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Review

A review on endocrine disruptors and their possible impacts on human health

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ABSTRACT

Endocrine disruption is a named field of research which has been very active for over 10 years, although the effects of endocrine disruptors in wildlife have been studied mainly in vast since the 1940s. A large number of chemicals have been identified as endocrine disruptors and humans can be exposed to them either due to their occupations or through dietary and environmental exposure (water, soil and air). Endocrine disrupting chemicals are compounds that alter the normal functioning of the endocrine system of both humans and wildlife. In order to understand the vulnerability and risk factors of people due to endocrine disruptors as well as the remedies for these, methods need to be developed in order to predict effects on populations and communities from the knowledge of effects on individuals. For several years there have been a growing interest on the mechanism and effect of endocrine disruptors and their relation with environment and human health effect. This paper, based on extensive literature survey, briefly studies the progress mainly in human to provide information concerning causative substances, mechanism of action, ubiquity of effects and important issues related to endocrine disruptors. It also reviews the current knowledge of the potential impacts of endocrine disruptors on human health so that the effects can be known and remedies applied for the problem as soon as possible.

Contents

Abbreviations: APE, alkylphenol ethoxylate; AR, androgen receptor; BaP, benzo[a]pyrene; BFR, brominated flame retardants; BPA-bisphenol A, (BPA); CD36, cluster of differentiation 36; CNS, central nervous system; DBP, di-n-butyl phthalate; DDD, 1,1-dichloro-2,2-di(chlorophenyl)ethane; DDT, 1,1,1-trichloro-2,2-di(chlorophenyl)ethane; DEHP, di(2-ethylhexyl) phthalate; DES, diethylstilbestrol; DIDP, diisodecyl phthalate; DNA, deoxyribonucleic acid; DNHP, di-n-hexyl phthalate; DnOP, di-n-octyl phthalate; ED, endocrine disruptor; EDC-, endocrine disrupting chemicals; ER, estrogen receptor; EPA, U.S. Environmental Protection Agency; FD&C, federal food drug and cosmetic act; FFA, free fatty acid; HBCDD, hexabromocyclododecane; HCB, hexachlorobenzene; IL-1β, interleukin 1 beta; IL-10, interleukin 10; IRS-1, insulin receptor substrate 1; NAT, N-acetyltransferase; NIEHS, National Institute of Environmental Health Sciences; NIS, sodium/iodide symporter; NP, nonylphenol; MFO, mixed functional oxidase; PAH, polycyclic aromatic hydrocarbon; PBB, polybrominated biphenyls; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated bisphenols; PCDF, polychlorinated dibenzofuran; PCOS, polycystic ovary syndrome; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonate; POP, persistent organic pollutant; PPAR, peroxisome proliferator activated receptor; PTU, 6-propyl-2-thiouracil; STP, sewage treatment plant; T3, triiodothyronine; T4, thyroxine; TCDD, tetrachlorodibenzo-p-dioxin; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TPO, thyroperoxidase; TR, thyroid receptor; TSH, thyroid stimulating hormone; WHO, World Health Organization; UNEP, United Nations Environment Programme.

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1. Introduction

1.1. What are endocrine disruptors?

An endocrine-disrupting compound has been defined by the U.S. Environmental Protection Agency (EPA) as 'an agent that interferes with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development and/or behaviour' (Kavlock et al., 1996). Simplified, this means that endocrine disruptors are chemicals, or chemical mixtures, that interfere with normal hormone function.

EDCs are highly heterogeneous (Blumberg, 2009; Grun, 2010) and can be classified in the following two ways.

A. They can be classified in two categories (Diamanti-Kandarakis et al., 2009):
   (i) Those that occur naturally.
      • Natural chemicals found in human and animal food (e.g. phytoestrogen: genistein and coumestrol) and
   (ii) Those that are synthesized. These can be further grouped as follows:
      • Synthetic chemicals used as industrial solvents or lubricants and their byproducts (e.g. polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dioxins)
      • Plastics (e.g. bisphenol A (BPA))
      • Plasticizers
      • Pesticides (e.g. dichlorodiphenyltrichloroethane (DDT))
      • Fungicide (e.g. vinclozolin) and
      • Some pharmaceutical agents (e.g. diethylstilbestrol (DES)).
B. The EDCs can also be grouped according to their origins (Caliman and Gavrilescu, 2009):
   (i) Natural and artificial hormones (e.g. fitoestrogens, 3-omega fatty acids, contraceptive pills and thyroid medicines).
   (ii) Drugs with hormonal side effects (e.g.naproxen, metoprolol and clofibrate).
   (iii) Industrial and household chemicals (e.g.phthalates, alkylphenoletoxilate detergents, fire retardants, plasticizers, solvents, 1,4-dichloro-benzene and polychlorinated bis-phenols (PCBs).
   (iv) Side products of industrial and household processes (e.g., polycyclic aromatic hydrocarbons (PAHs), dioxins, pentachlorobenzene).

However, from different observations, endocrine disruptors can also be categorized into three groups apart from the classification based on occurrence according to Gore, et al.

(i) *Pesticides*: Pesticides are usually designed in such a way so that they can be highly sensitive toward the reproductive and neural systems of the organisms. But the similarity of these processes with normal human physiological system indicates that these chemicals can also affect normal human body. The pesticides that are used commonly include DDT and chlorpyrifos (Gore et al., 2014).

DDT has a long history as an endocrine disruptor. The compound was once used randomly as a pesticide in the agricultural sectors, in production of crops and livestock, in household, gardens, public places and institutions, but because of its hazardous nature it was banned few years back. However, the compound is still in use in some countries. DDT can interfere with thyroid, estrogen, androgen, rennin-angiotensin, insulin and neuroendocrine systems which can directly influence the reproductive, cardiovascular and metabolic systems of human body. These have obviously made it one of the most potential candidates of endocrine disruptors (Gore et al., 2014).

Organophosphorus pesticides are the most commonly used insect killer and chloropyrifos is a unique example of this class of insecticides. The insecticide is used in both in household and agriculture sectors to control pests such as cockroaches, flies, termites, fire ants, mosquitoes. However, it is confirmed from studies that the compound is highly toxic since it has a huge effect on nervous systems (Gore et al., 2014).

(ii) *Chemicals in products*: EDC is present in the products that we use in our day to day life, starting from the products that include children products, electronics, personal care products, textile/clothing to building contact materials. However, in most of the cases, we are not aware of these facts since it is not always included in their chemical compound list. This is a matter of concern since there is a huge possibility of these chemicals to be released into the environment and come in contact with us. Also in the children's product where EDCs are mainly found, it is always seen that the children might pick up those products and put them into their mouth. Apart from these, EDCs are frequently found in personal care products starting from toothpaste, the products that we apply on our skin, soaps, in which antimicrobial agents are used. However for ease of understanding we may subclass this class into two groups: children's product and electronics (Gore et al., 2014).

Lead is a natural compound and is being regularly used in mining, smelting, refining, leaded petrol (gasoline), lead-acid batteries, paints, jewellery, children's products and in many other products. The children are the potential candidates of lead poisoning, since the amount they ingest per unit body weight is obviously higher, they may ingest high quantity of them and also they do not have a fully developed blood-brain

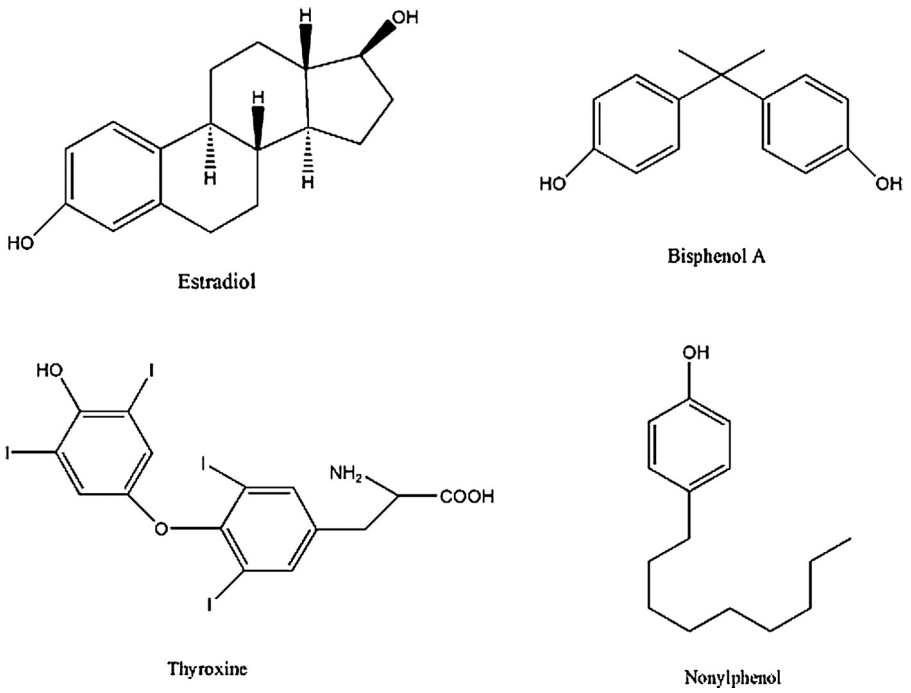


Fig. 1. Structures of some endocrine disruptors (Kidd et al., 2012).

barrier. This should be seriously considered as neurological effects are always higher in children when it is compared to adults (Gore et al., 2014).

Brominated flame retardants (BFR) are now being widely used in different products that we use regular in our daily life. These products may range from computers, electronics and electronical equipment, textiles, foam furniture, insulating foams and other building materials. The product is selected as a potential source of endocrine disruptors, since the compound is not bound to the products, and as a result they are easily released into the environment. However, although the compound has been prohibited in many countries, it is still being considered as a vulnerable source, since high half life of the compound makes it to persist in the environment for longer period of time (Gore et al., 2014).

(iii) *Food contact materials*: Bisphenol A was once used frequently in plastic based containers, and also in the epoxy based lining of canned food. However, because of the hazardous effects on human being, the compound is no longer used in baby bottles. The compound is still found in use in many containers, especially in epoxy based lining canned foods which are used for soups, vegetables etc. The lining is used to give protection from pathogens. But since it is in direct contact with the food, they may find their way into food and finally into human being (Gore et al., 2014). Table 1 lists some common EDCs and their uses.

Table 1
Common EDCs and their uses (Gore et al., 2014; Dodson et al., 2012).

Common EDCs used in our daily life	Uses
DDT, chlorpyrifos, atrazine, 2,4-dichlorophenoxyacetic acid, glyphosate	Pesticides
Lead, phthalates, cadmium	Children's products
BPA, phthalates, phenol	Food contact materials
Brominate flame retardants, PCBs	Electronics and building materials
Phthalates	Personal care products, medical tubing
Triclosan	Antibacterials
Perfluorochemicals	Textiles, clothing
Parabens, phthalates, glycol ethers, fragrances, cyclosiloxanes	Cosmetics, personal care products, cleaners
Tributylin	Antifoulants used to paint the bottom of the ship
Nonylphenol (alkylphenols)	Surfactants-certain kinds of detergents used for removing oil and their metabolites
Ethinyl estradiol (Synthetic steroid)	Contraceptive

Considering the structural features of EDC, it is very difficult to establish a relationship between them. This is because of the diverse mechanism of action of EDC in the human body. Additionally, sometimes, it is the metabolites of EDC that is more hazardous than the parent compound itself. Although, there are some structural features that are indicative of endocrine disruption, it is also generally not possible to determine whether a compound is an EDC based on its structure. From different observations, as seen in Fig. 1, that a phenolic ring with no halogens, sulphone functional groups, chlorine and bromine substitution next to OH group in phenolic ring is required for EDC activity (Kidd et al., 2012). Some of the common structures of EDC are given below:

1.2. History of endocrine disruption

Interest in the public health effects of endocrine disrupting chemicals with regard to the effects of long-term low-dose exposures is increasing (Veerasingam and Ali, 2013). The study of endocrine disruption began with the famous meeting at the Wingspread Conference Center, Racine, Wisconsin in July 1991 organized by Theo Colborn and coworkers (Colborn and Clement, 1992). Even though there is a misconception among the people regarding EDC, there is no doubt about the current interest in this subject area as a named research field that dates from that time. Using the search term 'endocrine disruptor' with science citation index (ISI Web of Science) in May 2002, it was found that about 1346

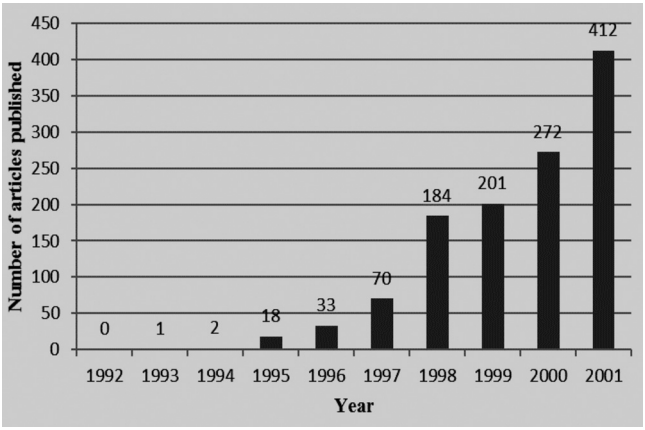


Fig. 2. Numbers of annually published scientific articles those refer to endocrine disruption (Matthiessen, 2003).

research articles were published and the first paper being Colborn and Clement (1992) (Colborn et al., 1993). Fig. 2 shows how the field has evolved since then in terms of published works, considering that many relevant articles do not contain endocrine disruption in their titles, abstracts, or keywords.

In reality, the study of endocrine disruption has been in progress for much more than 20 years, although the full range of early work is not represented in Colborn and Clement (Colborn, Theo, Coralie, 1992). Theo Colborn's major achievement in 1991 was to pull together information from very disparate fields of study (including both wildlife and humans) and come up with a new paradigm of toxicant action, but research in fields that would now be labeled as endocrine disruption had in fact been published since the 1940s and 1950s. The use of steroidal compounds in the livestock industry for the improvement of the reproductive and growth system began in the 1940s. Additionally steroidal compounds like ethinyl estradiol, mestranol, norethynodrel, and megestrol acetate were also being used in human beings as contraceptives and to treat diseases. With the advancement of these developments, investigations regarding the harmful effect of these compounds also started to take place at the same time. One such example is diethylstilbestrol, which was being prescribed for preventing miscarriage and premature births. However, in 1971, the compound was then advised by the Food and Drug Administration (FDA) to stop being prescribed, mainly because of the increased incidence of clear-cell carcinoma, a rare vaginal cancer was found in many women who had used them (Marty et al., 2011).

Endocrine disruption is sometimes dismissed as an issue of primarily academic interest (or even self-interest), with little if any relevance for real ecosystems. This follows in a long tradition employed by critics with various dimensions to grind either deliberately or accidentally overlook the abundance or significance of evidence for particular phenomena. The present study, therefore, takes an attempt to concise information that shows endocrine disruption is a common mechanism whereby a range of pollutants causes harmful effects in human, as well as in wildlife and to the environment.

1.3. Role of EDC in the environment

As mentioned earlier, we are surrounded by a wide range of endocrine disrupting chemical in our daily life. It is observed from different studies that endocrine disruptors are present in the air that we breathe, the water that we drink and even in the soil in which our food is cultivated. One class of endocrine disruptors, neuroendocrine disruptors, recognized as environmental pollutants are found to mimic/antagonize or modulate the synthesis and metabolism of neuropeptides, neurotransmitters or neurohormones (Cristina et al., 2012). These finally result in the several diverse modifications of physiological, behavioral or hormonal processes of animal body, the modifications might include altered reproduction, development, ability to deal with challenges and many other abnormalities (Cristina et al., 2012).

Endocrine disruptors are known to mainly work by altering hormonal and homeostatic system of living system. These systems are of primary importance since they are involved in the regulation of several significant processes like metabolism, sexual development, insulin production and utilization, growth, stress response, gender behavior, reproduction and even in the fetal development of living body. This is also seen in wild lives. Below are two experimental studies (prenatal and postnatal) conducted on mice gives an idea about the harmful effects that may have EDCs on animal bodies:

- *Study-1*: Prenatal exposure of BPA on mice had shown the following effects on offsprings: accelerated puberty, increased body weight, altered mammary gland, altered female genital tract, altered structure and function of the ventral prostate in male mice (Somm et al., 2009).
- *Study-2*: Studies were also conducted on perinatal subjects by BPA exposure from which following observations were reported: decreased fertility and fecundity, masculization of behaviors and brain structures in female mice CD-1 and decreased fertility in male offspring (Nicolas et al., 2013).

There are a number of evidences all of which have indicated that endocrine disruptors are also responsible for different wildlife crisis. However, wildlife is not exposed to single contaminants, but is exposed to a complex mixture of endocrine disruptors. The exposure route of wild lives to endocrine disruptors is also very critical and crucial. This is because many of the endocrine disruptors do not persist in environment and organism. At the same time there is a huge number of chemicals which persists in their food and habitat. Although it largely depends on the properties and persistent nature of endocrine disruptors, wild lives are normally exposed to them by air, water, food, soil and sedimentation. Many of the endocrine disruptors are degraded in the environment for example by sunlight, bacteria and chemical processes, while other persists in the environment in different time range. The organism may follow the same uptake route as the human like ingestion or by absorption through skin (Kidd et al., 2012).

For better understanding of the exposure level of endocrine disruptors to wildlife, studies were conducted both on polar bears and fishes as examples of remote and localized places respectively. High level of exposure to EDC is often expected to be for fishes because of their existence near the localized area. The water source as well as the low level land is continuously being exposed to EDCs due to sewage treatment process, urban and agricultural runoff and industrial run off. Moreover, exposure can occur from oil tankers, ships, fuel extraction processes, oil splits and from many other sources. Although EDC cannot persist in water for longer periods of time, regular disposal of these chemicals into water make the aquatic wildlife to be in contact with endocrine disruptors continuously. However, in spite of being in remote places, highest levels of PFOS, PCBs and organochlorine pesticides were also detected in the polar bears which may be due to the long distance transport of these chemicals into those areas (Kidd et al., 2012). Table 2 is a list of the common EDCs that are found in animal tissues.

However for the animal lives, three sources can be considered as the potential sources of exposure. Primary source of exposure can be thought to be the water source. Some endocrine disruptors are found to be highly soluble in water and might be present in water from the level of parts per trillion to parts per billion. From this water source, fish take up these contaminants through their

Table 2
Common EDCs that are found in animal tissues (Kidd et al., 2012).

Common EDCs	Exposed wildlife
Benzotriazole, UV stabilizers, parabens, triclosan, organophosphorus.	In tissues of wildlife living near sewage treatment works outfalls.
Triclosan.	Aquatic organisms that include algae, invertebrates, fish and dolphins.
Pharmaceuticals like antiepileptic carbamazepine and the active ingredients of several antidepressants (fluoxetine, sertraline, venlafaxine, citalopram, norfluoxetine, diphenhydramine, diltiazem).	In muscle or liver of wild fish or fish caged downstream of wastewater outfalls.
Human contraceptives (EE2 and levonorgestrel).	In fish muscle and plasma.

gills, wild birds and mammals may take up these contaminants through drinking water. Again, some EDCs are found to be bound with the soil and sediments, from which EDCs can concentrate on the organisms and finally get into the complex food web. Apart from these, endocrine disruptors have high affinity for fats. As a result they are found to be concentrated in organisms and because of the complex food web they finally reach into high level animal bodies (Kidd et al., 2012).

After being exposed, EDCs travel across the body and go through metabolic and elimination processes. Since some of the EDCs have strong affinities toward fat tissues, they get accumulated into them from where they are eliminated from the body by taking variety of routes. For example, they can be end in eggs which are laid by fishes and birds exposed to EDCs. This property also makes the EDC to be eliminated from the body through lactation and pass into the offspring. However, in the animal body liver is the main site of their metabolism, after which they are eliminated through urine and feces (Kidd et al., 2012).

Various analyses have been done in the previous years to understand the effects of EDCs on wild lives. These analyses have provided a strong link between these chemicals and their effects. However, because of the shorter half-lives of some EDCs, the tasks were sometimes difficult to be performed. The chemicals that were intensively studied in wildlife included the Persistent Organic Pollutants (POPs) which include DDT, chlordanes, dieldrin, PCBs, dioxins, PBDEs etc. These observations of EDCs level on wildlife have provided some of the following information:

- *Observation-1*: Studies conducted on teleost fishes in endocrine disruptors contaminated areas showed the high prevalence of liver tumors. The primary cause was thought to be the exposure to polyaromatic hydrocarbons (PAHs) and to a lesser degree, PCBs and DDT. However there was no exact indication that EDC was involved in causing the effects (Robert et al., 1996).
- *Observation-2*: The level of mercury was observed for over 40 years on the wildlife which provide a large database of their storage in the fish muscle. Mercury is primary stored as methylmercury in fish body from which it is transferred to other fish eating marine mammals as methylmercury (Kidd et al., 2012).
- *Observation-3*: DDT level was monitored in an area of South Africa, where DDT was sprayed for eradication of malaria. DDT concentration was found to be about seven hundred times higher in fat of chicken in the sprayed region (Kidd et al., 2012).
- *Observation-4*: The muscle and plasma of fishes which are exposed to municipal waste water were found to contain high levels of human contraceptives at low parts per billion levels (Kidd et al., 2012).

Table 3
Sources of endocrine toxicity (Dodson et al., 2012).

Sources	Category	Substances
Incineration, landfill	Polychlorinated Compounds (from industrial production or by-products of mostly banned substances)	Polychlorinated dioxins, polychlorinated biphenyls
Agricultural runoff/ Atmospheric transport	Organochlorine Pesticides (found in insecticides, many now phased out)	DDT, dieldrin, lindane
Agricultural runoff	Pesticides currently in use	Atrazine, trifluralin, permethrin
Harbors	Organotins (found in antifoulants used to paint the fulls of ships)	Tributyltin
Industrial and municipal effluents	Alkylphenols (Surfactants, – certain kinds of detergents used for removing oil – and their metabolites)	Nonylphenol
Industrial effluent	Phthalates (found in placticizers)	Dibutyl phthalate, butylbenzyl phthalate
Municipal effluent	Natural Hormones (Produced naturally by animals);	Estradiol, estrone, and testosterone; ethinyl estradiol
Agricultural runoff	synthetic steroids (found in contraceptives)	
Pulp mill effluents	Phytoestrogens (found in plant material)	Isoflavones, lignans, coumestans
Consumer products	Cosmetics, personal care products, cleaners	Parabens, phthalates, glycol ethers, fragrances, cyclosiloxanes

Therefore, it is clear that a strong monitoring process of assessing EDC level on wildlife has been going on for several years. But this information is still not enough to provide a visible indication of the level of EDCs exposure in many areas, especially in tropical and subtropical areas. At this point, it is crucial to conduct more studies on wildlife to save our endangered wildlife as well as our precious ecological systems.

1.4. Sources of endocrine toxicity

The sources of EDC exposure are usually diverse and widely distributed all over the environment and society of the world. But the situation is neither constant nor can be predicted easily since there is a significant usage difference of these substances among the countries. The whole scenario becomes more complicated as some of these chemicals have been banned in some countries while others remain the same in other countries.

Globally, it can be seen that the endocrine disruptors are mainly steroid hormones, synthetic steroids, polychlorinated dibenzo dioxins, biphenyls etc. and from the discussion of earlier studies, it is obvious that these chemicals have notable toxicities in human as well as in wildlives (Diamanti-Kandarakis et al., 2009). But endocrine disruptors like alkylphenol ethoxylate, gonadotropin compounds, pesticides etc. have not been discussed so much in the previous studies. These endocrine disruptors are either produced naturally or produced in the industries depending upon their diverse applications (Endocrine Disruptors, 2001). Table 3 lists some potential sources of endocrine disrupting chemicals.

However, although there are several examples of toxicities and contamination from PCBs and dioxins which may show a direct casual relationship between a chemical and manifestation of an endocrine or reproductive dysfunction in humans and wildlife, there is no representation of a common widespread persistent exposure to a broad mixture of contaminants. Nevertheless, exposure to endocrine disruptors may occur through drinking contaminated water, breathing contaminated air, ingesting food or contacting contaminated soil that are exposed to a number of pesticides, plasticizers, alkylphenols and flame retardants the

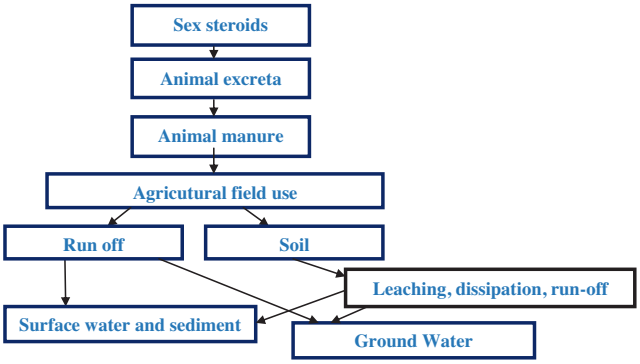


Fig. 3. Routes of potential exposure of sex steroids from livestock (Kjaerstad et al., 2010).

compounds commonly used in agriculture, industry and household applicants.

Many of these endocrine disruptors might end up in the aquatic environment and make water a potential source of EDCs. The reasons are may be incomplete removal of the contaminants during sewage treatment processes, soil run off or indiscriminate discharges of them into the waterways (Veerasingam and Ali, 2013). Some water treatment system like flocculation, sedimentation, filtration and chlorination even are not able to eliminate or remove these contaminates from water (Westerhoff et al., 2005; Gibs et al., 2007; Kim et al., 2007; Schenck et al., 2012). The situation is quite alarming as it is seen that when endocrine disrupting chemicals are released into waterways such as lakes, streams etc. can have toxic effects on the environment even though they are present in low concentrations.

Waste water from pharmaceutical and other industries can act as a major source of exposure due to their potential adverse effects on environment (Stumm-Zollinger and Fair, 1965.). They can contain natural human hormones, hormones from pharmaceutical products like birth control pills and potential EDCs from different detergents, soaps, plastics, food, and personal care products such as fragrances etc. It is observed from studies that endocrine disruptors like estrogen and androgen which are ubiquitously present in environment in trace quantities are released from the municipal wastewater of different industries (Halling-Sorensen et al., 1998; Daughton and Ternes, 1999). EDCs can end up in this wastewater through a variety of routes. For example, spillage during production and open air transportation in a developing country can act as an exposure to these substances to the environment.

However, industries can also be considered as a potential source of endocrine disruptors. The daily used products like pesticides containing DDT, plastic items containing bisphenol A and phthalates, personal care products containing antimicrobials are regularly being manufactured in the industries. These are some of the most potential candidates of endocrine disruptors. From these industries, chemicals are easily released into the environment for example through leaching into the soil and water. These are then taken up by microorganisms, algae and plants which are then taken up by animals. After this, endocrine disruptors find their way in the food chain from the animals to finally into human being (Gore et al., 2014).

Besides the water and industrial sources, livestock in agriculture can also act as a very important source of endocrine disrupting chemicals. Sex steroids like estradiol, progesterone and testosterone that are identified as endocrine disruptors have growth promoting effects in man and animal. As a result, these chemicals have been used in agricultural practice for many years where they are exogenously administered to meet producing animals for the improvement of weight gain and feed efficiency. However, these chemicals have hazardous great impact on environment because hundreds of animals may live in one area which result in high concentration exposure of these chemicals to the environment. These chemicals further contaminate the soil, water and air of the environment of that particular area as well as of other areas. The influence and presence of natural sex hormones as one of the environmental pollutants were first experimented by Shore et al. (Kim et al., 2005). Potential pathways of exposure are presented in Fig. 3.

A summary of the exposure route of human to EDC is given in Fig. 4:

However, EPA researchers have documented that chemical mixtures in some wastewaster effluents (or outflows) can result in ferminization of fish populations downstream of treatment plants. Additionally ecological impacts of these effluents and of effluents from other sources on the plants and overall environment are highly significant and disastrous. Extensive research has been

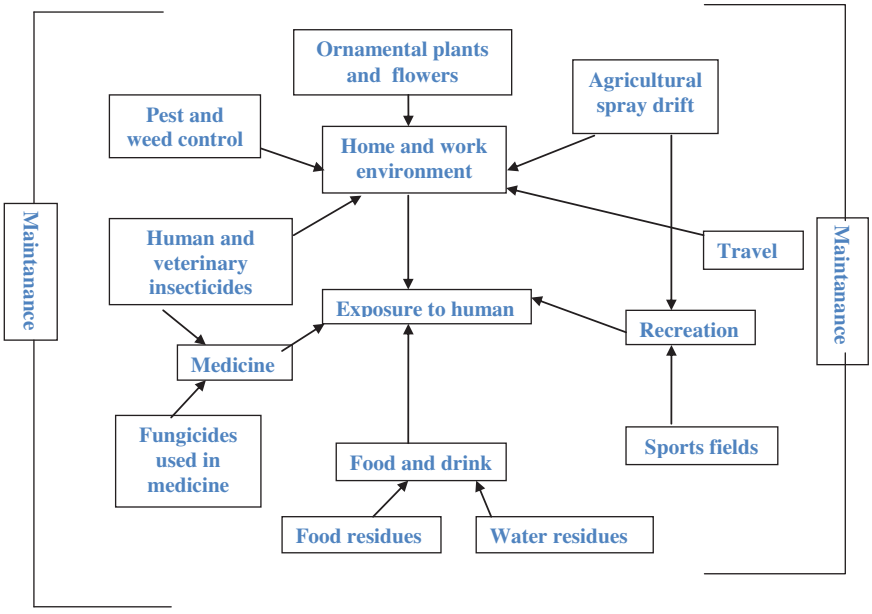


Fig. 4. Different exposure routes of human to EDCs (Cristina et al., 2012).

conducted on these endocrine disrupting chemical issues and their exposure to the environment which has raised a major concern in the global sector regarding these pollutants. The evidences from different studies, showing an alarming condition of EDC exposure mainly from industries and raw sewage, has made a huge impact on environmental health related cases which may lead to the immediate necessity of improving regularity issues.

1.5. Stability of EDC in the environment

Man-made chemicals have become an important part of the present life. There is no way that human and wildlife populations can avoid coming into contact with the chemicals employed in food production (plants and meat), in pathogen control (e.g. insecticides), in the production of modern materials (e.g. plastics), or in the built environment (e.g. insulations, flame retardants). Considering the widespread presence of these chemicals in the environment, it is important that strategies are developed to preclude widespread environmental contamination with endocrine disruptors. Endocrine disruption has been a central point of concern since many years because of the hazardous nature of endocrine disruptors in the environment. EDC can be found almost everywhere in the environment such as – water, air, soil and sediments. Moreover, the chemicals have high half-lives. Therefore, even if the compound was in use years ago, it can still persist in the environment (Gore et al., 2014). It is alarming since very low amount of these can be very hazardous for us. This is why it is essential to completely remove endocrine disruptors from the environment.

The concern is also because of the reason that many treatment processes are unable to complete remove them from environment. For example, major source of EDC is considered to be the sewage water effluents. This is because of the fact that different types of waste products usually find their way finally into sewage water effluents. Sewage water effluent is mainly contaminated by EDC from the domestic sewage which is discarded into the municipal water. Though municipal waste water undergo different traditional treatment process to remove these contaminants, water treatment systems like flocculation, sedimentation, filtration and chlorination, are not able to eliminate or remove these contaminates from water (Westerhoff et al., 2005; Gibs et al., 2007; Kim et al., 2007; Schenck et al., 2012). This makes it essential to conduct more studies in order to have more information on the stability of EDC in environment so that they can be completely removed from the environment.

However, stability of EDC largely depends on its persistent nature in environment. Some EDCs are found to be degraded quite fast in the environment by sunlight, bacteria and many other chemical processes, while some EDC can persist in the environment ranging from months to years (Kidd et al., 2012). The nature of some EDCs is discussed below (Kidd et al., 2012):

Polychlorinated biphenyls (*PCBs*):
PCBs are highly stable in nature which makes them widely distributed in the environment by air and water. As a result, some PCBs congeners, especially congeners with 2, 4 and 2, 4, 5 substitutions at their rings are found to be concentrated in humans.
Dichlorodiphenyltrichloroethane (*DDT*):
As a result of the persistent character of DDT, it can be found in the environment for long period of time, even 10–15 years after their application. Major metabolites of DDT, dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD) are also quite stable in the environment and cause bioaccumulation in living body.
Perfluorooctanesulfonate (PFOS):
PFOS do not easily undergo any transformation process, as the compound is formed by perfluoronation process from PFOS containing moity.
Polybrominated diphenyl ethers (*PBDEs*):
Although PBDE is quite stable in the environment, persistent characters of its metabolites vary largely. While 'Penta' and 'Octa' BDEs are easily degraded, some lower brominated congeners can additionally act as a source of their emission.
Hexabromocyclododecane (*HBCDD*):
Because of their stability, these compounds are found to be present in both human and wildlife in nano gram level.
Perfluorooctanoic acid (*PFOA*):
There is no exact indication about their transformation process.
Di(2-ethylhexyl) phthalate (*DEHP*):
The compound undergoes rapid transformation process in normal environment rather than in abiotic environment. It is quite rapidly taken by biota where they undergo metabolic processes by lipase and esterase enzyme.
Benzo[a]pyrene (*BaP*):
When released from their sources they get accumulated in soil and sediments and in this way they can travel a long distance. This is why their presence can be detected further away from their actual sources. However, in the gaseous state, they are rapidly degraded by photooxidation process.
Triclosan:
Because of their strong binding nature to soil and sediment, they are not easily released to the environment. They are commonly found in the large water source usually attached state with soil and sediment.
Bisphenol A (*BPA*):
They undergo rapid degradation process.
Atrazine:
This compound is not easily absorbed to soil, making it to further contaminate other sources. Additionally, it is highly stable in cold environment. However, it undergoes hydroxylation and dealkylation process as part of metabolic process.
Vinclozin:
Vinclozine and its residues have moderate half life ranging from 179 days to 1000 days.
Fluoxetine:
Fluoxetine is not affected by effluent treatment process and can be released into the environment in its intact state.
Levonorgestrel:
The compound is highly stable and is also not easily affected by effluent treatment process.
Cyclic methyl siloxanes:
These compounds have half-lives of more than three days. As a result, they can be found in remote places in addition to their actual place of release. Although, the compound is found to undergo limited metabolic process in both soil and sediments, it undergoes hydrolysis process as a transformation process.
Methylmercury:
Methylmercury is highly affected by different physical, chemical or biological processes. However, the compound has high attraction toward particles and dissolved organic carbon in the water and their presence is mainly detected in bacteria, plants and algae from which they ultimately enter into the complex food web.

Although stability of EDC in the environment has been a great concern, advanced techniques are coming forward for the complete removal of EDC from environment. Several studies have been conducted, for example oxidation of EDC has proved to be a great success. It is observed that oxidation by ozone, chlorine, TiO_2, potassium permanganate can efficiently decompose EDC. A complete degradation (>90%) of ethinyl estradiol in Lake Zurich was shown by potassium permanganate. Because of these successful oxidation approaches science is now thinking about degradation of EDC by UV oxidation process (Rosenfeldt and Linden, 2004). As a result the day is not far behind when EDC can be successfully removed from the environment.

1.6. Important issues in endocrine disruption

There are a number of issues that should be considered to have a clear understanding on endocrine disruption. Some of them are briefly discussed below:

1. *Age of exposure*: Endocrine disruptors may have different effects in adults and in developing fetus or in infants. The environment of a developing organism, which includes the maternal environment (eutherian mammals), the egg (other vertebrates) and the external environment, interacts with the individual's genes to determine the propensity of that individual to develop a disease or dysfunction later in life. This propensity is also dependent on exposure to EDC from fetal period to the early postnatal developmental period when organs continue to undergo

substantial development. Hence, in one paper, endocrine disruptor was related with the terminology 'the developmental basis of adult disease' (Diamanti-Kandarakis et al., 2009).

2. Effects of endocrine disruptors may begin early and be persistent: It is evident from researches that endocrine disruptors pose greater risk in the early developmental period rather than in adult period. Moreover, research from NIEHS (National Institute of Environmental Health Sciences) showed that, the adverse consequences of endocrine disruptors may be passed to subsequent generations even though they were not directly exposed to the endocrine disruptors. The mechanisms might involve altering gene function without altering DNA sequence (National Institute of Environmental Health Sciences, 2010).
3. Latency from exposure: The diseases resulting from endocrine disruptors may not be apparent during the exposure period; it might be manifested in adulthood or during aging. The latency between the exposure and the occurrence of diseases creates a challenge in determining the involvement of EDC in particular disease (Diamanti-Kandarakis et al., 2009).
4. Involvement of other pollutants: Environmental pollution does not involve single compound. Thus, if individuals and populations are exposed to an EDC, it is also possible that other environmental pollutants might also be involved. Furthermore, effects of different classes of EDCs may be additive or even synergistic (Diamanti-Kandarakis et al., 2009).
5. *Low dose effects*: Since last two decades the hypothesis of endocrine disruption has been an interesting and well reviewed area of science among scientists. Various scientists have gone through different kind of studies and provided their hypothesis. Some scientists debated that high levels of chemicals contamination have affected health and different systems of body but generally the level of contamination in human body to show health effect have been far too low. During 1990s the US National Academy of Sciences set up a committee to examine and study on the evidences of endocrine disruption and they considered the hypothesis xeno-estrogen was 100 times less potent to show any harmful severe effect which was proved to be false by various experiments. The information that very low dose internal exposures to cadmium and organochlorine contaminants are associated with detectable change in serum hormone level, sex maturation, height or in body mass index is proved by the observation made under Flemish biomonitoring campaign 2007–2011 (Dhooge et al., 2011; Den et al., 2002).
6. *Concentrations of EDCs*: Endocrine disruptors enter in the environment from various sources. Today, people are exposed to endocrine disruptors in everyday life, as these compounds can be found in low doses in almost all products ranging from drinking water to consumer products, drugs, foodstuffs etc. (Shudong et al., 2011). The concentrations of some EDC in some of their common sources are given in below in Table 4.

Even though wildlife and human matrices are available for extraction and analysis these days, the measured levels that are to be translated into an internal dose is not as simple. It is not always possible to do detailed comparisons between studies or assessments of effects of mixtures, since chemical analyses and exposure assessments still lack standardization. It is necessary to take into consideration that it is not the mass-based concentrations but the number of molecules that count when mixture doses are assessed. Therefore, the level of contaminants in humans and wildlife can only be currently compared on a molar basis (UNEP and WHO, 2013).

Table 4
Concentrations of some EDCs in some of their common sources (Kidd et al., 2012).

EDC	Source	Concentration
Triclosan	Municipal effluents	Upto 3 μg/l
	Biosolids	Upto 33 μg/g
	Receiving waters	Less than 2.3 μg/l
	Sediments	Less than 800 ng/g
Bisphenol A	Ground and surface water	Upto 20 μg/l
	River sediments	Upto 1.63 mg/kg
Fluoxetine	Effluents	Upto 99 ng/l
	River water	Upto 46 ng/l
	Treated sewage sludge	Upto 0.37 mg/kg
Levonorgestrel	Municipal effluents	At low ng/l

There is also a high demand for developing screening analytical methods that will accommodate a wide variety of analytical functional groups of the EDCs at low detection levels. Existing methodologies for chemical analyses of the EDCs having variable persistence, short half-lives in vivo and highly different structures need to be improved. The analytes need to be pure compounds as well as characterized in detail to promote methodological advances. The analysis of target analytes can be viewed as a top-down approach that only scratches the surface of the number of chemicals that can be measured. This is shown in Fig. 5. Authentic standards are ultimately needed, although larger numbers can be tentatively identified based on mass spectra. Larger numbers cannot be readily identified, even if they can be isolated by the conventional extraction and separation technology widely employed in trace organics analysis laboratories. Furthermore, the analyst has to make a decision about how to best allocate analytical resources for this task. While the "spectrum of the EDC chemicals" (not isomers or congeners) is very large, only a subset can be extracted and separated by chromatography, and even less numbers identified. The use of effects directed analysis (EDA) and quantitative structure-activity relationship (QSAR) directed non-target analyses are two techniques that are currently being used to address this challenge (UNEP and WHO, 2013).

2. Uptake of endocrine disruptors in human body

Endocrine disruptors can enter human body by a variety of routes. They can enter human body by simple oral consumption of food and water or by using more complicated intravenous route. From different observations, it is seen that adults come in contact with EDC mainly through ingesting contaminated drinking water, meat, fat-dairy products and also by inhalation of polluted air. Infants get contaminated with EDC by breast feeding, contact with baby products and also by inhalating polluted air (Polyzos et al., 2012). Some of the routes are discussed below:

1. *Oral consumption of food and/or water*: They can enter human body by oral consumption of food and water. Endocrine disruptors such as PCBs, dioxins, perfluorinated compounds, DDT, commonly found in industrial waste or pesticide contaminated soil or ground-water can get entry into human body by oral consumption of food and water. Leaching of chemicals like BPA, phthalates from food and beverage containers and pesticides residues in food or beverage can also enter human body by this route (Gore et al., 2014).
2. *Contact with skin and/or inhalation*: Human body can come in contact with pesticides, commonly used in agriculture, homes, or public disease vector control (DDT, chlorpyrifos, vinclozolin, pyrethroids) through contact with skin and/or by inhalation. It is also seen from observation that chemicals like BFR (brominated flame retardants), a flame retardant which is commonly used in household furniture uses this route to get entry in human body. Additionally, it is also quite known that cosmetics, personal care products, antibacterials, sunscreens, medications (phthalates, triclosan, parabens and insect repellants) that we apply on

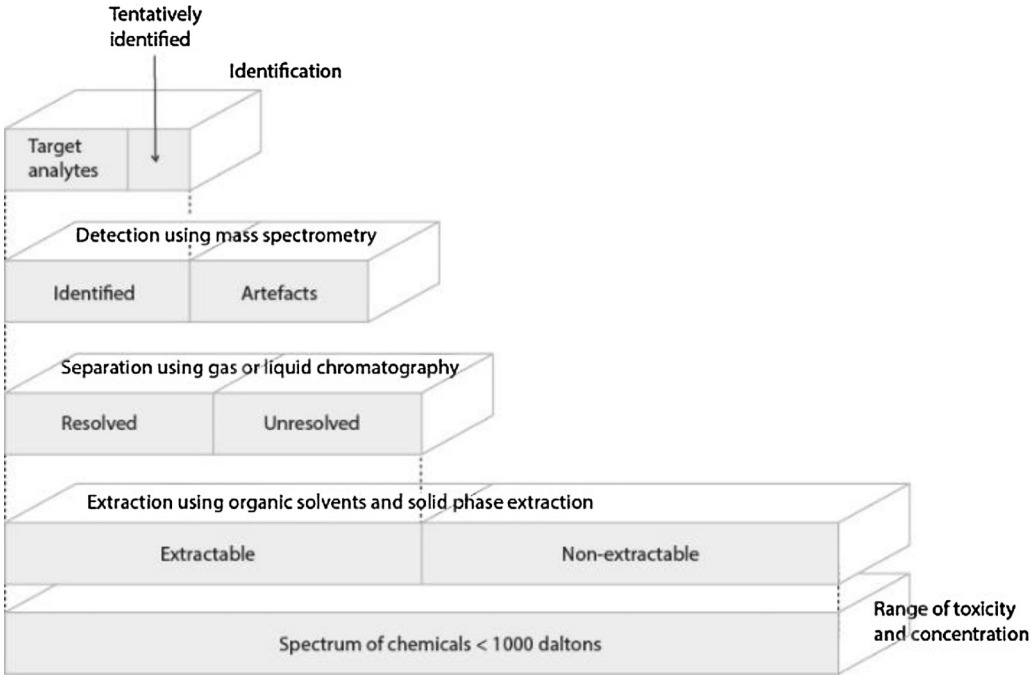


Fig. 5. An illustration of the possibility of complexity of measuring potential EDCs in environmental media (UNEP and WHO, 2013).

our skin on a daily basis uses the skin route for enter into human body (Gore et al., 2014).

3. *Intravenous route*: It is seen from observation that endocrine disrupting chemicals like phthalates which is commonly used in intravenous tubing use the intravenous route to enter the human body (Gore et al., 2014).
4. Biological transfer from placenta and maternal milk: Human body can get exposed to endocrine disrupting chemicals without being actually in contact with them. This may occur by biological transfer of EDC from placenta and mother's milk of maternal body if the woman has EDC previously in her body (Gore et al., 2014).

2.1. Mechanism of action

Over the last 30 years many interests regarding endocrine disrupting chemicals, their generation and behavior have been found to be published (Hutcheon et al., 1983; Irigaray et al., 2006). Since the substances identified as endocrine disruptor chemicals are diverse in many ways and do not seem to share specific similarities in structures and natures, it is quite hard to predict their mechanisms of actions but in broad term analysis it can be seen that some endocrine disruptors like dioxins, PCBs, PBBs, and pesticides may contain halogen substitutions by chlorine and bromine while some endocrine disruptors are just heavy metals or metalloids which may have estrogenic activities or act as antiandrogens or thyroid hormone receptor agonists or antagonist. These may be considered as endocrine disruptors as well as generalized toxicants (Kandarakis et al., 2009).

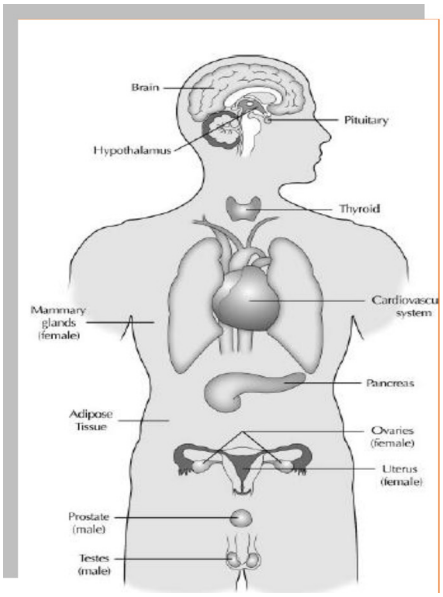
The understanding of the mechanisms by which endocrine disruptors exert their effect has grown tremendously. Endocrine-disrupting chemicals (EDCs) were originally thought to exert actions primarily through direct interaction with nuclear hormone receptors which include estrogen receptors (ERs), androgen receptors (ARs), progesterone receptors, thyroid receptors (TRs), and retinoid receptors, among others. Today, basic scientific research shows that the mechanisms are much detailed than originally recognized (Diamanti-Kandarakis et al., 2009).

To understand endocrine disruption, we must have a clear concept about the endocrine system, a system consisting of many interacting tissues that talk to each other and the rest of the body using signals mediated by molecules called hormones. It is responsible for controlling a number of processes in the body that start from our early development processes such as cell differentiation for development and bone formation to our adulthood controlling tissue and organ functions. The human endocrine system is shown in Fig. 6. The system acts via hormones which travel through blood to produce effects on distant cells and tissues via integrated complex interacting signaling pathways usually involving hormone receptors. There are about 50 different hormone and hormone related molecules (cytokines and neurotransmitter) in humans that integrate and control normal body functions across and between tissues and organs over the lifespan. Hormones and their signaling pathways are very critical for the functioning of every tissue and organ in both vertebrates and invertebrates and are often very similar across the species (UNEP and WHO, 2013).

Endocrine disruptors exhibit the same characteristics as hormones (Table 5). They interfere in some way with the function of these hormones and in doing so can alter endocrine function such that it leads to adverse effects on human and wildlife health (UNEP and WHO, 2013). The mechanisms through which endocrine disruptors may interrupt the endocrine system and alter hormonal functions were predicted by the researchers from animal studies (National Institute of Environmental Health Sciences, 2010).

They can:

- Imitate and partly imitate naturally occurring hormones in the body like estrogens (the female sex hormone), androgens (the male sex hormone), and thyroid hormones, potentially producing overstimulation.
- Act as antagonists, where they bind to the receptors of endogenous hormone within a cell. Thus, the normal endogenous hormone cannot bind to the receptors and no signal occurs. Eventually, the body fails to respond properly. Examples of chemicals that block or antagonize hormones are anti-estrogens and anti-androgens.



The endocrine system keeps our bodies in balance by maintaining homeostasis and guiding proper growth and development.

On the other hand, endocrine disruptors interfere with the endocrine system and cause adverse effects both in human and wildlife.

Fig. 6. Model of endocrine systems that include brain and hypothalamic neuroendocrine system; pituitary; thyroid; cardiovascular system; mammary gland; adipose tissue; pancreas; ovary and uterus in females, and testes and prostate in males physiology (Diamanti-Kandarakis et al., 2009).

- Interfere or block the natural hormones or their receptors, for example, by altering their metabolism in the liver.

Chemical exposures during pregnancy have been reported to affect the health of several subsequent generations of people (UNEP and WHO, 2013). Fig. 7 shows the changes in animal studies where EDC exposure during the period of germ cell programming can result in alteration of tissue development and thus in adult disease via an unknown mechanism (UNEP and WHO, 2013).

Table 5
Comparison of hormone and endocrine disruptors (UNEP and WHO, 2013).

Hormones	Endocrine disruptors
Act via hormone receptors	Act via hormone receptors and multiple receptors
Some have multiple receptors	Will cause abnormal receptor function
Tissue-specific receptor classes and subtypes	Likely isoform-specific interactions
Hormones normally bind similarly to all receptor subtypes	
Active at low doses	Some act at low doses, others variable
Blood levels do not always reflect activity	Blood levels do not always reflect activity
May be bound to serum proteins in blood with a small percentage free	May be bound to serum proteins
No bioaccumulation	Effects on human blood levels may not reflect on hormone action
	Possible bioaccumulation
Non-linear dose-response relationships	Non-linear dose-response relationships
Always saturable with variable dynamic range	Always saturable with variable dynamic range
Can exhibit non-monotonic dose-response relationships	Can exhibit non-monotonic dose-response relationships
High dose effects are not same as low dose effects	High dose effects are not same as low dose effects
Tissue-specific and life stage-specific effects	Tissue-specific and life stage-specific effects
Developmental effects permanent	Developmental effects permanent
Programs brain and endocrine system for adult function	Interferes with programming processes
Different end-points vary in sensitivity	Different end-points vary in sensitivity

Endocrine disruptors can exert their effects generally in two pathways: either a directly on hormone-receptor complex or directly on the specific proteins that are involved in the control of delivery of hormones at the right place at the right time (UNEP and WHO, 2013). Table 6 lists some proposed mechanism of action of some known EDCs.

Though we know the mechanisms by which endocrine disrupting chemicals (EDCs) work in biological systems, we cannot say with certainty that EDC is involved for a particular disease. A number of challenges like unique exposure rate of different persons to a variety of known and unknown EDCs; individual differences in metabolism and body composition (which may lead to the variation of half-life, persistence and degradation of EDC in body fluids and tissues, etc.) as well as differences in genetic polymorphisms etc. may be required to be ascertained to determine their involvement. In addition, human disorders are more likely to be the result of chronic exposure of low amounts of mixtures of EDCs. The latency between exposure to EDCs and occurrence of clinical disorders

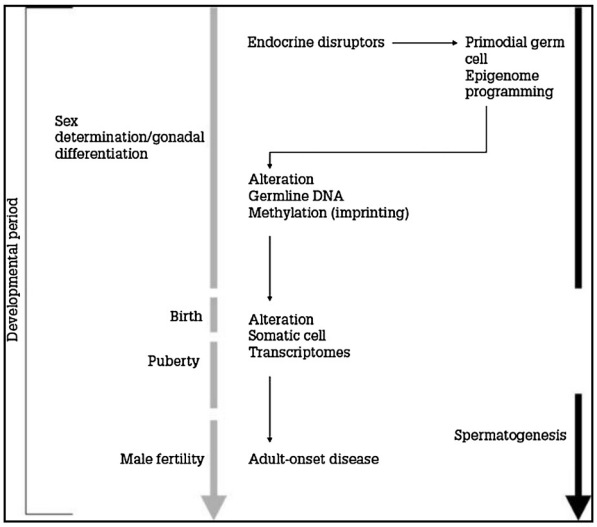


Fig. 7. Potential mechanism by which EDCs may affect disease transmission across generations.

Table 6
Proposed mechanism of action of some known EDCs (Polyzos et al., 2012).

Endocrine disruptors	Mechanism
Bisphenol A	Incrementation of insulin and leptin. Incrementation of TNF-α, IL-1β. Decreasing adiponectin. Interfering glucose tolerance induction. Incrementation of adipogenesis. Accumulation of lipid in adipocytes and hepatocytes. Increasing oxidative stress. Decreased anti-oxidant capacity.
Phthalates	Increased lipid peroxidation. Increased oxidative stress. Interference with insulin receptor. Altered glucose tolerance induction. Reduced glucose oxidation.
Dioxins	Initiation of steatosis, periportal fibrosis, hepatocellular ballooning, sinusoidal dilatations, activated kupffer cells. Abnormal lipids and lipoproteins. Incrementation of TNF-α, IL-1β and TGF-β. Decreased lipoprotein lipase activity. Decreased hepatic vascular endothelial cadherin. Altered glucose tolerance induction. Induction of hepatic expression of CD36. Decreased regulation of insulin receptor β-subunit, IRS-1 and Glut-4. Incrementation peripheral fat mobilization and hepatic FFAs uptake. Decreased hepatic FFAs β-oxidation Increased oxidative stress. Decreased anti-oxidant capacity. Inducing apoptosis
Other POP's	Altered glucose tolerance induction. Reduced anti-oxidant capacity. Incrementation of oxidative stress. Incrementation of lipid peroxidation. Introduction of steatosis, inflammation, lipid granulomas and portal fibrosis. Incrementation of TNF-α, IL-10 and interferon-λ. Incrementation of monocyte chemoattractant protein-1 and keratinocyte chemoattractant-1. Reduction of adiponectin. Decreased regulation of hepatic haptoglobin and fatty acid-binding protein. Altered function of mitochondria.

creates a further challenge when one attempts to establish a relationship at the level of given (Diamanti-Kandarakis et al., 2009).

2.2. Biotransformation of EDC in human body

So far, there is no exact indication about the biotransformation of endocrine disruptors in human body. But it is predicted that metabolites of several EDCs may exhibit stronger endocrine disruption properties than the parent compounds and may even lead to more persistent compounds that will accumulate in the tissue (Kidd et al., 2012). However, studies on biotransformation of several endocrine disruptors have been conducted extensively in rats and mice both in vivo and in vitro. Taking 1,2-dichloroethane as an example of endocrine disruptors, it was observed that the major metabolite of 1,2-dichloroethane is glutathione conjugate, which is ultimately eliminated from the body as nonvolatile urinary metabolites. However, involvement of another enzyme N-acetyltransferase (NAT) at subsequent steps of glutathione conjugation is also assumed from different observations (ATSDR, 2001). The pathway of predicted metabolism of 1,2-dichloroethane is shown in Fig. 8.

From the studies conducted on male rate bodies it is predicted that most of the 1,2-dichloroethane is initially conjugated with glutathione followed by inhalation and ingestion. However, followed by intraperitoneal exposure, it is expected from studies on female albino mice that 1,2-dichloroethane undergoes hydrolytic dehalogenation initially, after which it is reduced to give 2-chloroethanol. The compound 2-chloroethanol is then expected to be oxidized to 2-chloroacetic acid by microsomal oxidation. One in vitro study, conducted on isolated rat hepatic microsomes indicated the major involvement of hepatic nuclear cytochrome P-450 in the metabolism of 1,2-dichloroethane to chloroacetaldehyde, the metabolic pathway of which is proposed by Guengerich et al. (1980). The pathway showed the involvement of two enzymes in this oxidation process such as microsomal cytochrome P-450 (in presence of oxygen and nicotinamide adenine dinucleotide phosphate [reduced form][NADPH]) and MFO. In this pathway, oxygen is inserted into 1,2-dichloroethane to yield unstable chlorhydrin, followed by prompt dechlorination to 2-chloroacetaldehyde. 2-Chloroacetaldehyde may then further be reduced to chloroethanol or oxidized to chloroacetic acid (ATSDR, 2001).

Other urinary metabolites were also observed from both in vivo and in vitro studies. These compounds were the clear indication of glutathione conjugation of 1.2-dichloroethane. In vitro studies showed that 2-chloroacetic acid is conjugated with glutathione by a nonenzymatic process to give *S*-carboxymethylglutathione which is further converted to glycine, glutamic acid and *S*-carboxymethylcysteine. Of these metabolites, *S*-carboxymethylcysteine is expected to be further oxidized to thiodiglycolic acid. In vivo studies on mice and rats showed the presence of both *S*-carboxymethylcysteine and thiodiglycolic acid (ATSDR, 2001).

2.3. Excretion

Excretion of endocrine disruptors is highly dependent on the nature of the chemical substances. Endocrine disruptors can be persistent and non persistent. If the substance is non persistent it is usually predicted that they are metabolized by liver then finally eliminated from the body through urine and feces. Persistent endocrine disruptors are accumulated in different parts of human body especially in fats and from these places they are released slowly. One way of excretion of these persistent endocrine disruptors is thought to be by mother to infants though breast feeding. It is observed in many studies that the daily intake of breast milk containing persistent organic pollutants (POPs) may exceed the tolerable limit (Kidd et al., 2012).

2.4. Harmful effects of endocrine disruptors on human health

From a physiological perspective, an endocrine-disrupting substance is a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that otherwise enable the organism to communicate with and respond to its environment. Different studies conducted on animal bodies, clinical observations and epidemiological studies have indicated the potential role of endocrine disruptors in affecting reproductive systems, prostate, breast, lung, liver, thyroid, metabolism and causing obesity (Polyzos et al., 2012).

Some endocrine disruptors known to cause harmful human health effects have been banned in the United States. Even some prescription drugs have had unexpected effects on the endocrine system. In 1971, the U.S. Food and Drug Administration advised physicians to stop prescribing DES (diethylstilbestrol) because it was linked to a rare vaginal cancer. U.S. production of PCBs was stopped in 1977 because of the suspected harmful health and environmental effects; exports and imports of PCBs were eventually stopped in 1979. The general use of DDT was banned by the U.S. EPA in 1972 because it had posed unacceptable risks to the environment and potential harm to human health. Epidemiological data

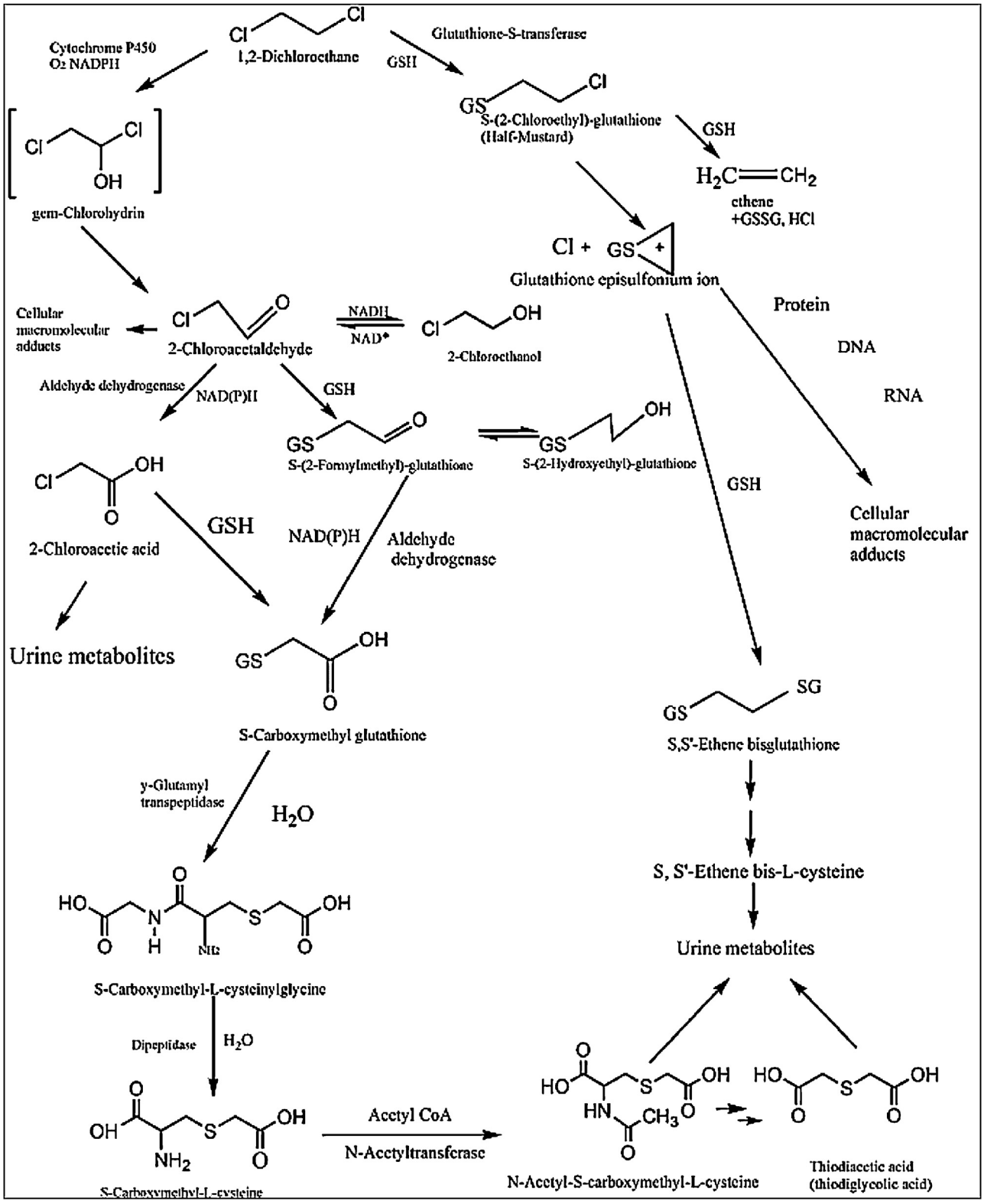


Fig. 8. The predicted metabolic pathway of 1,2-dichloroethane (ATSDR, 2001).

showed evidences that increase in the incidences and prevalence of some diseases are associated with endocrine-disrupting chemicals, such as cancer specially breast, prostate, and testis cancer, as well as diabetes, obesity, and decreased fertility which had been observed for over the last 50 years. These increases might partly reflect an increase in the likelihood of diagnosis but do not constitute proof of the impact of endocrine-disrupting chemicals. Time trends and ecological studies are not well suited to study a possible association between exposure to endocrine disrupting chemicals and risk of disease, as assessment of exposure is extremely difficult. The data on time trends are, however, consistent with such an impact, as are data on the incidence or prevalence of some diseases in migrants and on differences in function of geographical area. Huge geographical differences in cancer incidence are well

documented in the report "Cancer incidence in five continents, volume IX" of the International Agency for Research on Cancer (Curado et al., 2007) often showing higher risks of hormone-related cancers in more industrialized countries.

Cancer: In Great Britain, from 1978 to 2007, the overall age-standardized incidence rate of cancer has increased by 25%, an increase of 14% in men and a 32% increase in women (Sam and Nicolas, 2012).

Diabetes: The United States Centre for Disease Control and Prevention (CDC) reports the prevalence of diabetes incidence from 1980 through 2011 increased by 176% (from 2.5% to 6.9%) (Center for Disease Control and Prevention, 2014).

Obesity: Childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years. In the United States, the prevalence of obesity in children aged 6–11 years increased from 7% in 1980 to nearly 18% in 2012. Similarly in adolescents, the prevalence in creased from 5% to nearly 21% over the same period (Center for Disease Control and Prevention, 2014).

Some of the effects on endocrine disruptors on human health are discussed below.

2.4.1. Disruption of thyroid function

Thyroid hormone has many essential role in human physiology, for example, it is involved in normal brain development, control of metabolism, and many other important aspects of normal adult physiology. Therefore, adverse effects may results in development, metabolism, or adult physiology if there are changes in the function of the thyroid gland or interference with the ability of thyroid hormone to exert its action (Diamanti-Kandarakis et al., 2009). From previous studies and significant amount of literature reviews it is found that there are many endocrine disrupting chemicals which can directly disrupt the regular functions of thyroid gland. The primary environmental chemicals identified as thyroid disruptors may include PCBs; bisphenol A (4,4′-isopropylidenediphenol or BPA); perchlorate, tetrachlorodibenzo-p-dioxin [TCDD]; polychlorinated dibenzofuran [PCDF] (both commonly referred to as dioxins); pentachlorophenol (measured in mammals as the source chemical hexachlorobenzene [HCB]), a common pesticide that breaks down into pentachlorophenol; triclosan; polybrominated diphenyl ethers [PBDE] and tetrabrominated diphenyl ethers commonly known as flame retardants; naturally occurring chemicals such as soy isoflavones, thiocyanate in cruciferous vegetables and etc. Phthalates (di[2-ethylhexyl] phthalate [DEHP], di-n-octyl phthalate [DnOP], diisodecyl phthalate [DIDP], di-n-hexyl phthalate [DNHP], and di-n-butyl phthalate [DBP], used as plastic emollients in feeding tubes and plastic containers), have also been shown to alter thyroid function in animal studies. Evidences also exist that parabens, used in cosmetics, pesticides like dichlorodiphenyltrichloroethane [DDT], HCB, methoxychlor, chlordane, and endosufane have thyroid disrupting effects in animals and humans (Patrick, 2009).

Thyroid disruptors can affect thyroid physiology in many phases of thyroid regulation. The complex system of iodine uptake, thyroid hormone production, interconversion of thyroid hormones, cellular uptake, cell receptor activation, and hormone degradation and elimination can be directly altered by thyroid disruptors (Patrick, 2009).

The first step in thyroid hormone synthesis is the uptake of iodide into the thyrocyte by the sodium/iodide symporter (NIS). Iodine is essential for thyroid hormone synthesis. Today, iodine deficiency has become a worldwide problem. Thus, chemicals that interfere with NIS can interfere with the thyroid hormone synthesis thereby may exerbarate the iodine deficiency problem. A good example would be in this case is perchlorate, commonly used as oxidant in rocket propellants, in ordnance, fireworks, airbag deployment systems, and others. As the chemical is quite stable in the environment it has become a worldwide contaminants in drinking and irrigating waters and in foods. It is observed from experimental studies that in humans the serum half life of perchlorate is about 8 h and a dose of about 5.2 g/kg d is sufficient to begin to reduce iodide uptake into thyroid gland (Diamanti-Kandarakis et al., 2009).

Thyroperoxidase (TPO) (an heme-containing enzyme, responsible for the oxidation of iodide into iodine before it is transferred to the precursor of thyroid hormone, thyroglobulin) was also observed to be blocked by a number of compounds. An example would be 6-propyl-2-thiouracil (PTU), a methyl mercaptoimidazole, used therapeutically to treat patients with Graves disease. It was found in an experiment that as a class (the 2-mercapto-4-hydroxy-6-propyl-pyrimidines), PTU can effect thyroid function. Other TPO inhibitors may include isoflavones, especially those found in soy protein (e.g., genistein, coumestrol). From observation, it is seen that, infants fed with soy formula are reported more with goiter. Also, in teenage children, who were diagnosed with autoimmune thyroid disease, occurrence rate is twice in those children who were fed with infant soy formula (Diamanti-Kandarakis et al., 2009). In Table 7, several thyroid disruptors with their mechanism and effects have been shown.

Table 7
Mechanisms and effects of thyroid disruptors (Patrick, 2009).

Thyroid disruptors	Mechanism	Effect
Perchlorate, thiocyanate, nitrate, bromates, phthalates	Blocking uptake of iodide into thyroid cell	Decreased synthesis of T3 and T4
Methimazole, amitrole, soy isoflavones, benzophenone 2	Blocking production of TPO in thyroid follicles	Decreased synthesis of T3 and T4
PCBs, pentachlorophenols, flame retardants, phthalates	Competitive binding to thyroid transport protein (TTR)	Possible effect on fetal brain T4 production
Dioxin, PBDE, chlordane	Altering transport across cell membrane	Increased biliary elimination of T3 and T4
Acetochlor (herbicide), PCBs	Enhanced hepatic metabolism	Increased biliary metabolism of T3 and T4
PCBs, triclosan, pentachlorophenol, dioxin, difuran	Inhibition of sulfation	Decreased sulfation of thyroid hormones leading to possible decrease of peripheral T3 synthesis
FD&C red dye #3, PCBs, octyl-methoxycinnamate	Inhibition of deiodinase activity	Decreased peripheral T3 synthesis
PCBs, bisphenol A, hexachlorobenzene, flame retardants	Altering binding to thyroid receptor	Altered thyroid hormone directed gene transcription
DDT, PCBs	Inhibiting TSH receptor	Decreased production of T3 and T4

2.4.2. Corticoid function dysfunction

Many evidences have shown that corticoid hormonal function can be affected by endocrine disruption. For example, hexachlorobenzene induces oxidative stress, disruption of arachidonic acid metabolism and porphyria (Lelli et al., 2007).

Metabolic disorders: The peroxisome proliferator activated receptor (PPAR) is composed of three types of isotypes which are alpha, beta and gama and play very important roles in controlling cellular differentiation programs and in transcriptional control of lipid and carbohydrate metabolism (Casals-Casas et al., 2008). PPAR alpha is present in liver and when associated with the presence of endocrine disruptors mainly causes the metabolic disorders (Feige et al., 2006).

Interference with hormonal feedback regulation and neuroendocrine cells: Neuroendocrine systems functioning as link between central nervous system and peripheral endocrine system control the homeostatic processes which include reproduction, growth, metabolism, energy balance and stress response. Endocrine disrupting chemicals causing disruption of neuroendocrine homeostasis can lead to perturbations and evidence exists that neuroendocrine disruption of hypothalamic pituitary thyroid system has certain effects on metabolism and energy balance. For example PCBs reduce the thyroxin and thyroid stimulating hormone (TSH) in response to thyrotropin releasing hormone which result in hypothalamic and pituitary deregulation (Gore, 2010). Moreover exposure to EDCs which can be hormonally active substances may result in improper hypothalamic programming consequently decreasing reproductive success in adulthood (Gore, 2008).

2.4.3. Effect on nervous system

Nervous system, one of the most important body systems, needed to keep all the body parts synchronized and working perfectly, can be exposed and affected by endocrine disruptor chemicals and this effect can be induced by various mechanisms. The hormonal balance and function in the body may be altered due to the direct effect of endocrine disrupting chemicals on endocrine glands. On the contrary the compounds may initially affect the central nervous system (CNS) for example neuroendocrine disruptors which can consequently influence the endocrine system. Effect on any of those would cause neuroendocrine disruption and the indications might be alteration in metabolic rate, indirect effect in behavior, alteration in sexual differentiation in the brain which could affect sexually dimorphic reproductive and nonreproductive neural endpoints and also some neuroteratogenic effects. There are some studies and human or animal literature which provide examples about the exposure of EDCs and their effects on behavior, learning, memory, attention, sensory function and neurological development as well. Examples of neuroendocrine disruptors which may affect directly or indirectly or both include some PCBs, dioxins, DDT and related chlorinated pesticides and metabolites, heavy metals like mercury, lead, organotins, insect growth regulators, dithiocarbamates, synthetic steroids, tamoxifen, phytoestrogens and atrazine herbicides (Mellanen et al., 1996).

2.4.4. Effect on male and female reproduction

The diseases we experience throughout life, some of which are related to endocrine disruptors (EDs), can be sexually dimorphic. It is known that estrogen and androgen largely mediate male sexual differentiation, whereas female differentiation occurs largely independent of estrogen and androgen. Therefore, it might be expected that endocrine EDs might produce different disorders in male and female where EDs may act as estrogen and/or androgen antagonists (Diamanti-Kandarakis et al., 2009).

The diseases of female reproductive system that might be associated with EDC include precocious puberty, polycystic ovary syndrome and premature ovarian failure (Costa et al., 2014). In female, some unwanted side effects like increased growth of endometrium and higher risk of breast cancer can also occur because of the EDCs. Because of these the offspring of these women had to fight with some severe diseases for example, vaginal cancer. Some of the other adverse effects of EDCs on female reproductive system are:

Puberty: It is observed from over the last century that the age of menarche has been diminished from 16 or 17 years to less than 13. This early onset of puberty may be associated with a greater prevalence of many other disorders, such as insulin resistance, metabolic syndrome, breast and reproductive system cancers (Costa et al., 2014).

Primary ovarian failure: Studies showed that primary ovarian failure (POF) occurs in about 1% of the female population who are less than 40 years old. Several causes have been studied and EDC might have some association with it (Costa et al., 2014).

Irregularities in menstruation cycle: EDC may interfere with the hormonal regulation of menstruation cycle and thereby causing irregularities, such as long cycles which may reduce fecundability (ability to conceive in a menstrual cycle) (Costa et al., 2014).

Polycystic ovary syndrome (*PCOS*): This is a prevalent endocrine disorder in women. The disease is characterized by anovulation and hyperandrogenism, and associated with higher prevalence of obesity, insulin resistance and metabolic abnormalities (Costa et al., 2014).

Men may also suffer from malfunctions of the sexual organs such as sperm anomalies, hypospadias, and ectopic testes. There exists a strong possibility that these diseases were caused by perinatal exposure to EDs during sensitive stages of sexual differentiation of the developing fetus (Fechner et al., 2011; Santodonato, 1997). There are some other effects which are as follows.

Sperm quality: A number of studies reported a decline (since the 1930s) in sperm quality in several countries, such as sperm count, proportion of normal sperm, semen volume, which might be expected to affect fertility. However, not everyone agrees with these results. Several surveys refute this downward trend in human sperm quality. Even if there is not a worldwide decline in sperm quality, there are clearly variations in sperm quality, both within and between countries. From what is known about testis development and function, it is plausible that endocrine-active chemicals could affect sperm quality. But so far, no research has studied the relationship between exposure to endocrine disrupting chemicals and sperm quality (Endocrine Disruptors, 2001).

Fertility: In men, fertility has decreased in the last decades, at least in some countries. Similar observations were also seen by Comhaire et al. (2007) in Denmark, in France, (Bay et al., 2006) and in the United Kingdom. Some human and experimental animal studies have shown that occupational or environmental exposure to high levels of certain chemicals, such as pesticides and PCBs, can impair fertility, but any relationship to endocrine disruption remains speculative (Nicolopoulou-Stamati and Pitsos, 2001).

3. Need for public awareness

Following is a list of findings about EDC, according to a report by UNEP and WHO (2013):

- EDCs are exogenous in nature and can interfere with any aspect of hormone action.
- They can act directly on hormone receptors as well as on any number of proteins that control the delivery of a hormone to its normal target cell or tissues.
- There is no direct relationship between the affinity of an endocrine disruptor for a hormone receptor and its potency. Chemical potency on a hormone system is dependent upon many factors including receptor abundance.
- Endocrine disruptors produce complex, nonlinear dose responses both in vitro and in vivo; can often include non-monotonic dose responses.
- The responses due to EDCs can be due to a variety of mechanisms. No response threshold can be assumed since the endogenous hormone levels fluctuate.
- The effects due to endocrine disruptors are tissue-specific.
- Endocrine disruptors can act on membrane or nuclear receptors.
- Endocrine disruptor activity can be exerted by environmental chemicals on estrogen, androgen, thyroid hormone action. Some

are known to interact with multiple hormone receptors simultaneously.
- Sensitivity to endocrine disruption is not the same with every receptor, tissue or organ. It is highest during tissue development; developmental effects will occur at doses lower than are required for effects in adults. Some of the endocrine disruptors can work together to produce combination effects when even combined at low doses. The extent of combination effects is governed by the number of endocrine disruptors and their individual potency.
- Testing for endocrine disruption must encompass the developmental period and include lifelong follow-up to assess latent effects.
- Not all endpoints of hormone action will exhibit the same sensitivity to chemical exposures (example, uterine response to BPA).
- The toxicity due to endocrine disruption must be taken into consideration when interpreting the results of studies of endocrine disrupting chemicals, or when designing studies to clarify the effects of endocrine disrupting chemicals and quantifying the risks to human and wildlife health since it represents a special type of toxicity.
- The toxic effects exerted by the endocrine disruptors are also quite complex and are not always captured using strategies designed to detect acute toxicity.

Developing and low lying economic countries are in a vulnerable situation to go for significant risks on human health due to these endocrine disruptors. Endocrine disruptors are one of the major toxicants that cause varieties of health complications ranging primarily from disruption of the homeostasis of the hormone system to nervous system, thus affecting majority of the organs of the human body. These groups of chemicals have a high degree of stability with low degree of degradability that helps its presence in the environment in its unchanged form. Thus, the hazard lies in exposure to the environment after its discharge as waste. This gives the emphasis of endocrine disruptors not as a problem of certain group of individuals suffering from its toxicological effects rather it serves as a major concern of public health. This leads to public health awareness about endocrine disruption. Now, the query comes about the strategies and methodology of awareness of the public in the hope of developing public health stature of the country. Public health is indeed a vast field, with a lot of stakeholders involved having purposes of different dimensions and different league. Concerning public health awareness lies the general mass that plays the role of individual awareness of knowing the role of these toxicants, the healthcare professionals that serves as guidance how to address these issues and the policy makers who will make the governing rules as a result of massive public health awareness.

But the alarming news is that, no such initiatives has been taken from the government, private or other sectors due to the lack of knowledge sharing about EDCs. The current state of the law and regulation does not support the unwanted exposure of endocrine disrupting chemicals but lack of implementation of the rules about the use of EDCs is being underestimated. World health organization on their 2012 report already gave an outline about the key concern to raise the awareness about EDCs. Among them reproductive system and development were of the major concern. This review article also reflects the toxic effect of EDCs even at long-term low dose exposure but the information needs to be disseminated among the mass people and workers from being exposed to these deadly chemicals. Particular concern should be built in the area of the following:

1. Rise of endocrine related disease.
2. Increase of the global rate of endocrine related cancers.
3. Rise of obesity and type II diabetes has been increasing over time (UNEP and WHO, 2013).
4. Prostate cancer risk among occupational workers are increasing due to large amount pesticide especially PCB and arsenic.
5. Sewage water must undergo effluent treatment as we know that EDCs are stable compounds having low degree of biodegradability. The manufacturing industries having various uses of EDCs must be promoted to have effluent treatment plant in their manufacturing sites.
6. More epidemiological data must be available to interpret accurately the impact of EDCs on human health or disease prevalence.
7. Endocrine disrupting chemicals having a low degree of water solubility is indicative of high degree of lipophilicity, thus facilitating their easy entry into the bloodstream (Safe et al., 2009). Public awareness should, therefore, be created on a more informative manner of how exposure of these chemicals can rapidly cause toxicological impacts in the body.
8. Treatment of EDCs toxicity should be such that the medication competitively binds with the receptor responsible for the action of the EDC. For example, GPR30, a seven transmembrane receptor can be used for EDC treatment as this receptor has been found to have a very high binding affinity for bisphenol A, genistein, zealozone and nonylphenol (Andersen et al., 2002). Suggestions to prepare optimized therapy for patients suffering from the toxicological implications of EDCs may be proposed to drug manufacturers.
9. Issues of environmental causes of trends in endocrine disease and disorders must be addressed.
10. Strategies must include the use of media, both printed and electronic, in order to reach the people in an appropriate manner, thus increasing peoples' awareness of the harmful picture of EDCs.

All these key issues concerning the risk of the human life to these chemicals have not yet been adequately addressed in the developing and low income countries. Public awareness needs to be raised before EDCs affect the human and wildlife at a large scale. Heavy metals like lead and others like POPs, tributylin, di (2-ethylhexyl) phthalate, nonylphenol have been banned in many countries but sometime these bans concern specific uses only. The rate of men suffering from prostate cancer due to EDCs is found to also be increasing, particularly due to lack of occupational safety. Nonetheless, there have been clear benefits for human and wildlife health from the declining use of these chemicals. Understanding of the current need to improve human and wildlife health by prevention of environmentally induced diseases is extremely essential.

This review article has taken an attempt to outline the different EDC chemicals with their possible effects. The necessity of immediate action to ban most of the EDCs chemicals has been emphasized, particularly in the low-income countries. This may be possible if the following are taken into serious consideration:

1. Assessments of EDC action by researchers and all concerned bodies need to take into account the characteristics of endocrine system and mechanism behind its effect in order to get a full grip of how EDCs work and damage human and wildlife.
2. Raising awareness among the different government, private and NGO sectors about the fate of EDC exposure and thus to take serious implementation to reduce the exposure.
3. More collaborative work need to be done so that more tests on the toxic impacts of EDCs can be conducted and also help to bridge the gaps through knowledge sharing among the developed and developing countries.
4. People should be encouraged to come forward to learn about EDCs and their toxicological actions in order to be aware of the

harmful effects of these toxicants. This will also help the policy makers in an effective manner to minimize the chemical exposure of these chemicals below optimum levels.

5. The public should also be encouraged to help the policy makers in the effective implementation of the policies created in the awareness and in the minimization of these chemicals by discouraging people involved with the manufacture, import and use of these toxicants.

All these gaps need to be urgently looked into by each respective government, NGOs and private sectors by incorporating proper initiatives. It may also be necessary to give specific ideas to the policy makers to revise our legislation process so that these endocrine problems can be reduced. Management and framing of national occupational safety and health policy must also be incorporated in to the National Policy. Awareness regarding the safety and health of the workers in their working place must be ensured by their owners, as well as enforced by the government agencies.

4. Conclusion

This study has taken an attempt to describe the evolution of the field of endocrine disruptors as well as the mechanism of effect of the different industrially and therapeutically important compounds in producing different levels of endocrine toxicity and current exposure to these environmental toxicants around the world. Despite the advances that are being made in many other fields in the developing countries, information regarding this field is still quite limited. There is no proper documented assessment available about the population exposed to endocrine disruptors, and the level of toxicity they might already be in. Although some policy changes were executed for example the ban of DDT, etc. but these were done after long time and had resulted in a huge damage. Sufficient studies need to be carried out and the necessary policy changes should be done in a definite frame of time in order to have a proper assessment of endocrine disruptor. The damage that has already been done also needs to be assessed and dealt with. Challenges will exist though the works need to be carried out in the midst of the constraints present in order to have a better healthcare in the future.

4.1. Recommendations

The present study provides information on the exposure of different endocrine disruptors present in different areas and the specific effects on the population of the country. There is no concrete data of the diseases concerned with these substances and also to prove their correlation with the vulnerable areas of endocrine disrupting chemicals. More experimental studies need to be carried out in order to find such data.

On the other hand, no specific mechanisms have yet been found through which endocrine disrupting chemicals affect different parts of human body. More studies and experiments need to be conducted so that the mechanism can be known in order to treat the abnormalities caused by EDCs in the body accurately.

From one study, it gives the idea that endocrine disruptor can be spread as far as the surface water of the paddy fields and lakes, but no proper channel has yet been identified to show the mechanism of these endocrine disrupting substances being distributed at the concentration concerned. So proper channels should be identified and proper disposal of the chemicals ensured.

Below are given two case studies, which discuss the presence of certain EDCs in raw sewage and industrial pollutants. Since the endocrine disruptor substance are present in high concentration in several water bodies which are important for our water supply owing to their low degree of biodegradation, the waste material should be filtered and also there should be a proper monitoring system for the implementation of use of affluent treatment plants by the industries of the countries.

The use of these toxicants in the field should be discouraged strictly on the basis of the area and their subsequent requirement. Sufficient data on the disturbance of the aquatic life both in the rivers and in the seas is also not available. Therefore, there is a huge area of research that can be done on the presence of these substances in both aquatic or soil environment.

Case Study 1: Survey of STPs (Sewage Treatment Plants) in different parts of the world: It was found that raw sewage in a Brazilian and a German municipal STP contained 17α-estradiol and estrone with average concentrations of 21 ng/l and 40 ng/l in Brazil and with average concentrations of 15 ng/l and 27 ng/l in Germany, respectively (Daughton and Ternes, 1999). Elimination in Brazil was higher (99 and 83%) than in Germany (64 and 68%). In a survey of STPs in the Netherlands, presence of 17β-estradiol, 17α-estradiol, 17α-ethinylestradiol, and estrone in surface and wastewater were examined. In most effluents of STPs, estrone and 17β-estradiol were detected (Belfroid et al., 1999). The highest concentration observed was 47 ng/l for estrone, while 17β-estradiol concentrations were between 1 and 12 ng/l. Concentrations of hormones in surface water were generally low (below 1–5 ng/l). The effluent concentrations of estrone and estradiol have been measured in Israel and the United Kingdom. In Tel Aviv, estrogen levels were between 24–48 ng/l, whereas, in the United Kingdom, concentrations in sewage water plant effluents varied from 1 to 50 ng/l for estrone and 2–50 ng/l for 17β-estradiol (Desbrow et al., 1998). Investigations in the United Kingdom revealed concentration of 17α-ethinylestradiol in effluents of STPs up to 7 ng/l, whereas concentrations between 2 and 15 ng/l was determined in the river water. (Desbrow et al., 1998) Higher exposures of these are found to be affecting not only the drinking water quality for human and wildlife but also the crops and environment.

Case Study 2: Study of industrial pollutants: Large amounts of PCBs (polychlorinated biphenyls) are found to be released from the industries due to inappropriate disposal, accidents or leaks in the industrial facilities. The widespread applications of PCBs with their persistence and mobility result in their worldwide distribution and as a result PCBs have been identified in nearly every environmental compartment. Even after being banned and production being stopped in most of the countries globally, the estimated level of PCB is almost 1.2 million tons with about one third of the quantity circulating in the environment (Puga et al., 2009). In another study, PCBs were detected in three out of five sediment samples from different locations in Japan with dry sample fractions in the range from less than 1.1 ppb to 3.7 ppb. In the Baltic Sea region, the concentration of total PCB congeners in air was found to have increased with the temperature (Agrell et al., 1999).

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Ethics

Any opinions, findings, and conclusions or recommendations expressed in this review article are those of the authors or/and already published in peer-reviewed journals that are properly referenced and bears no conflicts of interest.

Conflict of interest

The author declares that there is no conflict of interest.

Transparency document

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