REVIEW ARTICLE

THE PHYSIOLOGICAL ASPECTS OF ENDOCRINE DISRUTORS IN REPRODUCTION: A REVIEW

ABSTRACT

Endocrine disruptors are environmental compounds that affect the normal hormones synthesis, secretion, transport, binding, action or elimination. There interference occurs at certain doses of the chemicals and can cause birth anomalies, as well as sexual developmental problems in both males and females. These hormones play significant role in reproduction. Endocrine disruptors are chemical substances which interfere with the natural hormones in the body and thus affect the maintenance of normal cell metabolism. They are also called hormonally active agents, endocrine disrupting chemicals or endocrine disrupting compounds. Biologically, these effects cause obesity, diabetes, reproductive problems as well as hormone sensitive cancers in both male and female. This is because of the release of great quantity of chemical, following the expansion of the industrial revolution which in turn leads to the alteration in the balance of endocrine and reproductive system. Studies in recent times has shown decline in female fecundity and sperm count. Furthermore, in the United States, the average age at menarche, thalarche and sexual development among minors, has speedily progressed, hence the need to identify their place in reproduction and put in control measures to prevent its attendance complications.

Key words: physiological aspects, chemical substances, Endocrine Disrutors

Introduction

"Endocrine disruptors are chemical substances which interfere with the synthesis, secretion, transport, binding, action or elimination of natural hormones in the body that play roles in development, behavior, fertility and maintenance of normal cell metabolism" (Crisp *et al*, 1998). "This interference occurs at certain doses of the chemicals and can cause malignant tumors, birth anomalies and other developmental defects such as learning disabilities attention deficit disorders, brain malformation, macromelia as well as sexual developmental problems in both males and females. Biologically, these effects cause obesity, diabetes, reproductive problems as well as hormone sensitive cancers in both male and females" (Gore *et al*, 2015). "They are also called hormonally active agents, endocrine disrupting chemicals or endocrine disrupting compounds" (Diamanti-Kandarakis *et al*, 2009).

In a period of global focus on environmental sustainability, environmental preservation becomes a concern. This is because of the release of great quantity of chemical, following the expansion of the industrial revolution which in turn leads to the alteration in the balance of endocrine system (Bachega *et al*, 2011). A large number of environmental agencies world over have made reference to a given number of environmental chemicals with endocrine disrupting activity. This could explain the steadily increasing prevalence of diseases and ailments (Dechert and Demeneix, 2011). Decline in human reproductive health especially in the Western world has some epidemiological proof. About half a century ago, there has been decline in sperm count in the Western nations (Swan *et al*; 2000). As estimated, over 10% men and up to 30% of women in Denmark have sub-fertility problem (Joensen *et al*; 2008).

"There has also been depreciation in female fecundity especially among the young women but the rate at which it occurs has not been quantified" (Brannian & Hansen, 2006). Furthermore, in the United States, the average age at menarche, thalarche and precisely in sexual development among minors, has speedily progressed (Partsch & Sippel, 2001) just as similar trends are obtained among adopted children of developing countries by Western parents (Aksglaede *et al*, 2009). "The above events have complex and multi-faceted aetiology but whether endocrine disrupting chemicals are contributory is still a subject of debate and other factors such as diet, stress and obesity also could play a role" (Costa *et al*; 2014).

The Endocrine System

Most species of animals possess the endocrine system. The endocrine system consists of;

- **a.** Glands which secret hormones
- **b.** Receptors which detect and react to the hormones

The hormones are transported throughout the body where they function as chemical messengers and interact at the cell-receptors surface in a "key and lock" fashion. These hormones are secreted in response to environmental stimuli in order to effect the developmental and reproductive changes. The occurrences of these changes are brought about by biochemical adjustments. The serenity of the glands is usually limited by estrogen and androgens (sex steroids) as well as thyroid hormones via a feedback mechanism.

"Since hormones work at very minute doses, endocrine disruption can occur at low-dose exposure to exogenous and hormonally active chemical that alter the receptors for other processes" (Golden *et al*, 1998). Most vital stages of development occur in-utero especially the period of organogenesis; hence interfering with this stage will have deleterious effects on brain development leading to irreversible effects that may not manifest in adults exposed to the same dose for the same length of time (Castro *et al*, 2008). Animal studies have shown the critical developmental periods in utero and postpartum period when exposure to endocrine disruptors will have adverse effects that will manifest in adulthood (Szabo *et al*; 2009). Disruption of thyroid function in early developmental period could explain the abnormal sexual development in both male and females (Lilienthal *et al*; 2005, Talsness *et al*; 2005) as well as learning disabilities (Viberg *et al*; 2006). "However, fetuses and embryos whose growth and development are highly controlled by the endocrine system are more vulnerable to the exposure and may therefore suffer chronic reproductive abnormalities while pre-birth exposure may lead to permanent changes and adult disease" (Colborn & Carroll, 2007). "Explained further, phthalates seen in urine of pregnant women has been linked to specific genital changes in their male infants who manifest shorter, more feminine anogenital distance with associated partial testicular descent, smaller scrotum and penis" (Swan *et al*; 2005).

Principles of endocrine disruption

There are 3 key principles (the DES story) of endocrine disruption.

1. **Dose response curve**

"Claims have been made that endocrine disruptors follow a U-shaped dose-response curve (Calabrese and Baldwin, 2003). This means that very low and very high doses have more effects than mid-levels of exposure to the toxicant. Study has shown that a flame retardant (BDE-47) affects the reproductive system and thyroid gland of female rats in a dose system and thyroid gland of female rates in a dose or the order to which humans are exposed" (Talsness *et al*; 2003). "Lower concentrations can have synergistic effects in amphibians but evidence is lacking as to whether this is mediated through the endocrine system" (Hayes *et al*; 2006).

The learning and developmental disability initiative argued that "the very low dose effects of endocrine disruptors cannot be predicted from high dose studies, which contradicts the standard 'dose makes the poison' rule of toxicology" (Schug *et al*; 2011).

2. Long latency period between exposure and manifestations of dysfunction

The latency period can be extremely long. This concept has been recognized by behavioral endocrinologists exploring the mechanism by which fetal hormone exposure could change sexual behavior and sex specific neuroendocrine feedback system (Marter, 2005), but toxicologists made some breakthrough. Currently, this is the basis for the conceptual framework "fetal basis of adult disease", - a scientific idea that has gained interest in endocrine disruption area (Patisaul and Adewale, 2009).

Research is currently gaining ground on the concept that exposure to environmental factors (such as toxicants) during early human development can interact with the human genome and influence the emergence of such disease as cancer and infertility, precocious puberty and obesity in later years of life (Patisaul and Adewale, 2009).

3. Timing of Exposure

The availability and the degree of anomally common to DES sons and daughters differ greatly depending on

1. Timing of mother's first exposure
2. Total dosage at exposure and
3. Length of exposure (Faber *et al*; 1990).

Sensitivity to hormones and EDCs are usually higher during the critical periods of reproductive organs and brain development in humans. This concept also recognizes the fact that the placenta is penetrable to EDC and most of which would likely affect the developing fetus. Maternal estrogens are functionally secreted by α-fetoprotein but most estrogenic compounds fail to or weakly attach to α-fetoprotein and so, can enter fetal circulation unhindered (Vandenberg *et al*; 2007)

Routes of Exposure to Environmental Endocrine Disruptors

Various channels of exposure to the harmful effects of the environmental endocrine compounds exist. These include:

1. **Food**: This is a major route by which people are exposed to the pollutant. Diets account for up to 90% of polychlorinated biphenyl and Dichloro diphenyl trichloroethane burden in a person (Fürst, 2006). A study of 32 different common food products from three stores in Dallas showed that fish and other animal products were contaminated with polybrominated diphenyl ethers (PBDE) (Schecter *et al*; 2004). These compounds are known to be fat soluble and are likely to accumulate in the fatty tissue of the animals that humans consume. While some opined that fish consumption is a major source of environmental chemicals, both wild and famed Salmon have been shown to contain a variety of man-made organic compounds (Hites *et al*; 2004). Soya bean a phytoestrogen that is widely consumed has also been noted to contain endocrine disruptive substance (Ugoji *et al*; 2022, Ugoji *et al* 2023)

2. **Indoor air/House dust**: "This is possible due to rise in household product containing pollutants and decreased in quality to building ventilation (Weschler; 2009). People in homes with wood floors treated in the 1960s with polychlorinated biphenol (PCB) –

based wood finish have higher burden than the general population (Rudel *et al*; 2008). Recent studies suggested that contaminated house dust, not food, may be the only major source of PBDE in our bodies" (Anderson *et al*; 2008). "In light of the above, another study asserted that ingestion of house dust accounts for up to 82% of PBDE burden (Lober; 2008). According to environmental working group, 19 out of 20 children tested had level of PBDE in their blood about 4 times higher than that of their mothers" (Lunder and Jacob, 2008). "Contaminated house dust has been demonstrated to be a primary source of lead in young children" (Charney *et al*; 1980).

3. **Consumer goods: "**An analysis of 42 household cleaning and personal care products versus 43 chemical free products in terms of composition showed 55 different chemical compounds: 50 were found in 42 conventional samples while 41 were seen in 43 chemical free samples. In seven of the chemical free products, parabens (a class of chemicals that are associated with reproductive tract issues) were detected. Vinyl products (associated with wheezing and asthma in children) were found to contain 10% of the compound. Risk of exposure increases when conventional and chemical free products are used in combination. Therefore, a consumer who uses surface cleaner, tubs and tile cleaner, laundry detergents, bar soap, shampoo and conditioner, facial cleaner and lotion would be exposed to at least 19 compounds" (Dodson *et al*; 2012).

Chemical Compounds with Endocrine Disruption Activities

Endocrine disrupting chemicals are found in low doses in many products. This has been recognized by environmental agencies around the globe. They include pesticides, pollutants and plastic manufacturing substances (Bachega *et al*; 2011)

Endocrine disrupting chemicals are classified thus:

a. According to their usage (e.g pesticides)
b. According to its structural properties as
   → steroids,
   → polyaromatic hydrocarbons.

These are abundantly found in the environment and may be transported over long routes. Many of them can be stored for years in the body of animals and human but others are easily eliminated from the body but can still cause effects if exposed in critical periods of development (Schug *et al*; 2011).

Plastics:

Controversies exist on the possible adverse effects of plastic compounds on human health. Plastics contain two major chemicals – phthalates and bisphenol.

1. **Bisphenol A (BPA)**

This is a monomer applied in the production of polycarbonate plastics and in the covering of the inside surface of foods cans. It polymerizes leaving some molecules unbound, thereby migrating and contaminating foods and drinks.

It is also used as dental sealant. Over 6 million of BPAs are produced annually (Zoeller, 2006). Exposure to BPA is widespread. About 95% of urine samples of Americans contain the chemical. Serum of pregnant mothers, amniotic fluid and cord blood have demonstrated the presence of BPA which shows that human exposure occurs during the period of increased susceptibility (Schug *et al*; 2011). An estimated 6.6mg/person/day of BPA is consumed on intake of canned foods packaged with epoxy resins (Zoeller, 2006). Its major disrupting effect is on thyroid hormones and adipogenic activities. Associations have been found between serum and

urinary BPA concentration and the increased development of Hypothyroidism, Infertility, Cardiovascular Diseases, Diabetes, Mammary and prostate cancers, Low sperm count, Early puberty, Obesity etc (vom Saal & Myer; 2008). Regulatory bodies have made estimates of safety levels for humans but this has been questioned and is being reviewed as a result of new scientific studies (Beronius *et al*; 2010).

2. **Bisphenol S**

This is an analogue of BPA. It is usually found in thermal receipts, plastics and household dusts. Traces have been found in personal care products (Rchester and Bolden; 2015). Despite its use in place of BPA, it has been shown to contain as much endocrine disruptors as BPA (Eladak, 2015)

3. **Phthalates**

These are plasticizers which, because of their effect on flexibility, suppleness and elasticity of polymers are being used in polymer (PVC) industries. They are used in the production of industrial paints, solvents, toys, personal and medicare products (Cosmetics and blood transfusion bags). Its human contamination is via food and skin absorption as well as transplacental and breastfeeding mechanism (Zoeller, 2006).

The most lethal of the phthalates is the diethylhexyl phthalate (DEHP). Its low dose in a mite study showed toxicity to the reproductive system and also increased the proliferation and differentiation of adipocytes leading to visceral obesity (Hao *et al*; 2012)

Dioxins:

These are group of organochlorine compounds such as;

1. Polychlorinated dibenzodioxins (PCDD),
2. Polychlorinated dibenzofurans (PCDF),
3. Polychlorinated biphenols (PCB),
4. Polybrominated diphenylethers (PBDE).

Polychlorinated biphenols

"These are used as industrial coolants and lubricants. Direct contact of PCB with skin results in severe acne like condition called chloracne (Tang *et al*; 2008). Its exposure increased risk of Skin cancer, Liver cancer, Brain cancer. Generally, doxins are fat soluble and easily accumulates in adipose tissues. Human exposure to the doxin occurs via foods of animal origin" (Liem *et al*; 2000).

Pesticides:

The exposure of human to pesticides is certainly ubiquitous. Recent study in the UK reported that there are many pesticides with endocrine disrupting activity. The pesticides of importance here include Organophosphates, Carbamates, Organochlorides (dichlorodiphenyltrichloroethane-DDT).

1. **Dichloro Diphenyl Trichloroethane-DDT**:

This has been banned in most developed countries but contamination in samples from adipose tissues and breast milk still exist (Casals–Casas and Des vergne, 2011). High concentration of this compound has been demonstrated in carnivores as a result of biomagnifications via the food chain (Szlinder-Richert *et al*; 2008). Its effect on the reproductive development of laboratory animal has been documented especially in females (Tiemann, 2008).

Further studies suggest that profound reduction in adult male fertility may be as a result of exposure to DDT (Hallegue *et al*; 2003) but of recent, suggestion has been made that in utero exposure to DDT increases the likelihood of childhood obesity (Verhulst *et al*; 2009). This same compound is still being used as anti-malaria insecticide in Africa, though in minute amounts.

2. **Atrazine:**

This is the most common pesticide contaminant of ground and surface water. As an endocrine disruptor, it alters the reproductive tissues if exposure occurs during development (Hayes *et al*;2011).

Other Suspected Endocrine Disruptors

Some other chemicals believed to possess endocrine disrupting potentials include Furans, Polycyclic aromatic hydrocarbons, Endosulfan, Kepone (chlordecone), Vinclozolin (fungicide), 17- α- ethinylestradiol (contraceptive) (Hayes et al;2011), Natural occurring phytoestrogens – genistein (Ugoji et al; 2022, Ugoji et al 2023).

Mechanism of action of endocrine disrupting chemicals

There are three major mechanisms through which EDCs alter hormonal control of metabolism in the endocrine system (Sikka and Wang, 2008). These include:

- They mimic natural hormones.
- They inhibit the action of hormones.
- They alter the normal regulatory function of the endocrine system.

The EDCs potentially alter the production, secretion, metabolism, transport or peripheral effects of endogenous hormones through their binding to hormone receptors. Through this pathway, two possible responses can occur via

- Agonistic effect (mimicking action of hormones);
- Antagonistic effect (causing lack of response and preventing the binding of natural hormones (Frade *et al*; 2014)

Besides binding to hormone receptors, they also act by recruiting co-activators or co-repressors in enzymatic pathways leading to the alteration of hormones synthesis and metabolic pathways while modifying plasma clearance or acting directly on gene expression of epigenetic modification without revising the nucleotide sequences (Schug *et al*; 2011).

The pathophysiologic mechanisms of many diseases such as tumor development (Schug *et al*; 2011) has been attributed to the epigenetic modification which usually leads to genetic silencing. Similarly, another example of this modification was demonstrated following the exposure of a pregnant woman to diethyestillbesterol (DES), used to prevent abortions. Following the exposure, fetuses exposed in the 1st trimester of pregnancy had increased prevalence of infertility in adult life as well as greater incidences of vaginal tumors. The second generation of women exposed to this drug had highest report of reproductive anomalies (Christensen and Marsit, 2011). Besides the fetal period, other periods of higher sensitivity to the effects of EDCs are the childhood and adolescent ages (Diamanti-Kandarakis *et al*; 2009).

Females Reproductive Development & EDCS

Pubertal development:

Over a century ago, the mean age at menarche has drastically reduced in all socioeconomic and ethnic backgrounds from 16-17 years to less than 13 years. Stronger notions also support the fact that telarche occurs earlier (Fortes *et al*; 2007). Psychological disturbance or instability is a factor in precocious puberty but it is also associated with co-morbidities such as Insulin resistance and diabetes mellitus, Metabolic syndrome, Cancer of the breast and Reproductive system cancer (Buttke *et al*; 2013). Onset of puberty is also triggered by other factors as genetics, nutritional factors (obesity) and idiopathic causes but environmental factors can't be ruled out. These environmental factors can't be isolated from the influence of EDCs (Frade *et al*; 2014). These compounds act via post-receptor signaling and by stimulating the hypothalamic neurons – leading to the release of kisspeptin and promotion of hypothalamic maturation, thus causing onset of puberty (Patisaul, 2013). Consumption of soy milk formula (which contains phytoestrogens) has been associated with premature telarche (Fortes *et al*; 2007). Precocious puberty is also associated with the use of DES, Polybrominated biphenyls, DDT, Phthalates.

Reproductive tract:
Ovarian differentiation of germ cells starts during the first trimester of pregnancy and thereafter, these germ cells become the primordial follicles which develop and enter latency period that can last up to 50 years in a woman. The oocytes do not degenerate and has a longer half life but are influenced by environmental effects in its entire period of existence (Frade *et al*; 2014).

Ideally, the fetal ovarian follicle formation is dependent on the balance between systemic concentrations of 3 main hormones viz: Estrogen, Inhibin, Actin.

"It is important to point out that exposure of the fetus to estrogen during the critical period of follicular development can change follicular dynamics. It has been reported that EDCs effect on the ovaries accounted for the identification of mulli-oocyte follicles (MOF) in alligators inhabiting a lake in California City because these animals were exposed to estrogenic compounds in the early phase of development" (Guillette *et al*; 1994). This therefore, portrays that maintenance of the homeostasis of these hormones during follicular formation is needed for normal development and subsequent oocyte quality assurance. Meanwhile, the mechanisms by which EDCs alter the formation of follicles with subsequent impact on ovaries function in adult females remain unknown.

Questions have been constantly asked on the ovarian structures targeted by these EDCs before these changes are manifested. However, the reproductive disorders attributable to these ovaries include.

1. **Aneuploidy:**

Research has observed that mice that inhabited damaged cages made of polychloride plastics had higher incidence of meiotic changes in oocytes. This has warranted investigations into the effects of biphenol A (BPA) on oocytes (Hunt *et al*; 2003). Conclusion was made that BPA came from the water consumed by the animals which caused changes in oocytes which resulted in aneuploidy.

Researchers concluded that BPA exposure has damaging impact on maturation of oocytes and similar changes may occur in adult animals but this is possible on exposure to significantly higher doses during the fetal period of oogenesis. This is maintained through estrogenic receptor β (ERb) (Eichenlaub- Ritter *et al*; 2008).

2. **Primary ovarian Failure (POF):**

Primary ovarian failure occurs in about 1% of women under the age of 40years leading to some reproductive disorders, early menopausal manifestation and other co-morbidities (Nelson, 2009). The development of this anomaly involves three mechanisms viz:

a. Acceleration of apoptosis,
b. Inhibition of follicular maturation,
c. Premature activation of follicles.

There are several causes which have been postulated and these may have strong link with EDCs. These include:

a. Genetic mutations or chromosomal abnormalities (mainly involving the x-chromosome);
b. Disorders of metabolism such as galactosaemia and 17–Hydorxylase deficiency,
c. Viral infections such as HIV,
d. Iatrogenic causes – radiation,
   - chemotherapy,
e. Autoimmune disorders,
f. Other factors – smoking,
   - toxins.

The cause of many cases of POF is obviously multifactorial (Cooper *et al*; 2011). Many EDCs predispose to multi-oocyte follicles – a precursor of POF and this mechanism is mediated by ERb agonist (Kirigaya *et al*; 2009).

"A study involving the administration of BPA to pregnant mice at specific doses between 9th and 16th day of pregnancy showed a significant presence of ovarian cysts and adenomas in adulthood in the group that received the higher doses of BPA, but not in the controls, hence proving the fact that BPA is detrimental to the reproductive system if exposure occurs during oocyte differentiation" (Newbold *et al*; 2009). "Exactly the doses of BPA used in these animals are said to be relevant for exposure in humans because the assumed dose intake of BPA in infant's formula is about 1 – 13mg/kg. The increase manifestation of genetically ovarian meiosis can give answers to the effects of BPA on female germ cells" (Brieno-Enriquez *et al*; 2012).

- Parabens, is another EDC which affects follicular formation. It acts by stimulating mRNA expression on mullerian hormones and thus inhibits the early phase of follicular formation in newborn rat ovaries. It may as well control steroidogenesis through the inhibition of follicular Fox12- the main transcription protein (Ahn *et al*; 2012).
- 4-Vanylcyclohexane diepoxide (VCD): This is an occupational cytotoxic chemical whose repeated doses may propagate the process of atresia via apoptosis and selectively destroys primodial primary follicles both in rats and mice (Kappeler and Hoyer, 2012). Hence exposure of women to VCD increases the risk of POF.
- Methoxycholor (MXC): This is an organochloride pesticides used in place of DDT. It is an estrogen that was demonstrated to have lower binding potential for estrogen receptor (Cummings, 1997). Two of its major forms → 2,2-bis-(p-hydroxyphenyl)-1,1,1-trichloroethane and mono-OH MXC have estrogenic as well as anti-androgenic actions (Gaido *et al*; 2000). They cause growth inhibition and implantation of embryo as well ovarian atrophy due to follicular inhibition.
- Diethylstilbesterol: This is a synthetic non-steroidal estrogen prescribed to pregnant women as a prophylaxis against abortion but reproductive anomalies of cardiovascular and immunological origin were reported in offspring of women treated with it. This was validated in animal studies (Newbold, 2004). Studies have shown that neonatal exposure to 3 mcg/kg of diethylstilbesterol causes multi-oocyte follicles (Kirigaya *et al*; 2009).

3. Menstrual irregularity and fecundability:

Human studies have suggested that fetal and neonatal exposure to EDCs can alter the menstrual cycle as a result of hormonal influence (Chao *et al*; 2007). Shorter menstrual cycle is associated with organochloride exposure in women (Axmon *et al*; 2004) whereas exposure to non-organochloride in women increased the risk of developing longer cycles or absence of cycles by 60-100% (Farr *et al*; 2004). The above assertion are supported by animal studies and this is possible due to hypothalamic alteration in the control of LH secretion and ovulation (Rubin *et al*; 2006). Recent study in Brazil aimed at quantifying organochloride compounds in infertile women and comparing them with fertile group observed that organochlorine compounds was most prevalent in infertile women (Bastos *et al*; 2013).

4. **Polycystic ovarian syndrome (PCOS):**

This is an endocrine disorder characterized by chronic anovulation and hyperandrogenism but milder phyenotypic variants exist in which either anovulation or hyperandrogenism may occur. The affected women are frequently known to have characteristic polycystic ovarian morphology at ultrasound with associated high rate of Obesity, Insulin resistance, Metabolic abnormalities. Its pathogenesis is not well understood but facts suggest that genetic androgens and environmental factors enhance its clinical manifestation. A BPA (with estrogen like activity) has been implicated (Takeuchi *et al*; 2004). Facts abound to show that BPA act in various ways (including estrogenic and androgenic pathways) to influence reproductive processes. In vitro, BPA enhances testosterone synthesis in rats by stimulating the theca interstitial cells (Zhou *et al*; 2008) but in male rats, it appears to compete with endogenous androgens for the biosynthesis of steroid hormone binding globulin (SHBG), thus increasing serum free androgen. BPA also decreases hepatic androgen related hydroxylases and so, inhibits breakdown of testesterone leading to the rise in the level of the hormone (Hanioka *et al*; 1998). Neonatal exposure to BPA could result in PCOS (Fernamidez *et al*; 2010).

BPA may hinder insulin action and metabolism of glucose leading to insulin resistance in intact animals (Alonoso-Magdalena et al; 2006). Studies have demonstrated higher BPA levels in anovulatory women (Takeuchi *et al*; 2004) and in PCOS (Kandaraki *et al*; 2011) when compared with controls. The mechanism of the association between BPA and PCOs development is unknown but may be as a result of androgen secretion as proved by animal studies. The BPA was said to be positively correlated with the level of androgen in women with PCOS (Kandakari *et al*; 2011).

Dietary products:

This has been associated with the development of PCOS. Advanced glycated end-products (AGEs) are purely the reactive products of enzymatic glucose-protein reaction. The sources include (Pasquali *et al*; 2011):

- Endogenously as a result of Aging, Hyperglycemia, Oxidative stress.
- Exogenously by ingestion of
  - High temperature processed protein – rich foods.

    It activates protein Kinase-C leading to oxidative stress and insulin resistance in peripheral tissues (Uribarri and Tuttle, 2006). Serum AGEs levels are raised in PCOS and positive correlates exist between this and raised androgen levels (Diamanti-Kandarakis *et al*; 2008). They also seem to contribute to increased likelihood of diabetes and cardiovascular diseases in the general population (Uribarri and Tuttle, 2006). Also,

insulin –resistant PCOS women have elevated levels of serum AGEs and their respective receptor (RAGE) – which is concentrated in the theca and granulosa cells (Diamanti-Kandarakis *et al*; 2008). Therefore, AGES are related to the number of oocytes and pregnancy rates in women with PCOS (Jinno *et al*; 2011).

Male reproductive tract and EDCS

The Target Sites

An endocrine disruptor can damage several potential target areas in the male reproductive tract. Common among these sites include the testes (male gonads) which are the sites for spermatogenesis and androgen production. Various compartments of the tests are under paracrine and autocrine regulations and so, are under endocrine influences from pituitary and hypothalamus (Sikka and Wang, 2008). About 80% of testicular mass consists of spermatogenetic semniferous tubules and 20% consists of Leydig cells and sertoli cells which establish normal spermatogenesis.

Sertoli cells:

These are also called the "nurse cells" as they form a continuous and whole lining within the tubular walls which envelope the sperm during spermatogenesis. The tight junction of these cells establishes the blood-testis barrier. The luminal cells are under the control of FSH and inhibin. The sertoli cells basically;

- Provide nutrient to the developing sperm cells,
- Destroys defective sperm cells,
- Secrets transport fluids to the sperm as it moves into epididymis,
- Releases inhibin which regulates sperm production.

Sertoli cells differentiation and strong blood-testis barrier are needed for normal spermatogenesis during puberty. Therefore, many anomalies of sperm production as a result of EDC may alter the function of sertoli cells and not necessarily the pathology of the germ cells (Sikka and Wang, 2008).

Leydig cells:

These cells produce testosterone from cholesterol via various enzymatic pathways and steroidal intermediates under the control of pituitary LH. These cells are formed during the 8^{th} week of embryogenesis and are located in the connective tissue between the seminiferous tubules.

Spermatogenesis:

Spermatogenesis spans about 80 days in man and 40 – 50 days in rodent species. During this period, the immature germ cells (undifferentiated spermatogonia) develop into highly specialized spermatozoa in a cyclic manner. Spermatogonia undergo mitotic divisions to generate many spermatocytes, which in turn develope into haploid spermatids by two meiotic cell division.

"Most testicular volume which decreases during testicular damage consists of the germ cells. During mitotic arrest, the gonocytes become acutely sensitive to toxic agents. For instance, low dose irradiation may totally eradicate germ cells while causing little damage to developing sertoli cells, thus forming a sertoli-cell-only testes" (Mandl, 1964).

Role of EDC in Male Reproduction

"Many estrogenic pollutants (including phytoestrogens), industrial chemicals and heavy metals have significant reproductive consequences as a result of their multiple route of exposure, their

heavy presence in the environment and their propensity to bio-accumulate and resist degradation" (Sikka and Wang, 2008).

Environmental Agents

1. **Agricultural and industrial chemicals**:

Agricultural and industrial chemicals impair spermatogenesis as they alter the activity of various hormones and subsequently affect sperm concentration, motility and morphology (Whorton, 1977). The fertilizing capacity of the sperm may as well be result of abnormal sperm morphology resulting from secretion dysfunction of the leydig and sertoli cells. The chemicals culpable here are DDT, Epicholorhydrin, Ethylene dibromide, Kepone and dioxin (De Jager *et al*; 2009). DDT and its metabolites have estrogenic effects in males by inhibition of the activities at androgen receptors (Li *et al*; 2008). Exposure to certain chemical solvents such as those used in the production of gasoline and organochemicals has been reported to reduce semen quality, alter hormone levels and testicular size (Figa-Talamanca *et al*; 2000).

The levels of serum toxicants (whether bound or free) will influence the androgen – blocking capacity. The fate of these organochemicals are not well documented but disruption of the hypothalamo-pituitary-testicular axis can occur which affects the endocrine and reproductive functions (Sikka and Wang, 2008).

2. **Heavy metals:**

Heavy metals such as lead, mercury, cadmium among others are believed to reduced fertility both in men and women (Taskinen *et al*; 2011) . Exposure to lead at a blood level of ≥1.9 µmol/L is said to be detrimental to semen quality (Taskinen *et al*; 2011). Reduced sperm count and modest alteration in hormone level have been reported at the above level but this exposure according to other studies have only marginal impact on men's ability to procreate at occupational exposure levels (Taskinen *et al*; 2011). In men, lead is believed to alter sperm DNA chromatin stability which is essential in maintaining the sensitive fertilization processes (Shiau *et al*; 2004). Similar effect in the reduction of sperm quality and morphology has been reported with the exposure to mercury (Wirth and Mijal, 2010).

Cadmium is a testicular toxicant used in electroplating, galvanizing and battery electrode production, plastics and paint pigments (Friberg *et a*l; 1974) and has been shown to cause reduction in sperm quality via testicular necrosis (Wirth and Mijal, 2010).

3. **Biologic factors**

Chronic disease conditions, ageing, exposure to toxins and many environmental contaminants enhance specific biologic activities. This causes hyperthermia while also increasing free radicals leading to oxidative stress that can predispose to gonadal and gamete damage (Sikka *et al*; 1995). Nitric oxide generation as a result of toxic exposure associated with hormonal imbalance can cause poor sperm motility and function leading to infertility (Skka and Wang, 2008).

4. **Radiation:**

Radiation exposure (X-rays, neurons and radioactive materials) induces testicular damage that is expected to be more severe and hard to recover than those induced via chemotherapy (Sikka and Wang, 2008). The effect of radiation on the testes is dependent on the dose of radiation, number of doses and the duration of exposure. It also depends on the stage of development of testicular germ cells at the time of exposure (La Vignera *et al*; 2012).

Germ cell apoptosis is an informative marker of ionizing radiation and other toxicants (Delbes *et al*; 2010). Intracellular reactive oxygen species produced by radiation are the chief inducers of apoptosis (Aitken and De Iulus, 2010). The loss of male germ cells via apoptosis (which has the potential of causing infertility) could be a result of ionizing radiation (Liu *et al*; 2006).
Even the radiation emissions from mobile phones at certain frequencies alter sperm motility and morphology as a result of increased oxidative stress leading to sperm membrane-lipid and DNA damage (La Vignera *et al*; 2012).

5. **Drugs and phythoestrogens**

Synthetic pharmacologic agents, phytoestrogens and anabolic steroids affect the reproductive function in males. The phytoestrogens are found in soybeans, flaxseeds, oats etc. Anabolic steroid use among sports men and women has grown out of proportion. Severe oligospermia and reduced libido have resulted from the above phenomena (Sikka and Wang, 2008, Ugoji et al; 2022, Ugoji et al 2023). Severe impairment of normal sperm production among this population results from hypogonadotropic hypogonadism secondary to feeback inhibition of the hypothalamic-pituitary-gonadal axis (Knuth *et al*; 1989). Even though this defect is reversible following discontinuation, some of these effects such as azoospermia can persist (Jarow and Lipshuttz, 1990).

Chemotherapeutic agents

Antibacterial agents were reported to be harmful to spermatozoa (Ericsson and Baker; 1967). Many cytotoxic agents usually damage the germinal epithelia cells. They cause dose-dependent progressive reduction in sperm count (Meistrich, 1982). Chronic low dose cyclophosphamide treatment in men alters the decondensation ability of spermatozoa as a result of nuclear protein or DNA alkylation. This can cause congenital anomally in children. Moreover, the use of alkylating agents in combination therapy has induced sterility in adults due to germinal aplasia in testicular biopsy. Antimicrobial agents such as tetracycline, nitrofurantoin and erythromycin impair spermatogenesis and sperm function. This however depends on the total therapeutic dose and duration of treatment (Parvinen *et al*; 1984).

Action of endocrine disruptors on the HPG axis

1. **Alteration of hormone biosynthesis**

Many agents possess the ability to hinder the biosynthesis of range of hormones. Some fungicides inhibit biosynthesis of estrogen by inhibiting the activity of aromatase which convert testosterone to estrogen in adult testis. Environmental estrogen and anti-androgens also affect protein synthesis induced by gonadal steroids via series of signals at transcriptional and translational levels (Manavathi and Kumar, 2006). Estrogen and testosterone alter pituitary hormone synthesis directly or via glycosylation of LH and FSH, hence any environmental toxicant that mimics the action of the steroid hormones could also alter glycosylation (Sikka and Wang, 2008).

2. **Alteration of hormone storage and release**

"Any compound that hinders the LH receptor or the activation of the cyclic AMP- dependent cascade involved in testosterone biosynthesis can as well alter the secretion of this hormone. The release of many protein hormones is influenced by the activation of second messenger pathways such as Phosphatidylinositol 4,5-bisphosphate (PIP_2), cAMP, Inositol 1,4,5 – triphosphate (IP_3), Tyrosine kinase, Ca^{2+} channels.

The bioavailability of many hormones is altered if there is hindrance in any of these processes" (Sikka and Wang, 2008).

a. Alteration of hormone transport and clearance

Hormones are transported from the blood either in the free or bound state. Steroid hormones are transported via steroid hormone-binding globulin (SHBG) or testosterone-estrogen-binding globulin (TEGB). These bindings need to be regulated as either raised or reduced levels could affect steroid hormone bioavailability. For instance, DDT analogs which induce hepatic microsomal monoxygenase activity could cause a reduction in transport of androgen due to improved degradation (Bulger *et al*; 1978).

b. Alteration of hormone receptor recognition.

Specific binding of hormone to receptors is a critical step in hormone action (Sikka and Wang, 2008). Intracellular receptors for hormones regulate gene transcription in a ligand-dependent manner through their interaction with response elements. Many environmental agents may mimic these hormones and so act as antagonist. An example is the DDT, kepone and alkylphenols which can disrupt estrogen receptor function (White *et al*; 1994).

Many chemicals classified as environmental estrogens can hinder the attachment to more than one type of intracellular receptor. Receptors for protein hormones are localized with the cell membrane. Binding of these hormones to their receptors and signal transduction occurs and this is mediated through second messenger activation. These may include

- Alteration in G-protein/cAMP-dependent protein kinase A (following LH stimulation of leydig cells),
- Phosphatidylinositol regulation of protein kinase C and inositol triphosphate (following GnRH stimulation of gonadotrophs; thyrotropin releasing stimulation of thyrotrophs),
- Tyrosine kinase (following insulin binding to membrane receptors),
- Ca2+ - influx.

c. The endocrine receptors can as well alter hormone post-receptor activation.

This is via the modification of steroid hormone receptor activation such as down regulation of receptor as seen following tetrachlorodibenzo-p-dioxine exposure (Sikka and Wang, 2008).

Conclusion:

Exposure to EDCs can have adverse effects in reproductive physiology and behaviour both in animals and human. However, there are still controversies on this subject, but the recognition of the prevalence of these compounds in our environment and their potential hazardous effects is increasing among scientist, policy makers and the general public.

Efforts to fully understand the mechanisms of action are necessary to develop adequate public health strategy for preventing these effects. Researches surrounding this topic are not conclusive in human but evidences are sufficient to cause concerns about their potential long term effects in humans and wildlife.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

REFERENCES

Ahn, H.J., An, B.S., Jung, E.M., Yang, H., Choi, K.C., Jeung, E.B (2012). Parabens Inhibit the Early Phase of Folliculogenesis and Steroidogenesis in the Ovaries of Neonatal Rats. *Molecular Reproduction and Development;* 79(9): 626-636.

Aksglaede, I., Sorensen, K., Peterson, J.H., Skakkebaek, N.E., Juul, A. (2009). Recent decline in Age at breast development: The Copenhagen puberty study. Paediatrics; 123"e932-e939.

Alonso-Magdalena, P., Morimoto, S., Ripoll, C., Fuentes, E., Nadal, A (2006). The Estrogenic Effect of Bisphenol A Disrupts pancreatic Beta-cell Function in vivo and Induces Insulin Resistance. *Environmental Health Perspective;* 114(1): 106-112.

Anderson, H.A., Imm, P., Knobeloch, L., Turyk, M., Matthew J., Buelow, C., Persky, V (2008). "Polybrominated disphenyl ethers (PBDE) in Serum: Findings from a US Cohort of Consumers of Sports-caught Fish". *Chemosphe;* 73(2):189-194.PMID18599108.(https://www. nobi.n/m.nip.gov/pubmed/18 599108).

Atken, R.J., De Iuliis, G.N (2010). On the Possible Origin of DNA Damage in Human Spermatozoa. *Molecular and Human Reproduction;* 16: 3-13.

Axmon, A., Rylander, L., Strömberg, U., Hagmar, L (2004). Altered Menstrual Cycles in Women with a High Dietary and Persistent Organochlorine Compounds. *Chemosphere;* 56(8): 813 – 819.

Bachega, T.A.S.S., Verreschi, I.T., Frade, E.M.C., O'Abronzo, F.H., Lazaretti–Castro, M (2011). The environmental endocrine disruptors must receive the attention of Brazilian Endocrinologists. *Arquivos Brasileiros de Endocrinologia and Metabologia;* 55 (2): 175 – 176. Available from: http:// dx. dio.org/10.1590/s0004-27302011000 200011 [Retrieved August 02, 2017].

Bastos, A.M., de Souza-Mdo, C., de Almeida Filho, G.L., Krauss, T.M., Pavesi, T., da Silva, L.E (2013). Organochlorine Compound Levels in Fertile and Infertile Women from Rio de Janeiro, Brazil. *Arquivos Brasileiros de Endocrinologia and metabologia;* 57(5):346-353.

Beronius, A., Rudén, C., Håkansson, H., Hanberg, A (2010). Risk to All or None? A Comparative Analysis of Controversies in Health Risk Assessment of Bisphenol A. *Reproduction and Toxicology;* 29 (2): 132 – 146. Available from: doi:10.101 6/j.reprotox.2009.11.007 (https://dx.doi.org/10.1016%2fj.reprotox. 2009.11.007).

Brannian, J., and Hansen, K. (2006). Assisted Reproductive Technologies in South Dakota: The first Ten years. *South Dakota Medical Journal*; 59 (7): 291 – 293.

Brieno-Enriquez, M.A., Reig-Viader, R., Cabero, L., Toran, N., Martinez, F., Roig, I., Garcia, C. M (2012). Gene Expression is altered by Bisphenol A Exposure in Human Fetal Oocytes in vitro. *Molecular and Human Reproduction*; 18(4): 171-183.

Bulger, W.H., Nuccitelli, R.M., Kupfer, D (1978). Studies on the in vivo and in vitro Estrogenic Activities of Methoxychlor and its Metabolite: Role of Hepatic Mono-oxygenase in Methoxycholor Activation. *Biochemistry and Pharmacology;* 27:2417-2423.

Buttke, E.E., Sircar, K., Martin, C. (2012). Exposures to Endocrine Disrupting Chemicals and Age of Menarche in Adolescent Girls in NHANES (2003-2008). *Environmental Health Perspective;* 120: 1613-1618.

Calabrese, E.J., and Baldwin L.A., (2003). Toxicology rethinks its central belief. Nature; 421 (6924); 691-692.

Casals- Casas, C., Desvergne, B (2011). Endocrine Disruptors. From Endocrine to Metabolic Disruption. *Annual Revision of Physiology;* 73: 135 – 162. Available from dio:10.1146/annisrev-physiol-012110-14200.

Castro, D.J., Lshr, C.V., Fischer, K.A; Pereora, C.B, Williams, D.E (2008). Lymphans and long cancer (&,1) pyrene: The Importance of in.utero vesus. Lactatimal Exposure. *Journal of Toxicology and Applied Pharmacology; 233 (3): 454-458. Available from: http://doi. org/10.1016%2Fj;taap.2008.09.009.*

Chao, H.R., Wang, S.L., Lin, L.Y., Lee, W.J., Papke, O (2007). Placental Transfer of Polychlorinated Dibenzo-p-dioxins, Dibenzofurans, and Biphenyls in Taiwanese Mothers in Relation to Menstrual Cycle Characteristics. *Food and Chemical Toxicology;* 45(2): 259-265.

Charney, E., Sayre, J., Coulter, M (1980). Increased Lead Absorption in Inner City Children: Where does the Lead come from? *Pediatrics;* 65 (2): 226 – 231. PMID 7354967 (http://www.ncbi.nlm.nih.gov /pubmed/73549697).

Christensen, B.C., and Marsit, C. J (2011). Epigenomics in Environmental Health. *Front Genetics*; 2: 84. Available from: doi.103389/fgene. 2011.00084.

Colborn, T., and Carroll, L.E., (2007). Pesticides, sexual development, reproduction and fertility current perspective and future. *Human and Ecological Risk Assessment: 13 (5): 1078-1110.*

Cooper, A.R., Baker, V.L., Sterling, E.W., Ryan, M.E., Woodruff, T.K., Nelson, L.M (2011). The Time is now for a New Approach to Primary Ovarian Insufficiency. *Fertilization and Sterility;* 95(6): 1890-1897.

Costa, E.M.E., Spritzer, P.M., Hohl, A., Bachega T.A.S.S (2014). Effects of endocrine distruptors in the development of the female reproductive tract. Arguivos Brasileiros de endocrinoolgia metabolism 58 (2): 153-161. Available from:http://dx. Dio.org/10.1590/004-273000000 3031. (Retrieved August 02, 2017).

Crisp, T.M., Clegg, E.D., Cooper, R.T., Wood, W.P., Adderson, D.G., Baetcke, K.P., Hoffmann, J.L., Morrow, M.S., Rodier, D.J., Schaeffer, J.E., Touart, L.W., Zeeman, M.G., Patel, Y.M (1998). Environmental Endocrime Disruption: an Effect Assessment and Analysis. *Environmental Health Perspective*. 106 (supplementary 1): 11-56. Available from : http://doi.org/10. 2307% 2F3433911.

Cummings, A.M (1997). Methoxychlor as a Model for Environmental Estrogens. *Critical Review and Toxicology;* 27(4): 367-379.

De Jager, C., Aneck-Hahn, N.H., Bornman, M.S., Farias, P., Later, G., Eleuteri, P., *et al* (2009). Sperm Chromatin Integrity in DDT-exposed young Man Living in a malaria area in the Limpopo Province, South Africa. *Human Reproduction* 24(10):2429-3810.

Decherf, S., Demeneix, B.A (2001). The Obesogen hypothesis: a shift of focus from the periphery to the hypothalamus. *Journal of Toxicology and Environmental Health 3 Critical Review*. 14 (5-7): 432 – 448. Available from doi:10.1080/10937404.2011-578561.

Delbes, G., Hales, B.F., Robaire, B (2010). Toxicants and Human Sperm Chromatin Integrity. *Molecular and Human Reproduction;* 16:14-22.

Diamanti-Kandarakis, E., Bourguignon, J.P., Guidice, L.C., Hauser, R., Prins, G.S., Soto, A.M., Zoeller, R.T., Gore, A.C (2009). Endocrine disrupting chemicals; an Endocrine society scientific statement. *Endocrine Reviews*; 30 (4); 293 – 342. Available from http://doi. org/10.121% 2Fer.2009-0002.

Diamanti-Kandarakis, E., Katsikis, I., Piperi, C., Kandaraki E., Piouka, A Papavassiliou, A.G., *et al* (2008). Increases Serum Advanced Glycation End-products is a Distinct Finding in Lean Women with Polycystic Ovary Syndrome (PCOS). *Oxford Journal of Clinical Endocrinology;* 69(4): 634-641.

Dodson, R.E., Nishioka, M., Standley, L.J,. Perovich, L.J., Brody, J.G., Rudel, R.A (2012). Endocrine Disruptors and Asthma-associated Chemicals in Consumer Products. *Environmental Health Perspective;* 120 (7): 935 – 943. Available from: doi:10.1289/ehp.1104052 (https://doi .org/ 10.1289%2fehp. 1104052).

Eichenlaub-Ritter, U., Vigt, E., Cukurcam, S., Sun, F., Pacchie rotti, F., Parry, J (2008). Exposure of Mouse Oocytes to Bisphenol A causes Meiotic Arrest but not Aneuploidy. *Mutation Research;* 651(1-2): 82–92.

Eladak, S., Grisin, T., Moison, D., Guerquin, M-J., N'Tumba- Byn, T., Pozzi-Gaudin, S., Benachi, A., Livera, G., Rouiller-Fabre, V., Habert, R (2015). A New Chapter in the Bisphenol A story: Bisphenol S and F are not Safe Alternatives to this Compound. *Journal of Fertility and Sterility;* 103(1): 11-21. Available from: doi.1016/j.fertinstert. 2014.11.005(https://doi.org/10.101 6%2fj.fertnstert.2014.11.005).

Ericsson, R.J., Baker, V.F (1967). Binding of Tetracycline to Mammalian Spermatozoa. *Nature;* 214: 403 – 404.

Farr, S.L., Cooper, G.S., Cai, J., Savitz, D.A., Sandler, D.P (2004). Pesticide use and Menstrual Cycle Characteristics among Premenopausal Women in the Agricultural Health Study. *American Journal of Epidemiology;* 160(12); 1194-1204.

Fernández, M., Bourguignon, N., Lux-Lantos, V., Libertun, C. (2010). Neonatal Exposure to Bisphenol A and Reproductive and Endocrine Alterations Resembling the Polycystic Ovarian Syndrome in Adult Rats. *Environmental Health Perspective;* 118(9): 1217-1222.

Figa-Talamanca, I., Traina, M.E., Urbani, E (2000). Occupational Exposure to Metals, Solvents and Pesticides: Recent Evidence on Male Reproductive Effects and Biological Markers. *Occupational Medicine (London)*; 15: 174-188.

Fortes, E.M., Malerba, M.I., Luchini, P.D., Sugawara, E.K., Sumodjo, L., Ribeiro-Neto, L.M et al (2007). High intake of Phytoestrogens and Precocious Thelarche: Case Report with a Possible Correlation. *Arquivos Brasileiros de Endocrinology and Metabologia;* 51(3): 500-503.

Friberg L., Piscator, M., Nordberg, G.E (1974). *Cadmium in the Environment*, 2nd Edition. Cleveland: CRC Press Inc. p37-53.

Fürst, P(2006). "Dioxins, Polychlorinated biphenyls and other Organohalogens Compounds in Human Milk. Levels, Correlation Trends and Exposure through Breastfeeding." *Molecular Nutrition and Food Research*; 50 (10): 922 – 33. Available from: https://www. nebi.nlm.nih.gov/pubmed/17009213.

Gaido, K.W., Maness, S.C., McDonnell, D.P., Dehal, S.S., Kupfer, D., Safe, S (2000). Interaction of Methoxychlor and related Compounds with Estrogen Receptors alpha and beta and Androgen Receptors: Structure-activity Studies. *Molecular Pharmacology;* 58(4):852858. Available from:dio:https://dio.org/10 /1124/mol.58. 4.852.

Golden, R.J., Noller, K.L., Titus- Ernstoff, L., kaufman, R.H, Mittendorf, R., Stillman, R., Reese, E.A (1998). Environmental Endocrime Modulators and Human Health: An Assessment of the Biological Evidence. Critical Prevuus and Toxocology; 28(2): 109-227.

Gore, A.C., Chappel, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoller, R.T(2015). Executive Summary to Environmental disrupting chemical-2: the endocrine society's second scientific statement on endocrine disrupting chemicals. *Endocrine Reviews*; 36 (6): 593-602.

Guillette, L.J.J., Gross, T.S., Masson, G.R., Matter, J.M., Percival H.F., Woodard, A.R (1994). Developmental Abnormalities of Gonad and Abnormal Sex Hormone Concentrations in Juvenile Alligators from Contaminated and Control Lakes in Florida. *Environmental Health perspective;* 102(8): 680-688.

Hanioka, N., Jinno, H., Nishimura, J., Ando, M (1998). Suppression of Male-specific Cytochorome P450 Isoforms by Bisphenol A in Rat Liver. *Archives of Toxicology;* 72(7): 387-394.

Hao, C., Cheng, X., Xia, H., Ma, X (2012). The Endocrine Disruptor Mono-(2-ethylhexyl) phthalate Promotes Adipose Tissue Differentiation and Induced Obesity in Mice. *Bioscience and Reproduction;* 32 (6): 619-629.

Hayes, T.B., Anderson, L.L., Beasley, V.R., de Solla, S.R., Iguchi, T., Ingraham, H., Willingham, E(2011). Demasculinization and Feminization of Male Gonads by Atrazine: Consistent Effects across Vertebrate Classes. *Journal of Steroid Biochemistry and Molecular Biology;* 127(2): 64-73.

Hayes, T.B., Case P., Chui, S., Chung, D., Haeffele, C., Haston, K., Lec, M., V.P., Marjuoa, Y., Parker, J., Tsai, M, (2006). Pesticide Mixtures, Endocrine disruption and amphibian declines: Are we underestimating the impact? Environmental health perspective: 144 (s-1): 40-50. Available from: doi:10.1289/ehp.8051.

Hites, R.A., Foran, J.A., Carpenter, D.O., Hamilton, M.C., Knuth, B.A., Schwager, S.J (2004). Global Assessment of Organic Contaminants in Farmed Salmon". *Science;* 303 (5655): 226-229. Available from: doi:10.1126/science.. 1091447(https://doi.org/10.1126%2fsceince.1091447).

Hunt, P.A., Koehler, K.E., Susiarjo, M., Hodges, C.A., Ilagan, A., Voigt, R.C., Thomas S., Thomas, B.F., Hassold, T.J (2003). Bisphenol A Exposure causes MeioticAaneuploidy in the Female Mouse. *Current Biology;* 13(7): 546-553. Available from: doi:10.1016/s0960-9833(03)00189-1.

Jarow, J.P., Lipshultz, I.I (1990). Anabolic Steroid-induced Hypogonadotropic Hypogonadism. *American Journal of Sports Medicine;* 18: 492-431.

Jinno, M., Takeuchi, M., Watanabe, A., Teruya, K., Hirohama, J., Eguchi, N., Miyazaki, A (2011). Advanced Gycation End-product Accumulation Compromises Embryonic Development and Achievement of Pregnancy by Assisted Reproductive Technology. *Human Reproduction;* 26(3): 604-610.

Joensen, U.N., Jorgensen, N., Rajpert-De Meyts, E., Skakkebaea, N. E (2008). Testicular Dysgenesis syndrome and leydig cell function. *Journal of Basic Clinical Pharmacology and Toxicology*; 102: 155-161.

Kandaraki, E., Chatzigeorgiou A., Livadas S., Palioura E., Economou, F., Koutsilieris, M., *et al* (2011). Endocrine Disruptiors and Polycystic Ovary Syndrome (PCOS): Elevated Serum Levels of Bisphenol A in Women with PCOs. *Journal of Clinical Endocrinology and Metabolism;* 96(3): E480-484.

Kappeler, C.J., and Hoyer, P.B (2012). Vinylcyclohexene Diepoxide: A Model Chemical for Toxicity. *Systemic Biology and Reproduction;* 58(1): 57 – 62.

Kirigaya, A., Kim, H., Hayashi, S., Chambon, P., Watanabe, H., Luguchi, T., Sato, T (2009). Involvement of Estrogen Receptors in the Induction of Polyovular Follicles in Mouse Ovaries Exposed Neonatally to Diethylstiybesterol. *Zoological Society of Japan;* 26(10): 704-712.

Knuth, U.A., Maniera, H., Nieschlag, E (1989). Anabolic Steroids and Semen Parameters in Body Builders. *Fertility and Sterility;* 52: 1041-1047.

La Vignera, S., Condorelli, R.A., Vicari, E., D'Agata, R., Caligero, A.E (2012). Effect of the Exposure to Mobile Phones on Male Reproduction: A Review of the Literature: 33(3): 350-356. (Journal?)

Li, J., Li, N., Ma, M (2008). In Vitro Profilling of the Endocrine Disrupting Potency of Organochlorine Pesticide. *Toxicology Letters*; 183(1-3): 65-71.

Liem, A-K., Fürst, P., Rappe, C (2000). Exposure of Populations to Dioxins and Related Compounds. *Food Addition Conference;* 17 (4): 241 – 259.

Lilientael, H., Hack, A., Roth-Harer, A., Grandes, S.W., Talsness, C.E: (2006). Effect of developmental exposure to 2,2,4,4,5-pentabromophenyl ether (PBDE-99) on sex steroids, sexual development and sexual dimorphic behaviour in rats. Environmental health perspective; 114 (2): 194-201. Available, from: doi: 10.1289/ehp.8391.

Liu, G., *et al* (2006). Effects of Low Level Radiation on the Death of Male Germ Cells. *Radiation Research;* 165: 379 – 389.

Lorber, M (2008). "Exposure of Americans to Polybrominated diphenyl ethers". *Journal of Exposure, Science and Environmental Epidemiology;* 18(1): 2-19. Available from: doi:10.1038 /sj.jes.7500572(https://doi.org/10.1038% 2fsj.jes.7500572).

Lunder, S., Jacob, A (2008). "Fire Retardants in Toddlers and their Mothers" *Environmental Working Group*; Available from: (http://www. ewg.org/ reports /pbdeintoddlers). (Retrieved March 14, 2009).

Manavathi, B., Kumar, R (2006). Steering Estrogen Signals from the Plasma Membrane to the Nucleus: Two Sides of the Coin. *Journal of Cell Physiology;* 207:599-604.

Mandl A.M (1996). The Radio-sensitivity of Germ Cells. *Biological Review of Cambridge Philosophy and Sociology;* 39: 288-371.

Meistrich, M.L (1982). Quantitative Correlation Between Testicular Stem Cell Survival, Sperm Production and Fertility in Mouse after Treatment with Different Cytotoxic Agents. *Journal of Andrology;* 3:58-68.

Nelson, L.M., (2009). Clinical Practice. Primary Ovarian Insufficiency. *New England Journal of Medicine;* 360(6): 606 – 614.

Newbold, R.R., (2004). Lessons Learned from Perinatal Exposure to Diethylstilbesterol. *Toxicology and Applied Pharmacology;* 199(2): 142-150.

Newbold, R.R., Jefferson, W.N., Padilla – Banks, E (2009). Prenatal Exposure to Bisphenol A at Environmentally Relevant Doses Adversely Affects the Murine Female Reproductive Tract Later in Life. *Environmental Health Perspective;* 117(6): 879-885.

Partsch, C.J., and Sippell, W.G. (2011). Pathogenesis and Epodemiology of Precocious Puberty: Effect of exogenous estrogens. Human reproductive and update; 7 (3) 292-302.

Parvinen, M., Lahdetie, J., Parvinen, L.M (1984). Toxic and Mutagenic Influences on Spermatogenesis. *Archives of Toxicology;* suppl 7: 128-139.

Pasquali, R., Stener-Victorin, E., Yildiz, B.O., Duleba, A.J., Hoeger, K., Mason, H., *et al* (2011). PCOs Forum: Research in Polycystic Ovary Syndrome Today and Tomorrow. *Oxford Journal of Clinical Endocrinology;* 74(4): 424-433.

Patisaul, H.B (2013). Effects of Environmental Endocrine Disruptors and Phylotesterogens on the Kisspeptin System. *Advanced Experimental and Medical Biology;* 784: 455-479. Available from: doi. 10.1007/978-1–4614- 6199-9-21.

Rochester, J.R., Bolden, A.L (2015). Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. *Environmental Health Perspective;* 123 (7): 643 – 650. PMC 4492270 (https://www.nchi.nlm.nih.gov/pubmed/25775505).

Rubin, B.S., Lenkowski, J.R., Schaeberle, C.M., Vandenberg, L.N., Ronsheim, P.M., Soto, A.M (2006). Evidence of Altered Brain Sexual Differentiation in Mice Exposed Perinatally to Low Rnvironmental Relevant Levels of Bisphenol A. *Endocrinology;* 147(8): 3681-3691.

Rudel, R.A., Seryak, L.M., Brody, J.G (2008). "PCB-containing Wood Floor Finish is a Likely Source of Elevated PCBs in Residents' Blood, Household Air and Dust: A Case Study of Exposure". *Environmental Health;* 7(1):2. Available from: doi: 10. 1186/1476-7-2 (https://doi. 0rg/10.1186%2f1476-069x-7-2).

Schecter, A., Päpke, O., Tung, K.C., Staskal, D., Birnbaum, L (2004). "Polybrominated diphenylethers Contamination of United States Food". *Environmental Science Technology;* 38 (30): 5306-5311. Available from: doi: 10.1021/eso490830 (https://doi.org/10/ 1021%2fes0490830).

Schug, T.T., Janesick, A., Blumberg, B., Heindel, J.J (2011). Endocrine Disrupting Chemicals and Disease Susceptibility. *Journal of Biochemistry and Molecular Biology.* 127 (3-5): 205 – 215.

Shiau, C. Y., Wang, J.D., Chen, P.C (2004). Decreased Fecundity among Male Lead Workers. *Occupation and Environmental Medicine;* 61: 915 – 923.

Sikka, S.C., and Wang, R (2008). Endocrine Disruptors and Estrogenic Effects on Male Reproductive Axis. *Asian Journal of Andrology;* 10: 134 – 145. Available from: doi:10.1111/j.1745-7262.2008-00370x.

Sikka, S.C., Rajasekaran, M., Hellstrom, N.J (1995). Role of Oxidative Stress and Antioxidants in Male Infertility. *Journal of Andrology;* 16: 464-468.

Swan, S.H., Elkin, F.P., Feuster, L. (2000). The question of declining sperm density Revisited: An analysis of 1010 studies published 1934-1996. *Environmental Health Perspective*; 108: 961-966.

Swan, S.H., Main; K.M., Liu, F., Stenerts, S.L., Krase, R.L., Calafat, A.M., Mao, C.S., Redmon, J.B., Ternand, C.L., Sullivan, S., Teague, J.L. (2005). Decreased in Ano-genital distance among male infants with prenatal phthalate Exposure. Environmental health perspective; 113 (8): 1056-1061.

Szabo, D.T., Richardson, V.M., Ross, D.G., Dliberto, J.J., Kodavanti, P.R., Birnbaum, L.S (2009). Effect of prenatal PBDE exposure on hepatic phase I, Phase II; Phase III and deiodinase I gene expression involved in thyroid hormone metabolism in male rat pups. Toxiocological science; 107(1): 27-39.

Szlinder–Richert, J., Barska, I., Mazerski, J., Usydus, Z (2008). Organochloride Pesticides in Fish from the Southern Baltic Sea: Levels, Bioaccumulation Features and Temporal Trends during the 1955-2006 Period. *Marine Pollution Bulletin*; 56 (5): 927-940. Available from: doi. 10. 1016/j. marpolbl. 2008. 01. 029 (https://doi.org/10.1016%2fj.marpolbul.2008.01.029).

Takeuchi, T., Tsutsumi, O., Ikezuiki, Y., Takai, Y., Taketani, Y (2004). Positive Relationship Between Androgen and the Endocrine Disruptor, Biphenol A in Normal Women and Women with Ovarian Dysfunction. *Journal of Endocrinology;* 51(2): 165-169.

Talsness, C.E., Kuriyama, S.N., Sterner-kock, A., Schnitker, P., Grande, S.W., Shakibaei, M., An drade, A., Grote, K., chahoud, I. (2008). In utero and lactatimal exposure to low doses of poly brominated diphenylether 47 alter the reproductive system and thyroid gland of female rat offspring. Environmental health perspective; 116 (3): 308-314.

Talsness, C.E., Shakibaei, M., Kuriyama, S.N., Grande, S.W., Sterner-kock, A., schnitker, P., de souza, C., Grote, K., chahoud I. (2005). Ultrastructural changes observed in rat ovaries following In-utero and lacpatunal exposure to low doses of a polybrounated flame retardant. Journal of toxicology letters; 157 (3): 189-202.

Tang, N.J., Liu, J., Coenraads, P.J., Dong, L., Zhao, L.J., Ma, S.W., Chen, X., Zhang, C.M., Ma, X.M., Wei, W.G., Zhang, P., Bai, Z. P (2008). Expression of AhR, CYP1A1, GASTA1, c-fos and TGF-alpha in Skin Lesions from Dioxin-exposed Humans with Chloracne. *Toxicology Letter;* 177(3):182-187. Available from:doi:10.1016/j.toxlet.2008. 01.011(https://dio.org/10.1016%2fj.toxlet. 2008 .01.011).

Taskinen, H., Lindbohm, M.L., Sallmeń, M (2011). *Occupational Exposure to Chemicals and Reproductive Health in Gupta, Rc (Ed)*. Reproduction and Developmental Toxicology, Elsevier Inc; San Diego. Pp 949-959.

Tiemann, U (2008). In vivo and in vitro Effects of the Organochlorine Pesticides DDT, TCPM, Methoxychlor and Lindane on the Female Reproductive Tract of Mammals: A Review. *Reproduction and Toxicology*; 25(3): 316-326. Available from: doi.10-1016/J.reprotox.2008-326.(https://doi. Org/10.1016%2fj.reportox. 2008.03.002).

Ugoji, D-P.C., Uwakwe, E.C., Oparaji, K.C., Igwe, J.C., Umahi, G., Besong, E., Ucha, S.E., UGOJI, U.C. (2022). Effect of Aqueous Extract of Soya Bean (Glycine Max) on the Reproductive Hormones and the Ovaries of Female Albino Wistar Rats. International Journal of Research and Scientific Innovation, 9(12); 59-62

Ugoji, D-P.C., Uwakwe E C, Ezenyirioha USJ , Ortuanya K E, Ucha S E , Umahi G, Besong E, Igwe J C (2023). Effect of Aqueous Extract of Soya Bean (Glycine Max) on the Male Reproductive Hormones and the Testes of Male Albino Wistar Rats. International Journal of Research and Scientific Innovation, 10(3); 29-34

Uribarri, J., and Tuttle, K.R (2006). Advanced Glycation end Products and Nephrotoxicity of High Protein Diets. *Clinical Journal of American Sociology and Nephrology;* 1(6): 1293-1299.

Verhulst, S.L., Nelen, V., Hand, E.D., Koppen, G., Beunekens, C., Vael, C., Schoeters, G., Desager, K (2009). Intrauterine Exposure to Environmental Pollutants and Body Mass Index during the First 3 years of Life. *Environmental Health Perspective*; 117(1): 122-126. Available from: doi:10.1289/ehp.0800003 (https://doi.org/10.1289% 2fehp.0800003).

Viberg, H., Johansson, N., Fredrikson, A., Eriksson, J., Marsh, G., Eriksson, P. (2006). Neonatal exposure to higher brominated disphenylethers, hepta-octa or nonabromodiphenylether, Impairs spontaneous behaviour and learning and memory functions of adult Mice. Toxicology and science journal; 92 (1): 211-218.

Vom Saal, F.S., Myers, J.P (2008). Bisphenol A and Risk of Metabolic Disorders. *Journal of American Medical Association;* 300 (11): 1353-1355. Available from: doi: 10. 1001/jama.300.11. 1353 (https://dx. doi.org/10.1001% 2fjama.300.11.1353).

Weschler, C.J (2009). Changes in Indoor Pollutants since the 1950s. Atmospheric and Environment; 43(1):153-169. Available from: dio:10. 1016/j.atmosenv.2008.09.044(https://doi.org/10.1016%2fj.a mosenv.2008.09.044).

White, R., Jobling, S., Hoare, S.A., Sumpter, J.P., Parker, M.G (1994). Environmentally Persistent Alkylphenolic Compounds are Estrogenic. *Endocrinology;* 135: 175-182.

Whorton, D., Krauss, R.M., Marshall, S., Milby, T.H (1977). Infertility in Male Pesticide Workers. *Lancet;* 2: 1259-1251.

Wirth, J.J., Mijal, R.S (2010). Adverse Effects of Low Level Heavy Metallic Exposure on Male Reproductive Function. *Systemic, Biological and Reproductive Medicine;* 56: 147-167.

Zhou, W., Liu, J., Liao, L., Han, S., Liu, J (2008). Effect of Bisphenol A on Steroid Hormone Production in Rat Ivarian interstitial and Granulosa Cells. *Molecular and Cellular Endocrinology;* 283(1-2): 12-18.

Zoeller, R.T (2006). Endocrine Disruptors: Do Family Lines Carry on Epigenetic Record of Previous Generations? *Endocrinology;* 147 (12): 5513 – 5514.