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Mini Review

Endocrine-Disrupting Chemicals and Related Medical Disorders

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Abstract

Endocrine-Disrupting Chemicals (EDCs) are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones. Over the past 60 years, the number of EDCs has markedly increased. Through air, water, and food, humans are regularly exposed to hundreds of EDCs. The *in utero* or lifetime exposure to EDCs can be a significant component of the environmental origin of several medical conditions. The prenatal damage caused by EDCs may have consequences later in life (developmental origins of adult disease). With EDCs, transgenerational effects are also possible. The medical disorders caused by EDCs include diabetes, obesity, Nonalcoholic Fatty Liver Disease (NAFLD), infertility, and cancers (non-exhaustive list). There is limited information on long-term effects of chronic, low-dose exposure to EDCs. Overall, EDCs represent a threat for human health and a financial burden for the society. The promotion of public knowledge and the initiation of preventive measures can minimize the deleterious consequences of EDCs.

Keywords: Chemical contaminants; Endocrine-disrupting chemicals; Medical disorders; Prevention

Abbreviations: AZ: Arizona; DNA: Deoxyribonucleic Acid; EDC: Endocrine-Disrupting Chemical; e.g.: Exempli Gratia; EPA: Environmental Protection Agency; EU: European Union; LLC: Limited Liability Company; MD: Medical Doctor; NAFLD: Nonalcoholic Fatty Liver Disease; US: United States; USA: United States of America

Introduction

EDCs are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones, causing a variety of medical disorders. Over the past 60 years, the number of EDCs has markedly increased. Modern life is associated with the daily use of multiple chemicals. Through air, water, and food, humans are regularly exposed to hundreds of EDCs [1-16].

The *in utero* or lifetime exposure to EDCs can be a significant component of the environmental origin of several medical conditions. Transgenerational effects are also observed with EDCs. The medical disorders caused by EDCs include diabetes, obesity, NAFLD, infertility, and cancers (non-exhaustive list) [1,3,4,8-15,17-40].

EDCs represent a threat for human health and a financial burden for the society [41]. By promoting public knowledge and initiating preventive measures, it is possible to minimize the deleterious consequences of EDCs for generations to come.

Characteristics of EDCs

In 2002, the International Programme on Chemical Safety belonging to the World Health Organization proposed the following definition for EDCs: "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 mainly man-made chemicals but can also be found in plants or fungi. The number of man-made chemicals is over 140,000. According to the Endocrine Disruption Exchange, there are approximately 1,000 chemicals considered as EDCs. The sources of EDCs include 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) [1-17,21,23,25-28,30,33,34,36,37,41-43].

The EDCs are present in a variety of products including dust, soil, water, food, cosmetics, soaps, shampoos, toothpastes, plastic containers, toys, nicotine, and fertilizers (non-exhaustive list) (Figure 1). According to the United States (US) Environmental Protection Agency (EPA), each day, children ingest 60-100 mg of dust from indoor environment. Contamination from plastic packaging is a serious concern [6,7]. The worldwide plastic production is around 400 million metric tons per year with almost half coming from Asia (mainly from China) and approximately 40% used for packaging (especially for beverages and food). The United States of America (USA), Japan, the European Union (EU), and China are the world largest producers while the African and the Central and South American countries are the world smallest producers of plastic packaging waste per capita. In most cases, plastic packaging is thrown away within few minutes of its first use. Plastic pollution in water could more than double by 2030. Most plastics do not biodegrade and when discarded, can take up to thousands of years to decompose. In terms of food contamination, monosodium glutamate (flavor enhancer), genistein (soy-based foods), and high-fructose corn syrup (sweetener) are relevant contributors.

Figure 1: Cosmetics contain a variety of EDCs.

EDCs can travel very long distances in the air. They accumulate in the food chain and are ingested. Exposure to EDCs begins before birth, even before conception. Air, water, food, skin, vein, breast milk, and placenta represent different routes of exposure to EDCs [1-18,22,23,27,33,34,37,42,43]. It is common to be exposed simultaneously to several EDCs. This multiple exposure can create difficulties during the interpretation of the results of epidemiological studies [44].

Numerous EDCs can be detected in human body fluids (e.g., blood and urine) and tissues (e.g., adipose tissue and liver). The majority of EDCs are highly lipophilic and stored in adipose tissue. Non-lipophilic EDCs are bound to albumin. Some EDCs have long half-lives (months or years, e.g., organochlorines) while others have short half-lives (minutes, hours, or days, e.g., bisphenol A) [1,10,11,14,18,20,28,43,44]. The liver metabolizes EDCs and may store lipophilic EDCs. Lipophilic EDCs are more resistant to degradation.

EDCs 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., Deoxyribonucleic Acid (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 (Table 1) [1,3,4,8,10-15,17-19,21,24-26,28-30,34,36,43-45]. EDCs are active at very low doses and can have persistent effects [1,4,8,9,11,14,17].

Mechanisms of Action of EDCs
Interaction with or activation of hormone receptors (membrane and nuclear receptors)
Antagonism of hormone receptors
Alteration of hormone receptor expression
Alteration of signal transduction in hormone-responsive cells
Induction of epigenetic modifications in hormone-producing or hormone-responsive cells (e.g., DNA methylation and histone modifications)
Alteration of hormone synthesis
Alteration of hormone transport across cell membranes
Alteration of hormone distribution or circulating hormone levels
Alteration of hormone metabolism or clearance
Alteration of fate of hormone-producing or hormone-responsive cells

Table 1: EDCs interfere with the action of hormones through multiple mechanisms.

Adverse Effects of EDCs

By altering the homeostatic systems through environmental or developmental exposures, EDCs have deleterious consequences for humans. A single EDC may be innocuous by itself but when combined with other EDCs, it may cause adverse effects (cocktail effects) [33]. No safe dose of EDC exposure can be established. Information on chronic low-dose exposure to EDCs is relatively limited.

The *in utero* or lifetime exposure to EDCs can be a significant component of the environmental origin of multiple medical conditions. The timing of exposure to EDCs has an important influence on the health consequences of EDCs. Pregnancy is a very sensitive window for EDCs exposure. Pregnant women can be exposed to multiple EDCs (e.g., bisphenol A, phthalates, parabens, and flame retardants) that are able to cross the placenta and affect the embryo/fetus. This exposure is associated with inflammatory cytokine levels in maternal circulation [16]. The oxidative stress caused by EDCs can be the mediator of several adverse health outcomes [46]. The Week 4 to Week 8 of the embryonic period is a sensitive and vulnerable window of organogenesis and any exposure to EDCs during that period can cause major congenital anomalies. The developing embryo/fetus and neonate are more sensitive than adults to the actions of EDCs (Figure 2) [1,4,8,11,14,16,18,21-24,26,30,31,35,42,44-47]. The prenatal damage may lead to adverse consequences later in life (developmental origins of adult disease). There is also a possibility to induce heritable changes that are propagated through multiple generations without any new exposure (transgenerational inheritance) [1,11,21,23-26,30,45].

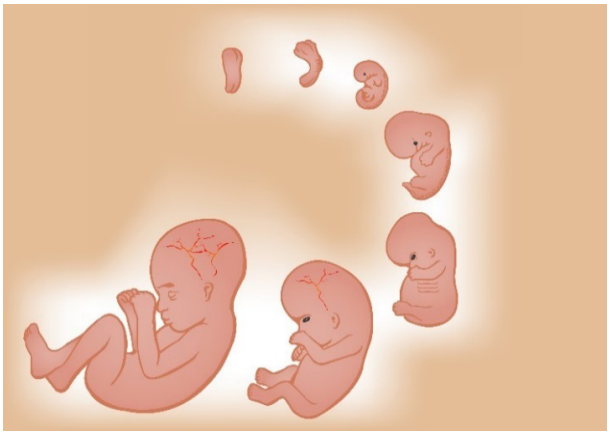

Figure 2: The developing embryo/fetus is very sensitive to the actions of EDCs.

Endocrine glands are particular targets for EDCs and every endocrine axis may be affected [10]. Gender may play a role in the impact of EDCs [10,11,26,32]. The sexually dimorphic effects of EDCs are likely through interactions with sex hormone receptors. The medical disorders caused by EDCs include diabetes, obesity, NAFLD, infertility, and cancers (non-exhaustive list) (Table 2) [1,3,4,8-15,17-40].

Medical Specialties Impacted by EDCs	Examples of Medical Disorders Caused by EDCs
Endocrinology/ Metabolism	Diabetes (type 1 and type 2), Overweight/ Obesity, NAFLD, Genital malformations, Precocious puberty, Polycystic ovary syndrome, Endometriosis, Uterine fibroids, Infertility
Oncology	Skin cancer, Thyroid cancer, Breast cancer, Endometrial cancer, Vaginal cancer, Testicular cancer, Prostate cancer, Lymphoma
Dermatology	Dermatitis, Chloracne, Hyperpigmentation, Aging
Neurology/ Psychiatry	Neurodevelopment disorders, Anxiety
Cardiology	Hypertension, Coronary heart disease
Pneumology	Asthma
Nephrology	Albuminuria
Ophthalmology	Dry eye disease
Immunology	Autoimmune diseases

Table 2: EDCs can impact multiple organs and systems resulting in a variety of medical disorders.

EDCs and Endocrinology/Metabolism

Diabetes

The incidence of diabetes has risen significantly over the last several decades and is expected to rise dramatically in the years to come [18,19,21,48]. The role of several EDCs in this rise has been extensively investigated. Prenatal and early-life exposures to EDCs can play a role in the development of type 1 diabetes [22]. 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 (Figure 3) [19,22]. Several EDCs that cause obesity may promote the development of type 2 diabetes through weight gain and the resulting insulin resistance. Exposure to bisphenol A can cause insulin resistance and type 2 diabetes [19]. In the USA, the higher burden of diabetes in the vulnerable populations (e.g., Latinos, African Americans, and low-income individuals) may be partly due to a higher exposure of these populations to several EDCs [21,49]. The confirmation of the current findings on exposure to EDCs and risk of developing diabetes re-

quires large prospective studies [1,4,8,11,12,18-22,49].

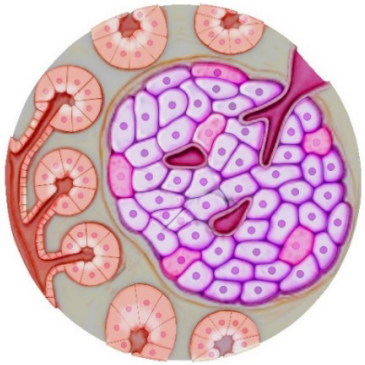

Figure 3: EDCs interfere with β-cell function, impair insulin secretion, and cause type 1 diabetes.

Obesity

Obesity is a worldwide pandemic responsible for increased morbidity/mortality and high cost for the society [50-52]. The current obesity pandemic cannot be fully explained by alterations in food intake and/or decrease in exercise. The important increase of the EDCs in the environment over the past few decades coincides with the obesity pandemic. Some EDCs called obesogens, impair the regulation of adipose tissue and food intake, reduce basal metabolic rate, and predispose to weight gain and obesity despite normal diet and exercise [1,3,4,9-14,20,23-31]. These EDCs can also cause resistance to weight loss in subjects on anti-obesity diet and/or drug. Approximately 50 obesogens have been identified including monosodium glutamate, nicotine, bisphenol A, phthalates, parabens, and tributyltin (non-exhaustive list). Obesogens impact several tissues and organs including adipose tissue, brain, liver, stomach, and pancreas. At the level of adipose tissue, obesogens increase the number of adipocytes by activating the nuclear receptor signaling pathways critical for adipogenesis and increase storage of fat, leading to obesity (Figure 4) [23-26,28-30]. Early-life exposure to obesogens can be responsible for overweight and obesity in children [14,31]. Transgenerational inheritance is also possible with some obesogens (e.g., bisphenol A and tributyltin) [23-26,30]. Since white adipose tissue is an important reservoir of lipophilic obesogens, a rapid weight loss, by increasing the plasma levels of lipophilic obesogens, may cause weight cycling (yo-yo effect).

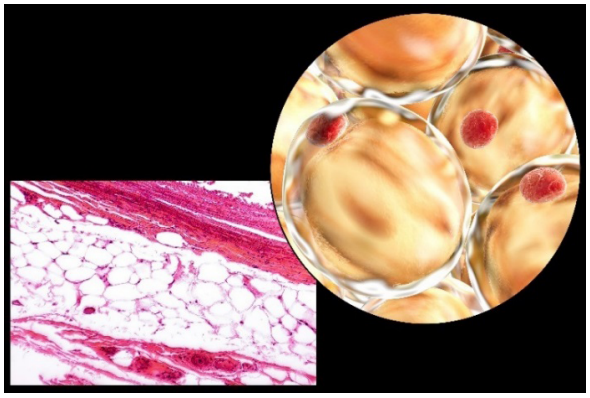

Figure 4: Obesogens increase the number of adipocytes and storage of fat and lead to obesity.

NAFLD

NAFLD is a pandemic with a prevalence of approximately 25% among adult population worldwide. It is commonly associated with overweight and obesity [32,53,54]. The liver is an ideal target for persistent EDCs particularly because it metabolizes EDCs and stores lipophilic persistent EDCs. EDCs can promote NAFLD by interfering directly or indirectly with liver lipogenesis [11,32].

Reproductive System Disorders

EDCs can cause several disorders in the hypothalamic-pituitary-gonadal axis including intersex variation (ambiguous genitalia), cryptorchidism (undescended testicles), hypospadias (abnormal opening of urethra), precocious puberty, polycystic ovary syndrome, endometriosis, uterine fibroids, and infertility [1,4,8-10,15,17,33-35,47,55]. In male subjects, the prenatal exposure to EDCs that have estrogenic and/or antiandrogenic activity (e.g., diethylstilbestrol, bisphenol A, and phthalates) may alter the secretion and/or action of the Leydig cell hormones (e.g., testosterone and insulin-like peptide 3) that regulate testicular descent, causing cryptorchidism in newborn [55]. In female subjects, the *in utero* exposure to diethylstilbestrol (given to millions of women 50-80 years ago to prevent miscarriage) had caused genital malformations, infertility, and vaginal adenocarcinoma while the exposed mothers had an increased risk of breast cancer [8,35]. Exposure to several EDCs during pregnancy is associated with increased risk of low birth weight in neonate [42].

EDCs and Oncology

The occurrence of several cancers can be promoted by exposure to some EDCs (e.g., dioxins, organochlorines, arsenic, cadmium, and diethylstilbestrol). These cancers include skin cancer, thyroid cancer, breast cancer, endometrial cancer, vaginal cancer, testicular cancer, prostate cancer, and lymphoma (non-exhaustive list) (Figure 5) [1,3,4,8-10,15,17,33-35,37-40].

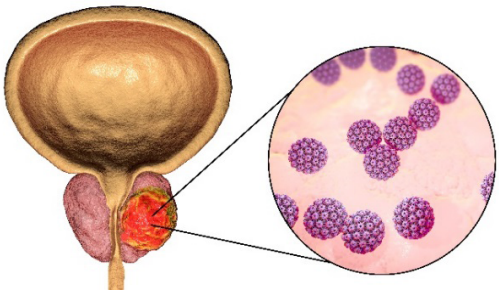

Figure 5: EDCs can promote the development of prostate cancer.

EDCs and Dermatology

EDCs can induce skin diseases through direct contact or indirect systemic absorption. 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 be responsible for a variety of disorders including dermatitis, chloracne, hyperpigmentation, and aging (coarse wrinkles, irregular pigment spots, and elastosis) [37].

EDCs and Other Medical Specialties

Increased incidence of neuro-psychiatric (e.g., neurodevelopment disorders, anxiety), cardiovascular (e.g., hypertension and coronary heart disease), respiratory (e.g., asthma), renal (e.g., albuminuria), ocular (e.g., dry eye disease), and immunological (e.g., autoimmunity) disorders has been reported in association with exposure to EDCs [1,4,8,9,36,43,56-60]. However, more robust epidemiological studies are needed before providing solid conclusions.

Preventive Strategies

EDCs represent a threat for human health and a financial burden for the society [41]. For a better understanding of the health risks related to EDCs it is important to conduct robust and well-designed epidemiological studies [61]. The promotion of public knowledge and the initiation of preventive measures can minimize the deleterious consequences of EDCs for future generations. Several agencies (e.g., US EPA and European Food Safety Agency) are regulating the EDCs. Countries have differences in regulations, including differences between the USA and the EU. Countries that have significant heavy chemicals industry are less open to promote greener chemicals production [8,62,63].

Although exposure to EDCs cannot be entirely avoided in many situations, every effort should be made to minimize it [4,8]. It is particularly important to identify windows of sensitivity to reduce or avoid the exposure to EDCs (e.g., fetal and neonatal periods).

The following recommendations should be considered as a guidance (non-exhaustive list):

- Wash hands before preparing or consuming food.
- Use filtered water by installing a filter on the faucet to minimize phthalates intake.
- 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 (e.g., for storing and for heating in microwave) with glass, ceramic, stainless steel, and bisphenol A-free products to reduce the intake 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.
- 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.
- Do not burn conventional candles and avoid air fresheners.

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

Cost of EDCs

The annual cost of EDCs is around hundreds of billions of dollars. According to a relatively recent report, the cost of EDCs-related medical disorders in the USA was $340 billion (2.33% of the gross domestic product), higher than in the EU where it was $217 billion (1.28% of the gross domestic product) [41]. Regulatory actions allowing the limitation of the most prevalent and hazardous EDCs could have significant economic benefits.

Conclusion

EDCs are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones. Through air, water, and food, humans are regularly exposed to hundreds of EDCs. The *in utero* or lifetime exposure to EDCs can be a significant component of the environmental origin of several medical conditions. The medical disorders caused by EDCs include diabetes, obesity, NAFLD, infertility, and cancers (non-exhaustive list). EDCs represent a threat for human health and a financial

burden for the society. The promotion of public knowledge and the initiation of preventive measures can minimize the deleterious consequences of EDCs.

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