IMPLICATIONS OF PLASTIC-DERIVED ENDOCRINE DISRUPTORS ON HUMAN HEALTH

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ABSTRACT

Endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), bisphenol S (BPS), phthalates, and micro- and nanoplastics, present substantial environmental and health hazards because of their potential to disrupt hormonal systems. Micro- and nanoplastics can release EDCs that disrupt reproductive and developmental processes, potentially affecting future generations. BPA, a common plasticizer and resin component, mimics estrogen and disrupts thyroid hormone metabolism, contributing to obesity, diabetes, and cardiovascular issues. BPS, a BPA substitute, exhibits similar endocrine-disrupting properties and persists longer in the environment. Phthalates, which are widely used as plasticizers, are associated with reproductive issues, metabolic conditions, and developmental issues in children. Combined exposure to multiple EDCs can amplify health risks, underscoring the need for further research on the synergistic impacts of these chemicals. This review underscores the urgent need for effective regulatory measures and further investigations into the health impacts of EDCs to mitigate their harmful impacts on the health of humans and the environment.

Keywords: Endocrine-disrupting chemicals; human health; bisphenol A; plastic

INTRODUCTION

One could argue that plastics are indispensable in today's world. Since its invention, many industries have been transformed due to its adaptability, sturdiness, and affordability. Plastic has become an integral component of everything we use daily, from electrical devices to medical equipment, vehicle parts, and packaging (Evode et al., 2021). Given how ubiquitous they are in today's world—home appliances, building supplies, kids' toys, packaging materials, and so forth—it is difficult to argue against them. According to Lattanzio (2018), the production of

plastic has increased more than twentyfold since the 1960s, reaching 322 million metric tons (Mt) in 2015. By 2035, it is predicted to have more than doubled in 2015, and by 2050, it will have quadrupled. The chemical structures of plastic materials vary widely, and their qualities can differ depending on how they are processed, whether they contain additives, and how they combine with other polymers (Guerreiro et al., 2018).
An extensive variety of additives, including stabilizers, plasticizers, fillers, flame retardants, lubricants, colorants, and agents to prevent sticking, have been developed to increase their functionality. Additionally, research suggests that chemicals such as plasticizers (softeners), UV stabilizers, and antioxidants are crucial for protecting against UV-induced or oxidative degradation, increasing material softness, and enhancing overall aesthetics.

The process of making plastic begins with the extraction of raw materials, mostly crude oil and natural gas. These nonrenewable resources undergo several chemical reactions to create several kinds of plastics, each of which is suitable for a particular use (Sharma et al., 2023). Owing to their nonbiodegradable nature and substantial contribution to environmental degradation, plastics are often frowned upon (Ilyas et al., 2018). Plasticizers, flame retardants, stabilizers, and colorants are just a few of the compounds found in plastics that can leak into the environment and endanger public health (Luo et al., 2022). Furthermore, polymers can adsorb and accumulate toxic compounds, including persistent organic pollutants, also called POPs, and the chemicals polychlorinated biphenyls (PCBs), which may circulate in the food system chain and disrupt the environment (Luo et al., 2022). Phthalates and bisphenols are commonly added to polymers such as polycarbonate and PVC to increase their versatility, longevity, and heat resistance. Nevertheless, there is evidence connecting these compounds to detrimental health outcomes, such as aberrant development, reproductive issues, and endocrine disruption (Luo et al., 2022). Phthalates and bisphenols, which are released from plastic items, can also be referred to as endocrine disruption chemicals (EDCs) because of their ability to modify the functioning of the endocrine system or disrupt the body's hormonal signals (Kawa et al., 2021). It has been widely reported that the presence of a chemical called bisphenol A in polymers might cause problems with metabolism, hormone production, or the body's natural homeostatic balance (Yilmaz et al., 2019; Frenzilli et al., 2020; Kang et al., 2023; Vacca et al. 2024).

Reproductive activity, hormone balance, and brain development can all be affected by exposure to EDCs, especially during important developmental stages. The effects of EDCs are particularly harmful to children, newborns, and pregnant women because of the rapid growth of mothers and children and the resulting hormonal changes (Predieri et al. 2022). The widespread use of polymers in consumer products, food containers, and healthcare equipment increases human exposure to plastic additives and contaminants (Belmaker et al., 2024). Commonly used chemicals that are released into the surroundings and endanger human health and the

environment include per- and polyphluoroalkyl substances (PFASs, such as PFOS and PFOA); phthalates such as bis-(2-ethylhexyl)-phthalate (DEHP) and dibutyl-phthalate (DBP); and bisphenol A (BPA) and its analogs (BPF, BPS, BPAF, BPB) (Adamovsky et al. 2024; Belmaker et al. 2024; Hasan et al., 2025). Research has connected phthalate and bisphenol exposure to an increased risk of heart disease, diabetes, obesity, and certain cancers (Fonseca et al., 2022). Furthermore, dangers to the respiratory and digestive systems are associated with the ingestion or inhalation of airborne contaminants, tiny particles, and microplastics resulting from the manufacturing and disposal of plastics (Hasan et al., 2025). Food, air, and skin (mostly through personal care products) are the entry points for these substances into our bodies (Bi et al., 2021). Because of prolonged storage or temperature fluctuations, they may seep into food through packing materials (FSANZ, 2014; Hasan et al., 2025). During processing, certain phthalate chemicals are discharged into the atmosphere. Living close to these enterprises exposes residents more to inhalation and dermal absorption by residents. One important chemical utilized in the creation of thermal paper receipts is bisphenol A. By cutaneous absorption, contact with such receipts can expose one to such materials. Table 1 displays the most commonly produced plastic polymers as well as the EDCs derived from plastic (Hermabessiere et al., 2017; Grigore, 2017).

This review provides a comprehensive overview of the current understanding of the threat of endocrine-disrupting chemicals (EDCs) originating from plastics. It complements the existing body of literature by synthesizing information across a wide spectrum of plastic additives, from commonly discussed phthalates and bisphenols to other plasticizers, flame retardants, and stabilizers, and meticulously tracing their pathways from material to human exposure. This broad scope aligns with recent calls for a more holistic view of chemical exposures (Sheriff et al., 2025). Furthermore, the review reinforces the critical focus on vulnerable populations, such as children and women, an area of ongoing concern (Tricotteaux-Zarqaoui et al. 2024), by detailing the heightened risks during critical developmental windows. By integrating discussions on various exposure routes, diverse mechanisms of action, including epigenetic modifications, and impacts on multiple endocrine glands and reproductive health, this review provides a valuable, updated synthesis that highlights the multifaceted nature of EDC-induced health challenges.

In addition to providing a comprehensive overview, this review makes a significant contribution by delving into more nuanced and emerging aspects of EDC toxicology that are often not central to broader surveys. A key strength is its dedicated attention to the complexities of nonmonotonic dose–response (NMDR) relationships for EDCs, a critical concept that challenges traditional toxicological paradigms and has profound implications for risk assessment, an area that continues to evolve (Stathori et al. 2024). Moreover, the study distinctively emphasized the escalating threat posed by microplastics and nanoplastics, not merely as pollutants but also as potent vectors that can increase the bioavailability and toxicity of adsorbed EDCs, potentially leading to synergistic effects (Ye et al. 2025). By exploring these advanced topics, alongside a

thorough examination of EDCs' roles in the increasing prevalence of metabolic disorders such as obesity and diabetes, the review pushes beyond standard summaries to highlight critical areas for future research and regulatory consideration, thereby offering fresh perspectives on the full scope of human health implications arising from plastic-derived EDCs.

RESEARCH METHODOLOGY

The relevant studies were identified through a comprehensive review of scientific articles in various databases (Scopus, Google Scholar, Springer, Wiley, PubMed, and Web of Science), which included the MeSH terms "endocrine disruptors", "bisphenol A", "bisphenol S", "obesity", "plastics", "toxicity", and "microplastics and nanoplastics." The primary search was divided into categories: (a). Related human health ("obesity", "reproductive health", and "cancer"), (b). related to reproductive health and (c). children health. In addition, the primary search filters, which included human data and clinical trials, were used to compile and evaluate the data obtained. To further elucidate the multifaceted health implications of exposure to plastic-derived endocrine-disrupting chemicals (EDCs), the integration of evidence from meta-analyses and longitudinal studies was also reported.

PLASTIC COMPOUNDS: IMPACT ON CELLS AND METABOLISM

Persistent organic pollutants (POPs), which are hazardous to the surroundings and healthcare systems, are discharged by plastics into the water, air, and soil. Owing to the widespread use of POPs as industrial materials and consumer goods, plastics and their main constituents, such as acrylonitrile, bisphenols, phthalates, dioxins, and polychlorinated biphenyls, accumulate in living organisms (Zwierełło et al., 2020). The bioaccumulation and bioamplification of POPs are also related to their lipophilicity and hydrophobicity, which cause significant biological toxicity, such as developmental defects, metabolic diseases, cancer, and even death (Tian et al. 2022). Diabetes, inflammatory conditions, insulin resistance, neurological disorders, allergies, and cancer can all result from exposure to these POPs (Niu et al., 2024). POPs can bioaccumulate in adipose tissues and are resistant to metabolic breakdown.

Since the hypothalamic–pituitary–gonadal axis is targeted at distinct levels by various polymers and their addition, exposure to these polymers can cause endocrine activity. POPs interfere with regular endocrine processes. Throughout a fetus's key developmental stage, exposure to POPs at even low levels can have long-term effects (Trasande, 2014, Barrea et al. 2024). Worldwide, exposure to substances generated from plastics is increasingly thought to have an impact on human health, particularly the pathogenesis of programming for the development of metabolic diseases associated with the endocrine system. These substances are widely present in the environment, in foods, and in quantities that may hasten the development of metabolic diseases such as overweight and diabetes (Celik and Yesildemir, 2025).

Because the large-scale use of plastic can cause significant health problems for humans and animals (due to the chemicals in plastics or the plastics themselves), various rules and measures have been introduced. These rules aim to reduce how much plastic we use and to decrease the ways in which people and animals come into contact with potentially harmful plastics (Belmaker et al. 2024; Li et al. 2024). However, substances such as bisphenol A and other endocrine disruptors, to which humans are normally exposed, may have an effect even at low levels (at tolerated daily intake, or TDI) (Vandenberg, 2014). Furthermore, these substances may persist and accumulate in the human body gradually, which could result in a variety of negative consequences, such as endocrine disruption leading to reproductive and developmental problems, an increased risk of certain cancers, immune system deficiencies, neurobehavioral disorders, and metabolic disorders such as diabetes and obesity (Yilmaz et al., 2019). According to recent studies, these toxic exposures may have long-lasting effects during embryonic life (Basak et al., 2020; Peivasteh-Roudsari et al. 2023; Li et al. 2024).

ENDOCRINE DISRUPTING CHEMICALS

Endocrine-disrupting chemicals are also known as endocrine-disrupting compounds (EDCs). Endocrine disruption occurs when external agents, known as endocrine-disrupting chemicals (EDCs), interfere with the body's hormonal system (Ghosh et al., 2022). "An external agent that affects the formation, release, transport, metabolic processes, linking action, or removal of naturally occurring blood-borne chemicals that accumulate in our bodies and are accountable for disrupting homeostasis, the process of reproduction, and growth-related process" is how the U.S. Environmental Protection Agency (EPA) defines EDCs (Diamanti-Kandarakis et al. 2009). Among the approximately 85,000 compounds manufactured, more than a thousand are regarded as EDCs (Gore et al. 2014). Soaps, plastic containers, polyethylene chloride tubes, personal care products, and toothpaste are the main products that include these kinds of chemicals. Through the receptor-mediated transmission of signaling pathways, receptors for estrogen (ERs) and receptors for androgen, which control reproductive activities, are particularly affected by endocrine-disrupting chemicals (EDCs). In particular, these substances bind to endocrine receptors to disrupt hormonal production and deterioration. Endocrine disruptors are extremely diverse in nature (Ghosh et al., 2022, Macedo et al. 2023). EDCs can enter the body through breathing, lactation, the birth canal, etc. By activating, inhibiting, and altering hormonal processes, these chemical substances cause several clinical consequences, including diabetes, fertility problems, obesity, neurodegenerative conditions, coronary heart disease, and thyroid malfunction (Ghosh et al., 2022, Macedo et al. 2023). According to Picone and Paolillo (2013), there are three main means by which endocrine disruptors enter the body: through food, skin contact, and inhalation. POPs are ECDs that do not undergo metabolism and are found in the environment for several years to decades at

significant concentrations. The composition of majorly synthesized and naturally occurring endocrine disruptors is depicted in Figure 1.

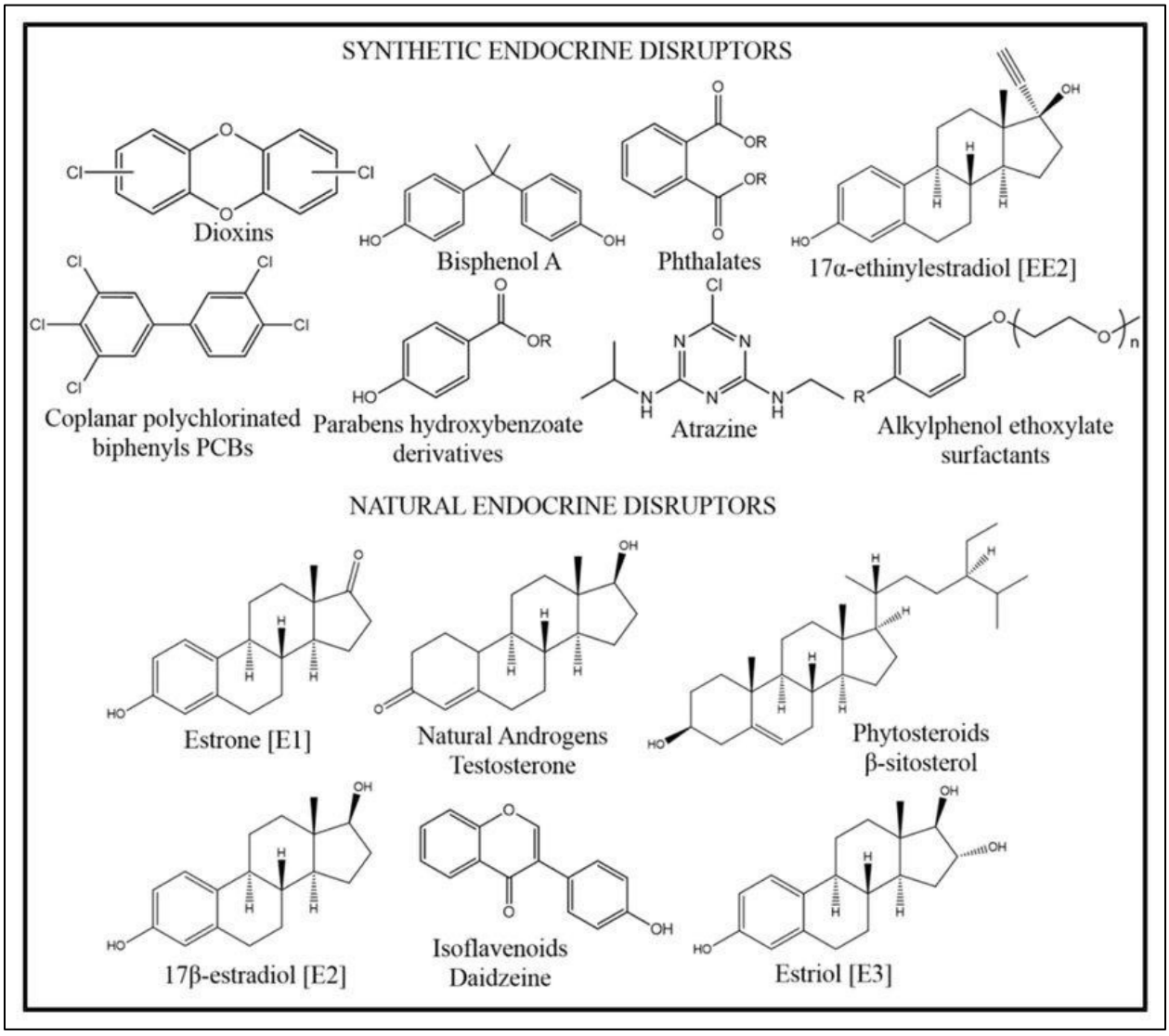

Figure 1: Structures of common synthetic and natural endocrine disruptors.

EDCS'S ACTION MODE

The mode of action of EDCs involves endocrine function, as reported by Zoeller et al. (2012); unhealthy or detrimental endocrine-mediated activity, as reported by Gore et al. (2015); and the causal connection between endocrine activity and substances in exposed subjects, as reported by Mnif et al. (2011), EFSA (2013), and Slama et al. (2016). The European Safety Authority (EFSA) claims that by attaching to hormone receptors or regulating the synthesis of specific genes, EDCs may interfere with the functioning of the endocrine system. Moreover, epigenetic changes, including histone modifications and DNA methylation and/or acetylation,

seem to be linked to pathways related to endocrine disruption (Zama and Uzumcu, 2010; Baldi and Mantovani, 2008).

EDCs primarily target receptors called nuclear hormone receptors (NHRs) (Combarnous and Nguyen, 2019). Therefore, endocrine-disrupting substances can imitate the action of naturally occurring hormones by functioning as antagonists or agonists (Monneret, 2017; Lubrano et al., 2013; Balaguer et al., 2017. Nuclear hormone receptors (NHRs) are stimulated by hormonal substances and can have a lasting effect on specific cells. Examples of NHRs include constitutive androstane receptors, retinoid X receptors, glucocorticoid receptors, thyroid hormone receptors, progesterone receptors, estrogen receptors, and mineralocorticoid receptors (Sever and Glass, 2013). Among the NHRs are the constitutive androstane receptor, retinoid X receptor, thyroid hormone receptor, progesterone receptor, estrogen receptor, glucocorticoid receptor, and mineralocorticoid receptor. In the end, EDCs can link to, contact, or stimulate hormone receptors; counteract hormone receptors; alter hormone synthesis and receptor activity; transfer through the cell membrane, hormone transmission levels, metabolic processes, and transmission of signals in hormone-responsive cells; and cause epigenetic changes in hormone-responsive cells (Schug et al., 2011; De Coster and Van Larebeke, 2012).

EDCs induce epigenetic changes through DNA methylation, histone modifications, and noncoding RNA dysregulation, altering the expression of genes critical for development, reproduction, and metabolism (Akanji et al. 2025). Changes in DNA methylation are an important mechanism in which EDCs such as bisphenol A (BPA) and phthalates modify methylation patterns at gene promoters, silencing tumor suppressors (e.g., hypermethylation of BRCA1 by BPA) or activating stress–response genes (e.g., hypomethylation of Fkbp5 in hippocampal neurons). Prenatal exposure to BPA, for example, reduces methylation at estrogen receptor (ERα) promoters, disrupting the signaling pathway between the hypothalamus, pituitary gland, and ovaries and causing reproductive problems that can be passed down through generations (Buha et al. 2022). Similarly, organotins change the methylation patterns of metabolic genes such as PPARγ, promoting adipogenesis and obesity. Histone modifications are equally targeted in which vinclozolin exposure increases H3K9 acetylation at stress-response genes, whereas heavy metals such as arsenic deplete methyl donors (e.g., S-adenosyl methionine), altering histone methylation. These changes persist across cell divisions, priming tissues for dysfunction even after EDC exposure ends.

Noncoding RNAs further amplify EDC effects. MicroRNAs (miRNAs), such as miR-155 and miR-210, are dysregulated by EDCs such as phthalates and dioxins, disrupting placental angiogenesis and immune tolerance. For example, BPA upregulates miR-34a, which silences SIRT1 to impair mitochondrial function and metabolic homeostasis (Singh, 2025).

Transgenerational effects occur when epigenetic marks in the germline (sperm and egg cells) evade the reprogramming process during embryogenesis. For example, paternal exposure to dioxins alters sperm miRNA profiles, predisposing offspring to metabolic syndrome, whereas maternal trenbolone exposure in fish induces heritable DNA hypomethylation at steroidogenic genes (CYP19A1), reducing fertility in unexposed F2 generations. Recent studies emphasize that these epigenetic "memory" effects are dose-dependent and sex specific, with female offspring often showing heightened sensitivity to maternal EDC exposure (Singh, 2025, Rani et al. 2025, Akanbi et al. 2025). These findings highlight the urgent need to include epigenetic markers to assess the risks posed by EDCs. The mechanism of action of endocrine-disruptive chemicals is shown in Figure 2.

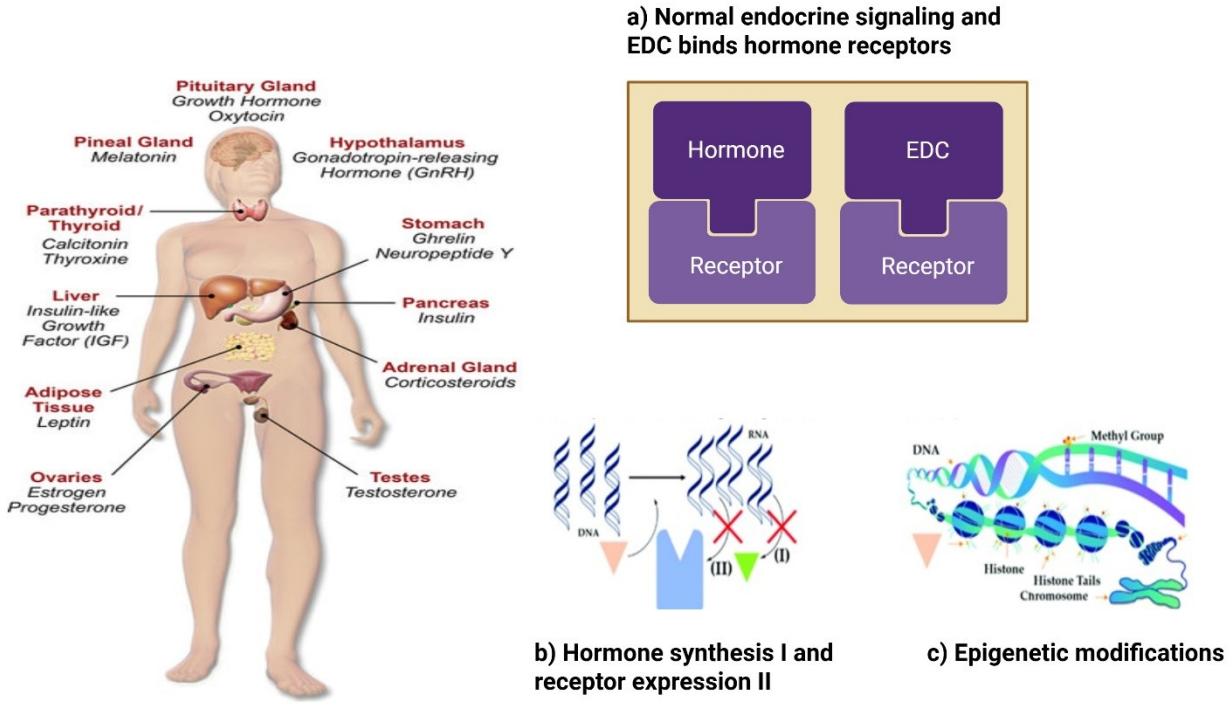

Figure 2: Schematic representation of the main of mechanism of actions of endocrine disruptors chemicals: (a) normal endocrine signaling and EDC binding to hormone receptor leading to cellular response; (b) alter hormone synthesis or receptor expression; (c) induce epigenetic modifications. Created from Biorender.com

MOLECULAR MECHANISM OF EDCS IN HORMONE RECEPTORS AND EPIGENETIC EFFECTS

Endocrine-disrupting chemicals (EDCs) interfere with hormonal systems through multifaceted molecular mechanisms; target nuclear hormone receptors such as PPARγ, AhR, ER, and TR; disrupt signaling pathways such as Nrf2; and induce epigenetic alterations. PPARγ

activation by organotin compounds (e.g., triphenyltin) promotes adipogenesis via ligand-binding domain interactions, whereas AhR agonists such as dioxins dysregulate xenobiotic metabolism and inflammation through transcriptional activation and cross-talk with ERs (Hall and Greco, 2020). Estrogen receptors (ERα/ERβ) are modulated by EDCs such as bisphenol A (BPA) and genistein, which alter genomic pathways (e.g., ERE-mediated transcription with coactivator recruitment) and nongenomic pathways (e.g., rapid PI3K/AKT activation via membrane ERs) (Lee et al., 2013, Hall and Greco, 2020). The Nrf2/ARE pathway, which is activated by atrazine to mitigate oxidative stress in placental cells, becomes overwhelmed under chronic exposure, exacerbating cellular damage. Epigenetically, EDCs such as BPA induce transgenerational effects by reducing DNA methylation at stress-response genes (e.g., *Fkbp5*) and promoting heritable ERα silencing in hypothalamic neurons, whereas genistein and vinclozolin alter histone acetylation and methylation patterns, disrupting steroidogenesis and tumor suppressor expression (Singh, 2025). These interconnected mechanisms—receptor cross-talk, oxidative stress pathways, and persistent epigenetic reprogramming—underpin EDC-driven metabolic disorders, cancers, and multigenerational health impacts.

EDCs disrupt steroid hormone synthesis by targeting relevant enzymes in the adrenal glands and gonads, such as steroidogenic acute regulatory protein (StAR) and cytochrome P450 enzymes (e.g., CYP17A1 and CYP19/aromatase). For example, phthalates suppress StAR and CYP17A1 activity in Leydig cells via PPARα activation, reducing testosterone synthesis, whereas bisphenol A (BPA) and atrazine dysregulate aromatase, increasing estrogen production and disrupting sex hormone balance (La Merrill et al. 2020). EDCs such as perchlorate also inhibit iodine uptake in the thyroid, thereby reducing thyroid hormone synthesis4. In addition, EDCs alter hormone transport by binding to plasma proteins such as sex hormone-binding globulin (SHBG) and transthyretin (TTR), which normally regulate the bioavailability of sex steroids and thyroid hormones. By competing for binding sites on SHBG, EDCs increase free estrogen or testosterone levels, exacerbating hormonal imbalances, whereas TTR binding disrupts thyroid hormone distribution, contributing to metabolic and developmental disorders (La Merrill et al. 2020).

TRANSPORT OF EDCS TO HUMANS

Endocrine-disrupting chemicals (EDCs) accumulate in organisms either through the consumption of contaminated food (biomagnification via diet) or by direct uptake from the surrounding environment (e.g., water, soil, or air). As EDCs move up the food system, their levels rise with every tier, with apex predators having the greatest amounts. Diet, particularly beverages, plays a significant role in human exposure to EDCs. Several EDCs were discovered in 116 common beverage samples in a Chinese study. These included triclosan, benzophenone-type

UV filters, parabens, phthalates, and bisphenol analogs. The phthalate concentration was greatest, at 14,400 ng/L. Despite these results, the daily consumption of these EDCs from beverages was less than the highest amounts that are safe and advised by several organizations, indicating a low danger to health (Wu et al., 2019).

ENDOCRINE DISRUPTING CHEMICALS AND CHILDREN HEALTH

Pediatric specialists express significant concern regarding hormone-disrupting chemicals because of the substantial physiological and developmental differences between children and adults, particularly during early life stages (Di Pietro et al., 2023). Children's organs undergo development at varying rates, and their detoxification systems, including cytochrome P450 enzyme functions, are often less mature or operate differently than adults are, making them potentially more susceptible (Di Pietro et al., 2023). Furthermore, children exhibit distinct exposure characteristics; for example, infant skin is more permeable (Di Pietro et al., 2023), and they have a longer lifespan ahead, increasing the duration of potential cumulative effects from early exposures (Di Pietro et al., 2023). Behavioral patterns unique to childhood, such as frequent hand-to-mouth activity and crawling on floors, can also increase contact with environmental contaminants (Di Pietro et al., 2023). Physiologically, children have a greater caloric, water, and air intake per unit of body weight than adults do (Di Pietro et al., 2023). Exposure can also occur through breastfeeding, as breast milk can contain fat-soluble endocrine-disrupting chemicals (Brambilla et al., 2025). These include changing hormone receptor expression or signal transduction in hormone-sensitive cells; activating or blocking hormone receptors; triggering epigenetic modifications in hormone-producing or hormone-sensitive cells; altering hormone formation, metabolic processes, or clearance; and influencing hormone transport across the membrane of cells (La Merrill et al., 2020, Di Pietro et al. 2023).

ENDOCRINE DISRUPTING CHEMICALS AND OBESITY

Globally, the prevalence of obesity is increasing quickly. Chemical exposure is one of the major contributing elements, although food and work-related habits are not the only elements of lifestyle that matter (Darbre et al., 2017). "Obesogens" are chemicals that cause weight gain by changing or modifying important endocrine system functions, including those that control hunger, the metabolic rate, and the distribution of energy. This results in obesity and related health problems. Studies have revealed that developmental exposure to these chemicals predisposes people to obesity and associated health issues, such as type 2 diabetes, heart disease, altered lipid metabolism, and decreased glucose awareness (Shahnazaryan et al., 2019; Lin and Yin, 2023; Tang et al. 2025). Human epidemiological studies, including cross-sectional, case–control, and prospective cohort designs, have provided evidence linking exposure to various EDCs with obesity and related metabolic outcomes. Meta-analyses have further synthesized these findings. For example, systematic reviews and meta-analyses have reported associations

between exposure to BPA or phthalates and increased odds of obesity, higher BMI, and larger waist circumference in both children and adults (Rancière et al., 2015; Stojanoska et al., 2017).

ENDOCRINE DISRUPTING CHEMICALS AND CANCER

Cancer is a complicated condition arising from the interaction of hereditary and environmental variables. Approximately two-thirds of cancer cases are thought to be caused by environmental factors, such as exposure to chemicals that disrupt the endocrine system (EDC). These hormone-interfering compounds are widely used in consumer and industrial products, and people are regularly exposed to them. EDCs are found in numerous settings, particularly in occupations involving excessive levels of chemical contact. Jobs in coal mining, latex and pulp production, painting, firefighting, and steel manufacturing are associated with increased cancer risk due to the prevalence of endocrine-disrupting chemicals (EDCs) in these occupational environments. These chemicals can alter hormonal regulation, disrupt metabolic processes, and cause cellular changes that contribute to cancer development (Ghosh et al., 2022). Owing to its xenoestrogen properties, EDC has been linked to various types of cancer, such as liver, gastrointestinal, breast, and skin tumors (Owingñas-Moreno et al. 2023).

ENDOCRINE-DISRUPTING CHEMICALS ON THE THYROID GLAND

Sodium-iodide symporter (NIS) channel inhibition is a common method by which various environmental chemicals trigger iodine absorption problems. Examples of prominent EDCs that disrupt thyroid metabolism by obstructing NIS include perchlorate and thiocyanate (Kabir et al., 2015). According to Gore et al. (2015), NIS is essential for the transfer of iodine into thyrocytes, which are the cells that produce thyroid hormones. In a study conducted by Braverman et al. (2005), 3,100 participants treated with thiocyanate, perchlorate, and nitrates showed a large decrease in thyroxine-free levels, especially in pubertal subjects, without a corresponding increase in TSH levels. These compounds contaminate numerous foods and sources of drinking water and are frequently employed in manufacturing processes. By binding to NIS, they block the iodide transporter, leading to thyroid dysfunction.

ENDOCRINE-DISRUPTING CHEMICALS ON A PITUITARY GLAND

The pituitary gland is impacted by several endocrine-disrupting chemicals, thereby impacting various endocrine systems. This can lead to a range of clinical issues related to exposure to these pollutants, including early or late maturity (Soriano-Guillen and Argente, 2019) and circadian rhythm disruption (Sen and Sellix, 2016). EDCs often target the diencephalic system, which may impair central nervous system functions by mimicking neurotransmitter actions in addition to interacting with endocrine transmitters (Gore et al., 2015).

ENDOCRINE DISRUPTING CHEMICALS ON REPRODUCTIVE GLAND

Hormonal signals can be disrupted by a variety of endocrine-disrupting chemicals, which can resemble sex hormones and attach to endocrine receptors. Exposure to EDCs can have an especially harmful effect on the reproductive system (Monneret, 2017). EDCs with poor estrogenic activity and anti-androgenic qualities fall into five broad categories. These include (1) synthetic estrogens and pharmaceuticals such as diethylstilbestrol and 17β-estradiol; (2) phytoestrogens such as cumestans, stilbenes, isoflavonoids, and lignans; (3) pesticides such as organophosphates, carbamates, and organochlorines; (4) chemicals and plasticizers arising from the partial combustion of polyvinyl chloride (PVC), paper, and waste products (such as dioxins); and (5) industrial materials such as phenols, flammable substances, dioxins, toxic metals, and perfluorooctanoic acid. The fertility of men and women is strongly impacted by EDCs, which also exacerbates illnesses such as polycystic ovarian syndrome (PCOS) and testicular hypotrophy (Ghosh et al., 2022). Undescended testicles, abnormal sperm development, and testicular cancer are developmental disorders linked to environmental factors. In women, endometriosis and ovarian pathology may be influenced by endocrine-disrupting chemicals (Caserta, Bordi, and Ciardo, 2013a; Caserta et al., 2013b). Compounds such as diethylstilbestrol, phthalates, and bisphenol A (BPA) have been associated with endometriosis, which affects 10% of women of reproductive age and results in infertility in 50% of those affected (Schug et al., 2011; Caserta, Bordi, and Ciardo, 2013a; Caserta et al., 2013b). BPA, paraben, PCB, dichlorodiphenyltrichloroethane phthalate (DDT), atrazine, genistein, TCDD, triclosan, and methoxychlor (MXC) exposure are associated with ovarian problems (Minguez-Alarcon and Gaskins, 2017).

ENDOCRINE-DISRUPTING CHEMICALS ON MALE REPRODUCTIVE HEALTH

Research shows that endocrine-disrupting chemicals, especially bisphenol A (BPA), may impede ATP synthesis through mitochondrial breakdown, leading to decreased motility of sperm (Rahman et al., 2017). GnRH is secreted by the hypothalamus and causes the anterior pituitary to release gonadotropins, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Exposure to endocrine-disrupting chemicals (EDCs) can cause disruptions at any point during this process. EDCs can harm Sertoli cells by upregulating lethal proteins or causing an increase in spermatocyte death (Zhang et al., 2019). Sertoli cells aid in the growth of spermatocytes, remove extra cytoplasm, and promote testosterone-driven sperm formation. The disruption of testosterone-bound androgen receptor-mediated gene transcription, which is essential for spermatogenesis, occurs when Leydig cells are unable to produce enough testosterone. Additionally, EDCs can produce an aberrant hormonal milieu that might lead to testicular aneuploidy and perhaps have repercussions for future generations.

ENDOCRINE-DISRUPTING CHEMICALS ON FEMALE REPRODUCTIVE HEALTH

The negative biological impacts of endocrine-disrupting chemicals (EDCs) on reproductive system development are linked primarily to disruptions in folliculogenesis. This process involves the transformation of fundamental follicles into primary, preantral, and antral follicles. Bisphenol A (BPA), methotrexate (MTX), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), phthalates, and other EDCs might disrupt the growth of these follicle types, leading to toxicity and potential infertility. BPA has been linked to several gynecological conditions, such as endometriosis, polycystic ovarian syndrome, and reproductive issues (Karman et al., 2012b). MTX disrupts folliculogenesis by increasing the expression of anti-Müllerian hormone in pre- and early antral follicles (Ghosh et al., 2022). Moreover, TCDD has antiproliferative effects on rat ovaries and can impair ovarian steroidogenesis (Karman et al., 2012a, 2012b). Research indicates that EDCs can influence the beginning of menopause, the rate of conception, and female genital growth. They are linked to a range of reproductive abnormalities, including ovarian dysgenesis syndrome, and can impact the duration of puberty, the adult ovarian system, the female hypothalamic–pituitary–gonadal axis, and trophoblast and placental function. Table 1 shows the identified endocrine-disrupting chemicals and their sources.

1 **Table 1: Origin-based classification of main endocrine-disrupting chemicals (EDCs) Source: (Cano et al. 2021)**

Type	Chemical Name	Abbreviation	Introduction date	Restricted/Banned	Countries	Source
		Residential				
Phenols	Bisphenol A Bisphenol S	BPA BPS	1960	Restricted	Sweden, France, Denmark, USA, Asia	Polycarbonate plastics, epoxy resins, plastic toys and bottles, lining of food cans
Phthalates	Mono-(2-ethylhexyl)-phthalate Di-(2-ethylhexyl)-phthalate Dibutyl-phthalate Dicyclohexyl phthalate	MEHP DEHP DBP DCHP	1920	Restricted	USa, Canada, China, South Korea and Japan	PVC: lubricants, perfumes, cosmetics, medical tubing, wood finishes, adhesives, paints, toys, emulsifiers in food, flooring, personal care products
Perfluorinated chemicals Perfluorooctanoic acid Perfluoroctanesulfonates Perfluorononanoic acid	Perfluorooctanoic acid Perfluoroctanesulfonates Perfluorononanoic acid Perfluorohexanesulfonic Acid	PFOA PFOS PFNA PFHxS	1940	Restricted	USA, Canada	Contaminated food and water, dust, floor waxes, firefighting foam, electrical wiring, lining of food wrappers, stain resistant carpeting
		Industrialist				
Dioxins	Polychlorinated Dibenzo P	PCDD	1872	Restricted	USA, Canada, China, Japan	By-product of chlorinated

						herbicide production, smelting, chlorine bleaching of paper
Polychlorinated biphenyls	Polychlorinated biphenyls Polybrominated biphenyls Polychlorinated terphenyls Polychlorinated naphthalenes	PCBs PBBs PCTs PCNs	1927	Banned	China, South Korea, UAE, Australia	Contaminated air and food, skin contact with old electrical equipment
Polycyclic aromatic hydrocarbons	Benzo[a]pyrene, anthracene, acenaphtylene, fluorene	PAH	-	Restricted	Usa, Canada, European union, China and Japan	Products of fuel burning
Alkylphenols	Nonylphenol Octylphenol	NP OP	-	Restricted and banned in certain areas of use in the USA	Japan, Austrialia	Surfactants, detergents, emulsifiers; fish, drinking water, personal care products
	Arsenic	As	-	Restricted		Pesticides, smelting, industrial waste, drinking water, soil, seafood, rice, mushrooms, poultry
	Mercury	Hg	-	Restricted		Mining, waste incineration,

						manufacturing; fish, shellfish,
Heavy metals	Cadmium	Cd	-	Restricted	USA, Canada, Japan, Australia	medical/dental procedures Soil, water, air; leafy vegetables, peanuts, soybeans, sunflower seeds; inhalation products of mining, combustion, waste incineration
			Agricultural			
Dicarboximide	Vinclozolin	Vnz	1981	Banned	Denmark, Finland, Norway, and Sweden	Diet and occupational
Organotins	Tributyltin oxide Triphenyltin	TBT TPT	-	Banned by many countries	EU, US, Canada, Australia	Used as a biocide (fungicide and molluscicide), especially as a wood preservative
Organochloride	Dichlorodiphenyltrichloroethane Dichlorodiphenyldichloroethylene	DDT DDE	1940	Banned	US, Canada, Australia, and most	Contaminated water, soil crops, fish, pesticides

					Asian and African	
Chlorotriazine	Atrazine	ATR	1959	Banned	EU, Switzerland, many African, Asian, and Latin American	Pesticide/herbicide, contaminated water and soil
Pharmaceutics						
Parabens	Butylparaben, methylparaben, ethylparaben, propylparaben, benzylparaben	Parabens	1924	Restricted	EU, USA, Denmark	Antimicrobial agents for the preservation of food, paper products, and pharmaceutical products
Non-steroidal synthetic estrogen	Diethylstilbestro	DES	1941–1947	Restricted	USA, Canada, Australia	Pharmaceutical

2 **Legend:** EU: European Union countries, USA: United State of America

DOSE RESPONSE AND RISK ASSESSMENT OF THE EDCS

The dose–response relationship is a cornerstone of toxicology, describing how the magnitude of an effect varies with the level of exposure to a chemical. For endocrine-disrupting chemicals (EDCs), traditional monotonic dose–response curves, where higher doses predictably yield greater effects, often do not apply. Instead, EDCs frequently exhibit nonmonotonic dose–response relationships, where effects may be more pronounced at low or intermediate doses than at higher doses, resulting in U-shaped or inverted U-shaped curves (Hilz and Gore, 2023; Cruz et al. 2025). Recent epidemiological studies, such as a 2025 investigation of Brazilian children and adolescents, have provided evidence of nonmonotonic and nonlinear associations between urinary EDC mixtures and oxidative stress biomarkers, highlighting the complexity of EDC actions at environmentally relevant exposures (Cruz et al. 2025). These findings challenge the conventional toxicological principle that "the dose makes the poison," as effects at low doses cannot be reliably predicted from high-dose data, necessitating a re-evaluation of safety testing and regulatory thresholds (Hilz and Gore, 2023).

Risk assessment for EDCs incorporates key toxicological benchmarks such as the no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL), which are derived from animal studies or short-term assays and inform regulatory limits such as the tolerable daily intake (TDI) (Choi et al., 2024). However, the prevalence of nonmonotonic dose–response curves complicate the identification of safe exposure thresholds, as adverse effects may occur below traditional NOAELs, particularly for developmental and reproductive endpoints (Choi et al., 2024). The margin of exposure (MOE) approach, which compares the NOAEL or LOAEL to estimated human exposures, is often used to assess risk but may underestimate hazards if low-dose effects are not adequately captured. Current frameworks, including those from the OECD and EFSA, recommend the use of larger safety margins and the integration of data from multiple endpoints and dose ranges to better protect public health in light of the unique dose–response characteristics of EDCs (Barton-Maclaren et al., 2022, Choi et al., 2024).

PLASTICS AS ENDOCRINE DISRUPTORS

Plastics consist of polymer chains composed of carbon, hydrogen, oxygen, and/or silicon atoms. Products made from petroleum and other chemicals mixed under particular circumstances are usually the source of these polymers (Halden, 2010). To increase the performance of polymeric materials, various substances, such as antioxidants, stabilizers, lubricants, antistatic agents, and antiblocking agents, are used (Al-Dayel et al., 2012). These additives enhance the elasticity, adaptability, strength, and transparency of polymers (Ullah et al. 2023). However, there are health risks associated with plastics and their constituent monomers, particularly bisphenol A (BPA), as well as additives such as phthalate plasticizers and their combinations (e.g., antimicrobial polycarbonate) (Darbre, 2020). Contact with these chemical additives has been linked to developmental issues, including problems with fertility,

sexual development, and other health concerns, such as cancer, diabetes, and obesity (Darbre, 2020, Ullah et al. 2023).

Plastic-derived endocrine-disrupting chemicals (EDCs) disrupt hormonal signaling by mimicking or blocking the actions of natural hormones. Bisphenols (e.g., BPA) bind to estrogen receptors (ERα/ERβ) and androgen receptors (AR), altering the expression of genes critical for reproductive health and metabolism. For example, BPA stabilizes the ligand-binding domain of ERα, triggering incomplete coactivator recruitment and dysregulated transcription of estrogen-responsive genes, potentially contributing to infertility or breast cancer. In contrast, phthalates act by antagonizing AR signaling, disrupting testosterone synthesis and spermatogenesis. Plastic additives such as organotins activate peroxisome proliferator-activated receptor gamma (PPARγ), promoting adipocyte differentiation and metabolic dysfunction. These receptor interactions are further complicated by nonmonotonic dose responses, where low-dose exposures paradoxically amplify effects, challenging traditional toxicological models (Pesonen and Vähäkangas, 2022; Ullah et al. 2023, Stevens et al. 2024).

Furthermore, plastic EDCs trigger oxidative stress and impair mitochondrial function. Microplastics and adsorbed pollutants such as dioxins generate reactive oxygen species (ROS), which can damage DNA and proteins while activating cellular stress response pathways such as the Nrf2/ARE pathway. When exposure is chronic, these protective mechanisms can be overwhelmed, leading to cell death (apoptosis) in reproductive cells and placental tissues. In addition, EDCs such as BPA alter epigenetic marks, such as DNA methylation at stress-response genes (Fkbp5) and histone modifications, thus disrupting hormone-sensitive developmental programs. These epigenetic changes can persist through generations, as reported in previous studies linking prenatal EDC exposure to transgenerational obesity and ovarian disorders (Basak et al. 2020; Ullah et al. 2023). Taken together, these pathways explain the wide-ranging impacts of plastic EDCs from neurodevelopmental delays to metabolic disorders.

PLASTICS' ENDOCRINE-DISRUPTING COMPOUNDS AND HOW THEY ALTER DEVELOPMENT, FERTILITY, AND REPRODUCTION

Numerous of these substances accumulate in tissue from living organisms and can have detrimental effects on human and animal health by interfering with endocrine functions or other functions in the body (Zoeller et al., 2016). Consequently, EDCs are ubiquitous harmful substances from the environment that can be inhaled, ingested, or come into contact with the skin. EDCs have a variety of long-lasting consequences for endocrine health and can exacerbate disorders related to the endocrine system (Gore et al., 2015). Basic components found in everyday products, such as per- and polyfluoroalkyl substances (PFAS), phthalates such as bis-(2-ethylhexyl)-phthalate (DEHP), and bisphenol A (BPA) and its analogs, are found in both the surroundings and living organisms, and they pose serious ecotoxicological and health risks

(Vandenberg, 2021). Scientists and medical professionals are well aware of these concerns. For example, a 2020 report from the International Pollutants Elimination Network and the Endocrine Society provided "discreet and comprehensive proof of the health impacts of various chemicals in typical plastic products," affecting ailments such as infertility, cancer, diabetes, metabolic problems, thyroid conditions, and neurological disorders, among others (Flaws et al., 2020). The environmental presence of micro- and nanosized plastics, which can make their way into the food chain, is another urgent concern. Micro- and nanoplastics are linked to several problems. First, these tiny plastics (<1 μm) have the same potential to produce endocrine-disrupting chemicals (EDCs) as larger plastic products do. Second, EDCs can be concentrated to higher levels than those normally present in the environment by using microplastics as molecular sponges (with the ability to attract and bind hydrophobic (water-repelling) EDCs) (Deng et al., 2021; Heindel and Vandenberg, 2015). The effects of environmental toxicants, such as those derived from plastics, on reproduction, fertility, and growth can vary on the basis of exposure level, timing, and stage (Vandenberg and Turgeon, 2021). The impacts of EDCs from plastics are especially harmful to gametogenesis, gamete quality, embryo growth, and pregnancy (Gore et al., 2015). Tissue destruction, low gamete performance, decreased fertility, and aberrant development are outcomes of these interactions. Significant contact phases include pregnancy and the first few postnatal months, even if effects in adults might only last temporarily. Notably, years or even decades may pass before the effects of initial growth exposures are felt (Deng et al., 2021). Additionally, through inherited epigenetic modifications or abnormalities in early embryonic development, the development of toxicants can impact not only vulnerable people but also future generations (Chianese et al., 2018; Santoro et al., 2019).

EMERGING CONTAMINANTS AND MICRO/NANOPLASTICS

Microplastics (MPs) and nanoplastics (NPs) have emerged as significant environmental contaminants, not only because of their persistence and ubiquity but also because they serve as vectors for endocrine-disrupting chemicals (EDCs) and other hazardous substances. These plastic particles possess a large surface area and hydrophobic properties, enabling them to adsorb and transport a wide range of EDCs, including bisphenols, phthalates, polybrominated diphenyl ethers, and heavy metals, which are either added during plastic manufacturing or absorbed from the environment (Zhang and Xu, 2020; Ullah et al., 2023; Khan and Jia, 2023). Since these chemicals are not covalently bound to the plastic matrix, they can readily leach into water, food, and biological fluids, increasing the risk of exposure for both wildlife and humans. The “Trojan horse effect” describes how MPs and NPs facilitate the entry and bioavailability of EDCs, leading to synergistic toxic effects on mammalian endocrine organs such as the hypothalamus, pituitary, thyroid, adrenal glands, testes, and ovaries, with documented impacts on hormonal balance, reproductive health, and metabolic function (Zhang and Xu, 2020; Ullah et al., 2023; Khan and Jia, 2023).

Microplastics (MPs) and nanoplastics (NPs) induce cellular and hormonal processes via a two-level mechanism: by producing reactive oxygen species (ROS) and by acting as carriers for endocrine-disrupting chemicals (EDCs). Their minute size and extensive surface area enable them to infiltrate tissues, where they trigger oxidative stress. This damage damages mitochondria and induces endoplasmic reticulum (ER) stress, potentially leading to cell death (apoptosis) and impaired cellular function (Donisiet al. 2024; Lee et al. 2025). In addition, MPs/NPs function as "Trojan horses," transporting EDCs such as bisphenols and phthalates that mimic hormones, binding to receptors such as estrogen and thyroid receptors, and disrupting hormonal equilibrium (Ullah et al. 2023). Smaller NPs (<1 μm) are especially detrimental because of their enhanced absorption and ability to release higher concentrations of adsorbed pollutants, thus amplifying their toxicity (Ullah et al. 2023). These combined effects—oxidative stress, disrupted signaling pathways, and hormone mimicry—contribute to reproductive, metabolic, and neurological disorders, emphasizing the dual threat of MPs/NPs as direct physical stressors and vehicles for chemical delivery (Donisiet al. 2024; Lee et al. 2025).

The capacity of MPs and NPs to increase bioaccumulation is closely linked to their size, surface chemistry, and polymer type. Smaller particles, particularly those in the nanosize range, are more readily absorbed and can cross biological barriers, including the gastrointestinal tract, blood–brain barrier, and placenta, allowing them to accumulate in secondary tissues such as the liver, brain, and kidneys. Recent studies have demonstrated that microplastics can increase the bioaccumulation of hydrophobic organic contaminants (HOCs) in organisms; for example, earthworm experiments using dual-labeling methods have shown that the presence of MPs in soil significantly elevates the uptake of HOCs, with concentration and polymer properties being major contributing factors (Wang et al., 2023). This enhanced bioaccumulation not only magnifies toxic effects within individuals but also promotes biomagnification in the food chain, raising concerns for ecosystem and human health (Wang et al., 2023; Ullah et al., 2023).

Of particular concern are the transgenerational and epigenetic effects associated with MP/NP-mediated EDC exposure. MPs and NPs have been detected in the human placenta and meconium, indicating the potential for maternal–fetal transfer. Experimental evidence shows that exposure during pregnancy can disrupt fetal development, immune balance, and angiogenesis while also inducing DNA damage and altering the expression of genes related to methylation and microRNA regulation. These epigenetic modifications can persist across generations, manifesting as developmental abnormalities, metabolic disorders, and reproductive dysfunction in offspring (Geng et al., 2023). The ability of MPs and NPs to act as carriers for EDCs thus amplifies their risk profile, underscoring the urgent need for further research into their mechanisms of action and long-term impacts on both environmental and human health (Ullah et al., 2023; Geng et al., 2023).

MNPs disrupt the gut microbiome by physically interacting with intestinal epithelial cells and altering the microbial community composition, resulting in dysbiosis characterized by reduced diversity and shifts in dominant taxa such as Firmicutes and Bacteroidetes. This imbalance impairs the production of short-chain fatty acids (SCFAs), such as butyrate, which are key for maintaining gut barrier integrity and regulating metabolic hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). Moreover, MNPs cause oxidative stress and inflammation in the gut, further destabilizing microbial ecosystems and promoting the growth of pathobionts such as proteobacteria (Ali et al. 2024). The increased permeability of the gut due to dysbiosis allows bacterial toxins (such as lipopolysaccharides) to leak into the bloodstream, causing low-level inflammation that can interfere with insulin signaling and estrogen metabolism, thereby increasing the risk of metabolic syndrome and hormonal imbalances. In addition, MNPs act as transporters for adsorbed EDCs (e.g., phthalates), concentrating these chemicals in the gut lumen and enhancing their uptake, which synergistically amplifies endocrine disruption. These interactions illustrate how MNP-induced gut dysbiosis serves as a key link between environmental plastic pollution and endocrine dysfunction (Ali et al. 2024; Dennis et al. 2025).

BISPHENOL A (BPA)

Among the diphenylmethane derivatives and bisphenols, bisphenol A (BPA) is an organic artificial molecule with the chemical formula $(CH_3)_2C(C_6H_4OH)_2$. It is a colorless, solid compound with two hydroxyphenyl groups that breaks down in organic solvents but has minimal solubility in water (0.344 weight percent at 83 °C) (Godswill and Godspel, 2019). Because BPA is estrogenic and has hormone-like qualities, it is considered a xenoestrogen, which raises questions about its application in food storage containers and other consumer goods (Kanlayaprasit et al. 2021). Many nations have tightened regulations and examined their safety since 2008, which has caused multiple retailers to remove BPA-containing polycarbonate items from their shelves. Owing to market trends rather than safety concerns, the Food and Drug Administration (FDA) decided to ban BPA from baby bottles and infant formula packaging (Neri et al., 2024). The European Union and Canada have outlawed BPA in infant bottles. BPA is not found in stiff PVC items such as siding, pipes, or windows, but it can be employed as an antioxidant in "flexible PVC" products, such as those made softer by plasticizers (Godswill and Godspel, 2019). BPA is linked to globular proteins, which typically connect to sex hormones such as estrogens and androgens, interfering with the healthy physiological production of sex hormones. The hormonal equilibrium between these sex hormones is disrupted by this interaction. Additionally, BPA can impact the breakdown of sex hormones. It frequently has antiestrogen or anti-androgen effects, which may interfere with the development of gonadal organs and the generation of sperm. Additionally, BPA affects the expression of genes linked to the thyroid gland hormone axis, which is important for metabolic processes and growth. BPA can reduce the levels of thyroid hormone-

binding proteins that bind to triiodothyronine and suppress thyroid hormone receptor (TR) activity by increasing the expression of TR transcriptional corepressors. Hypothyroidism may result from this interference with the thyroid hormone axis (Kanlayaprasit et al. 2021). To date, a substantial amount of literature indicates that maternal BPA exposure can have a negative effect on the outcomes of offspring in developing systems; for example, it increases the risk of behavioral problems associated with hyperactivity disorder, antisocial behavior, sleep-related issues, and language development (Kanlayaprasit et al. 2021).

EDCs such as bisphenol A (BPA) rapidly induce cellular responses by activating nongenomic signaling pathways via interactions with membrane-bound receptors, thereby bypassing direct gene transcription. BPA binds to G protein-coupled receptors (GPR30) and membrane estrogen receptors (mERs), initiating rapid kinase cascades such as MAPK/ERK and PI3K/Akt. For example, in breast cancer cells, BPA activates the ERK and PI3K/Akt pathways, promoting cell proliferation and survival while inhibiting apoptosis (Roy et al. 2010; Merzoug-Larabi et al. 2020). Similarly, in ovarian cells, BPA stimulates the PI3K/Akt pathway, accelerating primordial follicle activation and reducing degeneration (atresia), potentially leading to a depletion of ovarian reserves over time (Zhao et al. 2014). These pathways also modulate hormone release, as observed in pituitary cells, where BPA-induced ERK phosphorylation is correlated with altered prolactin secretion (Viñas and Watson, 2013). By manipulating these cellular communication networks, BPA can cause a variety of effects, ranging from metabolic disturbances to reproductive dysfunction, within minutes to hours, underscoring its capacity to disrupt the cellular balance without directly altering gene activity (Rahman and Pang, 2019; Sonavane, 2022; Urbanetz et al. 2023).

EXPOSURE ROUTES TO BISPHENOL A

Both humans and animals can become exposed to bisphenol A (BPA) through the skin, food, or inhalation. However, eating or drinking food and drinks tainting with BPA from plastic packaging and epoxy substance surfaces on containers is the main way to become exposed (Talpade et al., 2015).

DIETARY EXPOSURE

When consumed, BPA permeates easily. BPA can readily move into the surroundings and dissipate from the polymeric material products it is present because of its chemical makeup. When heat, acidity, or alkalinity hydrolyze the ester bonds tying BPA particles in polycarbonates or resins made from epoxy, free BPA is discharged into food, drink, and the surroundings. Furthermore, facilitating the migration of BPA includes frequent washing, rubbing, and sterilizing procedures (Mikolajewska et al., 2015).

BISPHENOL INTERACTIONS AND PATHWAY DISRUPTIONS

Research has demonstrated that BPA interferes with the endocrine system via various receptor-mediated mechanisms, establishing it as a model endocrine-disrupting chemical (EDC). As a xenoestrogen, BPA binds to receptors for estrogen (ER) and stimulates them. Although its affinity for the genomic ER is lower than that of estradiol, the circulating levels of BPA are higher and within a biologically active range. BPA is at least as effective as estradiol in eliciting some responses, especially those mediated by nongenomic signaling pathways. Additionally, to counteract androgens, BPA binds to androgen receptors, inhibiting the normal effects of androgens, altering steroid hormone synthesis, and affecting circulating steroid hormone levels. It also disrupts thyroid hormone synthesis by inhibiting the conversion of T4 (thyroxine) to T3 (triiodothyronine) (Kang et al., 2023).

Bisphenols, mainly bisphenol A (BPA) and its analogs, mainly disrupt the endocrine system through direct interactions with nuclear hormone receptors, notably estrogen receptors (ERα and ERβ), estrogen-related receptor gamma (ERRγ), and the androgen receptor (AR) (Pathak and Kim, 2024; Pathak et al. 2024; Stanojević and Sollner Dolenc, 2025). Structural studies have shown that BPA binds strongly to ERRγ and acts as a selective estrogen receptor modulator (SERM). It partly activates ERα and ERβ by triggering conformational changes in the receptor's ligand-binding domain (Delfosse et al., 2012; Pathak and Kim, 2024). Unlike the natural hormone 17β-estradiol, bisphenols act as partial agonists, stabilizing the N-terminal activation function (AF-1) but failing to fully stabilize the C-terminal activation function (AF-2), which is critical for coactivator recruitment and robust gene transcription (Delfosse et al., 2012). This incomplete activation results in altered transcriptional responses, potentially disrupting normal hormonal signaling and cell functions. In addition, BPA analogs have been reported to bind the androgen receptor, interfering with its normal activity and possibly disrupting androgen-dependent processes (Pathak et al. 2024).

In addition to receptor binding, bisphenols interrupt multiple intracellular signaling pathways and cellular processes. For example, BPA exposure has been linked to the initiation of various cell death pathways, including apoptosis and autophagy, which can negatively impact tissue health and function (Yukta et al., 2025). These disruptions also affect metabolic regulation and tumorigenesis, as BPA can modulate gene expression related to body weight, glucose metabolism, and cancer risk via both ER-dependent and ER-independent mechanisms (Cimmino et al. 2020). More importantly, the effects of bisphenols are not restricted to a single pathway or receptor but rather involve a network of interactions that collectively disturb endocrine homeostasis. This complexity underscores the need for comprehensive risk assessments of BPA and its analogs, particularly given their extensive use and the potential for additive or synergistic effects when exposures occur as mixtures (Stanojević and Sollner Dolenc, 2025).

BIOTRANSFORMATION OF BISPHENOL A

One artificial lipophilic organic molecule is BPA. Following consumption, it passes via the digestive system and into the liver, where it undergoes metabolism and becomes hydrophilic. In hepatocyte microsomes, BPA is broken down and becomes dormant by sulfation by phenol sulfotransferases and glucuronidation by uridine diphosphate glucuronosyltransferases. According to Herczegh et al. (2023), combined dormant types of BPA acquire hydrophilic qualities and are eliminated through bile and urine. Nevertheless, the development of the β-glucuronidase enzyme (present in the liver, kidneys, lungs, and placenta of humans and animals) enables the deconjugation of BPA and, consequently, the discharge of its effective component to the blood and circulation within the body. This process is essential because conjugated BPA, which penetrates the placenta and undergoes deconjugation during pregnancy in animals and humans, exposes the fetus indefinitely (Carstens et al., 2020).

THE IMPACT OF THE BISPHENOL ON HEALTH

BPA acts as both an antiestrogen agent and an anti-androgen agent, potentially disrupting sperm production and gonadal development. Research has shown that BPA exposure in the surrounding environment may increase the risk of obesity and diabetes. Studies have indicated that even minimal BPA exposure can prevent human fatty tissue from releasing adiponectin, which is crucial for regulating insulin sensitivity and glucose metabolism (Ramskov Tetzlaff et al., 2020). Additionally, BPA may promote fat accumulation, leading to weight gain. It influences thyroid hormone axis-related gene expression, which impacts metabolism and development. By increasing the activity of the TR corepressor, BPA reduces the activity of the thyroid hormone receptor (TR), reducing thyroid hormone-binding proteins and potentially causing hypothyroidism, which is associated with obesity. Compounds that disrupt lipid and glucose metabolism, leading to weight gain, are termed "obesogens" (Martínez et al., 2020). Because these substances are lipophilic, they tend to accumulate in fat tissues, creating a cycle where fat retention increases their persistence and the retention of other harmful pollutants. This cycle can contribute to obesity and its related health issues, including cancer (Frenzilli et al., 2020; Vacca et al. 2024). Moreover, elevated risks of cardiovascular disease as well as diabetes have been associated with significant urine BPA levels (Kang et al., 2023). To address these concerns, many companies have started using alternatives such as diphenyl sulfone and bisphenol S (BPS), although these substitutes also raise health concerns (Frenzilli et al., 2020; Vacca et al. 2024).

PHTHALATES

Phthalates refer to esters of phthalic acid or phthalate esters. Phthalates are mostly used as plasticizers. Plasticizers are added to plastics throughout the production process to increase

their malleability, flexibility, and strength. The main function of these materials is to make polyvinyl chloride (PVC) softer. Health concerns have caused several plastic and nonplastic products in the US, Canada, and the EU to gradually phase out practically all smaller-molecular-weight phthalates or those made from C3–C6 alcohols (Godswill and Godspel, 2019). Phthalates are classified as having a high molecular weight with backbones longer than C6, which confers greater durability. Because plasticized polymers are common, most people are exposed to phthalates to some degree. For example, the majority of U.S. citizens had urine that contained several phthalate metabolites when examined by the U.S. Centers for Disease Control and Prevention (Godswill and Godspel, 2019).

An estimated 3 million tonnes of phthalates are consumed annually worldwide by humans (Wang et al., 2018). Food, water, and other goods used in the human body can readily absorb phthalates. The main exposure routes are ingestion, breathing, and skin contact, mostly through PCPs (Wang et al., 2018). There is evidence that certain dairy products, fish, seafood, and oils contain significant levels of phthalates. There is evidence that substantial amounts of phthalates are present in several dairy products, fish, seafood, and oils. Because of their fugitive emission, phthalates are semivolatile chemical compounds that are more prone to enter the body through skin absorption and contaminated air in the vicinity of phthalate manufacturing plants. Dermal absorption is another effect of the use of PCP compounds, such as phthalates, daily. Additionally, infants are exposed when they suckle on toys that contain DEHP, DBP, and BBP or when they are breastfed by mothers who have been exposed to DEHP and DNP. Phthalates are found in modern electronics as well as in medical uses, such as catheter devices and blood transfusions (Wang et al., 2018).

PROPERTIES OF PHTHALATES

Phthalate esters are the esters of dialkyl or alkyl aryl phthalic acid, also known as 1,2-benzene dicarboxylic acid. When phthalates are incorporated into plastics, the lengthy polyvinyl acid molecules can glide over one another. Phthalates have transparency, syrupy liquid uniformity, minimal volatility, low solubility in water, and excellent oil solubility. Unless R' and R (e.g., methyl or ethyl groups) are relatively small, the polar carboxyl group affects the physical properties of phthalates. When the proper type of alcohol—typically one with six to thirteen carbons—reacts with phthalic anhydride, colorless and odorless liquids known as phthalates are produced (Giuliani et al. 2020).

EXPOSURE ROUTES TO PHTHALATES

Phthalates are readily absorbed by their natural surroundings, but they quickly undergo anaerobic, photo, and biodegradation-related processes. They usually do not present severe toxicity danger, and they are more frequently discovered at greater levels in suburban and urban

regions than in distant or rural regions. Compared with less volatile and denser DEHP, more volatile phthalates, such as DMP and DEP, are more frequently found in the air. The number of phthalates in the air is greater at increased temperatures (Pei et al. 2018). Dust frequently contains BBP and DEHP, which can be found in relatively large proportions when polyvinyl chloride (PVC) flooring is installed (Godswill and Godspel, 2019). Phthalates from flooring made of PVC can enter children's bodies via contact with the skin, inhalation, and food consumption, according to a 2012 Swedish study (Carlstedt et al., 2013). Recently, Wang et al. (2020) reported that dust ingestion is the main exposure pathway for indoor exposure to PAEs, contributing 74.4% of preschool children in kindergarten in Beijing. The general public's main source of DEHP and other phthalates is thought to be diet, with fat-laden foods such as meats, milk, and butter as major sources. Studies suggest that some meals may expose consumers to more phthalates than plastic goods, such as water bottles (Wang et al., 2020; Giuliani et al. 2020; de Paula et al. 2024). Low-molecular-weight phthalates, such as BBzP, DBP, and DEP, can penetrate through the skin, whereas inhalation is a major mode of exposure for very volatile phthalates (Godswill and Godspel, 2019).

Two particular phthalates, DiNP and DEHP, were found to be substantially more prevalent in the urine of people who ate fast-food eateries, according to a study performed on 9,000 participants between 2003 and 2010. Phthalate levels increased even with occasional fast-food consumption; individuals who consumed it had 15.5% higher DEHP levels and 25% higher DiNP levels (Alp and Yerlikaya, 2020). Usually, children are at risk of more phthalates than adults are. Body care products containing phthalates also contribute to infant exposure. A 2008 study revealed a stronger correlation between higher levels of phthalate radicals in infant urine and the use of baby shampoo, lotion, or powder (Sathyanarayana et al. 2008). This study revealed that younger babies are especially susceptible to the harmful effects of phthalates because of their evolving reproductive and endocrine systems, greater doses per unit of body surface area, and faster metabolic rate.

PHTHALATES METABOLISM IN THE HUMAN BODY

Phthalates have a short half-life of approximately 12 hours, which causes them to be metabolized quickly. After ingestion, phthalates are broken down into physiologically active monoester phthalates by lipases and esterases in the liver and intestines (Calafat et al., 2006). Certain low-molecular-weight phthalates are eliminated through direct excretion, whereas others undergo phase two metabolic processes. In these reactions, the active monoester phthalates are processed by the enzyme uridine 5'-diphosphoglucuronyl transferase to produce biologically inactive glucuronides (Zhang et al. 2021). The toxicological fate of phthalates in the body is contingent upon their kind. While short-branched phthalates are often hydrolyzed to monoester

phthalates and then excreted in the urine, long-branched phthalates typically undergo numerous biotransformations, such as hydroxylation and oxidation, before being removed in the urine and feces. The metabolism of DEHP (di(2-ethylhexyl) phthalate) in humans is shown in Figure 3.

Phthalates exert antiandrogenic effects primarily by disrupting critical steps in testosterone synthesis within Leydig cells and interfering with androgen receptor (AR) signaling. At the cellular level, phthalate metabolites such as mono-(2-ethylhexyl) phthalate (MEHP) suppress the expression and activity of crucial steroidogenic enzymes, including steroidogenic acute regulatory protein (StAR) and cytochrome P450 17A1 (CYP17A1), both of which are vital for cholesterol transport and androgen biosynthesis (Chauvigné et al. 2011). This suppression is partly mediated through nuclear receptors such as PPARα, which, when activated by phthalates, downregulate the transcription of these steroidogenic genes, resulting in decreased testosterone levels (Chauvigné et al. 2011). More importantly, recent studies highlight that these disruptions can occur at environmentally relevant exposure levels and may contribute significantly to reproductive disorders and developmental abnormalities, underscoring the importance of understanding phthalates' multilevel interference with androgenic pathways (Chauvigné et al. 2011; Hlisníková,et al. 2020; Zhao et al. 2022; Kolena et al. 2025).

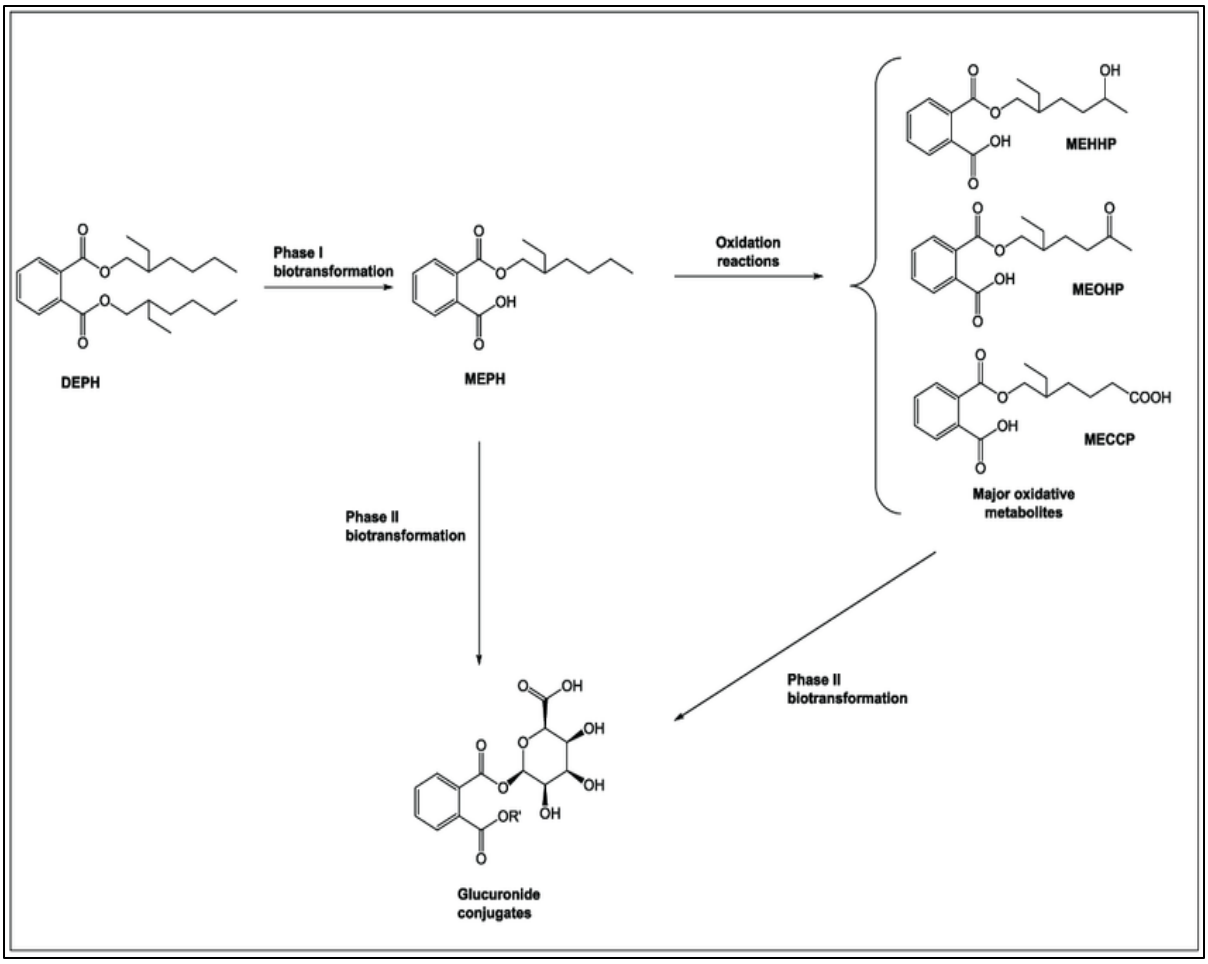

Figure 3: Metabolism of di(2-ethylhexyl) phthalate (DEHP) in humans

HEALTH EFFECTS OF PHTHALATES

Numerous studies have shown that phthalate levels and maternal body mass during pregnancy are strongly associated with care, and African American women are expected to have increased urine phthalate levels compared with those of expectant Caucasian women (Wenzel et al., 2018). The most prevalent phthalate metabolite discovered in the urine of pregnant women is MEP. The third-trimester urine excretion of humans was correlated with altered placental dimension and form and with prenatal phthalate contact. Additionally, it has been reported that the placenta may thicken and round out rather than be oval with an umbilical cord inserted in the center of the placenta as a result of exposure to certain phthalates (Zhang et al., 2020). Research conducted on adult male humans has demonstrated that contact with phthalates is linked to a decrease in male reproductive markers, such as the quantity of destruction of DNA in sperm, the size and quality of semen, sperm movement, and other measuring factors (Caporossi et al. 2020). Research on the potential harm that phthalates can cause to the male reproductive system is still ongoing. Additionally, preliminary studies indicate that phthalate consumption may be linked to metabolic issues, weight gain, resistance to insulin, diabetes,

breast cancer, endocrine disruption, and immune system dysfunction. Exposure to phthalates may be linked to adverse brain development in children, including the onset of ADHD and autistic traits, in addition to impaired cognitive and motor development, although these associations are not conclusive (Balalian et al., 2019).

Furthermore, 128 pregnant women were selected for a research study performed in South Korea, and blood and urine samples were collected. At the time of delivery, initial urine and blood samples from the umbilical cord were also taken. The anthropometric assessments of newborns included cord serum assessments of leptin levels, total cholesterol levels, and triglyceride (TG) levels, as well as length, weight, head diameter, and the ponderal index (PI) (Sol et al. 2020; Vuong et al. 2021). A urine sample was used to identify and study 2 metabolites of diethyl phthalate (DEHP): mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl5-oxohexyl) phthalate (MEOHP) (Su et al. 2019). A different study revealed links between elevated phthalate metabolite levels and a range of chronic conditions, such as hypertension (Mariana et al., 2023) and coronary heart disease (Su et al. 2019). The metabolite of DEHP, mono-ethylhexyl phthalate (MEHP), connects with all three-peroxisome proliferator-activated receptors (PPARs) (Wang and Qian, 2021). The synthesis of phthalate metabolites, such as DEHP, DnBP, DiBP, and BBzP, was inversely linked with genes associated with trophoblast transformation (PPARγ, AhR, and HCG). PPARγ is one of the major regulators of reproductive and growth functions, encompassing steroidogenesis, differentiation, fatty acid uptake and transport, and inflammation associated with parturition (Hasan et al., 2025). Human trophoblasts express PPARγ, which is necessary for placental development and operation. The breakdown products of phthalates may function as PPARγ agonists to control the differentiation of trophoblasts. Exposure of a metabolite of DEHP to a rat placenta during pregnancy caused dose-dependent activation of PPARγ and alterations in the expression of its downstream targets, such as cytochrome oxidase-2 and fatty acid transport proteins. These findings imply that phthalates and their metabolites modify placental function by acting as endocrine disruptors.

Phthalates disrupt both reproductive and metabolic health via numerous intertwined pathways, primarily acting as endocrine disruptors that interfere with hormonal production, receptor signaling, and gene regulation. In the reproductive system, phthalates impair the function of ovaries and testes by altering the synthesis and release of essential hormones such as estradiol and progesterone, disrupting the hypothalamic–pituitary–gonadal (HPG) axis, and inhibiting receptor signaling pathways necessary for normal follicle growth, ovulation, and spermatogenesis (Hlisníková et al. 2020; Land et al. 2025). These effects can result in decreased fertility, altered pubertal timing, increased risk of conditions such as polycystic ovary syndrome (PCOS), premature ovarian failure, and testicular dysgenesis syndrome, with evidence of impacts spanning multiple generations (Hlisníková et al. 2020; Land et al. 2025). Metabolically, phthalates induce oxidative stress, disrupt the metabolism of lipids and glucose, and modulate

nuclear receptors implicated in energy balance, thus contributing to increased risks of obesity, insulin resistance, and metabolic syndrome (Sedha et al. 2021; Hasan et al. 2025). The combination of hormonal disruption and cellular stress highlights the growing concern regarding phthalates for both reproductive and metabolic health in humans, as supported by recent research from 2020--2025.

EFFECTS OF THE SYNERGISTIC EFFECTS OF EDC BLENDS: COCKTAIL EFFECTS

Previous research has predominantly examined the effects of individual chemicals that disrupt the endocrine system, but recent research has focused on the combined effects of multiple EDCs. Baralić et al. (2020) performed an in vitro investigation on rats by comparing the subacute toxic effects of low doses of bis(2-ethylhexyl) phthalate (DEHP), di-butyl phthalate (DBP), and bisphenol A (BPA) with the effects of their mixture through different biochemical, hormonal, and hematological parameters. Compared with the impacts of single substances, the combination of small quantities of DEHP, DBP, and BPA caused drastic changes in body weight gain, water and food consumption, thyroid gland hormone levels, testosterone levels, cholesterol levels, liver-related biochemical metrics, and blood glucose levels. The mixture's more noticeable impacts are likely the result of the higher overall exposure, suggesting a dose-addition effect. Additionally, Caporossi et al. (2020) and Tassinari et al. (2021) investigated the reproductive risk of BPA and phthalates in binary and multicomponent combinations, with a focus on diseases of the male reproductive system. This study revealed that prenatal exposure to a mixture of DEHP and DBP changed the expression of the FSH, LH, and TSH genes and the generation of fetal testosterone, which in turn caused cumulative dose–additive spikes in disruptions of the reproductive tract.

Studying the "cocktail effects" of endocrine-disrupting chemicals (EDCs) faces significant challenges due to the complexity of real-world exposures, where humans encounter hundreds of chemicals simultaneously at low, environmentally relevant doses. Traditional toxicological methods, which focus on single chemicals at high doses, fail to capture synergistic or additive interactions that amplify toxicity even when individual components are below their no-observed-adverse-effect levels (NOAELs). For example, mixtures of phthalates, bisphenols, and pesticides may impede hormone signaling through overlapping pathways (e.g., ER, PPARγ), leading to reproductive or metabolic effects. Nonmonotonic dose responses further complicate risk assessment, as low-dose EDC combinations can paradoxically trigger stronger effects than higher doses can. Regulatory frameworks also lag, relying on outdated assumptions that ignore cumulative exposures, while testing all possible mixtures (e.g., >1,000 chemicals in consumer products) is logistically impossible (Kortenkamp, 2007).

Recent advances have aimed to bridge these gaps through integrated in vitro and in silico strategies. Projects such as EDC-MixRisk have used human brain organoids, zebrafish,

and mice to test mixtures that mimic real-life prenatal exposures, revealing sex-specific neurodevelopmental and metabolic disruptions at concentrations matching human biomonitoring data. In silico tools, such as the EuroMix toolbox, employ computational models (e.g., concentration addition, independent action) to predict mixture toxicity and prioritize high-risk combinations. High-throughput screening platforms now assess EDC interactions across nuclear receptors (PPARγ, ERα) and stress pathways (Nrf2), whereas omics technologies identify epigenetic or metabolic biomarkers of mixture effects. These approaches, combined with epidemiological data, are shifting regulatory paradigms, as evidenced by EFSA's 2023 guidance, which recommends the use of mixture-specific assessment factors to better reflect the "cocktail effect" and protect vulnerable populations (Kortenkamp, 2007).

EVIDENCE FROM METALAYSES AND LONGITUDINAL STUDIES

The adverse health effects of plastic-derived endocrine-disrupting chemicals (EDCs) are strongly supported by a growing body of evidence from human epidemiological research, particularly meta-analyses and longitudinal studies. Significant health concerns are linked to common plastic additives such as phthalates and bisphenols, with longitudinal cohort studies and meta-analyses consistently demonstrating these risks. For example, a recent global prospective cohort study and cost analysis by Hyman et al. (2025) directly implicated phthalate exposure from plastics in increased cardiovascular mortality, particularly in the 55–64 year age group, supporting the claim that these chemicals pose tangible public health threats. Similarly, meta-analyses have pointed to associations between bisphenol A (BPA) exposure and an increased risk of type 2 diabetes, as noted by Cart (2025), who referenced a 2018 meta-analysis by Lehmler et al. (2018). While specific meta-analyses on PFASs from plastics were not the primary focus of the immediate search, the general understanding is that PFAS compounds, which are widely used in some plastics, are persistent and linked to various health issues, a claim that further human cohort studies continue to be conducted.

The heightened vulnerability of children and pregnant women to EDCs is a critical aspect of this review, and longitudinal studies provide compelling evidence in this area. A study by Stratmann et al. (2024) suggested that prenatal exposure to a mixture of EDCs can adversely affect the behavioral development of children, especially girls. Furthermore, a systematic review by Brambilla et al. (2025) on EDCs in breastmilk highlighted the potential negative effects of early EDC exposure on mental and psychomotor development. Moreover, a general consensus from multiple studies, including a report by Toledano et al. (2024), indicates that prenatal EDC exposure can alter fetal development and lead to disorders in childhood or adulthood, reinforcing the review's emphasis on critical developmental windows.

The assertion linking plastic-derived EDCs to metabolic diseases such as obesity and diabetes is also well supported by recent research. A study discussing phthalates and bisphenols in foods explicitly reported that BPA exposure is associated with obesity in humans and disrupts

metabolic function (Calcaterra et al. 2024). The same study also strongly links BPA to type 2 diabetes risk on the basis of meta-analytic evidence, directly substantiating this claim.

Furthermore, studies concerning the potential role of EDCs in cancer are backed by comprehensive analyses. A wide-scope analysis by Zeng et al. (2024), which systematically integrated observational studies and randomized controlled trials over 20 years, revealed that exposure to most EDCs significantly increases the risk for most tumors in humans. This provides strong justification for including cancer as a major health outcome of concern. While meta-analyses and longitudinal studies in humans primarily establish associations and long-term outcomes, their findings are consistent with the mechanisms of bioaccumulation and endocrine disruption at multiple levels. The observed health effects across various organ systems (reproductive, metabolic, and neurological) support the idea that EDCs interfere with hormonal pathways. With respect to the emerging threat of microplastics and nanoplastics as vectors, direct longitudinal data establishing their specific contributions to EDC-related health outcomes are still lacking, as noted in a recent article by Li and Robaire (2025). However, the established risks from the EDCs they carry, as evidenced by the studies above, strongly suggest that microplastics can exacerbate human exposure and subsequent health problems.

CONCLUSION

The pervasive presence of plastics and their associated chemical additives, such as BPA, BPS, and phthalates, poses significant challenges, as these substances can leach into the environment and disrupt crucial hormonal systems essential for normal bodily functions. While human bodies may tolerate very low concentrations, escalating use and exposure lead to adverse health outcomes, a problem compounded by the ability of many of these endocrine-disrupting chemicals (EDCs) to cause significant disruptions even at low individual doses owing to additive or synergistic effects. Key findings indicate that these EDCs interfere with hormone levels, resulting in a range of detrimental health consequences, including impaired development, metabolic diseases, and reproductive problems, with their persistence, accumulation, and potential for combined impacts further exacerbating their threat to both human health and ecological stability.

Addressing the widespread impact of these endocrine disruptors necessitates a multifaceted approach. Comprehensive regulatory strategies must be implemented alongside concerted efforts to increase public awareness to effectively reduce exposure to these harmful chemicals. Continued and rigorous scientific investigations are paramount to fully understand the long-term and combined effects of EDCs, which will, in turn, inform the development of effective interventions to minimize associated health risks. Furthermore, prioritizing the development and adoption of safer alternatives to hazardous chemicals in consumer products,

coupled with improved and transparent product labeling, will play a crucial role in mitigating the adverse effects of these pervasive environmental contaminants and safeguarding public health.

FUTURE DIRECTIONS

Despite growing evidence linking plastic-derived endocrine disruptors (EDCs) to a range of adverse health outcomes, including reproductive, metabolic, neurodevelopmental, and oncological disorders, significant knowledge gaps persist regarding their mechanisms of action, cumulative effects, and long-term impacts on human health, especially at low and environmentally relevant doses. There is limited understanding of the health risks associated with chronic exposure to complex mixtures of EDCs and micro/nanoplastics, the effects of emerging plastic additives and BPA alternatives, and the potential for transgenerational toxicity, particularly in vulnerable populations such as pregnant women and children. Furthermore, research is needed to identify reliable molecular biomarkers, clarify dose–response relationships (including nonmonotonic effects), and elucidate the epigenetic and immunological pathways involved.

Future research should prioritize longitudinal human studies, comprehensive hazard assessments of new plastic chemicals, and the development of predictive models to better inform risk assessment and regulatory frameworks, ensuring adequate protection against the evolving threat of plastic-derived EDCs.

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