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Overview on Endocrine disruptors in food and their effects on infant's health

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ABSTRACT

Endocrine disruptors (EDs) are natural or synthetic chemicals that cause changes in the body's hormonal and homeostatic systems. Children, especially developing fetuses and infants, are more likely to be affected by these chemicals than adults. Intake through food is one of the primary pathways for EDs to enter the body. While EDs can be found naturally in some foods, synthetic EDs primarily contaminate food, including breast milk and water. Although safe doses have been reported for many EDs, this issue may be controversial because of the low-dose effects and non-monotonic dose responses of EDs. Because of their epigenetic effects, their effects may occur in subsequent generations that are not directly exposed. Some EDs are persistently present in the environment. These chemicals are transported through water and air currents, as well as migratory animals and enter the food chain even if the chemical is banned or not produced in that specific area.

In this article, we aim to provide information on EDs by emphasizing those found in food and their effects especially on the health of children including developing fetuses. Some suggestions have also been given to reduce the danger due to EDs.

1. Introduction

Endocrine disruptors (EDs) are substances that can be natural or synthetic, which can cause changes in the hormonal and homeostatic systems of the organisms exposed to their action. Some EDs are thought to mimic natural steroid hormones and interact with their receptors as analogues or antagonists due to the presence of a phenolic moiety. Thus, they can act as estrogens, androgens, and antiandrogens. They could also act as thyroid hormone receptor agonists and antagonists.

Phytoestrogens are one of the main natural EDs found in our food. Synthetic endocrine disruptors include chemicals used as industrial lubricants/solvents and their byproducts:Some examples include plastics [bisphenol A (BPA), pharmaceutical agents [diethylstilbestrol (DES)], dioxins, fungicides (vinclozolin), pesticides [methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT)], polybrominated biphenyls (PBB), plasticizers (phthalates), polychlorinated biphenyls (PCBs)][1].

The developmental age at which exposure to an endocrine disruptor occurs is critical. In the case of exposure to a presumptively "safe" dose during a life stage such as the intrauterine period, when there is no endogenous hormonal exposure, the potential effects of exposures even at very low doses should be considered[2]. In addition, there is evidence indicating that very low doses of EDs might be more effective than higher doses, and nonmonotonic dose responses are not uncommon findings when EDs are studied[3].

Endocrine disruptors are taken into the body mainly in three ways: inhalation, ingestion, and dermal contact[4]. Some EDs are not metabolized and remain in high levels in the environment for a long time; they are called persistent organic pollutants (POPs). Thus, EDs that were banned even decades ago can be found in human and animal bodies. On the other hand, some can change into compounds that are even more toxic and can be detected at distances from where they were produced or released. These chemicals are transported through water and air currents, as well as migratory animals and enter the food chain. Others, such as BPA, do not remain in the environment for very long but are

Abbreviations: AGEs, Advanced glycation end products; BPA, bisphenol A; DES, diethylstilbestrol; DDT, dichlorodiphenyltrichloroethane; DEHP, Di-etylhexyl Phthalate; DINP, Di-isononyl Phthalate; DIDP, Di-isodecyl Phthalate; DOHaD, Developmental Origin of Health and Disease; EDs, Endocrine disruptors; EU, European Union; PBBs, polybrominated biphenyls; PCBs, polychlorinated biphenyls; PE, polyethylene; PET, polyethylene terephthalate; POPs, persistant organic pollutants; PVC, polyvinyl chloride; TNC, transnonachlor; WTO, World Trade Organization.

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quite widespread in their use[1].

The age of exposure to an ED might be associated with different outcomes. During specific periods of development, exposure to environmental chemicals, drugs, altered nutrition, infections, or stress may cause functional changes in tissues, whereas the same effects may not be seen at other stages of life.

Nowadays, it is well known that changes that occur in the early years of life can pave the way for disease in later stages of life[5]. The term "the fetal basis of adult disease" has been used to describe observations of the maternal environment, the egg, and the external environment and identifies an individual's propensity to develop a disorder later in life[6]. Thus, the fact that EDs can be effective at critical periods of development could coincide with the concepts of fetal basis of adult disease and Developmental Origin of Health and Disease (DOHaD)[7].

Another important factor to be considered about EDs is the latency from exposure, which represents the time it takes for an endocrine disruptor to show its effect. The effect is more likely to be achieved when exposure occurs at a younger age, as survival will be longer.

Individuals may be exposed to several EDs in the same time interval, and although the individual components at doses considered safe have no effect on physiology or homeostasis, they cause synergistic effects when taken together, which is called the "cocktail effect." This is caused by enhancement of ligand binding affinity and recruitment of transcriptional coactivators. For example, transnonachlor (TNC) (a banned organochlorine pesticide) and 17α-ethinyl estradiol can bind to the same nuclear receptor (pregnane X receptor-PXR) at the same time with up to 100-fold higher affinity than the individual compounds. This synergistic activation leads to changes in the regulation of several physiological functions, whereas the separate effects of the individual components would be negligible[8].

Another interesting point about EDs is that there is not necessarily a linear relationship between dose and endocrine disruptor effect; a U-shaped or inverted U-shaped curve can be seen. Therefore, low doses may also cause more potent effects than higher doses[1,3].

The effects of EDs can be seen in subsequent generations by being transmitted through changes in factors that regulate gene expression through their epigenetic effects (transgenerational effect). Three main mechanisms of epigenetic regulation have been described are DNA methylation, posttranslational modifications of histones, and through noncoding RNAs. Alteration of any of these epigenetic regulators in germ cells is associated with increased disease risk[9].

2. Endocrine disruptors and children's health

Endocrine disruptors are of special importance to pediatricians because children, especially young children, are different from adults in many ways. Their rates of organ development are variable, they have greater absorption from the skin when adjusted for body weight, longer life expectancy, and lower cytochrome p450 enzyme activities. Children consume more daily calories, fluids, and oxygen per body weight, are exposed to breast milk, dairy products, and fat-soluble endocrine disruptors, put everything in their mouths, and crawl on the floor.

Endocrine disruptors, as the name suggests, affect the hormonal system in many different ways: They interact with hormone receptors by activating or antagonizing them, alter hormone receptor expression or signal transduction in hormone-sensitive cells, induce epigenetic changes in hormone-sensitive or hormone-producing cells, alter the synthesis, metabolism, or clearance of hormones, and alter the transport of hormones across cell membranes[10].

2.1. Risks posed by EDs to children's health

EDs could have several effects on different body functions; these effects seem to be increasing as the results of extensive studies are published. For now, these effects can be listed as follows:

Breast cancer (both prenatal and pubertal effects could be responsible), prostate cancer, diabetes, obesity, thyroid disease, puberty disorders, reproductive system disorders, infertility, weakened immune system, neurological and behavioral changes[11].

The observation of these diverse effects has led to the need for regulations regarding endocrine disruptors. REACH (EC 1907/2006) aims to improve the protection of the environment and human health by better and earlier identifying the intrinsic properties of chemicals through the four processes: Registration, Evaluation, Authorization, and Restriction of Chemicals.

2.2. Chemicals with endocrine disrupting properties found in food

- **Phytoestrogens**

Phytoestrogens are the main natural endocrine disruptors that can be found in human and animal food. Genistein is a phytoestrogen found naturally in soybeans. In infants fed soy formula, urinary concentrations of genistein have been found to be about 500 times higher than those fed cow formula. This substance binds to estrogen receptors and also has goitrogenic activities. Evidence also shows an association between feeding soy infant formula and autoimmune thyroid disease[12,13].

- **Phthalates (PAEs)**

Phthalates are widely used as major plasticizers in industry. These substances are used to improve the extensibility and elasticity of polymers, such as polyvinyl chloride (PVC), polyethylene (PE), and polyethylene terephthalate (PET).

Phthalates are a global human health concern. Di-ethylhexyl phthalate (DEHP) is considered "toxic to reproduction" in the European Union (EU) and a "priority hazardous substance" under the EU Water Framework Directive. The widespread use of phthalates in food packaging causes "putative food toxicity" due to the migration of these substances into food.

According to a recent EU risk assessment, more information is still needed on the risk in infants fed DEHP-contaminated breast milk. To minimize the health risk, DEHP has been replaced by two substances that are not considered hazardous under REACH: Di-isononyl phthalate (DINP) and Di-isodecyl phthalate (DIDP)[14].

The World Trade Organization (WTO) announced an EU proposal to change the restriction of three phthalates (DEHP, DBP, and BBP) in March 2018 under entry 51 of Annex XVII of REACH (Safeguard 54/18). In January 2019, the number of restricted phthalates was expanded from three (DEHP, DBP, and BBP) to four (DEHP, DBP, BBP, and DIBP). The EU has set specific migration limits in food and beverage contact plastics for five phthalates, namely DBP, DEHP, BBP, DINP and DIDP. DIBP is not permitted in food contact materials. DBP and DEHP are only allowed in plasticizers in repeated-use materials and nonfat food contact articles. DINP, DIDP and BBP may only be used in plasticizers in repeated-use and single-use materials and articles in contact with non-fatty foods (except infant formulae and follow-on formulae as defined by Directive 2006/141/EC or processed cereal-based foods and baby foods as defined by Directive 2006/125/EC)[14].

Di-ethylhexyl phthalate is the most abundant phthalate in water in PET bottles, followed by DBP and DIBP, and their levels increase when stored at high temperatures. Because 0.5 L PET bottles have a higher surface area/volume ratio, PAE concentration was found to be the highest in 0.5 L bottles compared to larger bottles. PAE levels increase even more when the bottles are stored in sunlight or when hot water is placed in these bottles. Soft drinks are more likely to be contaminated with PAEs than mineral water due to their higher acidity. Also, longer duration of contamination leads to higher levels.

As for dairy products, PAE contamination can occur during all stages of production. On the other hand, raw milk has also been found to be contaminated with DIBP and DEHP due to contaminated feed. The mechanical milking process with PVC pipes is also considered important for contamination. Cooling tanks may lead to further increases in DEHP levels. In Belgian farms, the highest levels of DEHP were found in creamers while the lowest levels were in light milk. Replacement of DEHP with other types of plasticizers has led to a decrease in DEHP levels in European cow's milk, while outside Europe (Canada and South Korea), DEHP levels in milk are still high. During the pasteurization process, DEHP content has been reported to increase most likely due to tubes and sealants that are DEHP-containing contact materials[14].

2.3. Prenatal exposure to DEHP

There are studies showing the effects of DEHPs as a result of in-utero exposure. Barakat et al.[15-18] conducted many animal studies on this topic. The results of these studies showed that male mice prenatally exposed to DEHP had increased germ cell apoptosis, oligo/azoospermia, and degenerated seminiferous tubules, i.e., induces premature reproductive senescence. This effect has been reported to be dose dependent[15]. In addition, it has been shown that these reproductive effects are passed on to subsequent generations through epigenetic modification of germ cells[16]: In experimental animals, when a pregnant female is exposed to an endocrine disruptor, one might expect that the first generation would be directly affected, and the second generation would be affected because germ cells of the first generation would also be affected. However, Barakat et al.[18] reported that in the third generation (those not directly exposed to DEHP), fertility and reproduction were also affected as a surprising finding suggesting epigeneticity.

Another effect of prenatal DEHP exposure in mice has been reported as impaired recognition memory and elevated anxiety behavior. These effects have been attributed to neurodegeneration due to inflammation and oxidative damage in the hippocampus, as well as decreased testosterone levels and androgen receptor expression in the brain[17].

- **Advanced glycation end products (AGEs)**

The Maillard reaction is a chemical reaction that occurs during the processing or cooking of foods at high temperature: As a result of the glycation of proteins in foods, AGEs appear; they are found in various foods such as bread, cheese, processed meats, cookies, and peanut butter. AGEs have been associated with the pathophysiology of several diseases, such as type 2 diabetes mellitus, polycystic ovary syndrome, and allergies. When the mother is exposed to exogenous AGEs, these glycated proteins are passed to the baby through lactation. Kutlu T.[19] described that infants may receive up to 15 kU/kg of AGEs directly from breast milk, which could increase to 76 kU/kg by the age of 6 months. Infants may also be exposed to exogenous AGEs from the diet through formula feeding. Dry heating of milk readily increases dietary AGEs in infant formula compared with normal cow's milk products. CML (Nε-carboxymethyl-lysine) is the major glycotoxin in infant formula and is found 7 to 12 times less in goat milk formula than in cow's milk products[20].

- **Persistant organic pollutants (POPs)**

The development of industry has brought with it environmental pollution. POPs are man-made chemicals that are lipophilic, highly resistant to degradation, and concentrate in living organisms (bioaccumulation). Animals and humans in the food chain not only absorb these chemicals, but also spread them as they travel. As a result, they can be found miles away from the original source. Exposure to POPs can cause many health disorders, such as impairment of neurodevelopment, reproductive and immune function, as well as disruption of endocrine system function. The severity of these effects can vary depending on the developmental period during exposure to POPs[21,22].

In May 2001, the Stockholm Convention on Persistent Organic Pollutants took place in Sweden with the participation of more than 90 countries. The goal was to protect the environment and human health from POPs, and 12 POPs (the dirty dozen) were chosen to be eliminated and/or reduced: aldrin, chlordane, DDT (dichlorodiphenyltrichloroethane, dieldrin, endrin, heptachlor, mirex, toxaphene, PCBs, hexachlorobenzene, dibenzodioxins, and dibenzofurans[23].

- **Pesticides**

Pesticides can pollute soil, water, grass, and flora. In addition to killing insects or weeds, pesticides may be poisonous to other creatures such as birds, fish, beneficial insects, and non-target vegetation. Exposure of males to pesticides may affect sex hormones, sperm (morphology, concentration, and motility), and semen quality[24].

In a retrospective study conducted in Belgium, which later became a pioneering study indicating the effect of pesticides on the timing of puberty, it was determined that 28% of the 145 cases treated with the diagnosis of precocious puberty were patients who had migrated from developing countries. When pesticide levels were checked in these cases, p,p'DDE (a derivative of the organochlorine pesticide DDT) was found in immigrants with precocious puberty, whereas this chemical could not be detected in most native Belgian cases. This suggested that the mechanism of precocious puberty might involve previous exposure of endocrine disruptors[25]. Other studies have also shown the effect of prenatal pesticide exposure on early menarche and early breast development[26,27].

Dichlorodiphenyltrichloroethane had been banned in the early 1970s. However, the effects of DDT have recently been demonstrated in granddaughters whose grandmothers were exposed to the pesticide DDT. These granddaughters had higher rates of obesity and early menstrual periods. These may increase the granddaughters' risk for breast cancer, as well as high blood pressure, diabetes, and other cardiometabolic diseases[28].

Measures can be taken on an individual basis to limit pesticide exposure, such as washing, peeling, and eating organic food. In particular, some fruits and vegetables that absorb high levels of pesticides (strawberries, cherries, apples, grapes, potatoes, peppers, spinach) could be purchased organic[29].

It is well known that the pre-harvest interval, i.e., the time between the last application and harvest, is important when dealing with pesticides. For example, for strawberries, many types of insecticides are widely used, as this soil-grown fruit is the target of many insects, A recent study showed that with respect to different pre-harvest intervals, the amount of thiacloprid residues showed variability[30]. In another study, residual levels of fosthiazate, a widely used nematicide, was measured in tomatoes and cherry tomatoes, and the 3-week preharvest interval was determined to be safe to consume[31]. For fungicide-treated pomegranates, the half-life of fluopyram and tebuconazole varied by pomegranate part. Pre-harvest intervals for combined tebuconazole and fluopyram treatment were 47 to 59 days in pomegranate fruits but 158 to 173 days in leaves[32].

Herbicides are widely used in dicot crops, and residues are of great concern. A recent study showed that vegetables, especially those with a short growing season could be easily contaminated with the herbicide aryloxyphenoxy-propionate (except propaquizafop). Vegetables treated with fluazifop and lettuce and cauliflower treated with quizalofop are declared unsuitable for infant feeding[33].

- **Parabens**

Parabens are p-hydroxybenzoic acid esters commonly used in cosmetics, food, and pharmaceuticals as preservatives[34]. They increase adipogenesis and reduce basal lipolysis in white adipose tissue, while attenuating adrenergic stimulation of lipolysis in brown adipose tissue[35]. Thus, parabens are obesogenic endocrine disruptors present in foods. Estimated daily intake values of total parabens were reported as 307, 273, 470, 879, and 940 ng/kg body weight/day for adults, adolescents, children, toddlers and infants, respectively, and among the 8 food categories (beverages, fruits, vegetables, dairy products, fats and oils, cereals, fish and shellfish, and meat), the highest amount of parabens was found in cereals[34].

- **Bisphenol A (BPA)**

Bisphenol A is a synthetic organic compound that is used to make polycarbonate plastics. It is commonly found in food and beverage packaging, medical devices, and dental materials. It can contaminate air, soil, food and beverages. Especially in children, 99% of BPA exposure occurs through the diet, with beverages and canned food being the main sources.

Bisphenol A, as an endocrine disruptor, exhibits hormone-like properties and causes hormone-dependent cancers and has negative effects on reproduction and immune regulation. It can bind to estrogen, androgen, and thyroid hormone receptors.

Acidic or basic conditions and heating increase the migration of BPA from plastics into foods and beverages. Thus, heating foods in plastic packages or bottles increases BPA exposure. In addition, the release of BPA from materials is increased by contact with sodium chloride or vegetable oils, making canned food a major source.

Therefore, to avoid the harmful effects of BPA, the consumption of plastic materials should be restricted and the use of BPA-free products should be promoted[36]. At the governmental level, restrictions should be lifted in the use of BPA and also for other alternatives, such as bisphenol S (BPS) and bisphenol F. At the individual level, BPA- and BPS-free bottles should be purchased or bottles containing the number 7 inside the recycling symbol should be avoided, and fresh foods should be consumed instead of canned foods[29].

3. Foodstuff exposed to the risk of contamination by endocrine disruptors

- **Eggs**

In a recent study conducted in Turkey, endocrine disruptors were analyzed in three types of eggs (battery, free-range, and organic)[37]. The results of the study showed that PAEs were the most abundant in battery eggs, while total DDT concentrations, although low, were highest in free-range eggs, although DDT was banned in Turkey more than 35 years ago. The eggs were found to be contaminated with more than one chemical; however, all were within the acceptable risk limit. There was no difference between the eggs in terms of PCB and PBDE concentrations; however, PBDEs have never been produced and PCBs are banned in Turkey[3]. This result supports that these chemicals are found in the environment despite restrictions and bans. From the authors' point of view, the term of acceptable limits should be stated very carefully, since it is well known that when it comes to EDs even very low levels can produce effects[3].

- **Breast milk**

The World Health Organization recommends breastfeeding until 2 years of age, and breastfeeding is undoubtedly the accepted mode of infant feeding for the first six months; however, infants can also be exposed to endocrine disruptors through breast milk. Highly lipid-soluble chemicals are concentrated in the mammary gland in lactating women. Thus, especially breast milk with a high fat content carries a higher risk. In addition, the degree of exposure is influenced by maternal age, duration of lactation, and number of pregnancies. The most prevalent chemicals in breast milk are: heavy metals, pesticides, organochlorine cyclodienes, semivolatile organohalogens, dioxins, furans, DDT, parabens, octylphenols, bisphenols, and other organic compounds including PAEs[4]. In a study conducted in Germany, 15 phthalates were measured in 78 breast milk samples. Of these, DEHP, DnBP, and DiBP levels were measured at significantly higher concentrations, whereas other phthalates were found in only a few of the samples or were not detectable in any of the samples. However, it was stated that the elevated values were still well below the recommended tolerable daily intake[38]. Again, the debatable question of acceptable or tolerable limits from the authors' point of view might come into the picture for breast milk as well. On the other hand, these chemicals have been shown to be at much higher levels in infant formula, and it was concluded in the study by Fromme et al.[38] that exposure through breast milk does not pose a significant health risk to infants.

- **Drinking water**

Drinking water is one of the main ways people can be exposed to endocrine disruptors. Brazilian researchers evaluated 15 articles published in the last decade to study chemical contamination in Brazilian drinking water. Of the 77 parameters studied in groundwater, surface, and rainwater sources, 10 parameters exceeded health limits for potability. In particular, 17 α-ethinylestradiol, widely used in contraceptive pills, exceeded 52,549 times the proposed guideline value. Its presence in water is thought to be due to contamination of the urine of women taking these drugs, and indirect exposure of pregnant women and thus the developing fetus to this chemical is a major concern. The authors concluded that instead of removing these chemicals from water, it would make more sense to prevent their contamination by reducing pesticide use and improving wastewater treatment[39].

4. Conclusions

Endocrine disruptors are mostly synthetic molecules introduced into our lives in an attempt to make living more convenient and easy. However, they have brought with them their own health risks. Children, especially developing fetuses and infants, are more likely to be affected than adults. Studies over time show that the health risks they cause are not only for people today but also for future generations. The use of some EDs has been banned and restricted. However, industry tries to compensate for the restricted chemicals by producing new molecules that in turn could also cause problems. Studies have been done to find out the maximum acceptable levels of these chemicals; however, the atypical dose-response curves of some EDs make determining these levels difficult and questionable from the authors' perspective, especially when fetuses and developing children are affected. One of the most important steps to reduce the health effects of EDs is to increase awareness of the risks in the general population. On the other hand, the many issues related to EDs require the involvement of scientists from different disciplines. Thus, an international multidisciplinary council of scientists must work together to reduce or eliminate health risks related to EDs now and in the future.

Declaration of Competing Interest

The authors declare no conflict of interests.

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