in genes involved in estrogen signaling pathways (*ESR1*), DNA repair (*BRCA1*), and immune function (*IL-6*) [47,48,90].

In addition to DNA methylation, BPA exposure alters histone modification patterns. It has been shown to reduce levels of H3K9 acetylation and H3K27 trimethylation by interfering with histone-modifying enzymes such as HATs and HMTs [91]. These modifications alter chromatin accessibility and gene expression profiles critical for cellular homeostasis. Moreover, BPA exposure disrupts non-coding RNA expression, with studies reporting miR-146a upregulation (linked to

Table 1
Summary of epigenetic effects by EDC.

EDC	DNA Methylation	Histone Modifications	ncRNA Alterations	Health Implications	Environmentally Relevant Concentration (ERC)	Environmental Matrix	Ref
Bisphenols (BPA, BPF, BPS)	- <i>Agouti</i> viable yellow locus hypomethylation - <i>BRCA1</i> promoter hypermethylation - Global hypomethylation in hypothalamus	- ↓ H3K27me3, ↓ H3K9ac in hippocampus & cortex - ↑ EZH2 expression in mammary tissues	- ↑ miR-146a (neural), - ↓ miR-29 (metabolic regulation)	Developmental abnormalities, metabolic disorders, reproductive dysfunction; transgenerational effects	1-1000 ng/L	Surface water, sediment, soil	[46–49]
Diethylstilbestrol (DES)	- Hypomethylation at <i>Svs4</i> enhancer in seminal vesicles, -Hypermethylation of estrogen-responsive genes (<i>lactoferrin</i> , <i>calsequestrin 2</i>)	↑H3K27me3 (tumor suppressors), Aberrant acetylation (WNT7A)	- ↑ miR-21 (oncogenic), - ↓ miR-200 family (EMT regulation)	Reproductive tract anomalies, carcinogenesis, cardiac abnormalities; heritable epigenetic marks	~0.5-5 ng/L	Surface water, sediment	[50–58]
Phthalates (DEHP, DBP)	- ↑ Methylation at <i>Igf2</i> , <i>H19</i> - Imprinting errors in early embryonic tissues	-↓H3K4me3 in fetal oocytes - SMYD downregulation in ovarian cell	- ↓ miR-155-5p (immune), lncRNA misregulation in testis	Reproductive toxicity, metabolic dysfunction, reduced fertility; transgenerational effects	0.1-10 µg/L	Indoor dust, wastewater	[59–62]
Parabens (MPB, nBuP)	- Hypermethylation of <i>POMC</i> promoter - Global DNA hypomethylation (e.g., <i>CCND2</i>)	Not well characterized; potential HDAC involvement suggested	Not well defined; epigenetic silencing inferred	Obesity, insulin resistance, increased breast cancer risk; early-life exposure concern	10-500 ng/L	River water, wastewater, sediment	[63,64]
PCBs	- Hypomethylation at <i>CYP1A1</i> enhancer - <i>LINE-1</i> hypomethylation in blood	↓ H4K16ac, ↓ H3K4me2 in neuronal tissue	- ↑ miR-1537, disruption in miRNAs linked to neural development	Immunosuppression, Neurodevelopmental impairments, Reproductive dysfunction	5-50 ng/L	Soil, air, surface water	[65–67]
Vinclozolin	- Sperm promoter hypermethylation (<i>Stk31</i> , <i>Foxa3</i>) - Persistent methylation changes across generations	Transgenerational ↑ H3K27me3 in sperm - ↓ H3K9ac in reproductive tract	Dysregulation of germline-specific miRNAs (e.g., <i>miR-23b</i> , <i>miR-21</i>)	Reproductive abnormalities (e.g., decreased sperm count, testicular atrophy), Hormonal imbalance	10-100 ng/L	Agricultural runoff, surface water, soil	[68–70]
Nonylphenol	Not well characterized;	- Not well defined; epigenetic silencing inferred in Sertoli cells - ↓ H3K27ac, ↓ p300 activity; chromatin condensation in zebrafish	- Altered miR-21 (proliferation), miR-135a (ROS)	Sertoli cell damage, inflammation, testicular atrophy, hormone imbalance	Unknown	Wastewater, sediment, soil	[71,72]
Tetrabromobisphenol A (TBBPA)	Not well characterized;	- ↓ H3K27ac, ↓ p300 activity; chromatin condensation in zebrafish	Not well characterized	Cognitive dysfunction, impaired neurogenesis, Cancer cell metastasis	5-500 ng/L	Sludge, wastewater	[73]
Atrazine	- ↓ Activity of DNMT1-Epimutations in sperm DNA	- ↑ H3K9me3 in human kidney cells lines	- ↑ AMPK levels concurrent with a ↓ <i>miR-322-5p</i>	Transgenerational reproductive toxicity, endocrine disruption	1-10 µg/L	Ground water	[74–77]
Dioxins (TCDD)	- Disrupts Dynamic DNA Methylation in cardiomyocyte- Persistent DNA methylation at AhR target genes	- ↑ H3K4me3, ↓ H3K9me3, H3K27me3 in thymocytes	- Altered <i>miR-26a-5p</i> , <i>miR-193a-3p</i> , <i>miR-30c-5p</i> expression	Immune dysfunction, developmental defects, carcinogenesis	1-10 ng/kg	Air, food, placenta	[78–81]
Triclosan	- ↑ 5-hydroxymethylcytosine- ↓ DNMT3A, DNMT3B	- ↓ phospho-Histone H3 and activate Bmp4 signaling	Not well characterized	Hormone disruption, breast cancer risk, liver toxicity	50-300 ng/ml	Wastewater, sediment, sludge	[82,83]

inflammation and cancer) and miR-29 downregulation (associated with extracellular matrix remodeling) in various tissues [92,93].

Recent research has raised concerns about BPA analogs, particularly BPS and BPF. BPS exposure has been associated with altered DNA methylation in imprinted genes and reduced expression of chromatin-modifying enzymes, including DNMTs and HDACs [94,95]. Similarly, BPF has been linked to disrupted histone acetylation and methylation *in vitro* and *in vivo* [22]. These findings suggest that BPS and BPF may share mechanistic toxicity with BPA and should not be assumed safe alternatives without rigorous toxicological evaluation.

Epigenetic alterations induced by bisphenols are not limited to directly exposed individuals. Several animal studies have shown that these changes can persist across generations when exposure occurs during early developmental windows, highlighting the potential for transgenerational inheritance of epigenetic dysregulation [96,97]. These findings emphasize the importance of understanding bisphenol-induced epigenetic mechanisms and support the need for stronger regulatory oversight in consumer product safety and chemical risk assessment.

3.1.2. Diethylstilbestrol (DES)

Diethylstilbestrol (DES) is a synthetic estrogen that was widely prescribed between the 1940s and 1970s. It is now well established that prenatal DES exposure leads to persistent epigenetic alterations, contributing to disease susceptibility and transgenerational health effects.

Prenatal exposure to DES results in abnormal DNA methylation of regulatory genes. For example, neonatal DES exposure in mice leads to hypomethylation of the *Svs4* promoter, an androgen-responsive gene in seminal vesicles, causing reduced gene expression and impaired androgen signaling [50,51]. Conversely, DES induces hypermethylation of the *lactoferrin* promoter—normally active only in female reproductive tissues—in male tissues, a phenomenon termed "molecular feminization." These changes are mediated via estrogen receptor alpha (ER α), as they are absent in ER α -knockout models [52]. DNA methylation alterations induced by DES are tissue-specific and have been linked to a variety of disease processes. For instance, perinatal DES exposure has been associated with hypermethylation of genes in the uterus, contributing to the development of vaginal clear cell adenocarcinoma and dysregulation of DNMT expression [53]. Furthermore, gestational DES exposure affects cardiac development by increasing *Dnmt3a* expression and hypermethylating the *calsequestrin 2* promoter, resulting in structural abnormalities in the heart [98].

DES also influences histone modifications. Elevated levels of H3K27me₃, a repressive histone mark, have been observed at tumor suppressor gene promoters following DES exposure. This histone-based repression is linked to increased cancer risk [54]. Additionally, abnormal histone acetylation patterns affecting genes such as *WNT7A*, which is critical for reproductive tract development, have been implicated in DES-induced carcinogenesis [55,56].

Emerging evidence suggests that DES exposure can modulate the expression of specific miRNAs, which play a crucial role in post-transcriptional gene regulation. Dysregulated miRNA expression profiles have been linked to developmental anomalies and increased susceptibility to various diseases, including cancer [57,99]. Certain miRNAs, such as miR-21, which is known to promote FasL and Fas expression, have been found to be significantly upregulated in DES-exposed individuals, further highlighting the compound's long-term epigenetic impact [57]. In contrast, downregulation of *miR-200* family members—key repressors of epithelial-mesenchymal transition (EMT)—has been associated with a higher risk of metastatic progression in hormone-related cancers [58].

Importantly, DES-induced epigenetic changes are not confined to directly exposed individuals. Several studies have shown that prenatal DES exposure results in heritable modifications of germline epigenetic marks, leading to increased risks of reproductive abnormalities and

malignancies in subsequent generations [100,101]. These findings highlight the far-reaching and multigenerational consequences of DES-induced epigenetic dysregulation and underscore the critical need for long-term mechanistic and epidemiological research.

3.1.3. Phthalates

Phthalates are a group of synthetic chemicals commonly used as plasticizers in a wide array of consumer products, including food packaging, medical devices, toys, and personal care products. Among them, di(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP) are the most studied and are known for their endocrine-disrupting potential. Emerging evidence also implicates these compounds in the epigenetic regulation of genes essential for development, metabolism, and reproduction.

Maternal exposure to phthalates can induce persistent DNA methylation changes, particularly in placental and embryonic tissues. In rodent models, in utero exposure to DEHP leads to hypermethylation of imprinted genes such as *H19* and *Igf2*, which are critical for fetal growth and development. These alterations often persist into adulthood, suggesting stable epigenetic reprogramming [59,60,102,103]. Additionally, DEHP has been shown to disrupt the expression of *Tet1* and *Tet2*, enzymes responsible for active DNA demethylation, thereby contributing to impaired epigenetic homeostasis and metabolic dysfunction in offspring across multiple generations [104,105].

Beyond DNA methylation, phthalate exposure also affects histone modifications. Although direct mechanistic studies are limited, recent findings identify H3K4me₃—histone H3 lysine 4 trimethylation—as a key target in developing ovaries. DEHP exposure in fetal mouse oocytes significantly reduces H3K4me₃ enrichment, impairing the formation of primordial follicles (PFs). This disruption is associated with downregulation of *SMYD3*, a methyltransferase required for proper H3K4 di-/tri-methylation [61]. Importantly, overexpression of *SMYD3* during follicle pool establishment partially rescues PF assembly, reinforcing the role of H3K4me₃ signaling in phthalate-induced ovarian toxicity. Similar epigenetic disturbances have been observed in genes related to steroidogenesis and spermatogenesis, supporting a mechanistic link to reproductive dysfunction.

Phthalates further impact non-coding RNA networks. For example, *miR-155-5p* is downregulated following DEHP exposure, affecting cell cycle progression and extracellular matrix remodeling [62]. Changes in long non-coding RNAs (lncRNAs) have also been reported, particularly in association with disrupted reproductive and metabolic phenotypes [41].

Crucially, the epigenetic effects of phthalates are not confined to the exposed generation. Several animal studies have reported transgenerational inheritance of altered DNA methylation and histone marks, leading to phenotypic outcomes such as reduced fertility, insulin resistance, and altered metabolic function in descendants. These findings underscore the heritable nature of phthalate-induced epigenetic reprogramming and highlight the need for comprehensive risk assessments that consider multigenerational effects.

3.1.4. Parabens

Parabens—including methylparaben (MP), ethylparaben, propylparaben, and butylparaben (nBuP)—are widely used as antimicrobial preservatives in cosmetics, pharmaceuticals, and food products. Due to their structural similarity to estrogen, these compounds can bind to estrogen receptors and disrupt hormonal signaling. Beyond their endocrine-disrupting properties, increasing evidence indicates that parabens also exert epigenetic effects that may contribute to metabolic disorders, reproductive dysfunction, and cancer [106].

Maternal exposure to nBuP has been shown to induce hypermethylation of the *proopiomelanocortin* (POMC) gene promoter in offspring, impairing hypothalamic appetite regulation and increasing susceptibility to obesity and related metabolic syndromes [63]. Consistent with this, animal studies have reported that prenatal nBuP

exposure leads to increased body weight and insulin resistance, phenotypes associated with silencing of metabolic regulatory genes. Notably, these effects are at least partially reversible through the use of DNA methyltransferase inhibitors such as 5-azacytidine, confirming an epigenetic mechanism. In human studies, paraben exposure has similarly been linked to aberrant DNA methylation. Elevated urinary MP levels have been associated with global hypomethylation in breast tissue, including at promoter regions of tumor suppressor genes such as *CCND2*, potentially contributing to breast cancer risk [64]. Moreover, high paraben concentrations have been correlated with increased breast cancer incidence, possibly through hypomethylation-mediated activation of cell proliferation pathways.

While the epigenetic impact of parabens on non-coding RNAs and histone modifications remains less well-characterized than that of other EDCs, preliminary evidence suggests possible modulation of miRNAs involved in adipogenesis and estrogen signaling. Further research is warranted to delineate these mechanisms. The transgenerational effects of parabens are still underexplored. However, emerging findings suggest that early-life paraben exposure may result in stable, heritable epigenetic alterations affecting long-term disease risk. Given the widespread use of parabens and the vulnerability of the developing epigenome, these findings support the need for cautious regulatory oversight and further mechanistic research to better understand the scope of paraben-induced epigenetic toxicity.

3.2. Heavy metals

Heavy metal exposure—especially to arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg)—represents a critical environmental and public health concern due to widespread contamination and bioaccumulation [107]. These toxicants exert harmful effects not only

through direct biochemical interactions but also via epigenetic mechanisms that alter gene regulation without modifying DNA sequence. Such changes are increasingly linked to the development of cancer, neurodevelopmental and metabolic disorders, and heritable disease susceptibility. While each metal elicits unique epigenetic profiles, common pathways include disruption of DNA methylation, histone modifications, and non-coding RNA expression (Table 2).

3.2.1. Arsenic (As)

Arsenic (As) is a naturally occurring metalloid and a well-established environmental toxicant. Chronic exposure, primarily through contaminated drinking water and food, has been associated with a range of health effects including skin lesions, cardiovascular dysfunction, diabetes, and multiple cancers. Increasing evidence suggests that arsenic mediates its pathogenic effects by remodeling the epigenome. Among the most prominent epigenetic effects of arsenic is its capacity to induce aberrant DNA methylation. Long-term exposure leads to global hypomethylation—particularly in peripheral blood leukocytes—contributing to genomic instability and increased cancer risk. Concurrently, arsenic promotes hypermethylation of key tumor suppressor gene promoters such as *p16INK4a*, *RASSF1A*, and *p53*, resulting in transcriptional silencing and oncogenic transformation [139–142]. Notably, prenatal arsenic exposure alters methylation of imprinted and metabolic regulatory genes, reflecting its capacity to disrupt developmental programming [143].

Arsenic also influences histone modification profiles. In vitro studies have shown reduced levels of histone H3 lysine 9 acetylation (H3K9ac) and histone H4 lysine 16 acetylation (H4K16ac), alongside elevated H3K27me3—a repressive chromatin mark—following arsenic trioxide exposure [42,108,144]. Additionally, elevated H3S10 phosphorylation has been linked to heightened oncogene expression and cellular

Table 2
Summary of epigenetic effects by heavy metals.

Heavy metal	DNA Methylation	Histone Modification	ncRNA Alteration	Health Implications	Environmentally Relevant Concentration (ERC)	Environmental Matrix	Ref
Arsenic (As)	Global hypomethylation; hypermethylation of tumor suppressor genes (e.g., <i>p16INK4a</i> , <i>RASSF1A</i>)	↓ H3K9ac, ↓ H4K16ac, ↑ H3K27me3, ↑ H3S10ph	↑ miR-21, ↓ miR-200 family, dysregulation of <i>MALAT1</i>	Cancer, diabetes, cardiovascular diseases, developmental disorders; transgenerational effects	10 µg/L	Drinking water, Soil, sediment	[108–112]
Lead (Pb)	Global hypomethylation; hypermethylation of <i>IGF2</i> , <i>H19</i> , <i>BDNF</i> , and <i>LIN-1</i>	↓ H3K9ac, ↑ H3K27me3	↑ miR-222, ↓ miR-148a, ↓ miR-21	Neurodevelopmental deficits, immune dysregulation, chronic inflammation; potential heritability	0.1–1 µg/m ³	Air, soil, dust, drinking water	[113–117]
Cadmium (Cd)	Dose-dependent hypo-/hypermethylation; altered imprinting genes (<i>ATP9A</i> , <i>PEG3</i>)	Altered H3K4me3, H3K9me3, H3K27me3; ↓ histone phosphorylation	↑ miR-101, miR-144, miR-1537, miR-27a-3p	Endocrine disruption, kidney damage, cancer, metabolic disorders; sex-specific transgenerational effects	1–5 ng/m ³	Air, soil, sediment	[21, 118–121]
Mercury (Hg)	Global and locus-specific methylation changes; hypermethylation of <i>BDNF</i> promoter	↓ H4 acetylation, ↑ HDAC3/4/6, ↓ H3 acetylation	↓ miR-206, miR-9-5p, miR-27a-3p	Neurotoxicity, cognitive deficits, depression-like behavior; persistent effects on brain development	2–20 ng/m ³	Air (vapor), fish, sediment	[122–125]
Chromium (Cr VI)	- Promoter hypermethylation (e.g., <i>MGMT</i> , <i>HOGG1</i> , <i>RAD51</i>) in 16HBE cell- Global methylation changes (e.g., <i>CDH4</i> , <i>IL1RAP</i> , <i>USP1</i> , <i>PXDNL</i> , <i>ALDH3A1</i>)	- ↑ H3K9me2, H3K27me3- ↓ H4K16ac via induction of Nupr1	- ↓ miR-210 in human lung cells - ↓ miR-142-3p, miR-15b-5p, miR-3940-5p, miR-451a	Pulmonary carcinogenesis, DNA repair inhibition, oxidative stress	0.1–10 µg/L	Water, industrial site, soil	[126–131]
Nickel (Ni)	- Gene-specific hypermethylation - Inhibits DNMT activity	- ↑ H3K9me2, ↓ H4 acetylation - ↑ H3K4me3 in BEAS-2B	- Altered miR-21 in TGF-β1/Smad signaling	Epigenetic silencing of tumor suppressors, fibrosis, lung cancer	1–10 µg/L	Soil, air, sediment, drinking water	[132–135]
Aluminum (Al)	- ↑ DNMTs, TET expression in brain tissue- Methylation of <i>APP</i> and <i>BACE1</i> genes	- Decreased H2BK20, ↑ HDAC3 expression in neurons	- miR-98-5p upregulation (neurotoxicity)	Neurodegeneration, Alzheimer's-like pathology	5–50 µg/L	Water, soil, sediment	[136–138]

proliferation [109].

Non-coding RNAs also represent a key layer of epigenetic regulation influenced by arsenic. Upregulation of oncogenic miRNAs, such as *miR-21*, and downregulation of tumor-suppressive miRNAs, including *miR-200* family members, enhance carcinogenic potential by promoting proliferation and epithelial-to-mesenchymal transition (EMT). Moreover, altered expression of lncRNAs such as *MALAT1* further highlights arsenic's broad epigenomic impact [110,111].

Importantly, arsenic's epigenetic effects are not restricted to the directly exposed generation. Rodent studies have shown that prenatal arsenic exposure results in persistent DNA methylation changes that are inherited across generations, increasing susceptibility to metabolic disease and cancer. These findings identify arsenic as a potent transgenerational epimutagen and reinforce the value of epigenetic biomarkers for risk assessment and environmental health surveillance.

3.2.2. Lead (Pb)

Lead (Pb) is a pervasive environmental pollutant with a long history of use in paints, gasoline, and industrial processes. Despite regulatory efforts, lead exposure remains a serious public health concern, particularly due to its neurotoxic and immunotoxic effects during critical developmental windows. Recent research increasingly implicates epigenetic mechanisms as mediators of the long-term biological consequences of lead exposure.

Prenatal and early-life Pb exposure has been consistently linked to alterations in DNA methylation. Multiple birth cohort studies report global hypomethylation in cord blood, indicating increased genomic instability and potential oncogenic risk [113,145]. Gene-specific changes, including hypermethylation of *IGF2*, *H19*, *LINE-1*, and *HSD11B2*, suggest silencing of imprinted and regulatory genes important in growth and endocrine regulation [114]. These findings are supported by animal studies demonstrating persistent methylation changes in neurodevelopmental genes such as *BDNF* and NMDA receptor subunits [115,146].

Pb also disrupts chromatin architecture by modulating histone marks. Reduced H3K9 acetylation and elevated H3K27me3 levels have been observed following Pb exposure, contributing to heterochromatin formation and downregulation of genes involved in synaptic plasticity and neurogenesis [116].

In contrast to other heavy metals such as arsenic or cadmium, lead's epigenetic toxicity appears to predominantly affect the developing brain, partly via dysregulation of non-coding RNAs. For instance, *miR-222*, which regulates cell cycle and apoptosis, is upregulated, whereas *miR-148a* and *miR-21*—associated with anti-inflammatory responses—are downregulated, implicating lead in immune dysregulation and neuroinflammation [117,147].

Emerging data suggest that these epigenetic changes may be long-lasting and potentially heritable. The effects of lead are highly dependent on developmental timing, dosage, and sex, highlighting the need for precision-oriented risk assessments. Advancing our understanding of Pb-induced epigenetic dysregulation is essential for the development of early biomarkers and targeted preventive strategies against lead-related disease.

3.2.3. Cadmium (Cd)

Cadmium (Cd) is a non-essential heavy metal classified as a Group I human carcinogen. It enters the human body primarily through occupational exposure, cigarette smoke, and contaminated food. Unlike lead and arsenic, cadmium is especially associated with endocrine disruption, renal toxicity, and carcinogenesis, with a unique epigenetic signature.

Cd contributes to genomic instability, a hallmark of cancer, by inducing DNA damage such as mutations, DSBs, and chromosomal aberrations [148,149]. One genotoxic mechanism involves the formation of Cd-DA adducts through direct interaction with purine bases, particularly adenine and guanine [150]. Additionally, Cd disrupts DNA repair by

displacing zinc in zinc finger proteins, impairing repair enzyme function and suppressing expression of key repair genes. These combined effects contribute to impaired genomic maintenance and Cd-induced carcinogenic transformation.

Cd modifies DNA methylation in a manner dependent on both dose and exposure duration. Acute Cd exposure suppresses DNMT activity, leading to global hypomethylation. In contrast, chronic exposure often results in overexpression of *DNMT3A* and *DNMT3B*, promoting global hypermethylation and silencing of tumor suppressor genes such as *RASSF1A* and *p16* [118]. In utero Cd exposure has been associated with differential methylation of imprinting genes such as *ATP9A* and *PEG3*, with female offspring showing greater susceptibility—suggesting sex-specific epigenetic effects [151,152]. Methylation changes in other imprinting control regions (*IGF2R*, *KvDMR*, *GNASXL*) have also been linked to altered birth outcomes and blood pressure regulation [153].

Although histone modifications have been less studied, available evidence indicates significant cadmium-induced effects. Altered levels of H3K4me3, H3K9me3, and H3K27me3 have been reported in Cd-transformed human bronchial epithelial cells [21]. Cd also impairs histone phosphorylation by downregulating vaccinia-related kinases (VRK1/2), which may alter chromatin dynamics and transcriptional regulation [119]. Notably, prenatal Cd exposure elevates *H3K27me3* during cardiomyocyte differentiation and reduces *H3K27me1* in embryonic stem cells, indicating its role in developmental epigenetic programming [154].

Cd exposure also dysregulates miRNA expression, including upregulation of *miR-101* and *miR-144*, both of which target *CFTR*, a gene essential for epithelial ion transport. This leads to diminished *CFTR* expression, potentially contributing to pulmonary dysfunction [120]. Moreover, maternal Cd exposure modifies placental and fetal miRNA expression, including increased levels of *miR-1537* and *miR-27a-3p*, which are implicated in endocrine disruption and metabolic reprogramming [121,155].

Taken together, Cd's epigenetic toxicity involves a complex interplay of DNA methylation dynamics, histone mark alterations, and non-coding RNA dysregulation. These mechanisms contribute to its broad systemic toxicity and potential for transgenerational health impacts, underscoring the need for long-term epigenetic monitoring and exposure regulation.

3.2.4. Mercury (Hg)

Mercury (Hg), particularly in its organic form methylmercury (MeHg), is a potent neurotoxin with heightened vulnerability during prenatal and early postnatal development. Owing to its lipophilic nature, MeHg readily crosses the blood–brain barrier and placenta, disrupting key processes in fetal neural development. Among heavy metals, mercury's epigenetic effects are particularly pronounced in the central nervous system [156,157].

MeHg exposure triggers both global and locus-specific alterations in DNA methylation. In human dopaminergic neurons, it induces the upregulation of *DNMT1* and *DNMT3A*, resulting in increased global methylation [158]. Conversely, low-dose exposure in rat neural stem cells reduces *DNMT3B* expression and global methylation levels, with persistent epigenetic alterations observed in descendant cell populations [159]. Notably, region-specific hypermethylation of *BDNF* promoter IV in the hippocampus has been linked to reduced *BDNF* expression and depression-like behaviors in mice [122].

Mercury exposure also disrupts histone acetylation dynamics. In SH-SY5Y cells and the mouse cerebellum, MeHg decreases histone H4 acetylation and upregulates HDAC4, leading to neuronal apoptosis—a process reversed by HDAC inhibitors [123]. Additional studies report increased HDAC3 and HDAC6 levels with concurrent reductions in histone H3 acetylation in LUHMES neurons and fetal mouse brain, impairing neurite outgrowth and synaptic maturation [158].

Among heavy metals, mercury exhibits the most consistent effects on neurodevelopment via miRNA dysregulation. *miR-206*, which regulates

BDNF expression, is notably downregulated after MeHg exposure in rat cortical neurons, with its restoration rescuing neurotoxicity [124]. Similarly, reduced expression of *miR-9-5p* and *miR-27a-3p* impairs synaptic protein translation. In *C. elegans*, genetic disruption of the miRNA processing pathway increases vulnerability to MeHg toxicity, suggesting a protective role for miRNAs in cellular stress responses [125, 160].

Collectively, mercury's epigenetic modifications—especially during critical developmental windows—underscore its lasting impact on neural function. The integration of epigenetic biomarkers into neurotoxicological frameworks may facilitate earlier diagnosis and targeted interventions for mercury-associated neurodevelopmental disorders.

3.3. Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) are a class of ubiquitous environmental pollutants generated during the incomplete combustion of organic matter such as coal, oil, tobacco, and wood. Among them, *benzo[a]pyrene* (BaP) is the most studied due to its potent carcinogenicity. Upon metabolic activation, PAHs produce reactive intermediates capable of covalently modifying DNA and reprogramming the epigenome (Table 3).

One of the principal genotoxic mechanisms of PAHs is the metabolic conversion of parent compounds into electrophilic intermediates, such as diol epoxides, which form covalent DNA adducts [178,179]. These DNA adducts, especially BPDE-DNA lesions derived from BaP, frequently target guanine residues and disrupt DNA replication fidelity, leading to point mutations and strand instability [180]. The presence of PAH-DNA adduct is considered a hall mark of early carcinogenesis and has been linked to elevated cancer risk in both experimental models and human biomonitoring studies [181]. Additionally, redox cycling of PAH metabolites generates reactive oxygen species (ROS), compounding DNA damage and mutagenesis [182]. Thus, DNA adduct formation serves as both a mechanistic driver and a biomarker of PAH-induced carcinogenesis.

In parallel with direct genotoxicity, a growing body of evidence indicates that PAH exposure induces widespread changes in DNA

methylation, histone modifications, and non-coding RNA expression, which collectively contribute to carcinogenesis, developmental abnormalities, and chronic diseases.

PAH exposure profoundly impacts DNA methylation patterns. BaP modulates DNA methyltransferase activity by suppressing *DNMT3a* while paradoxically increasing *DNMT1* expression in murine embryonic fibroblasts [183]. These shifts promote aberrant methylation, including significant global hypomethylation and selective promoter hypermethylation. For instance, human bronchial epithelial cells (16HBE) show up to 43 % reduction in global methylation at high BaP concentrations [161]. Oxidative stress, mediated by BaP-generated ROS, further destabilizes methylation homeostasis by impairing methyl-CpG-binding proteins and DNMT interactions [184]. Notably, promoter-specific hypermethylation of tumor suppressor genes such as *RAR-β2* and *APC* has been observed in both esophageal cancer models and peripheral blood mononuclear cells from exposed individuals, alongside *cyclooxygenase-2* hypomethylation—suggesting a dual mechanism that silences protective genes while enhancing inflammatory pathways [162,185]. These findings underscore how PAHs generate a methylation landscape conducive to malignant transformation and chronic inflammation.

PAHs have also been shown to influence histone post-translational modifications. BaP downregulates HATs while upregulating HDAC2/3, leading to reduced H3/H4 acetylation and repression of tumor suppressors like p53 [186]. Conversely, in MCF7 breast cancer cells, BaP induces genome-wide H3K9ac, relaxing chromatin structure to facilitate proto-oncogene transcription [43]. These opposing effects may reflect cell-specific differences in HDAC/HAT equilibrium or crosstalk with DNA methylation pathways. Histone methylation marks, such as H3K27me3 and H3K4me2, are also perturbed by BaP. Murine studies demonstrate that BaP reduces H3K27me3 at promoters of pro-inflammatory genes, fostering a tumor-promoting microenvironment. Simultaneously, it increases H3K4me2 at antioxidant response element (ARE)-containing genes [187,188]. Together, these chromatin-level alterations reflect the dual role of PAHs in silencing tumor suppressors while activating stress-adaptive pathways that paradoxically contribute to long-term damage.

Table 3
Summary of epigenetic effects by PAH compound.

PAH Compound	DNA Methylation	Histone Modifications	ncRNA Alterations	Health Implications	Environmentally Relevant Concentration (ERC)	Environmental Matrix	Ref
Benzo[a]pyrene (BaP)	Global hypomethylation; hypermethylation of <i>p16</i> , <i>RAR-β2</i> , <i>APC</i>	↓ H3K9ac, ↑ H3K27me3, ↑ H3K4me2	↓ <i>miR-34a</i> , ↑ <i>miR-21</i> , <i>miR-29a</i> , <i>miR-330</i>	Carcinogenesis, inflammation, developmental toxicity	0.1–5 ng/m ³	Air, sediment, soil	[43, 161–164]
Phenanthrene	Altered methylation in immune signaling molecules	↓ H4K12ac, ↑ H3K9me2	↑ <i>miR-398</i> , ↓ <i>miR-133a</i>	Immune dysregulation, inflammation, potential tumor promotion	100–1000 ng/L	Surface water, sediment, soil, air	[165–168]
Fluoranthene	Reduced methylation of <i>CYP1A</i> promoter	↓ H3K4me3	↑ <i>miR-181</i> , altered lncRNAs	Detoxification impairment, inflammation, cancer risk	200–3000 ng/L	River water, air, soil, sediment	[169–171]
Anthracene	- Induced methylation in skin cancers	Not well characterized; alter histone variants expression	- ↑ <i>miR-134</i> , <i>miR-132</i> , and <i>miR-124-1</i> in female mice	Pulmonary inflammation, vascular dysfunction	< 100 ng/L	Air, dust, surface water	[172–174]
Naphthalene	Not well characterized	- ↓ HDAC activity (cancer therapy)	- ↑ <i>miR-19b-3p</i> (inflammation)	Respiratory epithelial damage, inflammation, oxidative stress	Variable	Air, combustion site, groundwater, soil	[175,176]
Benzo[k]fluoranthene (BkF)	- ↑ <i>CYP1A4</i> promoter developing chicken embryos	Not well characterized	- ↑ <i>miR-181a</i> , <i>miR-181b</i> , and <i>miR-181d</i> (hepatocarcinogenesis)	Development, tumorigenesis	~50–500 ng/L	Soil, industrial waste, air, sediment	[169,177]

In addition to DNA and histone-level changes, PAHs alter the expression of several miRNAs involved in cell proliferation, apoptosis, and inflammation. These include downregulation of tumor-suppressive *miR-34a* and upregulation of oncogenic *miR-330*, *miR-29a*, and *miR-9* family members [163,164]. The miRNA dysregulation observed may link PAH exposure to inflammation-driven tumorigenesis. Recent transcriptomic studies in PAH-exposed lung epithelial cells have further identified miRNA changes linked to DNA damage response regulation, contributing to a pro-inflammatory and pro-oncogenic cellular phenotype [49].

Collectively, PAHs induce multilayered epigenetic alterations involving DNA methylation remodeling, histone code disruption, and miRNA-mediated gene regulation. These changes not only exacerbate direct genotoxicity but also establish persistent epigenetic footprints that underlie disease pathogenesis. As such, epigenetic markers may serve as early indicators of PAH exposure and provide insight into preventive strategies against PAH-induced disorders.

3.4. Air pollution and epigenetic modifications

According to the latest WHO's Ambient Air Quality Database (v 6.1, updated Jan 2024), more than 99 % of the global population lives in areas where concentrations of PM_{2.5} and NO₂ exceed the WHO Air Quality Guideline limits (WHO, 2024) [189]. Unlike single-compound toxicants such as PAHs or heavy metals, ambient air pollution is a complex mixture of gaseous (e.g., NO₂, SO₂, O₃) and particulate (PM_{2.5}, black carbon, ultrafine particles) pollutants. This chemical complexity, combined with its widespread and lifelong nature, leads to systemic and multi-organ epigenetic effects. These effects are increasingly recognized as key mediators in pollution-associated conditions such as asthma, cardiovascular disease, metabolic syndrome, and neurodevelopmental disorders (Table 4).

Table 4
Summary of epigenetic effects by air pollution.

Pollutant	DNA Methylation	Histone Modifications	ncRNA Alterations	Health Implications	Environmentally Relevant Concentration (ERC)	Environmental Matrix	Ref
PM _{2.5}	Altered methylation at <i>AHRR</i> , <i>IL-6</i> , <i>TLR4</i> , <i>APOE</i> ; persistent in blood and placenta	↑ H3/H4 acetylation at enhancer regions; ↑ H3K9me2, H4K20me3	↑ miR-155, ↓ miR-21; changes in vascular tone and inflammation-related miRNAs	Asthma, cardiovascular disease, metabolic dysfunction; developmental epigenetic imprinting	10–150 µg/m ³	Ambient air, indoor air	[190–193]
Diesel Exhaust Particles (DEP)	Promoter methylation of antioxidant genes; EWAS-identified loci	HAC activation; degradation of HDAC1	biomarker of miRNAs in liver (e.g., miR-122-5p, miR-342-5p)	Chronic lung inflammation, oxidative stress, reduced tissue repair capacity	20–100 µg/m ³	Urban air, roadside air, tunnel air	[194–196]
NO ₂	Reduced methylation at inflammation and oxidative stress genes	Inhibits KDM3A, which alter histone methylation patterns	↑ miR-451a, ↓ miR-146a linked to inflammation	Immune dysfunction, chronic inflammation, increased disease risk	20–80 µg/m ³	Urban air, indoor air, surfaces	[197–199]
O ₃	Altered methylation patterns (e.g., <i>PLSCR1</i> , <i>HCAR1</i> , and <i>LINC00336</i>)	Not well characterized; potential involvement suggested	miR-132, miR-143, miR-145 (inflammatory diseases)	Neurotoxicity, pulmonary damage, inflammation	50–100 µg/m	Tropospheric air, indoor air	[200,201]
Carbon Monoxide (CO)	- Hypomethylation during Pregnancy (e.g., <i>LMO7</i>) - Alteration of <i>Foxp3</i> and <i>IL10</i>	- ↑ Histone arginine methylation, ↑ PRMT1 activity - H3K3me, acH3 in endothelial cells	↓ miR-195-5p during osteogenic differentiation	Hypoxia-related injury, vascular inflammation, impaired neural development	0.5–5 ppm	Urban air, ambient air, indoor air	[202–206]
Black Carbon	Hypomethylation FOXP3 promoter	- ↓ H3K27me2, H3K36me3	- Altered MicroRNA Processing Genes (e.g., <i>DICER</i> , <i>GEMIN4</i> , <i>DGCR8</i>)	Respiratory inflammation, immune dysregulation, early-life developmental risk	1–5 µg/m ³	Traffic air, ambient air	[207] [208] [209]
Ultrafine Particles (UFPs)	- Not well characterized; potential associated with altered methylation in immune-related genes	↑ H3K9ac and H3K36me3	- ↑ miR-21, ↑ miR-222	Neuroinflammation, cardiovascular dysfunction, aging acceleration	< 1 µg/m ³	Urban air, indoor air	[208,210]

In addition to epigenetic remodeling, air pollution—particularly PM_{2.5} and PM₁₀—also induces direct DNA damage through adduct formation. Epidemiological studies have shown that individuals exposed to urban or traffic-related air pollution exhibit elevated DNA adduct levels in leukocytes, with similar findings reported in maternal and cord blood following gestational PM and PAH exposure [211,212]. In vitro studies further support that PM exposure upregulates CYP1A1 and CYP1B1, enhancing PAH bioactivation and subsequent adduct formation [213]. Notably, the extent of genotoxicity varies by PM source and season, with industrial and wintertime particles inducing significantly more DNA lesions [214]. DNA adducts have thus emerged as sensitive molecular biomarkers of air pollutant exposure and may serve as early initiators of mutagenesis that precede or synergize with epigenetic alterations.

DNA methylation changes associated with air pollution exposure are well documented across multiple tissues, including blood, placenta, and lung. Unlike localized pollutants, ultrafine airborne particles can translocate from the lungs to the bloodstream, initiating systemic inflammatory cascades and multi-tissue epigenetic remodeling. Large-scale epigenome-wide association studies (EWAS) have revealed altered methylation at genes regulating oxidative stress (*AHRR*, *NOS2*), immune response (*IL-6*, *TLR4*), and lipid metabolism (*APOE*, *ABCA1*), particularly following prenatal and early-life exposure to PM_{2.5} and NO₂ [215–217]. These methylation shifts are often dose-responsive and may persist for years, supporting the concept of an “epigenetic memory” of early-life air quality. Such sustained DNA methylation alterations may contribute to the developmental origins of chronic disease.

Emerging evidence indicates that air pollutants, particularly diesel exhaust particles, modulate histone-modifying enzymes, leading to persistent changes in chromatin accessibility. Both in vitro and in vivo studies have shown that PM exposure reduces histone acetylation at enhancer regions while promoting repressive methylation marks such as

H3K9me2 and H4K20me3 [218]. These changes suppress the transcription of protective genes associated with oxidative stress defense and tissue repair. Cumulatively, such chromatin remodeling contributes to the persistent low-grade inflammation and endothelial dysfunction commonly observed in urban-exposed populations. This histone-mediated repression reinforces the long-term biological impact of air pollution beyond acute exposure.

Air pollution further modulates gene expression post-transcriptionally through non-coding RNA pathways. For instance, PM2.5 exposure upregulates *miR-155*, a pro-inflammatory regulator, while downregulating *miR-21*, which exerts anti-inflammatory and pro-survival effects [190]. Additional studies have reported air pollution-induced dysregulation of miRNAs implicated in vascular tone (*miR-126*), coagulation (*miR-223*), and neurodevelopment (*miR-124*, *miR-9*), indicating that pollutants act as pleiotropic epigenetic disruptors [219,220]. These miRNA alterations highlight the widespread and organ-specific effects of airborne toxicants.

As a ubiquitous and persistent exposure, air pollution reshapes the epigenome across developmental stages—from prenatal life into adulthood. The resulting molecular changes may encode long-term health trajectories and help explain observed disparities in disease burden across polluted environments. A deeper understanding of these epigenetic mechanisms is critical for identifying sensitive windows of exposure, developing predictive biomarkers, and informing public health interventions aimed at mitigating the lifelong consequences of air pollution.

3.5. Lifestyle factors as epigenetic modulators

Lifestyle factors exert a profound influence on the epigenome, modulating DNA methylation, histone modifications, and non-coding RNA expression across tissues and life stages. These changes shape individual susceptibility to disease or resilience under environmental stress. Accumulating evidence distinguishes between causal epigenetic modulation, demonstrated in experimental or interventional settings, and associative evidence from population-based observations (Table 5).

3.5.1. Causal evidence from experimental and interventional studies

Controlled dietary and behavioral interventions have provided direct causal evidence that lifestyle factors can actively remodel epigenetic states. Nutritional components such as folate, resveratrol, and omega-3

fatty acids regulate DNA methylation by altering methyl-donor availability and DNMT expression, thereby influencing genes like NF-κB and MTHFR involved in oxidative and inflammatory balance [236,237]. Physical activity represents another robust causal modulator: experimental training studies demonstrate promoter demethylation of PGC-1α and activation of mitochondrial biogenesis pathways in skeletal muscle [238]. At the mechanistic level, SIRT1-FOXO3 signaling, activated by caloric restriction and metabolic stress, mediates histone deacetylation and longevity-associated transcriptional reprogramming [239]. Collectively, these findings indicate that specific nutritional and behavioral interventions can causally reprogram the epigenome, enhancing metabolic and stress resilience.

3.5.2. Associative evidence from epidemiological and cohort studies

Epidemiological studies complement experimental findings by revealing population-level correlations between lifestyle patterns and epigenetic profiles, though these do not establish direct causality. Nutritional status has been associated with gene-specific methylation patterns in metabolic disorders, such as MTHFR promoter hypermethylation linked to diabetic complications [237]. Psychosocial stress and insufficient sleep correlate with hypermethylation of NR3C1 and circadian regulators (CLOCK, BMAL1), affecting neuroendocrine and metabolic pathways [240,241]. Tobacco smoke and alcohol consumption are consistently associated with global DNA hypomethylation (e.g., LINE-1) and promoter hypermethylation of tumor-suppressor genes [242]. While these associative patterns are robust at the population level, they remain subject to confounding by genetics, environment, and behavior. Integrating both causal and associative frameworks thus provides a comprehensive understanding of how modifiable lifestyle factors shape the human epigenome and influence long-term health trajectories.

3.6. Comparative evidence for heritable epigenetic alterations across pollutant classes

To move beyond a purely descriptive overview, we performed a structured literature mapping of epigenetic studies published between 2010 and 2025 for the pollutant classes covered in this review. Table 6 summarizes, for each class, the total number of epigenetic studies, the subset reporting multigenerational or transgenerational epigenetic effects (F1–F3 or germline transmission), the predominant species and

Table 5
Summary of epigenetic effects by lifestyle factor.

Lifestyle Factor	DNA Methylation	Histone Modifications	ncRNA Alterations	Health Implications	Environmentally Relevant Concentration (ERC)	Biological Matrices	Ref
Diet (e.g., folate, polyphenols, omega-3)	Modulates methylation of NF-κB, MTHFR; supports antioxidant gene regulation	Polyphenols (e.g., resveratrol) modulate HATs/HDACs	Regulates miRNAs involved in inflammation and metabolism	Reduced inflammation, cancer prevention, improved metabolic health	N/A	Dietary intake (folate, polyphenols), blood, urine	[221,222]
Physical Activity	Demethylation of PGC-1α; improves metabolic function	Increases H3 acetylation in muscle tissue	↑ miR-873-3p; supports muscle regeneration	Enhanced mitochondrial function, anti-aging effects	N/A	Muscle tissue, blood, hair	[223,224]
Psychosocial Stress / Sleep Deprivation	Hypermethylation of NR3C1, CLOCK, BMAL1; disrupts stress/circadian genes	Alters histone acetylation; represses protective genes	↓ miR-132, miR-138; associated with sleep loss	Neuropsychiatric disorders, metabolic dysfunction	N/A	Saliva, blood, hair	[225–228]
Smoking & Alcohol	Global hypomethylation (p53), oncogene activation	↓ H4K20me3, Alters Chromatin Remodeling	Disrupts miRNAs (miR-193b-3p, miR-122-5p, miR-3937)	Liver disease, cancer, immune dysfunction	N/A	Blood, urine, buccal swabs	[229–232]
Mindfulness / Caloric Restriction / Fasting	age-related DNA methylation drift	Activates SIRT1/3-mediated deacetylation; chromatin relaxation	↑ protective miRNAs (e.g., miR-713); improved stress resilience	Extended healthspan, stress resistance, disease prevention	N/A	PBMCs, serum, brain tissue	[233–235]

Table 6
Comparative evidence for heritable epigenetic alterations across major pollutant classes (2010–2025).

Pollutant class	Example compounds from this review	Total epigenetic studies*	Studies on transgenerational / heritable epigenetics, n (%)	Main species (human vs. rodent)	Dominant epigenetic endpoints	Strength of evidence (★)
EDCs	BPA, BPF, BPS, DES, DEHP, DBP, parabens vinclozolin, nonylphenol, TBBPA, atrazine	168	42 (25.0 %)	Predominantly rodent; limited human cohort data (DES, phthalates, BPA)	DNA methylation (imprinted genes, sperm DMRs), histone marks (H3K4me3, H3K27me3, acetylation), miRNAs/lncRNAs	★★★★
POPs	Dioxins (TCDD), PCBs	94	18 (19.1 %)	Mostly rodent; few human birth cohorts	DNA methylation at xenobiotic, endocrine, and immune genes; some histone modifications and ncRNA changes	★★★★
Heavy metals	As, Cd, Pb, Hg, Cr(VI), Ni, Al	142	13 (9.2 %)	Rodent prenatal/multigenerational models; human cohorts mainly F0–F1	Global hypomethylation plus promoter hypermethylation, selected histone marks, limited ncRNA data	★★★
PAHs	BaP, phenanthrene, fluoranthene, anthracene, naphthalene, BkF	86	5 (5.8 %)	Rodent (germ-cell and developmental studies)	DNA adduct-associated methylation changes; some histone and transcriptomic alterations in germ cells	★★★★
Air pollutants	PM2.5, DEP, NO ₂ , O ₃ , CO, black carbon, UFPs	109	6 (5.5 %)	Rodent inhalation/instillation; human cohorts for F0/F1	DNA methylation in blood, lung, placenta and sperm; emerging data on histone marks and ncRNAs	★★★★
Lifestyle factors	Diet, physical activity, psychosocial stress/sleep loss, smoking, alcohol, caloric restriction/fasting, mindfulness	76	4 (5.3 %)	Human cohorts (F0–F1) plus rodent models (maternal diet, stress, alcohol)	DNA methylation at metabolic, neuroendocrine and inflammatory genes; histone acetylation; miRNAs	★★★★

exposure routes, and the main epigenetic endpoints examined. On this basis, we also provide a qualitative rating of the overall strength of evidence for heritable epigenetic alterations.

Across pollutant classes EDCs (e.g., BPA, phthalates, vinclozolin) and POPs (e.g., dioxins, PCBs) emerge as having the most robust support for transgenerational epigenetic effects. These classes not only account for the largest number of epigenetic studies overall but also include a substantial fraction of reports documenting persistent DNA methylation and chromatin changes in the germline and in F2–F3 offspring, often linked to reproductive or metabolic phenotypes [8,48]. Heavy metals (e.g., As, Cd, Pb) show a moderate level of evidence: several rodent studies report multigenerational methylation and histone-mark alterations, particularly following prenatal or early-life exposure, but the dataset is smaller and less consistent than that for EDCs and POPs [139,143,153]. By contrast, PAHs, air pollutants (e.g., PM2.5, diesel exhaust particles, NO₂, O₃), and lifestyle-related factors (such as parental diet, stress, or smoking) currently have relatively few studies that demonstrate clear heritable epigenetic transmission [186,191,211,212]. For these categories, most available data describe epigenetic changes in directly exposed individuals or their immediate offspring, with only isolated reports extending to later generations. Taken together, the comparative analysis in Table 6 indicates that EDCs and POPs provide the strongest evidence for heritable epigenetic alterations, heavy metals occupy an intermediate position, and PAHs, air pollutants, and lifestyle factors presently offer more limited or emerging evidence. This framework helps prioritize pollutant classes for future multigenerational studies and highlights where additional mechanistic work is needed to substantiate transgenerational toxicoepigenomic effects.

4. Retained intron as an emerging post-transcriptional epigenetic signature

Retained intron (RI), a regulated form of alternative splicing in which introns are retained in mature mRNAs, is gaining recognition as a sensitive post-transcriptional mechanism that responds to environmental stress. Unlike canonical splicing events, RI is tightly linked to chromatin architecture and epigenetic marks, which influence spliceosomal recognition and co-transcriptional splicing decisions [243]. This chromatin-splicing interface provides a regulatory checkpoint whereby environmental exposures can affect transcriptomic output without altering the underlying DNA sequence.

Several studies support the plausibility of RI as a toxicoepigenomic response. For instance, BPA exposure has been shown to disrupt splicing patterns in human retinoblastoma Y79 cells, with gene ontology analyses indicating enrichment in RI-associated pathways [244]. Similarly, methylparaben exposure induces early-phase RI in H1299 human lung carcinoma cells, particularly during the initiation of apoptosis [44]. These findings suggest that RI may be an early molecular signature in the cellular stress response to environmental toxicants. To detect RI events, studies have employed a multi-tool pipeline integrating rMATS, IRFinder, and iREAD, which leverage junction counts, intronic read coverage, and intron-exon read balance, respectively [245–247]. RI events supported by at least two tools and showing consistent directionality across replicates were considered high confidence, ensuring robust and reproducible identification. Functionally, intron-retaining isoforms frequently harbor premature termination codons and are subject to nonsense-mediated decay (NMD), serving as a mechanism to fine-tune gene expression. Fig. 3A illustrates this process, where environmental triggers disrupt canonical splicing and induce IR, leading to reduced protein output through NMD. In support of these observations, genome browser visualization demonstrates increased intronic read coverage in the *VPSS2* gene following PP exposure, indicated of RI. In addition, isoform-level transcriptome analysis revealed that PP treatment also promotes alternative-splicing-mediated transcript switching, independent of RI (Fig. 3B). For instance, in the *ABCC1* and *NBAS* genes, distinct transcript isoforms (e.g., *ABCC1-202*, *NBAS-201*) were

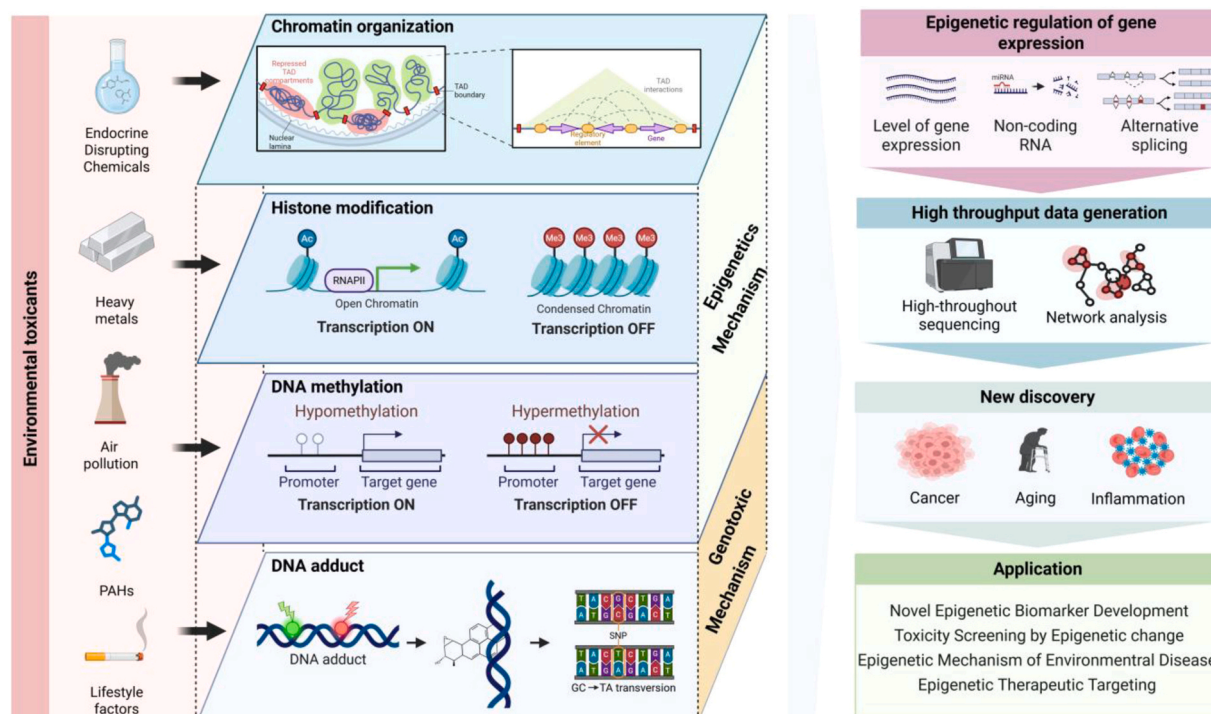


Fig. 2. Toxicoepigenomics framework linking environmental exposures to molecular mechanisms and translational applications. A broad range of environmental toxicants—including EDCs, heavy metals, PAHs, air pollution, and lifestyle factors—can induce both genotoxic and epigenetic alterations. Genotoxic effects such as DNA adduct formation can lead to mutations (e.g., GC→TA transversions) or disrupt transcriptional fidelity. In parallel, epigenetic mechanisms are altered through changes in DNA methylation, histone modifications, and chromatin organization, thereby modulating transcriptional activity. These chromatin-level changes further affect post-transcriptional regulation via non-coding RNAs (e.g., miRNAs, lncRNAs), alternative splicing, and RI events. High-throughput technologies such as next-generation sequencing and network-based integrative analysis enable the comprehensive profiling of these molecular responses. This framework supports novel discoveries in cancer, aging, and inflammatory disease, and facilitates the development of early epigenetic biomarkers, toxicity screening platforms, and therapeutic strategies targeting reversible epigenetic changes. Created with BioRender.com.

selectively upregulated, while others (e.g., *ABCC1-205*, *NBAS-202*) were downregulated (Fig. 3C). These results highlight that environmental stress can reshape the splicing landscape through both intron retention and isoform remodeling. RI has been linked to a range of biological processes, including inflammation, oxidative stress response, and tumor progression—each of which is commonly affected by environmental toxicants. Integrating RI analysis into comprehensive epigenetic frameworks may therefore provide deeper insight into how environmental exposures reprogram gene expression across multiple regulatory layers.

Beyond IR, researchers are increasingly exploring other emerging epigenetic signatures such as chromatin accessibility profiles, non-canonical histone modifications, and RNA-based epigenetic marks. As the field advances toward integrative multi-omics approaches, connecting alternative splicing events with DNA methylation and chromatin architecture may uncover novel axes of epigenetic vulnerability and adaptive potential.

5. Emerging epigenetic biomarkers and technologies

Recent advances in environmental epigenetics have identified a growing repertoire of molecular biomarkers that reflect exposure to environmental toxicants and predict disease risk. DNA methylation signatures—such as hypomethylation of *LINE-1* and *AHRR*, and hypermethylation of tumor suppressor loci like *p16INK4a* and *RARβ2*—have emerged as robust indicators of pollutant exposure and early carcinogenic transformation [248]. Circulating microRNAs and long non-coding RNAs (e.g., *HOTAIR*, *MALAT1*) have also been proposed as minimally invasive biomarkers for monitoring exposure to heavy metals, PAHs, and particulate air pollution [249,250].

A particularly promising class of biomarkers is the epigenetic clock. Models such as Horvath's clock and GrimAge leverage DNA methylation at select CpG sites to estimate biological age and detect age acceleration in response to chronic exposures like smoking, air pollution, and psychosocial stress [251–253]. These clocks offer quantitative metrics that bridge environmental stressors with long-term health trajectories and may inform early detection and intervention strategies.

The feasibility and resolution of epigenetic biomarker discovery have been transformed by recent technological innovations. High-throughput methylation arrays and WGBS now support EWAS across diverse cohorts and exposure scenarios [254,255]. In parallel, chromatin-focused assays such as ChIP-seq, ATAC-seq, and CUT&RUN enable fine-scale mapping of histone modifications and DNA accessibility. Advances in small RNA sequencing and single-cell epigenomic profiling further allow high-resolution assessment of non-coding RNA landscapes and epigenetic heterogeneity at the cellular level (Fig. 4). These platforms collectively support a shift from candidate gene approaches to data-driven, systems-level epigenetic toxicology (Fig. 4). They also enable integrative analyses that combine epigenetic information with transcriptomic, proteomic, and metabolomic data—providing a comprehensive picture of how environmental exposures shape molecular phenotypes.

The integration of epigenetic biomarkers with longitudinal epidemiological data and multi-omics profiling offers immense potential for translational toxicoepigenomics. Such biomarkers may enable retrospective exposure reconstruction, early disease prediction, and assessment of interventions such as caloric restriction, physical activity, or pollution mitigation strategies [256]. However, to realize their full potential in public health and precision medicine, further efforts are needed to standardize analytic pipelines, improve reproducibility, and

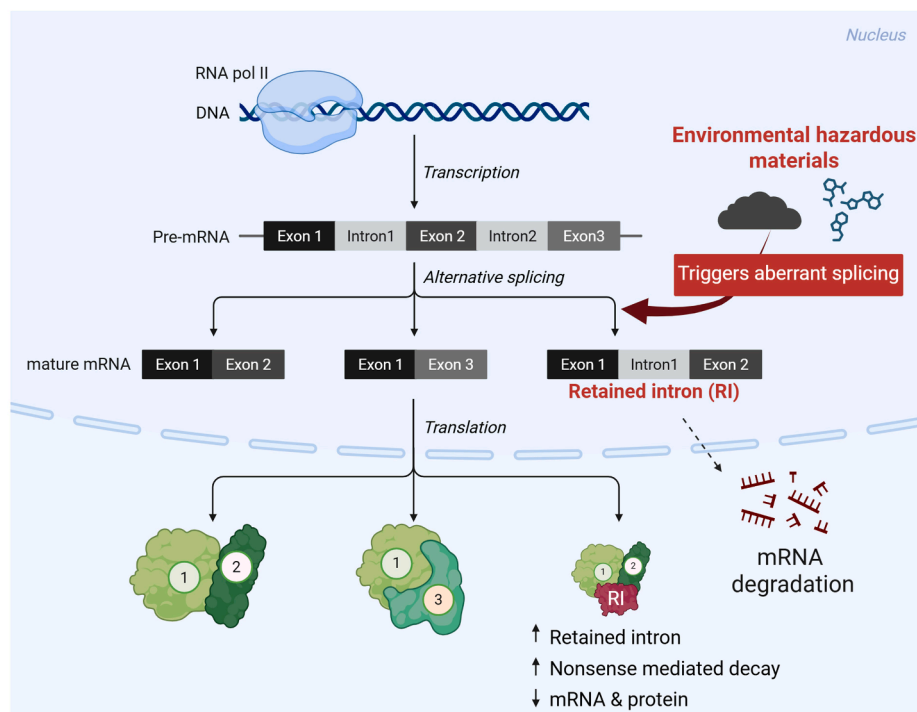
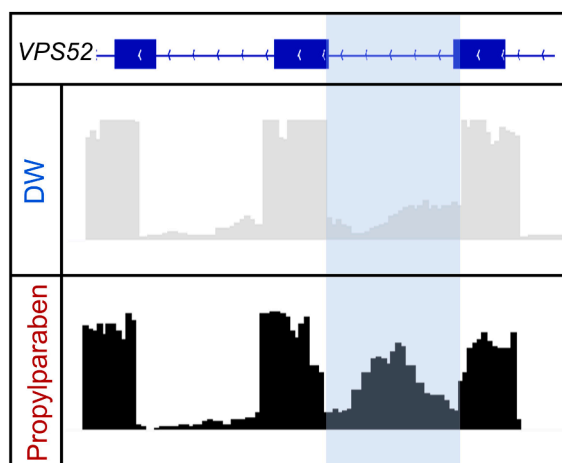
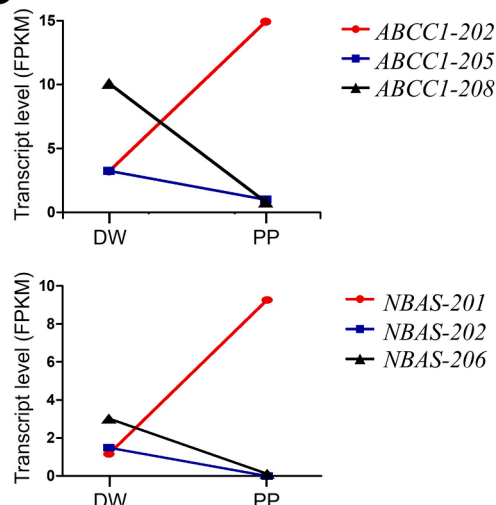
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Fig. 3. Environmental exposure modulates alternative splicing with a focus on RI events. A) Schematic overview of how environmental toxicants disrupt normal co-transcriptional splicing. Upon exposure, splicing fidelity is impaired, resulting in aberrant RI. These RI-containing transcripts frequently harbor premature stop codons, leading to NMD, decreased transcript stability, and reduced protein synthesis. B) Genome browser view of RNA-seq data showing a representative RI event in the *VPS52* gene in HepG2 cells treated with propylparaben. The highlighted intronic region (blue shaded regions) displays increased read accumulation in the propylparaben-treated group compared to DW (distilled water) control, indicating enhanced intron retention under chemical exposure. C) Isoform-specific expression analysis of the *ABCC1* and *NBAS* genes illustrates how alternative splicing leads to differential regulation of individual transcript isoforms. Upon propylparaben exposure, expression of *ABCC1-202* and *NBAS-201* is markedly upregulated, whereas *ABCC1-205*, *ABCC1-208*, *NBAS-202*, and *NBAS-206* are downregulated. This highlights that toxicant-induced splicing disruption does not merely alter total gene expression but selectively modulates the abundance of specific transcript isoforms in a context-dependent manner. Created with BioRender.com.

validate findings across large, diverse populations.

5.1. Dose-response relationships in epigenetic alterations

Understanding the dose-response dynamics of epigenetic changes is essential for the validation of exposure biomarkers and the development of predictive toxicological models. While many toxicants show monotonic, concentration-dependent shifts in DNA methylation or non-coding

RNA expression, others display non-linear or biphasic responses, reflecting the complex regulation of the epigenome. For instance, bisphenol A and other endocrine disruptors frequently exhibit inverted U-shaped or low-dose effects due to receptor saturation, feedback activation of DNMTs and HDACs, or hormetic cellular adaptation [48,87, 91]. Similarly, cadmium and arsenic induce global hypomethylation at lower doses but hypermethylation of tumor-suppressor genes at higher exposures, suggesting threshold-dependent switching of epigenetic

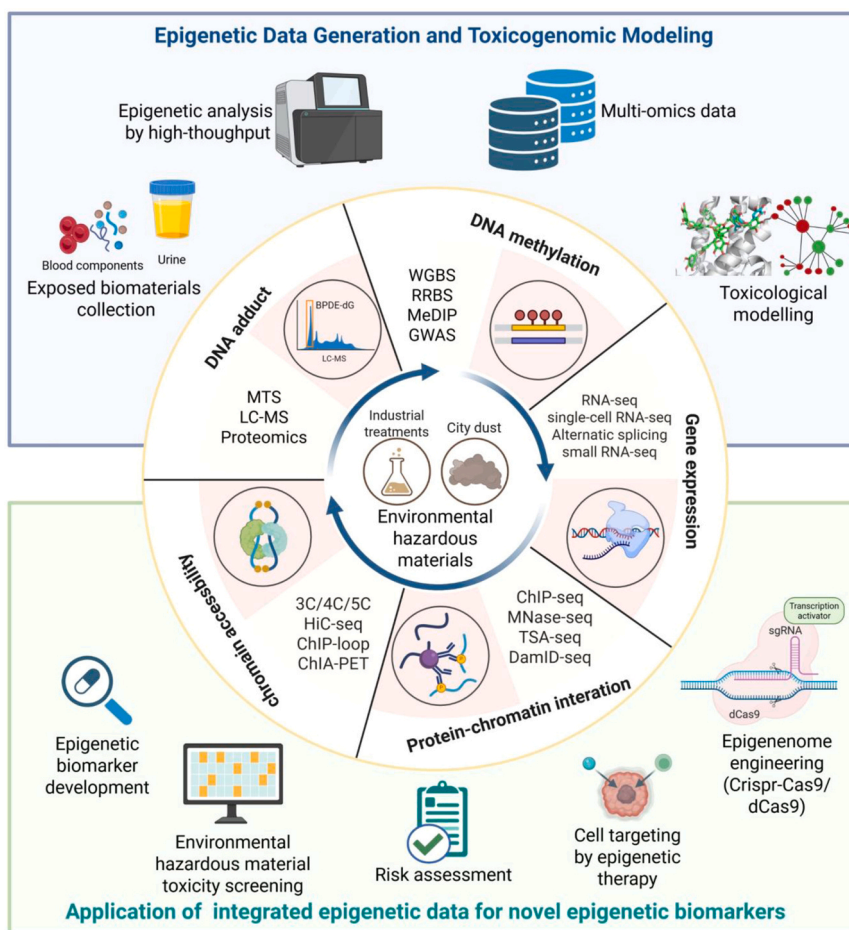


Fig. 4. High-throughput sequencing technologies for the identification of epigenetic biomarkers. Biological specimens such as blood and urine are collected from environmentally exposed individuals and subjected to high-throughput multi-omics analysis. Technologies including whole-genome bisulfite sequencing (WGBS), reduced representation bisulfite sequencing (RRBS), methylated DNA immunoprecipitation (MeDIP), RNA sequencing (RNA-seq), single-cell RNA-seq, ChIP-seq, MNase-seq, ATAC-seq, and LC-MS-based proteomics enable comprehensive profiling of DNA methylation, histone modifications, chromatin structure, gene expression, non-coding RNA activity, and DNA adducts. Integration of these datasets through computational toxicogenomic modeling allows for the identification of early-stage, exposure-sensitive epigenetic alterations. These findings support a range of downstream applications including biomarker discovery, environmental toxicity screening, risk assessment, epigenome editing (e.g., CRISPR-dCas9), and targeted cell-based interventions. Created with BioRender.com.

states [140,142]. These observations highlight that epigenetic biomarkers must be interpreted within a dynamic dose–response framework that accounts for non-monotonic and context-dependent patterns of environmental exposure [4,6]. For biomarker validation, this implies that quantitative assays should include multiple exposure levels to capture potential inflection points, low-dose plateaus, or biphasic responses, rather than relying on single-dose extrapolation. In risk modeling, incorporating such non-linear epigenetic trajectories into exposure–response curves can enhance the precision of threshold estimation and improve the prediction of long-term health outcomes. In addition to dose–response complexity, the temporal persistence of epigenetic alterations represents another key determinant of their reliability as exposure biomarkers.

5.2. Persistence and stability of epigenetic marks

A key determinant of the biomarker utility of epigenetic alterations is their persistence following exposure cessation. Numerous studies have shown that environmentally induced DNA methylation changes, and, in some cases, specific histone methylation marks, remain detectable long after the initiating exposure, consistent with a form of molecular “memory.” For instance, arsenic- and lead-associated methylation signatures persist in accessible biospecimens such as blood, buccal swabs, and cord blood well beyond the exposure period. Likewise, smoking

leaves durable methylation imprints at sentinel loci (e.g., *AHRR*, *F2RL3*), which are still evident years after cessation [257,258]. Prenatal and early-life exposure to air pollutants has similarly been linked to persistent methylation changes extending into childhood. In contrast, other epigenetic changes, particularly histone acetylation and stress-responsive miRNA programs, appear more labile and reversible, often fluctuating with tissue turnover or short-term physiological adaptation. This heterogeneity underscores that the temporal dynamics of epigenetic marks are highly context- and layer-dependent: DNA methylation and select histone methylation states are generally more stable and suited for long-term exposure assessment, while dynamic marks may serve as indicators of recent or reversible changes.

From a biomarker development perspective, these differences have practical implications. Assays should incorporate multiple exposure levels and longitudinal time points to distinguish transient responses from persistent molecular imprints. Modeling non-monotonic or time-dependent trajectories can enhance risk prediction, particularly in the context of chronic or cumulative exposure.

5.3. Limitations, validation, and comparison with traditional biomarkers

Epigenetic biomarkers hold strong promises for environmental exposure assessment and disease risk prediction, yet several limitations constrain their broader applicability. Key challenges include

pronounced tissue and cell-type specificity, temporal variability (mixtures of persistent and transient changes), and susceptibility to confounding by age, inflammation, smoking, and medication use. Technical variability across platforms (e.g., arrays vs. whole-genome bisulfite sequencing), preprocessing pipelines, and limited cross-tissue consistency further reduce reproducibility. In parallel, causal attribution remains difficult, as epigenetic changes may reflect exposures, mediate biological responses, or emerge secondarily as disease consequences. These constraints highlight the need for harmonized quality control, longitudinal sampling, and multi-cohort validation to enhance interpretability and translational relevance.

Despite these limitations, epigenetic biomarkers offer several advantages over conventional exposure indicators such as proteins or metabolites. Traditional biomarkers often lack sensitivity at environmentally relevant doses and may respond non-specifically to physiological or behavioral stressors. In contrast, locus-specific DNA methylation and chromatin-associated RNA signatures provide gene- and pathway-resolved readouts that respond sensitively to low-dose exposures and are mechanistically anchored in cellular stress-response programs. These signals often persist beyond the immediate exposure window, capturing both acute and cumulative effects.

Validated examples include hypomethylation at *AHRR* and *F2RL3*, which serve as robust markers of tobacco exposure and predict cardiovascular disease and mortality outcomes [257,258], as well as reproducible methylation signatures associated with air pollution that track cardiometabolic trajectories across multiple cohorts [167,168]. With standardized protocols, rigorous confounder control, and external cohort validation, epigenetic biomarkers represent a sensitive and mechanism-based framework for advancing precision environmental health.

5.4. Reversibility and translational potential of epigenetic alterations

The reversibility of environmentally induced epigenetic changes is a critical factor for both biomarker development and therapeutic translation. Unlike fixed genetic mutations, many epigenetic marks, particularly DNA methylation and histone modifications, retain a degree of plasticity and may be modifiable through environmental, behavioral, or pharmacologic interventions. This dynamic nature enhances their value not only as historical indicators of exposure but also as potential endpoints to track molecular recovery. Accumulating evidence suggests that methylation alterations linked to air pollution and metals decline after improved air quality or removal from exposure, albeit at variable rates. Nutritional and behavioral interventions also play a role. Supplementation with methyl donors (e.g., folate, vitamins B6/B12, choline) has been shown to restore methylation balance and buffer against pollutant-induced epigenetic shifts [221,223]. Lifestyle modifications, such as physical activity, smoking cessation, and caloric restriction, have demonstrated the ability to favorably remodel epigenetic profiles, particularly in inflammation- and metabolism-related pathways. At the pharmacological level, epigenetic enzyme modulators such as DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors have been used to restore expression of silenced genes in preclinical models. These therapies offer proof of principle that chromatin structure and gene expression are modifiable, although concerns remain regarding their specificity, safety, and off-target effects in environmental prevention settings. Importantly, the degree of reversibility varies across molecular layers. Histone acetylation and certain microRNAs respond rapidly to changes in exposure or cell state, while DNA methylation and histone methylation in low-turnover tissues (e.g., brain, placenta) tend to exhibit long-term persistence. Therefore, interpretation of reversibility requires attention to the molecular target, tissue kinetics, and timing of intervention. In this context, epigenetic biomarkers serve a dual function: (i) as sensitive recorders of prior exposure and (ii) as actionable endpoints for monitoring the efficacy of interventions aimed at restoring molecular homeostasis. This

reversibility dimension positions toxicoepigenomic signatures not only as diagnostic tools but also as key components in prevention and recovery frameworks within environmental health.

6. Conclusions

Environmental exposures influence health outcomes not only through direct toxic effects but also by reshaping the epigenome in complex and often long-lasting ways. This review highlights the expanding field of toxicoepigenomics, emphasizing how environmental toxicants—including EDCs, heavy metals, PAHs, and air pollution—disrupt epigenetic regulation through mechanisms such as DNA methylation, histone modifications, non-coding RNA expression, and emerging phenomena like RI.

By synthesizing evidence across molecular layers and pollutant classes, we underscore that epigenetic dysregulation serves as both a mediator and a marker of environmental toxicity. The review also identifies several epigenetic signatures—including LINE-1 hypomethylation, RAR β 2 hypermethylation, miR-21 downregulation, and epigenetic clock acceleration—as promising biomarkers for exposure and early disease risk assessment. Importantly, we introduce RI as a novel and underexplored post-transcriptional epigenetic signature with emerging relevance in environmental health research. This expands the conventional view of epigenetic toxicology and paves the way for integrative multi-omics frameworks that capture regulatory complexity. Despite these advances, key challenges remain. The context-specificity, reversibility, and inter-individual variability of epigenetic responses complicate biomarker standardization and interpretation. Moreover, many findings rely on *in vitro* or animal models, necessitating validation in large-scale, longitudinal human cohorts. There is also a need for improved exposure quantification, high-resolution single-cell analysis, and more robust causal inference methods.

Looking ahead, integrating epigenetic biomarkers into environmental surveillance, risk assessment, and precision prevention strategies holds significant promise. Efforts to harmonize methods, validate cross-species conservation, and assess modifiability of epigenetic marks will be critical for translating toxicoepigenomic insights into actionable public health interventions.

Environmental Implication

Environmental toxicants can disrupt the epigenome at exposure levels relevant to real-world settings, leading to altered gene expression and disease susceptibility. This review highlights multilayered epigenetic changes—including DNA methylation, histone modifications, and non-coding RNAs—induced by hazardous chemicals under environmentally realistic conditions. These mechanistic insights support the development of epigenetic biomarkers for environmental health monitoring and risk assessment.

CRediT authorship contribution statement

Ji-Young Kim: Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation, Conceptualization.
Jung-Woong Kim: Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

Data will be made available on request.

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