ENDOCRINE DISRUPTING CHEMICALS; MYTHS & FACTS

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ABSTRACT

Background: Recognition that some environmental chemicals pose the ability to interact with hormone receptors and mimic their activity has been regarded as one of the most significant developments in both endocrinal and toxicological research of the last century. **Objective:** Despite the myths related to the actions, hazards and effects of endocrine disrupting chemicals (EDCs), this review article briefly throws light on the evidence- based facts concerning such chemicals. An EDC is a chemical that alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment. Default drinking, eating and other every-day events can carry the risk of disrupting our endocrine homeostasis. A challenge to the field of endocrine disruption is that these substances are diverse and may not appear to share any structural similarity other than usually being small molecular mass (<1000 Daltons) compounds. Moreover, it is not surprising that a variety of mechanisms are used by EDCs to influence the endocrine system, these include all stages of hormonal life cycle. **Conclusion:** This review has tried to provide insights into the current state of the scientific evidence on the ubiquity, chemical diversity, variability & complexity of mechanisms and transgenerational effects of EDCs. Of course, the breadth of this topic precludes comprehensive coverage of all EDCs which, in turn, highlights the need for further epidemiological research on these classes of environmental chemicals

Keywords: Endocrine disrupting chemicals, EDCs, endocrine disruptors, environmental chemicals, hormone mimics.

1. INTRODUCTION

The delicate hormonal balance may be at risk, in part because a growing number of contaminants in the environment can accumulate in exposed individuals and may have adverse consequences due to their action as endocrine disrupting chemicals (EDCs). Thousands of chemicals, some banned and some still in use, have been classified as EDCs. They produce their effects by mimicking, antagonizing, or altering endogenous steroid levels (androgens or estradiol, E2) via changing rates of their synthesis or metabolism and/or expression or action at receptor targets **(McCarthy et al., 2009).**

2. DEFINITION OF ENDOCRINE DISRUPTING CHEMICALS

It was proposed that the most commonly used definition of an endocrine disruptor is that provided by **Kavlock et al. (1996)** whose study defines the endocrine disruptor as "An exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes".

The Natural Resources Defense Council (NRDC) (1998) defined an endocrine disrupter as "Synthetic chemicals that when absorbed into the body either mimic or block hormones and disrupts the body's normal functions through altering normal hormone levels, halting or stimulating the production of hormones, or changing the way hormones travel through the body".

Definitions reported by Kavlock and NRDC have later been criticized as being too inclusive and virtually include all chemicals, thus creating an ambiguity **(Kavlock, 1999).** Under such definitions, one could easily classify such innocuous things as a change in room temperature, consumption of a meal, and day light as endocrine disrupters as each is known to induce changes in circulating thyroid hormone **(Thompson et al., 2004),** insulin **(Sheehan, 2004),** and melatonin levels **(Stevens and Rea, 2001)** respectively.

The World Health Organization **(WHO, 2002)** identifies an endocrine-disrupting chemical or an endocrine disrupter as "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". Endocrine disruptors screening and testing advisory committee (EDSTAC), Canada centre for occupational health and safety (CCOHS), and international program for chemical safety (IPCS) agree with the aforementioned WHO definition being a more appropriate definition that readily accounts for the fact that many alterations of the endocrine system are not necessarily deleterious and poses no hazard to the organism **(Agzarian and Foster, 2004).**

The endocrine society defines an EDC as "A compound, either natural or synthetic, 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". This definition, reported in the Endocrine Society Scientific

Statement, is widely accepted worldwide until now **(Diamanti-Kandarakis et al., 2009).**

3. CLASSIFICATION OF EDCs:

Agzarian and Foster (2004) have propose that a suitable method of categorizing endocrine toxicants would be based on a classification system similar to that used by international agency for research on cancer (IARC) to categorize chemical carcinogens. In their proposed system, chemicals would be classified within one of three classes **(table 1)** based on the available published data, yet to that date, regarding their proved or probable effects on human. This disclaims the myth That endocrine disruption is of no concern to human health because the chemicals implicated are weak in comparison to natural estrogen.

With continuous research, more toxic insults on human, laboratory and/or wild animals are revealed and consequently many agents changed their class within this classification **(Diamanti-Kandarakis , 2009).**

Best example is the heavy metals, particularly cadmium that, up to the date of that classification, was classified as class III due to its proved estrogenic activity in a culture system and lack of evidence of effects in whole animals. Later, many studies proved its effects on animals **(Yang et al., 2006 & Pillai et al., 2010)** and human being **(Reid et al., 2009).**

In addition to detrimental effects of NP such as being uncoupler of the oxidative phosphorylation and its estrogenic and antiandrogenic effects proved via in vitro ER and AR reporter gene assays **(Xu et al., 2005),** in vivo studies of NP, held on male rats, have also shown adverse effects on sexual development: reduction of testicular spermatid count, decreased size of testes, epididymis, seminal vesicle and ventral prostate **(Han et al., 2004)**. As well, it causes extensive proliferation of lobular development and mammary glands in rats as a weakly estrogenic substance **(Calafat et al., 2005).**

Moreover, despite that phytoestrogens were neglected in this classification, they have been found to exert pleiotropic effects on cellular signaling. Due to activation/inhibition of the estrogen receptors ERα or ERβ, these compounds may induce or inhibit estrogen action and, therefore, have the potential to be an active EDC in the human body **(Mueller et al., 2004)**

Table (1): Agzarian and Foster classification for endocrine toxic chemicals **(Agzarian and Foster, 2004)**.

Class	Compound	Rationale
Class I (evidence of human exposure, and documented adverse effects in human populations)	**Tetrachlorodi-benzodioxin (TCDD)**	-Human exposure incident in Seveso Italy reported long-term effects of: spontaneous abortion, cytogenetic abnormalities, congenital malformation, impaired liver function and lipid metabolism, as well as neurologic and immunologic impairment **(Baccarelli et al., 2003).** -Ranch Hand's human exposure study to dioxin among Vietnam veterans indicated adverse effects on thyroid hormone metabolism and function resulting from increased levels of pituitary thyroid stimulating hormone **(Pavuk et al., 2003).**
	Polychlorinated biphenyls (PCBs)	-Human effects include irregular menstrual cycles, altered immune responses and increased levels of blood thyroxin and triiodothyronine **(Aoki, 2001).** - Evidence of thyroid toxicity due to PCB exposure produced from human epidemiologic studies is supported by even stronger evidence for thyroid toxicity from animal studies **(Wilhelm et al., 2008).** -They interact with a human hydroxy-steroid sulfotransferase causing sulfation of endogenous steroid hormones and bile acids **(Ekuase et al., 2011)**

	Dichlorodiphenyl-dichloroethylene (DDE)	-It enhance basal and FSH-stimulated granulosa cell aromatase enzyme activity (at normal levels in human follicular fluid) **(Younglai et al., 2004).** -Investigation of human effects showed that p,p' DDE did not affect serum hormone levels of LH or FSH nor SHBG **(Cocco et al., 2004).**
Class II (experimental animal data or evidence from wildlife and fish studies indicating their potential to induce adverse effects on the endocrine system, but evidence of adverse effects in humans is inconsistent)	**Methoxychlor**	affects embryonic testis cellular composition, germ cell numbers, and germ cell survival and appears to cause a reduced spermatogenic capacity **(Cupps et al., 2003).**
	Mirex	-It's a chlorinated hydrocarbon that was commercialized as insecticide, has been shown to be responsible for tumor promotion in female mice through the ovarian hormone 17-beta estradiol **(Porter et al., 2002).**
	Perchlorate	-It induces hypothyroidism by hindering iodine uptake in animal models **(Clewell et al., 2003).** -Its effects on humans even at levels up to 36 times those of normal exposure have been physiologically insignificant **(Greer et al., 2002).**
	Perfluorooctanesulfonic acid (PFOS)	**-** Exposure to it has lead to decrease in the serum levels of T4 and T3 in treated rat dams **(Thibodeaux et al., 2003).** - PFOS can have detrimental effects on development possibly through affecting thyroid function **(Inoue et al., 2004).**
	Dichlorodiphenyltrichloro-ethane (DDT)	-Large dose intoxication of in laboratory animals leads to effects on the nervous system, resulting in tremors and shivers, as well as detrimental effects on reproduction **(Greaves, 2007).** - Human research on DTT shows some debate, it has indicated adverse effects on DNA as well as apoptosis of human peripheral blood mononuclear cells **(Younglai et al., 2004).** However, cumulative exposure does not appear to have effects on human serum hormone levels **(Cocco et al., 2004).**
Class III (Evidence of adverse effects in animal models or in vitro but human exposure is too low or not expected to occur)	**Bisphenol A (BPA)**	-At low dose, it was proved to be equally as potent as 17-beta estradiol in activating the transcription factor cAMP response element-binding (CREB) in an alternative mechanism, involving non-classical membrane estrogen receptors **(Quesada et al., 2002).** **-**Exposure of male rats to environmentally low levels lead to a reduction in daily sperm production 5 weeks later **(Sakaue et al., 2001).**

	Nonylphenol (NP)	-Has been shown to cause extensive proliferation of lobular development and mammary glands in rats as a weakly estrogenic substance **(Odum et al., 1999).** -It has adverse effects on male rat sexual development: reduction of testicular spermatid count, decreased size of testes, epididymis, seminal vesicle and ventral prostate **(Chapin et al., 1999).**
	Dibutylphthalate (DBP) and di-2-ethylhexylphthalate (DEHP)	-Controversy exists regarding its effects on sexual development: reported a reduction in testis size, whereas other studies have refuted these findings **(Ashby et al., 1997).** - It has been reported to affect sperm motility **(Wang et al., 2004).** -Exposure at high levels caused "rapid and reversible diminution of the expression of several proteins required for cholesterol transport and steroidogenesis in the fetal testis, resulting in decreased testosterone synthesis and consequent male reproductive maldevelopment" **(Thompson et al., 2004).**

The European Union Commission reported about potential endocrine disruptor candidate list of 553 substances. From which, a sub-set of 106 compounds was chosen for further investigation due to their reliable literature data collected about several effects related to their endocrine disruption potential and potency (table 2) **(Novi and Roncaglioni, 2004).**

Table (2): Categories of suspected endocrine disrupting chemicals studied by the EU Commission **(Novi and Roncaglioni, 2004).**

Category	Labeling	Description
1	Endocrine disrupter	At least one study was found providing the evidence of endocrine disruption in an intact organism. Not a formal weight of evidence approach.
2	Potential endocrine disrupter	In vitro data indicating potential for endocrine disruption in intact organisms. Also includes effects in vivo that may, or may not, be ED-mediated. May include structural analyses and metabolic considerations.
3	Undefined activity or Non-endocrine disrupter	No scientific basis for inclusion in list of endocrine disrupters.
3A	Undefined activity– No evidence for non-ED	No data available on wildlife and/or mammal relevant effects.
3B	Undefined activity– Some evidence for non-ED	Some data are available but the evidence is insufficient for identification
3C	Non-endocrine disrupter– Certain evidence for non-ED	Some data are available but the evidence is insufficient for identification.

A third computational/in silico model for classification of endocrine disrupter activity of compounds of known chemical structures, is proposed giving each group a discrete class number **(Novi and Roncaglioni, 2004).** In silico is an expression used to mean "performed on computer or via computer simulation". The phrase was coined in 1989, as an analogy to the Latin phrases in vivo and in vitro which are commonly used in biology and refer to experiments done in living organisms and

outside of living organisms, respectively **(University Of Surrey, 2007).** Advances with cell and tissue cultures, computer modeling, and genetic research help to reduce the need for animals to test substances that can harm humanity, but they probably will not totally eliminate that need. Computers allow toxicologists to develop mathematical models and algorithms that can predict the biological effects of new substances based on their chemical structure. If a new chemical has a structure similar to a known poison in certain key aspects, then the new substance also may be a poison **(Keijsers, 2010)**.

4. SOURCES OF EDCs

4.1. Natural Sources :

4.1.1. Environmental**:**

Barcelo and Kettrup (2004) reported that EDC can enter surface water by a variety of mechanisms including direct discharge of industrial and domestic wastewater, discharge of sewage treatment plant (STP) effluents, agricultural drainage to streams & rivers and overland flow after rainfall. Both surface and ground water are exposed to pollution by steroid medications and their metabolites **(Zuehlke et al., 2004)**. Administration of drinking water treated with chlorine-based disinfectants was shown in multiple studies to interfere with thyroid function of laboratory animals. One possible mechanism is that intra-alimentary redox interactions, between chlorine oxides and organic & inorganic contents of the gastrointestinal tract, cause formation of iodinated and chlorinated nutrients **(Qingdong et al., 2006).**

4.1.2. Plants (Phytoestrogens):

Phytoestrogens are chemicals naturally found in plants and are present in fruits, veggies, beans and grasses. They may occur in the environment as mixtures where the dietary sources make more than one phytoestrogen or herbal compound could be consumed together from an individual food **(Assinder et al., 2007).**

Flax, cereals and seaweed are sources of phytoestrogens, e.g. lignans, Soy contains isoflavones including daidzein, equol, genistein and glycetein. Fungal growth on grains also are sources of resorcylic acid lactones. Grapes and peanuts contain resveratrol **(Charles et al., 2007).** There are a variety of compounds in plants and herbs used to make teas, including ginseng that serve as sources of phytoestrogens. The activity of some of these compounds is dependent on modification of precursor molecules that are contained in the food products. This often requires the action of gut bacteria and enterohepatic modifications **(King et al., 2007).**

4.1.3. Food products:

Exposure to EDCs is either through the food stuffs (soybeans, legumes, flax, yams, and clover), which are also referred to as phytoestrogens, or through the contaminants, additives or preservatives that can be found in food products. **(Chavarro et al., 2008).**

Concerning negligible exposures to xenobiotics with weak hormone like activities, the potent endocrine disruptor licorice is freely given to children. The active ingredient of licorice, glycyrrhizic acid, is present in confectionary products, sweets and health products at concentration average of 2mg/g. In sensitive individuals, a regular daily intake of about 100 mg glycyrrhizic acid (about 50g of licorice sweets) will induce clinical signs of mineralocorticoid dysfunction after 1 week **(Stokes-Riner et al., 2003).** Canned foods and plastic containers involve compounds considered as well known EDCs. For instance, DEHP and dipentyl phthalate are found in the food industry as a part of foil/plastic heat seal caps. Also BPA is used as a component in many resins and polycarbonate plastics **(Adler, 2007).** In addition, human exposure to TCDD via foods has recently shifted from phenoxy herbicides contaminants to the products of combustion and waste disposal which could contain TCDD and contaminate animal feeds and such human foods as milk, meat and vegetables. The total uptake of TCDD from foods by the maximally exposed population will usually be about 500- to 1000-fold greater than that due to inhalation **(Fries and Paustenbach, 2009).**

It's worth mentioning, as well, that fish and shellfish concentrate mercury in their bodies, often in the form of methylmercury. Species of fish that are long-lived and high on the food chain, such as marlin, tuna, shark, swordfish, king mackerel and lake trout contain higher concentrations of mercury than others **(Nilsson, 2006 & Balshaw et al., 2008).**This has an impact on the belief of the importance of maternal fish consumption during pregnancy that, unfortunately exposes the fetus simultaneously to both methylmercury and long chain polyunsaturated fatty acids each of which has different effect on neurological and psychomotor development of the offspring. Significant association of these exposures of opposite directions emphasizes the need for adjustment of maternal

nutrition to achieve balanced non hazardous exposure **(Stokes-Riner et al., 2011).**

Acrylamide, a well known carcinogen and EDC first discovered to be present in food by the Swedish National Food Authority in 2002, forms naturally in many plant-based, high-carbohydrate foods including baked and fried potatoes, cereals, crackers and bread when they are heated **(De Wilde et al., 2005& Olesen et al., 2008).** Production of acrylamide in the heating process was shown to be temperature-dependent. Browning during baking, deep-frying and over-cooking foods will produce acrylamide. Acrylamide cannot be created by boiling, and very few uncooked foods contain detectable amounts like olives, asparagus, prune juice and dried fruit **(Ciesarová et al., 2010).** Acrylamide may be a natural decay product of the polyacrylamide used in some commercial herbicides as heat and light can decompose polyacrylamide into acrylamide. Cigarette smoking is a major acrylamide source, also drinking coffee may contribute to more than 10% of acrylamide exposure **(Spivey, 2010).**

4.2. Synthetic, Anthropogenic and Industrial Sources:

4.2.1. Household products:

They mainly include breakdown products of detergents and associated surfactants, e.g. NP and octylphenol which are persistent toxic degradation product of alkylphenol ethoxylates (APEs) used in institutional cleaning agents, textiles, agricultural chemicals, plastics, paper products, household cleaning agents and personal care products **(Acevedo et al., 2005).** As a consequence of their wide use in a variety of products, APEs are quite common in rivers and other aquatic environments that receive sewage discharges **(Adler, 2007).**

4.2.2. Body care products:

Many over-the-counter daily body care products can carry the risk of hurting our endocrine system; for example, the role of underarm or body care cosmetics in the rising incidence of breast cancer in women in recent decades, has been proved on a scientific basis **(Darbre et al., 2004).** This is another disclaimer to the myth that chemicals used in products sold to consumers have been tested and found safe from health effects.

Parabens have been suggested as the agents in body care formulations potentially involved in breast cancer because of their ready absorption through the skin (e.g. as intact esters), their hormonal activity and their reproductive toxicity **(Harvey & Everett, 2004)**, but other suggestions are for a role of aluminum as another incriminated agent **(McGrath, 2003).** Additionally, the siloxanes or cyclosiloxanes are present in high proportions in personal care products, e.g. octamethylcyclotetrasiloxane is present at 40–60% by weight in such products as antiperspirants and cosmetics. The cyclosiloxanes are reported to concentrate in ovaries and uterus of mice following a single subcutaneous injection and also have an 'affinity' for the estrogen receptor **(Harvey and Darbre, 2004).**

It's noteworthy also that over the past several years there has been growing concern over exposure to dioxins such as polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and TCDD, through the use of tampons and other sanitary products **(DeVito and Schecter, 2002).** However, the exposure to dioxins from the diet is more than 30,000–2,200,000 times the exposure through tampons and diapers in nursing infants **(Shin and Ahn, 2007).**

An important study held by **Henley et al. (2007)** has shown that the common use of products containing lavender oil, tea tree oil, or both, by three boys, otherwise healthy, show prepubertal gynecomastia. All of whom had normal serum concentrations of endogenous steroids and none of whom had been exposed to any known exogenous endocrine disruptor such as medications or soy products. Resolution of gynecomastia occurred within months after ceasing use of those products.

4.2.3. Pesticides:

Organochlorine pesticides such as DDT & its metabolite DDE, endosulfan, atrazine, nitrofen, lindane, as well as chlordane and dieldrin can act as estrogens, antiestrogens or antiandrogens **(Čeh and Majdič, 2010).** The herbicide linuron and the organophosphorous fenitrothion have been shown to compete for binding to the human androgen receptor, then altering androgen-dependent gene expression **(Guerrero-Bosagna and Valladares, 2007).**

4.2.4. Plastics:

Bisphenol A, the most famous endocrine disrupting plasticizer, has been used also as a fungicide, antioxidant, flame retardant, rubber chemical and polyvinyl chloride (PVC) stabilizer. Polycarbonates/PVC are frequently used as components of food processors, micro-wave ovens, tableware, refrigerator drawers, food storage containers, water containers, juice containers, milk containers, infant feeding bottles and interior coatings of cans **(Takahashi and Oishi, 2000).**

Howdeshell et al. (2003) conducted a study investigating if used and new polycarbonate animal cages would release BPA into water at room temperature. They found that as much as 310µg/l and 0.3µg/l BPA was released into water from the used and new cages respectively. No BPA was detected when water was stored in glass. BPA is able to migrate from plastics into food, especially at high temperatures. Even plasticware labeled as dishwasher and microwave safe may pose some risk **(vom Saal and Hughes, 2005).** Although BPA is rapidly metabolized, as its half-life is less than 1 day important forms of EDCs **(McNab, 2002).**

and it apparently does not tend to accumulate in the body, its ubiquity in frequently used consumer products results in regular and continuous exposure **(vom Saal and Hughes, 2005).**

4.2.5. Pharmaceuticals:

Many drugs are hormones in nature, moreover, other drugs are hormone modulating chemical compounds (table 3). Unlike the common concepts regarding safety of pharmaceutical drugs, such drugs are very

Table (3): Some endocrine modulating pharmaceuticals **(Arky, 2010).**

Endocrine modulator drug	Human condition of exposure
Cytadren/ aminoglutethemide (adrenocortical steroid inhibitor)	Cushing syndrome
Anadrol/ oxymetholone (anabolic steroid)	Erythrocyte production deficiency anemia
Android / methyltestosterone (androgen)	Hypogonadism, puberty stimulation
Tapazole / methimazole (antithyroid)	hyperthyroidism
medroxyprogesterone (progestin)	2ry amenorrhea, abnormal uterine bleeding, endometriosis
Estratab (estrified estrogengs)	Various symptoms of menopause and hypogonadism
Levonorgestril + estradiol	Contraception
Eulexin / Flutamide (antiandrogen)	In cancer prostate (non steroidal competitive inhibitors)
Nizoral/ ketoconazole (antiandrogenic properties)	Fungal infections, especially in immunocompromised patients such as those with AIDS

It's worth mentioning that all chemically induced changes in the endocrine system cannot be considered undesirable, indeed synthetic steroids are used purposely to inhibit pituitary gonadotrophines thus providing a chemical method of birth control for millions of women **(Smith et al., 2010).**

4.2.6. Fuel combustion and industrial products**:**

Ueng et al. (2004) have tested the endocrine disrupting activity of motorcycle exhaust particulate (MEP) extract and its constituent compound benzo(a)pyrene. The results have shown their antiestrogenic activity mediated by cytochrome P450 induction in addition to replacement of estrogen from estrogenic receptor in a time- and concentration-dependent manner. On the other hand, examples of industrial EDCs include PCBs that are used in many applications especially as dielectric fluids in electric transformers, capacitors, and coolants **(Rudel et al., 2008).** Other examples include dioxins and benzo(a)pyrene. Exposure to these chemicals occurs through direct contact in the workplace or at home, or through ingestion of contaminated water, food, or inhalation of air **(Birnbaum, 2010).**

5. CHEMICAL STRUCTURE OF EDCs

It has been believed for long time that an EDC should resemble the natural hormone, hence the name hormone mimic. By continuous research, it's proved that variable factors and mechanisms play great role in the process of endocrine disruption, so it's not a must for an EDC to mimic the hormone molecule to disrupt its function **(Singleton and Khan, 2003).** Also, EDCs sharing similar hormonal properties don't necessarily

share the same structure, e.g. both the pesticide DDT and PCBs have estrogenic activity, but their chemical structures are quite different **(Hadley and Levine, 2006).**

5.1. Endocrine Disruptors Structurally Mimic to Natural Hormones:

The **glycyrrhizic acid** (figure1), the active principle of licorice, whose consumption cause hypertension and edema (water retention). These effects are related to the competitive inhibition of cortisol metabolism within the kidney, its accumulation and the subsequent stimulation of mineralocorticoid receptors. So, consumption of black licorice can mimic disorders of excess aldosterone **(Stokes-Riner et al., 2003).** Glycyrrhizic acid has recently shown to increase total and free dihydroepiandrosterone (DHEA) levels in both males and female saliva. Conjugated DHEA, predominantly DHEA sulphate synthesized in the adrenal gland, levels were decreased. This reflects inhibition of DHEA sulphation by the adrenal sulfotransferase enzyme **(Al-Dujaili et al., 2010).**

A conspicuous feature of the chemical structure of **phytoestrogens** (figure 2) is the presence of a phenolic ring which, with few exceptions, is a prerequisite for binding to the sex hormone, especially estrogen, receptors. For this reason, phytoestrogens can act as estrogen agonists or antagonists (**Rowlands et al., 2011).** It's worth mentioning that due to this estrogenic property, phytoestrogens have been shown to exert cardioprotective effects. Genistein, for example, is associated with reduced levels of TNF-α and blunted myocardial intercellular adhesion molecule-1 expression. Moreover, it was shown that in people at high risk of cardiovascular events, a greater isoflavone intake is associated with better vascular endothelial function and lower carotid atherosclerotic burden. There are some epidemiological studies that suggest that high phytoestrogen intake is inversely associated with cardiovascular risk factors and development of cardiovascular disease **(De Coster and van Larebeke, 2012).**

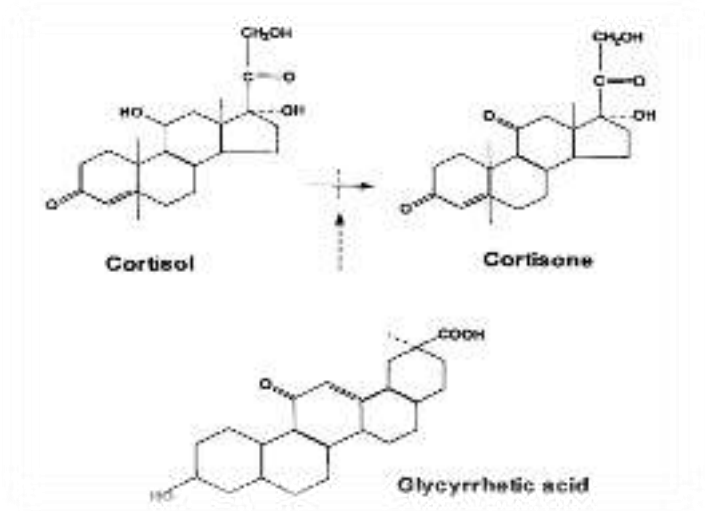

Figure (1): Glycyrrhizic acid **(Stokes-Riner et al., 2003).**

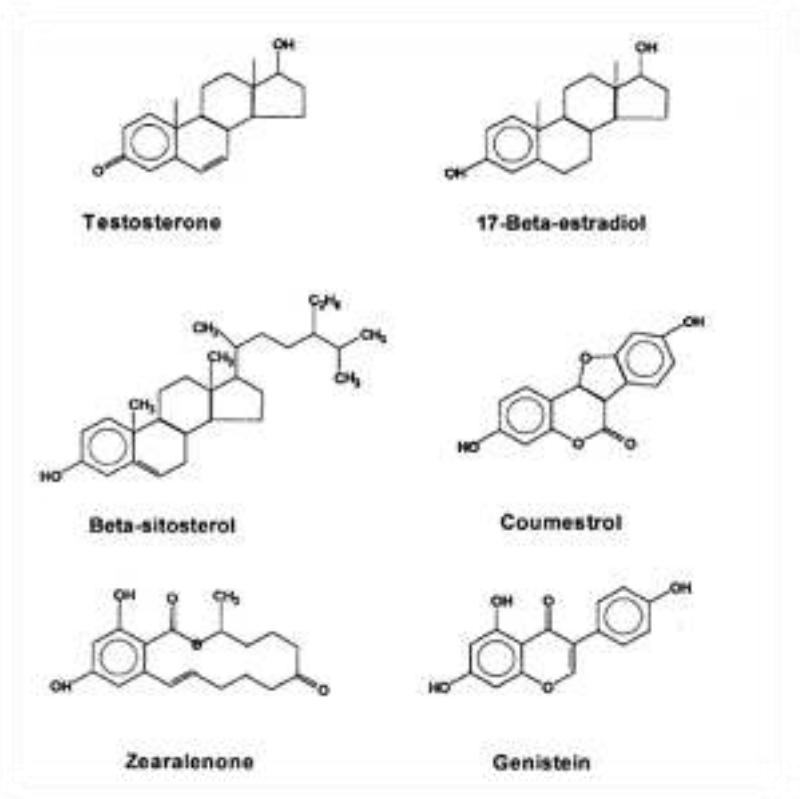

Figure (2): Structural comparison between some phytoestrogens and the sex hormones **(Chavarro et al., 2008).**

In addition there are synthetic chemicals in the environment that share similar sites of action or an active chemical moiety, especially hydroxyl group, with the natural estrogens, thus being able to act on the estrogen receptor also as agonists and antagonists (figure 3) **(Harvey and Johnson, 2002 & Coster and van Larebeke, 2012).**

Most antiandrogens, are competitive antagonists of testosterone and the more potent form dihydrotestosterone (DHT). These distinct chemicals share quite similarity to androgens. Figure (4) displays structure of putative competitive antagonists with relatively high potency ($IC_{50} \leq 1.5$ µM) **(Jones et al., 2009 a).**

However, the clinically used antiandrogen flutamide (figure 5) inhibits also androgen receptor translocation from the cytoplasm to the nucleus, indicating that receptor mechanisms extend beyond simple binding **(Jones, 2009).**

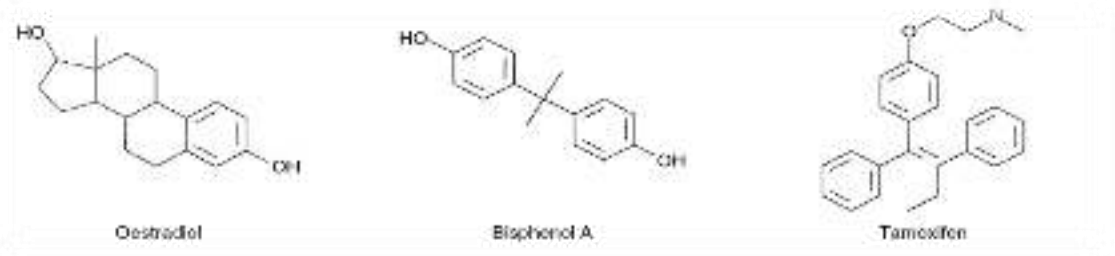

Figure (3): Compounds that act on the estrogen receptor **(Harvey and Johnson, 2002).**

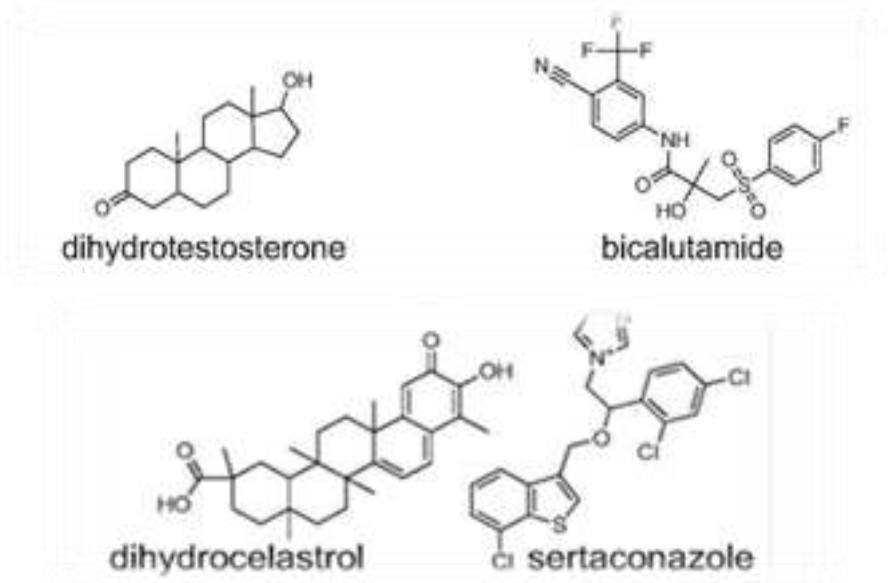

Figure (4): Structures of some competitive androgen antagonists **(Jones et al., 2009 b).**

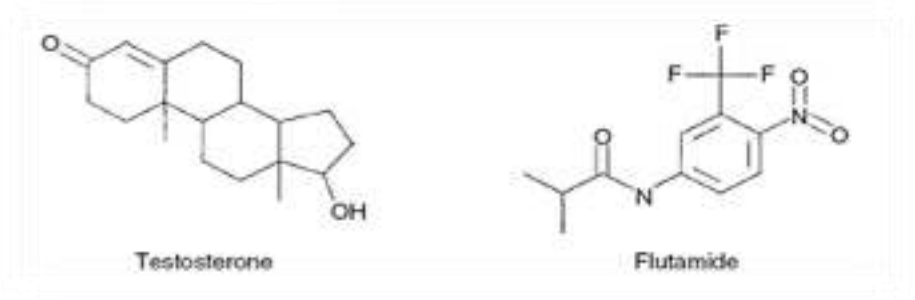

Figure (5): Testosterone and flutamide **(Harvey and Johnson, 2002).**

Polychlorinated biphenyls (figure 6), and their hydroxylated metabolites, are groups of synthetic chemicals, as per their molecular structure they exist in various states of chlorination either containing no ortho chlorine atoms (coplanar) or with one or more chlorine in the ortho position. These structural features affect the ability of PCBs to bind to various hormone and neurotransmitter receptors and to act as agonists, antagonists, or mixed agonists/antagonists **(Walker and Gore, 2006).**

Because they resemble the structure of the thyroid hormone and its precursor, polyhalogenated aromatic hydrocarbons, such as PCBs, dioxins, and flame retardants released into the environment by industrial activity, have been suspected for several years to interfere with thyroid hormone signaling **(Boas et al., 2006).** On the other hand, thyroid peroxidase inhibitors (figure 7) are considered the most famous antithyroid agents, so that they're used medically for treatment of hyperthyroidism. The mechanism of their action is typically competitive inhibition of tyrosine iodination **(Chernov'yants et al., 2010).**

The parabens, esters of p-hydroxybenzoic acid shown in figure 8, are widely available in body care products and female cosmetic preparations. The characteristic phenolic ring and the attached hydroxyl groups are essential for binding to estrogen receptors eliciting their estrogenic effects **(Darbre and Harvey, 2008).**

5.2. Endocrine Disruptors Structurally Diverse from Natural Hormones:

Steroidogenic cytochrome P-450 inhibitors, (figure 9), are chemically diverse members of endocrine disruptors that act by inhibiting steroidogenesis through their enzyme inhibiting properties regardless of their structural formulations **(Barcelo and Kettrup, 2004).**They include: formestane, anastrozole and letrozole, used clinically to inhibit aromatase (CYP19); aminoglutathimide, inhibiting side-chain cleavage of cholesterol to pregnenolone (CYP11A1, CYP scc) which is the first stage of

steroid production; etomidate, a potent inhibitor of CYP11β/18 blocking cortisol production; and ketoconazole (an antifungal) inhibiting 17-lyase (CYP17) **(Harvey and Johnson, 2002).**

Moreover, A diverse group of pesticides, such as DDT, DDE, dieldrin, endosulfan, lindane, chlopyrifos, and methoxychlor, can act as weak estrogens; antiandrogens, some alter thyroid function, interfere with immune function, or act upon neurotransmitter synthesis, degradation, and/or receptors **(Čeh and Majdič, 2010).** Their chemical formulae are not chacteristically similar to a certain natural hormone. Further, although they may share some actions, they do not have structural similarities among one another and sometimes to the natural hormones of interest **(Sebire et al., 2009).**

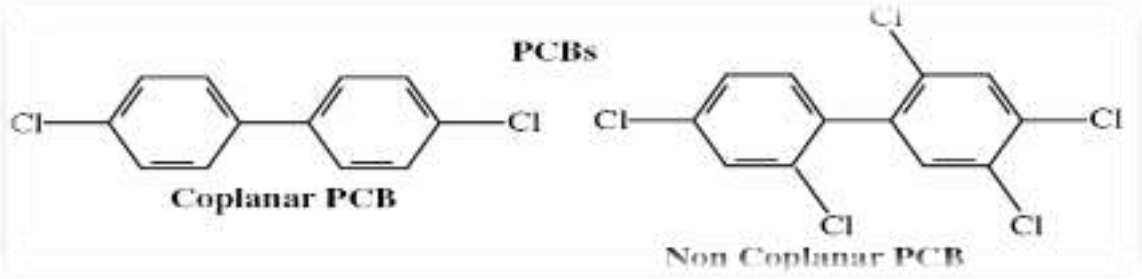

Figure (6): Polychlorinated biphenyls **(Walker and Gore, 2006).**

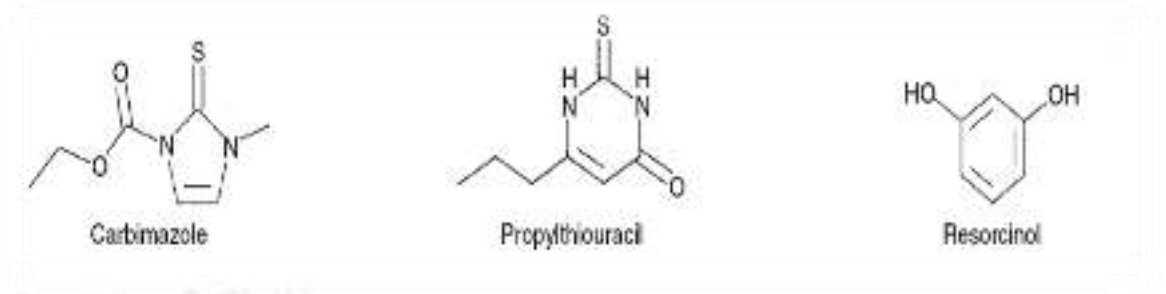

Figure (7): Structural similarity to tyrosine of anti-thyroidal competitive peroxidase inhibitors **(Chernov'yants et al., 2010).**

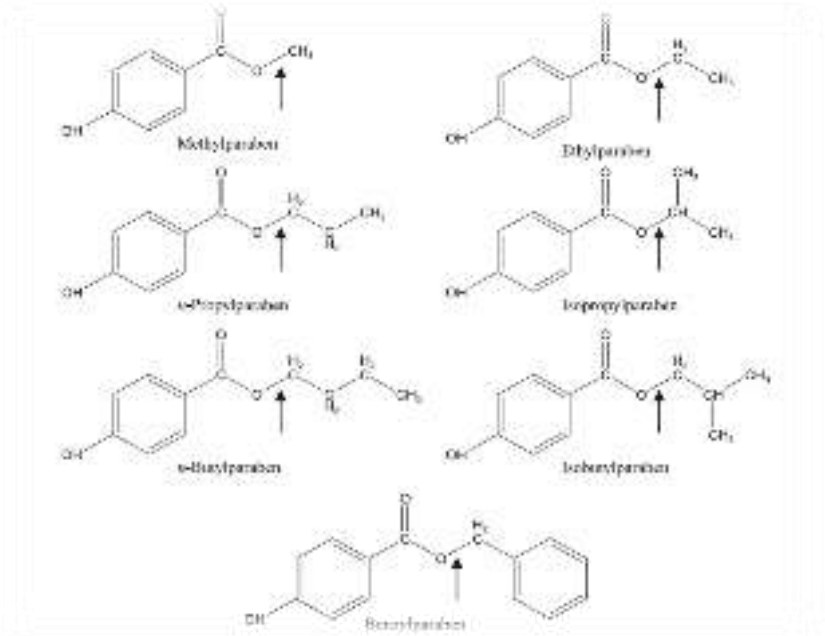

Figure (8): Chemical structure of seven parabens **(Darbre and Harvey, 2008).** 'Hydrolysis at the arrow yields p-hydroxybenzoic acid'

6. MECHANISMS OF EDCs' ACTION:-

Humans and animals are constantly exposed to substances in food and other environmental media that interact with the endocrine system but seldom compromise normal physiological functions. Altered hormone concentrations in response to chemical exposure could be an adaptation response, therefore, It alone is not a sufficient indicator of toxicity unless the equilibrium control, or hormonal homeostasis, mechanisms are overwhelmed **(Chou, 2005).**

Mechanisms for EDCs' action are not only complex but also exerted upon multiple targets; all stages of the natural hormone life can be involved. Therefore, it is predictable that single compounds that interact with multiple endocrine systems will exert complex actions **(Welshons et al., 2006).**

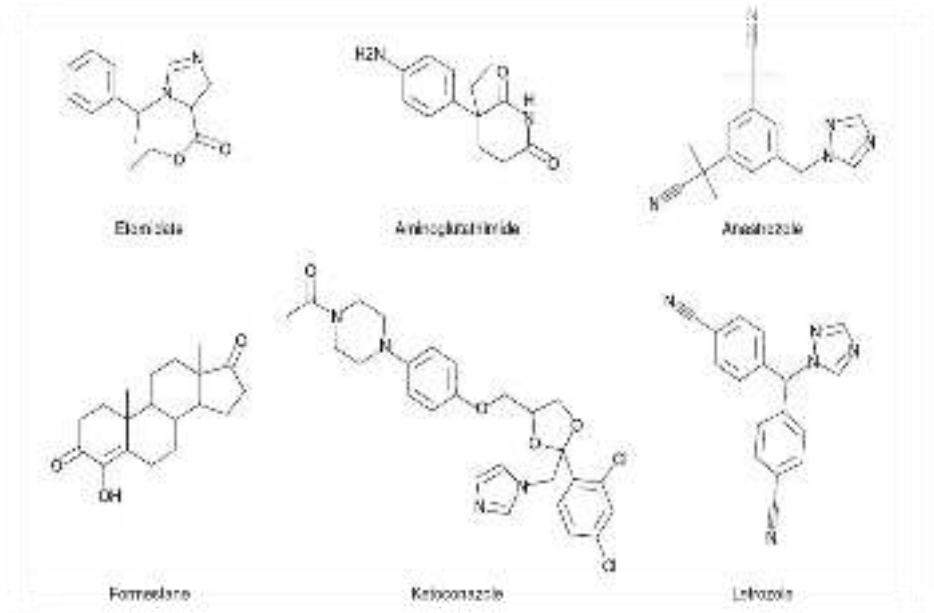

Figure (9): Steroidogenic cytochrome P-450 inhibitors **(Harvey and Johnson, 2002).**

6.1. Mode of EDCs' Action:

A major difficulty in the study of endocrine disruption is the apparent complexity of mechanisms of action. Often, non monotonic dose-response curves are observed, such as U- or inverted U-shaped dose responses **(Fenton, 2006).** This reflects the concept of **hormesis** that can be defined as a dose–response relationship in where there are inverse effects at low and high doses, resulting in a non sigmoid, non-monotonic dose–response curve **(Calabrese and Baldwin, 2003, Viñas et al., 2012).** The same concept is applied to nutrients and natural hormones where both low and high concentrations cause adverse health effects. High doses of selenium, nutrient trace element, can affect the brain, and high doses of estrogens may increase the risk of breast and endometrial cancers, while low doses of both of these substances cause severe disease conditions. produce an inhibitory effect. A similar observation might result from changes in metabolic processing of the chemical at the higher dose **(Smith et al., 2006).** Moderate levels of both are essential for life **(Eaton and Klaassen, 2001).**

Consideration of nonlinear dose–response relationships for EDCs is not surprising, given that some hormones can act on multiple receptor types (and subtypes) with potentially different intracellular signaling pathways **(Smith et al., 2006).** It is believed, as well, that the effects of an endocrine disruptor at the high end of its dose-response spectrum result from perturbation of more than one pathway, whereas at lower concentrations, only a single endocrine component may be involved **(Singleton and Khan, 2003).**

It's proposed also that at low concentrations an EDC may bind with high affinity to receptor A and produce a stimulatory effect, whereas at higher concentrations it may bind with low-affinity to receptor B and

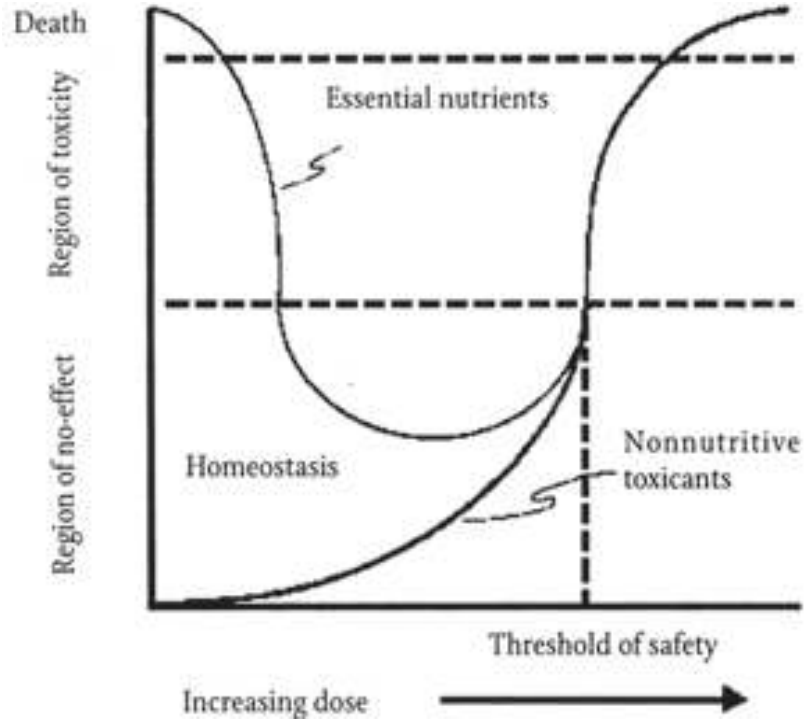

Figure (10): Typical dose–response curves for hormetic and other toxic non-hormetic chemicals **(Eaton and Klaassen, 2001).**

Other explanations of the non monotonic action of EDCs is the common exposure to mixtures, the different estrogenic potency of EDCs and the additive or modifying effect of xenoestrogen (XE) on the effect of endogenous physiological estrogens especially estradiol (E2) **(Henley and Korach, 2010).** Figure (11) is a working model of XE alteration of physiologic estrogen response effects. XEs of increasing dose were used to challenge the responses of the E2. In each case the vehicle control (V) and E2 responses are shown by horizontal bars. The response to an XE alone is shown by a solid line, and the combination of E2 plus the XE is shown by a dashed line. The types of combination responses are: (A) A weak XE enhances the physiologic E2 response; (B) A moderate XE response enhances the E2 response at low concentrations, and inhibits it at higher concentrations; (C) The strongest XE inhibits the E2 response at all concentrations, with increasing inhibition as the XE concentration increases; and (D) If the XE exhibits a fluctuating non-monotonic estrogenic response, the effect on the E2 response also fluctuates **(Viñas et al., 2012).**

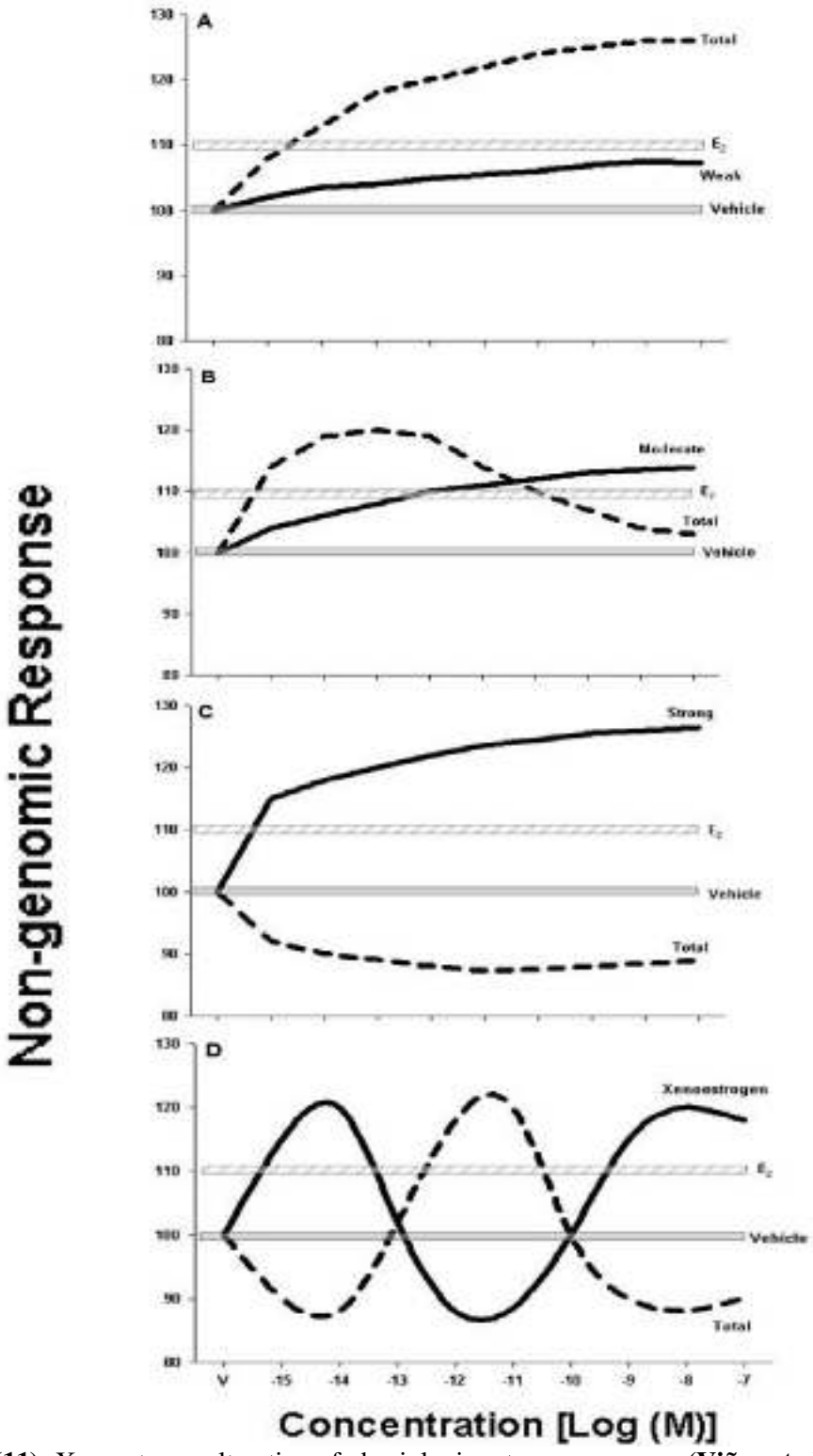

Figure (11): Xenoestogen alteration of physiologic estrogen response **(Viñas et al., 2012).**

6.2. Mechanisms of EDCs' Action:

6.2.1. **Altred Hormone Synthesis**:

a- Changes in the size and population of hormone producing cells:

Exposure to acrylamide monomer causes growth stimulation of the cellular volume of the thyroid gland, as partial mechanism of inducing thyroid cancer, with subsequent increase in T4 and a decrease in TSH in blood **(Dourson et al., 2008).**

b- Modification of the activity of hormone synthesizing enzymes:

Synthesis of glucocorticoids can be inhibited or blocked by several drugs that inhibit the steroidgenic CYP450 enzymes **(Rajapakse et al., 2002).** The role of these cytochrome enzymes in adrenal and gonadal androgen synthesis has made it a therapeutic target for intervention in prostate cancer and has fueled the development of a number of CYP450 inhibitors. They include: formestane, anastrozole and letrozole, used clinically to inhibit aromatase (CYP19); aminoglutathimide, inhibiting side-chain cleavage of cholesterol to pregnenolone (CYP11A1, CYP scc) **(Harvey and Johnson, 2002).** Moreover, the fungicide
fenarimol inhibits the enzyme aromatase, which converts testosterone to estrogen **(Sugni et al., 2010).** Iodination of tyrosine, in synthesis of thyroid hormones, is accomplished by the enzyme TPO, the antithyroid drugs propylthiouracil and methimazole act by inhibiting the activity of this enzyme **(Howdeshell, 2002).**

a- Causing lack of precursors:

Exposure to the plasticizers DBP and DEHP, at high levels, has shown to cause "rapid and reversible diminution of the expression of several proteins required for cholesterol transport and steroidogenesis in the fetal testis, resulting in decreased testosterone synthesis and consequent male reproductive maldevelopment **(Thompson et al., 2004).** Cadmium at high concentrations inhibits placental progesterone synthesis by inhibiting expression of the low-density lipoprotein receptor that is needed to bring cholesterol substrate into the cells leading to its depletion thus resulting in premature labour **(Yang et al., 2006).** By the same mechanism, cadmium inhibits ovarian steroidogenesis by causing marked depletetion of ovarian cholesterol content together with strong down regulation of the StAR protein **(Pillai et al., 2009).**

b- Interference with enzyme cofactors:

Divalent cation chelating compounds cause depletion of enzymes cofactors. Dithiocarbamates and carbon disulfide, for example, suppress the conversion of dopamine to norepinephrine and subsequently to epinephrine by this mechanism **(Cheng et al., 2010).**

6.2.2. **Storage and Release:**

The release of hormones from the storage compartments in cells also controls the amount of hormones in circulation **(Chou, 2005).** Reserpine and amphetamine are examples of compounds that affect hormone storage in granular vesicles causing excessive release of catecholeamines with later subsequent depletion **(Clausius et al., 2009).** Chemicals that activate LH receptors, such as manganese, could potentially cause hypersecretion of testosterone from the Leydig cells, site of testosterone synthesis and storage in the testes **(Lee et al., 2006).**

6.2.3. **Carrier Proteins (Delivery):**

The availability of hormones for physiological functions depends on the total concentration of the hormone as well as the amount of hormone existing in the free state; protein-bound hormones are not readily available for receptor binding. While lack of carrier proteins could impair the transport of hormones to target organs, excessive amounts may decrease the availability of free hormones **(Hadley and Levine, 2006).**

a- The endocrine disrupter may displace the natural hormone, preventing it from reaching its target cells and allowing the liver and kidneys to eliminate it from the body:

Salicylate was found to inhibit T4 binding to all 3 major T4 binding proteins; thyroid binding globulin (TBG), transthyritin (TTR) and albumin, and displaced proportionately more T4 from TBG compared with TTR and albumin **(Wang et al., 2003).** Certain PCB breakdown products can bind and saturate TTR displacing T_4 and allowing the liver and kidney to dispose of the free-floating hormone too quickly which can explain observed lowered levels of THs **(Gutleb et al., 2010).**

b- An endocrine disrupter can attach to the transport protein, denature it, and destroy its ability to bind to other molecules:

Equol, a phytoestrogen, causes significant increase in the level of sex horone binding globulin (SHBG) and also denature its protein properties increasing its affinity to testosterone, so the net result is marked decrease in sex hormone levels and too little hormone reaches the target cells, consequently, the body perceives a false low hormone level impression **(Tanaka et al., 2009).**

c- An endocrine disruptor could change how quickly or slowly the transport protein unloads hormone molecule:

Pentachlorophenol, a persistent organohalogen used as a herbicide, pesticide, and product additive, greatly slows down testosterone unloading from the sex steroid transport protein (SHBG) at the target cell **(Dorsey and Tchounwou, 2004).**

d- An endocrine disruptor can change the concentration of binding proteins:

Some compounds with estrogen activity, such as PCBs and polybrominated diphenyl ethers (PBDEs), are known to increase the amount of testosterone–estrogen-binding globulin (TEBG) **(Turyk et al., 2008).** While high doses of androgens and glucocorticoids may decrease the TEBG concentration in plasma **(William et al., 2008). Tanaka et al. (2009)** have found that the serum levels of sex hormone-binding globulin significantly increased, and the serum levels of free testosterone and dihydrotestosterone (DHT) decreased significantly after 3-month supplementation of soy isoflavones.

6.2.4. Receptor and Ligand Interactions (Docking):

This mechanism of action greatly participates in the complexity of an EDC action on a biological system. For example, an EDC may be an agonist at one hormone receptor but an antagonist at another. It may also act at a different range of dosages from one system to another **(Chou, 2005).** Endocrine disruptors may act as selected modulators of estrogen receptors, androgen receptors, thyroid receptors, and others **(Petersen et al., 2006)**.

a- Classic binding to specific hormone receptors:

Binding to intracellular hormone receptors was considered, for long time, the mainstay in the mechanisms involved in endocrine disruption. Many endocrine disruptors can bind to more than one type of receptor as agonist, antagonist or both **(Masuyama et al., 2005).** For example, DDT and chlordecone bind to both estrogen and progesterone receptors, while nonylphenol and metabolites of methoxychlor, bind with the same affinity to estrogen, progesterone, and androgen receptors **(Welshons et al., 2006).**

Agonist effect occurs when the hormone analogs act like the endogenous hormone where the analog receptor complex in the target cell mimics the function of the hormone–receptor complex. For instance, hydroxy metabolites of both DDT and methoxychlor bind to 17β-estradiol receptors and cause estrogenic effects **(Tiemann, 2008).** The agonist property of DES on estrogen receptors is incriminated in the detrimental effects occurring in the adult reproductive system of men and women exposed to DES in utero **(Volle et al., 2009).**

Antagonist effect occurs when an EDC compete with endogenous hormones at the receptor binding site, but elicit no cellular response. An example of estrogen antagonist is tamoxifen which binds competitively to the estrogen receptor and also alters the effectiveness of the hormone–receptor complex in regulating gene expression **(Clarke and Khosla, 2009)**. The metabolites of both vinclozolin and the organochlorine DDT (DDE) act as androgen antagonists; these metabolites block the androgen receptor causing abnormalities in male sexual development **(Jones et al., 2009 a).**

b- Receptor modulation and post binding modifications:

Endocrine disruptors may also interfere with hormone function by altering the nature of the receptors or interfering with interactions between the hormone– receptor complex, gene expression or involved cellular components. For example, TCDD and some of the PCBs act as antiestrogens by decreasing the sensitivity of ERs to estrogen. In such cases, despite adequate estrogen production, organisms respond as if in an estrogen-deficient condition **(Oenga et al., 2004).**

It has been suggested that certain compounds that can act as ligands for ERs also function through non-receptor-mediated pathways, perhaps by interactions with proteins, with which activated ER interacts. Effects of tamoxifen on calmodulin regulation have been invoked to explain some of its actions, it has also been shown to inhibit protein kinase C directly through non-ER mechanisms **(Adler et al., 2006).** Harmol, a naturally existing plant alkaloid used in herbal medicine, prevents DNA binding by the activated nuclear androgen receptor (AR), while pyrvinium, an antihelminthic, permits AR promoter binding, but interferes with assembly of a productive transcription initiation complex **(Jones et al., 2009 b).** Selective estrogen and, recently, androgen receptor modulators (SERM and SARM respectively) can act as agonist and antagonist on the same receptor type but in different tissue locations and this is most likely through modification of the steps involved in post binding gene expression **(Clarke and Khosla, 2009)**.

c- Action through uncommon receptors :

Pregnane X receptor (PXR), identified as a human nuclear receptor in 1998, is present in different tissues like liver, intestine, kidney, heart, stomach, testes and both normal & neoplastic breast cells, and generally regarded as a sensor activated by exogenous and endogenous chemicals. Following ligand binding, PXR forms a heterodimer with the **retinoid X receptor (RXR)** that binds to PXR

response elements on DNA resulting in their transcriptional activation **(Dussault et al., 2003).** Unlike other nuclear receptors such as the steroid receptors that interact selectively with their physiological ligands, PXR ligands are structurally diverse and include prescription drugs e.g. tamoxifine, doxorobicin, carbamazepin, dexamethazone, nifedipine, clotrimazole, phenytoin & phenobarbetal, herbal medicines e.g. Ginkgo biloba, dietary supplements, environmental pollutants such as pesticides, PCBs, NP & BPA and endogenous chemicals like steroids &bile acids **(Feero, 2010).**

Environmental estrogenic chemicals, as well as endogeneous estrogens, can exert rapid actions on **membrane estrogen or non estrogen receptors**, such as receptors shared by neural transmitters, dopamine, epinephrine, and norepinephrine **(Feero et al., 2010).** Bisphenol A at very low concentrations stimulated certain human testicular seminoma cell-line in vitro, this action doesn't involve classical ERs because it could not be reversed by ER antagonists nor reproduced by E2 or by DES. This activation was reproduced only by E2 coupled to bovine serum albumin (BSA), which is unable to enter the cell, i.e. through a non classical membrane G-protein coupled receptor (GPCR) **(Bouskine et al., 2009).**

Peroxisome proliferator - activated receptors (PPARs), figure 12 are a group of nuclear receptors that are distributed in adipose tissue in addition to liver, intestine and brain, they are regulators of fatty metabolism, increasing insulin sensitivity, and controlling adipocyte development, thus being involved in endocrinal homeostasis **(Waki et al., 2010)**. **PPAR-α** has been proved to be involved in modulation of both the activity of enzymes metabolizing thyroid hormone in the liver and the sensitivity to thyroid hormones by upregulating TRα-1 in response to peroxysome proliferators (PPs) like clofibrate, gemfibrozil, DBP and DEHP. This pathway adds to the metabolic and mitogenic properties of THs **(Michalik et al., 2006).** The antidiabetic drugs thiazolidinediones (TZDs) play their action through **PPARγ** receptors decreasing insulin resistance and modifying adipocyte differentiation**.** Since PPARγ is a master regulator of adipocyte development, chemicals that act through PPARγ, have been, and will continue to be a major focus of investigations into environmental obesogens. Organotins (such as tributyltin) and phthalates (such as monoethylhexylphthalate) are two classes of obesogenic compounds that target PPARγ **(Janesick and Blumberg, 2011).**

Induction of UDP-glucuronosyltransferase, an enzyme that conjugates UDP-glucuronic acid with T4 and other steroid hormones, can be achieved by TCDD and polychlorinated dibenzodioxins (PCDDs) via an **arylhydrocarbon receptor (AhR)-dependent mechanism (Boas et al., 2006).**

6.2.5. **Metabolism and Clearance (Disposal):**

a- Enzyme induction:

Nonyl phenol, DDT, BPA and similar compounds are potent inducers of cytochrome P450-dependent monooxygenases, an enzyme system that degrades endogenous androgens. These compounds, therefore, potentially have antiandrogenic activity **(Daaboub et al., 2008), also they play role in** induction of cancers in endocrine sensitive organs, such as gonads, adrenals, thyroid, prostate, and breast, due to long-term hormone imbalance as they are retained in the body, therefore causing a long-term CYP450 induction**(Ociepa-Zawal et al., 2010).** On the other hand, lindane has been reported to decrease the amount of circulating estrogen by increasing estrogen clearance **(Di Consiglio et al., 2009).**

b- Enyme inhibition:

Ketocoazole and some other members of azole fungicide derivatives are potent enyme inhibitors that result in increasesd estrogen level in plasma due to decreased metabolism **(Harvey and Johnson, 2002).**

c- Compete with endogenous hormones for the binding sites of metabolic enzymes:

Structurally similar compounds can also compete with endogenous hormones for the binding sites of metabolic enzymes and make the enzyme unavailable for normal hormone degradation. This would lead to a decreased clearance rate and prolong the half-life of circulating endogenous hormones **(Wilhelm et al., 2008).** Glycyrrhizic acid blocks cortisol metabolism in this way leading to its accumulation and subsequent stimulation of aldosterone receptor with development of hyperaldosteronism- like state **(Stokes-Riner et al., 2003).**

6.2.6. **Epigenetic mechanism and transgenerational effects:**

Effects of endocrine disruption may be manifested across multiple generations (i.e. transgenerational), but the mechanisms often do not involve an overt gene mutation. Rather, epigenetic effects of EDCs may occur whereby an action is exerted upon the genome to alter gene expression without modifying the sequence of the DNA itself **(Anway and**

Skinner, 2006). Such changes, methylation and/or histone modifications, can affect gene function and can be transmitted from generation to generation with a higher penetrance than mutations themselves. Such mechanisms of EDCs are difficult to diagnose through simple means such as DNA sequencing **(Gore et al., 2006).** The timing of exposures is transmission **(Schermelleh et al., 2005 & Fleisch et al., 2012).** crucial, because the receipt of a signal at an inappropriate developmental period may permanently influence gene expression by an epigenetic mechanism. Transgenerational effects of EDCs have been reported for up to four generations of male rats via matrilineal/patrilineal germ-line

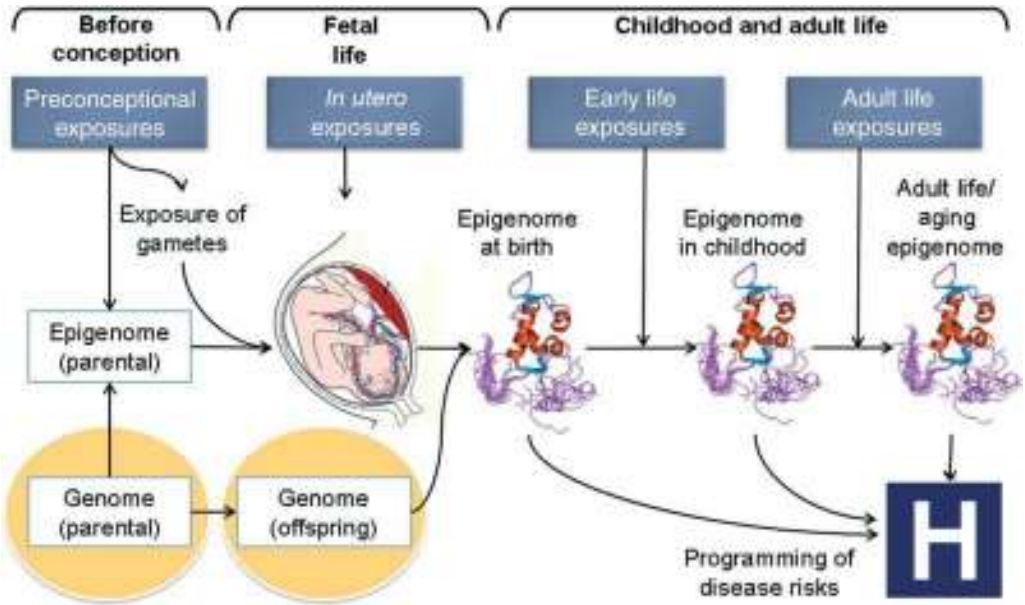

Figure (12): Exposures that occur preconceptionally, in utero, in early life and in adult life may result in epigenetic dysregulation **(Fleisch et al., 2012).**

7. CONCLUSIONS

In this review we have provided examples of the activity and actions of several different EDCs of varying chemical structure, properties, and sources. Findings from reported human cases, experimental animal studies and/or in vitro cell based assays have provided evidence of their hormonal biological actions. As expected, further observations of other types of toxicities and development of additional experimental models will be required for the evaluation of the mechanisms involved. To do so will undoubtedly require a large dataset of both genomic and non-genomic cellular responses. The effects of EDCs can vary greatly, depending upon cell, tissue, and organ type. Complications due to the potential non-monotonic nature of responses and variations in the makeup of mixtures will also require further systematic evaluation.

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الكيماويات المعطلة للغدد الصماء:الأكاذيب و الحقائق

تعتمد حياة الكائنات متعددة الخلايا إلى التنسيق بين أنسجتها وأعضائها ويقوم جهاز الغدد الصماء بهذه الوظيفة عن طريق إفرازه للهرمونات كإستجابة لمختلف التأثيرات الطبيعية والبيئية. ومن هنا فإن الإختلال الهرمونى يمكن تعريفه على انه إختلال فى تركيبه أو وظيفة هذا الجهاز نتيجة التعرض لمادة كيميائية معينة مما يؤدى إلى العديد من الاضطرابات فى وظائف الجسم بالإضافة إلى التحولات السرطانية. وبدورها فإن الكيماويات المعطلة للغدد الصماء يمكن أن نجدها فى كل مكان فى البيئة المحيطة بنا حيث يمكن التعرض لهذة الكيماويات عن طريق مصادر طبيعية كالنباتات،الأطعمة،الماء،الهواء،التربة أو مصادر صناعية كالوقود، أدوات التجميل، الأدوية، مخلفات المصانع أو المبيدات الحشرية. ومن المثير للدهشة أن التركيب الكيميائى لهذة المواد الضارة بالغدد الصماء غير ثابت وليس من الضرورى وجود شبه بينه وبين التركيب الكيميائى للهرمونات الطبيعية. وعلى هذا الأساس فانه أيضا من الصعب تقدير الأثر السلبى لأى من هذة الكيماويات بمجرد النظر الى تركيبها الكيميائى الجزيئي. إن آلية عمل الكيماويات المسببة للإختلال الهرمونى ليست معقدة فحسب بل إنها أيضا متعددة ومتشعبة، فالمادة الكيميائية الواحدة يمكنها أن تعمل على أكثر من هدف فى الغدد الصماء والهرمونات وكذلك فان الانسان لا يتعرض لمادة كيميائية واحدة فى الطبيعة بل لأكثر من مادة مختلطين بنسب متفاوتة فى الماء والهواء. و مع تنامى الإهتمام بمجال البحث فى الإختلال الهرمونى والكيماويات المعطلة للغدد الصماء ثم اكتشاف مدى تعقيد الية عمل هذة الكيماويات وطبيعة عملها والآثار الصحية السلبية الناتجة عن تعرض الإنسان لمثل هذة الكيماويات.