©IDOSR PUBLICATIONS

ISSN: 2579-0811

International Digital Organization for Scientific Research IDOSR JBBAF2026/101
IDOSR JOURNAL OF BIOCHEMISTRY, BIOTECHNOLOGY AND ALLIED FIELDS 11(1):31-35, 2026.
https://doi.org/10.59298/IDOSR/JBBAF/2026/1023135

Environmental Endocrine Disruptors and Epigenetic Toxicity: Linking Molecular Modifications to Transgenerational Health Impacts

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ABSTRACT

Endocrine-disrupting chemicals (EDCs) are widespread environmental contaminants capable of mimicking, antagonizing, or altering endogenous hormone signaling. Beyond classical toxicological endpoints, a growing body of evidence shows that EDCs induce epigenetic modifications - heritable changes in gene expression that do not involve alterations to DNA sequence. These include DNA methylation, histone modification, chromatin remodeling, and altered expression of non-coding RNAs. Such changes may persist across developmental stages and, in some cases, be transmitted across generations, amplifying health consequences long after initial exposure. This review synthesizes current knowledge of the mechanisms by which common EDCs such as bisphenols, phthalates, pesticides, heavy metals, and persistent organic pollutants exert epigenetic toxicity. We explore the molecular pathways implicated, highlight evidence from animal and human studies, and examine critical periods of susceptibility including fetal development, puberty, and gametogenesis. Particular attention is paid to transgenerational inheritance of altered epigenetic marks and the associated risks for endocrine, reproductive, neurodevelopmental, and metabolic disorders. Finally, we discuss methodological challenges, emerging biomarkers, and implications for risk assessment and regulatory policy. Understanding the interplay between EDC exposure and epigenetic programming provides a vital framework for preventing long-term and transgenerational health impacts in the Anthropocene.

Keywords: endocrine disruptors, epigenetics, DNA methylation, transgenerational inheritance, reproductive health

INTRODUCTION

Endocrine-disrupting chemicals (EDCs) are a diverse group of exogenous substances that can interfere with the synthesis, secretion, transport, binding, or action of natural hormones in the body [1]. Even at very low concentrations, these compounds have the capacity to disturb finely regulated endocrine signaling networks. Common EDCs include industrial by-products, pesticides, plastic-derived compounds such as bisphenols and phthalates, pharmaceuticals, and certain heavy metals including cadmium and arsenic [2]. Their widespread distribution in food, water, air, and consumer products has raised global concern, particularly because exposure often begins during sensitive life stages such as fetal development and childhood [3]. The health consequences associated with EDC exposure are wide-ranging. Experimental and epidemiological studies link them to reproductive disorders, altered sexual development, metabolic dysfunctions such as obesity and diabetes, neurobehavioral changes, and increased risk of hormone-related cancers [4]. Historically, the evaluation of EDC toxicity focused largely on overt clinical outcomes or organ-specific pathology after acute or chronic exposure [5]. However, research over the past two decades has revealed that EDCs can induce subtler yet profound changes at the molecular level, particularly through disruption of epigenetic programming. Epigenetic mechanisms, including DNA methylation, histone modification, chromatin remodeling, and regulation by non-coding RNAs, determine how genes are expressed without altering the underlying DNA sequence [6]. These mechanisms are especially active during development, when environmental exposures can permanently shape gene expression profiles. Because many epigenetic marks are mitotically and, in some cases, meiotically heritable, their disruption raises the possibility of health effects that persist long after exposure and may even extend to subsequent generations.

2. Epigenetic Mechanisms Relevant to Endocrine Disruption

2.1 DNA methylation

DNA methylation, primarily at cytosine residues in CpG dinucleotides, regulates gene expression by influencing transcription factor binding and chromatin accessibility. Several EDCs have been shown to alter DNA methylation patterns [7]. For instance, prenatal bisphenol A (BPA) exposure leads to hypomethylation of estrogen receptor promoters, increasing receptor sensitivity. Similarly, phthalates and organochlorine pesticides induce aberrant methylation in imprinted genes critical for fetal growth and reproductive development [8].

2.2 Histone modifications

Histone tails undergo covalent modifications, including acetylation, methylation, phosphorylation, and ubiquitination, which collectively shape chromatin structure and transcriptional outcomes [9]. EDCs such as vinclozolin and diethylstilbestrol (DES) disrupt histone methylation marks in germ cells, reprogramming chromatin organization. Altered histone modifications have been linked to impaired spermatogenesis, ovarian dysfunction, and increased susceptibility to cancers [10].

2.3 Non-coding RNAs

MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) regulate gene expression post-transcriptionally and interact with epigenetic machinery [11]. EDC exposure modifies miRNA profiles that govern endocrine signaling pathways. For example, BPA exposure alters miRNAs regulating insulin signaling, contributing to metabolic dysregulation. Persistent disruption of non-coding RNA networks may serve as a mechanistic link between environmental exposure and systemic disorders [12].

2.4 Chromatin remodeling

ATP-dependent chromatin remodelers orchestrate nucleosome positioning and accessibility. Emerging evidence suggests that EDCs impair chromatin remodeling complexes, disrupting normal developmental programming. Such disruptions may compromise embryonic development and predispose offspring to disease susceptibility [13].

3. Critical Windows of Susceptibility

3.1 Embryonic and fetal development

Embryogenesis represents one of the most vulnerable stages of life, as it involves extensive cellular differentiation and genome-wide epigenetic reprogramming [14]. During this period, epigenetic marks such as DNA methylation and histone modifications are erased and re-established to establish developmental gene expression programs. Exposure to endocrine-disrupting chemicals (EDCs) during pregnancy can interfere with these processes, leading to permanent alterations in gene regulation [15]. For example, maternal exposure to bisphenol A (BPA) has been linked to changes in DNA methylation of imprinted genes, resulting in altered growth trajectories and increased risk of obesity and metabolic syndrome in offspring. Similarly, exposure to diethylstilbestrol (DES) during fetal life has been associated with structural abnormalities of the reproductive tract and a higher lifetime risk of hormone-related cancers [16]. These findings highlight the developmental origins of health and disease (DOHaD) paradigm, in which early-life EDC exposure imprints long-lasting effects on health outcomes.

3.2 Puberty and adolescence

Puberty is another critical window characterized by intense endocrine activity and epigenetic remodeling that orchestrates sexual maturation [17. EDC exposure during this stage can disrupt hormone signaling pathways, delay or accelerate pubertal onset, and impair fertility later in life. For instance, phthalate exposure has been associated with altered timing of menarche in girls, while pesticides and heavy metals have been linked to reduced testosterone levels and impaired spermatogenesis in boys [18]. Because puberty is also a sensitive period for brain development, epigenetic disruption at this stage may predispose individuals to neurobehavioral disorders, including anxiety and depression.

3.3 Germline transmission

A particularly concerning aspect of EDC exposure is its ability to affect germ cells sperm and oocytes through epigenetic modifications that can be stably inherited [19]. Normally, epigenetic marks in germ cells are erased and reprogrammed each generation, but some EDC-induced alterations escape this reprogramming, leading to epimutations that persist across multiple generations. Animal studies with compounds such as vinclozolin, dioxins, and BPA have demonstrated transgenerational reproductive defects, metabolic dysfunction, and behavioral abnormalities in descendants up to the F3 or F4 generation [20]. This phenomenon underscores the potential for EDCs to exert health impacts far beyond the directly exposed population, raising significant concerns for public health and regulatory policy.

4. Evidence from Animal and Human Studies

4.1 Animal models

Experimental studies in animals have provided some of the most compelling evidence linking endocrine-disrupting chemicals (EDCs) to persistent epigenetic alterations [21]. Rodents, in particular, have been widely used to demonstrate how developmental exposure to EDCs can reprogram the epigenome in ways that persist throughout the life course and across generations. For example, exposure to vinclozolin, a fungicide with anti-androgenic

properties, in pregnant rats leads to reduced sperm counts, decreased fertility, and increased tumor susceptibility in the male descendants of exposed animals [22]. These outcomes are strongly associated with altered DNA methylation patterns in germline cells, which are transmitted through the paternal lineage to subsequent generations. Bisphenol A (BPA), one of the most studied EDCs, has also been shown to disrupt neuroendocrine pathways in rodents. Prenatal BPA exposure alters DNA methylation and histone modifications in the hypothalamus, leading to changes in neuropeptide expression that regulate behavior, stress responses, and energy balance [23]. These molecular changes manifest as anxiety-like behaviors, altered sexual differentiation of the brain, and metabolic disturbances in offspring. Similarly, exposure to diethylstilbestrol (DES) in animal models produces epigenetic alterations in reproductive tissues, predisposing offspring to uterine and testicular abnormalities [24]. Fish models have also proven valuable, as their rapid development and transparent embryos allow direct observation of epigenetic changes during early development. Studies in zebrafish exposed to phthalates and polychlorinated biphenyls (PCBs) show disrupted DNA methylation in genes controlling growth and reproduction, with effects persisting across generations [25]. Together, these animal studies establish a mechanistic link between EDC exposure, epigenetic modification, and adverse health outcomes.

4.2 Human epidemiological findings

In humans, the picture is more complex due to heterogeneous exposure profiles, genetic diversity, and confounding lifestyle factors [26]. Nonetheless, mounting evidence suggests that EDCs exert epigenetic effects that contribute to disease risk. Maternal exposure to BPA, phthalates, and pesticides has been associated with altered DNA methylation in cord blood, placental tissue, and fetal germ cells. These changes have been linked to variations in birth weight, disrupted neurodevelopment, and increased risk of obesity during childhood.

One well-documented example is prenatal exposure to DES, prescribed to prevent miscarriage in the mid-20th century [27]. Daughters of exposed women (the "DES daughters") exhibit elevated risks of reproductive tract abnormalities and breast cancer, while emerging data suggest epigenetic alterations in estrogen-responsive genes may underlie these effects. Similarly, populations exposed to persistent organic pollutants (POPs) such as dioxins show evidence of long-term reproductive and immune dysfunction, potentially mediated by epigenetic disruption [28].

Epigenome-wide association studies (EWAS) are increasingly used to investigate the relationship between environmental exposures and DNA methylation patterns at the genome level. While causality remains difficult to prove, these studies consistently identify epigenetic signatures associated with EDC exposure. For example, prenatal phthalate exposure has been correlated with hypomethylation in genes linked to endocrine function and neurobehavioral regulation [29].

5. Transgenerational Health Impacts

The concept of epigenetic inheritance suggests that EDC exposure can influence not only directly exposed individuals but also their descendants [30]. Evidence from both animal and human studies supports the idea that altered epigenetic marks in germ cells can persist through reprogramming events, giving rise to heritable disease risks [31]. Documented health impacts are wide-ranging. Reproductive dysfunction includes reduced sperm quality, impaired spermatogenesis, and ovarian follicle depletion. Neurodevelopmental disorders manifest as cognitive deficits, impaired social behaviors, and altered stress reactivity [32]. Metabolic syndromes such as obesity, insulin resistance, and type 2 diabetes have been linked to disrupted energy balance and altered epigenetic regulation of metabolic genes. Additionally, increased susceptibility to hormone-sensitive cancers including breast, prostate, and testicular cancers- has been observed in descendants of exposed populations.

These findings challenge traditional risk assessment frameworks, which focus on direct exposure and immediate toxicity. The potential for epigenetic inheritance underscores the need for regulatory approaches that account for long-term, transgenerational effects of EDCs on human health.

CONCLUSIONS

Environmental endocrine disruptors represent a unique toxicological challenge due to their capacity to induce epigenetic modifications that persist across life stages and generations. Mechanistic evidence highlights DNA methylation, histone modifications, and non-coding RNAs as key mediators of EDC-induced toxicity, with impacts spanning reproductive, neurodevelopmental, metabolic, and oncogenic outcomes. Integrating epigenetic insights into research, regulation, and risk communication will be vital to safeguarding future generations from the silent but lasting consequences of endocrine disruption.

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CITE AS: Mwende Wairimu G. (2026). Environmental Endocrine Disruptors and Epigenetic Toxicity: Linking Molecular Modifications to Transgenerational Health Impacts. IDOSR JOURNAL OF BIOCHEMISTRY, BIOTECHNOLOGY AND ALLIED FIELDS 11(1):31-35. https://doi.org/10.59298/IDOSR/JBBAF/2026/1023135