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REVIEW ARTICLE

Endocrine Disrupting Chemicals: An Overview of Their Toxicity and Implications

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ABSTRACT: Endocrine disrupting chemicals (EDCs) present a substantial threat to human health and the environment due to their adverse impacts on endocrine systems. EDCs disrupt hormonal signalling pathways by mimicking, blocking, or altering natural hormones, leading to developmental, reproductive, metabolic, neurological, and immune disorders. Challenges in assessing and regulating EDCs are discussed, emphasizing the need for continued research, surveillance, and regulatory measures. The review highlights the importance of understanding EDC complexities, types and sources, mechanism of action of EDCs, toxic consequences on the health of humans, and regulatory measures needed for safeguarding human and environmental health. Exposure occurs through dermal contact, inhalation and ingestion, with vulnerable populations, such as those exposed during prenatal and early life stages, particularly at risk. Endocrine-disrupting chemicals (EDCs) interfere with hormonal activity, potentially causing a range of health problems and diseases. In recent years, there has been increasing concern about the impact of EDCs on the environment and health, as they have been connected to numerous adverse effects in both humans and wildlife. EDCs are emerging contaminants that can cause significant health issues, even at low concentrations. This review highlights the environmental mobility of EDCs, their sources, and the various health problems they can cause.

INTRODUCTION

The Endocrine Disruptor Screening and Advisory Committee characterizes EDCs as external chemical substances or mixtures that disrupt the structure or function of the endocrine system, resulting in negative effects on individual organisms, their offspring, or groups of organisms. This definition is based on scientific evidence, the weight-of-evidence approach, and the precautionary principle. EDCs are substances that interfere with the body's endocrine system, which is responsible for regulating hormones. These chemicals have the ability to imitate hormones, obstruct hormone receptors, or disrupt the processes of hormone production, release, transport, metabolism, or elimination in the body. Consequently, they can interfere with the normal operation of the endocrine system, potentially causing a variety of health issues and developmental disorders. EDCs are present in numerous products, such as pesticides, plastics, cosmetics, food packaging, personal care items, and household cleaners. EDCs originate from various sources, including industrial processes, consumer products, and agricultural activities. These chemicals can enter the environment through manufacturing, use, and disposal, contaminating air, water, soil, and food. Examples of common endocrine-disrupting chemicals include phthalates, bisphenol A (BPA), dioxins, certain pesticides, and polychlorinated

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biphenyls (PCBs). Exposure to EDCs has been linked to several adverse health effects, including reproductive disorders, developmental abnormalities, immune system dysfunction, metabolic disorders, and certain types of cancer. Due to their potential to disrupt hormonal balance and impact human health, there is rising distress about the widespread presence of EDCs in the environment and their effects on both human and wildlife populations. EDCs interrupt the endocrine system by interfering with the synthesis, secretion, transport, binding, action, or elimination of natural hormones, thereby affecting processes vital for homeostasis, reproduction, development, and behaviour. EDCs exhibit estrogenic or androgenic activity and can originate from both anthropogenic and natural sources, including industrial processes and wastewater[1] Their interference with normal hormonal functions occurs through blocking or mimicking endogenous hormones and exhibiting endocrine-modulating characteristics[2-3] .Steroid estrogens and phenolic xenoestrogens, such as estrone, 17β-estradiol, 17α-ethinylestradiol, estriol, 4-nonyl phenols, and bisphenol A, are particularly concerning due to their potency in disrupting the endocrine system[4-7] .Even at low concentrations ranging from ng L^{-1} to g L^{-1}, these chemicals can cause birth defects, cancer, developmental disorders, and other adverse health effects[8-9] . EDCs exert their effects through various mechanisms, including receptor-mediated pathways, alterations in hormone synthesis, epigenetic modifications, disruption of metabolic pathways, and nonmonotonic dose responses[10-12]. EDCs change the regular functioning of the endocrine system through mechanisms such as blocking hormone receptors, disrupting hormone synthesis, and inducing epigenetic modifications. These disruptions can lead to adverse health effects, including reproductive disorders, developmental abnormalities, and metabolic disorders.

Wastewater treatment facilities face challenges in effectively removing EDCs, leading to their accumulation in activated sludge and effluents, posing potential risks to public health[13]. Human exposure to EDCs through environmental sources raises concerns about long-term health consequences, especially when contaminated sludge is used in agricultural practices[14] Additionally, EDCs are detected as trace-level pollutants in various aquatic environments, exacerbating environmental contamination[15,7]. EDCs can disrupt homeostatic systems through environmental or developmental exposures, potentially targeting any endocrine axis. Exposure to these chemicals, whether in utero or throughout life, may play a significant role in the environmental origins of various medical conditions, including diabetes, obesity, reproductive disorders, and cancers. The global concern over the occurrence, bioaccumulation, and persistence of EDCs highlights the urgent need for effective removal strategies and regulatory measures. The regulatory framework for EDCs operates at both international and national levels. Internationally, organizations such as the United Nations Environment Programme (UNEP), the World Health Organization (WHO), and the Organization for Economic Co-operation and Development (OECD) play crucial roles in assessing and managing the risks associated with EDCs. These organizations develop guidelines, methodologies, and conventions to address EDCs globally. At the national level, countries implement their regulatory frameworks based on scientific research and risk assessment. These frameworks typically involve conducting risk assessments, regulating chemical production and use, monitoring EDC levels, and promoting public awareness and education about EDCs and their potential health impacts (UNEP, WHO, OECD). Here we provide an overview of the sources, toxicity, and human health impacts of EDCs, as well as the challenges associated with their assessment and regulation. Finally, the review outlines public health concerns and suggests future research directions for addressing EDC contamination effectively. Future directions in EDC research and regulation require comprehensive approaches and collaboration to effectively address the challenges posed by these pervasive environmental pollutants.

Types of EDCs

EDCs encompass a diverse array of compounds classified based on various criteria such as chemical composition, origin, health effects, exposure sources, and mechanisms of action. Figure 1 outlines the types of EDCs [16,17,11,18]. These chemicals, including natural, synthetic, and metabolized derivatives of estrogen and

similar hormones, have drawn significant attention due to their potential harmful consequences on human health. Among the notable types of EDCs are phthalates, commonly found in plastics, personal care products, and medications, known to disrupt reproductive health by interfering with the endocrine system[19] . BPA, prevalent in epoxy resins, polycarbonate plastics, and consumer goods like food containers, mimics estrogen, posing risks to hormone regulation[20]. Polyfluoroalkyl substances used in industrial and commercial products like firefighting foams, and nonstick cookware leach into the environment and contaminate water, soil, and air. PCBs, extensively used in industrial applications such as those in the manufacture of electrical equipment, including transformers and capacitors, disrupt thyroid hormone function and possess endocrine-disrupting properties[21]. Organophosphate pesticides like chlorpyrifos and diazinon affect thyroid function and reproductive health by inhibiting acetylcholinesterase and interaction with hormone receptors[22]. Perfluorinated compounds (PFCs), present in non-stick cookware and waterproof clothing, disrupt hormone regulation, including thyroid function and reproductive hormones[23]. Dioxins, byproducts of industrial processes like metal smelting, chlorine bleaching, and waste incineration, are linked to reproductive and developmental issues[24]. Organochlorine pesticides, such as dichlorodiphenyltrichloroethane (DDT) and its metabolites, disrupt hormone function and impact reproductive health and development[25]. DDT (Dichlorodiphenyltrichloroethane) is a highly persistent insecticide used extensively in the mid-20th century to control pests like mosquitoes. Its widespread use led to environmental and health concerns due to its persistence, bioaccumulation, and impacts on wildlife. Phytoestrogens, naturally occurring compounds in plants like soybeans and flaxseeds, mimic estrogen, potentially disrupting hormone balance[26]. Heavy metals like lead, mercury, and cadmium disrupt endocrine function and interfere with hormone regulation, leading to various health problems[27]. They can disrupt the endocrine system by interfering with hormone synthesis, transport, and function. They can mimic or block the action of hormones, leading to hormonal imbalances and disrupting normal endocrine function. Additionally, heavy metals can accumulate in endocrine glands, impairing their function and affecting the release of hormones. Flame retardants, like PBDEs (Polybrominated diphenyl ethers) and OPFRs (organophosphate flame retardants), are recognized as EDCs due to their ability to disrupt hormone signaling pathways, potentially impacting reproductive, developmental, and metabolic health [28]. These chemicals can interfere with hormones like estrogen, androgen, and thyroid hormones, posing risks, especially during critical periods of development [20]. The understanding of these diverse EDCs is critical for addressing their potential risks and mitigating their impacts on human health and the environment.

Figure 1. Types of EDCs

Phthalates

Phthalates (pronounced "thalates") constitute a group of chemicals frequently added to plastics to enhance their flexibility and durability, making them versatile components in numerous consumer products (United States Environmental Protection Agency). These chemicals can be found in various items such as flooring, furnishings, paints, clothing, toiletries, certain toys and materials used in food packaging[29]. Phthalates enter our bodies through multiple routes, including ingestion of food and beverages stored in containers containing phthalate[30]. Inhalation of phthalates can occur when they leach from plastic products and combine with indoor dust, with children being particularly susceptible due to behaviors like hand-to-mouth contact and crawling on floors. Phthalate exposure during pregnancy has been associated with disruptions in the development of reproductive organs in boys, early onset of puberty in girls, and delayed language development.

Bisphenols

Bisphenols, including bisphenol S (BPS), bisphenol A (BPA), and bisphenol F (BPF), constitute a group of chemicals extensively utilized in the manufacturing of polycarbonate plastics and resins, notably in food packaging applications[31]. Among these, BPA stands out as the most prominent and widely employed bisphenol globally, being pervasive in several consumer products. Exposure to bisphenols primarily occurs through the consumption of food and beverages stored in containers or cans lined with bisphenol-containing resins, as well as handling thermal paper receipts and tickets. Research conducted across Europe has revealed the presence of bisphenols in the blood and urine of individuals, indicating widespread exposure. However, concerns arise due to their disruptive effects on the body's hormone system, with documented associations between BPA exposure and adverse health outcomes such as reproductive disorders, obesity, hormonal cancers, cardiovascular disease, and impaired brain development in children. These findings underscore the importance of regulating bisphenols to mitigate potential risks to human health.

Per and Poly Fluoroalkyl Substances (PFAS)

PFAS encompass a diverse family of more than 4,500 fluorinated chemical compounds prized for their grease and water-repellent properties, making them ubiquitous in various consumer products (EPA). These chemicals raise significant concerns due to their persistent nature, earning them the moniker "forever chemicals" as they exhibit minimal breakdown in the environment, persisting for generations (World Health Organization (WHO). Moreover, PFAS compounds are characterized by their bio accumulative properties, accumulating in the bodies of both wildlife and humans (Agency for Toxic Substances and Disease Registry (ATSDR)). Among the extensively studied members of this chemical group, many are recognized as endocrine disruptors, with documented associations with thyroid disease, obesity, and other adverse health effects[32]. These findings highlight the urgent need for stringent regulation and management of PFAS to safeguard public health and environmental well-being.

Poly Chlorinated Biphenyls (PCBs)

PCBs act as endocrine disruptors through various mechanisms. They can mimic or interfere with natural hormones, such as estrogen and thyroid hormones, by binding to their receptors, thus disrupting normal hormone signalling pathways[33]. PCBs can also alter hormone synthesis, metabolism, and transport, leading to dysregulation of hormone levels in the body [20]. Furthermore, PCB exposure can induce oxidative stress and inflammation, which can indirectly affect endocrine function[34].

Organophosphate Pesticides

Organophosphate pesticides (OPs) like chlorpyrifos and diazinon can act as endocrine disruptors through various mechanisms. They primarily exert their effects by inhibiting the activity of acetylcholinesterase, an enzyme involved in neurotransmission, leading to excessive accumulation of acetylcholine in the synaptic cleft[35] .This neurotoxicity can indirectly impact the endocrine system by disrupting neural signalling pathways involved in the regulation of hormone secretion and function[20]

Additionally, some OPs have been shown to interfere with hormone synthesis, metabolism, and receptor binding, particularly affecting the hypothalamic-pituitary-adrenal (HPA) axis and the thyroid gland[36] . Furthermore, OP exposure has been associated with modifications in reproductive hormone levels and adverse reproductive outcomes[35].

Perfluorinated Compounds

PFCs are known to disrupt endocrine function through various mechanisms, including interaction with hormone receptors, alteration of hormone synthesis, and interference with signalling pathways[37]. Synthetic chemicals like perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) can imitate or obstruct natural hormones by binding to estrogen and androgen receptors. PFCs may also interfere with signalling pathways, leading to dysregulation of hormone-responsive genes[38].

Dioxins

These toxic compounds bind to the aryl hydrocarbon receptor (AhR), triggering a cascade of events that disrupt normal endocrine function[39]. Through activation of AhR, dioxins can alter gene expression patterns, leading to dysregulation of hormone-responsive genes. Additionally, dioxins can affect steroid hormone synthesis and metabolism, further contributing to endocrine disruption[40].

Dichlorodiphenyltrichloroethane

DDT functions as an endocrine disruptor by interfering with hormonal signalling pathways, particularly those involving estrogen receptors[40]. Through its metabolite DDE (dichlorodiphenyldichloroethylene), DDT can bind to estrogen receptors and mimic the action of natural estrogens, leading to dysregulation of estrogen-responsive genes[41]. Moreover, DDT has been shown to disrupt thyroid hormone homeostasis by altering thyroid hormone synthesis and metabolism, potentially affecting neurodevelopment and reproductive function.

Phytoestrogens

Phytoestrogens, naturally occurring compounds found in plants, can act as EDCs by exerting estrogenic or antiestrogenic effects in the body[42]. These compounds, such as genistein and daidzein found in soy products, have structural similarities to estrogen and can bind to estrogen receptors, influencing hormone signalling pathways[43]. Additionally, phytoestrogens can modulate the activity of enzymes involved in hormone metabolism, impacting hormone levels and receptor activation[44].

Heavy metals

Lead, for example, can disrupt the hypothalamic-pituitary axis and interfere with hormone synthesis and secretion[45]. Cadmium has been shown to mimic the action of estrogen and interfere with hormone receptors, affecting reproductive function and bone metabolism[46]. The exposure has been linked to alterations in thyroid hormone levels and function, as well as disruption of the hypothalamic-pituitary-thyroid axis[47].

The Flame retardants

Flame retardants constitute a group of chemicals incorporated into numerous household products to mitigate or slow down the propagation of fires[48]. These substances are commonly added to items such as sofas, mattresses, electronic devices, carpets, building materials, and car seats[49]. Flame retardants are frequently released from the products they are applied to, including instances where flame retardant coatings on fabrics degrade and mix with household dust, leading to their accumulation in indoor environments (United States Environmental Protection Agency). Furthermore, these chemicals enter the environment through various pathways, including during product manufacturing, disposal, and recycling processes[50]. Of particular concern for human health are brominated flame retardants (BFRs) and organophosphorus flame retardants (OFRs), with many BFRs facing bans due to their adverse effects[51]. However, similar chemicals are often used as replacements, perpetuating similar health risks[52]. Despite bans, these chemicals persist in household goods, contributing to ongoing exposure[53]. BFRs are known to bioaccumulate, accumulating in the bodies of wildlife and humans, with some identified as

carcinogenic, endocrine disruptors, or neurodevelopmental toxins[54]. Several banned BFRs are internationally regulated as persistent organic pollutants (POPs) by the United Nations due to their enduring presence and global dispersion.

Sources of EDCs

EDCs are a significant concern due to their potential to interfere with hormone function, posing risks to both human health and the environment. These chemicals originate from various sources, including pesticides and herbicides, which often contain substances like atrazine known to disrupt endocrine function[55]. Plasticizers such as phthalates and BPA commonly found in plastics can leach into food, water, and the environment, leading to endocrine disruption. Additionally, personal care products like cosmetics and shampoos contain chemicals like parabens and triclosan, which have been identified as EDCs[56] . Industrial chemicals such as polychlorinated biphenyls (PCBs) and dioxins, often byproducts of industrial processes, can persist in the environment and act as EDCs[57]. Moreover, certain chemicals used in food packaging materials, like perfluoroalkyl substances (PFAS), can migrate into food, posing further risks as EDCs[58]. Understanding these diverse sources of EDCs is essential for implementing effective regulatory measures to minimize their detrimental effects on both human health and the environment. Figure 2 outlines the sources of EDCs.

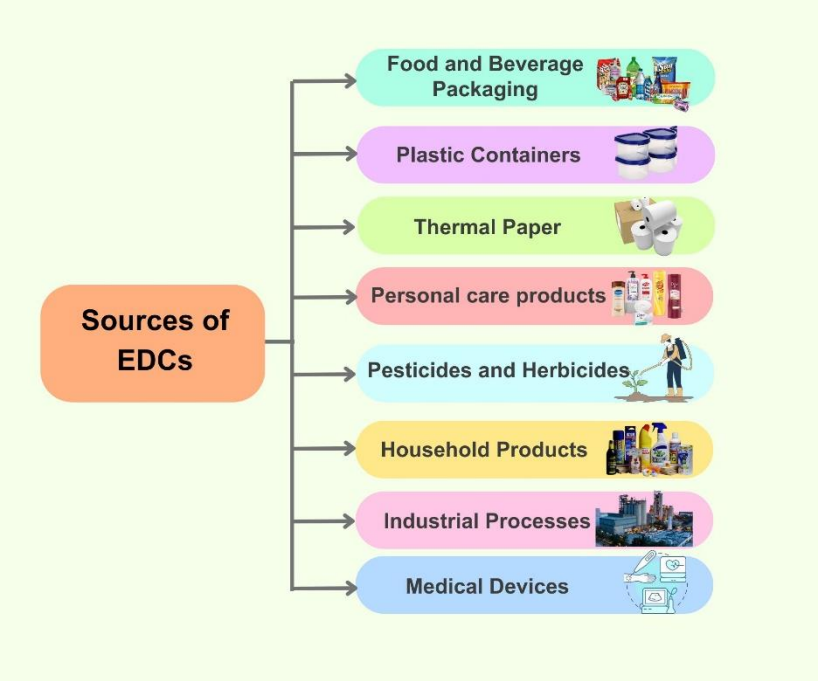

Figure 1. Sources of EDCs

Personal care products

Personal care products such as shampoos, conditioners, moisturizers, cosmetics, and others commonly contain EDCs, with phthalates being one prominent example[59]. Phthalates, a group of EDCs, are known to interfere with hormonal balance, leading to feminization effects in males across various species. This disruption in the endocrine system has been observed in wildlife, including polar bears, deer, whales, and otters, resulting in adverse effects such as testicular cancer, genital deformities, reduced sperm counts, and infertility[60] .Furthermore, triclosan, another EDC, can be found in certain toothpaste brands, adding to the array of potential exposures from personal care products[56]. To mitigate EDC exposure, individuals may opt for natural or homemade personal care products, thereby reducing the risk associated with synthetic chemicals commonly found in commercial products.

Drinking water

Drinking water poses a potential risk of contamination with EDCs such as atrazine, arsenic, and perchlorate, all of which have been associated with disruptions to the endocrine system[61]. Sources of contamination include septic systems, treated wastewater, stormwater runoff, industrial waste, oil spills, agricultural runoff, household products, and airborne pollutants, leading to both surface water (rivers and lakes) and groundwater contamination. Unfortunately, most wastewater treatment facilities are not equipped to effectively remove EDCs from sewage, resulting in the discharge of these chemicals into surface water. To mitigate exposure to EDCs in drinking water, employing high-quality water filtration systems both at the tap and in the shower/bath can be beneficial[62]. These filtration systems help in reducing the levels of EDCs, thus protecting against potential health risks associated with EDC exposure.

Canned foods

A study analysing 252 canned food brands found that 78 of them still utilize BPA, despite its well-established status as an endocrine disruptor[63]. BPA has been associated with various health issues, especially in vulnerable populations such as pregnant women, fetuses, and young children, but also in adults. In North America, BPA coats approximately 75 percent of cans, indicating that canned foods are a significant source of BPA exposure for consumers[64].

Conventionally grown produce

Pesticides, herbicides, and industrial runoff may coat conventionally grown fruits and vegetables in endocrine-disrupting chemicals. Recent studies have highlighted the presence of EDCs in conventionally grown produce. These chemicals, stemming from the use of synthetic pesticides, herbicides, and fertilizers, pose concerns due to their persistence in the environment and potential accumulation in crops. The research underscores the contribution of environmental contamination, including industrial runoff and packaging materials, to EDC exposure in food. While regulatory measures aim to mitigate pesticide residues, ongoing concerns prompt some individuals to opt for organic produce or thorough washing of conventionally grown fruits and vegetables to minimize EDC exposure.

CAFO Meat, poultry, and dairy products

Meat, poultry, and dairy products from concentrated animal feeding operations (CAFOs) often harbour antibiotics, hormones, and other industrial chemicals known to potentially disrupt the endocrine system[65]. To minimize exposure to these EDCs, consumers are advised to opt for animal products sourced from free-range, organic, and locally-raised livestock, preferably from small farms that eschew the use of such chemicals[66]. CAFOs, where animals are housed in high densities, often use hormones and antibiotics to promote growth and prevent diseases. These substances can enter the environment through waste runoff and contaminate soil and water sources surrounding CAFOs, potentially exposing animals to EDCs. Research has found residues of EDCs such as synthetic hormones, antibiotics, and persistent organic pollutants in meat and dairy products sourced from animals raised in CAFOs. These findings underscore concerns about EDC exposure through the consumption of animal products and highlight the need for monitoring and regulatory measures to address EDC contamination in the food supply.

High-Mercury fish

Fish contaminated with high levels of mercury and other heavy metals are problematic because such metals disrupt hormonal balance[67]. Shark, swordfish, king mackerel, marlin, and tilefish are among the worst offenders but even tuna has been found to be contaminated with dangerously high levels of mercury and heavy metals[68] Farmed fish (the "CAFOS of the sea") also tend to be higher in contaminants and are best avoided. When eating seafood, smaller fish such as sardines, anchovies, and herring tend to be low in contaminants and high in omega-3 fats. Consuming fish contaminated with high levels of mercury and other heavy metals poses a risk to hormonal balance[69].

Kitchen products

Kitchen products such as plastic containers and non-stick cookware, commonly found in households, represent another potential source of exposure to EDCs. Plastic containers may contain BPA or other EDCs, which can leach into food, particularly when exposed to heat[70]. Additionally, PFAS used in non-stick cookware to create surfaces resistant to stains and water are known to be toxic and persistent both in the body and the environment[71]. Heating non-stick cookware can lead to the release of perfluorooctanoic acid (PFOA), which is associated with thyroid disease, infertility, and developmental and reproductive issues[72]. Healthier alternatives include ceramic and enamelled cast iron cookware, which are durable, easy to clean (even stubborn cooked-on residues can be removed after soaking in warm water), and completely inert, ensuring they do not release EDCs into food.

Cleaning products

Household cleaning products commonly used for various surfaces like floors, toilets, ovens, and windows may harbour potential EDCs. For example, nonylphenol ethoxylates (NPEs), frequently found in laundry detergents and all-purpose cleaners, are banned in Europe due to their potency as endocrine disruptors, which can induce male fish to undergo feminization[65]. Fortunately, creating cleaning solutions using simple ingredients like vinegar, baking soda, essential oils, and coconut oil is a viable alternative. These homemade alternatives offer effective cleaning properties without the risk of exposure to harmful EDCs.

Office products

Ink cartridges, toner, and other solvents common in office environments are sources of endocrine-disrupting chemicals. However, it's worth noting that certain office products, such as thermal paper receipts, ink cartridges, and plastics used in office equipment, may contain chemicals that have been identified as EDCs or have the potential to disrupt endocrine function. For example, BPA, a well-known EDC, has been used in the production of thermal paper receipts and some plastics commonly found in office supplies. Studies have investigated the presence of EDCs in plastics, including those used in consumer goods and electronics, as well as in paper products like receipts. Reports from regulatory agencies that monitor chemical safety in consumer goods highlight the emerging concerns and findings related to EDCs in various products, including those commonly found in office settings.

Cash register receipts

Cash register receipts, commonly printed on thermal paper, are coated with a substance that darkens when exposed to heat (BPA). The process involves the application of heat by the printer in a cash register, allowing for the printing of numbers and letters. Thermal paper contains BPA, and simply handling thermal paper can lead to an increase in bodily levels of BPA[73]. (Research indicates that holding thermal paper for just five seconds is sufficient to transfer BPA onto the skin, with the amount of BPA transferred increasing by approximately tenfold if fingers are wet or greasy)[74]. Moreover, given that receipts are often stored alongside paper currency in wallets, there's a possibility that paper currency may also be contaminated with BPA due to contact with receipts.

Toxicity for human health

EDCs pose various risks to human health due to their ability to interfere with hormone function. Briefly, these risks include reproductive disorders, with exposure linked to infertility, reduced fertility, and impaired development of reproductive organs[20]. Additionally, exposure to EDCs during critical periods of fetal development can lead to adverse effects on neurodevelopment, cognition, behaviour, and growth, contributing to developmental disorders [75]. Metabolic disorders such as obesity, diabetes, and metabolic syndrome have also been associated with EDC exposure, possibly due to effects on insulin signalling and lipid metabolism[76]. Furthermore, some EDCs have been implicated in the development of hormone-related cancers, including breast, prostate, and testicular cancers, through their estrogenic or androgenic effects[20]. Immune system dysfunction is another concern, as EDC

exposure may disrupt immune function, leading to increased susceptibility to infections, autoimmune diseases, and allergic reactions. These references highlight the significant health risks associated with exposure to endocrine-disrupting chemicals, underscoring the importance of regulation and mitigation strategies to protect human health.

Exposure to EDCs is increasingly linked to disruptions in human health, particularly concerning reproductive and developmental systems, prompting urgent research priorities to understand these mechanisms[77]. Despite the complexity of human studies conducted under various experimental designs and exposure conditions, deciphering the exact impact of EDCs on health remains challenging. Nevertheless, exposure to EDCs has been associated with numerous adverse health outcomes affecting various systems.

Reproductive systems

EDCs are known to significantly impact the reproductive system, affecting both male and female fertility. These chemicals, commonly found in everyday products such as plastics, pesticides, and personal care items, have the ability to mimic or interfere with hormones, thereby disrupting normal endocrine function[78]. Studies have shown that in males, exposure to EDCs can lead to reduced sperm quality, altered hormone levels, and increased risk of reproductive disorders such as testicular cancer. Conversely, females exposed to EDCs may experience menstrual irregularities, decreased fertility, and complications during pregnancy[79]. Moreover, the effects of EDC exposure extend beyond immediate reproductive health, potentially influencing future generations through epigenetic changes[80]. Given these concerns, there is a pressing need for mitigation strategies, including the regulation of EDCs in consumer products and environmental conservation efforts, to safeguard reproductive health and overall well-being[81]. Following Figure 3 details the effects of EDCs on male and female reproductive systems.

Male reproductive system

In the male reproductive system, EDCs have been commonly linked to two primary effects: impaired reproductive function resulting in decreased semen quality and infertility [82]. Moreover, EDC exposure during fetal development can lead to urogenital abnormalities like cryptorchidism and hypospadias[83,36], although temporal trends in these effects remain poorly explained by existing studies and meta-analyses. Evidence from human and animal studies suggests that several chemicals can disrupt the development of the male reproductive tract through endocrine mechanisms. A comprehensive review of the correlation between environmental chemical exposure and prostate cancer incidence and testosterone levels reveals consistent outcomes across diverse investigations, albeit with certain discrepancies. Notably, occupational exposure to pesticides, as evidenced by studies such as the American Agricultural Health Study and research conducted in Canada, France, and the USA, consistently links such exposure with an increased risk of prostate cancer American Agricultural Health Study[84] Nevertheless, a study from the Netherlands reported an inverse association with self-reported occupational pesticide use, while another study from Australia failed to establish a significant correlation. Regarding testosterone levels, the testicular dysgenesis syndrome theory suggests that prenatal exposure to EDCs affects fetal Leydig cell proliferation and development, leading to lifelong reduced testosterone production. Cross-sectional studies across various age groups showed a negative association between DEHP (di ethyl hexyl phthalates) or its metabolite (mono ethyl hexyl phthalate) and testosterone levels[85]. However, findings from studies on prenatal exposure were less consistent, with some showing negative associations at birth and during childhood but not in adulthood[86]. The longitudinal Raine study from Australia reported a positive association between prenatal exposure to certain phthalates and testosterone levels at ages 20–22 years.

There is consistent evidence linking certain environmental chemicals to prostate cancer risk and testosterone levels, the relationship with semen quality parameters varies across different chemicals and study populations. Further research is needed to elucidate the mechanisms underlying these associations and to develop effective strategies for mitigating the adverse effects of EDC exposure on human health.

Female reproductive system

Various disorders of the female reproductive system, including polycystic ovary syndrome (PCOS), lactation disorders, breast diseases, endometriosis, and uterine leiomyomas, have been associated with EDC exposure[87]. Exposure to specific EDCs like phthalates and DDT has been tentatively linked to these conditions. Additionally, the increase in breast cancer incidence among women in industrialized nations over the past decades has been attributed to exposure to hormonally active EDCs, particularly xenoestrogens[88,89]. Moreover, daughters of mothers who received DES during pregnancy have shown an increased incidence of rare vaginal cancers, possibly due to in-utero exposure to high doses of DES (di ethyl stilbesterol) activating various pathways[90].

Research into the association between EDCs and PCOS has revealed significant evidence linking PCOS to PFAS and BPA. Several cross-sectional studies have consistently reported positive associations between PCOS and various PFAS, including perfluoro dodecanoic acid in China, PFOA and PFOS in the United States, and PFOS in the UK (China [91]. Accumulating evidence suggests a potential link between BPA exposure and PCOS, with six cross-sectional studies reporting positive associations, although some variability exists in these findings. However, the understanding of the relationship between other EDCs, such as PBDEs, phthalates, polycyclic aromatic hydrocarbons (PAHs), and triclosan, and PCOS is still in its infancy, and conclusive conclusions cannot be drawn at this time. While some studies show no significant associations, others report positive or mixed associations with PCOS, highlighting the need for further research in this area.

The evidence linking PFAS and BPA exposure to PCOS is relatively strong, additional research is required to fully understand the role of other EDCs in PCOS development. Furthermore, further investigations into the associations between EDCs and other female reproductive conditions are warranted to elucidate potential health risks and develop effective mitigation strategies. Figure 3 represents the effects of EDCs on male and female reproductive systems.

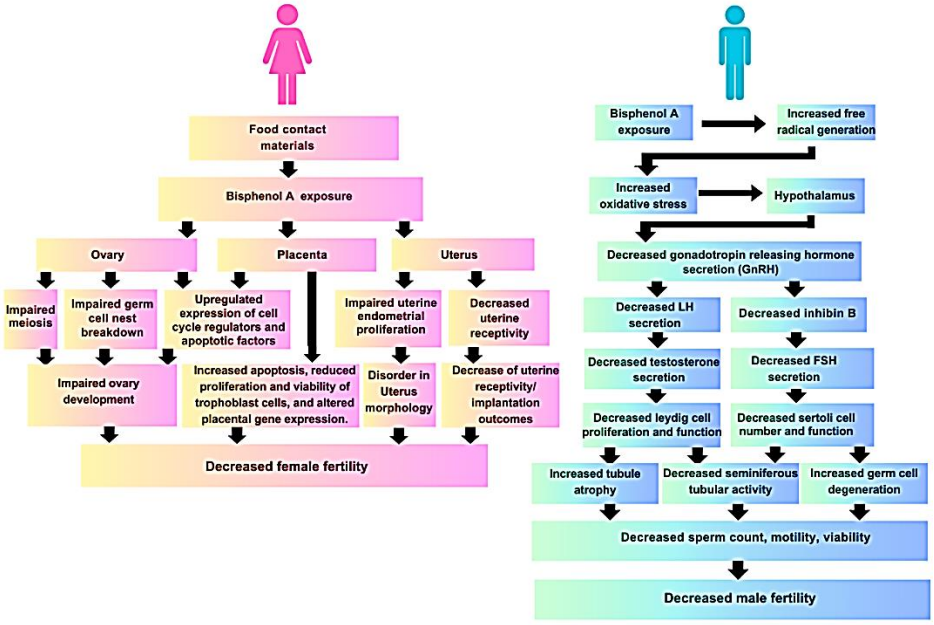

Figure 2. Effect of EDCs on Male and Female Fertility.

Neurodevelopment

EDCs may exert neurobiological and neurotoxic effects, particularly on neuroendocrine cells in the brain[92]. Exposure to EDCs during pregnancy can impact fetal neurodevelopment through distinct hormonal pathways.

Maternal thyroid imbalance, particularly during the first trimester when the fetus relies on transplacental thyroid hormone supply, can lead to permanent neurodevelopmental consequences in children, including attention-deficit disorder, autism spectrum disorder, and cognitive and behavioural dysfunction. Additionally, disruptions in sex hormone function can have differing effects on brain development. Epidemiological studies, drawing from extensive toxicological literature on EDC effects in animals, have generally mirrored these findings in humans. Recent research supports associations between prenatal exposure to PBDEs and organophosphate pesticides with decreased intelligence quotient (IQ) and between PBDEs, BPA, organophosphate pesticides, and pyrethroids with behavioural outcomes. Furthermore, associations have been identified between prenatal exposure to organophosphate pesticides and pyrethroid pesticides with autism spectrum disorder. Research investigating the association between prenatal exposure to EDCs and autism spectrum disorder (ASD) has faced challenges due to the relatively low frequency of these conditions. However, some compelling evidence has emerged, particularly regarding organophosphate pesticides. Studies conducted in various regions, including California, New York State, and Cincinnati (OH, USA), have reported associations between prenatal exposure to organophosphate pesticides and an increased risk of ASD or higher scores on autism-related scales. Additionally, investigations into pyrethroids have suggested a similar association with ASD risk, particularly in children residing in areas with higher pyrethroid use[93]. However, studies examining other EDCs have not provided clear evidence regarding ASD risk. In contrast, research on prenatal exposure to EDCs and child behavioural outcomes, particularly attention-deficit disorder (ADD) and related behaviors, has yielded more consistent findings. For instance, prenatal exposure to PBDEs has been associated with adverse behavioural outcomes in children across various regions, including the Salinas Valley (CA, USA), Cincinnati (OH, USA), and New York City (NY, USA), although some European studies did not identify such associations, possibly due to differences in exposure prevalence. Similarly, studies from France, the USA, and Denmark have linked urinary pyrethroid concentrations during pregnancy to increases in ADD scores and internalizing and externalizing symptoms in children[94].

Furthermore, evidence regarding prenatal exposure to BPA and child behaviour is substantial, with numerous studies reporting detrimental associations, including increased externalizing behaviors and other behavioural effects, particularly in boys[95]. Similarly, studies investigating other EDCs such as organophosphate flame retardants (OPFRs) have shown consistent albeit sparse evidence of associations with behavioural problems, while findings regarding phthalates have been more diverse.

Obesity and diabetes

Obesity and metabolic disorders have been linked to EDCs, which interfere with various metabolic signalling pathways including peroxisome proliferator-activated receptors, estrogen receptors, and thyroid hormone receptors. Prospective studies measuring exposure in utero and cross-sectional studies in adults have demonstrated this disruption. Recent data further support previous findings of prenatal exposure to BPA being associated with childhood obesity, and indicate potential associations between prenatal exposure to PFAS and phthalates with child adiposity. Evidence is also emerging linking adult exposure to PFAS and phthalates with gestational diabetes, impaired glucose tolerance, and obesity. Furthermore, these chemicals, along with bisphenols, may be linked to the development of type 2 diabetes.

Recent research has shed light on the potential impact of environmental exposures, particularly to EDCs, on pregnancy outcomes and metabolic health. Specifically, studies have highlighted the association between EDC exposure during pregnancy and the development of gestational diabetes, as well as the role of adult exposure in contributing to weight gain and type 2 diabetes [96-98]. During pregnancy, exposure to perfluoroalkyl substances (PFAS) has emerged as a significant concern, with several cohort and case-control studies implicating PFAS exposure in gestational diabetes and impaired glucose tolerance. Studies from various countries including China, the USA, Canada, Denmark, and Spain have reported associations between PFAS exposure and

gestational diabetes[6]. Similarly, some studies have linked phthalate exposure during pregnancy to impairments in glucose tolerance and gestational diabetes, although findings have been inconsistent across studies[99]. Additionally, bisphenols and parabens have been suggested as potential contributors to gestational diabetes, although the evidence for this association remains limited. In the context of adult exposure, mounting evidence suggests a link between phthalate exposure and weight gain, particularly in women. Studies have consistently reported associations between urinary concentrations of phthalate metabolites and weight gain, supporting previous findings from large cohort studies[100]. Similarly, serum concentrations of PFAS have been associated with weight gain across both sexes, with mechanistic insights suggesting that certain PFAS compounds may influence resting metabolic rate and energy expenditure. However, findings from communities with high PFAS exposure levels have been mixed, highlighting the complexity of environmental exposures and their effects on metabolic outcomes. In terms of type 2 diabetes, occupational studies have provided initial evidence of the diabetogenic effects of persistent EDCs, particularly PFAS. While some populations exposed to PFAS-contaminated drinking water did not show associations with diabetes, blood concentrations of PFAS have been linked to diabetes risk in Swedish and American cohorts[101]. Moreover, bisphenols and other non-persistent chemicals have also been implicated in diabetes risk, with case-control studies and prospective cohort studies reporting associations between (BPA) exposure and increased diabetes risk[102].

4.4 Birth Outcomes:

Fetal growth and gestational length, particularly low birth weight and preterm birth are significant indicators of future health[103]. There is a growing awareness that environmental exposures, particularly EDCs, can trigger the "thrifty phenotype" concept initially proposed by Barker and colleagues. This phenomenon involves fetal metabolism being programmed conservatively, which proves maladaptive outside the womb, leading to increased adiposity in childhood and cardiovascular risks later in life. Laboratory studies increasingly demonstrate that EDCs can affect gestational length, intrauterine growth, and metabolic programming[104]. Additionally, anogenital distance measurements at birth have been found to persist into adulthood and can predict infertility and reduced sperm count[105].While previous assessments did not establish probable evidence for causation between prenatal EDC exposure and birth outcomes, there are three noteworthy associations: between PFAS exposure and reduced birth weight, phthalate exposure and preterm birth, and phthalate exposure and reduced anogenital distance in male offspring.

Effect of EDC on blood pressure

The impact of endocrine-disrupting chemicals (EDCs) on blood pressure has garnered attention in recent research. A cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES) investigated the relationship between urinary EDCs, such as phthalates, and blood pressure in children aged 6–19 years. The findings indicated a significant increase in blood pressure associated with a threefold rise in urinary phthalate levels, specifically di(2-ethylhexyl) phthalate (DEHP)[106]. Moreover, a study conducted on individuals residing near a dioxin-contaminated area demonstrated a correlation between elevated serum dioxin levels and increased diastolic blood pressure[107]. Furthermore, research conducted on Taiwanese and Florida adults exposed to dioxins revealed a correlation between hypertension prevalence and serum levels of polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Similarly, elevated blood pressure was associated with high serum levels of polychlorinated biphenyls (PCBs). While these studies provide insights into the potential effects of EDCs on hypertension, further research involving larger and more diverse cohorts is warranted to validate the association between EDC exposure and the risk of hypertension.

Effect of EDCs on various glands

EDCs exert profound effects on various glands throughout the body, disrupting the delicate balance of hormone secretion and regulation. These chemicals, ubiquitous in modern environments due to their presence

in plastics, pesticides, and personal care products, have been extensively studied for their impact on endocrine function[108]. EDCs can interfere with the normal functioning of glands such as the thyroid, adrenal, and pituitary glands, leading to dysregulation of hormone production and signalling pathways[20]. Moreover, exposure to EDCs has been linked to disruptions in pancreatic function, potentially contributing to metabolic disorders such as diabetes. Understanding the effects of EDCs on these glands is essential for elucidating their role in various health conditions and developing strategies to mitigate their adverse effects.

Adrenal gland

The adrenal gland is a crucial component of the human endocrine system, yet studies examining the effects of EDCs on this gland are limited. The adrenal glands possess unique structural and biochemical characteristics that make them particularly susceptible to the actions of EDCs. These features include high blood flow, a lipophilic structure due to the abundance of polyunsaturated fatty acids in cell membranes, and the presence of cytochrome P450 (CYP450) enzymes that produce toxic metabolites and free radicals[109].

The primary focus of studies investigating the effects of EDCs on the adrenal gland has been their interference with the biosynthesis and metabolism of steroidal hormones. Key enzymes involved in adrenal steroidogenesis, such as aromatase, 5-α reductase, and various hydroxysteroid dehydrogenases, play critical roles in metabolic pathways, and EDCs can disrupt their function. Xenoestrogens, in particular, have been shown to impair adrenal function by inhibiting these enzymes[110]. Additionally, the Steroid Acute Regulatory Protein (StAR), which regulates the initial step of adrenal steroidogenesis, is also a target of EDCs [111].The complex interplay between hundreds of chemicals and drugs and the HPA axis means that each step of steroidogenesis may be affected by EDCs, with different chemical disruptors acting on various stages of the process[112]. It is crucial to recognize that even partial impairment of adrenal function due to EDC exposure can have significant ramifications for human health. Moreover, the bioaccumulation of these chemicals in adipose tissue can lead to the formation of a "cocktail" of EDCs, with clinical effects potentially manifesting only after years of constant, low-dose exposure. (For example, studies have shown that hexachlorobenzene can disrupt corticoid hormone function in animal models, such as Wistar rats)[113]. These chemicals have the potential to interfere with crucial hormonal pathways, posing significant risks to human health. Further research in this area is warranted to fully elucidate the impact of EDCs on adrenal function and to develop strategies for mitigating these effects. Following Figure 4 details the effect of EDCs on the adrenal medulla.

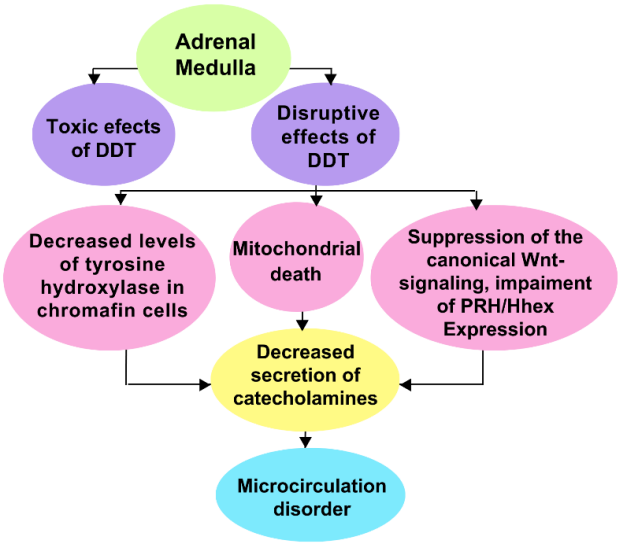

Figure 3. Effects of EDCs on adrenal medulla.

Pituitary gland

The diencephalic system is particularly susceptible to the effects of EDCs, which have the potential to disrupt proper central nervous system (CNS) function by mimicking neurotransmitter actions and binding to endocrine receptors[20]. Among the various components of the diencephalic system, the pituitary gland is a significant target for EDCs. Consequently, these chemicals can exert influence over multiple endocrine axes, leading to a diverse range of clinical manifestations associated with exposure to pollutants. One notable consequence of EDC action on the pituitary gland is the disruption of normal puberty timing. EDCs can interfere with the secretion and regulation of pituitary hormones involved in the initiation and progression of puberty. As a result, individuals may experience either precocious puberty, characterized by the premature onset of sexual maturation, or delayed puberty, where the onset of puberty is significantly postponed[114]. These alterations in pubertal timing can have profound effects on physical and psychological development, impacting overall health and well-being. Additionally, exposure to EDCs can disrupt the circadian rhythm[115] which is regulated in part by pituitary hormones. Circadian disruption refers to disturbances in the body's internal clock, leading to irregular sleep-wake cycles and other physiological processes that follow a daily rhythm. EDC-induced changes in pituitary hormone secretion patterns can contribute to circadian disruption, resulting in sleep disturbances, fatigue, and other related symptoms. EDCs exert significant effects on the pituitary gland, disrupting its normal function and subsequently influencing various endocrine axes. This disruption can manifest in clinical outcomes such as alterations in puberty timing and disturbances in circadian rhythms. Understanding the impact of EDCs on the pituitary gland is essential for elucidating the mechanisms underlying these clinical manifestations and developing strategies to mitigate their adverse effects on human health.

Thyroid gland

EDCs have been linked to disruptions in thyroid hormone levels, affecting hormone synthesis, release, transport, metabolism, and clearance, thereby potentially contributing to various health issues[116]. Studies have demonstrated that EDCs can disrupt various metabolic signalling pathways, including peroxisome proliferator-activated receptors, estrogen receptors, and thyroid hormone receptors, both in prospective studies measuring in-utero exposure and in cross-sectional studies involving adults.

Numerous environmental chemical substances have been identified as capable of interfering with iodine absorption by inhibiting the Sodium-Iodide symporter channel. Among these substances, perchlorate and thiocyanate stand out for their ability to disrupt thyroidal metabolism by inhibiting NIS (an integral plasma membrane protein) function. The NIS channel is responsible for transporting iodine into thyrocytes, and given the critical role of iodine in the biosynthesis of thyroid hormones, any alteration in NIS function can significantly impair thyroid function. Perchlorate, commonly found in explosives, fertilizers, and airbags, has been detected at high levels in various sources, including foods such as milk, vegetables, fruits, and eggs in the United States. Thiocyanate, present in cigarette smoke and Brassicaceae plants, is another notable inhibitor of NIS function. Studies involving 3,100 subjects exposed to perchlorate, thiocyanate, and nitrates revealed a significant decrease in free thyroxine levels, particularly pronounced in pubertal individuals, without a corresponding increase in TSH (thyroid stimulating hormone) levels. The widespread presence of perchlorate, thiocyanate, and nitrates in various environmental sources, including industrial products, foods, and potable water, underscores the potential for widespread exposure to these EDCs. These substances can disrupt NIS function by binding to the NIS transporter and blocking iodide transport, ultimately leading to reduced iodine bioavailability. Consequently, individuals exposed to high doses of these EDCs, especially in areas with iodine deficiency, may be at increased risk of developing hypothyroidism. While current data do not provide conclusive evidence, the implementation of iodine supplementation during pregnancy and in children may offer protection against the adverse effects of these EDCs. However, further studies are warranted to better understand the dose-

effects relationship and to explore potential preventive measures in populations at risk of exposure to perchlorate, thiocyanate, and nitrates. Perchlorate and thiocyanate are prominent examples of EDCs capable of disrupting thyroid function by inhibiting NIS activity. Their widespread presence in various environmental sources underscores the importance of continued research to elucidate their effects and identify strategies for mitigating their impact on thyroid health.

Endocrine glands cancer

Numerous scientific institutions, including the European Commission, European Environmental Agency, The Endocrine Society, WHO/UNEP, and IARC (International Agency for Research on Cancer), have conducted studies investigating the association between EDCs and various cancers affecting the testis, prostate, thyroid, and breast, suggesting that exposure to certain EDCs may serve as a risk factor in the development of these tumours. For instance, fungicides, pesticides, PBDEs, organochlorides, PCBs, dichlorodiphenyldichloroethylene (DDE), arsenic, and cadmium have been implicated in the etiopathogenesis of testicular cancer, potentially contributing to the development of testicular dysgenesis syndrome (TDS)[117]. Similarly, pesticides, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), PCBs, and solvents have been associated with thyroid cancer. Biocides, defined as substances capable of destroying, eliminating, or rendering harmless harmful organisms, have also emerged as potential contributors to cancer development. A study utilizing data from a Connecticut case-control study found a significantly increased risk of thyroid cancer associated with occupational exposure to pesticides and biocides, particularly among male adults[118].Furthermore, PCBs, dioxins, cadmium, phytoestrogens, diethylstilbesterol (DES), furans, and ethylene oxide have been implicated in the development of breast cancer, highlighting the diverse range of EDCs potentially involved in breast carcinogenesis. Additionally, arsenic, cadmium, PCBs, and pesticides have been linked to prostate carcinogenesis.

A recent study investigated the incidence of these tumours in polluted areas in Italy known as the Italian National Priority Contaminated Sites (NPCSs). The study found a significantly higher incidence of breast and prostate cancers in these areas. Interestingly, while breast cancer incidence appeared to be increased in each area, prostate cancer incidence varied, showing increases in certain areas and decreases in others[119]. These findings suggest that a wide range of chemicals, including pesticides, biocides, PCBs, dioxins, and heavy metals, may contribute to the development of various cancers, emphasizing the importance of further research and regulatory measures to mitigate exposure to EDCs and reduce cancer risk [120].

6. Mechanisms of Action of EDCs

The mechanisms by which EDCs exert their effects on the body are multifaceted and complex. These chemicals can disrupt normal physiological activities through various pathways, including binding to hormone receptors, altering gene expression, and interfering with hormone synthesis or metabolism[20]. EDCs often mimic the actions of hormones by binding to hormone receptors, thus activating signalling pathways and eliciting physiological responses. Additionally, they may inhibit the activity of endogenous hormones by occupying receptor sites or interfering with downstream signalling pathways[121]. Some EDCs can modulate hormone biosynthesis independently of receptor interaction, while others inhibit hormone biosynthesis or degradation, altering hormone levels without directly binding to receptors[122]. Moreover, EDCs can compete with natural hormones for binding proteins in the blood, affecting hormone availability, or influencing the synthesis or degradation of hormone-binding transport proteins, thereby impacting total hormone concentration[123]. Furthermore, certain EDCs may mimic endogenous hormones and stimulate receptor activity, while others may inhibit hormone receptor expression, reducing receptor availability and altering endocrine function[124]. Understanding these diverse mechanisms of action is crucial for comprehending the broad-ranging effects of EDCs on endocrine function and overall health. These mechanisms have been depicted in Figure 5.

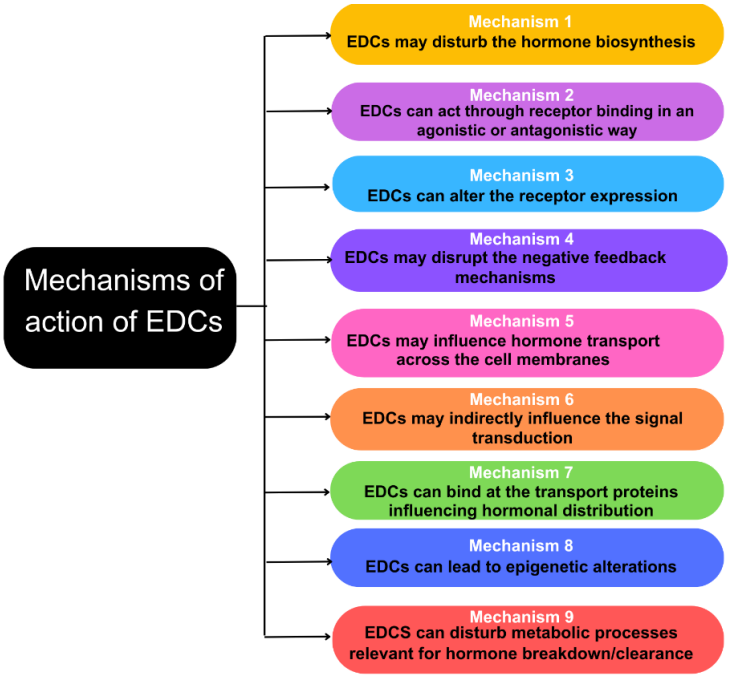

Figure 4. Mechanism of action of EDCs

Direct hormonal activity

Direct hormonal activity is a significant mechanism through which EDCs exert their effects on the endocrine system. This mechanism involves EDCs directly interacting with hormone receptors, mimicking or blocking the action of endogenous hormones and subsequently modulating cellular signalling pathways. Several studies have elucidated the direct hormonal activity of various EDCs, providing insights into their potential adverse effects on human health.

BPA, a well-studied EDC, exemplifies this mechanism by exhibiting estrogenic activity. BPA can bind to estrogen receptors (ERs) α and β, mimicking the action of natural estrogen[125]. This binding activates estrogenic pathways, leading to downstream effects on gene expression and cellular functions associated with estrogen signalling. Furthermore, BPA can also act as an antagonist to estrogen receptors in certain contexts, interfering with normal estrogenic signalling[126].The direct estrogenic activity of BPA has been linked to adverse health outcomes, including reproductive abnormalities, metabolic disorders, and carcinogenesis [127].Similarly, certain pesticides and herbicides possess direct hormonal activity, impacting the function of androgen receptors (ARs) and disrupting androgen signalling pathways. For instance, vinclozolin, a fungicide, acts as an antiandrogen by binding to ARs and inhibiting the action of endogenous androgens such as testosterone[128]. This interference with androgen receptor function can lead to impaired reproductive development and function, as well as other androgen-dependent physiological processes. Phytoestrogens, found naturally in certain plants, also exhibit direct hormonal activity by binding to estrogen receptors and modulating estrogenic signalling pathways. Examples of phytoestrogens include genistein and daidzein, which are commonly found in soy-based products. These compounds can bind to estrogen receptors with varying affinities, exerting both agonistic and antagonistic effects depending on the tissue and hormonal context. Consequently, exposure to phytoestrogens during critical periods of development may disrupt normal endocrine function and contribute to adverse health outcomes. Furthermore, pharmaceuticals and personal care products containing synthetic hormones, such as contraceptive pills and hormone replacement therapies, can also act as EDCs and directly influence hormone receptor signalling. For instance, synthetic progestins commonly used in hormonal contraceptives can bind to progesterone receptors and elicit biological responses similar to natural progesterone, albeit with varying

degrees of potency and selectivity. Direct hormonal activity is a crucial mechanism underlying the actions of EDCs on the endocrine system. Through interactions with hormone receptors, EDCs can disrupt normal hormonal signalling pathways, leading to a myriad of adverse health effects.

Receptor inhibition

Receptor inhibition is a pivotal mechanism through which EDCs exert their effects on the endocrine system. This mechanism involves EDCs binding to hormone receptors and blocking the action of endogenous hormones, thereby disrupting normal cellular signalling pathways. Numerous studies have elucidated the receptor inhibition activity of various EDCs, shedding light on their potential adverse health effects. For instance, certain pesticides like vinclozolin act as antiandrogens by binding to androgen receptors (ARs) and inhibiting the action of endogenous androgens such as testosterone, thereby interfering with androgen signalling pathways[129]. This disruption of androgen receptor function can lead to impaired reproductive development and function, as well as other androgen-dependent physiological processes. Similarly, some EDCs exhibit antiestrogenic activity by antagonizing estrogen receptors (ERs), thereby interfering with estrogenic signalling pathways. For example, certain phytoestrogens found in plants can act as ER antagonists, competing with endogenous estrogens for binding to ERs and attenuating estrogenic responses[126]. Additionally, synthetic chemicals such as BPA can also exert antiestrogenic effects by blocking ER activation, thus disrupting estrogen-dependent cellular processes[130]. Furthermore, receptor inhibition can occur through competitive binding, where EDCs compete with endogenous hormones for receptor binding sites, or through allosteric modulation, where EDCs bind to receptor sites distinct from the hormone-binding site, altering receptor conformation and function.

Interaction with signalling pathways

EDCs exert their effects on the body by interacting with various signalling pathways, disrupting normal physiological processes. These chemicals can interfere with signalling pathways involved in hormone regulation, leading to dysregulation of endocrine function. EDCs may disrupt signalling pathways by binding to hormone receptors and activating downstream signalling cascades, mimicking the actions of natural hormones[123]. Additionally, they can inhibit the activity of endogenous hormones by occupying receptor sites or interfering with downstream signalling components, thereby antagonizing hormone actions and inducing endocrine disruption[131]. Furthermore, EDCs may interact with components downstream of hormone receptors in signalling pathways, leading to diverse direct, non-endocrine, and toxic effects[72]. These interactions can have profound effects on cellular function, ultimately impacting various physiological processes regulated by hormones.

Stimulation

Stimulation serves as a significant mechanism of action for EDCs, contributing to their adverse effects on endocrine function. EDCs can mimic the actions of natural hormones by stimulating hormone receptors, thereby activating downstream signalling pathways and eliciting physiological responses[132]. Despite structural differences from endogenous hormones, EDCs can bind to hormone receptors and induce receptor activation, leading to dysregulation of endocrine processes. This mechanism of action allows EDCs to interfere with normal hormonal signalling and disrupt homeostasis within the endocrine system.

Inhibition of biosynthesis

Inhibition of biosynthesis stands as a significant mechanism through which EDCs exert their effects on the body's endocrine system. EDCs can disrupt normal hormone levels by inhibiting the synthesis or degradation of endogenous hormones, independent of direct interaction with hormone receptors[133]. By interfering with the production or breakdown of hormones, these chemicals can alter hormone concentrations in the body, leading to dysregulation of endocrine function. This mechanism allows EDCs to impact various physiological processes regulated by hormones, ultimately contributing to adverse health outcomes.

Binding to transport proteins

Binding to transport proteins serves as a crucial mechanism through which EDCs exert their effects on the endocrine system. These chemicals, often hydrophobic in nature, can compete with small hydrophobic hormones for binding sites on transport proteins in the bloodstream, thereby altering the availability of hormones to target tissues[134]. By interfering with hormone transport, EDCs can disrupt normal hormone signalling and contribute to endocrine dysfunction. This mechanism operates independently of direct interaction with hormone receptors, highlighting the diverse ways in which EDCs can impact endocrine function.

Regulation of binding protein synthesis

Regulation of binding protein synthesis serves as a significant mechanism through which EDCs influence endocrine function. These chemicals can impact the biosynthesis or degradation of hormone-binding transport proteins, thereby altering the total hormone concentration and its active fraction in the bloodstream[135]. The liver, as a primary organ for detoxification, is commonly targeted by EDCs for these effects. By modulating the synthesis of binding proteins, EDCs can disrupt hormone transport and signalling, contributing to endocrine dysfunction. This mechanism operates independently of direct interaction with hormone receptors, highlighting the complex ways in which EDCs can interfere with endocrine regulation.

Receptor stimulation

Receptor stimulation stands as a significant mechanism through which EDCs exert their effects on the endocrine system.

Certain EDCs mimic endogenous hormone activity by directly stimulating hormone receptors, thereby interfering with endocrine homeostasis and eliciting physiological responses[136]. By activating receptor activity, these chemicals can disrupt normal hormone signalling pathways, leading to dysregulation of endocrine function. This mechanism operates independently of hormone mimicry or receptor inhibition, highlighting the diverse ways in which EDCs can impact endocrine regulation.

Target mechanism of EDCs: genomic modulation

Nuclear hormone receptors

NHRs play a pivotal role in mediating the effects of Endocrine-Disrupting Chemicals (EDCs) within biological systems. Initially identified as one of the primary mechanisms through which EDCs exert their actions, NHRs belong to a class of ligand-activated proteins that function as transcription factors upon entering the nucleus, thereby regulating gene expression. This process of ligand-induced gene expression serves as a key mechanism through which cellular functions are modulated, a process susceptible to modulation by EDCs. The Figure 6 below outlines the modulation of EDCs.

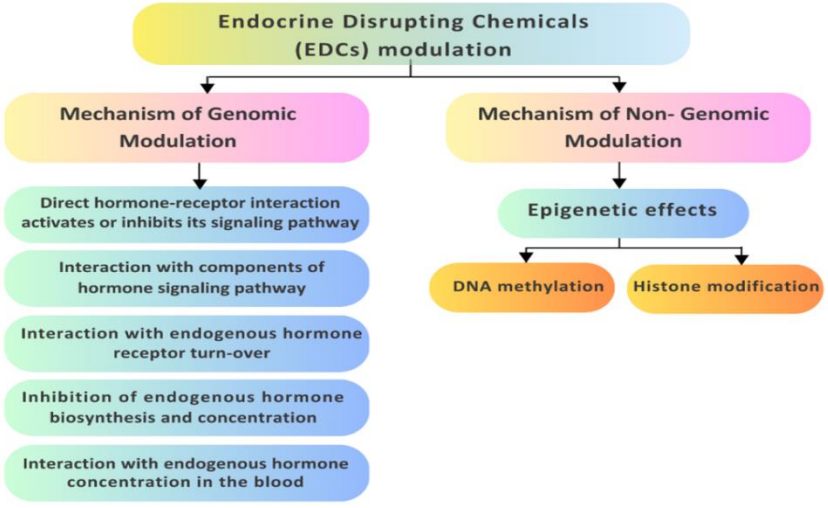

Figure 5. Modulation of EDCs.

NHRs are broadly categorized into three classes:

1. Type I NHRs: These receptors primarily respond to steroid hormones, including estrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR).
2. Type II NHRs: This class includes receptors responsive to non-steroid hormones, such as thyroid receptor (TR), retinoic acid receptor (RAR), and retinoid X receptor (RXR).
3. Type III NHRs: This category consists of receptors lacking a known ligand or orphan receptors, such as G-protein coupled receptor (GPCR), farnesoid X receptor (FXR), and liver X receptor (LXR).

Activation of NHRs occurs when the ligand binds to the activation domain of the receptor, inducing a conformational change in the protein. This conformational change subsequently activates or inhibits the receptor's ability to function as a transcription factor. The activity of NHRs is often mediated through the recruitment of co-activator or co-repressor accessory proteins, which facilitate the initiation or repression of gene transcription.[70].An exemplary illustration of NHR activity is provided by the estrogen receptor (ER). ER exists in two classical forms, ER-α and ER-β, which may exhibit antagonistic behaviour towards each other. For instance, ER-β can antagonize the proliferative effects mediated by ER-α. In the absence of ligand binding, ER remains in an inactive state within the cytosol, forming complexes with various proteins, including heat shock protein-90 (HSP90). Upon ligand binding, ER monomers dimerize, and the ligand-bound ER dimer translocate to the nucleus. Here, it binds to specific genes containing a recognition sequence termed a hormone-responsive element (HRE). In addition to promoter binding, the recruitment of co-activators or co-repressors further modulates gene expression, thereby regulating cellular responses to hormonal signals.

Androgen receptor-mediated endocrine disruption

During the perinatal period, the endocrine axis undergoes programming, rendering it particularly vulnerable to both endogenous and exogenous stimuli[137]. Critical during this programming phase is the feedback loop of hormones from the gonads to the hypothalamus and pituitary. Testosterone, primarily synthesized by the testis around gestational day 65 in humans plays a pivotal role in establishing sexual behaviors, male reproductive tract development, and masculinization of other organs. The androgen receptor (AR), the nuclear hormone receptor for testosterone and its metabolite dihydrotestosterone (DHT), is expressed in various organs including the hypothalamus, pituitary, kidney, prostate, adrenals, and ovary [138]. Aromatization of testosterone to 17β-estradiol by the enzyme aromatase (CYP19) is crucial for proper brain development[139]. Disruptions in testosterone production, such as exposure to antiandrogens, AR genetic mutations, or impaired testosterone metabolism, can lead to phenotypic female development in male fetuses. While the sensitivity to EDCs exposure decreases in adults once the hypothalamic-pituitary-gonadal (HPG) axis is established, exposure to antiandrogens in adult males can still impact sperm production and libido[140]. Therefore, EDC exposure during male reproductive tract development, affecting testosterone binding to AR or its metabolism, can permanently reprogram male reproductive tract development and its coordination with the HPG axis.

Endocrine-disrupting chemicals disrupt androgen homeostasis through various mechanisms, including decreasing AR levels, altering LH stimulation, or interfering with AR ligand-binding domain folding. Misfolding of the ligand-binding domain prevents co-activator recruitment, thereby inhibiting transcriptional initiation and AR activity. EDCs acting as antiandrogens via this mechanism include vinclozolin, DDT, tris-(4-chlorophenyl)-methanol, procymidone, linuron, atrazine, lindane, dieldrin, methoxychlor, nonylphenol, octyl phenol, and BPA[141] Another mechanism involves reducing AR expression, a shared mechanism among multiple EDCs including PCBs, DES, cyproterone acetate (CPA), and hydroxyflutamide (OHF)[142] (Ultimately, EDCs disrupting AR function, dimerization, DNA binding, or receptor levels can impair AR target gene expression, affecting downstream cellular responses such as differentiation and cell communication.

Estrogen receptor-mediated endocrine disruption

Estrogen receptor (ER)-)-mediated endocrine disruption has gained significant attention due to the effects of xenoestrogens like DES in humans and the identification of numerous estrogenic anthropogenic chemicals[143]. Analogous to testosterone, estrogen (E2) plays critical roles in female reproductive tract development, brain function, bone health, cardiovascular system maintenance, and male development. In adult females, E2 is vital for metabolism and orchestrating morphological changes during the menstrual cycle and pregnancy, as well as the differentiation and proliferation of hormone-responsive tissues. Estrogens transactivate estrogen-responsive genes by binding to ERs, with xenoestrogens acting as agonists to induce estrogen-responsive gene expression, as demonstrated by DES, 7-methyl-benz[a]anthracene-3,9-diol (MBA), coumestrol, and genistein (GEN)[144] among others. Estrogen-responsive genes contain estrogen-responsive elements (EREs) or recognition sequences for other transcription factors like SP1 and AP1, to which ER binds. Until liganded by E2 or a xenoestrogen, ER remains bound in an inactive state by heat shock protein 90 (HSP90). Upon binding by ERs, an anognist/ER complex is formed, leading to transcriptional activation of estrogen-responsive genes.

Xenobiotics as EDCs

To counteract the effects of xenobiotics, some of which function as EDCs, organisms have developed a sophisticated system of xenobiotic sensors that activate metabolic pathways to aid in the detoxification and elimination of these potentially harmful compounds. These sensors encompass various Nuclear Hormone Receptors (NHRs), including the steroid and xenobiotic receptor/pregnane X receptor (SXR/PXR), constitutive androstane receptor (CAR), peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), farnesol X receptor (FXR), and the aryl hydrocarbon receptor (AhR)[145]. These receptors play a crucial role in xenobiotic metabolism by binding to a diverse array of genes, thereby initiating Phase I (activation) and Phase II (conjugation) metabolic pathways. Despite being expressed in various tissues such as the brain, ovaries, testes, liver, and intestines, xenobiotic receptors exhibit a broad spectrum of ligand-binding affinity, being activated by pesticides, pharmaceuticals, xenobiotics, and steroid hormones.

Xenobiotics can also disrupt steroid hormone homeostasis by activating xenobiotic receptors or inducing the expression of cytochrome P450 enzymes, which modulate the production of steroidogenic metabolites. This mechanism has been elucidated in several in vitro studies conducted in rat hepatocytes, where compounds like methoxychlor and its estrogenic metabolites, such as bisphenol-OH-methoxychlor (HPTE), were found to induce cytochrome P450 enzymes CYP2B and CYP23A, along with the orphan nuclear receptor CAR[146]. Another mechanism involves xenobiotics altering the availability of co-regulators shared between xenobiotic receptors and NHRs, such as the estrogen receptor (ER). For instance, the CAR agonist 1,4-bis-(2-(3,5-dichloropyridoxyl)) benzene can competitively inhibit the expression of estrogen-responsive genes. The aryl hydrocarbon receptor (AhR) is one of the most important xenobiotic sensors, playing a crucial role in the detection and detoxification of environmental pollutants and toxins. It responds to a wide range of ligands, including polycyclic aromatic hydrocarbons (PAHs), dioxins, and certain phytochemicals, initiating a cascade of events leading to the activation of detoxification enzymes and the elimination of xenobiotics from the body[147].

Target mechanisms of endocrine-disrupting chemicals: non-genomic signalling

Target mechanisms of EDCs often involve non-genomic signalling pathways. Steroid hormones, for instance, activate Nuclear Hormone Receptors (NHRs) through two main pathways: genomic signalling, occurring within the nucleus where NHR-DNA binding regulates gene expression, and non-genomic signalling, which takes place in the cytoplasm without NHR-DNA binding. While various steroid hormone receptors are involved in non-genomic signalling, such as Glucocorticoid Receptor (GR), Thyroid Hormone Receptor (TR), Mineralocorticoid Receptor (MR), Progesterone

Receptor (PR), Retinoid X Receptor (RXR), and Androgen Receptor (AR), research predominantly focuses on Estrogen Receptor (ER) in understanding both potential and confirmed pathways of hormone- and EDC-mediated non-genomic signalling[148].

Modulation of hormone activity

The modulation of hormone activity stands as a pivotal target mechanism for EDCs. Metabolism is crucial in maintaining hormone homeostasis, rendering proteins involved in steroid hormone balance susceptible to endocrine disruption. Xenobiotics activate receptors that trigger the expression of enzymes crucial in the activation, conjugation, and elimination of both endogenous hormones and xenobiotics. These enzymes fall into two main categories: Phase I enzymes (including hydrolases, reductases, and oxidases) and Phase II enzymes (comprising conjugation enzymes). Phase I enzymes, notably cytochrome P450, predominantly facilitate the activation of xenobiotics, with many being up-regulated upon ligand binding to xenobiotic receptors. Moreover, P450s play a role in xenobiotic elimination through hydroxylation. Notably, P450s also partake in steroid hormone metabolism, such as the aromatization of testosterone to 17β-estradiol and the conversion of progesterone to testosterone. Other Phase I enzymes contribute to the inactivation and elimination of steroid hormones, including steroid reductases and hydroxy steroid dehydrogenases. By altering the activity of enzymes involved in hormone synthesis and metabolism, xenobiotics can function as endocrine disruptors[149]. The understanding of epigenetic modulation as a target mechanism of EDCs traces back to the concept introduced by Conrad Waddington, who proposed the term "epigenetics" to describe heritable changes in gene expression and phenotype not attributable to alterations in DNA sequence. Epigenetic regulation plays a pivotal role during development, where cells with identical DNA differentiate into diverse specialized cell types. Among the various epigenetic alterations, DNA methylation stands out as the first identified mechanism. This modification occurs at cytosine bases adjacent to guanine (CpG dinucleotides) in DNA, predominantly within CpG islands (CGIs) located in gene promoter regions[150]. While CGIs are typically unmethylated, methylation of promoter CGIs can inhibit gene expression, leading to gene silencing, a phenomenon observed in normal gene regulation and pathological states such as cancer[151]. DNA methyltransferases (DNMTs) catalyse the methylation of cytosines at CpG sites, with DNMT1 serving as a maintenance methylase, ensuring the faithful transmission of methylation patterns during cell division, while DNMT3a and 3b act as de novo methylases, crucial for establishing methylation patterns during embryonic development[152].

The intricate interplay between epigenetic modifications and environmental cues underscores the susceptibility of the epigenome to disruption by EDCs, emphasizing the importance of understanding these mechanisms in assessing the impact of environmental factors on developmental and health outcomes.

Histone modification

Histone modification is a crucial mechanism in chromatin regulation, wherein histone proteins, including core histones (H2A, H2B, H3, and H4) and linker histone (H1), play a central role in compacting DNA into chromatin structures. Besides their structural role, histone proteins serve as dynamic platforms for receiving environmental signals through post-translational modifications (PTMs) of their "tails." These modifications, such as methylation, phosphorylation, sumoylation, ubiquitination, and acetylation, occur on the protruding tail-like extensions of histones within nucleosomes. The enzymes responsible for these PTMs are regulated by upstream signaling pathways[153]. The specific combination of PTMs, often referred to as "marks," creates binding motifs that are recognized by various proteins, including those containing bromo and chromodomains. These proteins then bind to the modified chromatin, thereby regulating chromatin structure and gene transcription[154]. Generally, histone acetylation correlates with active chromatin, whereas histone methylation can either activate or repress gene expression, in contrast to DNA methylation, which is typically associated with gene repression or silencing[155]. The dynamic interplay between histone modifications and chromatin structure highlights the intricate regulatory mechanisms governing gene expression and cellular processes. Understanding these

processes is crucial in deciphering the impact of environmental factors, including EDCs, on gene regulation and health outcomes[156] Phenotypic alterations inherited across multiple generations, known as transgenerational effects, can result from both chemical and behavioural exposures[157]. These effects are hypothesized to be transmitted through germline alterations. Apart from Diethylstilbesterol (DES), other EDCs such as PCBs, vinclozolin, and methoxychlor have been demonstrated to induce phenotypic changes in rodents across several generations[158]. An early example of transgenerational epigenetic inheritance was illustrated by the transgenerational impacts of vinclozolin and methoxychlor on spermatogenesis and fertility in males following gestational exposure to these EDCs. Their research revealed that gestational exposure to vinclozolin or methoxychlor could modify DNA methylation patterns, affecting spermatogenesis in offspring from F1 through F4 generations. Subsequent investigations by the same group identified transgenerational effects of vinclozolin in both male and female offspring, although these studies did not integrate epigenetic analyses. In females exposed to vinclozolin during gestation, F1–F3 offspring exhibited pregnancy abnormalities and increased tumour incidence compared to control offspring (6.5% vs. 2%). While other studies have not yet replicated the transgenerational effects observed with vinclozolin or methoxychlor, they propose an intriguing hypothesis suggesting that alterations in DNA methylation may contribute to the transgenerational inheritance of EDC-induced phenotypic changes associated with exposure to these chemicals.

EDCs have been shown to disrupt normal hormone homeostasis, thereby impacting the reproductive function of both wildlife and human populations through direct and indirect pathways [20]. The mechanisms through which EDCs exert their effects are diverse and encompass several primary pathways. These pathways include (1) modulation of nuclear hormone receptor activity, (2) alteration of non-genomic hormone receptor signalling, (3) interference with xenobiotic and hormone metabolism, and (4) induction of epigenetic modifications. Disruption of any of these pathways has the potential to trigger endocrine disturbances, resulting in various diseases and compromised reproductive function[20,57] Importantly, even brief developmental exposures to EDCs can lead to lasting effects in adults and heritable alterations in subsequent generations[159]. Therefore, understanding the intricate mechanisms underlying EDC-induced endocrine disruption is paramount for devising strategies to manage and prevent their detrimental effects on exposed individuals and populations[20,57,159].

Regulation of endocrine disrupting chemicals

Regulating endocrine-disrupting chemicals (EDCs) is paramount due to their potential adverse effects on human health and the environment. Internationally, organizations such as the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) collaborate to develop guidelines and strategies for managing EDCs globally (WHO, UNEP). The Stockholm Convention on Persistent Organic Pollutants (POPs) identifies certain EDCs as substances of concern due to their persistence and harmful effects (Stockholm Convention). At the national level, countries have established regulatory frameworks to address EDCs. For example, the United States Environmental Protection Agency (EPA) regulates EDCs under statutes like the Toxic Substances Control Act (TSCA), while the European Union (EU) has regulations such as REACH and the Biocidal Products Regulation (EPA, EU). Regulatory approaches typically involve risk assessments considering factors like exposure routes, toxicity levels, and vulnerable populations, though challenges like data gaps and scientific uncertainty persist (EPA, EU). Specific chemicals, including phthalates, bisphenols, and flame retardants, have faced regulatory actions due to their endocrine-disrupting properties, with agencies prioritizing chemicals for assessment based on various factors (EPA, EU). Collaboration among governments, industries, and scientific communities is crucial, facilitated by initiatives like the Strategic Approach to International Chemicals Management (SAICM) and the OECD's Endocrine Disrupter Testing and Assessment Task Force (SAICM, OECD). Innovative approaches such as computational modelling and high-throughput screening assays are being developed to assess EDCs more efficiently (OECD). This multi-stakeholder approach to regulating EDCs aims to mitigate risks and

protect human health and the environment. Key scientific statements and regulatory documents from entities such as the European Commission, the United States Environmental Protection Agency (EPA), and international guidelines from the World Health Organization (WHO) provide essential guidance in this endeavour (European Commission, EPA, WHO).

Future prospects

The prospects of endocrine-disrupting chemicals (EDCs) encompass a multifaceted landscape shaped by advancements in scientific understanding, technological innovation, regulatory initiatives, and public awareness. Advancements in research and understanding are crucial, involving the exploration of molecular pathways through which EDCs disrupt endocrine function, deciphering the role of epigenetic modifications in mediating transgenerational effects, and investigating interactions between different classes of EDCs. Integrative approaches, combining experimental studies, computational modelling, and systems biology, provide comprehensive insights into the complexities of EDC exposure[160]. Technological innovation holds immense potential for enhancing detection methods, monitoring strategies, and exposure assessment tools for EDCs. Innovations in analytical techniques, such as high-throughput screening assays and biomonitoring technologies, enable rapid detection in diverse environmental matrices and biological samples. Additionally, novel remediation technologies facilitate the removal of EDCs from contaminated sites and wastewater streams.

The regulatory frameworks are expected to prioritize the identification, assessment, and management of EDCs to protect public health and the environment. Efforts to harmonize regulatory standards, strengthen risk assessment methodologies, and implement precautionary principles will enhance effectiveness. Initiatives promoting safer alternatives to EDCs and sustainable production practices will reduce exposure and associated risks[161]. Public awareness and education are critical for informed decision-making and behavioural changes to reduce EDC exposure. Educational campaigns and community initiatives empower individuals to advocate for policy reforms and support sustainable practices[162] Global collaboration and partnerships are essential for addressing the complex nature of EDCs. By leveraging collective expertise and resources, stakeholders can develop holistic approaches to tackling challenges and promoting sustainable development[161]. By harnessing synergies between scientific innovation, technological advancement, regulatory action, and public engagement, stakeholders can work towards minimizing the risks associated with EDC exposure and fostering a healthier and more sustainable environment.

CONCLUSIONS

In conclusion, the impact of EDCs on human health is a multifaceted issue with significant implications. Extensive research suggests that exposure to EDCs can disrupt the endocrine system, leading to various health concerns such as reproductive disorders, metabolic dysfunction, and even developmental abnormalities. Addressing this challenge requires interdisciplinary collaboration, robust monitoring, and effective policies to safeguard public health and environmental integrity for current and future generations. Through extensive research, it has become increasingly evident that EDCs exert diverse effects on endocrine systems, disrupting hormonal balance and contributing to a spectrum of adverse outcomes across various biological systems. Firstly, EDCs exhibit remarkable versatility in their mechanisms of action. They can mimic, block, or interfere with the synthesis, transport, metabolism, and action of endogenous hormones, often by binding to hormone receptors or altering signalling pathways. This intricate interference can lead to dysregulation of physiological processes, spanning reproductive, metabolic, immune, and neurodevelopmental functions. Transgenerational impacts have emerged as a significant concern, with evidence suggesting that EDC-induced alterations in gene expression and epigenetic modifications can be inherited across multiple generations. This transgenerational inheritance underscores the enduring legacy of EDC exposure, potentially perpetuating adverse health outcomes in subsequent offspring. Furthermore, the ubiquitous presence of EDCs in the environment poses substantial challenges for regulatory agencies and public health initiatives. Additionally, the complex interactions

between different EDCs and their cumulative effects further complicate risk assessment and management efforts. Integrative approaches, combining epidemiological studies, mechanistic investigations, and computational modelling, offer valuable insights into the complexities of EDC exposure and inform evidence-based regulatory decisions. Addressing the pervasive threat of EDCs requires concerted efforts from multiple stakeholders, including policymakers, industry, healthcare professionals, and the public. By prioritizing research, enhancing regulatory frameworks, promoting awareness, and advocating for safer alternatives, we can work towards minimizing the adverse effects of EDCs and safeguarding human health and environmental integrity for current and future generations.

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Conflict of interests

The authors declare that there is no conflict of interest.

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