

Endocrine Disrupting Chemicals: Current Trends, Attributable Effects on Women's Health and Future Perspectives

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Abstract—Endocrine disruptors (EDCs) are chemicals that have the capacity to interfere with normal signaling systems. They may mimic, block or modulate the synthesis, release, transport, metabolism and binding or elimination of the natural hormones. Not all EDCs are man-made compounds; many plants also produce substances which can have different endocrine effects either beneficial or adverse in certain circumstances. We present a comprehensive overview of EDCs' sources, types, their different aspects of exposure like dose, range of effects, persistence and ubiquity, mechanism of action and effect on women's health. We have also discussed the different detection methods of investigating EDCs including physical and chemical fractionation methods, biomarkers' study in indicator species, in vitro and single mode of action (MOA) oriented in vivo and in ovo assays, and life cycle or multigenerational in vivo tests. Alongwith different methods adopted for their removal from the environment including coagulation, biofiltration, chlorination, ozonation, membrane treatment and lime softening of the environmental samples, we have also taken in account the potential of probiotics for countering the effect. The review also gives a special reference to sex hormones mimicking compounds like xenoestrogens and phytoestrogens consumed through diet, and their ability to cause hormonal disbalance and therefore leading to reproductive and urogenital abnormalities, making them a major matter of concern.

1. INTRODUCTION

Over the past decade, a growing body of evidence suggests that numerous chemicals, both natural and man-made, may interfere with the endocrine system and produce adverse effects in humans and wildlife.

In conjunction with the nervous and immune systems, the endocrine system forms the main regulatory mechanism that controls different pivotal functions in the human or animal body. The messengers of the endocrine system are hormones that are synthesized and secreted at very low quantities from specialized glands and transported to the target organ via the bloodstream. Hormones influence several essential regulatory, growth, developmental, and homeostatic mechanisms of the organism leading to normal functioning of the body.

Growing industrialization and modern ways of living have introduced chemicals that can disrupt the normal functioning of the body's various processes. Over the last 50-60 years, man-made chemicals have been manufactured and many have become widespread environmental contaminants (Simonich and Hites, 1995). Such chemicals have been given the name of 'endocrine disruptors'. These have been incriminated as a cause for a range of reproductive health problems and diseases like cardiovascular diseases and cancers. This review gives a comprehensive overview of endocrine disruptors, their sources, types and effect on health.

We electronically searched using Pubmed and Google. Grey literature and journal hand searching of scientific journals only were also done to explore more information. Data in only English language was searched and reviewed. Literature from the time period 1985 has been reviewed. The search was performed and articles were screened for suitability and read by the first author. Reviewing of the same was done by other co-authors.

We divided the data collected under major headings for better and clear understanding. These include definition of EDCs, likely routes and aspects of exposure, types, mechanism of action, spectrum of health effects, phytoestrogens in women's health, detection and elimination from the environment and a discussion over the protective effects of probiotics countering EDCs.

Definition

Endocrine disruptors are exogenous agents that interfere with the synthesis, secretion, transport, metabolism, binding action or elimination of natural blood borne hormones that are present in the body and are responsible for homeostasis, reproduction and development process (Diamanti-Kandarakis et al., 2009). They are heterogenous and include synthetic chemicals used as industrial solvents and their byproducts like polychlorinated biphenyls (PCBs), dioxins, plastics (Bisphenol

A), pesticides (DDT, methoxychlor), fungicides (vinclozolin), insecticides like malathion and even pharmaceutical agents (Diethylstilbesterol). In addition to these, natural chemicals found in human and animal food can also act as endocrine disruptors, for example, phytoestrogens. These chemicals do not necessarily remain where they are released into the environment but may be transported in water or through air across the globe, with increase in concentration at each trophic level in the food chain (Loganathan and Kannan, 1994).

2. LIKELY ROUTES OF EXPOSURE TO ENDOCRINE DISRUPTERS

Endocrine disruptors enter air or water as a byproduct 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. Hence, human exposure to endocrine disruptors may occur by the ingestion of food and water, through inhalation of air and even by absorption through skin (Hall, 1992).

Many Endocrine Disrupting Chemicals (EDCs) are classified as 'xenoestrogens' because their action mimics that of oestrogen hormones. On entering into the body system, these exogenous chemicals mimic the action of different hormones, in particular, the sex hormones, estrogen and androgen and disrupt the normal functioning by binding to specific receptors, thus leading to reproductive disorders. The first evidence for the effects of EDC came from observations of reduced fertility and hormonal perturbation in aquatic organisms living in polluted waters (Colborn et al., 1993; Guillette and Gunderson 2001).

3. FOUR ASPECTS OF EXPOSURE TO ENDOCRINE DISRUPTION

First, the effect of low doses: Normal endocrine signaling involves very small changes in hormone levels, yet these changes can have significant biological effects. That means subtle disruptions of endocrine signaling is a plausible mechanism by which chemical exposures at low doses can have effects on the body.

Second, the wide range of effects: Endocrine signals govern virtually every organ and process in the body which means that when outside chemicals interfere with those systems, the effects can be seen in many different diseases and conditions.

Third, the persistence of effects: It is being seen that the effects of exposure to endocrine disruptors can be observed long after the actual exposure has ceased. This is especially true for growth and development, processes that are very sensitive to endocrine regulation.

Fourth, the ubiquity of exposure: Both naturally occurring and manmade substances can be endocrine disruptors. Some, e.g., arsenic and agricultural chemicals, are ubiquitous in the environment. In addition to the growing use of hormonally-active pharmaceuticals that pass through the bodies of those taking them and end up in water treatment systems and surface waters, many of the chemicals that are being found to have endocrine effects are components of a wide range of consumer products, including plastic water bottles, cosmetics, sunscreens, and other personal care products. Substances applied to the skin can be directly absorbed but also end up getting washed off our bodies and into our water systems. As a result, chemicals with endocrine disrupting activity are widely dispersed in our environment, often at levels associated with biological effects.

4. TYPES OF ENDOCRINE DISRUPTING MOLECULES

Current knowledge about endocrine disruption is based on studies of growth, development, and reproduction. These processes are regulated by steroid and thyroid hormones that can be affected by many environmental chemicals. One of the more common mechanisms of endocrine disruption occurs when the chemical mimics a steroid hormone's effect by binding to the receptor for that hormone. A chemical that has this mechanism of action is termed an agonist. Other EDCs may be hormone antagonists, where their binding to hormone receptors reduces hormone activity by preventing the endogenous hormone from binding to that receptor and producing the intended cellular response.

Dioxin

Dioxin, the most toxic man-made chemical, is not an estrogen (Szabo et al., 2009). However, it can block the action of estrogens under certain conditions. Dioxin can also lower the levels of androgens and affect the amount of thyroid hormones in the body. It can decrease insulin levels and change the amount of glucocorticoids. Exposure of pregnant animals to extremely low levels of dioxin (doses that do not adversely affect the mother) leads to alterations in the reproductive system of the pups. Many of the effects are not detectable until the offspring reach puberty.

Polychlorinated Biphenyls

Unlike dioxin, which is an unwanted by-product of certain industrial processes and combustion, PCBs were commercially synthesized and used in transformers and capacitors. The very properties that made PCBs desirable in electrical equipment, such as their resistance to thermal degradation and stability, has led to their persistence and bioaccumulation in the environment. Short-term exposure to large amounts of PCBs can cause liver damage; the effects of smaller concentrations can be more subtle, affecting the reproductive development of children of exposed mothers.

Bisphenol A

Bisphenol A (BPA) is an industrial monomer used in the production of polycarbonates and epoxy resins. It mimics the action of endogenous estrogen 17- β -estrogen and is a putative endocrine disruptor known to have adverse health effects. Traces of it are known to leach from the linings of food cans, plastic wares and dental sealants, hence leading to human exposure (Honda et al., 2000; Olea et al., 1996). It is a known endocrine disruptor, and hundreds of studies published in the decade have found that laboratory animals exposed to low levels of it have elevated rates of diabetes, mammary and prostate cancers, decreased sperm count, reproductive problems, early puberty, obesity, and neurological problems. BPA has been associated with reproductive disorders in both males and females. Ikezuki et al have reported accumulation of BPA in fetuses and early exposure during the prenatal period in humans (Ikezuki et al., 2002). Human exposure to BPA can arise from a number of sources, particularly from the direct contact of food with BPA containing plastics. A study conducted by Brotons and colleagues detected BPA in the liquid portion of several types of vegetables (peas, artichokes, green beans, mixed vegetables, corn, and mushrooms) taken from cans with epoxy resin linings (Brotons et al., 1995).

Malathion

Malathion is an insecticide used to control outdoor insects in both residential and agricultural areas. Exposure to malathion can occur via skin contact, ingestion of food and water and through inhalation (Tomlin, 2006). This endocrine disruptor irreversibly binds to the enzyme acetylcholinesterase. Under normal conditions, acetylcholinesterase degrades the neurotransmitter acetylcholine and is present at the nerve junction and cholinergic synapsis where it terminates synaptic transmission. But when malathion binds to this enzyme, acetylcholine accumulates at the nerve junction and results in overstimulation of the nervous system (Reigart and Roberts, 1999).

Phthalates

Phthalates are found in some soft toys, flooring, medical equipment, cosmetics and air fresheners. They are of potential health concern because they are known to disrupt the endocrine system of animals, and some research has implicated them in the rise of birth defects of the male reproductive system (Swan et al., 2005).

Diethyl stilbestrol

Human diethylstilbestrol exposure occurs by diverse sources, such as medical treatment for certain conditions, which includes breast and prostate cancers. A study carried out by Sheehan in 1998 depicted reduced sperm quality, undescended testes and urogenital tract abnormalities were increased in the sons of mothers taking diethyl-stilbestrol (DES) compared with those who did not take them. Animal studies conducted with DES resulted in male genital abnormalities during

development including cysts, testicular lesions and lack of growth of the seminal vesicles and therefore concern has been raised about the effects of phytoestrogens on male development.

Phytoestrogens

Phytoestrogens are naturally occurring estrogens found in various plants which may enter human consumption. They are of biological interest because they exhibit both *in vitro* and *in vivo* weak estrogenic and antiestrogenic activity (Price and Fenwick, 1985). Many phytoestrogens have molecular configuration similar to mammalian sex hormones. They exert their effect primarily by binding to estrogen receptors (Turner et al., 2007). There are three main types of phytoestrogens namely isoflavones, coumestans and lignins. Isoflavones have been shown to stimulate uterine hypertrophy in laboratory animals, thus exhibiting estrogenic action. The isoflavonoides, genistein and diadzein, have an affinity for estrogen receptors and have been seen to induce sexual differentiation including delayed puberty onset in rats (Levy et al., 1995). Because phytoestrogens have an estrogenic effect, they have been shown to be responsible for permanent oestrous in mammalian females, alongwith vaginal hypersecretion, which impairs sperm progression into the female reproductive tract (Adam, 1990).

While considerable attention has been focused on the developmental effects of environmental contaminants, comparatively less attention has been directed towards potential actions of hormonally active dietary factors such as phytoestrogens. As the public has become increasingly aware of the health benefits associated with consuming an Asian-style diet, consumption of foods and health products containing dietary phytoestrogens has risen (Messina and Messina, 1991). While these chemicals may have health-related benefits in some age groups, they may also present a risk to immature estrogen-sensitive target tissues, such as the developing reproductive tract.

5. MECHANISM OF ACTION OF ENDOCRINE DISRUPTORS

The endocrine disruptors modulate hormonal function in the body and in particular affect steroid hormones. Changes in the effective concentrations of hormones can occur if an endocrine disruptor binds to a specific hormone receptor. This chemical substance may then either mimic the hormone or block the normal biological response by occupying the receptor site. Also, endocrine disruptors maybe able to react directly or indirectly with hormone structure to alter its function, change the pattern of hormone synthesis or modulate the number of hormone receptors and their affinities for specific molecules (Safe et al., 1991; DeRosa et al., 1998).

6. SPECTRUM OF HEALTH EFFECTS CAUSED BY ENDOCRINE DISRUPTORS

Health effects attributed to endocrine disrupting chemicals include a range of reproductive problems like reduced fertility, male and female reproductive tract abnormalities, loss of fetus and skewed male/female sex ratios along with abnormal thyroid function and structure and altered immune system function. A spectrum of disorders throughout life, some of which are sexually dimorphic, can be related to endocrine disruption. Male sexual differentiation is androgen-dependent (and potentially estrogen-dependent), whereas female differentiation occurs largely independent of estrogens and androgens.

Women are exposed to hormone disruptors more frequently than they know. These chemicals are a worrisome threat to their reproductive health. The role of endocrine disruptors in affecting the development of male reproductive organs is well studied and well known unlike their role in women's reproductive health which until recently was not clearly understood.

Phytoestrogens: Effect on Puberty

Pubertal onset maybe hastened, delayed or unchanged by early exposure to phytoestrogens, an effect to which females seem to be particularly susceptible, and that is dependent upon the compound, dose and timing of exposure. For example, while gestational and postnatal exposure to resveratrol delayed the onset of puberty in female rats (Kubo et al., 2003), postnatal exposure alone had no effect on the timing of puberty (Henry and Witt, 2006). The effects of phytoestrogens on puberty maybe species specific. For instance, short term postnatal exposure to genistein and gestational and lactational exposure to it, had no effect on timing of puberty in male mice (Wisniewski et al., 2005). These data suggest that puberty is a sensitive endpoint upon which perinatal phytoestrogens may exert their effects with a relatively long latency. However, it is not clear what the mechanisms are for these effects, nor is it clear whether pubertal exposure to phytoestrogens affects reproductive function during adulthood. This latter question is important because it has been posited that puberty is a second critical for brain organization (Sisk and Foster, 2005) and the pubertal brain maybe vulnerable to estrogenic EDCs.

Women's Hormonal Balance

Hormones of the female reproductive system which include estrogen and progesterone exist in a delicate balance, controlling a lifetime of reproductive cycles. These hormones which are made by the endocrine system are transported through the blood, and as chemical messengers they set up an intricate communication network between organs, the brain and different tissues. They work in concert with all the body systems, maintaining and controlling the development of the various systems including the reproductive system. A small shift in the balance can have disastrous effects on the

reproductive system leading to a lifetime of ailments. Hormone disruptors are not normally found in the body, but once inside they interfere with the natural hormone balance by scrambling the messages that the hormones are sending. They do so by binding to hormone receptors sites which either result in the blockage of messages or the sending of faulty messages.

Worrying trends in female health

The most common endocrine disruptor that affects the female reproductive system is Diethyl stilbestrol (DES). DES is a synthetic estrogen and is considered a potent neonatal endocrine disruptor. Human exposure to this endocrine disrupting molecule occurs usually through medical treatment for certain clinical conditions, including breast and prostate cancer. Numerous studies have proved the endocrine disrupting ability of this compound. From about 1940 to 1970, DES was given to pregnant females under the mistaken belief that it would prevent pregnancy complications and losses. However, in 1971, it was seen that young girls who were exposed to DES in utero developed a rare vaginal tumor (Goldberg and Falcone, 1999).

In addition to DES, the ubiquitous use of BPA provides great potential for exposure to both the developing fetus, indirectly through maternal exposure, and the neonate, directly through ingestion of tinned food, infant formula, or maternal milk. Indeed, BPA has been measured in maternal and fetal plasma and placental tissue at birth in humans.

Female hormone production

The organochlorine pesticide hexachlorobenzene is a worldwide persistent organic pollutant and has been detected in various tissues and human fluids including serum and ovarian follicular fluid (van der Venn et al., 1992). A study showed that exposure of cynomolgus monkeys to HCB for approximately three menstrual cycles significantly reduced the concentration of oestradiol during ovulation (Foster et al., 1995). Another endocrine disrupting organochlorine pesticide Heptachlor suppresses progesterone and estradiol concentrations in the blood and reduces the production of oestradiol by ovarian cells of treated rats (Oduma et al., 1995).

Menstrual Cycle

Endocrine disrupting chemicals may affect the function of oestrogen and progesterone and may alter the natural menstrual cycle, ovulation and fertility. In one of the studies conducted on the Great lakes which is the area most contaminated with persistent organic pollutants, it was seen that women who consumed fish from these lakes showed a reduction in the menstrual cycle length indicating the possible effect of PCBs through food on menstrual cycle (Mendola et al., 1997). On the other hand Van Birglene et al showed that rats exposed to organochlorine pesticides with oestrogenic properties including atrazine, methoxychlor showed oestrous irregularities and prolonged menstrual cycle length (van Birglene et al., 1999).

Fertility

The reasons for infertility might be because of the molecular and biochemical disorders in sperms resulting in an inability for fertilization, although their mobility and morphology is normal (Tulsiani et al., 1998). Lindane is a widely distributed organochlorine pesticide, which intercalates into the sperm membrane and alters the molecular dynamics of the lipid bilayer. It has been seen that high doses of lindane as found in the female genital tract secretions may inhibit sperm responsiveness to progesterone in vitro, which causes acrosome reaction at the site of fertilization. This could be one of the reasons for infertility in females exposed to lindane (Silvestroni and Palleschi, 2000).

7. DETECTION OF EDCS IN THE ENVIRONMENT

A wide variety of testing methods have been developed to investigate EDCs. These include physical and chemical fractionation methods, the study of biomarkers in indicator species, in vitro and single mode of action (MOA) oriented in vivo and in ovo assays, and life cycle or multigenerational in vivo tests.

Physical and chemical fractionation methods rely on analytical chemistry to separate and isolate suspected EDCs from environmental samples. Due to the wide variety of EDCs and other chemicals in the environment, these methods are most suitable to look for compounds frequently associated with endocrine disruption, e.g., 17 β -estradiol and its metabolites in sewage effluent (Huang and Sedlak, 2000; Smeds and Saukko, 2001; Sole' et al., 2000).

Biomarkers for the detection of endocrine disrupting chemicals are defined as measurable alterations within an organism indicative of exposure to or effects from environmental contaminants. These can range from repressed activity of metabolic enzymes to alterations in gross physiology or behavior. Sensitive species living in natural environments can provide a warning of deteriorating conditions or an indication that a damaged environment is recovering from previous stresses (Fossi, 1998). Biomarkers are needed that reflect both exposure to and effects of endocrine disruptors. They must also address species differences, sexual dimorphism characteristics, and be life stage specific. Importantly, they must be applied in long-term transgenerational studies to identify biomarkers in offspring that can be measured shortly after exposure and that are predictive of long-term or latent effects.

Effluent discharges from industries have been identified as a potential source of endocrine disruption activity in aquatic ecosystems (Hewitt et al., 2006; Orrego et al., 2009) leading to chronic toxicity in marine animals. The in vitro Yeast Estrogen Screen (YES) assay is a screening tool used to evaluate the potential endocrine disruption activity of a given substance or environmental sample. This assay is based on a *Saccharomyces cerevisiae* recombinant yeast strain containing

an expression plasmid for the human estrogen hormone receptor (ERE) and an appropriate reporter of β -galactosidase (lacZ) (Routledge and Sumpter 1996).

A more precise form of environmental testing involves in vitro or single Mode of Action –oriented in vivo and in ovo tests (Baker, 2001). Single MOA oriented in vivo assays use specialized biomarkers in test animals to detect only one type of endocrine disruption, such as estrogenic, androgenic, or thyroid-stimulating functions. Similarly, the hormone-driven maturation of certain amphibians is suitable for use as an in ovo or in vivo bioassay for specific types of endocrine-disrupting activity. The in vitro bioassays are rapid, straightforward, and inexpensive. Combining them with chemical and physical fractionation could potentially allow for the isolation and identification of all contaminants in an environmental sample that share the same endocrine-disrupting activity.

But because EDCs are varied and most environmental samples are composed of complex mixtures of pollutants, the in vitro assay, though rapid, will test only one MOA at a time. Hence, the best testing approach combines a variety of tests to efficiently cover the broadest possible spectrum of endocrine-disrupting activity. One such technique is that of DNA microarray. They provide a broad view of gene expression within the cell, as opposed to the single-gene responses measured in other assays, such as reporter gene assays.

Apart from these, certain nutritional biomarkers are gaining importance rapidly. One such nutritional biomarker is phytoestrogen that can be used as a dietary biomarker. Although identified originally for their weak estrogenic activity, many of these compounds have a variety of other biological activities that may influence disease risk (Setchell, 1998). Thus monitoring dietary exposure to these compounds is desirable for reasons beyond just their hormone like effects. Isoflavones and lignans in urine and serum or plasma are probably most pertinent to the application of their measurement as dietary biomarkers in human population-based studies. Several types of analytic methods have been used to determine phytoestrogens and their metabolites in body fluids. Chromatographic separation coupled with various detection systems is most commonly used for measuring phytoestrogens in urine and plasma. GC/MS SIM methods, which are adapted from the highly specific and sensitive approaches used for measuring steroid hormones and using deuterated internal standards of the phytoestrogens and their metabolites, have been used effectively for analysis of urine and serum. Improved levels of assay detection coupled with minimal sample extraction and the capacity to use small amounts of urine, serum or tissue will further the use of lignans and isoflavones as biomarkers in large population-based studies.

8. REMOVAL OF ENDOCRINE DISRUPTORS FROM THE ENVIRONMENT

During the last decade, various methods have been adopted for the removal of endocrine disruptors, pharmaceuticals and other personal care products from the environment. Some of the processes include coagulation, biofiltration, chlorination, ozonation, membrane treatment and lime softening of the environmental samples doubtful of the presence of endocrine disrupting chemicals. In general, removal of an EDC or personal care products is dependent upon their intrinsic chemical properties, including molecular weight, octanol-water partition coefficient, aromatic carbon content, and functional group composition. Therefore, as additional compounds are identified in different environmental samples, a fundamental approach can be utilized to evaluate their potential for removal. Apart from the chemical treatments employed for the removal of EDCs, biologically based assays seem to be a promising method for the identification of EDCs. Some studies on the biological degradation of EDCs and personal care products have been reported. Biological attenuation involves partitioning into biomass or metabolism by target organic pollutants (Akkanen et al., 2001).

On the other hand, mass-based analytical methods show excellent sensitivity and precision for their quantification. Several extraction techniques for the instrumental analysis have been developed since they are crucial in determining overall analytical performances. Conventional treatment techniques, including coagulation, precipitation, and activated sludge processes, may not be highly effective in removing EDCs, while the advanced treatment options, such as granular activated carbon (GAC), membrane, and advanced oxidation processes (AOPs), have shown satisfactory results.

Apart from the conventional chemical treatments used, effects of bacteria in effectively degrading and removing endocrine disruptors have also been reported. It is known that estrogens are either removed by direct use as electron donors for heterotrophs or via the co-metabolic degradation of ammonia oxidizing bacterium (AOB). Yoshimoto et al. (2004) showed that *Rhodococcus zopfii* and *Rhodococcus equi* isolates from activated sludge can degrade estradiol (E2), estrone (E1) and estriol (E3). This is also true of ethinylestradiol (EE2) at an initial concentration of 100 mg/L. Keeping in mind the effectiveness of bacterial cultures in degrading endocrine disrupting chemicals, the ability of probiotic bacteria that are considered to be beneficial, in degradation and subsequent removal of EDCs is the next stage of research to focus upon.

9. CAN PROBIOTICS COUNTER THE EFFECTS OF ENDOCRINE DISRUPTORS?

Probiotics are defined as live microorganisms which when ingested in appropriate amounts confer beneficial health effects (Fuller, 1990). Lactic acid bacteria and bifidobacteria

are the most common types of microbes used as probiotics but certain yeasts like *Saccharomyces* are also proven probiotics.

Probiotics have been used to treat various disorders like diarrhoea, hypercholesterolemia, lactose intolerance along with exhibiting anticarcinogenic effects. But recently, the role of probiotics has also shown great advancement in degrading environmental chemicals and compounds that have adverse effects on the endocrine system of living beings. There have been reports on the degradation of chemicals like BPA using microorganisms and enzymes. Lobos et al. (1992) and Spivack et al. (1994) found that gram-negative aerobic bacterium could degrade BPA and its analogues. Kang and Kondo (2002) reported biodegradation of BPA using microorganisms isolated from river. However, it is difficult to apply these microorganisms and enzymes to foods and feeds contaminated with BPA from the point view of food hygiene. Yasushi et al (2007) conducted a study to remove BPA from media using lactococci as lactic acid bacteria, which did not adhere with the intestine mucosa and was easily excreted and they concluded that lyophilized cells of lactococci could effectively adsorb and remove BPA from the medium. They suggested that lactococci might be adsorbing BPA by hydrophobic-binding effect of proteins on cell surface.

It is well-known that lactococci are widely used as starter bacteria in manufacturing cheese and other fermented dairy products. Recently, lactococci are being considered as helpful probiotics because they have the ability to bind toxic compounds such as mutagens and aflatoxin (Peltonen et al., 2001). Mergler et al (2004) have also reported the adsorption of BPA by yeast *Pichia pastoris*.

Probiotics have also been shown to be effective on malathion treated rats and it was seen that the group of rats fed with probiotic after the supplementation of toxic dose of malathion exhibited normal activity of the hormone acetylcholine which is otherwise disrupted by malathion endocrine disruptor, as compared to the control group which was barred of any probiotic. The results were further confirmed by carrying out in vivo studies using *C. elegans* as the model organism. *C. elegans* showed normal regeneration activity and normal reproductive activity when administered probiotics alongwith malathion in the treated group.

The role of probiotics in degrading endocrine disruptors and hence exhibiting protective effects clearly deserve extensive study. For now it seems that lactic acid bacteria through foods containing endocrine disrupting chemicals might be a safe and useful method in curbing the ill effects that these molecules exert on living beings.

10. CONCLUSION

The review provides an overview of Endocrine Disrupting Chemicals' sources, types, their different aspects of exposure, mechanism of action, effect on women's health, different methods of detection and removal from the environment.

Protective effects of probiotics over EDCs have also been touched upon, although which requires further exploration through extensive study. The attention seeking concern in the discussion remains spectrum of their health effects, especially the women.

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REFERENCES

- [1] Goldberg, J. M., Falcone, T. (1999) Effect of diethylstilbestrol on reproductive function. *Fertil Steril* 72:1–7.
- [2] Akhtar, N., Kayani, S., Ahmad, M. and Shahab, M. (1996). Insecticide-induced changes in secretory activity of the thyroid gland in rats. *J. Appl. Toxicol.*, 16 (5):397-400.
- [3] Akkanen, J., Penttinen, S., Haitzer, M., Kukkonen, J.V.K. (2001). Bioavailability of atrazine, pyrene and benzo[a]pyrene in European river waters. *Chemosphere* 45: 453-462.
- [4] Baker, V.A. (2001). Endocrine disrupters—testing strategies to assess human hazard. *Toxicol in Vitro*, 15:413– 9.
- [5] Brotons, J.A., Olea-Serrano, M.F., Villalobos, M., Pedraza, V. and Olea, N. (1995). Xenoestrogens released from lacquer coating in food cans. *Environmental Health Perspectives*, 103: 608-612.
- [6] Fossi, M.C. (1998). Biomarkers as diagnostic and prognostic tools for wildlife risk assessment: integrating endocrine disrupting chemicals. *Toxicol Ind Health*, 14:291–309.
- [7] Guillelte, L. J. and Gunderson, M. P. (2001) Alteration in development of reproductive and endocrine systems of wildlife populations exposed to endocrine-disrupting contaminants. *Reproduction*, 122: 857–864.
- [8] Henry, L.A., Witt, D.M. (2006). Effects of neonatal resveratrol exposure on adult male and female reproductive physiology and behaviour. *Dev Neurosci*. 28(3): 186-195.
- [9] Honda K, Sawada H, Kihara T, Urushitani M, Nakamizo T, Akaike A, and Shimohama S. (2000). Phosphatidylinositol 3-kinase mediates neuroprotection by estrogen in cultured cortical neurons. *J Neurosci Res*, 60: 321-7.
- [10] Huang, C.H. and Sedlak, D.L. (2000). Analysis of estrogenic hormones in municipal wastewater effluent and surface water using enzyme-linked immunosorbent assay and gas chromatography/tandem mass spectrometry. *Environ Toxicol Chem*, 20:133–9.
- [11] Ikezuki, Y., Tsutsumi, O., Takai, Y., Kamei, Y., and Taketani, Y. (2002). Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Hum. Reprod.*, 17:2839–2841.
- [12] Kang, J.H. and Kondo, F. (2002). Bisphenol A degradation by bacteria isolated from river water. *Arch Environ Contam Toxicol*, 43:265–269.
- [13] Kubo, K., Arai, O., Omura, M., Watanabe, R., Ogata, R., Aou, S. (2003). Low dose effects of bisphenol A on sexual differentiation of the brain and behaviour in rats. *Neurosci Res*, 45(3): 345-356.
- [14] Levy, J.R., Faber, K.A., Ayyash, L. and Hughes, C.L. (1995). The effect of prenatal exposure to the phytoestrogen genistein on sexual differentiation in rats. *Proc Soc Exp Biol Med*, 208:60-66.
- [15] Lobos, J.H., Leib, T.K. and Su, T.M. (1992). Biodegradation of bisphenol A and other bisphenols by a gram-negative aerobic bacterium. *Appl Environ Microbiol*, 58:1823–1831.
- [16] Loganathan, B. and Kannan, K. (1994). Global organochlorine contamination trends: An overview. *AMBIO*, 23:187-89.
- [17] Mergler, M., Wolf, K. and Zimmermann, M. (2004). Development of bisphenol A-adsorbing yeast by surface display of the Kluyveromyces yellow enzyme on Pichia pastoris. *Appl Microbiol Biotechnol*, 63: 418–421.
- [18] Peltonen, K., El-Nezami, H., Haskard, C., Ahokas, J. and Salminen, S. (2001). Aflatoxin B1 binding by dairy strains of lactic acid bacteria and bifidobacteria. *J Dairy Sci*, 84:2152–2156.
- [19] Price, K.R. and Fenwick, G.R. (1985). Naturally occurring oestrogens in foods—a review. *Food Addit Contam.* 2:73–106.
- [20] Reigart, J. R.; Roberts, J. R. Organophosphate Insecticides. Recognition and Management of Pesticide Poisonings, 5th ed.; U.S Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, 1999; pp 34-47.
- [21] Setchell, K. D. R. (1998) Phytoestrogens: the biochemistry, physiology, and implications for human health of soy isoflavones. *Am. J. Clin. Nutr.* 68(suppl. 6): 1333S–1346S.
- [22] Simonich, S.L. and Hites, R.A. (1995). Global distribution of persistent organochlorine compounds. *Science*, 269: 1851-54.
- [23] Sisk, C.L. and Foster, D.L. (2004). The neural basis of puberty and adolescence. *Nat Neurosci*, 7(10): 1040-1047.
- [24] Smeds, A. and Saukko, P. (2001). Identification and quantification of polychlorinated biphenyls and some endocrine disrupting pesticides in human adipose tissue from Finland. *Chemosphere*, 44:1463– 71.
- [25] Sole, M., de Alda MJL, Castillo, M., Porte, C., Ladegaard-Pedersen K, Barcelo' D. (2000). Estrogenicity determination in sewage treatment plants and surface waters from the Catalanian area (NE Spain). *Environ Sci Technol*, 34:5076– 83.
- [26] Spivack, J., Leib, T.K. and Lobos, J.H. (1994). Novel pathway for bacterial metabolism of bisphenol A. *J Biol Chem*, 269:7233–7239.
- [27] Swan, S.H., Main, K.M., Liu, F., Stewart, S.L., Kruse, R.L., Calafat, A.M., Mao, C.S., Redmon, J.B., TERNAND, C.L., Sullivan, S., Teague, J.L. (2005). Decrease in anogenital distance among male infants with prenatal phthalate exposure". *Environ. Health Perspect*, 113 (8): 1056–1061.
- [28] Szabo, D.T., Richardson, V.M., Ross, D.G., Diliberto, J.J., Kodavanti, P.R., Birnbaum, L.S. (2009). "Effects of perinatal PBDE exposure on hepatic phase I, phase II, phase III, and deiodinase 1 gene expression involved in thyroid hormone metabolism in male rat pups". *Toxicol. Sci.* 107 (1): 27–39.
- [29] Tomlin, C. D. S., The Pesticide Manual, A World Compendium. 14th ed.; British Crop Protection Council: Alton, Hampshire, UK, 2006; pp 642-643.
- [30] Turner, J.V., Agatonovic-Kustrin S. and Glass, B.D. (2007). "Molecular aspects of phytoestrogen selective binding at estrogen receptors". *J Pharm Sci*, 96 (8): 1879–1885.

-
- [31] Wisniewski, A.B., Cernetich, A., Gearhart, J.P., Klein, S.L. (2005). Perinatal exposure to genistein alters reproductive development and aggressive behaviour in male mice. *Physiol Behav*, 84(2): 327-334.
- [32] Yoshimoto, T., Nagai, F., Fujimoto, J., Watanabe, K., Mizukoshi, H., Makino, T., Kimura, K., Saino, H., Sawada, H., Omura, H. (2004). Degradation of estrogens by *Rhodococcus zopfii* and *Rhodococcus equi* isolates from activated sludge in wastewater treatment plants. *Appl. Environ. Microbiol.* 70 (9), 5283–5289.
- ling measurement in objectoriented systems", *IEEE Transactions on Software Engineering*, 25, 1, January 1999, pp. 91-121.