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ENDOCRINE DISRUPTORS.

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INTRODUCTION.

An endocrine disruptor (ED) is a synthetic chemical that when absorbed into the body either mimics or blocks hormones and disrupts the body's normal functions. This disruption can happen through altering normal hormone levels, halting or stimulating the production of hormones, or changing the way hormones travel through the body, thus affecting the functions that these hormones control. Chemicals known to be human ED include diethylstilbestrol (DES), dioxin, PCBs, DDT, and other pesticides. Many chemicals, particularly cosmetics (UV filters) and plasticizers, are suspected to be endocrine disruptors based on experimental studies in animals **(see Table 1)**.

Sources	Category	Substances
Incineration, landfill	Polychlorinated Compounds (from industrial production or by-products of mostly banned substances)	Polychlorinated dioxins, polychlorinated biphenyls
Agricultural runoff / Atmospheric transport	Organochlorine Pesticides (found in insecticides, many now phased out)	DDT, dieldrin, lindane
Agricultural runoff	Pesticides currently in use	Atrazine, trifluralin, permethrin
Harbours	Organotins (found in antifoulants used to paint the fulls of ships)	Tributyltin
Industrial and municipal effluents	Alkylphenols (Surfactants - certain kinds of detergents used for removing oil - and their metabolites)	Nonylphenol
Industrial effluent	Phthalates (found in placticizers)	Dibutyl phthalate, butylbenzyl phthalate

Sources	Category	Substances
Municipal effluent Agricultural runoff	Natural Hormones (Produced naturally by animals); synthetic steroids (found in contraceptives)	Estradiol, estrone, and testosterone; ethynyl estradiol
Pulp mill effluents	Phytoestrogens (found in plant material)	Isoflavones, lignans, coumestans

***Table 1**. Endocrine Disruptors.*

Exposure to endocrine disruptors can occur through direct contact with pesticides and other chemicals or through ingestion of contaminated water, food or air. Chemicals suspected of acting as endocrine disruptors are found in insecticides, herbicides, fumigants and fungicides that are used in agriculture as well as in the home. Industrial workers can be exposed to chemicals such as detergents, resins, and plasticizers with endocrine disrupting properties. Endocrine disruptors enter the air or water as a bioproduct of many chemical and manufacturing processes and when plastics and other materials are burned. Further, studies have found that endocrine disruptors can leach out of plastics, including the type of plastic used to make hospital intravenous bags. Many endocrine disruptors are persistent in the environment and accumulate in fat, so the greatest exposures come from eating fatty foods and fish from contaminated water.

All vertebrates (fish, amphibians, reptiles, birds, and mammals, including humans) are fundamentally similar during early embryonic development. Scientists can therefore use the evidence acquired on other species to make predictions about endocrine disrupting effects on humans.

In the 1950s and 1960s pregnant women were prescribed diethylstilbestrol (DES), a synthetic estrogen, to prevent miscarriages. Not only did DES fail to prevent miscarriages, but it also caused health problems for many of the women's children. In 1971, began reports of high rates of unusual vaginal cancers in teenage girls. Investigations of the girls' environmental exposures traced the problem to their mothers' use of DES. The girls also suffered birth defects in the uterus and ovaries, and immune system suppression.

Other evidences are more ambiguous. Several studies have found a worldwide lowering of sperm counts and blamed it on the rise of the concentration of estrogens mimics in the environment. Some scientist proposed that estrogen mimics could also explain the growing incidence of breast cancer and perhaps prostate cancer.-

The endocrine disruptors affect the development of the body's vital organs and hormonal systems; infants, children and developing fetuses are more vulnerable to its exposure. And as it was the case with DES, parents' exposure to certain chemicals may produce unexpected and tragic effects in their children, even decades later.

The majority of more than 2,000 chemicals that come into the market every year do not go through even the simplest tests to determine toxicity. Even when some tests are

carried out, they do not assess whether or not a chemical has endocrine interfering properties.

Hormone disruptors have lots of ways to confuse the body signaling system when they occupy a hormone receptor. A) Normal hormones activate the receptor at the appropriate level to obtain a physiological response. B) ED blocks the receptor and interfere with the signall from the body hormone and no effect of this hormone is induced on the cell (Antagonist). C) ED act on the receptor inducing an effect on the cell (Agonist) but this effect could be stronger or weaker than that of the body hormones **(Fig.1)**. The consequence is and excessive or else aninsufficient cellular response.

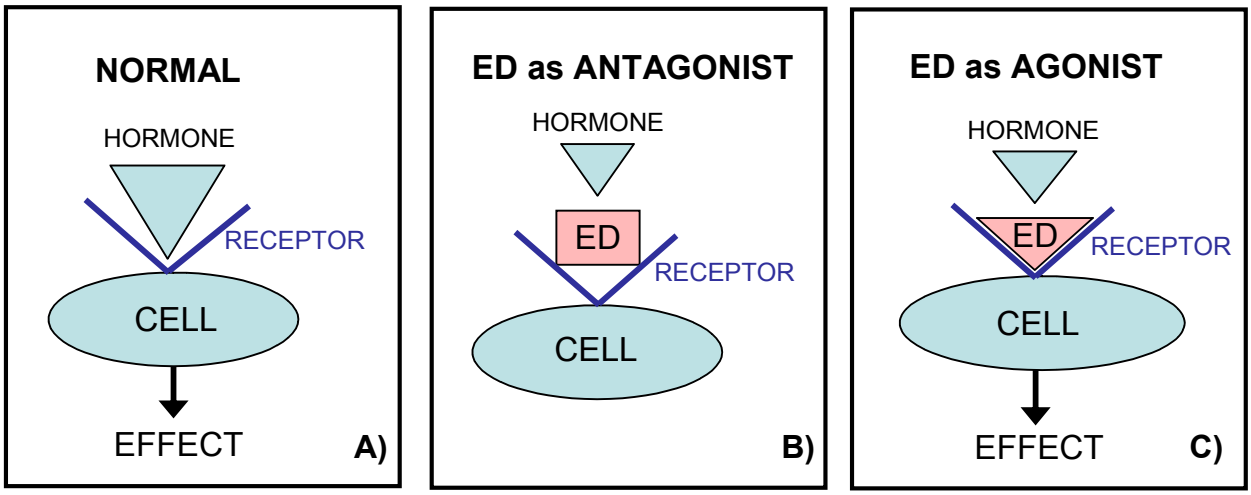

Fig. 1.

Endocrine disruptors and reproduction.

The possibility that environmental exposure to chemicals might affect human reproduction is not new. Apparently, exposure to Ed could result in decreased sperm count and or quality and in increased incidences of testicular cancer, testicular maldescence (cryptorchidism) and male reproductive tract malformations, such as hypospadias and testicular cancer (seminoma). Apparently all of these disturbances have been connected to disturbances in normal endocrine control of male reproductive function.Significantly decreased fertilization rates were observed in couples with male partners exposed to pesticides and enrolled in an in vitro fertilization program.

The possible influence of dietary phytoestrogens should also be considered. It has long been known that grazing on clover rich pastures high in phytoestrogen precursors causes infertility in sheeps (Bennets et al., 1946). More recent studies have shown prolongation of the menstrual cycle in healthy women given soy protein daily. The problem was attributed to prolongation of folicular phase due to suppression of the normal midcycle surge in FSH and LH (Cassidy et al 1994,1995. Lu et al. 1996).

Exposure of humans to pesticides increases the risk of abortion (Ashengrau and Monson 1989, 1990). On the other hand there is evidence that organochlorine and carbamate pesticides cross the plancenta and probably cause fetal death (Arbuckle and Server 1999).

Experimental studies in animals demonstrated that exposure to ED during prenatal and perinatal period induce reduction in weight testes, (Begelow et al 1998); and seminiferous tubule degeneration.

Experiments performed in animals demonstrated the estrogenic activity of alquilphenols, and biophenol-A substances that are used in food plastics different containers.

Almost all the evidences obtained on the effects of ED in human are connected to disturbances in normal endocrine balance.

Ultraviolet filters (UV) represent a new class of endocrine active chemicals. UV filters are lipophilic with high production volume and an increasing diverse spectrum of use. This substance showed estrogenic and antiadrogenic activity. Possible exposure scenarios are various as human and animals can be exposed through the food and humans also through the skin.

A number of absorbers of UV light particularly those of the cinnamate line appear to be endocrine disruptors (Holbech et al 2002; Ma el al 2003; Schumpf et al 2003). Sun protection products contain a variety of UV-filters, among others octyl-methoxycinnamate (OMC). Recent in vitro and animal studies have reported estrogen-like activity of this substance which is used in unknown quantities in sunscreen, cosmetic and plastic products to protect against UV light . Under various conditions in mice and rats OMC was shown to have estrogenic activity in the uterus and in the vagina. (Klamermer 2005; Schumpf et al 2003). On the other hand, in MCF-7 breast cancer cells OMC increased cell proliferation.(Klamermer 2005). These chemicals are able to bind to sexual hormone receptors and influence hormone signaling pathways although several of them have structures that differ substantially from the endogenous hormones (Holbech 2002). In the humans OMC is absorbed by the skin and is present in the blood and urine(Hyden et al 1997).

It is a well known fact that estrogens modify gonadotrophin secretion both in male and female rats acting at pituitary and hypothalamic levels (Kordon et al 1994). At hypothalamic level the effect of sexual hormones is connected with modifications in the hypothalamic neurotransmitters that regulates hypothalamic release of LHRH (Kordon 1994). Recent studies have demonstrated that, besides its estrogenic effect, OMC acts at hypothalamic level decreasing the hypothalamic synthesis of the hypothalamic luteinizing releasing hormone, a hypothalamic hormone that control the hypothalamic-pituitary axis. (Carbone et al in press). Moreover this ED also modified the nervous neurotransmitters involved in the nervous regulation of the gonadal function.

It is very probable that other ED also have multiple effects on the body, modifying the hormonal homeostasis as well as inducing cell alterations. It is clear that more experimental evidences are needed to clarify the effects of these substances in humans.

Endocrine Disruptors and the Nervous System.

The nervous system plays an integrative role along with the endocrine and immune system in orchestrating important physiological functions of the body. These integrative functions are critical for normal development, cognitive functions and behavior. A number of environmental chemicals: organochlorine pesticides such as DDT and/or its metabolite

DDE, chlordecone (kepone), some fungicides (methoxychlor, fenarimol), polyhalogenated aromatic, the polychlorinated dibenzodioxins (PCDD), polychlorinated/ brominated biphenyls (PCB, PBB), and dibenzofurans (PCDFs) etc. have shown to induce neurotoxic effects since it has been described from motor impairment and memory loss to subtle behavior changes (Spencer and Schaumburg, 2000). Of particular concern are the potential effects of exposures on the developing nervous system, because both the nature and adversity of the outcome may depend on the time window during which chemical exposure occurs and may result in irreversible neurobehavioral changes later in life (Yilson 1998).

Endocrine Disruptors and Cancer.

Increases in the incidence of certain cancers in many regions of the industrialized world are often cited as evidence that widespread exposure of the general population to ED has had adverse impacts on human health. Of particular concern are the observed increased incidences of cancers at hormonally sensitive sites, such as breast, uterus, prostate, and testis. It has been argued that these trends coincide roughly with the increasing use and release of industrial chemicals into the environment. Furthermore, these concerns are also based on plausible mechanisms of action because both human and experimental model studies have demonstrated that these cancers are either dependent or modulated by the hormonal milieu. *Breast cancer*: Although numerous human epidemiological studies have been conducted to determine whether environmental ED may contribute to an increased risk of breast cancer, the results remain inconclusive. Overall, the current scientific evidence (from human and animal studies) does not support a direct association between exposure to environmental ED and increased risk of breast cancer. However, all the studies published to date have measured ED exposure levels in adult women. The claim that the time of life when exposure takes place (e.g., prenatal, neonatal, childhood, adolescence) may be the most critical factor is supported by human data on radiation and smoking and by basic research in animal models. Adult women currently at risk for breast cancer may have been exposed to exogenous ED in uterus or during infancy, childhood, and adolescence in the mid-1900s, when contaminant levels of organochlorines were higher. Risk factors for *testicular cancer* are associated with disorders of androgen production or activity. There are also limited data from animal studies about that the exposure of the male fetus to high levels of estrogen may increase the risk of developing testicular cancer. However, there are no published analytical epidemiologic studies that examine a connection between exposure to estrogenic and/or antiandrogenic (e.g. dichlorodiphenyl dicholoroethylene) compounds and testicular cancer.

The *thyroid gland* plays a key role in numerous endocrine, metabolic and physiological functions. The thyroid hormones are particularly important to processes involving growth and development and some environmental chemicals (e.g. certain polychlorinated biphenyls PCBs) have been shown to possess antithyroidal activity (Porterfield and Hendry, 1998). Thyroid hormones are also involved in the carcinogenic process and can affect tumor formation, growth, and metastasis (Guernsey and Fisher, 1990). Thyroid cancer is an uncommon and largely nonfatal tumor with incidence rates two to three times higher in females than in males (Landi et al. 1998). Nordic countries appear to have the highest incidence rates (Coleman et al. 1993). In contrast to clinically apparent disease, small occult thyroid tumors are noted at autopsy in up to about 50% of cases surveyed. The only known human thyroid carcinogens are x-rays and ionizing radiation

(NRC, 1990; Lomat et al., 1997). Persons living in iodide-deficient areas of the world are unable to synthesize adequate levels of thyroid hormones and develop hyperplasic thyroid lesions. There is some evidence that sustained stimulation of TSH receptors is important for development of thyroid cancer in chronic goiter cases (Shi et al., 1991). To date, no environmental chemical has been identified as being carcinogenic to the human thyroid. The etiology of thyroid cancer in humans is largely unknown, and limited trend data are available.

Rodents and humans share a common physiology in regard to the hypothalamic-pituitary-thyroid feedback system, and the thyroid is a commonly affected target organ in rodent chemical carcinogenicity studies (Huff et al., 1991a, 1991b). In a review of potential carcinogenicity of 240 pesticides, at least 24 (10%) produced thyroid follicular cell tumors in rodents (Hurley et al., 1998). Mutagenicity does not appear to be a major determinant in thyroid carcinogenicity for pesticides (except possibly for acetochlor), in contrast to some other chemicals, such as aromatic amines (Hill et al., 1989). The mechanism of action by nongenotoxic agents is thought to be due to a sustained increase in serum TSH levels (Kanno et al., 1996), which can occur through various perturbations of the hypothalamic-pituitary-thyroid axis. The most potent thyroid carcinogens are thyroid peroxidase inhibitors (TPOs), which can cause a drastic decrease in serum thyroid hormone levels and trigger TSH hypersecretion from the pituitary gland via release from negative feedback. Highly potent TPOs are thionamides (thiourea, ethylene thiourea, propylthiouracil, etc.) and aminotriazole (Hill et al., 1989). It is also postulated that during these reactions, free radicals are generated that interfere with other enzymes and bind to other proteins and possibly to DNA (Krauss and Eling, 1987). Other chemicals (e.g., the pesticides clofenzetine, fenbuconazole, pentachloro nitrobenzene) appear to enhance the hepatic metabolism and excretion of thyroid hormones.

The environmental chemicals 2,3,7,8 tetrachlorodibenzoyl-p-dioxin (PCBs), polychlorinated biophenyls polybrominated biphenyls (PBBs) also increase the metabolism of thyroid hormones, resulting in potential increases in thyroid neoplasms (Barter and Klaassen, 1992). PCBs have also been shown to block the binding sites for T4 to serum transport proteins that cause enhanced clearance from serum and decreased availability in tissues (Brouwer and Van den Berg, 1986). PCBs do not bind directly to the thyroid receptor (Cheek et al., 1999).

A direct association between exposure to specific EDCs and thyroid cancer is not supported by human experimental data. However, some ED chemicals can affect the hypothalamic-pituitary-thyroid axis, and the basic mechanisms of interaction among various hormonal systems need to be elucidated to understand the process of thyroid carcinogenesis in humans.

As a summary about the effects of ED and cancer it is clear that there are biological plausibility and some experimental evidence that ED may contribute to hormonally influenced human cancer, the current state of the science has not provided clear evidence for a causal link. In the case of testis cancer, human studies have not yet explored this possible link. Where possible associations with ED exposure have been explored (mainly for breast cancer), the overall strength of the evidence of a causal association is weak.

However, there is not enough information to completely reject the hypothesis that endocrine disruptors such as PCBs, dieldrin, or some other not yet evaluated compound(s) could play a role in the incidence of (female and/or male) breast, endometrial, prostatic, and testicular malignant tumors. Further research should focus on the assessment of

exposure to endocrine disruptors during critical periods of human development (intrauterine life, adolescence, etc.), in relation to the occurrence of cancer at endocrine-sensitive sites during childhood or at later stages of life.

The presence of ED in our environment raises concerns because: harmful effects have been observed on reproduction, growth and development in certain species of wildlife, there are increases in some human reproductive disorders and some cancers which could be related to disturbance of the endocrine system. Adverse effects from some environmental chemicals known to act on the endocrine system have been observed in laboratory animals.

Endocrine disruptors could act in a number of ways in different parts of the body, they may reduce the production of hormones in endocrine glands, affect the release of hormones from endocrine glands, copy or counteract the action of hormones at target tissues, or speed up the metabolism of hormones and so reduce their action. In many cases, it is not yet clear exactly how ED act, even in some cases where a link has been shown between ED exposure and an adverse effect. The most controversial issue is whether low level exposures to ED can have adverse effects. Some scientists have found effects at low doses in laboratory experiments, while others have not been able to corroborate these findings.

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