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ENDOCRINE DISRUPTORS IN THE ENVIRONMENT AND THEIR IMPACT ON HUMAN HEALTH

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Abstract

International health organizations recognize the increasing importance of environmental exogenous agents in relation with endocrine system. The endocrine disruptors alter the proper functioning of the endocrine pathway with important consequences on human health. In recent years, more studies came to asses the exposure to multiple endocrine disrupting chemicals on animals and humans. This article summarizes data concerning the effects of different types of endocrine disruptors such as: phytoestrogens, bisphenol, diethylstilbestrol, phthalates, dioxin and pesticides on endocrine system and the sequelae on endocrine functions. Many endocrine disrupting compounds adversely impact the following functions: metabolic rate, sex development, insulin production and utilization, growth, stress response, gender behavior, reproduction. The action to disrupt the endocrine pathway is possible via nuclear receptors, through membrane receptors, neurotransmitter receptors, orphan receptors and enzymatic pathways involved in the hormonal synthesis. Elucidation of the role of endocrine disruptors in human health will provide insights into the assessment of environmental exposure and risk. Further epidemiological and toxicological studies are needed to evaluate the exposure to multiple endocrine disrupting compounds.

Key words: bisphenol, endocrine disruptors, hormone receptor, pesticides, phytoestrogens

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1. Introduction

A great number of natural or synthetic substances have been identified to disrupt the functioning of the endocrine system and to produce effects in hormone targets tissues and organs in both human and animals. These substances (chemicals) are referred to as endocrine disrupting chemicals (EDCs) (Henley and Korach, 2010; Mnif et al., 2011).

According to the WHO, a EDCs is an exogenous substance or mixture that alters function(s) of endocrine system and consequently causes adverse health effects in an intact organism, or its progeny or (sub) population (Danulescu et al., 2011; Bruni et al., 2002; Parent et al., 2011; Robu et al., 2007). The Environmental Protection Agency (EPA), define EDCs as an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are responsible for homeostasis, reproduction, and developmental processes (Craig et al., 2011).

A subtype of EDCS are the neuroendocrine disruptors defined as *pollutants in the environment that are capable of acting as agonists/antagonists or modulators of the synthesis and/or metabolism of neuropeptides, neurotransmitters, or neurohormones which subsequently alter diverse physiological, behavioral, or hormonal processes to affect an animal's capacity to reproduce, develop and grow, or deal with stress and other challenges* (Van Voorhis et al., 1992).

The present review focuses on: endocrine disruptors mechanisms of action, examples of

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compounds that alter the endocrine system and the effect on human health.

2. Endocrine disruptors- general data

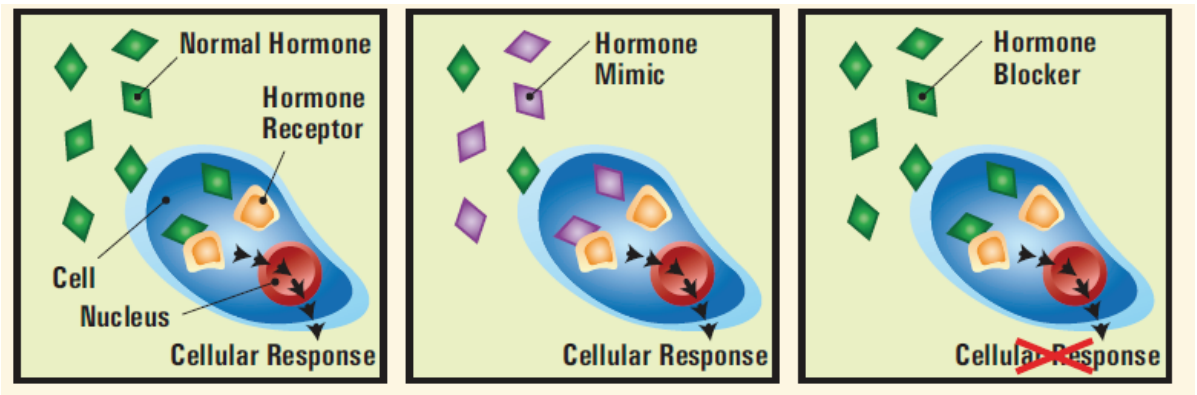
Endocrine Disruptors (EDCs) are compounds, of natural or synthetic provenience, which through environmental or inappropriate developmental exposures alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment (Diamanti-Kandarakis et al., 2009) (Fig. 1). EDCs can influence the normal function of the endocrine system by affecting glands and hormones that regulate vital body functions: metabolic rate, sex development, insulin production and utilization, growth, stress response, gender behavior, reproduction. EDCs may also disrupt the gene-controlled, normal signaling systems that determine the fetal development (Bernal and Jirle, 2010; Newbold, 2010) and act via nuclear receptors, through membrane receptors, neurotransmitter receptors, orphan receptors and enzymatic pathways involved in the synthesis of hormones (Craig et al., 2011).

The studies on endocrine disruption are not of recent data, since the phenomenon accompanied the industrial development, in particular industrial chemical synthesis (Solomon and Schettler, 2000). In the 1930s studies on laboratory animals demonstrated estrogenic effects of some industrial chemicals including bisphenol A, now widely used in plastics, resins and dental sealants (Solomon and Schettler, 2000; McCally, 2002). The feminizing effect of the pesticide DDT (dichlorodiphenyltrichloroethane) in roosters was reported in the 1950s (Saalu and Osinubi, 2009). EDCs are environmental pollutants (pesticides, industrial by-products and chemical used in manufacturing-particularly plastics) (Caliman and Gavrilescu, 2009; Robins et al., 2011) which are taken up through food, drinks or through the air and they are also absorbed transdermally (Wuttke et al., 2010). The mechanism of action of EDCs is actively studied, but the consequences of endocrine disruption at the population level and the adaptations to cope with chronic EDCs exposure have been overlooked (Carere et al., 2006).

A recent report of Euopean Environment Agency reveals that, in the last 10 years, "many new computational predictors and both *in vitro* and *in vivo* assays for EDCs have been developed that greatly enhance the ability to study mechanisms of action and to screen large numbers of new and existing chemicals for hormone activity, so as to ensure their safety" (EEA, 2012).

Humans and animals are exposed to a complex range of chemical substances from the environment (Fig. 2). Chemicals in air, water soil and food, professional conditions and lifestyle factors, all contribute to a complex exposure situation in our daily life (Olujimi et al., 2010; Silins and Hogberg, 2011). The ability of exogenous substances to interfere with the endocrine system was known from the past: for centuries, farmers have observed reproductive problems in female sheep and cows grazing on pastures rich in certain clover species (containing estrogenic compounds such as coumestrol) (Marty et al., 2011). A decade ago, the focal point of both concern and action regarding EDCs was on hormone receptor agonists and antagonists, in particular oestrogen receptor (ER) agonists. The screening and assessment systems for ER- or androgen receptor (AR)-mediated hormone activity continue to be broadly used (EEA, 2012; Heinlein and Chang, 2002; Napoli et al., 2012).

The development and improvement of risk assessment procedures for EDCs exposure is an issue of many authorities world-wide (Hlihor et al., 2009; WHO, USA and the European Union). Several recent studies indicate that endocrine chemicals may interact in complex ways even in a way similar to that of many carcinogens (Caliman and Gavrilescu, 2009; EEA, 2012). The existence of specific receptors in target cells allows the hormone-mimicking effect of endocrine disruptors. The 16th-century Paracelsus observation's that "the dose makes the poison" is no longer valid. Very low dose can enhance the production of receptors (receptor up-regulation) resulting in a stronger response, while higher doses can inhibit receptors (receptor down-regulation) resulting in a weaker response (Peterson Myers et al., 2009).



a b c

Fig. 1. Schematic representation of EDCs action when absorbed in the body: a) can decrease or increase normal hormone levels, b) mimic the body's natural hormones, c) alter the natural production of hormones (NIEHS, 2010; Swedenborg et al., 2009)

The timing of exposure to EDCs is important in determining its specific effect. Even low exposure during foetal or early life periods on EDCs has caused concern due to serious consequences later in life (Silins and Hogberg, 2011). Early in life exposure to endogenous sex hormones particularly in fetal life and infancy, organize the brain in a sexually dimorphic manner that becomes activated later in life. Exposure to exogenous substances such as EDCs is likely to have more profound detrimental consequences in developing organisms than in adults (Gore, 2010). How the early life exposure can promote an adult onset disease is a serious question and is presumed to involved epigenetic mechanisms (Skinner et al., 2010). Synthetic EDCs such as: industrial lubricants, pesticides and plasticizers are frequently associated with alarming statistics regarding reproductive diseases, obesity and cancer (Patisaul and Jefferson, 2010).

3. Phytoestrogens

The increased effort to implement healthier eating lifestyles resulted in increased consumption of soy products which in turn has caused an important exposure to phytoestrogens (Newbold, 2010).

Phytoestrogens are plant compounds that are similar (as structure and/or function) to mammalian estrogens and their active metabolites, they have poly-phenolic structures and can be classified in three major classes (Shanle and Xu, 2011).

One major classes is the flavonoids with subgroups as: **flavanones** (eriodictyol, hesperetin, homoeriodictyol, naringenin) found in citrus fruits and juices, **flavones** (apigenin, luteolin, tangeritin) found in parsley, celery, capsicum pepper, **flavonols** (fisetin, kaempferol, myricetin, pachypodol, quercetin, rhamnazin) found in kale, broccoli, onions, tomatoes, lettuce, apples, grapes, red wine and **catechins** (proanthocyanides) found in chocolate, green tea, beans, apricots, cherries, berries. Another major class is the isoflavonoids with subgroups as: **isoflavones** (biochanin A, clycitein, daidzein, formononetin, genistein) found in soy beans, **isoflavans** (equol- metabolite of daidzein), **coumestans** (coumestrol) found in clover, alfalfa, spinach. The lignans are also a major class of phytoestrogens and they are components of plant cell walls and found in many fiber-rich foods such as: grains, seeds, nuts and fruits (Senti, 1974; Thomas and Lutz, 2001; Patisaul and Jefferson, 2010).

Exposure to phytoestrogens occurs through dietary intake of food and beverages containing herbs, fruits and vegetables (mainly soy) (Shanle and Xu, 2011).

Soy is a popular food additive because is a vegetable protein high in fiber and unsaturated fats and free of lactose and cholesterol. Energy bars, sports drinks, cereals, granola bars and imitation dairy products are enriched with soy protein (Patisaul and Jefferson, 2010). About 25% of infant formulas are soy-based and urinary concentration of phytoestrogens- daidzein and genistein was 500 times higher in infants fed with soy-based formula compare with those fed with cow milk (Shanle and Xu, 2011).

Also textured soy protein is a meat substitute found in: hamburgers, sausages and hotdogs (Patisaul and Jefferson, 2010). Isoflavones are also used as an alternative for hormone replacement therapy in menopaused women in order to prevent osteoporosis or arteriosclerosis (Wuttke et al., 2010).

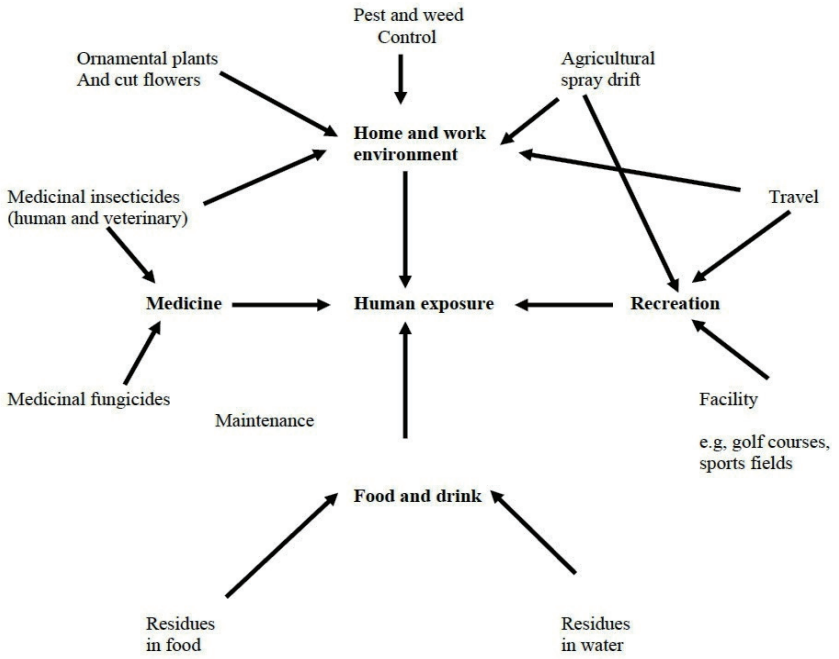


Fig. 2. Exposure routes of humans to EDCs (McKinlay et al., 2008; Olujimi et al., 2010)

The impact of soy or soy phytoestrogens consumption on human health, according with clinical and experimental studies is still unclear. The answer is complex and may depend on: health status, age, level of consumption (Patisaul and Jefferson, 2010). The phytoestrogens acts via estrogen receptors (ER). There are two subtypes: ERα and ERβ and after phytoestrogen binding an ER-dependent, gene transcription is activated. Once bound isoflavones do not act as estrogen agonists but more like selective estrogen receptor modulators (SERM) (Patisaul and Jefferson, 2010).

Most phytoestrogens bind ERβ and this fact is significant in relation with the differentially distribution of ER throughout the body and the brain. Another pattern for the phytoestrogens action is the binding on membrane receptors with activation of the second messenger pathways (the first accepted transmembrane ER, GPR30, is capable of binding a wide range of EDCs including genistein) (Patisaul and Jefferson, 2010).

By stimulating sex hormone binding globulin (SHBG) synthesis in liver cells and competitively displacing either 17β-estradiol or testosterone from plasma SHBG, phytoestrogens can manipulate steroid synthesis and transport (Patisaul and Jefferson, 2010). Some phytoestrogens (e.g. coumestrol, genistein) interferes with enzymes needed for steroid biosynthesis.

Administration of coumestrol and equol to newborn mice enhances DNA methylation involving alterations in epigenetic processes (Skinner et al., 2010). Genistein and other phytoestrogens have been shown to cross the placenta and - in utero- exposure may interfere with the ovarian function later in life (Zama and Uzumcu, 2010). Genistein can affect adipose tissue fat deposition according to recent studies, the effects being dose-dependent and gender specific (Newbold, 2010).

It is unclear how phytoestrogens administration may impact with breast cancer risk, precocious or delayed puberty (Ozen and Darcan, 2011), brain and reproductive tract disregulation (androgen insufficiency with undermasculinisation of the male uro-genital tract) (Svechnikov et al., 2010), behavior disturbances, uterine fibroids development.

Consumers should be aware that soy contains endocrine disrupting compounds and make dietary choices accordingly (Patisaul and Jefferson, 2010). Pregnant women or those who want to become pregnant should use soy foods with caution (Patisaul and Jefferson, 2010). Also the effects of dietary isoflavones in newborns and climacteric/ postmenopausal women are of great concern and need to be further investigated (Wuttke et al., 2010).

Bisphenol A (BPA)

BPA was first described in 1891, initially developed as a pharmacological for estrogen replacement therapy (Robins et al., 2011). In the 1950's BPA was rediscovered and polymerized to make polycarbonate plastic and then until now it has been used in the plastic industry (Alonso-Magdalena et al., 2010).

BPA is the primary building block of polycarbonate plastic and component of epoxy resins being used in the manufacture of: food cans, polycarbonate baby bottles, beverage containers, dental sealants and composites (Newbold, 2010; Zoeller, 2010). BPA is also halogenated (brominated or chlorinated) to produce flame retardants (Newbold, 2010; Zoeller, 2010). BPA is one of the highest volume chemicals produced worldwide, human population being routinely exposed to this chemical through numerous sources and routes (Newbold, 2010). Daily exposure is possible by: carbonless print paper, lining inside cans, baby formula cans and plastic food containers (when heated) (Badawi et al., 2000), milk cartoons and other paper-board containers commonly used to package food and beverages (McAllister and al., 2010). BPA exposure has become an important health concern based on it's capability to enter the materials contained within them (Craig et al., 2011). Studies report that BPA is found in serum of pregnant women, in the amniotic fluid of their fetus, in placenta and in cord serum taken at birth (Zoeller, 2010).

Regarding the structure, BPA is similar to diethylstilbestrol, having two fenolic rings and bind to the nuclear estrogen receptor α and β. Taking into account the low affinity of BPA for estrogen receptor, it is likely that the estrogenic effects of BPA are due to non-genomic estrogen receptor signaling. BPA's molecular structure is similar to that of estradiol, one of the human body's three main estrogens, suggesting that BPA binds to estrogen receptors (Fig. 3) (Parker, 2012). In binding to the estrogen receptor, BPA can disrupt the body's hormonal system, with the most troubling consequences for fetuses, infants and young children (Parker, 2012; Shanle and Xu, 2011). MBP has a 100-fold to 1,000-fold stronger bond to the estrogen receptor than BPA; however, the structural basis for MBP's high affinity for the estrogen receptor was not investigated further (http://www.foodproductdesign.com/news/2012/10/study-says-metabolized-bpa-poses-bigger-threat.aspx).

Also BPA may interact with a variety of other cellular targets including: non-classical membrane-bound form of the estrogen receptor, nuclear receptor termed estrogen-related receptor gamma (Newbold, 2010). General hormone imbalance, as a result of BPA exposure, has been well documented in animal system (humans included) with disregulation of all sex hormones (Speranza, 2010). BPA can contribute in developing psychological dependence on drugs through the brain adverse effects (Speranza, 2010).

Several experimental animal studies have shown that BPA decreases placental aromatase activity (Robins et al., 2011) and is associated with

abortion (Zoeller, 2010) and a variety of abnormalities in the male and female reproductive and mammary gland tissues (Newbold, 2010).

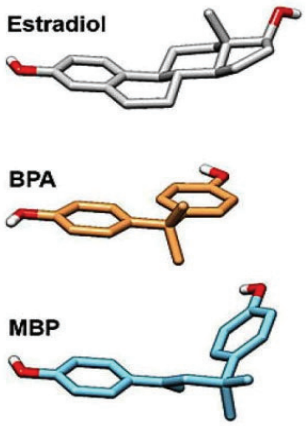


Fig. 3. Conformational structure of Estradiol, BPA and MBP with the relevant similarities (Parker, 2012)

The disruption of pancreatic β cell function and blood homeostasis (in mice) and the acceleration of adipocyte formation may connect BPA to the development of obesity (Newbold, 2010) and so considering as an "obesogen" (Hatch et al., 2010). In adult humans, epidemiological studies reflect BPA as an important risk factor for type 2 diabetes (Alonso-Magdalena et al., 2010). Also, BPA can interfere with thyroid receptor signaling both in vitro and in vivo (Zoeller, 2010). Perinatal exposure to low BPA doses caused: disrupted ovarian morphology, accelerated puberty and changes in body weight (Zama and Uzumcu, 2010). Disruption of the endocrine environment can alter metabolism and susceptibility to cardiovascular diseases may increase in humans (Speranza, 2010).

Much remains to be determined about the mechanism of action of BPA, haw BPA is metabolized, and whether animal models are relevant for modeling human exposure (Taylor et al., 2011).

Diethylstilbestrol (DES)

DES is a non-steroidal synthetic estrogen and during 1940-1971 was prescribed to pregnant women in an attempt to prevent miscarriages and premature births (Henley and Korach, 2010; Newbold, 2010; Craig et al., 2011). It was estimated that a range of 2 to 8 million pregnancies were exposed to DES (Newbold, 2010). Beginning with 1953 several studies showed that DES had no protective effects against miscarriages and premature births and the drug was banned on the use during pregnancy only in 1971 (Craig and al., 2011). The production or marketing of this this chemical is prohibited since 1997 (Ozen and Darcan, 2011). More than that, numerous studies showed multi-generational effects of DES on reproductive, cardiovascular, and immune system.

Today it is well known that perinatal DES exposure lead to a significant increase in neoplastic and benign lesions (Newbold, 2010) in both female and male offspring: anatomical malformations of the cervix, vagina and uterus, decreased fertility, vaginal clear cell adenocarcinoma, testicular hypoplasia, cryptorchidism and epididymal cysts (Henley and Korach, 2010).

DES has been a model for EDC action and has been studied due to its adverse impact on humans in utero (Shanle and Xu, 2011).

DES mimics the natural estrogen pattern, binding both α and β estrogen receptors; due to its high affinity for the receptors it is a potent transcriptional activator through genomic signaling (Shanle and Xu, 2011). More recent studies suggest another mechanism: non-genomic estrogen signaling (Nadal et al., 2000; Bredfeldt et al., 2010; Shanle and Xu, 2011). DES can be considered as an "obesogen" in relation with the development of obesity in perinatal DES treated individuals (Newbold, 2010). Also the effects on the sexual dimorphism of the brain in relation with DES use have been documented (Zama and Uzumcu, 2010). The DES paradigm was a clear example that prenatal exposure could lead to adult-onset disease (Newbold, 2010).

Phthalates

Phthalates are synthetic chemicals used to increase the flexibility of polyvinyl chloride plastics in beauty and infant products, medical devices and the enteric coating of some medication (Lovekamp-Swan and Davis, 2003; Craig et al., 2011; Robins et al., 2011), ink solvents, food packaging (Svechnikov et al., 2010). They are easily released in to the environment do to the fact that they are weakly bound to the plastic (Robins et al., 2011). The human exposure to these ubiquitous xenobiotics occurs by ingesting contaminated food and by applying make-up (Robins et al., 2011).

There are strong evidences that phthalates and their metabolites (diethylhexyl phthalate-DEHP and monoethylhexyl phthalate-MEHP) are potent reproductive teratogens in male and female animal models. Also in human granulosa-lutein cells, MEHP suppressed basal and stimulated estrogen secretion and decreased aromatase activity (Craig et al., 2011). Others than MEHP and DEHP, e.g. dioctylphthalate (DOP), diisononylphthalate (DiNP) and diisodecylphthalate (DiDP) posses endocrine-disrupting capacities, by interfering with the progesterone production of the ovary (Gregoraszczuk, 2002; Craig et al., 2011).

In male mice the phthalates exposure decreases the anogenital distance. In male, the development of testis is affected leading to abnormalities in spermatogenesis and hormonogenesis (Fig. 4) (Hu et al., 2009; Svechnikov et al., 2010; Robins et al., 2011).

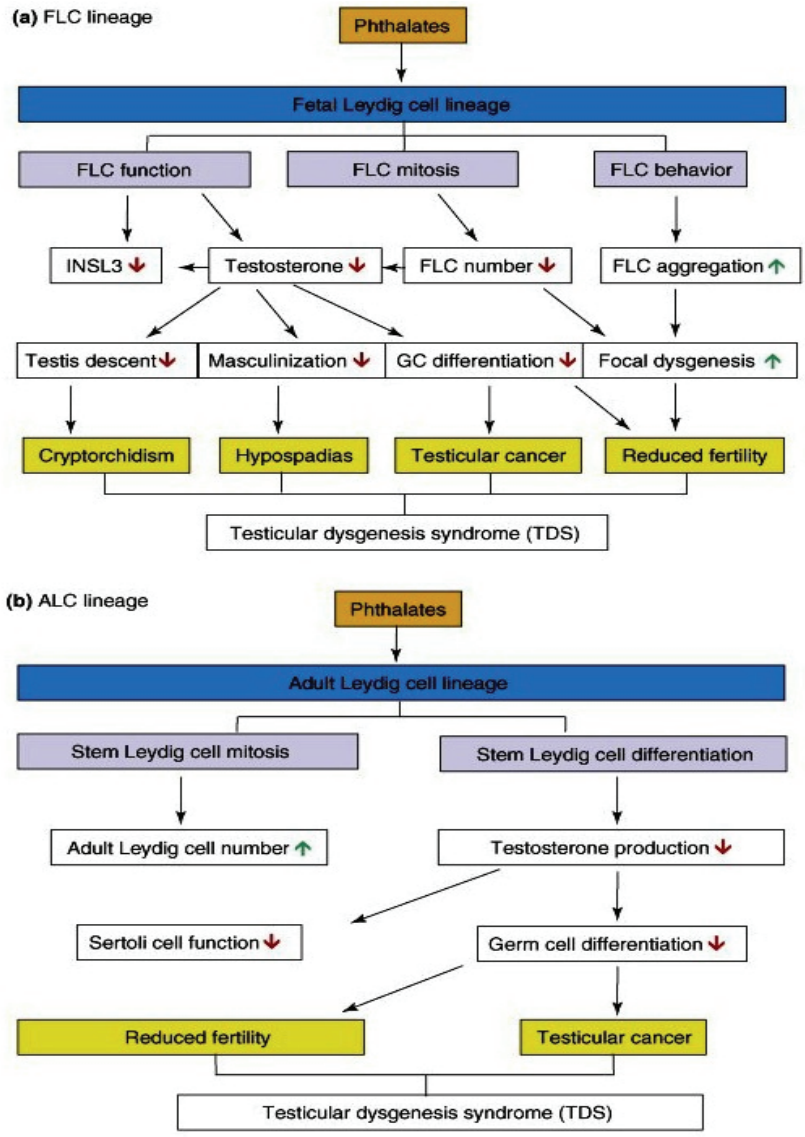


Fig. 4. Effects of phthalates on (a) fetal Leydig cell (FLC) lineage: (b) adult Leydig cell (ALC) lineage after in utero exposures, causing testicular dysgenesis syndrome (FLC, fetal Leydig cell; INSL3, insulin-like growth factor 3; GC, germ cell; ↓ = decrease or inhibition; ↑ = increase or stimulation) (taken from Hu et al., 2009)

Environmental effects have been assumed to contribute to the growing occurrence of testicular dysgenesis syndrome (TDS) in humans (i.e. cryptorchidism and hypospadias in newborn boys and testicular cancer and reduced sperm quality in adult males) (Hu et al., 2009). Also, prenatal exposure to phthalates affects Leydig cell function in the postnatal testis. Recent progress was performed in understanding of how Leydig cell factors contribute to phthalate-mediated TDS (Hu et al., 2009; Johnson et al., 2012).

In females phthalates have been associated with: uterine abnormalities, anovulation, and foetal development in pregnant women (Silins and Hogberg, 2011), implantation or placentation (Robins et al., 2011).

Several studies have correlated phthalates levels with abnormal pubertal development (Colon et al., 2000; Qiao et al., 2007; Robins et al., 2011) and with occurrence of obesity (Hatch et al., 2010).

However, additional studies are needed for more definitive conclusions regarding the consequences of phthalates exposure on human health.

Pesticides

In order to increase agricultural productivity, numerous pesticides have been discovered and used since 1939, without guidelines or restriction (Mnif et al., 2011; Gavrilescu, 2005). They are widely used not only for agricultural purpose but also for municipal, home and medical use. Despite the benefits (control of agricultural pests and plant disease vectors) pesticide may persist in soils and aquatic water sediments, move up trophic chains and affect top predators (Mnif et al., 2011).

It has been suggested that disease such as cancer, allergies, neurological disorders and reproductive disorders may be connected to pesticide exposure (Mnif et al., 2011).

About 105 substances can be listed as pesticides divided in three major groups: insecticides (46%), herbicides (21%) and fungicides (31%) with different chemical structures: organochlorides, organophosphates, carbamates (Čeh and Majdič, 2010; Mnif et al., 2011).

Human epidemiological studies have shown that there is an important correlation between occupational or nutritional exposure to pesticide and different human pathologies mainly in female fertility (Fuortes et al., 1997; Bretveld et al., 2006; Zama and Uzumcu, 2010).

Pesticide may act as endocrine disruptors via multiples mechanisms: agonist receptor (estrogen receptor, androgen receptor, estrogen related receptor, pregnane X receptor, arylhydrocarbon receptor), antagonist receptor and interfering with the synthesis, transport, metabolism and excretion of hormones (Andersen and Cook, 2002; Čeh and Majdič, 2010; Mnif et al., 2011).

The disruptive effect of pesticides has consequences on: reproductive and sexual development, gametogenesis and early development of the fetus, intellectual function and central nervous system function (Table 1) (Caliman and Gavrilescu, 2009; Zama and Uzumcu, 2010; Mnif et al., 2011).

Pesticides such as: thiram, molinate, metam sodium, chlordimeform, amitraz, triazole, dichloroacetic acid, atrazine, propazine, simazine and linuron may impair neuroendocrine functions through their effect on the central nervous system and the hypothalamic-hypophyseal-gonadal axis in animal models (Ozen and Darcan, 2011). The pesticide prochloraz suppresses both estrogen and androgen synthesis through enzymatic inhibition also in animals (Ozen and Darcan, 2011).

Dichlorodiphenyltrichloroethane (DDT) an organochlorine pesticide, used in the 1940's as a broad-spectrum insecticide, was banned in the 1970's due to the estrogenic effect and interference in pubertal development (Tiemann, 2008; Craig et al., 2011; Ozen and Darcan, 2011; Shanle and Xu, 2011).

Methoxychlor, an organochlorine pesticide introduced as an alternative to DDT, was also banned in the United States due to its endocrine disrupting proprieties (Shanle and Xu, 2011). It was detected in human adipose tissue, it was shown to impair reproductive behavior and functions in male rat but there are no studies on the effect of this pesticide on precocious puberty in humans (Ozen and Darcan, 2011; Shanle and Xu, 2011). Epigenetic analyses using bisulfite-sequencing PCR and methylation-specific PCR showed that methoxychlor caused hyper-metilation in ER β promoter sequences and had no effect in ER α promoter (Zama and Uzumcu, 2010).

Not only the direct contact with the pesticide is dangerous but also the residential proximity to agricultural activity may lead to: low birth weight, fetal death or childhood cancer (Reynolds et al., 2002; Mnif et al., 2011).

In a Danish study more frequent genital abnormalities in boys and earlier puberty in girls were observed in children of greenhouse owners even so, no pesticide analysis was done in this study (Ozen and Darcan, 2011).

Table 1. Pesticides disrupting the hormone and reproductive system (Andersen and Cook, 2002; Čeh and Majdič, 2010; Mnif et al., 2011)

Effects	***Pesticides***
Estrogenic activity	Amitraz Lindane Parathion-methyl Permethrin Triadimefon s-Triazines
Anti-androgenic activity	Atrazine Lindane Linuron Procynidon Vinclozolin Pyrethroids
Disrupt steroid metabolism	Atrazine Carbofuran Conazole Lindane
Disturb thyroid function	Amitrole Dithiocarbamates Ioxynil Metribuzin Certain pyrethroids Trifluralin
Influence on gonadothrophic hormones	Amitraz Atrazine Certain organophosphates Some dithiocarbamates
Influence on spermatogenesis	Cooper fungicides Certain pyrethroids Some dithiocarbamates Glyphosate Some organophosphates
Reproductive toxicity	2,4 – D Some dithiocarbamates Some organophosphates

The risk of breast-estrogen dependent cancer and prostate cancer is raised by several epidemiological studies but the relation with pesticide use is not yet formally demonstrated (Mnif et al., 2011).

The combined actions of pesticides are very important in the risk assessment process because mixtures of these substances may cause higher toxic effects that those from a single compound (Mnif et al., 2011).

Dioxins

Dioxins are a class of chemicals (polychlorinated dibenzo-p-dioxins) which are formed as by-products of incomplete combustion of

chlorinated waste and in contact of plastics with hot surfaces (Svechnikov et al., 2010; Ozen and Darcan, 2011).

Exposure to dioxins (such as 2,3,7,8-tetrachlorodibenzeno-p-dioxin: TCDD) is possible using products such as: plastic plates and glasses, cleaning substances or paper whitened by chlorine in contact with hot surfaces (Ozen and Darcan, 2011). Also they may be transferred to humans from animal meat or milk. Other sources and the evolution of total environmental releases of dioxins from all quantifiable sources between 1987 and 2000 are shown in Fig. 5 (USEPA, 2006).

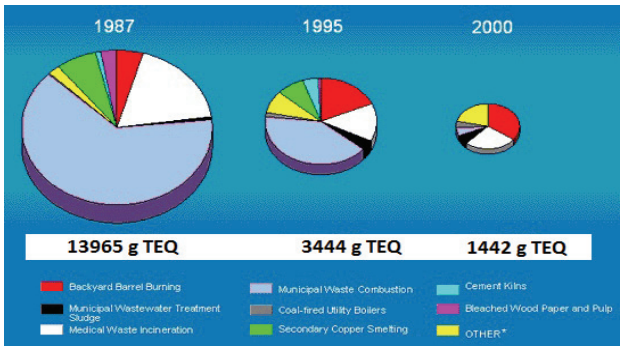


Fig. 5. Dioxin sources contribution (total environmental releases of dioxins from all quantifiable sources decreased by 90% between 1987 and 2000) (taken from USEPA, 2006)

Dioxins bind to aryl hydrocarbon receptor (AhR) and regulate the transcription of target genes (Svechnikov et al., 2010). AhR regulates expression of metabolic enzymes and have many similarities with ER signaling (Shanle and Xu, 2011).

The disruptive actions of dioxins may lead to: reduced expression of sex steroids and LH receptors, inactivation of steroid hormone synthesis or altered steroidogenesis (Badawi et al., 2000; Ohsako et al., 2001; Fukuzawa et al., 2004; Baba et al., 2005; Mutoh et al., 2006; Svechnikov et al., 2010).

3. Cigarette smoke compounds - endocrine disruptors

Constituents in cigarette smoke as: benzo (a) pirene and cadmium can operate as endocrine disruptors by different mechanisms resulting in either estrogenic or anti-estrogenic effects (Dechanet et al., 2011). Benzo (a) pirene has estrogen-like properties, but in human tissue this estrogenic effect must be demonstrated (Dechanet et al., 2011).

Cadmium also interferes in steroidogenesis and may act as an estrogen-like factor (by binding to ER). Given the fact that chemical structure of cadmium is close to that of calcium (they all have 2+ oxidation states and are similar in size when they are ionized) this may facilitates interaction with intra-cellular calcium signaling (Dechanet et al., 2011). Also the FSH and LH intra-cellular signaling mechanism can be altered by cadmium.

An abnormal endocrine profile as: higher level of FSH, higher level of testosterone and lower estrogen level during ovarian stimulation in vitro fertilization, was mentioned in several studies (Van Voorhis et al., 1992; Cooper et al., 1995; Barbieri et al., 2005) there for exposure to cigarette smoke affect every step of the reproductive process according to time, dose, type and duration of exposure (Dechanet et al., 2011).

4. Conclusions

Exposure to endocrine disrupting substances is a common circumstance in nature. Even the disrupting mechanism of action is actively studied, the consequences at the population level and the adaptation to chronic exposure have been disregarded. The impacts of endocrine disruptors on endocrine pathway are complex and often occur through multiple direct and indirect mechanisms making it hard to anticipate the endpoints of their toxicity in animals and humans. Moreover, exposure to EDCs may lead to different effects in different tissues at different life stages. The role of endocrine disruptors as epigenotoxic agents raise the issue of epigenome altering that may influence the health of actual and future population. The influence on reproduction, development and growth, metabolic rate, gender behavior convert EDCs into real health hazards.

The chronic exposure to low levels to an increasing number of chemicals (with possible endocrine-disruptig properties) must determine the regulatory agencies to embrace modern endocrine principles into their risk assessments methodology.

Further studies are necessary to understand the deleterious effects of endocrine disruptor compounds on the endocrine system.

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