# Endocrine Disrupting Chemicals (EDCs): Its Impact On Health

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**ABSTRACT:** Endocrine disruptors or EDCs are compounds that interfere with natural hormone functions and may produce reversible or irreversible biological effects in individuals or populations by interfering with hormone function. They may interfere with the synthesis, storage, release, secretion, transport, elimination, binding, or action of endogenous hormones. They may temporarily or permanently alter feedback loops involving the brain, pituitary, gonads, thyroid gland, or other organs. Their action is not limited to receptor binding. Some examples of endocrine disruptors are bisphenols, alkylphenols, DDT, diadzein, genistein, lindane, paraquat, benzoic acid, dibutylphthalates, diethylhexylphthalates, diethylstilbesterol and PCBs. Many are chemicals produced for such purposes as used in pesticides, plastics, cosmetics, electrical transformers etc. Some, like diethylstilbestrol (DES) and ethinylestradiol, are synthetic drugs, while others are natural plant compounds called phytoestrogens. Evidence that EDCs exerts adverse effect on wildlife is accumulating. Some of the well known examples are the feminization of fish by nonylphenol or estradiol, and masculinization of snail by organotin compounds. Many of known endocrine disrupters are environmental estrogens and it is for this reason that feminization is often observed in the environment. In addition to estrogen-like compounds, some other endocrine disrupter is known to show anti-estrogenic activity, or thyroid hormone activity. Disruption of the endocrine system will lead to the failure of reproduction and subsequently to the loss of biological species. Nationwide monitoring has been done in 2000 to 2003 in Malaysia to establish a baseline and a comprehensive database in Malaysia. The monitoring projects include several programmes on environment monitoring including river, drinking water, food products, human blood and cord blood of population.

**Keywords**: endocrine disrupter, phthalates, bisphenol, nonylphenol, health

## The endocrine system

The endocrine system is a complex and integrated network of glands and hormones that functions together in a balanced and harmonised manner. This system regulates many of the body's functions including growth, development and maturation, as well as the way various organs react to the current needs of the body.

Disorders of any of the endocrine systems, involving both overactive and underactive hormone secretion, result inevitably in disease, the effects of which may extend to many different organs and functions and may often be debilitating or life-threatening. Viewed from this general perspective, the threat posed from environmental chemicals with endocrine activity (either agonistic or antagonistic) is potentially serious. However, the fact that humans and wildlife are exposed to such chemicals, *ipso facto* does not imply that clinically recognizable disturbances of one or other endocrine system will result, because such an effect depends much on the level and duration and the timing of exposure.

In general, endocrine systems maintain some form of "homeostasis," avoiding extreme fluctuations in hormone levels/responses that might otherwise have detrimental metabolic effects on the organism. A good example is the role of insulin in maintaining blood glucose levels within the normal range. Failure of insulin to respond to changing blood levels of glucose will lead to emerging of diseases like diabetes.

However, in reality, each system is more complicated and integrated so that it can enable all of the endocrine systems of the body to be integrated via cross talk. For example, endocrines triggering reproduction need to take in to account the age, nutritional status, and in most animals, season of the year. Similarly, stress response related endocrines, and to a lesser extent, those regulating hunger, may need to have the ability to override other endocrine systems when danger threatens survival. This cross link is vital for survival and has important implications while evaluating endocrine disruptors. Exposure to an estrogenic chemical, for example, may affect not only the reproductive endocrine axis but also several other endocrine systems as well as bone, fat, and cardiovascular.

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**Endocrine disruptor**

Endocrine disrupting chemicals (EDCs) encompass a variety of chemical classes, including natural and synthetic hormones, plant constituents, pesticides, compounds used in plastics industry and in consumer products, and other industrial by-products and pollutants. They are often pervasive and widely dispersed in the environment. Some are persistent, can be transported long distances across national boundaries, and have been found in virtually all regions of the world. Others are rapidly degraded in the environment or human body or may be present for only short periods of time but at critical periods of development. The toxic effects of EDCs are not confined to their hormonal actions. The toxic effects of pesticides for example may be attributed to their mode of action as neurotoxins or their effects on enzymes involved in the digestive system.

Many pesticides and other EDCs are also categorised as either proven, probable or potential carcinogens. Most of the present research in this area however, has focused on the effects on animals. Endocrine-disrupting chemicals (EDCs) include a diverse group of chemicals, synthetic or natural, that can affect hormonal activity in living things. Many EDCs are regarded as significant organic pollutants in the environment. Environmental pollutants with well-established endocrine-disrupting properties currently number more than 50 and include industrial chemicals, pesticides and by-products of manufacturing processes as well as products of incineration of industrial and household wastes. These known EDCs include polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs) and other types of pesticides, dioxins, alkylphenol polyethoxylates, pentachlorophenols, bisphenol A, styrenes and phthalate esters.

Many of these chemicals are also classified as persistent organic pollutants (POPs). POPs are pollutants that resist degradation in natural ecosystems and include DDT, dieldrin, chlordane, heptachlor, mirex, toxophene, PCBs and dioxins. All of these chemicals rank high on the list of POPs. Because of the widespread use of many of the chemicals, exposure of biota including man to EDCs is a growing concern.

**The effects of EDCs on humans**

Studies on the main effects of EDCs on humans have concentrated largely on the reproductive system. The term xenoestrogen have been used to describe the diverse group of chemicals that exert an impact on reproduction. The majority of xenoestrogens do not bear any structural similarity to the natural oestrogens such as 17β-oestradiol but are nevertheless able to bind to the oestrogen receptor leading to either agonistic or antagonistic effects. Reproductive system is especially susceptible to these agents because the system acts in a 'fine-tuned' manner. The whole menstrual cycle, fertilization and implantation of the fertilized ovum is greatly dependent on the intricate functional relationship between the hypothalamus, pituitary gland, gonads and the endometrium. Every stage is vulnerable to disruption. Another function that is susceptible to disruption is spermatogenesis which is greatly dependent on the ordered secretion of hormones from the pituitary gland and testes.

The ordered development and sexual differentiation of the developing fetus is another area where EDCs may have a significant impact. The genotype or sex of the individual is determined by the genes it inherits. But the development of the external genitalia and to some extent the internal genital organs is determined by the hormones released from the gonads. Thus it can be anticipated that the presence of EDCs during the critical period of sexual differentiation may have profound effects not only on the type of genitalia ultimately formed, but on the subsequent sexual behavior of the animal. Available epidemiological data mostly relating to reproductive systems in humans indicate that EDCs may be exerting their effects. A tragic example is the synthetic hormone, diethylstilbesterol (DES), which was at one time prescribed to expectant mothers to prevent miscarriages and was shown to cause cancer in the offspring.

There have been numerous reports that sperm counts and/or quality have been declining over the past few years. The incidence of infertility in the female has been increasing. The incidence of hypospadias, an abnormal development of the male genital organs has been reported to be increasing. These can be probably related to the endocrine effects of EDCs on the menstrual cycle and ovulation.

When an endocrine disruptor is absorbed into the body, it may disrupt the body's normal hormonal functions. This disruption can happen when the compound either mimics or blocks hormones through altering normal hormone levels, and halting or stimulating the production of hormones, or changing the way hormones travel through the body, thus affecting the functions that these hormones control. Other EDCs may block the effects of a hormone in parts of the body normally sensitive to it. Others may alter or block the signaling pathways of the cell. By this process, cell function is disrupted. For this reason, EDCs are sometimes called imposters. Chemicals that are known to be endocrine disruptors include diethylstilbesterol (the drug DES), dioxin, bisphenol A, phthalates esters, PCBs, DDT, and some other pesticides. There are more than 70,000

chemicals tested to show some form of endocrine disrupting effects, but only a few showed significant effects on human body, while several showed effects on animals like rodents and fishes. Some of the well documented mechanisms of action of EDCs are discussed in the following sections.

**Effects of phthalates**

Phthalates are used as plasticizers in a number of manufacturing processes to soften plastics. The reproductive toxicity of some phthalates has been well described. For example, DEHP has been shown to target the testis of adults and juveniles rats (Gray and Butterworth, 1980; Sjoberg *et al.*, 1985). Monoethylphthalates acts on the sertoli cells in the testis, causing testicular toxicity, while dibutyl and diethylhexyl esters exert developmental effects via alterations in testosterone-synthesizing ability of the fetal testes.

Studies were also conducted on the effects of phthalates, including interactions with both estrogen and androgen receptors. In 1998, Zacharewski *et al.* reported that DBP, BBP, and DHP weakly competed with estradiol for binding to the estrogen receptor in competitive ligand-binding assays. Studies have shown that only selected phthalate esters (i.e., DBP, BBP, and DHP) exhibit weak estrogen receptor-mediated activity in some in vitro assays at high concentrations, but none of the eight phthalate esters elicited in vivo estrogenic responses based upon results obtained from uterotrophic and vaginal cornification assays. These results serve to raise caution in assessing the potential hazard of chemicals based solely upon results of in vitro experiments. More significantly, some phthalates (e.g., DEHP, DBP, BBP, di-isonyl phthalate, but not DEP, DMP or DOTP) induce antiandrogenic responses in fetal males. For example, male rat pups exposed during sexual differentiation to DBP or DEHP exhibit malformations in androgen-dependent tissues although apparently by a non-receptor-mediated mechanism (Gray *et al.*, 1999a and 2000). Importantly, because the critical window lies outside that of the traditionally defined "period of organogenesis," these effects have been missed in standard developmental toxicology studies (Ema *et al.*, 1992, 1993 and 1994; Tyl *et al.*, 1988; Narotsky *et al.*, 1995).

A recent study reported that a connection has been found between the physiological presence of phthalates and the occurrence of male obesity, insulin resistance and diabetes. Previous studies have suggested a connection between phthalates and adverse affects on testicular function in human males following a confirmed connection of synthetic chemicals, including phthalates, on reduced testicular function in animals. This connection is highly significant because one of the plausible causes for the growing incidence of obesity, insulin resistance and diabetes in men is lower testicular function.

**Effects of Bisphenol A (BPA) and Nonylphenol**

A study was conducted in our laboratory to assess the pubertal development and thyroid function in juvenile male rats after sub-chronic administration of bisphenol A and nonylphenol. Nonylphenol, an alkylphenol with a 9-carbon olefin side chain, is widely used in the manufacture of nonionic surfactants, lubricant additives, polymer stabilizers, and antioxidants. Bisphenol A (BPA) is an industrial chemical, used to manufacture polycarbonate and numerous plastic articles including compact disks, food can linings, thermal (fax) paper, safety helmet, adhesives, and powder paints. Both nonylphenol and bisphenol A are known to have endocrine-disrupting properties.

The effects of bisphenol A and nonylphenol on pubertal development and thyroid function in the intact juvenile/peripubertal male Sprague-Dawley rats were observed during our study. Two groups of rats were treated with either 100 mg/kg body weight of nonylphenol or bisphenol A. Another group of rats were treated with a mixture of 100 mg/kg body weight of nonylphenol and bisphenol A. The required endpoints that were observed in this study are: growth, age and weight at preputial separation, serum thyroxin (T4), thyroid, liver and kidney weight and histology, epididymal and seminal vesicle weight, testis weight and histology, serum testosterone, and serum insulin. Our studies revealed that nonylphenol and bisphenol A significantly delay the onset of puberty as well as testicular damage when compared to a control group; spermatogenesis was affected in most treated rats. Bisphenol A also caused the enlargement of the kidney and kidney defect (Benjamin *et al.*, 2003).

Nonylphenol and bisphenol A have been observed to cause delay in puberty onset as well as testicular damage in the treatment groups when compared to the control; spermatogenesis was affected in most treated rats. Bisphenol A also caused the enlargement of the kidney and hydronephrosis. Another interesting feature that was observed in this study was that administration of nonylphenol and bisphenol A as a mixture has caused less than additive effects.

**Studies on pesticides and antibiotics in the aquatic systems**

The occurrence of selected organochlorine and organophosphate pesticides was studied in the Selangor River, Malaysia over a period of 2 years. The pesticides detected were chlorpyrifos, lindane, heptachlor, endosulfan, endosulfan sulfate, diazinon, total DDTs, total DDEs and dieldrin. This study has shown the presence of organochlorine pesticides despite the fact that they have been banned for a considerable amount of time in Malaysia (Mustafa *et al.,* 2007). An analytical HPLC method for the simultaneous determination of eight sulfonamides in swine wastewater was developed (Nancy and Mustaffa, 2006). The study on selected swine wastewater showed that traces of sulfonamides are present in water from animal husbandry activities.

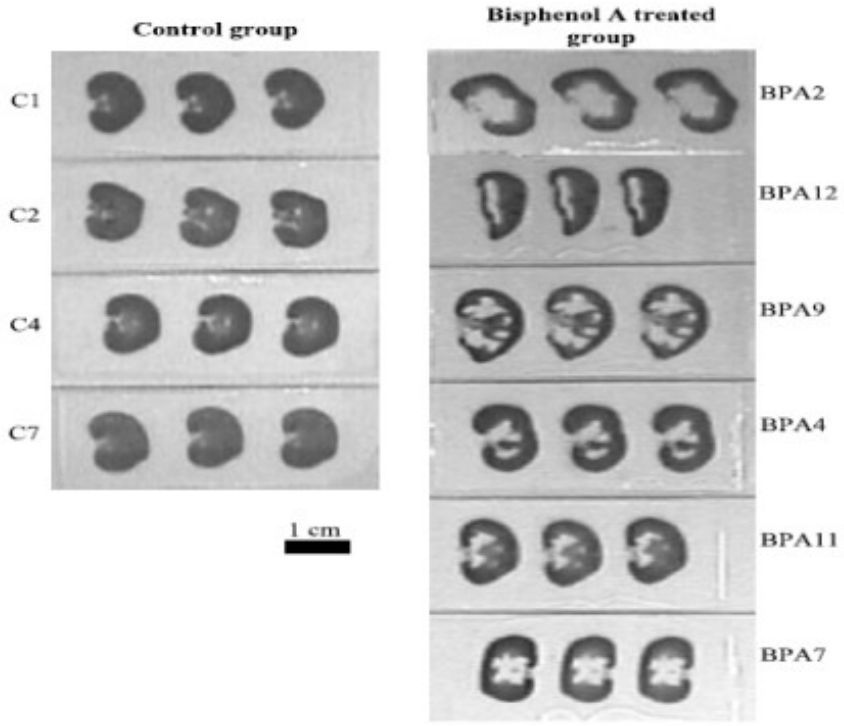


**FIG. 1**- Comparison between the kidney morphology of the control group and the six abnormal kidneys from the bisphenol A treated group. Bisphenol A treated group kidneys shown here have moderate to severe hydronephrosis. Scale bar_/1 cm.

**Conclusion**

The potential risks to humans and wildlife posed by EDCs in many other parts of the world (particularly in developing countries) have not been addressed adequately to date. Although it is clear that certain environmental chemicals can interfere with normal hormonal processes, there is weak evidence that human health has been adversely affected by exposure to endocrine-active chemicals. However, there is sufficient evidence to conclude that adverse endocrine-mediated effects have occurred in some wildlife species. Laboratory studies support these conclusions.

Generally, studies examining EDC-induced effects in humans have yielded inconsistent and inconclusive results, leading to classifying the overall data as "weak." This classification is not meant to downplay the potential effects of EDCs; rather, it highlights the need for more rigorous studies. This state-of-the-science assessment has revealed that our current understanding of the effects posed by EDCs to wildlife and humans is incomplete. There are numerous uncertainties and controversies in the mechanisms and expressions of the effects. Due to the requirement of more sophisticated techniques and instrumentations for the studies of EDCs, the research output has been significantly lesser in developing countries compared to the developed countries like USA, Japan, Europe and Korea.

A good quantum of work has been generated by the Malaysian team, especially when compared with other Asean countries. The evidence that high-level exposure may impact both humans and wildlife indicates that this potential mechanism of toxicity warrants our attention. Uncertainty over the possible effects of chronic, low-level exposures to a number of chemicals with endocrine disrupting potential and the fundamental roles played by the endocrine system in maintaining homeostasis make

understanding the potential effects posed by exposure to these chemicals an obvious international priority. There is a need to identify life stages and species that are more vulnerable to the effects of EDCs and to understand how this mechanism of toxicity may affect individual populations and communities.

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