Environmental estrogen: A Review

Paper subtitle: Effect of Xenoestrogen as endocrine disruptor: A Review

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Abstract: Environmental estrogens are chemicals present in the environment which have been a source of concern because of its possible health threats to human by interfering with hormone biosynthesis, metabolism of body, reproduction and cardiovascular endocrinology. These chemicals in the human body act through different mechanism like estrogenic, peroxisome proliferator-activated receptor γ, retinoid, and actions through other nuclear receptors, neurotransmitter receptors and systems which makes the study of the mechanism of action of these xenoestrogens complicated. Because of the fact that human being are exposed to these substances though wide variety of routes regularly including pesticides, plastics, agriculture, paper mill effluents, these chemicals are of growing concern. These environmental estrogens also interfere with the endocrine systems of wide variety of animals including invertebrates, fishes, reptile, aves and mammals. These have lead to depletion of wide variety of important species of wild life and also affected live stock of human. Understanding these topics is essential for educating the public and medical professionals about potential risks associated with exposure of endocrine disruptors, the design of rigorously researched programs using both epidemiological and animal studies, and ultimately the
I. Introduction:
Environment often changes with time and therefore many organisms have to adapt to the changes in the surrounding environment and they have the ability to adapt to these changes. However, tolerance range is not the same with all species and exposure to environmental conditions at the limit of a certain organism's tolerance range represents environmental stress.

It is widely believed that exposure to natural and synthetic chemicals in the environment, with potential to interfere with the endocrine system, may elicit a wide range of toxic effects in wild-life and in humans, in particular on the reproductive system and with respect to the induction of cancer (Atterwill & Flack, 1992, Neubert, 1997; McLachlan 2001; Baker, 2002; Eertmans et al., 2003)

II. Natural estrogen:

Natural estrogens are a group of compounds which are steroid in nature and are primary female sex hormones. The three major naturally occurring

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**Key words:** Environmental estrogens; endocrine disruptors; endocrine systems
Estrogens in women are estrone (E1), estradiol (E2), and estriol (E3). Although estrogen exists in men as well as women, it is found in higher amounts in women, especially those capable of reproducing. Estrogen contributes to the development of secondary sex characteristics, which are the defining differences between men and women that don’t relate to the reproductive system.

Estrogen is an essential part of a woman’s reproductive process. It regulates the menstrual cycle and prepares the uterus for pregnancy by enriching and thickening the endometrium. Two hormones, the luteinizing hormone (LH) and the follicle stimulating hormone (FSH), help to control how the body produces estrogen in women who ovulate.

A) Environmental Estrogens:

Environmental estrogens are natural or synthetic chemicals that mimic enhance or inhibit endogenous hormones. These are also called as Xenostrogenes, and are false estrogens found in chemicals that bind with estrogen receptor sites in the human body, causing cellular functions to change. They are of a great concern to all sectors of public interest including the Environmental Protection Agency (EPA). Exposure to these substances occurs through from food, air, water, soil, household products and probably through breast milk and during development in our mother's womb. The human health risks that may be associated with these low-level yet constant exposures which are still largely unknown and highly controversial.

Silent Spring is a book written by Rachel Carson and published by Houghton Mifflin on 27 September 1962. The book is widely credited with helping launch the environmental movement. In the late 1950s, Carson turned worked on the conservation and the environmental problems caused by synthetic pesticides. In her book she drew attention to the effect of manmade chemicals especially pesticides like DDT on bird and wildlife. DES (diethylstilbestrol), the medication given in the 50’s and 60’s to prevent miscarriages, had dangerous effect, as the daughters of women who took this medication developed vaginal cancers and other reproductive abnormalities.
Another example is the tragic effects which occurred on the development of limbs following the administration of the pharmaceutical drug thalidomide to pregnant women (Michal et al. 1993).

**B) Mode of action of endocrine disruptor (ED).**

Environmental estrogen act in wide variety of mechanisms to affect the endocrine system. Some of the ways by which endocrine disruptor acts on the endocrine system are:

*These disruptors, by blocking the cell receptors, prevent naturally occurring hormones from affecting cells in the usual way.

*These disruptors elicit unusual or abnormal reactions in cells.

*These disruptors are perceived by the body as genuine hormones because they elicit the same chemical reactions as natural hormones.

Exposure to these substances occurs throughout our lives from food, air, water, soil, household products and probably through breast milk and during development in our mother's womb. The human health risks that may be associated with these low-level yet constant exposures are still largely unknown and highly controversial.

1) **Pesticides:**

Many pesticides have now been found to have estrogenic or bind to estrogen receptors, which include: ortho-phenylphenol, DDT and metabolites (although the anti-androgenic properties of p,p'DDE may be of greater importance); methoxychlor; chlordecone; dieldrin, endosulfan; 1-hydroxychlorodene (a metabolite of chlordane); and toxaphene. Some of these can induce estrogenic effects at relatively low levels.

![DDT Chemical structure](image)

**Effect of pesticide on mammals:**

Numerous pesticides have been reported to affect hormone synthesis and or metabolism. These include: the imidazole pesticides (such as...
propiconazole, epoziconazole and ketoconazole); fenarimol; TBT; and several organochlorine pesticides.

Ketoconazole, for example, has been found to block steroid synthesis. Another pesticide, fenarimol, is known to inhibit aromatase activity, and this has also been shown to delay birth.

**Effect on other animals:**

TBT (Tributyltin) is also believed to act by inhibiting aromatase, as it appears to act by blocking the conversion of testosterone to estradiol. It therefore has well-known androgenic activity in molluscs, and for example, it can cause female dog whelk to grow penises (imposex) at concentrations as low as 2.5 nanogram per litre.

2) **Products associated with plastics:**

Bisphenol A and phthalates are sometimes called "everywhere chemicals" because they're so widely used. Bisphenol A, which is used to make plastics clear, strong and shatter-resistant, shows up in water bottles, food containers, baby bottles, some dental fillings and the coatings for the inside of cans containing foods. Phthalates which make plastic soft and flexible, are used in toys, rattles, car interiors and medical devices such as tubing, catheters and intravenous bags.

**Bisphenol A**

![Bisphenol A](image)

**Effect on mammals:**

In addition to its estrogenic activity, there is some evidence that BPA binds to thyroid hormone receptor, acting as a thyroid hormone antagonist.

**Effect on other animals:**

Intrauterine effects may occur in other species, including wild house mice, rats, ferrets, swine, hamsters, voles, and sheep. An interesting and probably related phenomenon is the freemartin in cattle, sheep, goats, and other farm animals.

**Phthalates:**
General chemical structure of phthalate

**Effect on mammals:**

In a study published in 2005, lead investigator Dr. Shanna Swan reported in the "Swan Study" that human phthalate exposure during pregnancy results in decreased anogenital distance among baby boys.

**Effect on other animals:**

Anti-estrogenic effects have been reported in a study on Japanese medaka (*Oryzias latipes*) water exposed to DEHP for three months post-hatching (Kim et al. 2002).

**3) Industrial chemicals:**

Exposures to poly-chlorinated dibenzo-p-dioxins (PCDDs), polychlorinated biphenyls (PCBs), and poly-chlorinated dibenzofurans (PCDFs), which are products and by-products of industrial or combustion processes, have the potential to disrupt multiple endocrine pathways and induce toxic responses.

**Effect on mammals:**

A wide variety of endocrine systems are affected by PCBs, including the estrogen and androgen system (3), the thyroid hormone system (4), retinoid system, corticosteroid system and several other endocrine pathways.

**Effect on other animals:**

* in birds it leads to alterations in behavior/reproductive success of colonial water birds (DDE, PCBs,) and abnormal reproductive morphology (dioxins), eggshell thinning (DDT/DDE).
* Amphibian population changes (DDT, DDE)
* PCB-induced reproductive and immune dysfunction in Baltic seals. Great Lakes trout populations were adversely affected by PCB and dioxin exposures in the 1960–1970’s, PCB-exposed cormorants displayed crossed-bills, great blue herons were infertile, and mink fed PCB contaminated fish from the Great Lakes either died after high exposures or were infertile at lower exposure levels.
4) **Ordinary household products:**

Octylphenol ethoxylates (OPEs) are widely used in cleaning agents. They are also added to paints, coatings, treatments for textiles and chemicals used in paper manufacture. OPEs also have some medical applications.

**Effect on mammals:**

Exposure to high levels of octylphenol ethoxylates may cause irritation of the lungs, digestive system, skin and eyes. Octylphenol ethoxylates are thought to interfere with hormones in animals and may therefore interfere with the development and reproductive system in animals.

**Effect on other animals:**

OPEs are known to be very toxic to wildlife, particularly aquatic organisms. OPs are accumulated and concentrated by aquatic organisms and birds.

5) **Pharmaceutical and Personal Care Products:**

Pharmaceutical and Personal Care Products (PPCPs) include medicines, insect repellents, sunscreens, perfumes, soaps, fragrances, and lotions.

**Effect on mammals:**

UV filters in sunscreen a good example of a ubiquitous endocrine disruptor and the dueling science surrounding its risk to human health.

**PARABENS** (alkyl-p-hydroxybenzoates) are one of the most widely and heavily used suites of antimicrobial preservatives in cosmetics (skin creams, tanning lotions, etc.), toiletries, pharmaceuticals, and even foodstuffs (up to 0.1% wt/wt). Although the acute toxicity of these compounds is very low, Routledge et al. (112) report that these compounds (methyl through butyl homologs) display weak estrogenic activity in several assays.

Fragrances (musks) are ubiquitous, persistent, bioaccumulative pollutants that are sometimes highly toxic. The polycyclic musks (substituted indanes and tetralins are the major musks used today, accounting for almost two-thirds of worldwide production) and especially the inexpensive nitro musks (nitrated aromatics accounting for about one-third
of worldwide production) are used in nearly every commercial fragrance formulation (cosmetics, detergents, toiletries) and most other personal care products with fragrance; they are also used as food additives and in cigarettes and fish baits (96). 'Musk xylol has proved carcinogenic in a rodent bioassay and is significantly absorbed through human skin; from exposure to combined sources, a person could absorb 240.5g/day. The human lipid concentration of various musks parallels that of other bioaccumulative pollutants such as PCBs”

**Effect on mammals:**

The pharmaceuticals and pharmaceutical metabolites salicylic acid, paracetamol, clofibrinic acid, and methotrexate were examined with regard to their biological degradability and toxicity toward algae, Daphnia, fish embryos, luminescent bacteria, ciliates, and the fish cell line BF-2.

6) **Phytoestrogens:**

Plants which contain phytoestrogens include many in our diet, such as whole cereal grains, seeds, soy, cabbage, beet, broccoli and peas (Barrett 1996).

Phytoestrogens are plant-derived xenoestrogens, also called "dietary estrogens", are a diverse group of naturally occurring nonsteroidal plant compounds that, because of their structural similarity with estradiol (17-β-estradiol), have the ability to cause estrogenic or and antiestrogenic effects.

Studies show they can result in lowering the biological activity of sex hormones in the body. Some also have antioxidant properties.

**Fig:** Chemical structures of the most common phytoestrogens found in plants (top and middle) compared with estrogen (bottom) found in animals.

**Effect on mammals:**
The soy isoflavone, genistein, at a concentration of 20 µmol/L, inhibited proliferation of estrogen-independent human breast cancer cells in culture by approximately 50% (Santell et al, 2000).

**Effect on other animals:**

The phytoestrogen beta-sitosterol alters the reproductive endocrine status of goldfish (MacLatchy DL, Van Der Kraak GJ. 1995).

Research suggests that phytoestrogens in the diet have many beneficial effects, but harmful effects have also been found. For example, in Australia, female sheep which grazed for prolonged periods on a species of clover containing phytoestrogens suffered sharp declines in fertility. Phytoestrogens may act as a defence mechanism, to deter herbivores from heavy predation on a single plant species (Adlercreutz 1995, Barrett 1996).

Beneficial health effects have been associated with eating a diet which is rich in grains and vegetables, containing high quantities of phytoestrogens. Studies on populations who consume such a diet suggest that it has a protective effect against several hormone-related diseases. These include estrogen-related cancers, such as breast cancer and prostate cancer, colon cancer, and possibly osteoporosis and cardiovascular diseases.

**Conclusion:**

The most challenging aspect of this problem is discovering how to eliminate these compounds from the environment and where to focus remediation efforts. Even pollutants no longer in production persist in the environment, and bioaccumulate in the food chain. Another challenging aspect of this problem is discovering how to eliminate these compounds from the environment and where to focus remediation efforts.

In 1998 the EPA announced the Endocrine Disruptor Screening Program by establishment of a framework for priority setting, screening and testing more than 85,000 chemicals in commerce. The basic concept behind the program is that prioritization will be based on existing information about
chemical uses, production volume, structure-activity and toxicity.

The potential seriousness of the effects of these substances has led to an increasing number of medical experts and scientists from all over the world to target environmental estrogen in their research.

By awareness of and potentially labeling foods that are likely to contain high amounts of pollutants the human exposure to environmental estrogen can be lowered to a certain extent. An understanding of how these chemicals, once in the environment, move through ecosystems is essential to designing ways to isolate and remove them.

ACKNOWLEDGEMENT

The authors are thankful to Department of Science and Technology for providing with the INSPIRE Fellowship for financial assistance during study period.

REFERENCES


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