

COMPREHENSIVE REVIEWS ON ADVERSE HEALTH EFFECTS OF HUMAN EXPOSURE TO ENDOCRINE-DISRUPTING CHEMICALS

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ABSTRACT

Endocrine disruption refers to the ability of chemicals or substances at a certain dose to interfere with hormonal systems in the body. This has brought genuine concern globally in recent years. Endocrine disruptive chemicals (EDCs) represent a serious health risk to human and wildlife and have the tendency to impact human health negatively. This review focuses on the health impact of EDCs. There is growing interest from researchers, scientists and standard organization across the globe on the possible health threat posed by endocrine disrupting chemicals (EDCs), which are substances we get exposed to on a daily basis in our environment, food, drinks and consumer products (creams, drugs, addictive, plastics, children toy etc.) that interfere with hormone biosynthesis, action resulting in a deviation from normal homeostatic control or reproduction and metabolism. Moreover, EDCs represent a broad class of molecules such as industrial chemicals and organo-chlorinated pesticides, plasticizers and plastics, fuels, and many more chemicals that are present in the environment or are in extensive use. This article focuses on making suggestions to broaden society knowledge of the health risk of EDCs, including enhancing increased basic and clinical research, invoking the precautionary principle, and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness.

KEYWORDS:

Endocrine Disruptive Chemicals, Endocrine disruptor, DDTs, PCBs, Health impact

INTRODUCTION

The production of chemicals and their introduction into the environment is turning out to be

progressively on a worldwide premise because of urbanization and industrialization. Some of these chemicals act as endocrine disruptors as they disturb endogenous hormone signaling pathways. Endocrine disruptors are chemicals that at a certain dose can interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. Some of different reviews indicate an association with cancer, diabetes, endometriosis and other ailments. There is confirmation that the rate of endocrine-related issue in people has expanded in recent years. Numerous causes underlie this pattern; however, confirmation is mounting that chemical exposure is involved. Close to 800 chemicals are known or suspected to be capable of interfering with hormone receptors, hormone synthesis or hormone conversion.

An extensive variety of substances, both natural and man-made, are thought to cause endocrine disruption, including dioxin and dioxin-like compounds, pharmaceuticals, polychlorinated biphenyls, organotin compounds, plasticizers such as bisphenol, DDT and other pesticides. Endocrine disruptors may be found in most of the products which we use every day including flame retardants, food, toys, plastic bottles, detergents, cosmetics, metal food cans, and pesticides [1]. The NIEHS studies help to determine whether exposure to endocrine disruptors may result in human health effects including male and female lowered fertility and an increased incidence of endometriosis and some cancers [2]. Research shows that endocrine disruptors may pose the greatest risk during prenatal and early postnatal development, when organ and neural systems are forming.

Endocrine disrupting chemicals (EDCs) and potential EDCs are usually man-made, discover in various materials such as additives or contaminants in food, pesticides, metals, and personal care products. EDCs have been suspected to be associated with altered reproductive function in males and females; increased incidence of breast cancer, ab-

normal growth patterns and neuro-development delays in children, as well as changes in immune function.

HISTORY OF ENDOCRINE DISRUPTORS

The first evidence of endocrine disruption was disclosed almost 40 year ago through observations of uncommon vagina adenocarcinoma in daughters born 15–22 year earlier to women treated with the potent synthetic estrogen Diethylstilboestrol (DES) during pregnancy [3]. The term endocrine disruptor was coined at the Wingspread Conference Centre in Wisconsin, in 1991. One of the early papers on the developmental effects of endocrine-disrupting chemicals in wildlife and humans was proposed by Colborn and co worker [4]. In the paper, she stated that environmental chemicals disrupt the development of the endocrine system, and that effects of exposure during development are often permanent. Although the endocrine disruption has been disputed by some, work sessions from 1992 to 1999 have generated consensus statements from scientists regarding the hazard from endocrine disruptors, particularly in wildlife and also in humans [5-8].

The Endocrine Society released a scientific statement outlining mechanisms and effects of endocrine disruptors on “male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology,” and showing how experimental and epidemiological studies converge with human clinical observations “to implicate EDCs as a significant concern to public health.” The statement noted that it is difficult to show that endocrine disruptors cause human diseases, and it recommended that the precautionary principle should be followed [9]. A concurrent statement expresses policy concerns [10].

Endocrine disrupting compounds encompass a variety of chemical classes, including drugs, pesticides, compounds used in the plastics industry and in consumer products, industrial by-products and pollutants, and even some naturally produced botanical chemicals. Some are pervasive and widely dispersed in the environment and may bioaccumulate. Some are persistent organic pollutants (POP's), and can be transported long distances across national boundaries and have been found in virtually all regions of the world, and may even concentrate near the North Pole, due to weather patterns and cold conditions [11]. Others are rapidly degraded in the environment or human body or may be present for only short periods of time [12]. Health effects attributed to endocrine disrupting compounds include a range of reproductive problems (reduced fertility, male and female reproductive tract abnormalities, and skewed male/female sex ratios, loss of foetus, menstrual problems [13];

changes in hormone levels; early puberty; brain and behaviour problems; impaired immune functions; and various cancers.

TYPES OF EDCS

Endocrine disruptors are chemicals, or chemical mixtures, that interfere with normal hormone function. EDCs are highly heterogeneous [14] and can be classified in the following two ways.

1. They can be classified in two categories [10]:

(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 by-products (e.g. polychlorinated biphenyls(PCBs), polybrominated biphenyls (PBBs), dioxins)

➤ Plastics [e.g. bisphenol A (BPA), organotin compounds]

➤ Plasticizers Pesticides [e.g. dichlorodiphenyltrichloroethane (DDT)]

➤ Fungicide (e.g. vinclozolin) and some pharmaceutical agents [e.g. diethylstilboestrol (DES)].

2. The EDCs can also be grouped according to their origins [15]:

(i) Natural and artificial hormones (e.g. fitoestrogens, 3-omegafatty 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, alkylphenolethoxylate detergents, fire retardants, plasticizers, solvents, 1, 4-dichlorobenzene and polychlorinated bis-phenols (PCBs, organotin compounds).

(iv) Side products of industrial and household processes (e.g. polycyclic aromatic hydrocarbons (PAHs), dioxins, pen-tachlorobenzene, organotin compounds).

Some other examples of putative EDCs are polychlorinated dibenzo-dioxins (PCDDs) and -furans (PCDFs), phenol derivatives and a number of pesticides (most prominent being organochlorine insecticides like endosulfan, Kepone (chlordecone) and DDT and its derivatives, the herbicide atrazine, and the fungicide vinclozolin), the contraceptive 17-alpha ethinylestradiol, as well as naturally occurring phytoestrogens such as genistein and mycoestrogens such as zearalenone [16]. Tributyltin (TBT) are organotin compounds that was used as a biocide in anti-fouling paint, commonly known as bottom paint [17,18].

TABLE 1
Some well-known EDCs and their uses
adapted from [19]

Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate, triphenyltins (TPT)
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol, organotin
Electronics and Building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterial	Triclosan
Textiles, clothing	Perfluorochemicals
Product Cleaner	Fragrances, cyclosiloxanes
Surfactants-certain kinds of detergents used for removing oil and their metabolites	Nonylphenol (alkylphenols)
Contraceptive	Ethinyl estradiol (Synthetic steroid)

SELECTED EDCS IN THIS REVIEW ARTICLE

Organotin Compounds (OTCs). Tributyltin (TBT) are organotin compounds that was used as a biocide in anti-fouling paint, commonly known as bottom paint. TBT has been shown to impact invertebrate and vertebrate development, disrupting the endocrine system, resulting in masculinization, lower survival rates, as well as many health problems in mammals [17,18,20,21]. High toxicity of tri-substituted organotin (effects seen in the aquatic environment at $<1 \text{ ngL}^{-1}$)(R_3SnX) has led to the ban of organotin compounds as a marine antifouling under the international convention on the control of harmful antifouling systems on ships [1,22]. Basically, there are numerous effects of TBT which are well reported in organotin compounds produce various effects when aquatic life are exposed to these chemicals. These effects include; larva mortality, growth impairment, developmental and reproductive effects [1,17,22]. Among other effects of organotin compounds which includes immune toxicity, carcinogenicity etc. Apparently, TBT and TPT have reported to induce toxic effects in both male and female reproductive organs of rodents, these contaminants have been confirmed to cause tumors I organs of rodents and may results in endocrine disruption [23].

Recent studies have released a significant reduction by TBT along coastlines as well as the biological recovering of many marine species [24]. In a study carried out by Okoro and his co-workers on Cape Town harbour, organotin compounds were

detected in Cape Town harbour in both sediments and seawater samples [25]. The observed values recorded for TBT could be the result of an increase or decrease in traffics of ships and boats. Ship reparations is one of the reasons suggested for TBT detection in sediments samples [25]. Tributyltin has been demonstrated by Okoro and co-workers to have effects on the stability of hemocytic lysosome membrane of the mussel, (*Mytillus galloprovincialis*), they found out that the two exposed groups of mussels exhibited appreciably increased whole body TBT concentration with decreases in Neutral Red Retention (NRRT) for lower and higher exposure groups. NRRT assay was found useful in this study for early warning and cellular biomarker of stress due to TBT exposure in *Mytillus galloprovincialis* [26], a similar trend was reported in *Tapes philippinarum* and *Mytilus galloprovincialis* [27,28].

Dichloro-Diphenyl-Trichloroethane (DDT).

DDT was first used as a pesticide against Colorado potato beetles on crops beginning in 1936 [29]. An increase in the incidence of malaria, epidemic typhus, dysentery, and typhoid fever led to its use against the mosquitoes, lice, and houseflies that carried these diseases [29]. It became used worldwide to increase monoculture crop yields that were threatened by pest infestation, and to reduce the spread of malaria which had a high mortality rate in many parts of the world. As early as 1946, the harmful effects of DDT on bird, beneficial insects, fish, and marine invertebrates were seen in the environment. The most infamous example of these effects was seen in the eggshells of large predatory birds, which did not develop to be thick enough to support the adult bird sitting on them [30].

Further studies found DDT in high concentrations in carnivores all over the world, the result of biomagnification through the food chain [31]. Twenty years after its widespread use, DDT was found trapped in ice samples taken from Antarctic snow, suggesting wind and water are another means of environmental transport [32]. Recent studies show the historical record of DDT deposition on remote glaciers in the Himalayas [[33]. More than sixty years ago when biologists began to study the effects of DDT on laboratory animals, it was discovered that DDT interfered with reproductive development [34,35]. Recent studies suggest DDT may inhibit the proper development of female reproductive organs that adversely affects reproduction into maturity [36]. Additional studies suggest that a marked decrease in fertility in adult males may be due to DDT exposure [37]. Most recently, it has been suggested that exposure to DDT in utero can increase a child's risk of childhood obesity [38]. DDT is still used as anti-malarial insecticide in Africa and parts of South East Asia in limited quantities.

Polychlorinated Biphenyls (PCBs). Polychlorinated biphenyls (PCBs) are a class of chlorinated compounds used as industrial coolants and lubricants. PCBs are created by heating benzene, a by-product of gasoline refining, with chlorine [39]. They were first manufactured commercially by the Swann Chemical Company in 1927. In 1933, the health effects of direct PCB exposure were seen in those who worked with the chemicals at the manufacturing facility in Alabama. In 1935, Monsanto acquired the company, taking over US production and licensing PCB manufacturing technology internationally. General Electric (GE) was one of the largest US companies to incorporate PCBs into manufactured equipment. Between 1952 and 1977, the New York GE plant had dumped more than 500,000 pounds of PCB waste into the Hudson River. PCBs were first discovered in the environment far from its industrial use by scientists in Sweden studying DDT [40]. The effects of acute exposure to PCBs were well known within the companies who used Monsanto's PCB formulation who saw the effects on their workers who came into contact with it regularly. Direct skin contact results in a severe acne-like condition called chloracne [41]. Exposure increases the risk of skin cancer [42], liver cancer [43] and brain cancer [42,44]. Monsanto tried for years to downplay the health problems related to PCB exposure in order to continue sales [45]. The detrimental health effects of PCB exposure to humans became undeniable when two separate incidents of contaminated cooking oil poisoned thousands of residents in Japan and Taiwan [46], leading to a worldwide ban on PCB use in 1977.

Recent studies show the endocrine interference of certain PCB congeners is toxic to the liver and thyroid [47]; increases childhood obesity in children exposed prenatally [38] and may increase the risk of developing diabetes [48,49]. PCBs in the environment may also be related to reproductive and infertility problems in wildlife. In Alaska it is thought that they may contribute to reproductive defects, infertility and antler malformation in some deer populations. Declines in the populations of otters and sea lions may also be partially due to their exposure to PCBs, the insecticide DDT, other persistent organic pollutants. Bans and restrictions on the use of EDCs have been associated with a reduction in health problems and the recovery of some wildlife populations [50].

Polybrominated Diphenyl Ethers (PBDEs). Polybrominated diphenyl ethers (PBDEs) are a class of compounds found in flame retardants used in plastic cases of televisions and computers, electronics, carpets, lighting, bedding, clothing, car components, foam cushions and other textiles. Potential health concern: PBDE's are structurally very similar to Polychlorinated biphenyls (PCBs), and

have similar neurotoxic effects [51,52]. Research has correlated halogenated hydrocarbons, such as PCBs, with neurotoxicity [47]. PBDEs are similar in chemical structure to PCBs, and it has been suggested that PBDEs act by the same mechanism as PCBs [47]. In 1972, in response to this situation, the National Commission on Fire Prevention and Control was created to study the fire problem in the US. In 1973 they published their findings in *America Burning*. Most of the recommendations dealt with fire prevention education and improved building engineering, such as the installation of fire sprinklers and smoke detectors.

The Commission expected that with the recommendations, a 5% reduction in fire losses could be expected each year, halving the annual losses within 14 years. Historically, treatments with alum and borax were used to reduce the flammability of fabric and wood, as far back as Roman times [53]. Since it is a non-absorbent material once created, flame retardant chemicals are added to plastic during the polymerization reaction when it is formed. Organic compounds based on halogens like bromine and chlorine are used as the flame retardant additive in plastics, and in fabric based textiles as well.

The widespread use of brominated flame retardants may be due to the push from Great Lakes Chemical Corporation (GLCC) to profit from its huge investment in bromine. In 1992, the world market consumed approximately 150,000 tonnes of bromine-based flame retardants, and GLCC produced 30% of the world supply [54]. PBDEs have the potential to disrupt thyroid hormone balance and contribute to a variety of neurological and developmental deficits, including low intelligence and learning disabilities [54]. Many of the most common PBDE's were banned in the European Union in 2006 [54]. Studies with rodents have suggested that even brief exposure to PBDEs can cause developmental and behaviour problems in juvenile rodents [55] and exposure interferes with proper thyroid hormone regulation [56].

Phthalates. Phthalates are found in some soft toys, flooring, medical equipment, cosmetics and air fresheners. They are of potential health concern because they are known to disrupt the endocrine system of animals, and some research has implicated them in the rise of birth defects of the male reproductive system [57-59]. Although an expert panel has concluded that there is "insufficient evidence" that they can harm the reproductive system of infants [60], California [61] and Europe have banned them from toys. One phthalate, Bis(2-ethylhexyl) phthalate (DEHP), used in medical tubing, catheters and blood bags, may harm sexual development in male infants [58]. In 2002, the Food and Drug Administration released a public report which cautioned against exposing male babies to

DEHP. Although there are no direct human studies the FDA report states: "Exposure to DEHP has produced a range of adverse effects in laboratory animals, but of greatest concern are effects on the development of the male reproductive system and production of normal sperm in young animals. In view of the available animal data, precautions should be taken to limit the exposure of the developing male to DEHP [62]. Similarly; phthalates may play a causal role in disrupting masculine neurological development when exposed [57].

Perfluorooctanoic Acid. PFOA exerts hormonal effects including alteration of thyroid hormone levels. Blood serum levels of PFOA were associated with an increased time to pregnancy or "infertility. PFOA exposure is associated with decreased semen quality. PFOA appeared to act as an endocrine disruptor by a potential mechanism on breast maturation in young girls. A C8 Science Panel status report noted an association between exposure in girls and a later onset of puberty.

Bisphenol A (BPA). Of the approximately 85,000 chemicals in use, 1000 have been identified as having the ability to disrupt normal endocrine function. Exposure to endocrine disrupting chemicals (EDCs) during critical period in brain differentiation (prenatal and neonatal life) via the mother can alter the course of the development of sexually dimorphic behaviours. Bisphenol A (BPA) has estrogenic activity and is one of the most studied EDCs. Jones and co worker [63] review evidence from studies in rodents using dose levels relevant to human exposure. BPA alters behaviour and eliminates or in some cases reverses sexually dimorphic behaviours observed in unexposed animals.

Other Suspected Endocrine Disruptors. Some other examples of putative EDCs are polychlorinated dibenzo-dioxins (PCDDs) and -furans (PCDFs), polycyclic aromatic hydrocarbons (PAHs), phenol derivatives and a number of pesticides (most prominent being organochlorine insecticides like endosulfan, Kepone (chlordecone) and DDT and its derivatives, the herbicide atrazine, and the fungicide vinclozolin), the contraceptive 17-alpha ethinylestradiol, as well as naturally occurring phytoestrogens such as genistein and mycoestrogens such as zearalenone. The molting in crustaceans is an endocrine-controlled process. In the marine penaeid shrimp (*Litopenaeus vannamei*), exposure to endosulfan result increased susceptibility to acute toxicity and increased mortalities in the postmolt stage of the shrimp [64]. Many sunscreens contain oxybenzone, a chemical blocker that provides broad-spectrum UV coverage, yet is subject to a lot of controversy due its potential estrogenic effect in humans [18].

ROUTES OF EXPOSURE

Food is a major mechanism by which people are exposed to pollutants. Diet is thought to account for up to 90% of a person's PCB and DDT body burden [65]. In a study of 32 different common food products from three grocery stores in Dallas, fish and other animal products were found to be contaminated with PBDE [66]. Since these compounds are fat soluble, it is likely they are accumulating from the environment in the fatty tissue of animals which we eat. Some suspect fish consumption has a major source of many environmental contaminants. Indeed, both wild and farmed salmon from all over the world have been shown to contain a variety of man-made organic compounds [67].

With the increase in household products containing pollutants and the decrease in the quality of building ventilation, indoor air has become a significant source of pollutant exposure [68]. Residents living in homes with wood floors treated in the 1960s with PCB-based wood finish have a much higher body burden than the general population [69]. A study of indoor house dust and dryer lint of 16 homes found high levels of all 22 different PBDE congeners tested for in all samples [70]. Recent studies suggest that contaminated house dust, not food, may be the major source of PBDE in our bodies [71,72]. One study estimated that ingestion of house dust accounts for up to 82% of our PBDE body burden [73].

Consumer goods are another potential source of exposure to endocrine disruptors. An analysis of the composition of 42 household cleaning and personal care products versus 43 "chemical free" products was performed by [74]. The products contained 55 different chemical compounds: 50 were found in the 42 conventional samples representing 170 product types, while 41 were detected in 43 "chemical free" samples representing 39 product types. Parabens, a class of chemicals that has been associated with reproductive-tract issues, were detected in seven of the "chemical free" products, including three sunscreens that did not list parabens on the label.

Vinyl products such as shower curtains were found to contain more than 10% by weight of the compound DEHP, which when present in dust has been associated with asthma and wheezing in children. The risk of exposure to EDCs increases as products, both conventional and "chemical free," are used in combination. "If a consumer used the alternative surface cleaner, tub and tile cleaner, laundry detergent, bar soap, shampoo and conditioner, facial cleanser and lotion, and toothpaste would potentially be exposed to at least 19 compounds: 2 parabens, 3 phthalates, MEA, DEA, 5 alkylphenols, and 7 fragrances [74]. An analysis of the endocrine disrupting chemicals in old Mennonite women in mid-pregnancy determined that they

have much lower levels in their systems than the general population. Mennonites eat mostly fresh, unprocessed foods, farm without pesticides, and use few or no cosmetics or personal care products. One woman who had reported using hairspray and perfume had high levels of monoethyl phthalate, while the other women all had levels below detection.

Three women who reported being in a car or truck within 48 hours of providing a urine sample had higher levels of diethylhexyl phthalate which is found in polyvinyl chloride, and is used in car interiors [75]. Additives added to plastics during manufacturing may leach into the environment after the plastic item is discarded; additives in micro plastics in the ocean leach into ocean water and in plastics in landfills may escape and leach into the soil and then into groundwater [76]. Esteban and co worker [77] determine the presence and origin of 30 substances of anthropogenic origin considered to be, or suspected of being, endocrine disruptors in the continental waters of the Antarctic Peninsula region.

HOW ENDOCRINE DISRUPTORS WORK

There are various mechanisms of ED action, one of which is their interference in the action of 11 β -hydroxysteroid dehydrogenase (11 β HSD) that maintains a balance between active and inactive glucocorticoids on the intracellular level. This enzyme has two isoforms and is expressed in various tissues. Inhibition of 11 β HSD in various tissues can have different consequences. Vitku and co worker [78] review on the effects of 11 β HSD inhibitors in the testis, colon, adipose tissue, kidney, brain and placenta. Clinical evidence, experimental models, and epidemiological studies suggest that EDC have major risks for human by targeting different organs and systems in the body. Multiple mechanisms are involved in targeting the normal system, through estrogen receptors, nuclear receptors and steroidal receptors activation. Maqbool and co worker [79] review summarize all evidence regarding different physiological disruptions in the body and possible involved mechanisms, to prove the association between endocrine disruptions and human diseases.

From animal studies, researchers have learned much about the mechanisms through which endocrine disruptors influence the endocrine system and alter hormonal functions.

HARMFUL EFFECTS OF ENDOCRINE DISRUPTORS ON HUMAN HEALTH

- Mimic or partly mimic naturally occurring hormones in the body like estrogens (the female sex hormone), androgens (the male sex hormone), and thyroid hormones as shown in Fig. 1B, potentially producing overstimulation.

- Bind to a receptor within a cell and block the endogenous hormone from binding. The normal signal then fails to occur and the body fails to respond properly. Examples of chemicals that block or antagonize hormones are anti-estrogens and anti-androgens.

- Fig. 1C explains the Interfering or blocking the way natural hormones or their receptors are made or controlled, for example, by altering their metabolism in the liver.

When absorbed in the body, an endocrine disruptor can decrease or increase normal hormone levels (left), mimic the body's natural hormones (middle), or alter the natural production of hormones (right).

Many endocrine-related diseases and disorders are on the rise [80-82], For example:

- Large proportions (up to 40%) of young men in some countries have low semen quality, which reduces their ability to father children.

- The incidence of genital malformations, such as non-descending testes (cryptorchidisms) and penile malformations (hypospadias), in baby boys has increased over time.

- Neurobehavioural disorders associated with thyroid disruption affect a high proportion of children in some countries.

- Global rates of endocrine-related cancers (breast, endometrial, ovarian, prostate, testicular and thyroid) have been increasing in past decade.

- The prevalence of obesity and type 2 diabetes has dramatically increased worldwide.

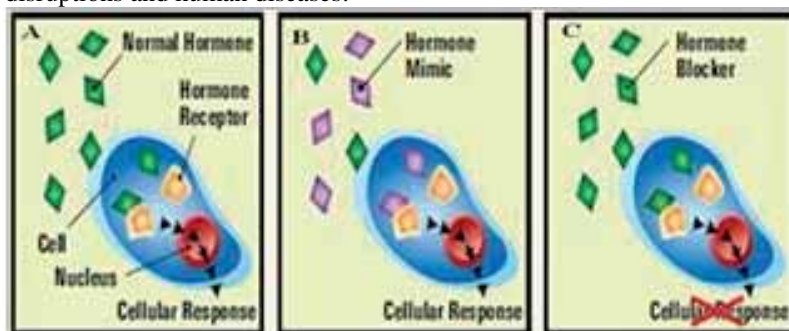


FIGURE 1
EDCs mechanisms

TABLE 2
Examples of EDC routes of exposures in humans

Exposure to EDCs	EDCs come from	EDC example(s)
Oral consumption of contaminated food or water	Industrial waste/ pesticides contaminating soil/ groundwater	PCBs, dioxins, perfluorinated compounds, DDT
Oral consumption of contaminated food or water	Leaching of chemicals from food/ beverage containers; pesticide residues in food/beverage	BPA, phthalates, chlorpyrifos, DDT
Contact with skin and/or inhalation	Household furniture treated with flame retardants	BFRs
Contact with skin and/or inhalation	Pesticides used in agriculture, homes/ for public disease vector control	DDT, chlorpyrifos, vinclozolin, pyrethroids
Intravenous	Intravenous tubing	Phthalates
Application to skin	Some cosmetics, personal care products, anti-bacterials, sunscreens, medications	Phthalates, triclosan, Parabens, insect repellants
Biological transfer from placenta	Maternal body burden due to prior/current exposures	Numerous EDCs can cross the placenta
Biological transfer from mother's milk	Maternal body burden due to prior/current exposures	Numerous EDCs are detected in milk

KEY: BFR: brominated flame retardant; BPA: bisphenol A; PCBs: polychlorinated biphenyls

EDCs are global and ubiquitous problem. People and animals are exposed to EDCs by a variety of routes (Table 2), including consumption of food and water, through the skin, by inhalation, and by transfer from mother to fetus (across the placenta) or mother to infant (via lactation) if a woman has EDCs in her body. Pregnant mothers and children are the most vulnerable populations to be affected by developmental exposures, and the effect of exposures to EDCs may not become evident until later in life. Research also shows that it may increase the susceptibility to non-communicable diseases. It was observed that increasing chemical production and use is related to the growing incidence of endocrine-associated paediatric disorders over the past 20 years, including male reproductive problems (cryptorchidism, hypospadias, and testicular cancer), early female puberty, leukaemia, brain cancer, and neurobehavioral disorders. Chemicals such as polychlorinated biphenyls (PCBs), BPA, and phthalates, are now detectable in serum, fat, and umbilical cord blood in humans around the globe.

One example of the consequences of the exposure of developing animals, including humans, to hormonally active agents is the case of the drug diethylstilbestrol (DES), a non-steroidal estrogen and not an environmental pollutant. Prior to its ban in the early 1970s, doctors prescribed DES to as many as five million pregnant women to block spontaneous abortion, an off-label use of this medication prior to 1947.

It was discovered after the children went through puberty that DES affected the development of the reproductive system and caused vaginal cancer. The relevance of the DES saga to the risks of exposure to endocrine disruptors is questionable, as the doses involved are much higher in these individuals than in those due to environmental exposures [83]. Aquatic life subjected to endocrine disruptors in an urban effluent have experienced decreased levels of serotonin and increased feminiza-

tion [84].

Childhood neuropsychiatric disorders are increasing in prevalence with as many as 1 in 6 children in the US now diagnosed with at least one [85]. These disorders include attention deficit hyperactivity disorder (ADHD) and Autism Spectrum Disorder (ASD), as well as depression and other mood disorders, learning disabilities, executive function deficits, and conduct disorders. PCBs have the strongest and longest-known associations with neurological disorders. In humans, there is evidence for impaired neurodevelopment [80,86], lower IQ, and problems with attention, memory, and fine motor skills such as writing. Similarly, polybrominated diphenyl ethers (PBDEs) are associated with reduced IQ, and other cognitive deficits [87]. PBDEs affect neurotransmitter activity, synaptic organization, and neuron viability suggesting that they impact not only brain development but also brain aging.

Brominated flame retardants, perfluorinated compounds, and pesticides (organophosphates such as chlorpyrifos and organochlorines), are linked to ADHD, ASD, and related learning disabilities [88]. Obesity rates are rising rapidly globally. Chemicals referred to as "Obesogens" are thought to enhance weight gain by altering or reprogramming key parts of the endocrine system governing metabolism, energy balance, and appetite, resulting in obesity and its related adverse health outcomes [89-92]. A brominated flame retardant, Firemaster 550, was shown to alter thyroid hormone levels in pregnant rats and their offspring, with the pups growing up to develop obesity, cardiac disease, early puberty and insulin resistance [93].

The increase in early puberty in girls, maybe attributed to many factors which includes; nutrition, stress, and ethnicity. Also, it may be due to exposures to estrogenic EDCs [94,95]. Such estrogenic compounds are also associated with uterine fibroids, ovarian dysfunction, and subfertility in humans and in animal models [96-98]. Several

chemicals, most notably phthalates, are associated with a variety of adverse effects on the male urogenital tract, including cryptorchidism, hypospadias, prostate disease and testicular cancer [99].

The list of known chemical carcinogens is long and includes metals [100,101], vinyl chloride, benzidine (used in dyes), solvents such as benzene, polycyclic aromatic hydrocarbons (PAHs), dioxins, fibers and dust (silica, asbestos, etc.), some pesticides including those on the Stockholm Convention's list of Persistent Organic Pollutants, and numerous pharmaceuticals including the synthetic estrogens. It was observed that estrogenic and other hormone-active chemicals such as BPA, phthalates and some pesticides, are thought to contribute to carcinogenic risk [102].

Vitku and co worker [78] reported the stimulatory effects of combined endocrine disruptors on MA-10 Leydig cell steroid production and lipid homeostasis. The author investigated direct effects and mechanisms of toxicity of Genistein (GEN) and plasticizer DEHP, MA-10 mouse tumor Leydig cells were exposed in-vitro to varying concentrations of GEN and MEHP, the principal bioactive metabolite of DEHP. The results suggest a deregulation of MA-10 Leydig function in response to a combination of GEN + MEHP. Hampl and co worker [103] provided the overview of the levels and sites at which endocrine disruptors (EDs) affect steroid actions. An important target for EDs is also steroid acute regulatory protein (StAR), responsible for steroid precursor trafficking to mitochondria. EDs influence receptor-mediated steroid actions at both genomic and non-genomic levels. This article is mainly focus on Endocrine disruptors & steroids.

Maqbool and co worker [79] reported the impact of environmental factors including the possible role of nutrition; stress and endocrine disruptors on the individual variations in pubertal timing and the possible underlying mechanisms. Estrogenic endocrine disruptors (EDs) were detected in 80% of 116 sports supplements investigated by biological in vitro reporter gene assays (RGAs). Palanza and co worker [104] quantify the hormonal activity in 50 of these sports supplement samples using a validated estrogen RGA and perform an exposure and risk assessment for human health. Palanza and co worker [104] investigated the highest activity samples presented a potential to influence the human daily exposure to 17 β -estradiol like activity in various risk groups with a predicted hormonal impact of greatest concern in young boys and postmenopausal women. Thus in conclusion, consumers of sports supplements may be exposed to high levels of estrogenic EDs.

Endocrine disruptors (EDs) are a class of environmental toxic molecules able to interfere with the normal hormone metabolism. Numerous studies involve EDs exposure to initiation and development of cancers, including prostate cancer. Bedia and co

worker [105] investigated three different EDs (aldrin, aroclor 1254 and chlorpyrifos (CPF)) were investigated as potential inducers of a malignant phenotype in DU145 prostate cancer cells after a chronic exposure. Epithelial to mesenchymal transition (EMT) induction, proliferation, migration, colony formation and release of metalloproteinase 2 (MMP-2) were analysed in 50-day exposed cells to the selected EDs. As a result, aldrin and CPF exposure led to an EMT induction (loss of 16% and 14% of E-cadherin levels, respectively, compared to the unexposed cells).

Aroclor and CPF presented an increased migration (134% and 126%, respectively), colony formation (204% and 144%, respectively) and MMP-2 release (137% in both cases) compared to the unexposed cells. Thus Bedia and co worker [105] concluded that some lipid compounds and lipid metabolic pathways could be involved in the acquisition of the malignant phenotype in exposed prostate cancer cells to the selected EDs. Milk and dairy products are a major component of our diet, thus it is important to monitor them for EDs. However, most methods developed to date are devoted to one group of compounds at a time. Wielogórska and co worker [106] described UHPLC/MS/MS method has been validated according to EC decision 2002/657/EC and allows simultaneous extraction, detection, quantitation and confirmation of 19 EDs in milk. This method facilitates fast, reliable, quantitative and confirmatory analysis of sub mg kg⁻¹ levels of a range of EDs in milk.

Corticoid hormonal function can be affected by endocrine disruption. For example, hexachlorobenzene induces oxidative stress, disruption of arachidonic acid metabolism and porphyria [107] PPAR α is present in liver and when associated with the presence of endocrine disruptors mainly causes the metabolic disorders [108]. PCBs reduce the thyroxine and thyroid stimulating hormone (TSH) in response to thyrotropin releasing hormone which result in hypothalamic and pituitary deregulation [19]. The diseases of female reproductive system that might be associated with EDC include precocious puberty, polycystic ovary syndrome and premature ovarian failure [109]. EDC may interfere with the hormonal regulation of menstruation cycle and thereby causing irregularities, such as long cycles which may reduce fecund ability (ability to conceive in a menstrual cycle) [109]. Certain EDC such as estrone (E₁), 17 β -estradiol (E₂), diethylstilbestrol (DES), nonylphenol (NP), octylphenol (OP), Biphenol A (BPA), dibutyl phthalate (DBP), and di-(2-ethylhexyl)phthalate (DEHP) was determined in lakes and rivers of Wuhan city, China [110]. Dun and co worker [111] establish the behavior and potential risks of phenolic endocrine disrupting chemicals in surface water and suspended particle matter of the Xiaohu river, north china plain, china.

In response to these concerns, WHO published

several publications, including the latest information on the subject in the State of the Science of Endocrine Disrupting Chemicals 2012, which was done in collaboration with UNEP and key scientific experts? A resolution to include EDCs as an emerging issue under Strategic Approach to International Chemicals Management (SAICM) which was adopted in September 2012 by the third International Conference on Chemicals Management (ICCM) in Nairobi during which WHO and UNEP jointly raised public awareness on EDC issues during a side-event and technical briefing session (partially supported by the National Institute of Environmental Health Sciences). Since endocrine disrupting chemicals (EDCs) are substantially diverse in character, vary widely in physical and chemical properties, how they are used, as well as how they exist in the environment, discussion of fate and transport is very difficult unless the chemicals are categorized in some manner [112].

CONCLUSION AND RECOMMENDATIONS

Daily use of chemicals is an essential part of modern society. Yet with the exponentially increased production and release of synthetic chemicals, an unwanted effect includes introduction of toxic and persistent substances into the environment. Today, humans and wildlife are constantly exposed to thousands of chemical residues, through air, food, and water. However, scientific information regarding the long-term effects of this chronic, low-dose exposure to complex mixtures of chemicals is very limited. The literature provides highlights and insights to the fate, history and health impact of EDCs on both human and wildlife. The overview was not meant to be an exhaustive review of the evidence, but rather a synthesis of the current knowledge in an ever-changing field of inquiry and discovery. Although there is current scientific, public, and governmental interest in the potential health risks of exposure to EDCs, the human evidence of EDCs with altered human and wildlife health endpoints remains limited and, in certain instances, inconsistent across studies. This highlights the need for further research on these classes of EDCs, more comprehensive testing methods are required to identify other possible endocrine disruptors, their sources, and routes of exposure, more scientific evidence is needed to identify the effects of mixtures of EDCs on humans and wildlife (mainly from industrial by-products) to which humans and wildlife are increasingly exposed, many sources of EDCs are not known because of insufficient reporting and information on chemicals in products, materials and goods, more data sharing between scientists and between countries can fill gaps in data, primarily in developing countries and emerging economies.

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REFERENCES

- [1] Okoro, H.K, Fatoki, O.S, Adekola, F.A, Ximba, B.J, Snyman, R.G. Opeolu, B. (2011a) Human exposure, biomarkers, and fate of organotins in the environment. *Reviews of Environmental Contamination and Toxicology* Volume 213: Springer. pp. 27-54.
- [2] Crisp, T.M, Clegg, E.D, Cooper, R.L, Wood, W.P, Anderson, D.G. (1998) Environmental endocrine disruption: an effects assessment and analysis. *Environmental health perspectives* 106: 11.
- [3] Herbst, A.L, Ulfelder, H, Poskanzer, D.C. (1971) Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *New England journal of medicine* 284: 878-881.
- [4] Colborn, T, Vom Saal F.S, Soto, A.M. (1993) Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environmental health perspectives* 101: 378.
- [5] Colborn, T. (1995) Statement from the work session on environmentally induced alterations in development: a focus on wildlife. *Environmental Health Perspectives*: 3-5.
- [6] Alleva, E, Brock, J, Brouwer, A, Colborn, T, Fossi, M. (1998) Statement from the work session on environmental endocrine-disrupting chemicals: Neural, endocrine and behavioural effects. *Toxicol Ind Health* 14: 1-8.
- [7] Colborn, T, Clement, C. (1992) Chemically-induced alterations in sexual and functional development: the wildlife/human connection: Princeton Scientific Pub. Co.
- [8] Rolland, R, Gilbertson, M, Peterson, R.E. (1997) Chemically induced alterations in functional development and reproduction of fishes. SETAC Press.
- [9] Short, P. (1999) Statement from the work session on health effects of contemporary-use pesticides: the wildlife/human connection. *Toxicology and Industrial Health* 15: 1-5.
- [10] Diamanti-Kandarakis, E, Bourguignon, J-P, Giudice, L.C, Hauser, R, Prins, G.S. (2009) *Endocrine-Disrupting Chemicals: An Endo-*

- crine Society Scientific Statement. *Endocrine Reviews* 30: 293-342.
- [11] Visser, M.J. (2007) Cold, clear, and deadly: Michigan State University Press.
- [12] Damstra, T, Barlow, S, Bergman, A, Kavlock, R, Van Der Kraak, G. (2002) Global assessment of the state-of-the-science of endocrine disruptors. Geneva: World Health Organization.
- [13] Harrison, P, Humfrey, C, Litchfield, M, Peakall, D, Shuker, L. (1995) Environmental oestrogens: consequences to human health and wildlife: Institute for Environment and Health.
- [14] Grun, F, Blumberg, B. (2009) Minireview: the case for obesogens. *Molecular Endocrinology* 23: 1127-1134.
- [15] Caliman, F.A, Gavrilescu, M. (2009) Pharmaceuticals, personal care products and endocrine disrupting agents in the environment—a review. *CLEAN—Soil, Air, Water* 37: 277-303.
- [16] Tumburu, L, Shepard, E.F, Strand, A.E, Browdy, C.L. (2012) Effects of endosulfan exposure and Taura Syndrome Virus infection on the survival and molting of the marine penaeid shrimp, *Litopenaeus vannamei*. *Chemosphere* 86: 912-918.
- [17] Okoro, H.K, Fatoki, O.S, Adekola, F.A, Ximba, B.J, Snyman, R.G. (2011b) Sources, environmental levels and toxicity of organotin in marine environment—a review. *Asian Journal of Chemistry* 23: 473.
- [18] Burnett, M.E, Wang, S.Q. (2011) Current sunscreen controversies: a critical review. *Photodermatology, photoimmunology & photomedicine* 27: 58-67.
- [19] Gore, A.C. (2010) Neuroendocrine targets of endocrine disruptors. *Hormones (Athens, Greece)* 9: 16.
- [20] Grun, F, Blumberg, B. (2006) Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology* 147: s50-s55.
- [21] Grün F, Watanabe H, Zamanian Z, Maeda L, Arima K, Cubacha R, Gardiner DM, Kanno J, Iguchi T, Blumberg B. (2006) Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Molecular Endocrinology* 20: 2141-2155.
- [22] Bedia, C, Dalmau, N, Jaumot, J, Tauler, R. (2015) Phenotypic malignant changes and untargeted lipidomic analysis of long-term exposed prostate cancer cells to endocrine disruptors. *Environmental research* 140: 18-31.
- [23] Okoro, HK, Fatoki, OS, Adekola, FA, Ximba, BJ, Snyman, RG. (2014) Organotin Compounds, In Wexler, P. (Ed). *Encyclopedia of Toxicology*, 3rd edition. Vol 3 Elsevier Inc., Academic Press. pp. 720-725.
- [24] Langston, W, Pope, N, Davey, M, Langston, K, O'Har,a S. (2015) Recovery from TBT pollution in English Channel environments: A problem solved? *Marine pollution bulletin* 95: 551-564.
- [25] Okoro, HK, Fatoki, OS, Adekola, FA, Ximba, B.J, Snyman, R.G. (2016) Spatio-temporal variation of organotin compounds in seawater and sediments from Cape Town harbour, South Africa using gas chromatography with flame photometric detector (GC-FPD). *Arabian Journal of Chemistry, Elsevier*. 9: 95-104.
- [26] Okoro, HK, Snyman, RG, Fatoki, OS, Adekola, FA, Ximba, BJ, MY, Slabber. (2015) Lysosomal Membrane Stability of the Mussel, *Mytilus galloprovincialis* (L), as a Biomarker of Tributyltin exposure. *Bulletin Environmental Contamination and Toxicology, Springer Media*. 94(5): 609-613.
- [27] Pagliarani A, Bandiera P, Ventrella V, Trombetti F, Pirini M, Borgatti AR. (2006) Response to alkyltins of two Na⁺-dependent ATPase activities in Tapes philippinarum and *Mytilus galloprovincialis*. *Toxicology in vitro* 20: 1145-1153.
- [28] Fiorini R, Pagliarani A, Nesci S, Pirini M, Tucci E, Ventrella V. (2012) Structural and functional changes in gill mitochondrial membranes from the Mediterranean mussel *Mytilus galloprovincialis* exposed to tri- n- butyltin. *Environmental Toxicology and Chemistry* 31: 877-884.
- [29] Davis, K.S. (1971) *The Deadly Dust: The Unhappy History of DDT*: American Heritage Publishing Company, Incorporated.
- [30] Lundholm, C. (1997) DDE-induced eggshell thinning in birds: effects of p, p'-DDE on the calcium and prostaglandin metabolism of the eggshell gland. *Comparative Biochemistry and Physiology Part C: Pharmacology, Toxicology and Endocrinology* 118: 113-128.
- [31] Szlinder-Richert, J, Barska, I, Mazerski, J, Usydus, Z. (2008) Organochlorine pesticides in fish from the southern Baltic Sea: levels, bioaccumulation features and temporal trends during the 1995–2006 period. *Marine Pollution Bulletin* 56: 927-940.
- [32] Peterle, T.J. (1969) DDT in Antarctic snow. *Nature* 224: 620-620.
- [33] Daly, G.L, Wania, F. (2005) Organic contaminants in mountains. *Environmental science & technology* 39: 385-398.
- [34] Tauber, O.E, Hughes, A.B (1950) Effect of DDT Ingestion on Total Cholesterol Content of Ovaries Of White Rat.*. *Proceedings of the Society for Experimental Biology and Medicine* 75: 420-422.

- [35] Stoner, H. (1953) Effect of 2, 2-bis (Parachlorophenyl)-1, 1-Dichloroethane (DDD) on the Adrenal Cortex of the Rat. *Nature* 172: 1044-1045.
- [36] Tiemann, U. (2008) In vivo and in vitro effects of the organochlorine pesticides DDT, TCPM, methoxychlor, and lindane on the female reproductive tract of mammals: a review. *Reproductive Toxicology* 25: 316-326.
- [37] Hallegue, D, Rhouma, K.B, Tebourbi, O, Sakly, M. (2003) Impairment of testicular endocrine and exocrine functions after dieldrin exposure in adult rats. *Polish Journal of Environmental Studies* 12: 557-562.
- [38] Verhulst, S.L, Nelen, V, Den Hond, E, Koppen, G, Beunckens, C. (2009) Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. *Environmental health perspectives* 117: 122.
- [39] Francis, E. (1994) Conspiracy of Silence: The story of how three corporate giants—Monsanto, GE, and Westinghouse—covered their toxic trail. *Sierra Magazine*.
- [40] Jensen, S. (1969) DDT and PCB in marine animals from Swedish waters. *Nature* 224: 247-250.
- [41] Tang, N-J, Liu, J, Coenraads, P, Dong, L, Zhao, L-J. (2008) Expression of AhR, CYP1A1, GSTA1, c-fos and TGF- α in skin lesions from dioxin-exposed humans with chloracne. *Toxicology letters* 177: 182-187.
- [42] Loomis, D, Browning, S.R, Schenck, A.P, Gregory, E, Savitz, D.A. (1997) Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. *Occupational and Environmental Medicine* 54: 720-728.
- [43] Brown, D.P. (1987) Mortality of workers exposed to polychlorinated biphenyls—an update. *Archives of Environmental Health: An International Journal* 42: 333-339.
- [44] Sinks, T, Steele, G, Smith, A.B, Watkins, K, Shults, R.A. (1992) Mortality among workers exposed to polychlorinated biphenyls. *American journal of epidemiology* 136: 389-398.
- [45] Grunwald, M. (2002) Monsanto hid decades of pollution. *Washington Post* 1.
- [46] Organization, W.H. (1976) Environmental Health Criteria 2. Poly chlorinated biphenyls and terphenyls: United Nations Environment Programme/WHO, Geneva, Switzerland.
- [47] Kodavanti, P.R.S. (2005) Neurotoxicity of persistent organic pollutants: possible mode (s) of action and further considerations. *Nonlinearity in Biology, Toxicology, Medicine* 3: dose-response. 003.003. 002.
- [48] Uemura, H, Arisawa, K, Hiyoshi, M, Satoh, H, Sumiyoshi, Y. (2008) Associations of environmental exposure to dioxins with prevalent diabetes among general inhabitants in Japan. *Environmental research* 108: 63-68.
- [49] Mullerova, D, Kopecky, J, Matejkova, D, Muller, L, Rosmus, J. (2008) Negative association between plasma levels of adiponectin and polychlorinated biphenyl 153 in obese women under non-energy-restrictive regime. *International Journal of Obesity* 32: 1875-1878.
- [50] Organization, W.H. (2013) Effects of human exposure to hormone-disrupting chemicals examined in landmark United Nations report. *ScienceDaily*.
- [51] Daso, A.P, Fatoki, O.S, Odendaal, J.P, Olujimi, O.O. (2013) Polybrominated diphenyl ethers (PBDEs) and 2, 2', 4, 4', 5, 5'-hexabromobiphenyl (BB-153) in landfill leachate in Cape Town, South Africa. *Environmental monitoring and assessment* 185: 431-439.
- [52] Eriksson, P, Fischer, C, Fredriksson, A. (2006) Polybrominated diphenyl ethers, a group of brominated flame retardants, can interact with polychlorinated biphenyls in enhancing developmental neurobehavioral defects. *Toxicological Sciences* 94: 302-309.
- [53] Organization WH (1997) Flame retardants: a general introduction. *Environmental Health Criteria*.
- [54] Ether, D. (2008) Toxicological Review Of Decabromodiphenyl Ether (BDE-209).
- [55] Costa, L.G, Giordano, G. (2007) Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. *Neurotoxicology* 28: 1047-1067.
- [56] Lema, S.C, Dickey, J.T, Schultz, I.R, Swanson, P. (2008) Dietary exposure to 2, 2', 4, 4'-tetrabromodiphenyl ether (PBDE-47) alters thyroid status and thyroid hormone-regulated gene transcription in the pituitary and brain. *Environmental health perspectives* 116: 1694.
- [57] Swan, S, Liu, F, Hines, M, Kruse, R, Wang, C. (2010) Prenatal phthalate exposure and reduced masculine play in boys. *International journal of andrology* 33: 259-269.
- [58] Fisher, J.S. (2004) Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. *Reproduction* 127: 305-315.
- [59] Barrett, J.R. (2005) Phthalates and baby boys: potential disruption of human genital development. *Environmental health perspectives* 113: A542.
- [60] Kaiser, J. (2005) Panel finds no proof that phthalates harm infant reproductive systems. *Science* 310: 422-422.
- [61] Bette, H. (2007) California bans phthalates in

- toys for children. *Chemical and Engineering News* 12.
- [62] Feigal, D. (2002) PVC Devices Containing the Plasticizer DEHP. FDA Public Health Notification (12 July 2002).
- [63] Jones, S, Boisvert, A, Naghi, A, Hullin-Matsuda, F, Greimel, P. (2016) Stimulatory effects of combined endocrine disruptors on MA-10 Leydig cell steroid production and lipid homeostasis. *Toxicology* 355: 21-30.
- [64] Knobeloch, L, Turyk, M, Imm, P, Schrank, C, Anderson, H. (2009) Temporal changes in PCB and DDE levels among a cohort of frequent and infrequent consumers of Great Lakes sportfish. *Environmental research* 109: 66-72.
- [65] Fürst, P. (2006) Dioxins, polychlorinated biphenyls and other organohalogen compounds in human milk. Levels, correlations, trends and exposure through breastfeeding. *Molecular nutrition & food research* 50: 922-933.
- [66] Schecter, A, Päpke, O, Tung, K-C, Staskal, D, Birnbaum, L. (2004) Polybrominated diphenyl ethers contamination of United States food. *Environmental science & technology* 38: 5306-5311.
- [67] Hites, R.A, Foran, J.A, Carpenter, D.O, Hamilton, M.C, Knuth, B.A. (2004) Global assessment of organic contaminants in farmed salmon. *Science* 303: 226-229.
- [68] Weschler, C.J. (2009) Changes in indoor pollutants since the 1950s. *Atmospheric Environment* 43: 153-169.
- [69] Rudel, R.A, Seryak, L.M, Brody, J.G (2008) PCB-containing wood floor finish is a likely source of elevated PCBs in residents' blood, household air and dust: a case study of exposure. *Environmental Health* 7: 2.
- [70] Stapleton, H.M, Dodder, N.G, Offenberg, J.H, Schantz, M.M, Wise, S.A. (2005) Polybrominated diphenyl ethers in house dust and clothes dryer lint. *Environmental science & technology* 39: 925-931.
- [71] Anderson, H.A, Imm, P, Knobeloch, L, Turyk, M, Mathew, J. (2008) Polybrominated diphenyl ethers (PBDE) in serum: findings from a US cohort of consumers of sport-caught fish. *Chemosphere* 73: 187-194.
- [72] Morland, K.B, Landrigan, P.J, Sjödin, A, Gobeille, A.K, Jones, R.S. (2005) Body burdens of polybrominated diphenyl ethers among urban anglers. *Environmental health perspectives*: 1689-1692.
- [73] Lorber, M. (2008) Exposure of Americans to polybrominated diphenyl ethers. *Journal of Exposure Science and Environmental Epidemiology* 18: 2-19.
- [74] Dodson, R.E, Nishioka, M, Standley, L.J, Perovich, L.J, Brody, J.G. (2012) Endocrine disruptors and asthma-associated chemicals in consumer products. *Environmental health perspectives* 120: 935.
- [75] Martina, C.A, Weiss, B, Swan, S.H. (2012) Lifestyle behaviors associated with exposures to endocrine disruptors. *Neurotoxicology* 33: 1427-1433.
- [76] Teuten, E.L, Saquing, J.M, Knappe, D.R, Barlaz, M.A, Jonsson, S. (2009) Transport and release of chemicals from plastics to the environment and to wildlife. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 364: 2027-2045.
- [77] Esteban, S, Moreno-Merino, L, Matellanes, R, Catalá, M, Gorga, M. (2016) Presence of endocrine disruptors in freshwater in the northern Antarctic Peninsula region. *Environmental research* 147: 179-192.
- [78] Vitku, J, Starka, L, Bicikova, M, Hill, M, Heracek, J. (2016) Endocrine disruptors and other inhibitors of 11 β -hydroxysteroid dehydrogenase 1 and 2: Tissue-specific consequences of enzyme inhibition. *The Journal of steroid biochemistry and molecular biology* 155: 207-216.
- [79] Maqbool, F, Mostafalou, S, Bahadar, H, Abdollahi, M. (2016) Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. *Life sciences* 145: 265-273.
- [80] Winneke, G. (2011) Developmental aspects of environmental neurotoxicology: lessons from lead and polychlorinated biphenyls. *Journal of the neurological sciences* 308: 9-15.
- [81] Porte, C, Janer, G, Lorusso, L, Ortiz-Zarragoitia, M, Cajaraville, MP. (2006) Endocrine disruptors in marine organisms: approaches and perspectives. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology* 143: 303-315.
- [82] Giulivo, M, de Alda, M.L, Capri, E, Barceló, D. (2016) Human exposure to endocrine disrupting compounds: Their role in reproductive systems, metabolic syndrome and breast cancer. A review. *Environmental Research* 151: 251-264.
- [83] Golden, R.J, Noller, K.L, Titus-Ernstoff, L, Kaufman, R.H, Mittendorf, R. (1998) Environmental endocrine modulators and human health: an assessment of the biological evidence. *Critical reviews in toxicology* 28: 109-227.
- [84] Willis, I.C (2007) *Progress in Environmental Research*: Nova Science Publishers.
- [85] Boyle, C.A, Boulet, S, Schieve, L.A, Cohen, R.A, Blumberg, S.J. (2011) Trends in the prevalence of developmental disabilities in US children, 1997–2008. *Pediatrics* 127: 1034-1042.
- [86] Stein, J, Schettler, T, Wallinga, D, Valenti, M.

- (2002) In harm's way: toxic threats to child development. *Journal of Developmental & Behavioral Pediatrics* 23: S13-S22.
- [87] Dingemans, M.M., van den Berg, M., Westerink, R.H. (2011) Neurotoxicity of brominated flame retardants:(in) direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. *Environmental health perspectives* 119: 900.
- [88] De Cock, M., Maas, Y.G., van de Bor, M. (2012) Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. *Acta paediatrica* 101: 811-818.
- [89] Casals-Casas, C., Desvergne, B. (2011) Endocrine disruptors: from endocrine to metabolic disruption. *Annual review of physiology* 73: 135-162.
- [90] Grün, F., Blumberg, B. (2007) Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. *Reviews in Endocrine and Metabolic Disorders* 8: 161-171.
- [91] Kirchner, S., Kieu, T., Chow, C., Casey, S., Blumberg, B. (2010) Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Molecular endocrinology* 24: 526-539.
- [92] Baillie-Hamilton, P.F. (2002) Chemical toxins: a hypothesis to explain the global obesity epidemic. *The Journal of Alternative & Complementary Medicine* 8: 185-192.
- [93] Patisaul, H.B., Roberts, S.C., Mabrey, N., McCaffrey, K.A., Gear, R.B. (2013) Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster® 550 in rats: an exploratory assessment. *Journal of biochemical and molecular toxicology* 27: 124-136.
- [94] Biro, F.M., Greenspan, L.C., Galvez, M.P., Pinney, S.M., Teitelbaum, S. (2013) Onset of breast development in a longitudinal cohort. *Pediatrics* 132: 1019-1027.
- [95] Mouritsen, A., Aksglaede, L., Sørensen, K., Mogensen, S.S., Leffers, H. (2010) Hypothesis: exposure to endocrine-disrupting chemicals may interfere with timing of puberty. *International journal of andrology* 33: 346-359.
- [96] Crain, D.A., Janssen, S.J., Edwards, T.M., Heindel, J., Ho, S-m. (2008) Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. *Fertility and sterility* 90: 911-940.
- [97] Jefferson, W.N., Patisaul, H.B., Williams, C. (2012) Reproductive consequences of developmental phytoestrogen exposure. *Reproduction: REP-11-0369*.
- [98] Newbold, R.R. (2008) Prenatal exposure to diethylstilbestrol (DES). *Fertility and sterility* 89: e55-e56.
- [99] Skakkebaek, N.E., Meyts, E.R., Main, K. (2001) Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Apmis* 109.
- [100] Titretir, S., Sakar, M.K. (2007) Determination of some metals in medicinal plants by flame atomic absorption spectrometry after different digestion procedures. *Fresen. Environ. Bull.* 16: 216-222.
- [101] Turner, E.A., Pye, C.C., Singer, R.D. (2003) Use of ab initio calculations toward the rational design of room temperature ionic liquids. *The Journal of Physical Chemistry A* 107: 2277-2288.
- [102] Soto, A.M., Sonnenschein, C. (2010) Environmental causes of cancer: endocrine disruptors as carcinogens. *Nature Reviews Endocrinology* 6: 363-370.
- [103] Hampl, R., Kubátová, J., Stárka, L. (2016) Steroids and endocrine disruptors—History, recent state of art and open questions. *The Journal of steroid biochemistry and molecular biology* 155: 217-223.
- [104] Palanza, P., Nagel, S.C., Parmigiani, S., vom Saal, F.S. (2016) Perinatal exposure to endocrine disruptors: sex, timing and behavioral endpoints. *Current opinion in behavioral sciences* 7: 69-75.
- [105] Bedia, A., Bedia, F.Z., Aillerie, M., Maloufi, N., Benyoucef, B. (2015) Morphological and Optical properties of ZnO thin films prepared by spray pyrolysis on glass substrates at various temperatures for integration in solar cell. *Energy Procedia* 74: 529-538.
- [106] Wielogórska, E., Elliott, C., Danaher, M., Chevallier, O., Connolly, L. (2015) Validation of an ultra high performance liquid chromatography–tandem mass spectrometry method for detection and quantitation of 19 endocrine disruptors in milk. *Food control* 48: 48-55.
- [107] Lelli, S.M., Ceballos, N.R., Mazzetti, M.B., Aldonatti, C.A., de Viale, L.C.S.M. (2007) Hexachlorobenzene as hormonal disruptor—studies about glucocorticoids: their hepatic receptors, adrenal synthesis and plasma levels in relation to impaired gluconeogenesis. *Biochemical pharmacology* 73: 873-879.
- [108] Feige, J.N., Gelman, L., Michalik, L., Desvergne, B., Wahli, W. (2006) From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. *Progress in lipid research* 45: 120-159.
- [109] Costa, E.M.F., Spritzer, P.M., Hohl, A., Bachega, T.A. (2014) Effects of endocrine

- disruptors in the development of the female reproductive tract. *Arquivos Brasileiros de Endocrinologia & Metabologia* 58: 153-161.
- [110]Xue, X, Wu, F, Zhang, X, Deng, N. (2008) Occurrence of endocrine disrupting compounds in rivers and lakes of Wuhan City, China. *Fresen. Environ. Bull.* 17: 203.
- [111]Dun, Y, Tang, C, Zhang, Y. (2014) Characteristics, behavior and potential risks of phenolic endocrine-disrupting chemicals in surface water and suspended particle matter of the Xiaohe River, North China Plain, China. *Fresen. Environ. Bull.* 23: 620-629.
- [112]Organization, W.H. (2012) State of the Science of Endocrine-Disrupting Chemicals. Geneva: International Programme on Chemical Safety.

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