Review Article

Exposure to environmental endocrine disruptors and human health

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Abstract: Exposure to environmental chemicals which have major risks for human by targeting different organs in the body has significant impacts on biological systems. For several years there have been a great amount of interest on the environmental endocrine disruptors (EEDs) and their relation with human health. Therefore, the aim of this review is to summarize all evidence regarding varieties and different physiological disruptions on the human and possible involved mechanisms, to discover the risk factors of EEDs and to prove the association between endocrine disruptions and human diseases.

Keywords: Environmental endocrine disruptors (EEDs); bisphenol A (BPA); reproduction; diabetes

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Introduction

Endocrine-disrupting compound is named 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 behavior" (1). Many chemicals have been identified as endocrine disruptors and they have been active for the past decade. These chemicals are related to many chronic diseases like breast cancer, ovarian problems, thyroid eruptions, testicular carcinoma, diabetes, reproductive abnormalities, nerve damage, obesity and many homeostatic imbalance (2).

Environmental endocrine disruptors (EEDs) are compounds altering the physiological function of endocrine system in both human and wild life. They can impact endocrine system by targeting different levels of the hypothalamic-pituitary-thyroid/gonad/adrenal axes, inhibiting or stimulating the production of hormones, or changing the way hormones travel through the body, the effects can range from hormone receptors to hormone synthesis or metabolism, so the EEDs can have negative health implications on human (3). Over the years, scientists, physicians and governments are paying more and more attention to potential links between exposure to EEDs and certain endocrine-related diseases, resulting form that exposure to many EEDs is now ubiquitous, coupled with suggested trends for increased rates of some endocrine-related diseases.

This review provides a brief introduction to some EEDs such as PAHs, contemporary use pesticides, bisphenol

A (BPA), phthalates, heavy metals, representing a small number of all known or suspected EEDs. Besides this, we also give a summarize of EEDs for adverse impacts on human development (reproductive tract development, thyroid function, effect on nervous system, obesity and diabetes), guidance and recommendations for future research.

Classification of EEDs

EEDs can be grouped according to different observations. In this paper, we categorized EEDs into five groups as following.

PAHs

PAHs are lipophilic chemicals with long half-lives that include polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and other brominated flame retardants (BFRs). PBDEs are now being widely used in carpet backing, furniture and other consumer products that we use regular in our daily life (4). Exposure to it can also occur through dietary sources, but contact with house dust may account for the primary source. Fortunately, use of PBDEs have already been prohibited or are currently being phased out in many countries. PCBs are widely used as transformer, hydraulic fluids and additives existing in paints and other building materials (5). PCBs exposure from building materials is possible, but continued exposures to PCBs can occur primarily through the diet (meat, higher trophic level fish etc.). BFRs and other flame retardants can be found in different products range from electronics, textiles, computers, foam furniture and so on (6). Since BFRs are not bound to the products and are easily released into the environment, these products are considered as potential source of endocrine disruptors. However, they have been banned in many countries, but BFRs are still being considered as pollution source since they persist in the environment for longer period because of their longer half-life (7).

There are scientific researchers suggesting that PAHs are associated with many adverse health effects such as thyroid effects (8), obesity (9), diabetes (10), reproductive problems (11,12) and endocrine-related cancers (13).

Contemporary use pesticides

Pesticides are composed of insecticides, fungicides, herbicides, rodenticides, etc. The most human research has been conducted for insecticides and the common types of insecticides are organophosphates, organochlorine, pyrethroids and carbamates. DDT which belongs to the pyrethroids was once used popular as a pesticide in agricultural sectors, household and public places, but it was banned few years back because of its hazardous nature. However, the compound is still in use in some countries. Organophosphorus pesticides (OPs) are the most commonly used pesticide and chlorpyrifos is a unique example. The insecticide is regarded as safe alternatives to arsenic-based pesticides after 1940s and is used in both household and agriculture field to control pests such as cockroaches, flies, mosquitoes, termites. However, it is confirmed from studies that the compound is highly toxic since it has a huge effect on nervous systems (14), some of heavily used organochlorine pesticides (OCPs) were banned in industrialized nations in the 1970s after reports of the negative effect on human, but the use of DDT still occurs in some developing countries as an effective method against vector-borne illnesses.

Today nearly all pesticides we used are designed to disintegrate after some hours or days (just called "non-persistent"). But it has been shown that many non-persistent pesticides can remain for years after applied in homes where they are protected from sunlight, moisture and other degradation mechanisms (15). Pesticides are usually designed to be highly sensitive toward reproductive and neural systems of the organisms, but due to the similarity with human physiological function, these chemicals can also be harm to normal human body (16), so they are known neurovirulence, especially in acute high-dose situations. DDT can interfere with thyroid, insulin, reproductive and neuroendocrine systems (17-20), which has made it one of the most potential candidates as endocrine disruptors.

BPA

BPA is a high production chemical that is used frequently in polycarbonate-plastic based containers, thermal paper and the lining of canned food. Because of the negative effects on human being, the compound is banned from using in baby bottles. But it is still found in many containers, especially in the epoxy based lining of canned foods which are used for soups, fruit jam etc. and in certain construction materials (21). Although the lining is used to give protection from pathogens, it is in direct contact with food and finally

Table 1 Lists some common EEDs and their uses

Common EEDs	Uses in our daily life
Polybrominated diphenyl ethers (PBDEs)	Carpet backing, furniture, dietary sources
Polychlorinated biphenyls (PCBs)	Transformer, hydraulic fluids, additives, building materials, diet (meat, higher trophic level fish etc.)
Brominated flame retardants (BFRs)	Electronics, textiles, computers, foam furniture
DDT, chlorpyrifos, atrazine, glyphosate	Pesticides
Bisphenol A (BPA)	Polycarbonate-plastic based containers, thermal paper, epoxy based lining of canned food, certain construction materials
Phthalates	Plastics, food packaging, home furnishings, personal care products, dietary supplements, medical equipment
Lead	Smelting, mining, refining, leaded petrol (gasoline), lead-acid batteries, paints, jewellery, children's products
Triclosan	Antibacterials
Perfluorochemicals	Textiles and clothing

EEDs, environmental endocrine disruptors.

grasp the opportunity entering food and then into human bodies. Exposure to BPA occurs mainly through diet, and measurable levels of BPA can be found in most people (5).

A diverse variety of developmental problems following exposure to BPA such as abnormal reproductive organ and neurobehavioral effects have been reported in some animal studies (22-24). However, human studies remain limited, a little ones have been suggested relationship between BPA exposure and reproductive endpoints, altered thyroid hormones, cardiovascular disease and diabetes (25-28).

Phthalic acid esters (PAEs)

PAEs can be used as solubilizing or stabilizing agents, and also service as plasticizer to make plastics more flexible, they can be found in a great deal of products. Due to their widespread use, phthalate-metabolites can be measured in urinary of virtually everyone. High molecular weight phthalates exist in flexible PVC commonly induced in food packaging, home furnishings and other materials. Low molecular weight phthalates can be found in personal care products, certain dietary supplements and other consumer goods. Unfortunately, elevated exposure to phthalates has been reported among infants as a result of phthalate-containing medical equipment or personal care products (29).

Several phthalates have demonstrated adverse impact on reproductive development and numerous other endpoints at high doses in rodents (30,31). In human studies, phthalates have been associated with abnormal in sex steroid, thyroid hormone levels (32), insulin resistance (33), poor sperm quality (34) and obesity (35), they have also something to do with type 2 diabetes in human populations (36).

Other chemicals

There are many other types of EEDs to which extensive approach of human exposure has been involved. Heavy metals are public health concern recently because they can persist in the environment for long time and some metals such as cadmium, lead and arsenic have biological half-lives of longer than 10 years (37). Cadmium, arsenic, mercury and lead included in heavy metals are classified as EEDs and thought to have estrogenic activity (38). Lead is a natural compound used in mining, refining, gasoline, lead-acid batteries, jewellery, children's products and many other products. It is worth mentioning that children are the potential candidates of lead poisoning, due to their high ingest quantity but do not have a fully developed blood-brain barrier (39). A large body of evidence shows that heavy metals, such as lead, cadmium, arsenic and mercury may impact endocrine function in addition to their other modes of toxicity (40-43).

There is also a growing list of other emerging EEDs including triclosan, parabens, perchlorate and fluorinated organic compounds such as perfluorooctane sulfonate (PFOS). There are researchers suggesting that many of these emerging compounds may be associated with endocrine endpoints in animals and humans (44-47).

Humans can be exposed to EEDs through dietary, occupations or environmental exposure (water, soil and air).

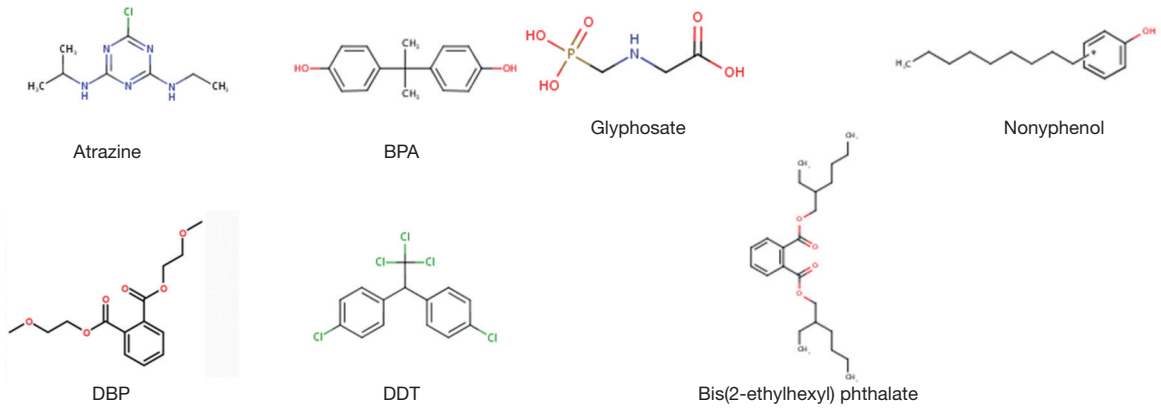

Figure 1 Structures of some common EEDs. EEDs, environmental endocrine disruptors.

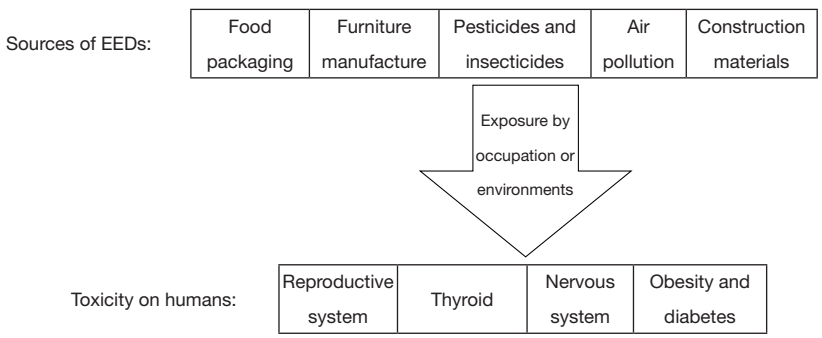

Figure 2 Routes of EEDs release to the environment and their toxic effects. EEDs, environmental endocrine disruptors.

Table 1 lists some common EEDs and their uses. Because of the diverse mechanism of EEDs in human body, it is very difficult to establish a relationship between EEDs if just considering the structural features of them (some of the common structures of EEDs are given in *Figure 1*). Actually, it is sometimes the metabolites of EEDs more hazardous than the compound itself. The rest of this article will pay attention to developmental endpoints associated with those EEDs and their metabolites introduced in previous paragraphs.

Developmental disease endpoints related to EEDs

EEDs may alter the homeostatic system through environmental exposure. Different studies (animal, clinical observations and epidemiological studies) have indicated the potential role of endocrine disruptors in affecting reproductive and nervous systems, thyroid, metabolism, breast, lung and causing obesity. Some effects of EEDs on human health are discussed below. *Figure 2* shows the routes of EEDs releasing into the environment and their toxic effects on humans.

Reproductive tract development

EEDs damage normal physiological reactions about the reproductive system. It is known that female sexual differentiation occurs independent of estrogen and androgen, which largely mediate male differentiation. There are some effects of EEDs on male and female reproductive system which are as follows.

Male reproduction and development

There is evidence that anomalies of the male reproductive tract such as sperm anomalies, hypospadias and ectopic testes may have increased in some countries recently (48). These diseases are possibly caused by perinatal exposure to

EEDs during sensitive stages of the developing fetus (49).

EEDs reduce number as well as quality of sperms, along with an increase in occurrence of testicular, prostate and breast cancer (50). Similarly, low sperm count due to toxicity of environmental pollutants has been reported (51-53). Testicular dysgenesis syndrome (TDS) is one of the main illnesses being associated with some environmental endocrine pollutants (54). It represents a series of reproductive disorders disturbing gonadal development (hypospadias, cryptorchidism and smaller reproductive organs) (55). TDS can effect on human as a reduction in semen quality, infertility and increasing risk for testicular cancer as they growing older.

Several studies that have been reviewed previously have assessed relationships between EEDs and male genital defects. A relationship between prenatal PBDE exposure and congenital cryptorchidism was reported in Denmark (56). A type of utero and lactational exposure of children to relatively low dioxin doses have been found to have permanently impact on reducing sperm quality (57). Gaspari *et al*. supported that the increased risk of cryptorchidism and hypospadias were related to parental occupational exposure to pesticides (58). Another study reported that consumption of fruits and vegetables with high levels of pesticide residues was associated with a lower total sperm count and a lower percentage of morphologically normal sperm among men presenting to a fertility clinic (59). A newer Chinese study recruiting 1,040 men from the Reproductive Center suggested that environmental exposure to di-n-butyl phthalate (DBP) and di 2-ethyl hexyl phthalate (DEHP) may contribute to a decline in semen quality (60). Another experiment conducted by Huang *et al*. show that in utero exposure to phthalates has generally threatened the health of newborns (61). There is evidence that PAEs and possibly other EEDs disrupt early male reproductive development, but additional studies are needed.

Female reproduction and development

EEDs may effect on female reproductive system when regarding to the diseases including irregularities in menstruation cycle, precocious puberty, polycystic ovary syndrome and primary ovarian failure (62).

Uterine fibroids (leiomyomas) occurring in 25% to 50% of all women are the most common tumors in female ones (63). Obesity, unopposed estrogen signaling, age during premenopausal years and at menarche have been shown to increase the risks of the development of uterine fibroids (64). Furthermore, there are studies showing that exposure to EEDs can also increase the incidence of fibroids in humans. Shen *et al*. recruited the subjects including 600 patients with uterine leiomyoma and 600 patients with non-uterine leiomyoma or healthy volunteers, they found that exposure to plastic products, cosmetics, and other chemicals probably containing EEDs may be the risk factor for uterine leiomyoma (65).

Some other side effects of EEDs in female like increased growth of endometrium and higher risk of breast cancer can also occur because of the EEDs (66). In addition, utero exposure of women to diethylstilbestrol (DES) is associated with a high lifetime risk of a broad spectrum of adverse health outcomes (infertility, preterm delivery, ectopic pregnancy, preeclampsia and stillbirth) (67). Altered cyclicity and body burdens have been noted in individuals exposed to OCPs (68). Indeed, cycle irregularities caused by epigenetic changes that may be transmitted to the next generation have been reported in female whose mothers were exposed in utero to DES (69). Meeker *et al*. found that PAEs exposure is prevalent among third-trimester urinary of pregnant women in Mexico and that some phthalates may be associated with preterm birth (70). Based on a pilot nested case control study, Cantonwine D also supported that low level BPA exposure may impact placental tissue and that urinary concentrations of BPA during the last trimester of pregnancy may relate to risk of delivering prematurely (71). In a study conducted in Taiwan on 33 girls of the general population, PCBs may result in lower estradiol concentrations in 8-year old children and impaired reproductive development in girls (12).

Thyroid function

Normal human metabolic control, for example, brain development, control of metabolism and many other important aspects of normal adult physiology are regulated by thyroid hormones. Disruption in thyroid hormones may results in brain damage or disruptions in metabolism, development and adult physiology if there are changes in the function of the thyroid gland (72).

OCPs as potential EEDs have been reported to influence the level of thyroid hormones, Blanco-Muñoz *et al*. have observed positive associations between the serum levels of p,p'-DDE and those of total T3 and total T4 (73). Data showed that exposure of children to OCPs produced a significant increase in serum total T3 concentrations (74). A positive association had been observed by Freire between exposure methoxychlor in males and presence of TPOAb, but not in females. He also found that TSH levels were

associated with higher beta-HCH in men (75). These results suggest that OCPs can affect the thyroid system through gender-specific mechanisms that may differ among compounds. Chevrier *et al*. suggested that dioxin exposure, particularly exposure before menarche, may have enduring impacts on women's total thyroxine levels (76). During the first trimester of pregnancy, exposure to burden of OH-PCBs at environmental levels can affect neonatal thyroid hormone status (77). There was also a tendency toward lower total T4 and higher free T3 with increasing PBDEs exposure. Jacobson *et al*. found that exposure to PBDEs could breakdown thyroid hormone function, with impacts in the direction of hypothyroidism (78). However, further detailed investigations and health monitoring should be warranted for humans.

Effect on nervous system

Nervous system is one of the most important body systems, it is needed to keep all the body parts synchronized, whereas it can be affected by endocrine-associated chemicals. Neural, behavioral and bipolar disorders have been observed in adults, infants and children due to exposure to EEDs that target different hormonal pathways (79-81). EEDs directly act on many neuro-steroids effecting brain regions causing schizophrenia and bipolar disorders, these steroids evoke psychiatric disorders that can be caused by many pathways like physical development, brain anatomy, cellular anatomy, neurotransmitters and receptors, hormone function, sexual development, immunology, social behaviors or physiological responses (82). There are researchers agreeing on the hypothesis that hypothalamic-pituitary-adrenal (HPA) axis activity may be relevant to the development and expression of psychotic disorders (83,84). Elevated glucocorticoid levels resulted from different causes damage hippocampal nerve and give rise to schizophrenia and anxiety disorders exerting change in HPA axis.

There are some studies providing examples about the exposure of EEDs and their effects on behavior, sensory function and other psychiatric and neurological development as well. Lesiak *et al*. identify non-dioxin-like polychlorinated biphenyls (NDL PCBs) as potential environmental risk factors for neurodevelopmental disorders (85). Caspersen *et al*. indicated that maternal dietary exposure to PCB-153 or dl-compounds during pregnancy was significantly associated with poorer expressive language skills in preschool girls (86). In addition, BPA has shown a close association with schizophrenia and other neuro-toxicological pathology (82). The association of perinatal dioxin exposure and autistic traits in 3-year-old children living in a contaminated area in Vietnam were reported, in the study, the high total dioxin-exposed group had significantly more poor neuro-developmental scores than the mild-exposed group in boys, demonstrating a specific impact of perinatal exposure to dioxin on autistic traits in children (81). There was also a case-control study aiming evaluation of level of essential trace elements and heavy metals in the hair samples of children with autistic spectrum disorder (ASD), the result showed high contamination of heavy metals such as lead, mercury and cadmium in ASD children compared to healthy ones, suggesting a possible pathophysiological role of heavy metals in the symptoms of ASD (87).

Obesity and diabetes

Endocrine disruption is a major cause for obesity, which further associate with metabolic disorders, such as diabetes, dyslipidemia, cardiac arrest hypertension, hyperinsulinemia and insulin resistance (88). Glucose metabolism includes estrogenic receptors (ERα and ERβ) as the key parameters. Estradiol (E2) and some EEDs (pesticides, dioxin and BPA) are similar in the way attacking these receptors to evoke changes of glucose homeostasis and insulin release (89,90), so any EED targeting these receptors can damage the normal glucose homeostasis, giving a necessary clue for diabetes (91).

Indeed, there is a growing body of literature involving EEDs such as PCBs, BPA, dioxin and pesticides with the incidence of metabolic syndrome, obesity and diabetes (92-94). Epidemiological studies established a link between type 2 diabetes mellitus (T2DM) and low-level environmental exposure to some dioxin and PCBs, which mainly accumulate in adipose tissue (95). The rapid rise in obesity and diabetes in young suggests that the influence of early-life exposure to EEDs may play an important role in the development of abnormal. Verhulst *et al*. demonstrated that cord blood PCB and DDE concentrations were associated with increased BMI or change during early childhood (from ages 1 to 3 years) (96). A cross-sectional study included 3,390 adults aged 40 yr or older indicated that BPA was positively associated with generalized obesity, abdominal obesity, and insulin resistance (97). Actually, even low doses of BPA have been indicated to damage α-cells of the pancreas which produce glucagon controlling glucose metabolism (98), thus the low doses of BPA can link to type 2 diabetes and obesity

by causing hyperinsulinemia (99). Huang *et al*. thought that exposure to dioxin being recognized as an EED is a risk factor for diabetes mellitus (DM), independent of age and BMI in both men and women (100). A kind of cross-sectional data reported several positive associations between PAE metabolites and obesity in girls (101). Al-Othman *et al*. confirmed the association between the body burden of the pesticide hexachlorocyclohexane (HCH) and the risk of T2DM in a sample of 280 adult subjects from Saudi Arabia (102).

Growing evidence also suggests that EEDs may affect not only the exposed individual but also the children and subsequent generations. However, EEDs cause a significant challenge to environment and human health. Consequently, due to their wide commercial use and adverse effect to human health the Endocrine Society had published a scientific statement indicating that endocrine disruptors pose a "significant concern for public health" (2). More research is in urgently needed to provide important insights into the etiology of these chronic disorders caused by EEDs, playing an important role in the design of effective prevention strategies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jphe.2016.12.09). BZ serves as an Editor-in-Chief of *Journal of Public Health and Emergency* from Jan 2017 to Dec 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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