Journal of Biomedicine and Biochemistry
Volume 4 Issue 1 (2025), pp. 14–26

Journal JBB

Print ISSN:3006-0532
Online ISSN:2958-0528

REVIEW ARTICLE

Endocrine Disrupting Chemicals and Human Health: A Review of Toxicological Mechanisms and Regulatory Challenges

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Received:January 20, 2025,
Revised:February 21, 2025,
Accepted:March 5, 2025,

DOI: 10.57238/jbb.2024.7432.1133

OPEN ACCESS

Access this article online

Abstract

The present review is to evaluate the current state of knowledge in regard to health effects of endocrine disrupting chemicals (EDCs) in humans, with a special reference to recently published research. The primary target audience aside from scientists will be policymakers, public health professionals, and health practitioners who need an up-to-date broad understanding of the issue in the form of a concise compilation of peer-reviewed literature. The main goal serves to synthesize recent research findings regarding the most important toxicological mechanisms associated with EDCs and recent advancements in understanding their health effects. A major emphasis is placed on research that has been published in peer-reviewed journals over the past years, with less attention being given to systematic reviews. Information found in the literature bears a description of current knowledge of the human health effects of EDCs, focusing on recent scientific publications. Greater familiarity with the complexities of EDC exposure routes, mechanisms, and the large variety of chemicals that have endocrine-disrupting properties is also aimed. By detailing the state of research, it is hoped that the review may help clarify the complexities for regulatory authorities, enabling for more accurate decision-making with regards to management of EDCs. Additionally, this contribution is intended to advance the current public health and regulatory debate about EDCs, by highlighting the challenges faced in regulation and proposing potential directions for their effective management.

Keywords: Endocrine; Regulatory Challenges; Toxicological mechanisms

1 Introduction

Endocrine disrupting chemicals (EDCs) have been the subject of intense concern in the public, regulatory, and scientific communities due to their implications for human health [1]. A growing body of evidence has implicated EDCs in a number of adverse health effects, including reproductive and developmental disorders, as well as non-targeted outcomes, such as neurological and immune disorders, which may share a developmental origin. This growing recognition has driven efforts by scientists, public health professionals, and policy-makers to better understand the mechanisms of

EDC action and to develop new regulatory and public health measures that protect vulnerable populations. Given the complexity and scope of the problem, the analysis is best framed from a multidisciplinary perspective that encompasses toxicological, public health, and regulatory challenges associated with EDCs. The outlines of the following discussion are an overview of the intertheoretical domains and how they intersect in describing where the science is today, and where there is a grand need for further research as it applies to EDCs. To provide a context for the following discussion, discussions include important current issues, in a broader context of emerging environmental awareness, and an overview of the areas to be covered in the following discussion [2]. The last four decades have seen a major international increase in environmental awareness, accompanied by a host of grass-roots environmental movements and a variety of governmental actions to address the health and safety aspects of an industrial society. While some of these steps have met with success, several highly consequential areas remain of great concern, in particular the question of exposure to anthropogenic xenobiotics and their putative implications for human and ecosystem health. This concern has been fueled by a large and growing body of evidence from laboratory studies, wildlife, domestic animal, and human monitoring suggesting that a variety of synthetic compounds can mimic, antagonize, or alter the synthesis, metabolism, or clearance of endogenous hormones, leading to a range of adverse consequences [3]. Periodically, particular groups of compounds were identified as posing risks, but the present situation, with highly complex synthetic mixtures of tens of thousands of compound classes, and the widespread nature of exposure, is unprecedented. It is in this context that a review of the current state of knowledge is presented, which reveals the urgent need for evidence-based regulation and public health interventions regarding EDC exposure [4]. See Figure 1.

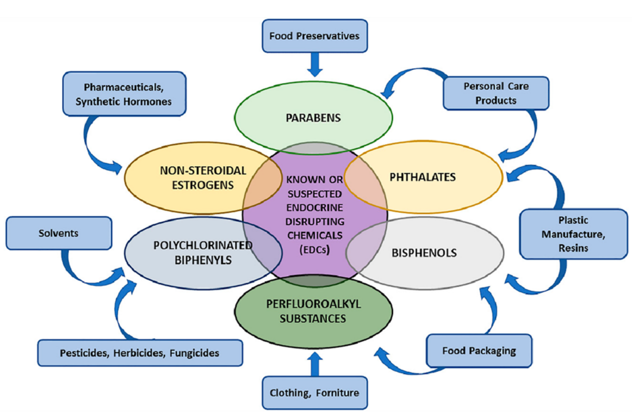

Figure 1: Endocrine-Disrupting Chemicals' (EDCs) [4].

1.1 Background and significance

Endocrine disruptors, otherwise known as endocrine disrupting chemicals (EDCs), have generated increasing public concern over the past few decades for a variety of reasons. This concern was greatly amplified in 2016 by reports that EDC-related health problems in the United States cost as much as 340 billion dollars annually in treatment, lost wages,... and other societal costs. This article reviews toxicological mechanisms of EDCs, then discusses the vast array of factors that have made them such a formidable challenge for public health policy, including unique complexities in scientific testing and classification. In the context of this discussion, EDCs simply are exogenous chemicals, different from biological hormones, that disrupt the endocrine system [5]. EDCs are found in food and various forms of packaging, the environment, as well as many other consumer products. These chemicals can interact with endocrine system receptors, similarly to natural hormones. EDCs can block binding of natural hormones to receptors, thereby inhibiting normal endocrine signaling, or they can imitate natural hormones, constantly stimulating receptors even when natural hormones are not present [6]. There are implications for affecting gene expression and DNA replication and repair. In short, these mechanisms allow EDCs to interfere with many different aspects of endocrine signaling pathways [7]. A wide range of populations can be affected by these chemicals, but children and pregnant women are at particular risk. The critical need to connect environmental exposures to health outcomes through a concerted research effort is outlined because toxicological mechanisms are often quite difficult to definitively establish. For these reasons, it is necessary to gain a more comprehensive understanding of the pathways in which these chemicals affect human health. At a more fundamental level, this includes pathways that occur in wildlife, when considering EDCs in the broader socio-environmental context. There can be reduced fertility rates, early, late or premature puberty, and even adverse health effects in utero. These effects can have profoundly unequal socio-economic implications. Similarly, understanding of the complex societal implications of the link between EDCs and health issues is still in its early stages. Thus, ongoing research and public awareness campaigns are crucial given the persistence and ubiquity of EDCs [8].

2 Endocrine system: Structure and function

Understanding of the structure and function of the endocrine system is essential for a complete appreciation of the toxicological mechanisms underlying endocrine disrupting chemicals (EDCs). The endocrine system is a unique collection of glands that secrete hormones, which circulate throughout the body and act as chemical messengers that regulate various physiological processes 3. It is intricately involved in the maintenance of homeostasis, governing processes such as metabolism, growth and development, and the stress response. Although the system is made up of multiple components that can be discussed individually, it is important to recognize that the glands of the endocrine system are interconnected. This plays a crucial role in the system's regulation, as the hormone(s) secreted by one gland can directly impact other glands in the system in a cascading, or domino-like, effect [9]. The interconnectedness of the endocrine system helps to ensure that it is attuned to changing circumstances, such as shifts in internal composition, in order to effectively facilitate the maintenance of homeostasis. Disruption of the endocrine system's normal functions is, by nature, a complex process, as it involves the dysregulation of a system that is highly integrated and exquisitely balanced. However, there are often a multitude of points where this balance can be perturbed, and even relatively minor disruptions could have sweeping effects. Similarly, understanding the layout of the endocrine system as a whole, along with the complex and dynamic nature of its hormonal interactions, is a necessary foundation for comprehending how endocrine function can be disrupted by EDCs [10].

2.1 Overview of the endocrine system

The endocrine system is one of the two main systems of intercellular signaling in humans, and conveys information by means of chemical signals that travel in the bloodstream. Hormones are the main type of signaling molecule within the endocrine system, and can influence various physiological processes in target cells [11]. The endocrine system is composed of a network of major glands, including the hypothalamus, pituitary, thyroid, pancreas, ovaries, testes, and adrenal glands, that work together to regulate metabolism, growth, development, and reproduction in the human body. Hormones and signaling molecules control a wide variety of bodily functions including but not limited to mood, growth, metabolism, and sexual differentiation. Hormones are used to communicate between organs and tissues for physiological regulation and behavioral activities, such as digestion, metabolism, respiration, tissue function, sensory perception, sleep, excretion, lactation, stress, growth and development, movement, and, for instance, mood [12]. The endocrine system has a role in multiple mechanisms – integrating behavior, life-histories, and evolution – affecting diverse systems including neural, immune and reproductive function.

The pituitary gland is a major component in the endocrine system, and is the primary regulator of homeostasis. It is located at the base of the brain and is closely connected with the hypothalamus. Adenohypophysis, or anterior section, releases hormones and influences the activities and production of other glands including the thyroid and adrenal cortices. The adenohypophysis is known as the master gland, as it is interrelated with a multitude of hormonal systems. This gland works in conjunction with the gonads and olfactory systems, and is essential in physiological processes and immunity. The posterior pituitary lobe, the neurohypophysis, is responsible for the release of hormones. This involves two main hormones, oxytocin and vasopressin, which regulate activities such as breast milk production and the conservation of water within the human body, respectively. This is an important function, as the body's requirement of oxytocin increases generally just before and during parturition, stimulating the contraction of the uterine muscles, and the pressing of the milk from the cells to the breastfeeding outlet. A deficiency in vasopressin is an underlying cause of diabetes insipidus [13]. The thyroid gland produces T3 and T4, which regulate metabolic function, growth and normal development in animals. It is controlled by the pituitary gland, which releases thyroid-stimulating hormone. The adrenal glands are two glands located above the kidneys, and secrete aldosterone and cortisol. The former assists in the regulation of salts, and the latter assists with metabolism regulation and the body's response to stress. Additionally, it works to regulate immune responses – more specifically, preventing the body from attacking itself.

2.2 Key hormones and their functions

The endocrine system is a complex network of glands that produces and secretes hormones. Hormones are chemical messengers that affect target cells, which are located far from endocrine glands, and regulate many physiological functions. Once hormones are released into the bloodstream, they spread rapidly throughout the whole body. The endocrine system is made up of several glands, each of them capable of producing different hormones. Metabolism is regulated by hormones such as insulin and cortisol. Thyroid hormones control metabolism as well as growth development. Stress response is under the control of more systems, such as the corticotrophin-releasing hormone system. It is mediated by the hypothalamic-pituitary-adrenals system, which controls the levels of cortisol. Immune cells are also targets for cortisol actions; it modulates immune cells proliferation, cytokines production and phagocytosis efficiency. Gonadal hormones, such as estrogen and testosterone, have a key role in the reproductive system and control the development of secondary sex characteristics [14]. Although their production starts at puberty, their synthesis is active starting from very early life to allow the correct development of primary sex characteristics.

Homeostasis is maintained by hormonal regulation through numerous negative feedback loops responding to internal changes. Whenever these changes occur, the system attempts to counteract them by compensating through the secretion of adequate hormones. When blood glucose levels raise over a certain value, the pancreas rapidly secretes insulin, that enables the absorption and storage of glucose by cells. Similarly, when blood glucose levels drop below a certain value, as a result of food deprivation, the pancreas secretes glucagon that stimulates the liver to synthesize molecules capable of increasing blood glucose levels. This and many other negative feedback loops allow the maintenance of physiological values. Indeed, disruptions in these systems can lead to the onset of diseases, such as diabetes or thyrosis. Furthermore, the same hormone may be produced in different glands depending on the target system. For instance, cortisol may be produced by the adrenal cortex in response to stress, or by the placenta during pregnancy, to increase cortisol levels in order to promote the maturation of fetal organs.

3 Endocrine disrupting chemicals (EDCs)

Endocrine disrupting chemicals (EDCs) are defined as “exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis, reproduction, development and/or behavior”. EDCs include a wide range of chemically diverse substances such as organochlorine pesticides, phthalates, dioxins, polychlorinated biphenyls, surfactants, fire retardants, food additives, and pharmaceuticals. Based on their chemical structure and effects, EDCs are classified into several groups including: e.g. estrogenic, anti-estrogenic, toxicant chemical that affects sex hormone system, toxicants. EDCs can be derived from various sources including plastic, industrial, and indoor and outdoor air. Plastics, bisphenol-A, alkylphenolethoxylates, and surfactants are released from industrial products and when they degrade have been found as pollutants in freshwater aquatic systems [15]. Although EDCs in water are filtered, they are still found in freshwater fish. Apart from industrial products, EDCs are also found in agricultural chemicals, household products such as cosmetics, cleaning products, and detergents. Women’s personal care products, e.g. sunscreen lotions, and household cleaning products have been shown to contain chemicals with a potential EDC effect. In addition, various other products such as pesticides, advanced coating materials, plastics, food preservatives, and food packaging can contain EDCs.

Understanding the classification of EDCs can clarify the modes of action they take on in disrupting endocrine function. There are numerous exposure routes through which humans and wildlife can encounter EDCs. These include: food substances, air inhalation, dermal exposure, etc. Although EDCs are known for being pesticides in agricultural products, however, EDC residues are also found in water that is present in the body through the food chain. EDCs are molecules that have been shown to persist in the environment due to their weak biodegradability [16]. Because of this, EDCs accumulate in the food chain, and due to the amount of EDCs that are constantly exposed to the human body in food and environment, they may disrupt the endocrine system. Long-term exposure of chemicals, which accumulate in fatty tissues, can pose a significant health risk to living beings. Recently, health problems associated with EDCs have attracted worldwide attention. In a study conducted on 26 children playing basketball in Sydney, it was reported that the children presented higher EDC levels than the adults and there was a rapid accumulation in the body. Therefore, the importance of public awareness should be underscored for daily exposure to EDCs. EDCs, which have a wide scope in terms of form and effect, are important today and are an issue that requires attention in terms of human health.

3.1 Definition and classification

A large number of chemicals are produced, used in everyday products, and spread throughout the environment. Some of these chemicals can interfere with hormonal systems and are sometimes termed "endocrine disrupting chemicals" (EDCs). There is a wide array of chemical classes that display endocrine disrupting properties, and based on one’s perspective some chemicals may or may not be considered as EDCs. To classify EDCs, a working definition is adopted regarding human health and the emphasis is placed on the ability of a compound to interact/interfere with hormonal targets [17]. Chemical substances considered as being of concern through their EDC capacity induce a variety of other modes-of-action (MOA) than mere "endocrine-like action". Discussing EDCs as a "class of chemicals" rather than as individual substances presents additional challenges, including whether to focus on intrinsic hazards of EDCs as a class of substances or on their effects considered "harm" in one’s context.

A broad definition of EDCs states that these chemicals "alter the function of the endocrine system and consequently cause adverse health effects in an intact organism, its progeny or sub-populations" [18]. Based on structural properties, EDCs can be divided into 3 main classes: pollutants, natural compounds, and hormones. Several other ways to classify EDCs have been proposed such as "dose dependent EDC" and the "stimulator inhibitor" classification. It is likely that EDCs acting through these MOA fall outside the at present predominantly considered EDC classification. Another issue with the EDC classification has been the overwhelming focus on only a few well-known POPs and synthetic compounds such as Bisphenol A [19].

3.2 Sources and exposure routes

Endocrine disrupting chemicals (EDCs) are compounds that have been shown to interfere with the hormone systems in humans, animals, and ecological receivers. They can be found in the air, dust, water, and soil, and they are present at levels up to several orders of magnitude higher when present in various commodities such as toys, cosmetics, building materials, textiles, detergents, and electronics, to name a few. This pathway is particularly relevant in the regulation of progesterone levels, which are directly related to ovulation. There are many substances that have the potential to act as EDCs. This is the case of parabens, for example, which are considered EDCs with estrogenic activity. Endocrine disruptors can be found in the following sources:

1. Environmental sources: air, soil, agricultural and domestic products;
2. Personal sources: personal hygiene products, cosmetics, detergents;
3. Food: processed and glycolic chemicals used in certain materials.

Even though the sources of EDCs are abundant, people are not aware of their exposure to them. The route of absorption involves ingestion, inhalation, and dermal exposure. Smaller compounds, with low molecular weight or high lipid solubility, tend to be more bioavailable. This is also related to the capacity of some compounds to dissolve in the phospholipids of cellular membranes. The route of exposure also determines where the EDC is absorbed. This requires knowledge to understand where the main exposure routes are and ways to reduce them. A vulnerable population deserves special attention: that of children, pregnant women, and fetuses. It is necessary to educate the population about the sources of EDCs, how they are absorbed by the human body, and what can be done to mitigate this exposure. Another reason why it is of the utmost necessity to educate the population about the risks of EDCs is their capacity to remain in the environment for long periods. Many EDCs are resistant to macroscopic, chemical, and microbiological degradation processes. Moreover, EDCs have the tendency to biomagnify and bioaccumulate [20].

4 Toxicological mechanisms of EDCs

Endocrine disrupting chemicals (EDCs) are a pernicious collection of compounds that have deleterious effects on the endocrine system. These harmful compounds have been found in a wide variety of everyday goods, such as toys, cosmetics, and even food, making them a major public health concern. Mechanistically, EDCs exert these effects through interfering with normal hormonal signaling. However, this is a vast array of cellular processes and cargo that together mediate essential physiological functions. This includes, most notably, cell proliferation, differentiation, motility and apoptosis. When these processes are disturbed, it can lead to a myriad of deleterious health outcomes. Furthermore, there are a large number of hormones in the human body, and these hormonal signals can be passed through a variety of genomic and non-genomic pathways. Additionally, different cell types will have differing responses to the same hormonal signal. Thus the mechanisms of EDC action are very complex [21]. Nonetheless, it is possible to categorize the mechanistic pathways through which EDC exposure can result in endocrine interference. Broadly speaking, this can be divided into receptor-mediated or non-receptor-mediated pathways, although hybrid categories exist as well.

Unquestionably the most studied and well understood interaction between EDCs and hormones is through their ability to physically interact with and modulate hormone receptors. The majority of EDCs are selective estrogen receptor modulators (SERMs), and similar to real estrogen, they can bind to and either activate or inhibit transcription through several different estrogen receptors. This can have a myriad of effects on a particular cell type depending on what products the hormone would normally induce. For instance, if the estrogenic chemicals mimic the ability of estrogen to trigger transcription of cyclins and growth factors, a cell that is not normally estrogen sensitive will start proliferating [22]. However, there are several others signaling pathways in widespread use by non-estrogenic EDCs as well, including androgen, thyroid, and corticosteroid pathways. In fact, there are now a list of proven disease states caused by EDCs acting on such pathways.

4.1 Receptor-Mediated mechanisms

The toxicological mechanisms of endocrine disrupting chemicals (EDCs) have been a significant concern to human health in the past few decades. They are a complex group of exogenous chemicals capable, with adequate exposure, of interfering with hormonal systems. These xenobiotic agents' mechanisms of action are variable and in most cases, still poorly understood. EDCs are reported to interfere with the endocrine system at many levels with different dose-response relationships. As hormones control many functions of the human body (including brain development, growth and metabolism, immune functions and different nutrients uptake), the possible effects of EDCs are also vast and the health outcomes go beyond cancers [2].

Interaction of EDCs with the endocrine system may occur with various mechanisms at different levels and by different ways. Several EDCs share a steroid hormone-like chemical structure and have high affinity for binding to specific receptors. The receptor-mediated mechanism of EDCs is based on the interaction with estrogen receptors (ERs), as established by single compound testing and by testing binary or ternary mixtures of full and partial agonists. Full agonists are preferably selected by ERs, whereas partial agonists induce unconventional conformational changes in ERs compared to the endogenous hormone. Enhancement or inhibition of the synthesis, transport, metabolism, binding to the plasma carrier proteins, and receptors of a natural hormone can occur with exogenous interferences [3]. The pertinent endocrine system of humans includes many hormones that control and coordinate the complex development and function of several body network and like a Cascade, qualified by the pituitary gland in response to body requirements. Each hormone can bind to different types of hormone receptors, triggering a variety of signal pathways with different effects (gene transcription activation or not, post-translational modification of proteins). Considering the variety of natural hormones and the intricate network of their receptor-mediated activities, it is not surprising that the interaction of endogenous hormones with their receptors might result in multiple biological outcomes, a concept poorly addressed by toxicological studies of single or even a few compounds.

4.2 Non-Receptor-Mediated mechanisms

Endocrine-disrupting chemicals (EDCs) interfere with hormonal balance in various ways, leading to adverse effects on humans and wildlife 6. The traditional mechanism of action for EDCs is receptor-mediated, altering the hormone activity by binding to hormone receptors 3. Besides this direct interaction, giving toxic effects for endogenous hormones, there are non-receptor-mediated EDC mechanisms that are focused on acting as modifiers downstream of the hormone receptor. EDCs can affect the endocrine system without the direct interactions of hormone receptors. The focus is on non-receptor-mediated routes, which can interfere hormone balance through other pathways that are endocrine-related and affect health.

Endocrine-related non-receptor-mediated mechanisms for EDCs are divided into 7 categories:

1. Modifying hormone synthesis,
2. Modifying hormone transportation,
3. Modifying hormone metabolism,
4. Modifying hypothalamic-pituitary feedback,
5. Modifying signal transduction pathways,
6. Modifying hormone activity,
7. Others.

These mechanisms discuss how EDCs act further downstream of the hormone receptor, therefore indirectly interfere with the activity of natural hormones. Different routes are explored for each of the 7 categories. It is generally attempted to regard the existing evidence of the postulated non-receptor-mediated EDC mechanisms on the basis of the literature search, but considerable gaps are found, leading to incomplete discussions and a recognition that this is an underdeveloped and important research area.

On the other hand, the reviewed evidence also demonstrates that the postulated non-receptor-mediated mechanisms of EDCs are diverse and complex and that they interact at multiple levels. In addition, they have crosstalk with themselves or stimulate receptor-mediated mechanisms. The application of high throughput analysis should also be considered as a useful approach to understanding the complex toxicity of EDCs with respect to non-receptor-mediated mechanisms. Those insights might be needed for a comprehensive risk assessment of EDCs, and it also suggests that the emphasis on non-receptor-mediated mechanisms of EDCs beyond the classical view become more developed [23].

5 Human health effects of EDCs

Endocrine disrupting chemicals (EDCs) include a variety of industrial chemicals and intermediates, such as plasticizers, solvents, and surfactants. These substances act on the neuroendocrine axes, competing with, or blocking, the sex hormones. As a result, EDCs have multiple toxicological targets, from the reproductive systems to various peripheral organs. This article aims to review, in a succinct manner, the current knowledge on the toxicological mechanisms of EDCs and their health risk assessment. Another topic covered is the identification of shortcomings and uncertainties that have an impact on public health regulatory decisions and discussing future research approaches.

The increasing spread of xenobiotics for multiple uses has brought substantial concern with the potential toxicological effects on living organisms, including human beings. Endocrine disrupting compounds target the neuroendocrine axes, modifying the synthesis, the concentration in blood or vital organs, and the binding of the steroid hormones. This kind of action translates into chemicals that can mimic the action of natural hormones (agonists), thus triggering early puberty in its various forms (premature thelarche, adrenarche, pubarche, telarche, and menarche in females), or vice versa, blocking the action of the steroids in the receptor organs, causing delay in pubertal development in either sex. Given the widespread nature of the phenomenon, this is a subject of concern and debate in the media. Apart from actual potent endocrine disruptors, the broad spread of chemicals for multiple uses alerts not only to individual but also to cumulative exposures. The scientific background on sex steroids has been reviewed in the endocrinology literature [24].

5.1 Reproductive health impacts

The awareness of population about potential toxic effects of many chemicals is low while the surveillance of the governments is not enough. Humans are exposed to an increasing number of chemicals in their daily life through food, water, air, soil, and used products. Numerous studies have demonstrated that many chemicals can have adverse effects on human health, including endocrine disrupting chemicals (EDCs). EDCs are a group of chemicals that can disrupt the endocrine system of humans and animals, leading to adverse effects at molecular, cellular, tissue, organ, individual, and even population levels. This article aims to provide a review on the toxicological mechanisms of EDCs affecting human health and the current regulatory situation and challenges. Based on the findings, the vulnerability of reproductive health, children's health, and immune health is further discussed. Impacts on the reproductive system EDCs have aroused increasing concern during the past two decades because of the adverse effects of wild animals found in field studies and laboratory tests. The potential ecological and health impacts of EDCs are reflected in their effects on wildlife species. Traditionally, the effects of EDCs have been viewed mainly in terms of their ability to feminize males or induce other abnormalities among wildlife populations. However, it is important to note that reduced reproductive fitness might be an equally important effect of EDCs in wildlife that is not necessarily mediated by easily observed abnormalities. Disruption of the reproductive system is one of the most potent ways that EDCs can compromise the health and fertility of individuals and populations. This study, focusing on the impacts on human reproduction, reviews the findings of the EDCs and human reproduction and their underlying mechanisms [25].

5.2 Metabolic disorders

Exposure to endocrine disruptor chemicals (EDCs) is an emerging cause for concern in association with the rising epidemic of obesity and metabolic diseases [26]. The increase in the prevalence of metabolic diseases observed worldwide has elicited intensive investigation on the pathogenesis of such a health issue. Genetic background, increased caloric intake, physical inactivity, sleep deficit, and aging have been recognized by the medical community as pivotal pathogenetic factors involved in metabolic diseases. Nevertheless, the observed upsurge of metabolic diseases cannot be fully ascribed to the aforementioned risks. Apart from the desire of any individual to possess and preserve an ideal physical appearance, this epidemic is also supported by economic bases. Metabolic interplay relies upon an abundance of well-coordinated signals communicated between various cells and tissues - the endocrine system. Within the endocrine system, hormonal signals regulate a plethora of life-sustaining processes. Additionally, endocrine signals are supplied by the gastrointestinal system, the kidneys, the adipose tissue, and other organs that are not traditionally regarded as endocrine glands [27].

However, over the past years, the spectrum of potentially endocrine active compounds has been greatly broadened due to an expansion of environmental xenobiotic chemicals capable of interfering with the endocrine system. These compounds do not resemble endogenous hormones in structure and bearing. The main concern with environmental EDCs is that they can perturb endocrine signaling, thus leading to the disruption of normal hormonal control and affecting the physiological functions regulated by the endocrine system. Data are growing that exposure to EDCs may promote weight gain and contribute to the development and progression of metabolic diseases. There are environmental chemical contaminants capable of perturbing human metabolism primarily by i) disrupting the control of energy and substrate metabolism, ii) influencing the metabolic function of multiple metabolically crucial organs, and iii) eliciting a cascade of events that alter the fine balance in the metabolism of energy-dense substrates, predisposing the body towards the establishment of a state of obesity while altering glycemic homeostasis and the lipid, lipoprotein profile and maybe contributing to hypertension as well. Since the containment of the metabolic disorder pandemic implicates numerous and well-coordinated measures, emerging data suggest that current environmental conditions should be to account for. Furthermore, increased focus is placed on the identification of particularly vulnerable population subgroups that are prone to the metabolic toxicity of EDCs [28].

5.3 Cancer risk

The role of endocrine disruptors (EDCs) in cancer development is very complex, as multiple effects often co-exist at various levels in various organs and tissues. The mechanisms by which EDCs interact with humans to induce cancer or promote tumoural growth are numerous [12].

Carcinogens may modify the risk of malignant tumours directly or may contribute to the tumorigenic process by other than hormonal pathways. As EDCs interfere with hormonal homeostasis and after they influence the hormone-receptor interaction in target tissues, it is conceivable that the EDC oncogenic action follows not only the classically known tumoural progression but also deviations in DNA repair process and alterations in cell growth signaling, both activated by nuclear receptor pathways. Nevertheless, many data on EDC carcinogenesis are insufficient to support conclusive remarks. Tumours that arise from hormone-sensitive organs are at increased risk following exposure to EDCs with estrogen-like effects. In various experimental models and in the human population, this association seems to be well documented. Breast cancer is the most common malignancy in women, being the most studied organ in relation to EDCs exposure. Unfortunately, definitive epidemiological human data are not yet attainable to make a formal statement concerning the association between EDCs and female hormone-dependent cancer risk. Among the EDCs, dioxins are probably those EDCs whose action as carcinogens is more compelling in exposed humans. Experiments in rats helped in defining in details different molecular events, which lead to an increased susceptibility to breast neoplasms after perinatal TCDD [29].

6 Regulatory framework for EDCs

Many compounds introduced into the environment by industrial activities are capable of disrupting the endocrine system of animals, including fish, wildlife, and also humans [30]. Endocrine disruption can be profound because of the essential role hormones play in controlling growth, differentiation, development, and homeostasis. Fifteen years ago the potential human and environmental health implications of exposure to chemically induced alterations in endocrine function were first discussed at a conference convened by a private organization. More studies were called for, including epidemiological studies to search for associations between exposure and health effects, in both wildlife and humans. This science has since shown substantial advancement and a much clearer picture is now emerging of the status of EDCs in the environment and their effects on human health [31].

The World Health Organization, European Commission, Food and Agriculture Organization, United Nations Environment Programme, US Environmental Protection Agency, and the Japanese Environment Agency are among international organizations that have active programs. In recent years national regulatory agencies in Europe and North America, and to a lesser extent elsewhere, have established regulatory programs focused on EDCs to varying degrees with less consistency than in international agencies. Despite the large amount of money spent on screening and testing programs, no national, international, or pan-European agreement has been reached on methods for regulating potential EDCs [32].

Limitations of many existing regulatory criteria were recognized in the scientific community, including perceived inconsistencies with the definition of EDCs. Regulations developed to address EDCs are often lucrative and inconsistent across treatment groups. Efforts to reassess how EDCs are evaluated, identified, and regulated are hampered by these inconsistencies. There is also increased recognition of the importance of regulatory harmonization among stakeholders from industry, academia, regulatory agencies, and the public sector. The need for such collaboration is increasingly being addressed as heightened concerns arise about the exposure to and potential impacts of EDCs [4]. However, determination of EDC exposure is not without difficulty; the lipophilic nature of many EDCs means they are stored in adipose tissue and can be present in blood and serum at concentrations several orders of magnitude lower than those within target tissues. Furthermore, metabolites of EDCs must also be considered, as in the case of bisphenol A.

6.1 International regulations and guidelines

Many international regulations and guidelines have been developed to manage endocrine disrupting chemicals (EDCs). These organizations include [13]. The EU has been very active in regulating EDCs, and in

Europe more generally, many frameworks are in place to manage them. The EU has developed a strategy for EDC management, while other regulatory bodies have published guidelines for the identification and regulation of EDCs. A framework interferes in both exports, which help developing and global countries improve their chemicals, and health-related policies to the global collaborative approach to EDC regulation.

This is to adapt to the global nature of EDC exposure and to ensure that the global advantages of EDC managements exceed the associated costs in the obstruction of trade. Implementation of harmonized scientific assessing of EDCs will be discussed, but an effort to identify opportunities to build on the international approach to EDC regulations around the world presents opportunities, challenges, principles, and strategies. Markets can place value on businesses, but incentives are needed to improve information. Reports show that increased production are of safer products, so EDCs also have sores for high-income marketing countries. The EU program of setting limits on the content of EDCs such as pesticides and in consumer products, as well as evidence of 10 times a decrease of EDCs in European water in recent years [33].

6.2 Challenges and gaps in regulation

This section discusses the challenges and gaps in the current regulatory framework that hinder addressing endocrine disrupting chemicals (EDCs) effectively [34]. There is no common scientific consensus on EDC definitions or even established mechanism of action. Lack of such alignment among the scientific community delays the development of regulation. The broad spectrum of EDCs sources and adverse effects makes it rather complex to assess health risks from those compounds. In some countries, regulations are not sufficient to effectively control EDCs, also varying enforcement practices may result in poor compliance. At the same time, there is a substantial dispersal of activities linked to the presence of EDCs. A proactive approach is also limited by a paucity of comprehensive meaningful data on the presence and impact of EDCs on humans. The combined gap analysis has identified a range of important operational areas, which require much attention and action to enhance policies. The dialogue between scientists, regulators, and industry is essential to advance on issues crucial for the development of more effective regulatory frameworks ensuring a high level of health protection, while at the same time compatible with the broader policy objectives of competitiveness and innovation. In order to promote this dialogue, the various participants in the study, especially stakeholders from the chemical industry, were identified that would be invited to participate in upcoming workshops [35].

7 Emerging issues and future directions

Recent advancements in scientific research on endocrine disrupting chemicals (EDCs) are producing new issues and stimulating future study needs. Over time, the development of new methodologies and technologies for detecting chemicals at progressively lower levels, and of new conceptual models to understand their potential health effects, is yielding a more holistic understanding of the health impacts of EDCs [1]. In parallel, researchers are coming to terms with the multifactorial nature of EDC exposure to humans, specifically that people are exposed to complex mixtures of EDCs in the environments in which they live. As such, the most recent investigations aim at studying human populations in as comprehensive a manner as possible.

There is at least anecdotal evidence of an increasing recognition within public and political domains of EDCs as a potential public health threat. Now, a combination of scientific and political factors is driving this recognition. Scientifically, there is a growing body of in vivo, in vitro, and epidemiological research findings that consistently point to the potential for EDCs to cause altered development of humans and wildlife and hormone-dependent cancers, fertility, and metabolic and behavioural issues in adults. As a result of this growing scientific consensus, numerous reviews and expert panels have urged a more proactive and precautionary approach to regulation. Politically, the European Commission and competent authorities in EU member states have committed themselves to a long-term strategy addressing the issue. At the very least, ensuring that the regulation of EDCs is commensurate with the state of science [36].

In this rapidly evolving field, unique forms of interdisciplinary and multidisciplinary collaboration are yielding interesting outcomes. For example, research into the health impacts of persistent organic pollutants (POPs)—many of which are EDCs—has spurred collaborations between toxicologists and epidemiologists, as well as other fields, leading to substantial public health benefits and decision-relevant scientific findings. In light of this, there is a strong argument for endocrinologists, toxicologists, epidemiologists, and environmental scientists to engage in dialogue on EDCs, given the potential for the outcomes of that dialogue to inform the drafting of public health, environmental, and insurance policies. Given these trends and developments, a timely analysis of recent and ongoing research in the field is not only appropriate, but is arguably necessary [37].

7.1 Advances in EDC research

Public and scientific awareness over the potential risks of endocrine disrupting chemicals (EDCs) have rapidly increased over the past three decades. Since then, research of EDCs has continued to evolve, expanding far beyond early studies focusing on known EDCs of concern. Much effort has been devoted to the development of more sensitive and sophisticated methods for the detection and monitoring of a wide range of environmental compounds with endocrine disrupting properties [1]. As a result, the body of evidence demonstrating the pervasiveness of potential EDCs in various environments has been rapidly growing. Apart from improvements in analytical technologies, there has been a proliferation of innovative research methodologies aimed at understanding the effects of complex mixtures and low-dose exposures on a variety of health outcomes, targeting at various stages throughout the life span [4]. There are now a number of powerful studies that have revealed critical links between environmental exposures and adverse health outcomes via endocrine disruption mechanisms, providing impetus for revisiting existing health policies and developing new strategies for both EDC reduction and robust exposure assessment. Moreover, recent findings suggest the promise of more sensitive and more specific risk assessment strategies that take advantage of advances in scientific understanding to be able to better adjust for uncertainties and data gaps. However, concerns have been raised about dwindling funding support in various countries, casting doubt on the sustainability of the anticipated advances in this field. Collaboration at an international level may bolster resources and expertise to re-energize the scientific and regulatory communities, providing a strong basis for improved policy decisions.

7.2 Technological innovations in detection

With the rising awareness of endocrine disrupting chemicals (EDCs) and their potential adverse health impacts, the need for real-time monitoring of this class of contaminants becomes increasingly important [38]. Recent technological advances have led to significant improvements in EDC detection that has broad implications for understanding EDC toxicology, regulatory compliance, and public health monitoring. Following intensive research efforts on EDC toxicology in recent years, a growing number of endocrine active chemicals have been identified in daily products, and the toxicological mechanisms of these pollutants have been well elucidated. However, the exposure risks associated with these chemicals are far to be efficiently monitored and controlled. To facilitate the toxicological studies of EDCs and protect human health, the monitoring of the EDCs in water, soil, and other matrices should be comprehensively addressed. In this regard, more precise and efficient detection tools should be developed to easily and timely monitor the emerging EDC concentration. With the development of the modern sensor techniques, numerous measurement strategies of the EDC concentration have been proposed and widely investigated in the past two decades. Recently, the synthesis of novel materials such as metal-organic frameworks, covalent organic frameworks, and graphene, operated as nanozymes, has received remarkable attention in the construction of EDC sensors. Moreover, the sensing assay based on molecularly imprinted polymers has been designed for detecting EDCs with high selectivity. Besides, with the combination of liquid chromatography (LC) and mass spectrometry (MS), numerous advanced monitoring systems have also been manufactured for determining the multi-class of EDC trails in the complex samples. These tools provide more options for the ensuing study of the EDC toxicology and the subsequent regulatory intervention. With the establishment of these high-performance instrumental setups, the EDC monitoring can be conducted on site continuously at a fast rate and with high sensitivity, which is beneficial for the exposure and potential risk assessment of the EDCs. Furthermore, these devices can also be combined with other facilities and expedite the establishment of real-time monitoring systems, which can be applied to rapidly evaluate the emergency occurrence and the actual regulation efficacy in the future [39].

8 Conclusion and recommendations

Endocrine-disrupting chemicals (EDCs) have become a threat to human health across the globe. Many of these chemicals are either man-made products or their by-products which interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body posing numerous adverse effects on human health. In recent years, significant efforts have been devoted to assessing the potential hazards of EDCs, clarifying their toxicological and regulatory implications, and finally offering corresponding countermeasures. Nonetheless, many important gaps still persist in our understanding of the human health risks posed by EDCs, highlighted the requirement for continued and sustained efforts among stakeholders worldwide. It is urgent to further regulate and manage EDCs in a scientific and effective manner to protect public health.

The complex environmental behavior, potential life-long exposure, atypical toxicological mechanisms, and non-linear, low-dose effects make challenges to the scientific understanding of EDCs and their regulations. Intensive research work is being developed based on these hot spots to address the knowledge gaps posing practical implications by developing widely accessible and implementable strategies. Implementation of comprehensive countermeasures regarding EDCs and the related mixtures are urged to be involved into national, regional, and international regulatory frameworks. Public outreach issues are anticipated to be filled with meaningful information on EDCs in a timely manner. Mechanistic understanding of EDCs exposures can be improved by raising questions, offering possible research solutions, and sharing consolidated opinions. It is ideal to complete the effective monitoring technology for EDCs in the environmental and biological media, including those to deal with the EDCs mixtures. Furthermore, the development of such databases should enhance data availability and harmonization to support ongoing actions. Thus, all possible EDC-related research should be presented with harmonized and transparent outputs to jointly face the challenge.

Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The ethical committee approved the study at Pharos University in Alexandria, Alexandria, Egypt.
Funding: This research received no external funding.

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How to cite this article

Youssef M.M.; Helal A.M.; Khedr Y.I.; Endocrine Disrupting Chemicals and Human Health: A Review of Toxicological Mechanisms and Regulatory Challenges. Journal of Biomedicine and Biochemistry. 2025;4(1):14-26. doi: 10.57238/jbb.2024.7432.1133