

Chapter 185

Xenoestrogens: The Curse of Civilization

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INTRODUCTION

"Xeno" literally means foreign. Xenoestrogens therefore mean foreign estrogens. They are also called "environmental hormones" or endocrine disrupting compounds (EDC) and have been defined by the United States Environmental Protection Agency as "an exogenous agent" that interferes with synthesis, secretion, transport, metabolism, binding action or elimination of natural blood borne hormones that are present in the body and which are responsible for homeostasis, reproduction and developmental process.¹ Xenoestrogens have been introduced into the environment by industrial, agricultural and chemical companies and their consumers in the last 70 years or so, as a consequence of modern civilization. Out of the 70,000 registered chemicals for use in the United States, many have hormonal effects in addition to toxic effects. List of few of these compounds commonly used in day-to-day practice is mentioned here (Table 1). Evidence is steadily growing that they are responsible for a wide range of human health problems. They are being implicated for precocious puberty,² higher incidence of breast cancer,³ lowered libido, impotency, sterility, fibroids, early menopause, endometriosis and osteoporosis in females⁴ and oligospermia,⁵ testicular cancer, cryptorchidism, hypospadias,⁶ gynecomastia, sterility and prostatic problems in males.⁷ More recently, they have been held responsible in pathogenesis of diabetes mellitus, hypertension and coronary artery disease.⁸ In children, they have been implicated in childhood obesity,⁹ neuropsychiatric disorders¹⁰ and endocrine disturbances.¹¹ The list seems to be ever increasing. One of the critical points of concern in relation to EDCs is the potential time lag between exposure and the manifestations of the clinical disorders. In humans, this period may be years or decades and hence consequences of developmental exposure may be manifested in adulthood or during aging process. The timing of exposure to EDC is the key to human diseases; exposure of an adult to an EDC may have very different consequences than a developing fetus or infant. In fact, the field of endocrine disruption has embraced the terminology "The fetal basis of adult disease."¹² Furthermore, effects of different classes of EDCs may be additive or synergistic¹³ even very low level of exposure may cause endocrine or reproductive abnormalities, particularly if exposure occurs during a critical developmental window.¹⁴ Recent evidence suggests that the mechanism of transmission may in some cases involve the germ line and may be nongenomic.¹⁵

EFFECT OF XENOESTROGENS ON AQUATIC LIFE SYSTEMS

It was the result of keen observations by many workers across the globe implicating disturbances in wildlife with atmospheric estrogenic exposure that led to the path for similar studies on human

TABLE 1 | Showing list of chemical substances which are commonly used in day-to-day living and have estrogenic effects

- Alkylphenols—Intermediate chemicals used in the manufacture of other chemicals.
- Atrazine—A commonly used weed killer.
- Butylated hydroxyanisole (BHA)—Used as food preservative.
- Bisphenol A—Commonly used monomer for polycarbonate plastic and epoxy resin.
- Dichlorodiphenyldichloroethylene—One of the breakdown products of DDT.
- Dieldrin—A banned insecticide in many countries.
- DDT—A banned insecticide.
- DEHP—Used as plasticizer for PVC.
- Diethylstilbestrol—Obsolete pharmacological estrogen, no more in clinical use.
- Endosulfan—Widely banned insecticide, not yet banned in India.
- Ethinylestradiol—A combined oral contraceptive pill, released into the environment as a xenoestrogen along with urine and feces.
- Heptachlor—Restricted insecticide, not in India.
- Lindane, hexachlorocyclohexane—A widely restricted insecticide.
- Metalloestrogens—A class of inorganic xenoestrogens.
- Methoxychlor—A banned insecticide.
- 4-methylbenzylidene camphor—Widely used in sunscreen lotions.
- Pentachlorophenol—Used as general biocide and wood preservative.
- Polychlorinated biphenyls—Formerly used in electrical oils, lubricants, adhesives, and paints banned these days in many countries.
- Parabens—Commonly used in lotions.
- Phenosulfathiazine—Used as a red dye.
- Phthalates—Used as plasticizers.
- Propyl gallate—Used as antioxidant to protect oils and fats from oxidation.

race. Hence, it is imperative to discuss a little about these horrifying experiences in aquatic life systems to get an inside of this massive global problem. Effects linked to endocrine disruption have been largely noted in invertebrates, reptiles, fish, birds and mammals. Details of these studies are out of scope here. This issue has been addressed in great detail in an excellent review by Mnif et al.¹⁶ A study on *Daphnia magna* showed that endosulfan sulphate disrupts the ecdysteroidal system and juvenile hormone activity of crustaceans.¹⁷ In another study, testosterone production in rats was significantly reduced after *in utero* exposure to linuron.¹⁸ On comparing fishes from above a wastewater treatment plant and below it, studies found disrupted ovarian and testicular histopathology, gonadal intersex, reduced gonad size, vitellogenin induction and altered sex ratios.¹⁹ Sperm concentrations and motility parameters were also reduced in male fish in addition to disruption of stages of spermatogenesis.²⁰

MECHANISM OF ACTION OF XENOESTROGENS

Endocrine disrupting compounds were originally thought to exert actions primarily through nuclear hormone receptors, including estrogen receptors, androgen receptors, progesterone receptors, thyroid receptors and retinoid receptors. Today, it is known that endocrine disruptors also act on neurotransmitter receptors such as serotonin receptor, dopamine receptor, nor epinephrine receptor and aryl hydrocarbon receptor as well. Alterations in acetyl cholinesterase activity has also been demonstrated.²¹ Dachaud et al. found that hSHBG binding may transport some contaminant xenoestrogens into the plasma and modulate their bioavailability to cell tissues, they may also displace endogenous sex steroid hormones from hSHBG binding sites and disrupt the androgen balance.²² Several xenoestrogens are now known to alter *HOX* gene expression.²³ Rodent studies have shown that BPA exposure *in utero* causes molecular changes in mammary tissue, altering estrogen sensitivity, mammary ductal hyperplasia and an increase in carcinoma *in situ* of the breast.²⁴ Increase in EZH2 expression and function in mice after *in utero* exposure to these chemicals have shown a potential for increased risk of breast cancer.²⁵

SOURCES OF XENOESTROGENS

Chemical Pesticides and Fertilizers

Since the discovery of dichlorodiphenyltrichloroethane (DDT) in 1939, numerous pesticides (organochlorides, organophosphates, carbamates) have been developed and used extensively worldwide with few guidelines or restrictions.²⁶ Some of these can persist in soil and aquatic sediments, bioconcentrate in the tissues, move up trophic chains and affect human beings.²⁷ Humans and wildlife are today continuously exposed to a number of pesticides via environment, food and drinking water.²⁸

Water

Both surface and ground water are contaminated with xenoestrogens; studies across the globe suggest that this contamination is nearly universal. Unfortunately, water treatment plants are currently not designed to remove hormonal pollutants, agricultural and pharmaceutical run off as it is not technically possible to remove them in the present set of knowhow. Even detection of their presence is extremely cumbersome and we are hardly aware of their safe limits for human consumption. Discharge of untreated waste, dumping of industrial effluents and run off from agriculture fields are some of the ways in which water is contaminated. Living near sites where pesticides are used, manufactured or disposed, significantly increase exposure.²⁹ Plastic or lead distribution pipes may also contaminate purified water. In India, drinking water is usually stored in plastic buckets and drums which too are not safe as phthalates from plastic are known to leach out in water on prolonged storage especially at high temperatures. Canned and bottled water so frequently used by the affluent class may not be safe for the same reason.

Cereals, Fruits, Vegetables, Meat, Dairy Products and Eggs

It has been found that out of all pesticides spread on the crop, only 1% falls on the insects or pests, whereas 99% falls on the crop itself and gets absorbed in the soil and water, besides being deposited on the crop, and thus finds its way to human and animal bodies. The growth hormones fed to cattle, pigs, poultry and their livestock are major sources of xenoestrogens.

Cosmetics and Toiletries

Unfortunately, one of the most effective ways to absorb xenoestrogen is through skin contact. Xenoestrogens absorbed by the skin are 10

times more potent than those taken orally, as they travel directly to the tissue instead of passing through the liver. Nail polish and sun screen creams are common sources of xenoestrogens including phthalates, benzophenone-3, homosalate, 4-methyl-benzlidene camphor (4-MBC), octyl-methoxy cinnamate and octyl dimethy-PABA. Other products including body lotion, moisturizers, shaving foams, tanning lotions, deodorants, tooth paste, soap, gels and hair sprays may contain xenoestrogens in the form of parabens and phenoxyethanol.

Plastics

Byproducts of the plastic and pesticide industries called organochlorines are one of the largest sources of xenoestrogens. Plastics especially soft plastic, contain phthalates; these compounds can leach out, volatilize over time or in response to heat and other stimuli. Phthalates are used during manufacturing of food storage containers, children's toys, clothing, footwear items, toiletries, IV bags. Bisphenol-A (BPA) is a chemical plasticizer with xenoestrogenic properties human exposure to BPA is ubiquitous and occurs primarily through the diet, from food and beverage containers. BPA is used in the lining of food cans and juice containers, to avoid metallic taste.

HOUSEHOLDS CLEANERS AND NONSTICK KITCHEN WARES

Many household cleaners contain xenoestrogens. Particularly dangerous are laundry detergents and fabric softeners, because residues on clothing, towels and other items are worn against the skin. Air fresheners and insect repellants are also major sources. Perfluorooctanoic acid (PFOA) which is used in the manufacture of Teflon nonstick polymers used in nonstick kitchen wares has been shown to increase the risk of cancer, reproductive problems and liver damage in laboratory animals.

Birth Control Pills and Spermicidal Gels

Birth control pills contain a synthetic estrogen and progestin to force the body to cycle in a normal manner; they are oil soluble and difficult for the body to get rid of them easily. Spermicidal gels containing nonoxynol have also been found to be xenoestrogenic.

HARMFUL EFFECTS OF XENOESTROGENS ON HUMAN RACE

It was only after the first World Wildlife Federation Conference that concerns were articulated about the endocrine disrupting effects of these chemicals for the first time. The potential hazardous effects of EDCs on human health and ecological well being are of global concerns. They have been implicated in a variety of medical problems during the last two decades.

XENOESTROGENS AND CANCEROUS ILLNESSES

Estrogens and their metabolites are known to be involved in the pathogenesis of cancerous illness of breast, uterus, ovary, testicle, prostate and kidney. Xenoestrogens having association with cancerous illnesses include—polychlorinated biphenyl congeners, food-related mycotoxins, fungicides, algicides, pyrethroid insecticides, pentachlorophenol and β -hexachlorocyclohexane.³⁰

Xenoestrogens and Breast Cancer

One of the most famous xenoestrogen implicated for a high incidence of breast cancer in females was DDT, which has been banned in many countries; unfortunately it can persist in soil for centuries, so despite the ban many people around the world are still being exposed to DDT on a regular basis. DDT persists in the human body for decades, where it is stored in fatty tissue such as breasts.

Miscellaneous

High levels of PCBs, DDE and DDT have been found in fat samples from women with breast cancer. The risk of breast cancer is said to be four times greater in women with increased blood levels of DDE.³¹ As environment pollutants, organochlorines are present everywhere. They are used in the production of plastics, to bleach paper products and for many other industrial and agricultural uses. When dumped into landfills, they leak into soil and water, and eventually collect in the tissue of living organisms. One of the latest epidemiological studies performed in Spain between 1999 and 2009 shows that among total of 2,661 cases of breast cancer reported in the female population 2,173 (81%) were observed in areas of high pesticide contamination.³² Numerous other studies support the hypothesis that pesticide exposure influences the risk of breast cancer but few of them are really conclusive due to some inconsistent data across the study.³³ Further research is required to explore long-term follow-up beginning in early life. Researchers also need to consider simultaneous co-exposures to these substances and presence of pesticide byproducts and whether they may act in an additive, synergistic, or antagonistic manner.³⁴

Prostate Cancer

Various studies have consistently demonstrated a higher risk of prostate cancer in agricultural populations than in the general population.³⁵ Quite recently, a study found a statistically significant higher rate of prostate cancer among farmers exposed to chlordecone (organochloride pesticide).³⁶ Nath and Singh from India found a consistent pattern of high incidence of the prostatic cancer from districts located closer to the Gangetic belt and attributed this to a high level of arsenic in ground water.³⁷

Xenoestrogens and Effect on Heart

Recent literature demonstrates the role of EDCs in the etiology of complex diseases such as obesity, diabetes mellitus and cardiovascular diseases; yet these processes are still poorly understood. Further research is required to elucidate all potential interactions between environmental substances and metabolic deregulations. A recent animal study found that exposure to EDC might play a role in arrhythmogenesis in the female heart;³⁸ in yet another study, high level of exposure to BPA has been associated with diabetes and heart disease by increasing the activity of Maxi-K channels in coronary smooth muscles.³⁹

Xenoestrogens and Childhood Obesity

It has been suggested that exposure to even low doses of BPA during development may be associated with increased susceptibility to obesity and diabetes later in life⁹ the rise in the incidence in obesity matches the rise in the use and distribution of industrial chemicals, suggesting that EDCs may be linked to this epidemic. Recent study by Damaskini et al.⁴⁰ suggests that prenatal exposures to polychlorinated bisphenyls may be associated with overweight in children and that sex and high-fat intake may influence susceptibility.

Endocrine Disruptors, Diabetes and Glucose Homeostasis

The incidence of diabetes mellitus has tripled over recent decades; epidemiological studies show an alarming increase in the incidence of diabetes mellitus in young population. Based on the links between EDCs and disturbances of reproduction, metabolism and cancer, it is reasonable to propose a connection between EDCs and diabetes as well as prediabetic state. Animal models also support this hypothesis.

Maternal Xenoestrogen Exposure and Breast Feeding

Fetuses and infants receive greater doses of xenoestrogens due to the mobilization of maternal fat reserves during pregnancy and breastfeeding⁴¹ fetal fat metabolism changes rapidly in the postnatal period, and differences in fat metabolism and adiposity between pre- and postpartum periods determine the pattern of EDC accumulation. This may explain that the children who were breast-fed had higher EDC levels than children who were exposed only in the uterus. In a recent study from IIT Kanpur, breast milk was found to contain endosulphan 800 times higher than permissible limit and pyriphos 400 times higher, which is mind boggling.

XENOESTROGENS AND NEUROPSYCHIATRIC DEVELOPMENT

Infants are extremely vulnerable to pre- and postnatal exposure to EDC, resulting in possible long-term impacts on intellectual function and delayed effects on the central nervous system functioning. In a recently conducted study, prenatal phthalate exposure was associated with childhood social impairment in a multiethnic urban population.⁴² Yet, another study on adult monkeys demonstrated that the capacity of BPA to disrupt neural circuitry goes beyond the vulnerable developmental stages.⁴³

XENOESTROGEN AND FERTILITY

Adverse effects of EDCs on male reproductive dysfunction are well recognized. Damage caused by EDC occurs during gametogenesis and the early development of the fetus. However, the effects may not become apparent until adulthood. Higher prevalence of cryptorchidism and hypospadias has been found in areas with extensive farming and pesticide use.⁴⁴ Many environmental studies have shown that animal species living near contaminated waters are unable to reproduce successfully. This can be extrapolated to explain why sperm count is rapidly decreasing in man⁵ and ectopic pregnancies are increasing in women. Xenoestrogens may account for the rapidly increasing rate of infertility and andropause in industrialized countries. In India also, rising infertility has been reported according to a study from AIIMS. The average sperm count of a normal Indian adult male which used to be 60 million/mL three decades ago, now stands at 20 million/mL. In women, dioxin can be linked to increasing rate of endometriosis and possibly polycystic ovarian syndrome, both related to infertility.

How to Avoid Daily Exposure to Xenoestrogens?

Seeing the universal distribution of chemicals with estrogenic properties in our day-to-day life, it seems impossible to avoid their exposure. However, the following simple measures could go a long way in ensuring protection, if followed meticulously.

- Avoid all synthetic pesticides, herbicides and fungicides. Use natural pest control.
- Wash your food well to get rid of pesticides.
- Don't switch to bottled water. Instead install a reverse osmosis water system.
- Eat organic foods as often as possible. Reduce your consumption of animal products in general.
- Do not heat food or water with plastic containers in the microwave. Use glass or ceramics.
- Do not leave plastic containers especially with drinking water in the sun. Avoid teflon and other nonstick cookware instead use cast iron.

- Minimize consumption of food from tin cans. Over 85% of tin cans are lined with BPA that leaches when exposed to heat.
- Don't drink from Styrofoam cups and container.
- Don't use fabric softeners and dryer as it puts petrochemical right on your skin.
- Use organic soaps and tooth paste. Avoid fluoride.
- Avoid shampoos, creams, sun screen lotions and cosmetic that has parabens, switch to more natural products.
- Avoid nail polish and nail polish removers.
- Use only naturally based perfumes. Most perfumes are petrochemically based.
- Use old-fashioned household cleaners like baking soda, borax and vinegar.
- Ventilate your house frequently; avoid use of air fresheners, insecticides, foggers that release chemicals into the air.
- Use a simpler method of birth control such as condom. Use one that does not use a spermicide such as nonoxynol.

Detoxification from Xenoestrogens

Obviously, one cannot completely avoid chemicals like xenoestrogens in one's life, so it is important to do some detoxification to help the body get rid of the xenoestrogens and other chemicals it is exposed to. We all know that liver breaks down all excess hormones for elimination, so supporting the liver is very helpful. Cruciferous vegetables contain compounds that help the enzyme pathways in the liver that breakdown excess estrogen. Eating broccoli, cauliflower, cabbage and other vegetables such as celery, carrot, beetroot and parsley is a great way to support liver's detoxification ability. One of the compounds in these vegetables is Indole 3 carbinol which is helpful in getting rid of excess estrogen.

Food rich in phytoestrogen can also help to protect the body as they tie up estrogen receptor site. So, the stronger xenoestrogen cannot attach to them. Soy products are widely promoted for their phytoestrogen effects, but too much soy is also not good. Flax seeds and flax seed oil that contain lignans are also sources of beneficial phytoestrogens. A number of herbs are also good sources of phytoestrogens, including black cohosh, licorice root and hops. Increasing progesterone level can also be helpful.

The other possible way to detoxify xenoestrogens:

- Vitamin C-500 milligrams
- Lipoic acid (100-500 mg daily)
- N-acetyl cystine (1,500 mg daily)
- Natural progesterone cream (20 mg/day)
- Improve circulation and sweating via hydrotherapy, sauna and exercise.
- Increase fiber intake because excess xenoestrogen binds to fiber and it is eliminated through bowels. Eat fresh raw fruits and vegetables to provide living enzymes.
- Drink plenty of water to support elimination of toxins through the kidney.

CONCLUSION

It is clear from the above discussion that xenoestrogens are responsible for numerous disturbances of reproductive systems including sterility. Their role in childhood obesity, neurological and endocrinal disorders is getting established day by day, beside their contribution in complex diseases such as obesity, diabetes mellitus and cardiovascular disease, the so called major epidemics of the modern world. This seems only a tip of the iceberg phenomenon, as many of these processes still remain poorly understood, the unfortunate part being that this is all a creation of so called modern civilization. Hence, it is apt to call xenoestrogens as "The Curse of Civilization". At the present juncture, the only way forward seems to

be taking preventive measures to minimize exposure and maximize their excretion from the body. This should not be limited by absence of the so called hardcore scientific evidence, besides of course strict international regulations for their use. Further extensive research is required to elucidate potential interactions between these endocrine disrupting substances and well being of mankind.

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