Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms

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ABSTRACT

Endocrine disrupting chemicals (EDC) are released into environment from different sources. They are mainly used in packaging industries, pesticides and food constituents. Clinical evidence, experimental models, and epidemiological studies suggest that EDC have major risks for human by targeting different organs and systems in the body. Multiple mechanisms are involved in targeting the normal system, through estrogen receptors, nuclear receptors and steroidal receptors activation. In this review, different methods by which xenobiotics stimulate signaling pathways and genetic mutation or DNA methylation have been discussed. These methods help to understand the results of xenobiotic action on the endocrine system. Endocrine disturbances in the human body result in breast cancer, ovarian problems, thyroid eruptions, testicular carcinoma, Alzheimer disease, schizophrenia, nerve damage and obesity. EDC characterize a wide class of compounds such as organochlorinated pesticides, industrial wastes, plastics and plasticizers, fuels and numerous other elements that exist in the environment or are in high use during daily life. The interactions and mechanism of toxicity in relation to human general health problems, especially endocrine disturbances with particular reference to reproductive problems, diabetes, and breast, testicular and ovarian cancers should be deeply investigated. There should also be a focus on public awareness of these EDC risks and their use in routine life. Therefore, the aim of this review is to summarize all evidence regarding different physiological disruptions in the body and possible involved mechanisms, to prove the association between endocrine disruptions and human diseases.

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1. Introduction

Endocrine system is a group of various glands that secrete hormones to control metabolism, growth and development in tissue, sexual and reproductive functions as well as sleep, and mood among other physiological changes. The use of synthetic chemicals by human has been increased extensively since the introduction of these chemicals. Endocrine-disrupting chemicals (EDC) are structurally diverse class of synthetic and natural compounds that possess the ability to alter various mechanisms of the endocrine system and potentially induce adverse health effects in exposed individuals and populations [1]. According to the latest report, about 800 chemicals that are being used in daily life possess endocrine disrupting properties [2]. Out of available EDC, only some of them have been examined. These chemicals are involved in many chronic diseases like cardiovascular problems, diabetes, obesity, reproductive abnormalities, thyroid problems, neoplasm and many homeostatic imbalances [3].

2. Search strategy

Data was obtained from different scientific databases such as PubMed, Google Scholar, ClinicalTrials.gov and ToxNet. The search terms were "various types of EDC" "endocrine disrupting chemicals and health effects", "reproductive system and EDC", "thyroid system and endocrine disruption", "EDC and cardiac system", "nuclear receptors and mechanism of EDC", "EDC and oxidative stress", "nervous system and endocrine toxicants", and "carcinogenicity and danger of EDC". The reference studies of animal models were also analyzed for further research and their applicability for studying different effects related to environment, food and occupational settings exposed to EDC. Effects of EDC in relation to different system, organs and sources of exposure have been explained in Table 1. Table shows different epidemiological studies conducted in different time periods with specific protocols and different doses of EDC. Full understanding of this review article will give us new direction to the future and guidance in endocrinology related toxicology.

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Table 1
List of studies whose results show association of EDC exposure and incidence of health effects.

Reference	Model	Source of exposure	Type of EDC	Duration of exposure	Concentration	Target system/organ studied	Results
Ikezuki et al. [24]	Epidemiologic	Food packaging and diet	(BPA)	15–18 weeks gestation	1–2 ng/mL	Ovarian fluids	Fetus damage
Gore [19]	Experimental	Pesticides and environment	Methoxychlor or chlorpyrifos	Acute 24 h	Methoxychlor (0, 1, 10, 100) μM, chlorpyrifos (0, 1, 10, 100) μM	Cell culture	Alteration in gonadotropin releasing hormone
Weidner et al. [21]	Epidemiologic (male)	Diet (vegetables, fruits)	Pesticides	Chronic		Testes	Cryptorchidism and Hypospadias↑
Staessen et al. [20]	Epidemiologic	Environmental and occupational	VOCs, PCBs and PAHs	Chronic		Reproductive	DNA damage and urinary dysfunctions
Hunt et al. [23]	Experimental (female)	Food packaging and diet	BPA	6–8 days	100 and 360 ng/mL	Reproductive	Mammalian oocytes failure and aneuploidy
Kelce et al. [124]	Experimental	Pesticides	DDE	4 days	100 mg/kg and 200 mg/kg	Reproductive	Testosterone ↑
Alexander et al. [31]	Epidemiologic (case control study mother–infants)	Environmental and occupational	Alcohol, benzene, cigarette and insecticides	Chronic		Leukemia	Leukemia in infants ↑
Cooper et al. [34]	Experimental (female rats)	Occupational	Atrazine	21 days chronic	50–300 mg/kg	Ovary	LH and Prolactin ↓
Wolff et al. [125]	Epidemiologic (cohort study female)	Environmental and occupational	PCB and DDE	Chronic		Breasts cancer	Breast cancer ↑
Schantz et al. [43]	Experimental	Environmental and occupational	PCBs	1 month	32 mg/kg, 16 mg/kg, 64 mg/kg, 8 mg/kg	Thyroid system	Hyper or hypo thyroid activity ↑
Hurley [47]	Experimental	Environmental and occupational	240 pesticides	Chronic		Thyroid system	10% ↑ thyroid follicle cell tumors and 12% ↑ thyroid tumors
McKinney et al. [49]	Experimental	Environmental and occupational	(PCB)	Acute		Thyroid hormones and liver	Thyroid hormones and nuclear receptors are targeted.
Darnerud et al. [50]	Experimental	Environmental	3,3′, 4,4′-tetrachlorobiphenyl (CB-77)	Chronic	1 mg/kg and 10 mg/kg	Thyroid hormones	TT4 and Ft4 ↓
Braverman et al. [126]	Epidemiologic	Occupational	Perchlorate, thiocyanate, and nitrate	Chronic		Thyroid system	4-h thyroid RAIU by 38% ↓
Hinton et al. [54]	Experimental	Food packaging and diet	Phathalic acid	Chronic		Thyroid system	Level of thyroid hormones ↓
Rousset [57]	Experimental	Food packaging and diet	Methylparaben		2.0×10^{-4} M	Thyroid system	Nonstimulated and TSH- or dibutyryl cyclic AMP-stimulated cells produced.
Lee et al. [67]	Epidemiologic	Environmental	POPs	Chronic		Diabetes	Prevalence of diabetes ↑
Alonso-Magdalena et al. [69]	Experimental (pregnant mice)	Food packaging and diet	BPA	Chronic	10 or 100 μg/kg/day	Diabetes	Insulin resistance ↑
Alonoso-Magdalena et al. [127]	Experimental	Contraceptive pills	17 beta estradiol	Chronic	10 μg/kg	Diabetes	Hyperinsulinemia ↑
Lind and Lind [75]	Epidemiologic	Food packaging and diet	BPA and phthalates	Chronic		Cardiovascular system	Atherosclerosis ↑
Kaneda and Ohmori [84]	Epidemiological (male schizophrenia patients)	Contraceptive pills	Estradiol	Chronic		Nervous system	Negative signs in male schizophrenia patients ↑
Ali et al. [98]	Experimental	Aquatic/sea food	Methyl mercury	Acute	5–40 μM 1–5 mg/kg	Nervous system	Oxidative strees in hippocampus ↑

BPA: bisphenol A; PCBs: polychlorinated biphenyls; DDE: dichlorodiphenyldichloroethylene; PAHs: polyaromatic hydrocarbons; DNA: deoxyribonucleic acid; VOCs: volatile organic compounds; POPs: persistent organic pollutants; TSH: thyroid stimulating hormone; AMP: adenosine monophosphate; TT4: tetra-iodo thyronine (thyroxin); Ft4: free T4 hormones; LH: luteinizing hormone; ↑: increase; ↓: decrease.

3. Human exposure to different types of chemical toxicants

The EDC are divided into major classes of chemicals containing various types of pesticides, industrial chemicals, plastic packaging components, fuels and other materials that are used in daily life [4,5]. The International Program on Chemical Safety (IPCS) suggests that "EDC are such exogenous substances that alter many endocrine and hormonal functions in the body, resulting in various abnormalities". Generally it can be said that EDC are substances entering into the body that affects synthesis, metabolism and excretion of hormones involved in homeostasis, and developmental processes [2]. It has been reported that from 120 indoor air and dust chemicals, 89 organic chemicals have been identified as EDC; most abundant of these are phthalates (plasticizers), o-phenyl phenols, 4-nonylphenols, and 4-tert-butylphenols [6]. Phthalates have been reported as one of the major components of food packaging materials which penetrate into the foods after leaching through packaging bags [7]. Phthalates used as polymer materials in shampoo bottles, and plastic food packaging pose high risk for human health, by targeting endocrine system [8]. Pesticides are involved in various chronic diseases like cancers, diabetes, neurodegenerative disorders, Parkinson, Alzheimer, amyotrophic lateral sclerosis (ALS), birth defects, and reproductive disorders [9,10]. The most abundant of phthalates are permethrins, and some banned pesticides like heptachlor, DDT (dichlorodiphenyltrichloroethane), and methoxychlor. These phthalates have been evidenced to cause indoor degradation of different organs in humans [6]. Even some studies support that some natural food components of animals and humans like phytoestrogens e.g. apigenin and naringenin can also behave as EDC [11,12]. In this study, damage and mechanisms involved for different organs and systems have been explained thoroughly and their impact on human health, as well as detailed understanding of different physiological systems is stated in Fig. 1.

4. Organ and systemic effects of EDC

4.1. Reproductive and developmental effects

EDC damage normal physiological reactions related to the reproductive system. In relation to this a number of in vitro and in vivo evidence are available about testicular and ovarian abnormalities [13]. EDC reduce number as well as quality of sperms, along with an increase in occurrence of testicular, prostate and breast cancer [14]. To a great
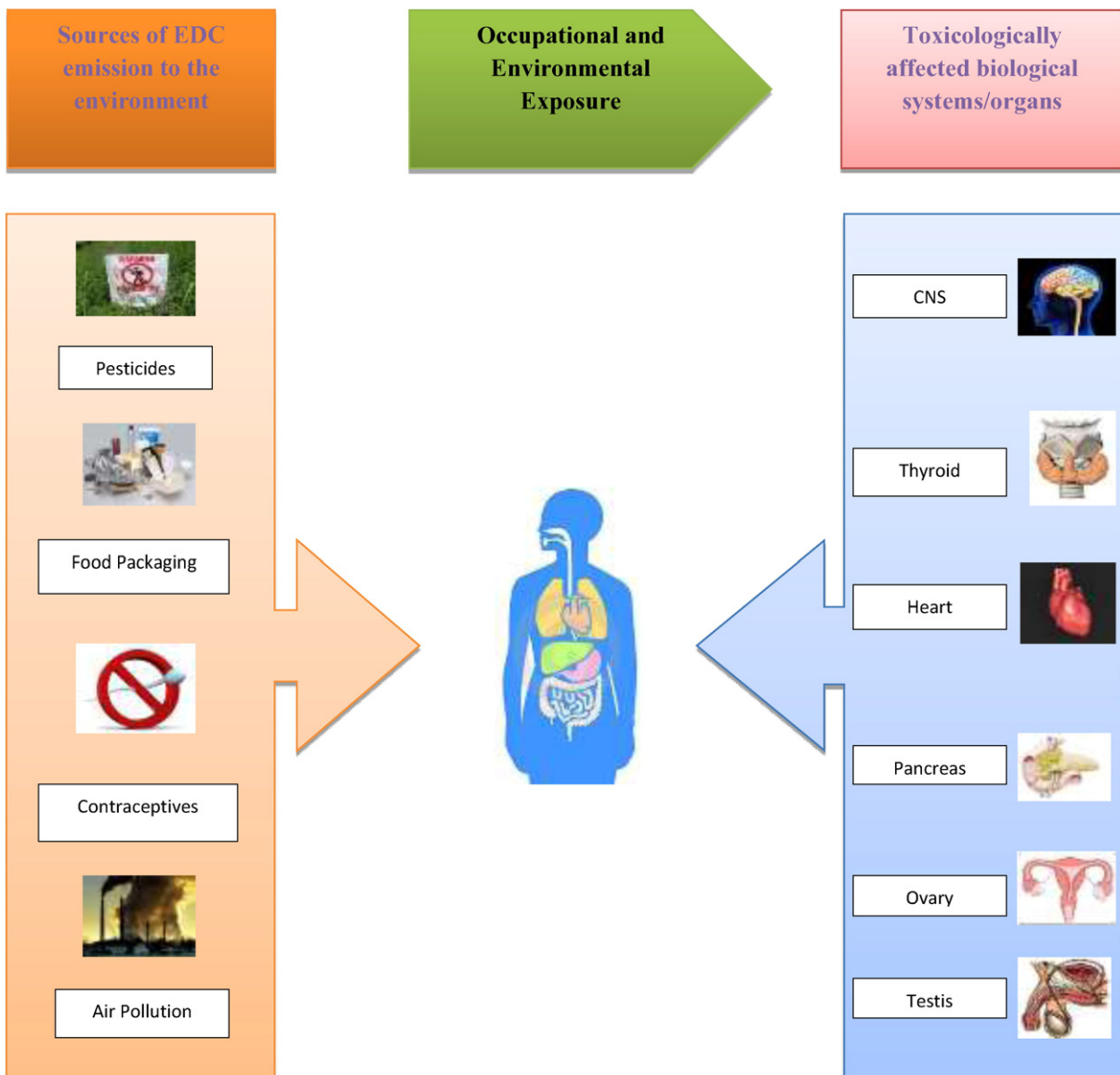

Fig. 1. Routes of EDC release to the environment and their toxic effects on human health from the viewpoint of biological systems and organs.

extent sexual defects have also been observed in the wildlife species, and for all these, environmental pollutants have been reported to play a key role [15]. Testicular dysgenesis syndrome (TDS), poor semen quality, and testicular carcinoma are main illnesses known to be associated with some environmental pollutants affecting the endocrine system [16]. Similarly, very low sperm count due to toxicity of environmental pollutants has been reported [17,18]. In the female reproductive system, diethylstilbestrol (DES) induces some morphological and functional changes [15]. In an in vitro study two organochlorine pesticides, methoxychlor and chlorpyrifos have caused alteration in the biosynthesis of gonadotropin hormone in hypothalamic GT1-7 cells [19]. So, toxicants target the whole system of hormone release in humans. In a study conducted in Belgium on 120 girls of the general population, polychlorinated biphenyls (PCBs) caused damage to developmental stages of the reproductive system [20]. There are also evidence of reproductive malfunctioning in children of pesticides exposed workers [21]. BPA (Bisphenol-A), commonly exposed EDC, leaches out from plastic packaging materials like reusable baby bottles, water carboys and other household materials. So, BPA also puts children at high danger of ED problems [22].

Accidental exposure of mice to BPA from cage and water plastic bottles causes different meiotic disturbances and aneuploidy in the oocytes [23,24]. Similarly miscarriages observed in woman are mostly because of aneuploidy [25]. Sugiura-Ogasawara et al., [26] observed that the risk of miscarriage was high in women exposed to BPA.

4.2. Carcinogenicity

After the Second World War, a large number of chemicals used as weapons have been analyzed for endocrine disrupting properties in the human body [27]. An analysis in animal studies has been conducted on about 48 EDC listed under CDC (center for disease control and prevention in the US), and the results have shown close linkage to mutagenicity, developmental effects and carcinogenicity [28]. A mathematical computerized based simulation study on animals showed that many endocrine disrupting chemicals have devastating effects like mutagenicity, thyroid gland cancer, prostate cancer and much more related to metabolic diseases and cardiovascular problems [29]. Natural or synthetic estrogens can also serve as carcinogenic and most cases of such tumors and toxicities develop during developmental stages of different organs. Maternal source proved to be main route of such toxicities [30]. A study on infants and children living in agricultural areas using household pesticides has proved an increased rate of leukemia and lymphoma [31]. Tobacco smoke, containing different constituents like alkenes, nitrosamines, aromatic and heterocyclic compounds is the main cause of lung and alveolar cancer. In addition, carbamates cause leukemia in offspring [32].

Similarly, atrazine is an extensively used pesticide for controlling the population of weeds in crops [33]. The atrazine exposure is associated with cancer of the mammary glands [34]. The American Cancer Society reported that prostate cancer cases are increasing rapidly [35]. Benign prostate hyperplasia is the major problem of prostate cancer observed in 50% of the men at age of 60 [36]. During the last fifty years, xenoesterogens have been assumed as the most probable cause for developing breast cancer [37]. It was studied that increased estrogen level during pregnancy causes breast cancer and other endocrine disruptions [2,38]. Toxaphene, DDT and other pesticides with endocrine disrupting properties have been proved to induce breast tumor.

4.3. Effect on thyroid system

Normal human physiology, metabolic control and brain developmental stages are regulated by thyroid hormones. Disruption in thyroid hormones or delayed release can cause growth, mental and metabolic disruptions and eventually brain damage [2]. Thyroid system pharmacokinetics have been studied as one of the targets for EDC, like PCB,

perchlorates, dioxins, BPA, flame retardants, pesticides, polycyclic aromatic hydrocarbons (PAHs), and phytoestrogens [39–41]. The EDC can affect the thyroid system via different ways. EDC can act as an agonist or antagonist altering the transport or pathways of thyroid hormones [42]. Organochlorines as potential EDC have been reported to reduce the level of thyroid hormones, particularly T4 in many species [43–46]. Other organochlorines like acetochlor and alachlor also cause a reduction in levels of thyroid hormones (T4) and increase in level of uridine diphosphate glucuronosyl transferase (UDPGT) [47,48]. Animal studies proved that PCBs have high affinity to thyroxin specific binding proteins, so highly damage normal physiology of thyroid hormones. This can alter the development, growth and adrenal functions of human body [49–51]. Exposure to phthalates causes damage in metabolism of thyroid hormones in neonates [52]. In rats, histopathological damages have been detected after exposure to different forms of phthalates [53–55].

Among other chemicals, parabens are the most commonly used preservatives in the foods. Some relationship has been established for potentiating estrogenic activity of parabens but no animal modeling studies are available to correlate it to thyroid toxicities [56]. Methylparaben has been evidenced for decreasing thyroid activity and a dose dependent inhibition of iodide functions was observed during in vitro studies [57]. So, there is some gap and need to be studied for parabens to link with thyroid system problems. Pesticides, like DDT and HCB (hexachlorobenzene) in addition to other EDC have shown developmental defects in thyroid hormone production. DDT decreases the thyroid hormones activity while HCB metabolize to give highly toxic compounds, targeting thyroid hormones [58]. A number of animal studies are available that support toxic effects of HCB on thyroid hormones like T3 and T4 [59]. Much more research is pending to find out the link with respect to the thyroid system.

4.4. Obesity and diabetes

Endocrine disruption is a major cause for obesity, which further links to diabetes and cardiovascular problems [60]. In hypothesis to explain obese epidemics, WHO has declared that the total number of obese patients in the world is now greater than total undernourished patients [61]. In addition to diabetes mellitus type 2 and cardiac arrest hypertension, dyslipidemia, insulin resistance and hyperinsulinemia are main metabolic disorders caused by obesity, which require novel drug approaches to avoid high mortality rate [62]. In animal modeling studies, significant rise in the weight of mice has been observed, when DES a pharmaceutical chemical was administered to neonatal mice. In addition to increase of abdominal body fats, inflammatory biomarkers were also raised in DES exposed animals [63].

Estrogenic receptors (ERα; estrogen receptors alpha) and ERβ (estrogen receptors beta) are the key parameters involved in glucose metabolism. Estradiol (E2) and environmental pollutants BPA, dioxins and pesticides are analogous to each other in targeting these receptors [64]. The EDC attack such receptors to evoke changes of glucose homeostasis and insulin release mechanism [65]. So any natural or environmental chemical attacking these receptors can damage the normal physiology of glucose homeostasis and can damage the cells of pancreas, giving a clear clue for occurrence of diabetes [66]. A study of Persistent Organic Pollutants (POPs), reveals that a close linkage between diabetes, obesity and such chemicals does exist in nature. So there are increased chances of diabetic incidence for human living in such an environment, having high concentration of environmental pollutants [67]. Epidemiological studies established a link between dioxins like compounds and diabetes, as different cases of diabetes and glucose homeostasis changes have been reported for susceptible populations in exposure to dioxins [68]. At very low doses, BPA causes hyperinsulinemia linking to type 2 diabetes mellitus and obesity [69]. Glucagon is one of the main hormones produced by α-cells of the pancreas and control glucose metabolism. Even low doses of BPA and DES have been indicated to damage

α-cells and glucagon pathway [70]. Some of EDC like pesticides, BPA, and dioxins that are slowly released from adipose tissues, after excessive accumulation disturb glucose homeostasis. Normally they cause hyperinsulinemia similar to the metabolic state seen during pregnancy. These hyperestrogenic concentrations ultimately lead to diabetes and obese condition [71].

4.5. Effect on cardiovascular system

In addition to obesity and diabetes, endocrine disruption also plays a pivotal role in cardiovascular problems [72]. Animal studies have proved a link between exposure of DES and cardiovascular problems [60]. Obesity caused by EDC has been evidenced to induce a number of coronary heart diseases proceeding toward stroke and blood pressure problems [73,74]. BPA and phthalates in cross-sectional study have proved a strong relation to endocrine disruptive mechanisms and cardiovascular injuries and seem to be involved in destroying both carotid arteries [75]. Cardiovascular and diabetic problems created by such endocrine disruption can lead to metabolic syndromes that can ultimately increase mortality rate [76,77].

High concentrations of persistent organic polymers have also been associated with increased rates of coronary heart disease [78–80]. Many man-made and natural substances like plastic bottles, dioxins like compounds, pesticides and pharmaceuticals are associated with hormonal imbalances, which are further involved with disturbed state of cardiac markers physiology [81]. WHO limitations for each component for making packagings and other daily used products are needed to be followed in order to favor human health and reduce cardiac risks.

4.6. Effect on nervous system

Many endocrine disrupting chemicals like herbicides and POP have an influence on the nervous system through various receptors, changing morphology and behavioral response. Some critical developmental stages like intrauterine, perinatal and puberty periods have very serious drawbacks as a result of EDC exposure [82]. In animal studies, BPA has shown a close association with schizophrenia and other neurotoxicological pathology. Neurotoxic problems are associated with abruptions in different pathways like physical development of organs, cellular anatomy, hormone, neurotransmitters and behavioral response [83]. Estrogen has been thought to have neuroprotective effects, but lower levels of estrogens may cause schizophrenia-like symptoms in both males and females [84–87]. Disturbed estrogenic functions may also lead to mutated genetic makeup. This could further lead to diseases such as Turner's syndrome and Klinefelter's syndrome which are contributing toward schizophrenia [88]. Genetic studies clearly give evidence of psychotic disorders due to Klinefelter's syndrome [89].

Neural disorders have also been linked with hypothalamic–pituitary–adrenal (HPA) axis. Animal studies show the effect of increased glucocorticoid concentrations on hippocampal nerve damage. In case of stress, elevated glucocorticoid levels exert change in HPA axis causing schizophrenia [90]. An altered concentration of corticosterone in animal studies has also been reported to exert change in the HPA axis, ultimately raising more chances of schizophrenia [91,92]. EDC directly target many neuro-steroids like allopregnenolone that regulate mechanism evoking psychiatric disorders. In addition to this, these steroids also effect brain regions causing schizophrenia and bipolar disorders. Altered levels of steroids are directly linked with changing estrogen levels in the body, but BPA apart from schizophrenia, also seem to be involved in the other brain disorders like attention deficit hyperactivity disorder (ADHD) [93,94].

Neural, behavioral and bipolar disorders have also been observed in infants, children and neonates due to exposure to BPA, that target different hormonal pathways [83]. Astrocytes, most often reported target for BPA, also lead to schizophrenia. Animal modeling studies interlink an increased concentrations of leukemia inhibitory factor (LIF) with schizophrenia. Higher level of LIF is involved in decreasing motor activity, similar to the abnormal physiology of autoimmune disease Alzheimer's disease and schizophrenia [95–97]. Likewise, methyl mercury an organic form of mercury has proved increase in oxidative stress of hippocampus in brain, thus causing neural problems in exposed animals [98]. Some PCB have shown a damaging effect during developmental stages. Contrary to this, aroclor1221 has shown positive effects on estrogen receptors in rats during analysis of sexually dimorphic brain circuits [99]. So, there is a need to critically evaluate different EDC and their toxicological profiles as some may be less harmful for humans. As other EDC like 2,3,8-tetrachlorodibenzo-p-dioxin (TCDD) have been reported to possess large effects on brain after administration in animals. In female rats, damaged myelin layer has been observed with single dose of 700 ng/kg at 18 gestational days [100–102]. Such evidence urge to do more clinical trials in order to get rid of endocrine toxicity related problems.

5. Mechanisms involved in chemicals induced endocrine disruption

EDC effect the normal human physiology in a number of ways. These may be genomic or non-genomic, via a receptor linked or a non-receptor linked pathway. The disruptions are caused by a similar mechanism as the estrogens and androgens produced naturally in the body, either through mimicking or opposing actions. Here different mechanisms for endocrine disruptions have been described [103].

5.1. Oxidative stress

It has been recently published that oxidative stress due to reactive oxygen species and free radical formation is a major cause for the occurrence of many diseases [104]. Some evidence have clearly described that not only human beings, but also the wildlife is in danger of EDC [105]. Production of reactive oxygen species (ROS) due to endocrine disruption leads to damaged DNA, protein and lipid production in the cell (Fig. 2).

EDC: endocrine disrupting chemicals; DES: diethylstilbestrol; BPA: bisphenol A; PCBs: polychlorinated biphenyls; ROS: reactive oxygen species; DNA: deoxyribonucleic acid.

5.2. Endocrine disruption by targeting metabolism of steroid hormones

Enzymes involved in the biosynthesis of steroids are ideal targets for EDC. Damage to normal physiology can cause cancer, reproductive problems, nervous disorders and growth abnormalities [106]. Cytochrome P450 (CYP450) has a fundamental role in steroid hormone biosynthesis regulated by different organs like, adrenal gland, testis, ovary, brain, placenta and adipose tissues. Organotin compounds widely used in paint, agriculture and industries have been evidenced to inhibit the activity of CYP450 and CYP1A1 and aromatase in fish [107]. All these lead to endocrine disruptive effects like "imposex (penis development in females)" by inhibition of aromatase in females [108].

Some derivatives of DDT like DDD (1,1-dichloro-2,2-bis(p-chlorophenyl)ethane), mitotane; 1-chloro-2-(2,2-dichloro-1-(4-chlorophenyl)-ethyl)-benzene have been reported to be adrenotoxic in dogs [109]. It is recently published that benzene is involved in many non-cancerous health effects like reproductive, immune, nervous, endocrine, and cardiovascular system problems [110]. In another study MeSO$_2$-DDE (methylsulfonyl-DDE) has shown adrenotoxic effects through inhibition of P450c11-mediated functions in adrenocortical cell lines Y1 and Kin-8 [111]. So toxicity of such daily used chemicals cannot be avoided, we need to take serious measurements. It has also been reported that PCB (polychlorinated biphenyls) and many methyl sulfonated metabolites of PCB inhibit CYP11B1 in Y-1 mouse originated adrenocortical cells [112]. For clear understanding its mechanism is explained in Fig. 3.
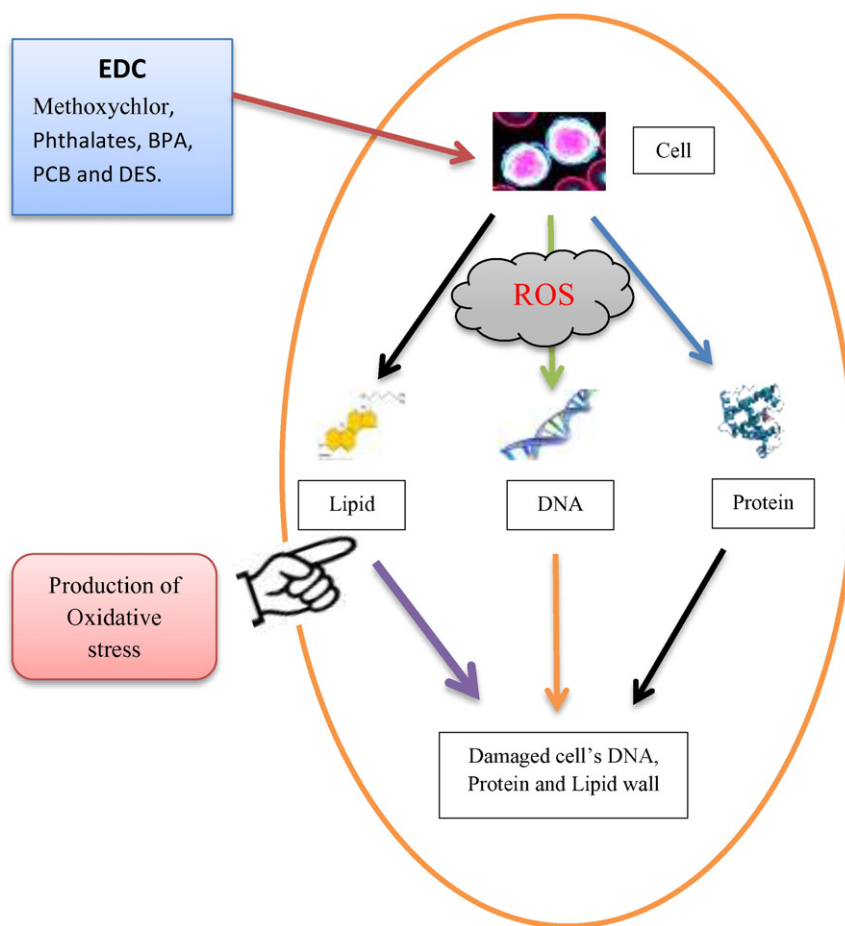
Fig. 2. Mechanism of action of endocrine disrupting chemicals through production of oxidative stress.

CYP 450: cytochrome 450; CYP 198: cytochrome 198; EDC: endocrine disrupting chemicals; P-160: protein-160; P-220: protein-220; P-205: protein-205/peroximal proliferator-activated receptor.

5.3. Endocrine disruption by targeting nuclear receptors

Nuclear receptors are actually ligand-inducible transcription factors that modulate the expression of specific genes involved in metabolism, differentiation and sexual functions. More than 100 nuclear receptors are present, which regulate the response in target cells to hormones such as sex steroids, adrenal steroids, vitamin D_3, thyroid and retinoid hormones. Natural or synthetic ligands have been known to stimulate the actions of nuclear receptors called co-activators [113]. Co-activators include p160 family with intrinsic histone acetyl transferase activity [114], thyroid hormone receptor activator protein 220, vitamin D receptor-interacting protein 205/peroximal proliferator-activated receptor [14] and binding protein lacking intrinsic histone acetyl transferase activity [115]. An increase in transcriptional activity of nuclear receptors has been observed in SERM (selective estrogen-receptor modulator) treated cells. Blockage of SRC (steroid receptor co-activator) family coactivators and CBP (CREB binding protein) has also been evidenced in proteasome mediated protein degradation. This happens due to alteration of gene expressions and inhibition of co-activators activity. In SERM treated mouse cells, response to 4HT and raloxifene shows broad biological actions of ligands, influencing transcriptional activity of nuclear receptors [116].

It has been reported that under the influence of high fat and high calorie diet, nuclear receptors become activated by organotins that can stimulate adipocyte differentiation and predisposition progressing toward obesity [117]. Exposure of humans to organotins is mostly observed through polluted food sources (seafood and shellfish), fungicides from crops, and contaminated water from textile industries [118]. Other than organotins, BPA and phthalates have also been evidenced for stimulating nuclear hormones and nuclear receptor's linked pathways resulting in metabolic syndrome [119].

5.4. Endocrine disrupters as hormone sensitizers

Hormones are involved in stimulating and catalyzing a series of biological reactions in the human body. EDC have been reported to affect every stage of hormone production cycle [120]. Exposure to xenobiotics has been observed to cause disturbance in the hormone conduction pathways. Many chemicals like PCB, dioxins and furans have been evidenced to cause thyroid stimulatory actions in the treated animal while flame retardants cause reduction of thyroid hormone levels in treated rodents. Phthalates have also been seen to induce the stimulatory actions of TH (thyroid hormones) in opposition to some other chemicals [40]. In case of short chain fatty acids, valproic acid and MAA (methoxyacetic acid), by action of EDC, mainly inhibition of histone deacetylases as well as stimulation of the protein kinases have been observed. Both of these exaggerate hormonal functions and signaling pathways (Fig. 3) [121].

Oral contraceptives and postmenopausal hormone replacement therapies are main causes of increasing hormonal disturbances. In the US, it has been reported that among 200 top prescriptions, valproic acid and EGME/MAA (ethylene glycol monomethyl ether/methoxy acetic acid) have high EDC properties [122]. MAA (methoxy acetic acid) administration in rats has shown hormonal disturbing mechanism like estrogens. They target estrogen receptor beta (ERb) and P450 aromatase and thus increases risk of testis cancer [123].
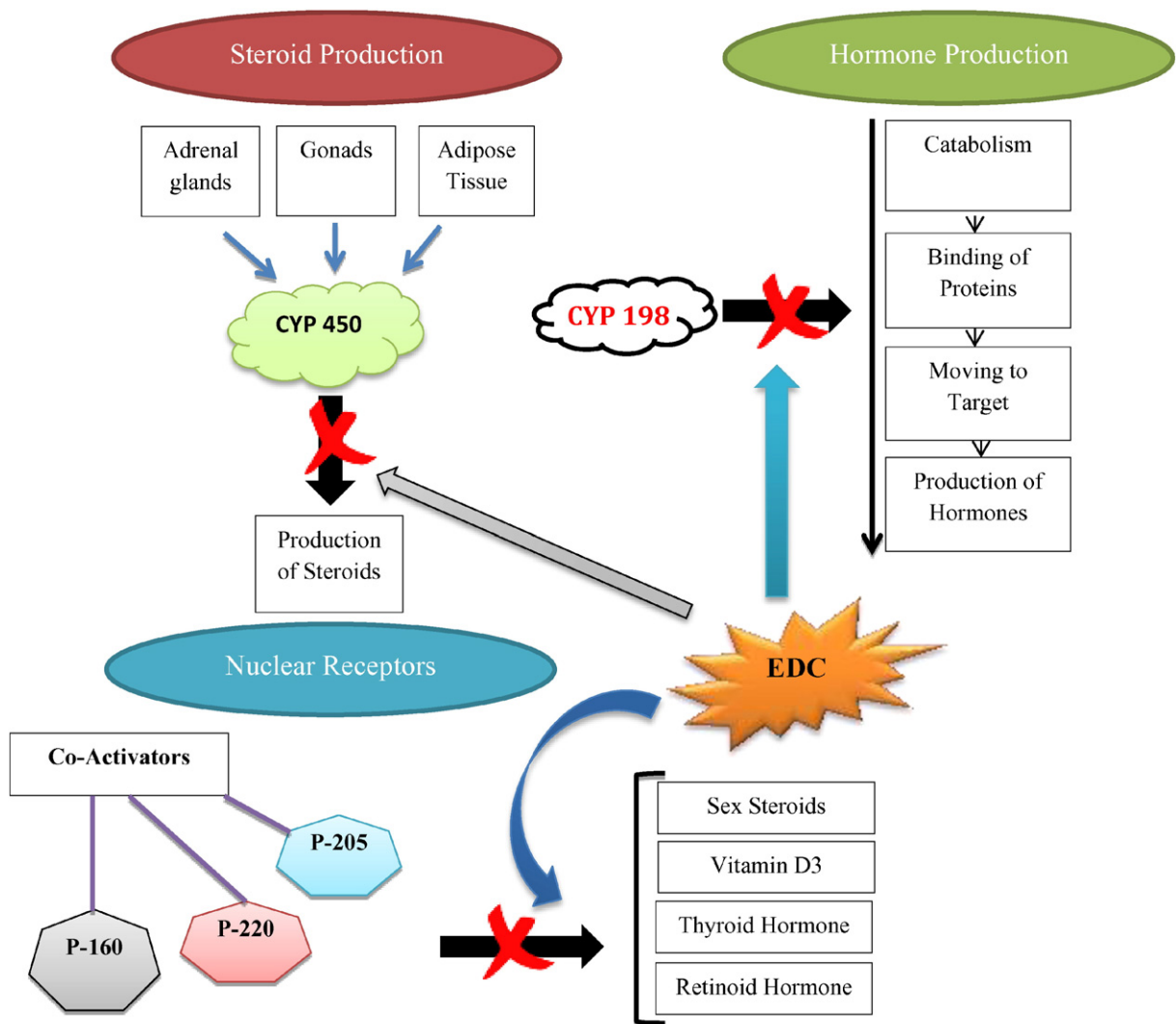
Fig. 3. Mechanism of action of endocrine disrupting chemicals at different hormonal and receptor level.

6. Conclusion

It is evident from the above gathered evidence that whole human physiology has been recognized as a target for EDC. Some risk factors for endocrine disruptions are seriously fatal for life. Humans as well as animals are at greater risk of environmental toxicants especially through inhalational exposure. EDC have damaging effects on central nervous system, the thyroid system, reproduction, and also have carcinogenic effects on different organs and system in the body. Luteinizing hormones, testosterone, ovarian fluids and some other endocrine hormones are main targets of endocrine disruptions in the reproductive system as well as carcinogenicity of reproductive organs. Nervous system disorders are nominated as a major target of endocrine disruptions, particularly targeting hippocampus and hypothalamus of the brain; giving dangerous outcomes like schizophrenia, and bipolar disorders. EDC mediate different interruptions in systems and organs via multiple mechanisms, either targeting steroid hormones or nuclear receptors which behave as hormone sensitizers. A number of endocrine disruptors, in routine life, like POP, pesticides, PAH (polyaromatic hydrocarbons), VOC (volatile organic compounds), plastic polymers, food additives, and preservatives have to be studied in more detail, to find a link between different biological systems, disorders and toxicants. Receptors that are linked to biological pathway disruptions, hormonal imbalances, and endocrine disruptions are needed to be disclosed. Studies on EDC compounds illustrate that these can function through receptor-mediated and/or non-receptor-mediated pathways to effect endocrine system. Most complicated and sometimes intermixed mechanisms of action of EDC, linked with the physical and chemical variation between members of the EDC group, propose that, there is possibility of several additional mechanisms that have yet to be elucidated. In addition, more progress in this field will depend on the expansion of modern laboratory techniques and experimental models that account for the diversity as well as novelty. However, the aim of the study has become so meaningful and enough to understand the risk factors of endocrine disruption for the global environment. Apart from these, there is a need to find safe measures to get rid of EDC in daily life.

Authors' contribution

FM searched, criticized, and drafted the whole manuscript. SM helped in review design and evaluating papers related to study. HB helped in collecting data related to mechanism of actions of endocrine disruptors and rearranging the study. MA conceived whole study and edited the manuscript for final form.

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