What is an endocrine disruptor?

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Chemicals are an essential component of our daily lives. But some chemicals, known as endocrine disruptors, can have harmful effects on the body's endocrine (hormone) system. Hormones act in very small amounts and at precise moments in time to regulate the body's development, growth, reproduction, metabolism, immunity and behavior. Endocrine disruptors interfere with natural hormone systems, and the health effects can be felt long after the exposure has stopped. Exposure to endocrine disruptors can have life-long effects and can even have consequences for the next generation

According to OMS, endocrine disrupting chemicals (EDCs) and potential EDCs are mostly man-made, found in various materials such as pesticides, metals, additives or contaminants in food, and personal care products. EDCs have been suspected to be associated with altered reproductive function in males and females, increased incidence of breast cancer, abnormal growth patterns and neurodevelopmental delays in children, as well as changes in immune function. Human exposure to EDCs occurs via ingestion of food, dust and water, via inhalation of gases and particles in the air, and through the skin. EDCs can also be transferred from the pregnant woman to the developing fetus through the placenta and to the young child through breast milk. 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.

Diethylstilbestrol, a proof of concept.

Diethylstilbestrol (DES) which was the first synthetic non steroidal estrogen was given from about 1940 to 1971, to pregnant women with the wrong idea [1], it would reduce the risk of pregnancy complications and premature delivery. In 1971, DES was shown [2] to cause clear cell carcinoma, a rare vaginal tumor occurring in girls and women who had been exposed to this drug *in utero*. Therefore, the United States Food and Drug Administration subsequently withdrew DES from use in pregnant women. In France, DES was withdrew in 1977.

Follow-up studies have indicated that DES also has the potential to cause a variety of significant adverse medical complications such as an increased risk of reproductive complications and infertility among DES daughters (Individuals who were exposed to DES during their mothers' pregnancies) as well as obesity [3]. Cumulative risks in women exposed to DES, as compared with those not exposed were reported as follow [4]: infertility (33.3 % vs. 15. 5%), spontaneous abortion (50.3 % vs. 38.6 %), and preterm delivery (53.3 % vs. 17.8 %). Concerning prenatally DES-exposed males, increased risk of testicular cancer, infertility and urogenital abnormalities in development such as cryptorchidism and hypospadias were also reported [5)

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Endocrine disruptors mechanism of action.

An endocrine disruptor may mimic or partly mimic natural hormone in the body like estrogens or androgens, but also thyroid hormones It may block the interaction of natural hormones with their receptor by altering their metabolism *in vivo*. It may also bind to a receptor within a cell and block the endogenous hormone from binding. Such as chemicals that block or antagonize hormones are anti-estrogens and anti-androgens.

By interfering with the body's endocrine system, it produces adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife

Endocrine disruptors origins.

A wide range of substances, both natural (hormones, phytoestrogens as genistein) and man-made, are thought to cause endocrine disruption, including pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and plasticizers such as bisphenol A. Endocrine disruptors may be found in many everyday products– including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides.

Some of the endocrine disruptors

Bisphenol A.

BPA is an industrial chemical that has been used to make certain plastics and resins since the 1960s. It is found in polycarbonate plastics that are often used in containers that store food and beverages, such as water bottles, and in other consumer goods. It is also found in epoxy resins which are used to coat the inside of metal products, such as food cans, bottle tops and water supply lines. Some dental sealants and composites also may contain BPA.

Under European legislation, it has been prohibited for use in polycarbonate baby bottles since 2011. Then during a first phase of France's ban, effective from January 1, 2013, BPA was banned in food contact materials (FCMs) intended for use by children up to three years of age. On January 1, 2015 the second phase of France's ban on bisphenol A (BPA) became effective. This law prohibits the use of BPA in all packaging, containers and utensils intended to come into direct contact with food

The French law is not harmonized with the European legislation. Thus, under the European Plastics Regulation (EU) No 10/2011, BPA is authorized to be used as a monomer for the production of plastic with a specific migration limit of 0.6 mg/kg food.

Phthalates.

Phthalates which are often called plasticizers are a group of chemicals used to make plastics more flexible and harder to break. They are used in a wide variety of products, such as vinyl flooring, adhesives, detergents, lubricating oils, automotive plastics, plastic clothes (raincoats), and personal-care products (soaps, shampoos, hair sprays, and nail polishes). Dibutyl-phthalate (DBP), di(2-ethylhexyl)-phthalate (DEHP), and dimethyl-phthalate (DMP) are the most commonly utilized phthalates.

People are exposed to phthalates by eating and drinking foods that have been in contact with containers and products containing phthalates. To a lesser extent exposure can occur from breathing in air that contains phthalate vapors or dust contaminated with phthalate particles.

The association between endocrine disrupting chemicals and human sperm quality is controversial. However a recent and systematic review [6] with meta-analysis has found there is a consistent increase in the risk of abnormal sperm quality with phthalate ester group as well as with organochlorine. Early phthalate exposure in pregnant women is also associated [7] with alterations in thyroid hormones leading to autism spectrum disorders and developmental delay. Moreover, phthalates may interfere [8] with testicular function by reducing testosterone and insuline-like factor 3 levels.

Polybrominated diphenyl ethers (PBDEs).

Polybrominated diphenyl ethers (PBDEs) are used as flame retardants in a number of applications, including textiles, plastics, wire insulation, and automobiles. Certain PBDE congeners are persistent, bioaccumulative, and toxic to both humans and environment. The critical endpoint of concern for human health is neurobehavioral effects. Various PBDEs have also been studied for ecotoxicity in mammals, birds, fish, and invertebrates. In some cases, current levels of exposure for wildlife may be at or near adverse effect levels.
It must be remained that PBDEs are not chemically bound to plastics, foam, fabrics, or other products in which they are used, making them more likely to leach out of these products

Parabens

Parabens are esters of p-hydroxybenzoic acid which are widely used as preservatives in cosmetics as well as in foods and drugs. The parabens used most commonly in cosmetics are methylparaben, propylparaben, butylparaben, and ethylparaben. Despite studies, no effective direct links between parabens and cancer have been established.
Animal experiments have shown that parabens have weak estrogenic activity, the effect of butylparaben was determined to be approximately 100,000 times weaker than that of estradiol, and was only observed at a dose level approximately 25,000 times higher than the level typically used to preserve products. The study also found that the *in vivo* estrogenic activity of parabens is reduced by about three orders of magnitude compared to *in vitro* activity. The estrogenic activity of parabens increases with the length of the alkyl group.
Based on the current posology of medicines containing methyl- and propylparaben, concentrations of 0.2% and 0.06% would correspond to maximal intakes of approximately 140 mg/day and 50 mg/day, respectively. Other parabens are also used in pharmaceuticals to a lesser extent, such as ethylparaben and butylparaben.
According to the European Medicines Agency, methylparaben has not been associated with adverse effects on the male and female reproductive organs in juvenile rats or in embryo-fetal development studies. This allows concluding that the use of methylparaben in oral formulations up to 0.2% of the product (as within the recommended effective concentrations as a preservative) is not a concern for humans including the pediatric population whatever the age group. Regarding propylparaben, certain oestrogenic activity has been seen in various experimental settings, but with much lower activity than oestradiol in *in vitro* pharmacological models. In conclusion, the EMA review [9], reported that additional information for parabens is not considered necessary due to the absence of sufficient clinical evidence of parabens-related effects in humans.

The cost of endocrine disruptors

According to a recent review[10], the disease costs of EDCs were much higher in the USA than in Europe ($340 billion [2·33% of GDP] vs $217 billion [1·28%]). The difference was driven mainly by

intelligence quotient (IQ) points loss and intellectual disability due to polybrominated diphenyl ethers (11 million IQ points lost and 43 000 cases costing $266 billion in the USA vs 873 000 IQ points lost and 3290 cases costing $12·6 billion in the European Union). Accounting for probability of causation, in the European Union, organophosphate pesticides were the largest contributor to costs associated with EDC exposure ($121 billion), whereas in the USA costs due to pesticides were much lower ($42 billion).

In conclusion, the deleterious effects of endocrine disruptors on development, reproduction, growth, metabolism, and obesity, constitutes a real public health issue. Moreover, nonlinear/nonmonotonique action (as opposed to toxic dose effect), cocktails presence of EDCs (additive effects and/or synergistic and/or antagonists), latency, window of exposure, and possibility of transgenerational effects provide as much data that underlying the complexity in this domain.
As concerning the mechanisms of action of EDCs, many questions remain unanswered, more research is needed to enable more precise effect estimates in epidemiology studies used for risk assessment. Nevertheless, considering the possible developmental early effects of endocrine disrupters on child health, a particular attention should be given to pregnant women, babies and young children.

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