3 The Role of Environmental Disruptor Chemicals in the Development of Non Communicable Disease

Maryam Zarean and Parinaz Poursafa

Abstract

The increasing prevalence of non communicable diseases (NCDs) poses main challenges to global public health. Various environmental exposures to different chemicals and pollutants might interact with genetic and epigenetic mechanisms resulting in the development of NCDs. Among these environmental exposures, endocrine disrupting chemicals (EDCs) consist of a group of compounds with potential adverse health effects and the interference with the endocrine system. They are mostly used in food constituents, packaging industries and pesticides. Growing number of *in vitro*, *in vivo*, and epidemiological studies documented the link of EDC exposure with obesity, diabetes, and metabolic syndrome, which are the underlying factors for development of NCDs. Prevention of exposure to EDCs and reduction of their production should be underscored in strategies for primordial prevention of NCDs.

Keywords

Endocrine disruptors · Non communicable diseases · Environment · Metabolic disorder · Obesity · Diabetes

3.1 Introduction

Exposure to environmental chemicals, especially in early life, is a notable risk for development of different diseases. Many environmental exposures to various agents might interact with genetic and epigenetic mechanisms, which in turn would affect the normal development [1]. Over the last decade, the scientific perception of the relationship between health and environment has made quick progress, and growing experience exists on the increasing trend of diseases related to environmental pollutants [2]. Studies in the US population revealed that in the past 40 years, non communicable diseases (NCDs) had rapid escalating trend; for instance, breast and prostate cancers have increased by 40% and 57%, respectively. In addition, in the past 30 years, obesity has doubled, and diabetes has tripled in the number of US adults. Since human genome has not changed over this short time-period, undoubtedly the role of environment should be highlighted as the main cause of such increase in NCDs. Environmental endocrine disruptors are probably the underlying

M. Zarean (✉) · P. Poursafa
Environmental Health Department, Environment Research Center, Research Institute for Primordial Prevention of Non Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
e-mail: m.zarean@mail.mui.ac.ir

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factor in the rise of many disorders and diseases [3]. Humans are abundantly exposed to chemicals like endocrine-disrupting chemicals (EDCs) in different periods of life with particular concern [1]. EDCs include environmental, industrial, nutritional, agricultural, and pharmaceutical compounds that might alter hormonal activity by either resembling natural hormones or antagonizing their actions and/or homeostasis in organisms and cells [4]. These compounds are the source of progression of some metabolic disorders such as obesity, metabolic syndrome, and diabetes, as well as endometriosis. Synthetic EDCs are commonly categorized into short-lived pollutants considered as persistent organic pollutants (POPs). Short-lived pollutants like phthalates and bisphenol A (BPA) abundantly detected in the environment [1, 5]. It is shown that exposure of girls to low-molecular weight phthalates is positively associated with later changes in indexes of generalized and abdominal obesity. It is indicated that exposure of 6–8-year-old overweight girls to monoethyl phthalate (MEP) (i.e. diethyl phthalate (DEP) metabolite) is associated with their body mass index and waist circumference 1 year later [6]. The targets of classical disrupting chemical are nuclear receptors like estrogen receptors (ER), androgen receptors (AR), thyroid receptors (TR), progesterone receptors (PR), mineralocorticoid receptors (MR), glucocorticoid receptors (GR), and peroxisome proliferator-activated receptors (PPAR). POPs include organochlorine pesticides, industrial byproducts, and flame retardants [7]. NCDs are a global health concern, especially in low and middle-income countries undergoing socio-economic development [8, 9]. In addition to rapid lifestyle changes, environmental exposures are considered as a main underlying cause of such increase. It is reported that ambient and indoor air pollution caused more than six million deaths from chronic respiratory diseases, lung cancer, and cardiovascular diseases in 2012 [10–12]. Over time, humans are often exposed to cumulative extents of these pollutants. Even low levels of exposure to environmental factors in early life might be associated with the development and progress of NCDs can many years later. It is documented that exposure to EDCs in early life can affect the metabolism and might influence mechanisms related to weight control or brain growth, and in turn it can interact with other risk factors resulting in increased risks of obesity, diabetes, cardiovascular disease, and cancer [13]. Increasing body of evidence suggest that EDCs exposure during vital periods of development can be associated with later life reproductive disorders, neurodevelopmental disruptions, thyroid-related diseases, diabetes and obesity, as well as cancers of breast, prostate and endometrium [14]. The rising prevalence of obesity and overweight during the last decades and a number of birth or pregnancy cohort studies suggested the possibility to explore the role of exposure to environmental factors very early in life, at specific critical windows, with growth velocity and obesity in childhood [7]. Obesity is a more serious concern for children and it is a health risk for adults [15, 16]. Moreover, metabolic syndrome (MetS) is a complicated condition consisting of abdominal obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia; its prevalence is rapidly growing along with the increasing trend of obesity. Metabolic disorders have been commonly linked to genetic background and changes in lifestyle, and aging. There is now substantial document that environmental pollutants, including EDCs, may be the cause of rapid increase in the incidence of such disorders including MetS [17].

3.2 Overview of EDCs

According to the US Environment Protection Agency (EPA), EDCs are defined as exogenous agents interfering with the production, release, transport, metabolism, binding, action, or omission of natural hormones responsible for the regulation of developmental processes and the maintenance of homeostasis. Moreover, the Endocrine Society defined EDCs as exogenous

chemical that can interfere with any aspect of hormone action. The World Health Organization/ United Nations Environment Program (WHO/ UNEP) defines these chemicals as "an exogenous substance that changes the function(s) of the endocrine system and consequently makes negative impacts in intact organism, or its progeny or population" [17]. EDCs are defined by three criteria based on the decision of the European Food Safety Authority (EFSA) Scientific Committee to use the World Health Organization/ International Programme on Chemical Safety (WHO/IPCS) definition: i) the presence of a negative impact in population or an intact organism; ii) the presence of an endocrine activity; and iii) a demonstrated causal relationship between the negative impact and the endocrine activity [18]. Some pollutants with particular chemical properties that interfere with endocrine systems have been of increasing interest. The information on environmental impact of EDCs is currently incomplete and these compounds are poorly regulated. Preliminary results from epidemiological and clinical studies, and *in vivo* models, have shown that EDCs play a role in different diseases. Therefore, it has become a global public health matter [19]. Recently, most studies examining associations between EDCs and measures like birth weight, birth length, head circumference, gestational age, have revealed notable inverse associations, i.e. lower birth weight, birth length and head circumference for increased endocrine disruptors levels [20].

3.2.1 EDC Categories

EDCs can be categorized according to their sources or their modes of action from a toxicological perspective:

EDCs can be initially classified as:

(i) natural and
(ii) synthetic.

In the second classifications, EDCs can be grouped as:

(i) EDCs affecting reproductive system
(ii) EDCs affecting pancreas
(iii) EDCs affecting thyroid
(iv) EDCs affecting central nervous system
(v) EDCs affecting other systems [1]

From a total of 564 chemicals suggested by various studies or organizations, 147 were shown to be persistent in the environment. In a first assessment, clear evidence of endocrine disrupting activity was noted for 66 out of them [21]. In summary, the most important EDCs are presented as follows:

3.2.1.1 Phthalates

Phthalic acid esters (i.e., phthalates/PAEs) are alkyl aryl or dialkyl esters of phthalic acid and are used to make plastic. Based on a number of studies, human urine and blood were used as biological fluids to evaluate the exposure to these compounds [1]. PAEs are used as plasticizers in many consumer products such as personal care products, floorings, pharmaceuticals, gelling agents, building materials, lubricants, medical devices, food packaging, dispersants and children's toys [22–24]. The major source of PAEs exposure people is diet. Another main source is medical exposure by blood transfusion equipment and blood storage bags during receiving blood transfusion or hemodialysis bags. PAEs are categorized into two distinct groups of low molecular weight (LMW) and high molecular weight (HMW) based on the length of their carbon chain. LMW phthalates, such as diethyl phthalate (DEP), di *n*-butyl phthalate (DnBP), dimethyl phthalate (DMP), and di-iso-butyl phthalate (DiBP) are usually used in the production of personal care products [1, 25–27]. HMW phthalates, such as bis(2-ethylhexyl) phthalate (DEHP), di-iso-decyl phthalate (DiDP), di-iso-nonyl phthalate (DiNP), and butyl benzyl phthalate (BBzP) are mostly used in the production of

medical devices and flexible plastics. Epidemiological studies with cross-sectional designs also suggest relationships between a variety of PAE metabolites, diabetes and insulin resistance [28]. The animal exposed in utero to DEHP include non-sex-specific increases in body weight, visceral fat mass, and circulating leptin, insulin and/or glucose concentrations [29].

3.2.1.2 Bisphenols

Bisphenols are synthetic lipophilic compounds used in the production of epoxy resins and plastics, which contain several related compounds, namely BPA, BPAP, BPAF, BPB, BPE, BPC, BPS, BPF, and BPZ. BPA is the most studied representative of this class [1, 29, 30]. It is used in consumer products like thermal receipts, food can linings, tableware, medical equipment, toys, water supply pipes and food/beverage storage containers [31]. Data from national studies in the US have presented that over 95% of the population have detectable levels of BPA in urine [32]. Water and food intake in children is an important source of exposure to these compounds. According to National Health and Nutrition Examination Survey (NHANES), in children aged 6–19 years, urinary BPA level was linked with increased risk of obesity and albuminuria [33]. The effects of BPA are of critical importance for fetuses, infants, and young children, because they lack mature systems of body detoxification. When they are exposed to the same weight-normalized dose, plasma levels of BPA in newborns were found to be 11 times greater than in adults [34]. Early-life exposure studies suggest significant association between BPA and excess adiposity and an increased risk of being overweight. Multigenerational obesogenic effect has also been stated in this regard [29].

3.2.1.3 Polychlorinated Biphenyls

POPs widely used as industrial solvents and pesticides. Polychlorinated biphenyls (PCBs) are amongst the 12 compounds documented as POPs in the 2001 Stockholm Convention. PCBs are aromatic, synthetic chemicals made by two connected benzene rings with some or all of the hydrogen substituted by chlorine atoms. These compounds are a large group of over 200 chemicals utilized in a range of industrial products, like transformers, hydraulic fluids, lubricants, cable insulation, or fiberglass. They have high environmental resistance to metabolize in organism and tendency to accumulate in lipids which favor their global presence in the environment. Low vapor pressure of PCBs and low water solubility coupled with air, water and sediment transport processes move them from regional contaminated sites to far regions [29, 35]. Oral is the primary route of exposure for this chemical. Over 10 PCBs have been recognized with different obesogenic potential. Notably, a positive relationship between dietary intake of PCBs and prevalence of obesity has been found [36, 37]. PCBs are recognized for their neurotoxic properties, particularly on the developing brain [38]. Some studies have provided convincing evidence for the obesogenic nature of some PCBs; however, the cumulative obesogenic burden of PCBs is still questionable [29].

3.2.1.4 Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons or polyaromatic hydrocarbons (PAHs) are organic compounds that are composed of multiple aromatic rings. PAHs distribute in the environment through sewage, road run-off, smelter industries and fossil fuel sources [35]. They can result from consumption of polluted water and food, contaminated air from occupational settings, inhalation of cigarette smoke, and automobile exhausts. The presence of these compounds in fish and shellfish are a result of contamination of fresh and coastal waters [39]. The coal and biomass burning for heating and cooking result in high indoor levels of PAHs in most developing countries [40]. The increased concern about carcinogen effects of PAH has triggered widespread attention at global level. A study showed that low molecular weight PAHs were present at highest levels and the more abundant compounds were naphthalene, acenapthalene, phenanthrene, and fluorine [35, 41]. As a component in all environmental PAH mixtures, pyrene is not mainly toxic, and only one phase I metabolite (1-hydroxypyrene)

is formed by biotransformation process in eukaryotic organisms. It is a widely used model compound in investigations of PAH metabolism. Moreover, 1-hydroxypyrene is a useful biomarker of human PAH exposure [40].

3.2.1.5 Pesticides

According to WHO, developed countries are consuming 80% of all pesticides. However, due to lack of specific legislation, agricultural workers from developing nations are exposed to higher concentration of pesticides. These compounds persistent organic pollutants are non-bio-degradable, lipid soluble, and EDCs [38]. Pesticides are responsible for several chronic diseases like cancers, diabetes, neurodegenerative disorders, Alzheimer, Parkinson, reproductive disorders, amyotrophic lateral sclerosis (ALS), and birth defects [42]. The finding of Duyzer (2003) indicated the level of 17 pesticides in precipitation exceeded the maximum permissible level for surface water and 22 exceeded the standard for drinking water of 100 ng/L [43]. Dichlorodiphenyltrichloroethane, commonly known as DDT has been used worldwide for pest and vector control. After finding its toxic effects for human, its use was banned in developed countries [38]. Illustrations of pesticides with endocrine disrupting characteristic include the organophosphorus (OPs) and the organochlorines (OCs) pesticides [44]. OPs can result in lower intelligence quotient (IQ) and attention deficit in children. Other pesticides have impact on Parkinson's disease [3]. They are metabolized by xenobiotic metabolizing enzymes and are not persistent in the environment. OCs pesticides are not, however, metabolized by human body. Therefore, such compounds appear to be much more persistent compared to OPs pesticides [44].

3.2.2 Sources and Pathways of Exposure to EDCs

Individuals are exposed to low levels of environmental abundant endocrine disruptors throughout their lives [4]. There are various sources of environmental pollutants [45]. The route and duration of exposure may have considerable influence on how the chemicals are metabolized and whether or not the chemical remains biologically active [46]. Around 1000 compounds have been recognized that meet the criteria of an EDC. These chemicals are utilized in a varied range of consumer products like building materials, food packaging, clothing and upholstery, pesticides, personal care products, cleaning agents, plastics and medical devices, and thermal paper [17]. EDCs are multimedia pollutants that are present in all parts of the environment: inland and seawaters, atmosphere, soils, sediments, and vegetation [35]. Contact with several consumer matters is a major source of exposure to organic pollutants. Such matters include the plastic linings inside food and beverage containers, thermal receipts, soft toys, household materials, dental sealants, flame-retardants in clothing in upholstery as well as water and air pollution from vehicular, industrial and agricultural waste products, with some compounds persisting in the environment well beyond the initial pollution. People living near motorways are at risk of higher exposure to endocrine disruptors (such as benzene and PAHs), which are often components of hazardous air compounds in diesel exhaust. Other probable routes of exposure are through personal care products such as cosmetics, sunscreens, soaps, and many of which contain PAEs [4, 30]. There are other sources of chemicals. For example, pesticides and herbicides, such as DDT and methoxychlor, get into the environment and have adverse consequences. In addition, BPA, are present beverage and food storage containers [45]. The US CDC's National Health and Nutrition Examination Survey (NHANES) evaluates exposures to environmental compounds in the population which has documented widespread exposures to a number of endocrine disruptors. However, a large number of EDCs are not studied and the typical levels of exposure remain to be determined [17].

3.3 EDCs Contributions to Major NCDs

3.3.1 EDCs and Metabolic Diseases

3.3.1.1 Obesity

The worldwide prevalence of obesity has nearly doubled during the past three decades. This increase in the prevalence of childhood obesity and its consequences are no more limited to developed countries, and it has also increased in both developing nations. About one third of US children are obese or overweight, and over 60% of them will become obese adults. Moreover, there is obesity epidemic among infants 6 months of age and younger [17, 47, 48]. In other words, obesity now affects one in every six children and adolescents. Evidence regarding the effect of environmental factors on obesity prevalence is increasingly supported by (i) epidemiological observations and (ii) experimental evidence supportive of global environmental EDCs [29]. The risk of becoming obese may begin during pregnancy, early childhood, or in the first few months of life. Exposure to chemicals proven to cause obesity in animals results in reduced insulin resistance and altered glucose tolerance as well [2]. Obesity has genetic background; however, the recent epidemic cannot be due to mere genetic changes in the population, and thus must result from changes in environmental factors [3]. A subcategory of EDCs called 'obesogens' can distort sensitive metabolic processes if exposure happens during early development, which would result in obesity, type 2 diabetes mellitus, and MetS. These compounds are believed to lead people to weight gain due to changes in metabolic 'set-points', particularly if exposure takes place during sensitive periods of early life. Animal studies showed that important EDCs such as BPA, PAEs, some pesticides (DDT), and PCBs, can lead to weight gain later in life. PAHs, a family of environmental chemicals found in oil, coal and tar deposits, have been shown to prevent lipolysis, and might cause increased fat accumulation in adult mice. Exposure to air pollutants can also lead to excess weight gain later in life [49]. Environmental obesogenic compounds consist of PAEs, non-steroidal estrogens, parabens, organotins, PCBs, and bisphenols which are proven to have an impact on one or more of the following traits: (i) an increase in adipose tissue mass by hyperplasia or hypertrophy, (ii) an induction of dyslipidemia, (iii) a distortion of adipocyte function leading to increased lipid production, (iv) a disruption in metabolic hormone profiles, (v) an increase in preadipocyte differentiation, or (vi) an increase in the fate of mesenchymal stem cells (MSCs) to undergo adipogenic differentiation [29]. Exposure to PCBs remains universal as a result of improper disposal and bioaccumulation in the environment. In some researches, these chemicals have been indicated to accumulate at high levels in adipose tissue and might be a contributing factor in obesity high frequency [49]. BPA, a synthetic estrogen, is broadly used in a wide range of products such as toys, drinking bottles, baby bottles, food containers, medical device, and water pipes. Animal studies have shown that prenatal exposure to BPA is associated with the prevalence of obesity, lipid metabolism, and impaired glucose tolerance [50].

3.3.1.2 Diabetes

Prediabetes, typically defined as blood glucose concentrations higher than normal, is an earlier phase in the hyperglycemic continuum that has been shown to be linked with higher risk of developing diabetes. Prevalence of prediabetes is growing and it is predicted that more than 470 million people will have become prediabetic by 2030. Every year, approximately 5–10% of people with prediabetes become diabetic, while the conversion rate varies with population characteristics and prediabetes meanings [32, 51]. The main environmental factor driving the increased prevalence of type 2 diabetes (T2D) is obesity; 70% of the risk related with T2D is connected to weight gain [17]. For example, according to the data from the NHANES (2001–2008), separately suggested that urinary PAEs metabolites, such as mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), and three DEHP metabolites, including mono(2-ethylhexyl) phthalate (MEHP),

mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl- 5-oxohexyl) phthalate (MEOHP), are positively associated with diabetes [23]. Moreover, there is accumulating in vitro data supporting a role of BPA in the development of diabetes [52]. A review article presented the role of several environmental exposures on the development of type 2 diabetes; in addition, it proposed the association of exposure to multiple classes of pesticides with risk factors for diabetes and obesity [3].

3.3.1.3 Metabolic Syndrome

The endocrine system involved in the control of metabolism is highly likely to cause EDCs to influence metabolic function. The possible effect of EDCs on the programming of glucose homeostasis during development and, thus, its role in obesity, diabetes, cardiovascular disease, and hypertension has received a lot of attention [2]. MetS is a complex disorder described by abdominal obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia; it is a risk factor for cardiovascular disease, T2D, cancers, stroke, and chronic kidney disease. In the medical community, epidemics of metabolic diseases are mostly linked to changes in diet and genetic background, exercise and aging. There is now significant evidence regarding the role of other environmental factors in the rapid growth of MetS [17, 53]. As a matter of fact, various environmental factors are linked to the increase in metabolic diseases like stress, lack of sleep, adenoviruses, childhood antibiotics and exposure to environmental chemicals. Although all of these environmental stressors may play some role in the epidemic of metabolic diseases, we focus here only on the possible role of EDCs. Household air pollution and ambient air pollution from cooking with polluting fuels are estimated to cause 17% and 13% of cardiovascular diseases, respectively [10]. Cardiovascular diseases are still the main cause of mortality with over 80% of them in low-and middle-income countries. It is estimated that by 2030, over 23.6 million people will die from cardiovascular diseases [54].

3.3.2 Effects on the Reproductive Health

EDC harm normal physiological reactions associated to the reproductive system. They decrease the number and quality of sperms as well as increase the risk of prostate, testicular, and breast cancer. Testicular dysgenesis syndrome (TDS), testicular carcinoma, and poor semen quality are main diseases known to be related with some environmental contaminants affecting the endocrine system [42]. Current studies on PAEs are especially focusing on their reproductive toxicity potential. PAEs were recommended to target mostly male reproductive system. Numerous studies have reported that fetal exposures to DEHP instigate TDS-like effects and reduce anogenital distance (AGD) in rodents. According to many reserachers, DEHP malfunctions Leydig and Sertoli cells. Exposure to PAEs, particularly to DEHP, resulted in reduced production of testicular testosterone in rodents, and most reprotoxic effects are thought to be related to their anti-androgenic potential [1]. AGD is an important clinical measure to health effects of EDCs in environmental toxicology and has been identified as one of the endpoints in the US EPA guidelines for reproductive toxicity studies [55]. A recent meta-analysis has also documented the association of exposure to some EDCs with shoortened AGD [56].

3.3.3 EDCs and Cancer

More than 70% of all cancer deaths happen in low and middle-income nations. Mortality from cancer is projected to continue increasing, with an estimated 11.5 million deaths in 2030 [57]. The results of an analysis in animal studies on about 48 EDCs listed under center for disease control and prevention (CDC) have shown close association to mutagenicity, carcinogenicity, and developmental effects. Moreover, a study on infants and children living in agricultural regions using household pesticides showed an increased rate of lymphoma and leukemia. Recently, xenoesterogens have been assumed as the most prob-

able source for developing breast cancer. Increased estrogen level during pregnancy might lead to breast cancer. Some pesticides including DDT, toxaphene, etc. are proposed to give rise to breast tumors [42].

3.3.4 EDCs and Respiratory Diseases

Chronic respiratory diseases (CRDs) are diseases of the airways and the other structures of the lungs including respiratory allergies, asthma, sleep apnea syndrome, occupational lung diseases, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension. The prevalence of these diseases is increasing, mostly among children and elderly people [58]. Exposures during fetal development are crucial and the consequences of these exposures are determined by the stage of development of the respiratory and immune systems when the exposures occur [59]. Researchers reported higher prenatal dialkyl phosphate levels with the occurrence of respiratory symptoms in early childhood during the period (0.5–5 years of age) [44]. Environmental factors related to asthma in childhood include respiratory viral infections, environmental tobacco smoke, aeroallergens, and inflammatory stimuli linked with ambient air pollution and indoor air pollution. Exposure to formaldehyde in early life would also greatly increase the risk of asthma [59].

3.4 Endocrine Disrupting Mechanism of Action

The various contaminants released into the environment create an enormous analytical challenge in quantifying people exposure while the physical properties of some chemicals contribute to their bioaccumulation and persistence in human tissues long after the exposure has ended [60]. The gene networks and target cell activities are managed by hormones and by binding to the responsive elements in the promoter of target genes [35]. EDCs affect human body through various pathways including: i) effect on hormone, nuclear, and nonnuclear receptors, ii) effect on enzymatic pathways, iii) effects on signaling pathways. EDCs were originally thought to exert actions mainly through nuclear hormone receptors. However, recent studies show that the mechanisms of their toxicity are much wider than previously thought. The properties of EDCs make them specifically well suited for activating or antagonizing nuclear hormone receptors. In fact, the nuclear hormone receptors are a super family of transcription factors that play major roles in both physiology and disease. The estrogen receptors (ERα and ERβ) are at the center of endocrine disruption studies. Findings of these studies may provide a model for how other nuclear receptors interact with hormone mimics. Identifying chemicals with estrogenic effect is now a main area of research. Some EDCs act as estrogen mimics. Although other EDCs have estrogenic effect, they are not true estrogens. For instance, BPA was designed as a synthetic estrogen and has been shown to bind to the estrogen receptors, resulting in a cellular signal transduction cascade indicative of an estrogen response. Hence, EDCs do display hormone ranging effects on cellular systems. These chemicals can affect the enzymatic pathways and can disrupt the action of enzymes involved in steroidogenesis, especially in the metabolism of estrogens. Additionally, they can affect cellular signaling pathways. PAEs and BPA are shown to actuate epithelial-to-mesenchymal transition (EMT). These compounds can also up-regulate or down-regulate the genes involved in the regulation of signal transduction [1]. Concern has increased since several EDCs are suspected of disrupting the programming of endocrine signaling pathways during the fetal development period [20]. In order to control exposure to disrupting chemicals, primary prevention and environmental interventions are required with major focus on early development to reduce the incidence of NCDs [59].

3.5 Conclusions

EDCs are commonly present in the environment. Serious measures must be taken to diminish the production of these chemicals as well as exposure to them; regulatory authorities of health and industry must be aware of their toxic effects. Studies in the field of EDCs have increased over the last decades, and increasing knowledge is provided in the areas of environmental toxicology and the risk of NCD development and progress. The growing scientific literature on the long-term effects of exposures adds new dimensions to the importance of preventing the harmful effects of environmental chemicals. Moreover, the novel insights require prospective long-term studies to define early-life exposures to environmental chemicals and provide new emphasis on trans-generational effects of EDCs. Environmental protection activities should be considered in policies and strategies related to primordial prevention of NCDs.

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