Chapter

Human Health Consequences of Endocrine-Disrupting Chemicals

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Abstract

Daily use of chemicals is an essential part of modern life. Endocrine-disrupting chemicals (EDCs) are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones and consequently cause adverse effects to humans and wildlife. The number of EDCs has markedly increased over the past 60 years. Humans are constantly exposed to hundreds of EDCs mainly through air, water, and food. Exposure to EDCs (*in utero* or lifetime) may be a significant component of the environmental origin of several medical conditions. The developing fetus and neonate are more sensitive than adults to perturbation by EDCs. The prenatal damage can cause adverse consequences later in life (developmental origins of adult disease). In many cases, the damage is irreversible. There is also a possibility of transgenerational effects. By interfering with hormonal functions, EDCs can contribute to a variety of dysfunctions and diseases including obesity, diabetes, reproductive disorders, and cancers. Information on long-term effects of chronic, low-dose exposure to EDCs is relatively limited. EDCs represent a global threat for human health and cause a high cost for the society. Promoting public knowledge and initiating preventive measures will help minimizing the health and economic consequences of EDCs for future generations.

Keywords: environmental contaminants, endocrine-disrupting chemicals, human health, preventive strategies

1. Introduction

Daily use of chemicals is an essential part of modern life. EDCs are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones and consequently cause adverse effects to humans and wildlife. They represent an emerging research field. The number of EDCs has markedly increased over the past 60 years. Humans are constantly exposed to hundreds of EDCs mainly through air, water, and food [1–9].

Exposure to EDCs (*in utero* or lifetime) may be a significant component of the environmental origin of several medical conditions. There is also a possibility of transgenerational effects. By interfering with hormonal functions, EDCs can contribute to a variety of dysfunctions and diseases including obesity, diabetes, reproductive disorders, and cancers [1–4, 10–46].

EDCs represent a global threat for human health and cause a high cost for the society [47]. Promoting public knowledge and initiating preventive measures will help minimizing the health and economic consequences of EDCs for future generations.

2. General characteristics of EDCs

2.1 Definition and identification of EDCs

In 2002, the International Programme on Chemical Safety belonging to the World Health Organization conducted a comprehensive evaluation of EDCs and proposed the following definition: "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

EDCs are chemicals, mainly man-made, but also naturally occurring substances that can be found in plants or fungi, that interfere with hormonal signaling pathways. The EDCs are active at very low doses, impact health, and can have persistent effects [1–5, 10, 11, 13, 16, 48].

The first scientific statement of the Endocrine Society in 2009 provided a wake-up call to the scientific community on the risks of EDCs for human health. The second statement of the Endocrine Society in 2015 provided a global update on EDCs based on the available data in the literature [10].

The experimental screening process of the EDCs using animal data is time-consuming and costly. Computer-based (*in silico*) methods have been developed to predict the effect of the EDCs on the endocrine receptor [5, 49]. One popular method is the molecular docking approach.

2.2 Origin of EDCs

There are over 140,000 man-made chemicals. In 2015, the total production of chemicals in the European Union (EU) was 323 million metric tons, 205 million metric tons of which were considered hazardous to health. The Endocrine Disruption Exchange lists approximately 1,000 agents that have been characterized as EDCs (**Figure 1**).

Figure 1.
EDCs are mainly man-made chemicals.

EDCs originate from several sources including phytoestrogens (e.g., genistein), industrial (e.g., dioxins and perchlorates), agricultural (e.g., organochlorines, organophosphates, and carbamates), residential (e.g., bisphenol A and phthalates), medical devices (e.g., bisphenol A and phthalates), and pharmaceutical (e.g., diethylstilbestrol and parabens) [1–8, 10, 11–13, 15–25, 31, 33, 44].

The EDCs can be found in our everyday lives in a variety of products including dust, soil, water, food, cosmetics, soaps, shampoos, toothpastes, plastic containers, toys, nicotine, and fertilizers. The United States (US) Environmental Protection Agency (EPA) estimates children ingest 60–100 mg of dust per day from indoor environment. Among multiple EDCs present in food, it is notable to mention monosodium glutamate (used as a flavor enhancer), genistein (found in soy-based foods), and high-fructose corn syrup (used as a sweetener). The use of plastic packaging is on the rise. The worldwide plastics production reached 380 million metric tons in 2015, with approximately 40% used for packaging. Around 60% of all plastic packaging is used for beverages and food.

2.3 Routes of exposure to EDCs

The exposure to EDCs is mainly unintentional. EDCs remain intact in the environment and become widely distributed geographically. They are able to travel very long distances in the air. EDCs can accumulate in the food chain and be ingested by humans. Exposure to EDCs begins before birth, and even before conception. There are several routes of exposure including air, water, food, skin, vein, breast milk, and placenta [2–8, 10–13, 15, 16, 18–21, 23, 25, 31, 39, 41]. Humans can be exposed simultaneously to several EDCs and this is a challenge for the interpretation of the epidemiological studies [14]. Professional workers (e.g., workers using pesticides) are at higher risk of exposure to EDCs.

2.4 Metabolism of EDCs

EDCs accumulate in adipose tissue or binds to proteins. Most EDCs are highly lipophilic and are stored in adipose tissue. Non-lipophilic EDCs are bound to albumin. EDCs may have long half-lives (months or years, e.g., organochlorines) or short half-lives (minutes, hours, or days, e.g., bisphenol A) [10, 12, 14, 36]. The liver is responsible for metabolizing EDCs and may also act as a storage site for lipophilic EDCs. Lipophilic EDCs are more resistant to degradation. Detectable levels of numerous EDCs exist in human body fluids (e.g., blood and urine) and tissues (e.g., adipose tissue and liver).

2.5 Mechanisms of action of EDCs

EDCs interfere with the action of hormones (**Figure 2**). They may interact with or activate hormone receptors (membrane and nuclear receptors), antagonize hormone receptors, alter hormone receptor expression, alter signal transduction in hormone-responsive cells, induce epigenetic modifications in hormone-producing or hormone-responsive cells (e.g., DNA methylation and histone modifications), alter hormone synthesis, alter hormone transport across cell membranes, alter hormone distribution or circulating hormone levels, alter hormone metabolism or clearance, and alter fate of hormone-producing or hormone-responsive cells [1, 3, 4, 9, 10, 12–21, 24, 27, 28, 33, 35].

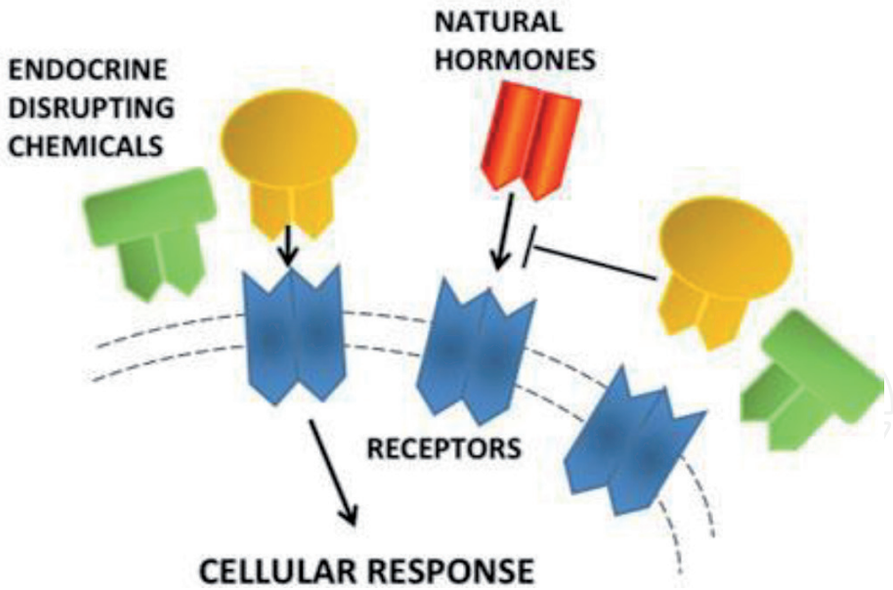

Figure 2.
EDCs interfere with the action of hormones.

3. Consequences of exposure to EDCs

The endocrine system is a complex network of glands (or tissues), hormones, and receptors controlling different functions and insuring the homeostasis of the organism.

EDCs pose a threat to humans. They alter the homeostatic systems through environmental or developmental exposures. By interfering with hormonal functions, EDCs can contribute to a variety of dysfunctions and diseases. Every endocrine axis may be the target of EDCs. Exposure to EDCs (*in utero* or lifetime) may be a significant component of the environmental origin of several medical conditions including obesity, diabetes, reproductive disorders, and cancers (**Figure 3**) [1–4, 10–46]. A specific EDC may be innocuous by itself but when associated with other EDCs may cause hazardous effects (cocktail effects). The EDC mixtures are the most complicated situations to investigate.

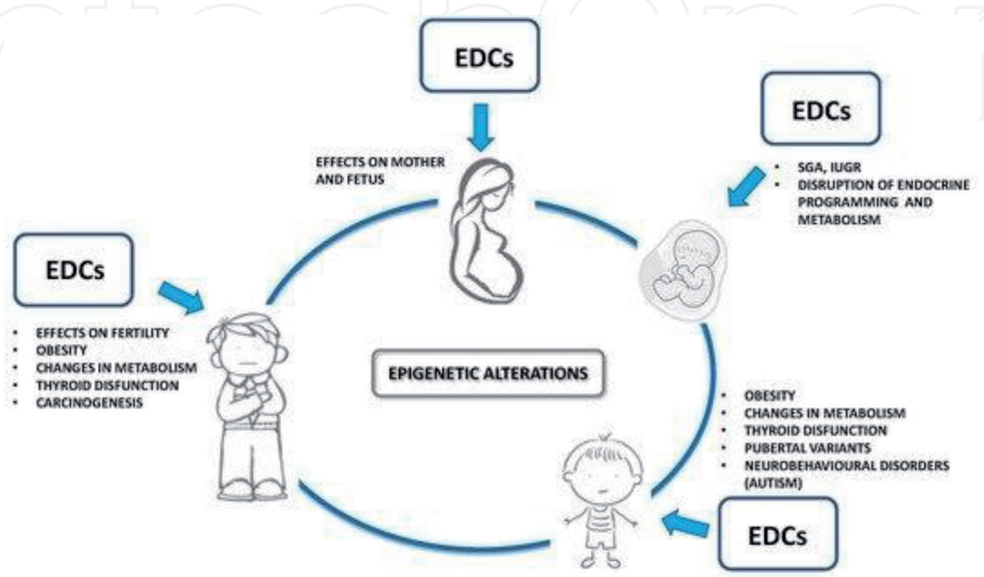

Figure 3.
EDCs can contribute to a variety of dysfunctions and diseases.

The susceptibility to EDCs and the resulting deleterious effects may be further enhanced by the current climate change.

3.1 Obesity

Obesity is a worldwide pandemic associated with increased morbidity/mortality and high cost for the society [50–52]. Although alterations in food intake and/or decrease in exercise are important contributing factors to obesity, they cannot fully explain the current obesity pandemic. Obesity pandemic coincides with the marked increase of the chemicals in the environment over the past 60 years.

Some EDCs can impair regulation of adipose tissue and food intake, reduce basal metabolic rate, and predispose to weight gain and obesity despite normal diet and exercise. They can also cause resistance to weight loss if subjects are on anti-obesity diet and/or drug. These EDCs are called obesogens (or metabolism-disrupting chemicals) [2, 4, 10, 12, 15–20, 26–33, 36]. The list of obesogens is continuously growing. Approximately 50 chemicals have been implicated. They include monosodium glutamate, nicotine, bisphenol A, phthalates, parabens, and tributyltin (non-exhaustive list).

Obesogens have several target tissues including adipose tissue, brain, liver, stomach, and pancreas. At the level of adipose tissue, obesogens promote obesity by inducing an increase in the number of adipocytes (by activating nuclear receptor signaling pathways critical for adipogenesis) and storage of fat (**Figure 4**) [17].

Perinatal exposure to obesogens is associated with overweight and obesity in children. Some obesogens (e.g., bisphenol A and tributyltin) are able to induce heritable changes that are propagated through multiple generations without any new exposure (transgenerational inheritance) [17].

White adipose tissue is an important reservoir of lipophilic obesogens (many obesogens are lipophilic chemicals). Rapid weight loss increases plasma levels of lipophilic obesogens and may contribute to weight cycling (yo-yo effect).

The dramatic increase in the prevalence of obesity, especially among children, shows that intervention actions are needed urgently. Exposure to obesogens should be reduced or avoided especially in fetus and neonate.

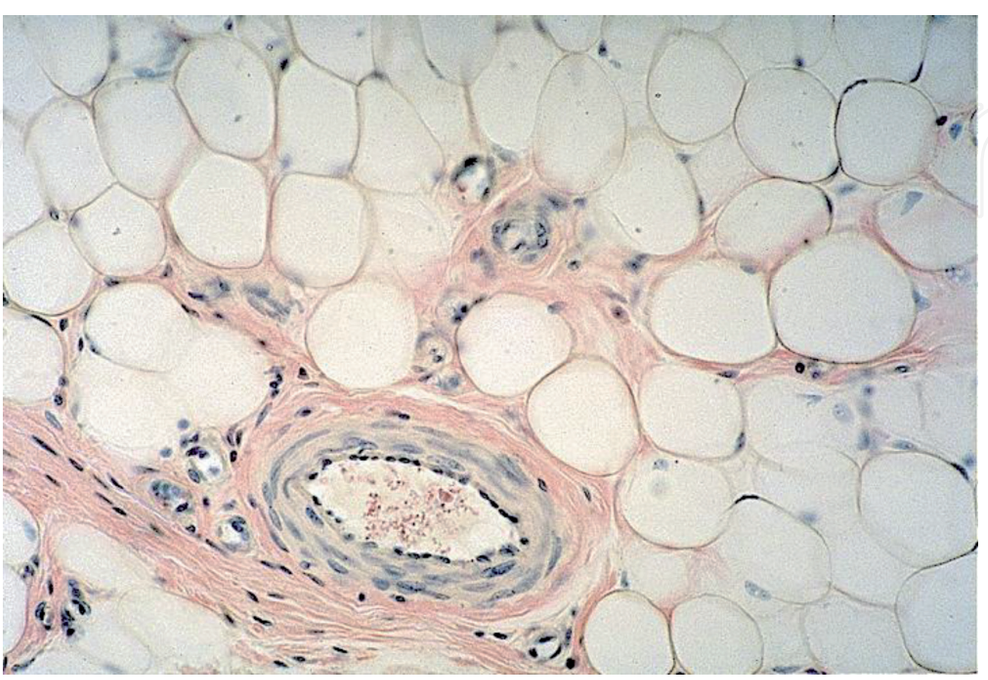

Figure 4.
Obesogens alter lipid homeostasis to promote adipogenesis and lipid accumulation.

3.2 Diabetes

Diabetes (type 1 and type 2) is a complex metabolic disease resulting from deficiency of insulin secretion and/or action [35, 53]. The incidence of diabetes has risen significantly over the last several decades [35, 54]. The role of several EDCs in the development of diabetes has been extensively investigated. However, prospective studies are still needed to support the current findings (**Figure 5**) [3, 4, 10, 15, 16, 34–37].

Prenatal and early-life exposures to EDCs can play a role in the development of type 1 diabetes by increasing the risk of autoimmunity and affecting β-cell development and function [37]. EDCs with androgenic activity (e.g., bisphenol A) may interfere with β-cell function, impair insulin secretion by accelerating insulitis, and cause type 1 diabetes [35].

Several EDCs (obesogens) may promote the development of type 2 diabetes through weight gain and the resulting insulin resistance. Exposure to bisphenol A leads to insulin resistance and type 2 diabetes [35].

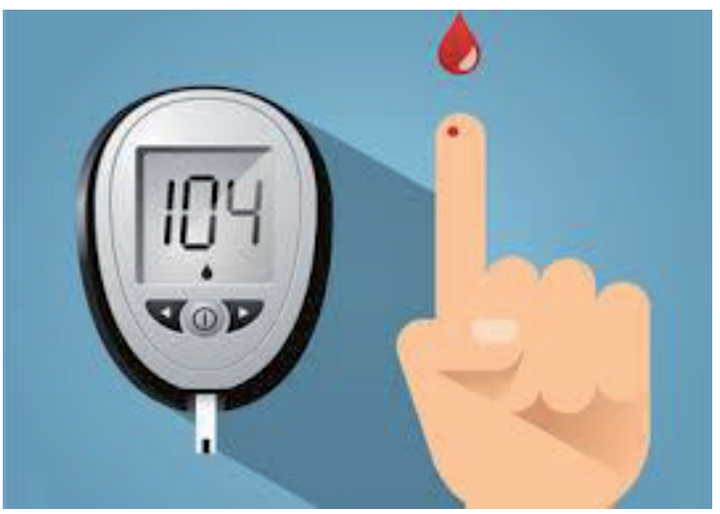

Figure 5.
Exposure to EDCs can cause diabetes through multiple mechanisms.

3.3 Reproductive disorders

The hypothalamic–pituitary-gonadal axis is the most vulnerable endocrine axis to EDCs action. Several disorders have been reported including intersex variation (ambiguous genitalia), cryptorchidism (undescended testicles), hypospadias (abnormal opening of urethra), precocious puberty, infertility, polycystic ovarian disease, endometriosis, uterine fibroids, and cancers [1–4, 10, 12, 13, 21–23, 25, 38–40].

3.3.1 Male reproductive disorders

Over the past several years, male reproductive health has been on the decline with the increase incidence of congenital malformations and poor semen quality [23, 40]. Experimental and epidemiological studies support the hypothesis that prenatal exposure to EDCs with estrogenic and/or antiandrogenic activity (e.g., diethylstilbestrol, bisphenol A, and phthalates) may disrupt the secretion and/or action of two Leydig cell hormones (testosterone and insulin-like peptide 3) regulating testicular descent, leading to cryptorchidism in newborn (**Figure 6**) [40].

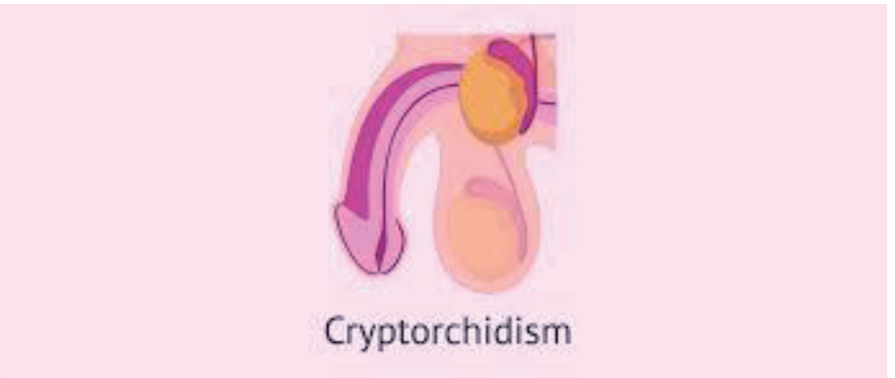

Figure 6.
Maternal exposure to EDCs may predispose to cryptorchidism in newborn.

3.3.2 Female reproductive disorders

The first clinical warning with EDCs came from diethylstilbestrol, a potent estrogen mimic, given to millions of women 50–80 years ago to prevent miscarriage. A large number of children exposed *in utero* to this chemical developed genital malformations and cancers (e.g., vaginal adenocarcinoma) while the exposed mothers had an increased risk for developing breast cancer [3, 38].

Exposure during pregnancy to several EDCs (e.g., bisphenol A and phthalates) is associated with inflammatory cytokine levels in maternal and neonatal circulation and increased risk of low birth weight [25, 41].

3.4 Cancers

Exposure to some EDCs (e.g., dioxins, organochlorines, arsenic, and cadmium) may promote the occurrence of different cancers including thyroid cancer, testicular cancer, prostate cancer, uterine cancer, breast cancer, skin cancer, and lymphoma (**Figure 7**) [2–4, 10, 12, 13, 18, 21, 22, 38, 44, 45].

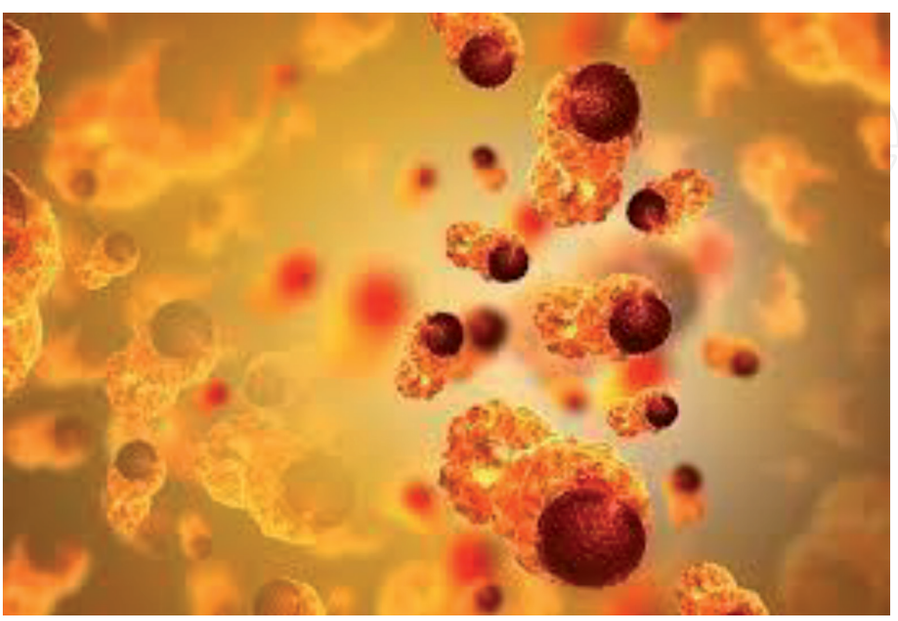

Figure 7.
EDCs can promote the occurrence of different types of cancer.

3.5 Others

Exposure to EDCs has been reported to be associated with increased incidence of cardiovascular, respiratory, liver, kidney, neurological/psychiatric, skin, and immunological disorders [2–4, 10, 13, 16, 24, 42–44].

Skin is a body barrier providing protection from environmental physical and chemical harm. Several EDCs (e.g., dioxins, phthalates, parabens, and arsenic) can act directly on different skin cells (e.g., keratinocytes, sebocytes, melanocytes, stem cells, and fibroblasts) and cause a variety of skin disorders such as chloracne, hyperpigmentation, allergic contact dermatitis, aging, and cancer (**Figure 8**) [44].

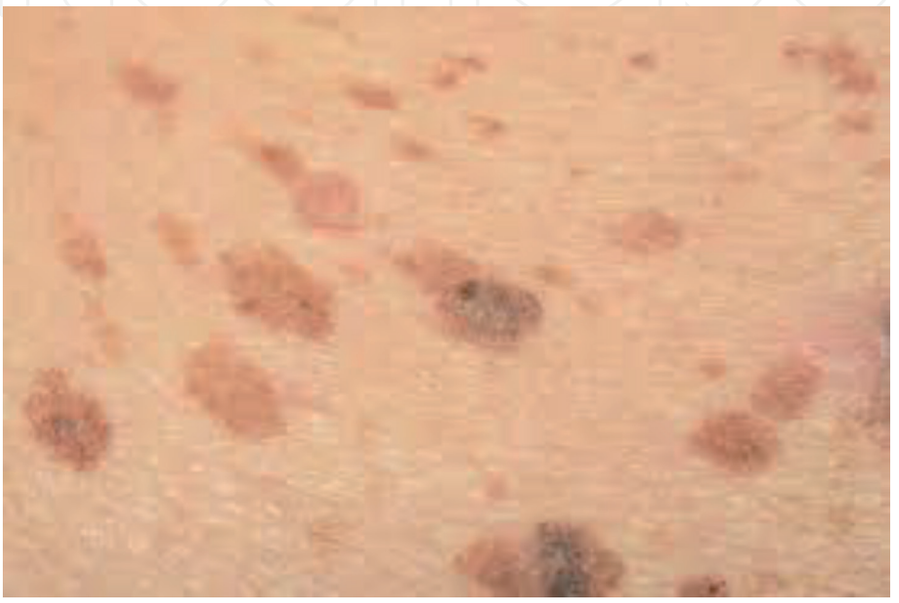

Figure 8.
EDCs can cause a variety of skin disorders.

3.6 Timing of exposure to EDCs

The timing of exposure to EDCs plays an important role for the health consequences of EDCs.

Pregnancy is a sensitive window for EDCs exposure. Pregnant women are exposed to numerous EDCs (e.g., bisphenol A, phthalates, parabens, and flame retardants) which can cross the placenta and affect the fetus. The developing fetus and neonate are more sensitive than adults to perturbation by EDCs (**Figure 9**) [3, 4, 9, 10, 14, 16, 17, 19, 25–28, 37–39, 41, 43, 46]. There is a higher sensitivity in fetus and neonate due to rapid cell division and differentiation, lack of protective mechanisms (e.g., DNA repair), competent immune system, or mature blood/brain barrier, and increased metabolic rates. During fetal development, different organ systems begin to develop at different time periods. Therefore, the susceptibility to EDC exposure and health consequences depends on the critical period for a given target organ system. The prenatal damage can cause adverse consequences later in life (developmental origins of adult disease). Effects on early development are of special concern as these effects are often irreversible. Oxidative stress caused by EDCs can be the mediator of several adverse health outcomes (e.g., obesity, diabetes, and cardiovascular disease in adulthood) [16, 19, 46]. With EDCs, there is also a possibility of damage to future generations (transgenerational inheritance) [10, 16, 17, 27, 28].

Figure 9.
EDCs can severely impact the developing fetus.

3.7 Dose and duration of exposure to EDCs

The intensity of exposure to EDCs varies between the United States of America (USA) and the EU because of differences in regulations. For example, EDC exposure is much higher for organophosphate pesticides in the EU and for polybrominated diphenyl ethers in the USA [47].

Humans are at the top of food chain. They may store large doses of multiple EDCs according to the process of bioaccumulation and bioamplification, generating effects with unknown consequences [12]. No safe dose of EDC exposure can be established. Information on chronic low-dose exposure to EDCs is relatively limited.

3.8 Gender effect of exposure to EDCs

Based on epidemiological studies, gender may play a role on the impact of EDCs (**Figure 10**) [12, 16, 42]. EDCs exert sexually dimorphic effects in metabolism regulation through interactions with sex hormone receptors. Bisphenol A appears to have specific effects on behavior of both sexes (increase in externalizing behavior in girls versus increase in internalizing behavior in boys).

Figure 10.
Gender may influence the health consequences of EDCs.

4. Preventive strategies to reduce exposure to EDCs

EDCs represent a global threat for human health and cause a high cost for the society [47]. Promoting public knowledge and initiating preventive measures will help minimizing the health and economic consequences of EDCs for future generations.

Policymakers are caught between competing interests, those of organizations acting to protect health, and companies working to increase commercial profits. EDCs challenge regulators on how to translate science into policy. It is important to establish and agree on the criteria defining and identifying the EDCs and the level of risk to human health.

Several agencies (e.g., US EPA and European Food Safety Agency) are regulating the EDCs. Legislation and regulation have been implemented over the last few years to control the exposure to EDCs. There are differences in regulations between countries, including between the USA and the EU. For example, countries with significant heavy chemicals industry are less open to changes towards greener chemicals production [3, 11, 48, 55].

Exposure to EDCs cannot be entirely avoided. However, it is possible to minimize the exposure to EDCs [3, 4]. The following recommendations should be considered (non-exhaustive list):

- Take the shoes off before walking into the house.
- Wash hands before preparing or eating food.
- Use filtered water to minimize phthalates intake (install a filter on the faucet).
- Consume low-fat low-meat fresh food (instead of processed and canned food) and organic produce to reduce the ingestion of EDCs (especially pesticides).
- Avoid beverages and foods stored in plastic containers. Replace plastics used in food preparation (for storage and heating in microwave) with glass, ceramic, stainless steel, and bisphenol A-free products to decrease the consumption of bisphenol A and phthalates. Keep water bottles cool to reduce bisphenol A leaching. Minimize the use of nonstick cookware. Throw away any scratched nonstick pans.
- Increase the recycling rates of packaging plastics.
- Use organic, natural cosmetics. Prioritize makeup and perfume products that are free of phthalates, parabens, and triclosan. For sunscreens, mineral-based products containing zinc oxide or titanium dioxide as active ingredients should be preferred.
- Minimize the use of bleached paper products containing dioxins (e.g., paper towels and disposable diapers).
- Prefer ecological household cleaning products.
- Avoid flame retardant-treated clothing and furniture.
- Use alternatives to plastic toys.

- Do not burn conventional candles. Avoid air fresheners (try a vase of dried lavender instead).

- Perform regular ventilation of the indoor environment. Open windows to allow clean air in when possible.

- Avoid touching receipts to minimize exposure to carbonless/thermal paper.

Some of the above recommendations are difficult to implement for practical and/or financial reasons.

5. Cost of EDCs

EDCs are costing society hundreds of billions of dollars each year. Due to regulatory divergence and according to a relatively recent report, the disease costs in the USA were around 2.3% of the gross domestic product, higher than in the EU (around 1.3%) [47].

Regulatory actions to limit the most prevalent and hazardous EDCs could have substantial economic benefits. The costs of regulatory actions should be compared with the costs of inaction.

6. Conclusions

EDCs are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones and consequently cause adverse effects to humans and wildlife. Humans are constantly exposed to hundreds of EDCs mainly through air, water, and food.

EDCs pose a threat to humans and the environment. Exposure to EDCs (*in utero* or lifetime) may be a significant component of the environmental origin of several dysfunctions and diseases including obesity, diabetes, reproductive disorders, and cancers.

Promoting public knowledge and initiating preventive measures will help minimizing the exposure to EDCs and the resulting health and economic consequences for future generations.

Conflict of interest

The author declares no conflict of interest.

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