# Effect of xenobiotic compounds on steroidogenesis in humans

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**Abstract**

Gonadal steroids are crucial hormones responsible for the proper functioning and growth of the body. The sex hormones are produced in the adrenal glands and gonads by a process called steroidogenesis. Steroidogenesis is an enzymatic reaction where cholesterol gets converted to active steroid hormones in the respective gonads and play a dominant role in determining the primary and secondary characteristics of organisms. Studies has revealed that highly divergent groups of xenobiotic compounds are known to obstruct with steroidogenesis and cause endocrine-disrupting effects. Environmental contaminants such as DDT and PCBs are known to affect steroidogenesis. Chemicals such as azole fungicides and antifungal drugs is known to function as powerful inhibitors of steroidogenic enzymes, resulting in endocrine disruption. With the increasing various hormonal disorders and decreased fertility rate due to stress and improper lifestyle, understanding the role and environmental impact of sex hormones on humans helps to manage and lead a healthy life. This review highlights the biosynthesis, functional mechanism of estrogen, progesterone and testosterone hormones including the effects of its varying levels and the influence of endocrine disrupting compounds (EDCs) on the steroidogenesis process.

**Keywords:** Steroidogenesis, Sex Hormones, Sexual Orientation, Endocrinedisrupting chemicals (EDCs)

## 1 INTRODUCTION

An endocrine disrupting compound (EDC) is an exogenous agent and is long known for its potential to interfere with the synthesis, secretions, transportation, binding action, metabolism, or elimination of hormones present in the blood that are responsible for the developmental process, homeostasis, and reproduction. These EDCs act via different types of receptors to interrupt

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processes like steroid biosynthesis. The nature of these compounds is heterogeneous, involving chemicals present in industrial solvents and their by-products such as polychlorinated biphenyls (PCBs), plastics such as bisphenol A (BPA), pesticides like chlorpyrifos and dichlorodiphenyltrichloroethane (DDT), fungicides like vinclozolin, and pharmaceutical agents such as diethylstilbestrol (DESI). Naturally occurring chemicals like phytoestrogens can also act as EDCs. The mimicking mechanism is implemented by these compounds in order to disrupt steroidogenesis. The phenolic moiety present imitates the bodily present steroid hormone, which allows these EDCs to bind to the hormone receptors as analogues or antagonists. These EDCs are constantly present indoors and outdoors, where they eventually enter the food chain and harm organisms (Diamanti-Kandarakis et al., 2009).

Gonadal steroids regulate secondary sex characteristics, sex differentiation, patterns of sexual behaviour, control inflammation, metabolism, immune functions, salt, and water balance, and withstand injury and illness. Cholesterol serves as the central precursor of steroid hormones. It is an organic waxy molecule and a lipid sterol found in animals (Razin & Tully, 1970). The oxidative enzymes located in mitochondria and the endoplasmic reticulum are the most essential part of the biosynthesis process. Steroid hormones are transported through the blood by carrier plasma proteins that bind to them and increase the solubility of hormones in blood. The complex is disassembled inside the lysosome, it then migrates into hormone that diffuses into the cell and then undergoes metabolism and has an impact at the genetic level (Cook-Botelho et al., 2017).

Steroid hormones can be majorly classified into five types: testosterone, progesterone, estrogen being the major sex steroids and cortisol/corticosterone (glucocorticoid) and aldosterone (mineralocorticoid) are referred to as corticosteroids. Testosterone is a multi-functional hormone present in men. It is at its peak during adolescence and is the main element accountable for the development of secondary sexual characteristics in males. Traces of testosterone can also be found in the females and it helps in determining the behaviour and assists in cell repair (MacGill, 2019). Progesterone is a well-known hormone that have a significant role in menstruation and pregnancy. It is a steroid hormone that belongs to the progestogen class of hormones (Davidge-Pitts & Burt Solorzano, 2019). Progesterone is an endogenous steroid hormone that is produced by the gonads as well as the adrenal cortex. Progesterone is also secreted by the adrenal glands in males as progesterone plays a role in sperm development. Estrogen is a steroid, sex hormone that plays responsible for in regulating the reproduction in mammals. Besides, it has an effect on mental health, bone health, cardiovascular and other vital bodily functions. Estriol are the most abundant estrogen produced in the body, but their levels are similar to that

of other forms of estrogen because of its high metabolic rate and excretion. They are synthesized by placenta making levels increasing sharply during pregnancy as their major role is to prepare the uterus and make it suitable for reproduction. The estriol levels in non-pregnant women is almost undetectable (Magon & Kumar, 2012). On the other hand, corticosteroids are hormone mediators synthesized by the cortex of the adrenal glands. They are further divided into glucocorticoids (the body's main glucocorticoid is cortisol), mineralocorticoids (the main mineralocorticoid is aldosterone), and androgenic sex hormones. They are used to treat a wide range of conditions, particularly dermatoses and steroid-responsive disorders (Muhammad Yasir & Sidharth Sonthalia, 2019).

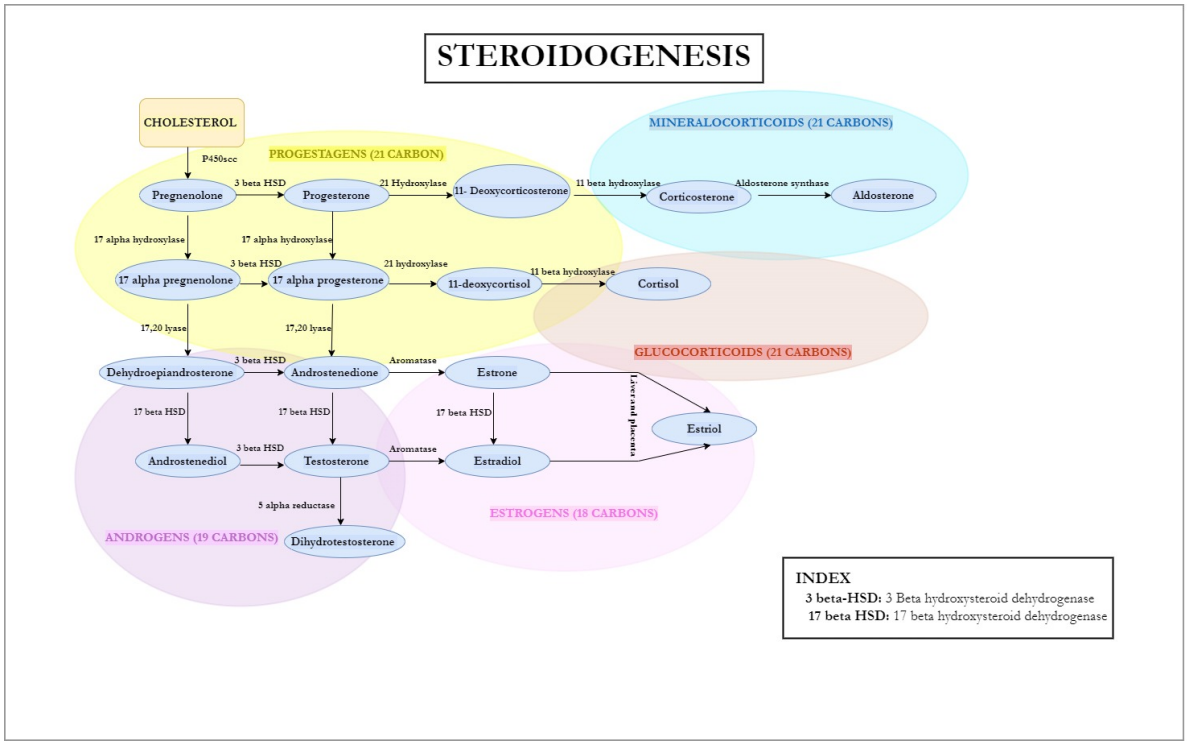


**FIGURE 1**

Schematic representation of steroid biosynthesispathway

biosynthesis of major sex steroid hormones,regulation in cellular levels, and the consequence of differing hormone level in both male and female.The action mechanisms of numerous categories of chemicals that have been theorised or proven to interfere with steroidogenesis and lead to endocrine disruption will be covered.

Cholesterol is the exclusive precursor for the synthesis of steroids. Cytochrome P450 cholesterol side chain cleavage enzyme (P450scc), catalyzes and converts cholesterol to pregnenolone from which various steroid products, mineralocorticoids, glucocorticoids, androgens and estrogens are synthesized by further enzymatic reactions.

## 2 STEROIDOGENESIS

The production of steroid hormones from cholesterol occurs in a multi-step process called steroidogenesis (Sewer & Li, 2008). The steroid hormones are categorized into five main types: testosterone, progesterone, estrogen, mineralocorticoids (cortisol/corticosterone), and glucocorticoids (aldosterone). While cortisol/corticosterone and aldosterone are referred to as corticosteroids; testosterone, progesterone, and estrogen are known as sex steroids (Miller & Auchus, 2011). Various organs are known to carry the ability for production of biologically active steroids, few include, adrenal gland, testis, ovary, brain, placenta, and adipose tissue (Sanderson, 2006). It is synthesized de novo by three main endocrine glands: ovaries, testes, and adrenal cortex (Holst et al., 2004). The steps involved in the synthesis of steroids from cholesterol is depicted in the Figure 1. They are mainly composed of many distinct hydroxysteroid dehydrogenases (HSDs), steroid reductases, and cytochrome P450 enzymes (CYPs) (Miller, 1988). The first step in the de novo production of all steroid hormones is the conversion of cholesterol by CYP11A (cholesterol side-chain cleavage) to pregnenolone

(Parker and Schimmer, 1995). The placenta is known to produce steroids such as estrogen and progesterone during pregnancy. They are transported through the bloodstream to the target sites to regulate a huge number of functions (Magon & Kumar, 2012).

### 2.1 BIOSYNTHESIS OF GLUCOCORTICOIDS AND MINERALOCORTICOIDS

Mineralocorticoids, glucocorticoids, and precursors of active androgens are produced by the cortex of the adult human adrenals (Odermatt et al., 2016). The adrenal cortex and adrenal medulla, two endocrine organs that are embryologically and functionally separate, make up the adrenals. Tyrosine is used by the medulla to make catecholamines, and cholesterol is used by the cortex to release steroid hormones. The zona glomerulosa, zona fasciculata, and zona reticularis are the three anatomically separate zones that make up the adrenal cortex. All animals' zona glomerulosa, which is primarily controlled by the renin-angiotensin system, produces the mineralocorticoid aldosterone. Depending on the species, glucocorticoids are produced in the zona fasciculata or reticularis under the control of ACTH (Johansson, 2002).

Due to their strict regulation of the Na/K balance in extracellular fluids, mineralocorticoids are crucial for survival. The development of the embryonic lung, immunological regulation, and preservation of normal tissue function are all influenced by glucocorticoids, which are also crucial for glucose homeostasis and the body's reaction to stimuli. The adrenal cortex is unable to store glucocorticoids. As a result, cholesterol serves as the starting material for the

immediate synthesis of all adrenocortical steroids (Johansson, 2002). Adrenocorticotropic hormone (ACTH), which increases mainly glucocorticoid and weak androgen production via the cAMP-mediated protein kinase A (PKA) pathway, activates factors like steroidogenic acute regulatory protein (Stocco, 2001) and steroidogenic factor-1 (SF-1) (Morohashi and Omura, 1996; Morohashi et al., 1992), and angiotensin II and potassium (Rainey, 1999). The adrenal cortex-specific enzyme steroid 21-hydroxylase (CYP21), which is required for the manufacture of both mineralo- and glucocorticoids, is crucial. It is responsible for converting progesterone and 17-hydroxyprogesterone into 11-deoxycorticosterone (through the mineralocorticoid pathway) and 11-deoxycortisol (via the glucocorticoid pathway), respectively. It is found in the smooth endoplasmic reticulum of all three adrenocortical zones (Sasano et al., 1988). These precursors are then transformed by the enzymes aldosterone synthetase (CYP11B2) and steroid 11-hydroxylase (CYP11B1) into the physiologically active hormones cortisol and aldosterone, respectively. In addition, only the adrenal cortex produces these two mitochondrial enzymes. According to Ogishima et al. (1992), CYP11B2 is only expressed in the zona glomerulosa and has additional 18-hydroxylase/aldosterone synthetase activity, which explains the zone selectivity of adrenocortical steroid biosynthesis. CYP11B1 is expressed in the zonae fasciculata and reticularis, and it has strictly 11-hydroxylase activity.

The single enzyme CYP17, which has both 17-hydroxylase and 17,20-lyase activity, is responsible for forming the adrenal weak androgens. Although the human placenta does not contain CYP17, the ovary and testicles do (Voutilainen and Miller, 1986). The same enzyme that is expressed in the smooth endoplasmic reticulum is responsible for the two actions due to different catalytic sites on it (Miller, 1988). Pregnenolone and progesterone are each converted into their corresponding 17a-hydroxysteroids by CYP17, a process that takes place in the zonae reticularis and fasciculata but not in the zona glomerulosa (Reincke et al., 1998). The two 17-hydroxylated steroids are converted to the weak androgens dehydroepiandrosterone (DHEA) and androstenedione by the 17,20-lyase activity of CYP17, which is only present in the zona reticularis of the adult adrenal cortex.

### 2.1.1 *Effects of Xenobiotic Compounds in Production of Glucocorticoids and Mineralocorticoids*

A test approach for identifying putative glucocorticoid disruptors was assessed using the human adrenocortical H295R cancer cell line. To do this, the effects of various well-known CYP inhibitors (ketoconazole, metyrapone, and aminoglutethimide) on catalytic CYP enzyme activity during hormone production were investigated. Metyrapone decreased the activities

of the mitochondrial CYP11A and CYP11B1 enzymes while ketoconazole inhibited all of the investigated CYP enzyme activities in H295R cells (CYP11A, CYP11B1, CYP17, and CYP21). Both drugs effectively and similarly inhibited CYP11B1. Aminoglutethimide was solely tested for its effects on CYP11A activity, and it was discovered to have weak inhibition of this enzyme (Johansson, 2002).

Being a metabolite of the still widely used insecticide DDT, MeSO2-DDE (3-methylsulfonyl-2,2-bis(4-chlorophenyl)-1,1-dichloroethene) is a global environmental problem. MeSO2-DDE bioaccumulates in the food chain due to its persistence and lipophilicity, even contaminating human breast milk (Jensen & Jansson, 1976). (Haraguchi et al., 1989). According to animal studies, MeSO2-DDE is adrenotoxic to a number of species after being bioactivated in the mitochondria of the adrenal cortex (Lund et al., 1988; Jönsson et al., 1992). In vitro bioactivation of MeSO2-DDE has also been shown to occur in human adrenal mitochondria (Jönsson & Lund, 1994). According to Johansson et al. (2002) and Lund & Lund (1995), the medication 3-MeSO2-DDE had a potency that was only marginally inferior to that observed in mouse Y1 cells when it came to inhibiting CYP11B1 activity in human H295R cells. The maximum dosage of 3-MeSO2-DDE (10 M) reduced cortisol production in human H295R cells to 66% of control (Johansson et al., 2002). In contrast, human adrenal tissue slices exposed to a 2.5-fold greater concentration of 3- MeSO2-DDE did not impact the production of cortisol, despite the medium accumulating other hormones such 11-deoxycortisol, 11-deoxycorticosterone, and androstenedione (Lindhe et al., 2002).

According to Brown and Fishman (2000), either an inhibition of CYP21 activity or an enzymatic conversion of 11-deoxycortisol to androstenedione can result in elevated levels of the hormone. Although at higher concentrations than those required to block CYP11B1 in H295R cells, 3-MeSO2-DDE showed inhibitory effects on CYP21 activity as well. This suggests that CYP21 inhibition may be the cause of the elevated levels of androstenedione. It is important to pay more attention to how 3-MeSO2-DDE affects the synthesis of androstenedione. On the other hand, it has been noted that in both mice and humans, 3-MeSO2-DDE is bioactivated and irreversibly attached to the regions of the adrenal cortex that express CYP11B1 (Lund et al., 1988; Jönsson and Lund, 1994).

### 2.1.2 *Varying Levels of Glucocorticoids and Mineralocorticoids in Humans and its Effects*

Clinical indicators of a mineralocorticoid shortage include hypotension, fatigue, a salt desire, and electrolyte imbalances (hyperkalemia, hyponatremia). Aldosterone levels that are dramati-

cally lowered and plasma renin activity levels that are dramatically raised (PRA) are indicators of mineralocorticoid insufficiency (Quinkler et al., 2015). If there is excessive mineralocorticoid activity, severe hypokalemia, metabolic alkalosis, or therapeutic responses to spironolactone may emerge as major clinical characteristics. These conditions are uncommon in pure glucocorticoid hypertension. Extracellular fluid (ECF) volume increases and hypertension results from increased Na+ retention in conditions where mineralocorticoid production is out of control (such as hyperaldosteronism); on the other hand, low blood pressure (hypotension) results from insufficient mineralocorticoid secretion. Furthermore, excessive H+ discharge and metabolic alkalosis can come from mineralocorticoid hypersecretion, while metabolic acidosis and greater H+ retention can result from mineralocorticoid hyposecretion (such as in Addison's disease) (Petroff & Greco, 2020). Typical mineralocorticoid-induced hypertension arises as a result of enhanced sodium reabsorption in the distal renal tubule, which raises body sodium content and expands plasma volume. Moreover, decreased body potassium content and metabolic alkalosis are caused by increased urine potassium and hydrogen ion secretion. The kidney's juxtaglomerular cells finally reduce renin production in response to elevated plasma volume and sodium, which results in low amounts of angiotensin II (Marie Freel, 2018). The side effects of excessive glucocorticoids include immunosuppression, muscular atrophy, central obesity, osteoporosis, hepatosteatosis, hypertension, insulin resistance, sleeplessness and depression (Peppa et al., 2011).

Due to the potential harm caused by elevated glucocorticoids, the hypothalamic-pituitary-adrenal (HPA) axis tightly regulates the hormones' synthesis. After the anterior pituitary receives a signal to release adrenocorticotrophin from the hypothalamus, corticotrophin-releasing hormone (CRH) is released (ACTH). Hence, the release of glucocorticoids, which have the ability to affect nearby tissues, is signalled to the adrenal gland's cortical layer (Herman et al., 2016). Elevated levels of circulating glucocorticoids eventually feed back to the hypothalamus and pituitary, preventing further production of CRH and ACTH, which in turn prevents glucocorticoid release. As a result, glucocorticoids are released in a pulsatile manner and exhibit a diurnal pattern, with peak levels of the circulating hormone occurring at the start of waking (Herman et al., 2016). Water retention and dilutional hyponatremia arise as a result of poor renal free water clearance caused by a lack of glucocorticoids. Low plasma osmolality combined with abnormally high urine osmolality and excessive urinary sodium content provide a biochemical profile like that of SIAD (Milionis et al., 2002)

## 2.2 BIOSYNTHESIS OF ESTROGEN

Estrogen, often known as oestrogen, is a sex hormone that affects secondary sex traits as well as the growth and regulation of the female reproductive system. Estrone (E1), Estradiol (E2), and Estriol (E3) are the three main endogenous oestrogens having estrogenic hormonal activity and their normal levels present in male and female is represented in Table 1 and 2. Estradiol is the most powerful and common estrane. Another oestrogen produced only during pregnancy is estetrol (E4). Estrogen has a four-ringed carbon atom backbone, or core, in its biological structure.

Glandular estrogen production takes place in the ovaries' granulosa and theca cells, the corpus luteum, as well as the fat cells and the bones which is known as the extra glandular synthesis. Theca interna is highly vascularized and generates substantial quantities of progesterone and androgens, which serve as precursors for oestrogen production in the granulosa cells (Sanderson, 2006). The luteinizing hormone stimulates the granulosa cells to produce pregnenolone which reaches the thecal cells. 17, 20-lyase and 3-HSD, which facilitate the conversion of pregnenolone to androstenedione via DHEA, are expressed in the theca cells. The pregnenolone is converted to 17-$\alpha$-hydroxy pregnenolone under the influence of the enzyme 17-$\alpha$-Hydroxylase in the presence of 3 $\beta$-HSD; It is also formed by progesterone in presence of the enzyme 17 $\alpha$-hydroxylase. These two precursors are converted into di-hydro epi-androsterone and androstenedione respectively by the action of the enzyme 17, 20-Lyase. Androstenedione and testosterone permeate into the nearby weakly vascularized granulosa cells where they are transformed to mainly estradiol, with the coordinated action of aromatase and 17b-HSD types 1 and 7, which encourage the conversion of estrone to estradiol (Mindnich et al., 2004; Luu-The, 2001). The estrone is converted into estradiol by the action of the enzyme 17- $\beta$ -HSD. The estrone and the estradiol in the liver and placenta are converted to estriol non-enzymatically (Cui et al., 2013). FSH stimulation regulates the expression of aromatase and 17-HSD (Christenson & Devoto, 2003) (Fuentes & Silveyra, 2019). Aromatase is a non-gonadal enzyme that aids in the peripheral aromatization of androgens into estrone. Fat cells convert androgen to estrone, which raises blood estrogen levels. Bone converts testosterone to local estrogen, which aids in epiphyseal maturation (Fuentes & Silveyra, 2019). Aromatase is a protein that helps peripheral target tissues in men convert circulating testosterone to estradiol and androstenedione to estrone. These oestrogens are thought to have low systemic effects since they are thought to act locally and be digested in the target tissues. In the bone, particularly in osteoblasts and chondrocytes, the male reproductive system, particularly in leydig cells, sertoli cells, and mature

spermatocytes, as well as adipose tissues, all express aromatase (Simpson & Santen, 2015) (Zhao et al., 2016).

Reduced LH levels and therefore reduced aromatase expression lead to decreased oestrogen production (Fitzpatrick et al., 1997), whereas concurrently increased CYP11A and 3b-HSD activity boosts progesterone synthesis and, via its receptor, triggers follicular rupture.

**TABLE 1**

Normal levels of estrone (E1) and estradiol (E2) in male and female. Source: (Denver et al., 2019, Jewell, 2019)

| | **Hormone** | |
|---|---|---|
| | **Estrone (E1)** | **Estradiol (E2)** |
| Prepubescent female | Undetectable-29 pg/mL | Undetectable-20 pg/mL |
| Pubescent female | 10-200 pg/mL | Undetectable-350 pg/mL |
| Premenopausal adult female | 17-200 pg/mL | 15-350 pg/mL |
| Postmenopausal adult female | 7-40 pg/mL | <10 pg/mL |
| Prepubescent male | Undetectable-16 pg/mL | Undetectable-13 pg/mL |
| Pubescent male | Undetectable-60 pg/mL | Undetectable-40 pg/mL |
| Adult male | 10-60 pg/mL | 10-40 pg/mL |

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**TABLE 2**

Normal levels of estriol (E3) in adult male and female Source: (Novkovic, 2019)

| **Estriol (E3)** | **Normal Range** |
|---|---|
| Adult male | $\leq$ 0.18 ng/mL |
| Adult female | |
| Pubescent female | $\leq$ 0.21 ng/mL |
| $1^{st}$ trimester | $\leq$ 2.50 ng/mL |
| $2^{nd}$ trimester | $\leq$ 9.60 ng/mL |
| $3^{rd}$ trimester | $\leq$ 14.60 ng/mL |

### 2.2.1 *Effects of Xenobiotic Compounds in Production of Estrogen*

EDCs (endocrine disrupting chemicals) are widely distributed in the environment, exposing people to them every day. This is concerning because it is known that many EDCs primarily target the ovaries and the female reproductive system. The ovary is a woman's primary organ for both reproductive and endocrine functions. Many issues with reproductive health, including infertility, early ovarian failure, and aberrant sex steroid hormone levels, are linked to exposure to EDCs (Patel et al., 2015).

Organochlorines that affect the endocrine system, including the pesticide dichlorodiphenyltrichloroethane (DDT), bind to and activate the ERs, which results in estrogen-like actions (Frigo et al., 2002). Yet another well-known endocrine disrupter are the PCBs. They have the potential to have a variety of effects on the endocrine system of an organism, including simulating the actions of natural hormones, opposing those of natural hormones, or altering the synthesis, metabolism, and transport of natural hormones (Balaguer et al., 2019).

BPA, a major industrial chemical, widely used in plastics has been recently studied as a major endocrine disrupting agent. In KGN cells and primary granulosa cells, it was discovered that bisphenol A (BPA) activated peroxisome proliferator-activated receptor (PPAR) and blocked FSH-stimulated insulin-like growth factor-1 (IGF1)-dependent activation of CYP19A1 expression and estradiol synthesis (Kwintkiewicz et al., 2010). While estradiol synthesis was decreased following treatment with 80 mM of BPA, there was a considerable blunting of the FSH-induced CYP19A1 expression at 40 mM. The BPA amounts used are exceedingly high, and it is unclear whether these findings have any application to humans. In a different investigation, CYP19A1 expression was found to be significantly reduced by BPA at 5 mM in both KGN cells and human foetal osteoblastic cells (Willcutt, 2012).

Heneweer et al., (2005) recently discovered that 3-MeSO2-CB-132, 4-MeSO2-CB-132, 4-MeSO2-CB-149, and 4-MeSO2-CB-91 reduced the catalytic activity of aromatase in H295R cells and in primary culture of human mammary fibroblasts. The researchers came to the conclusion, however, that biologically substantial aromatase inhibition was unlikely to happen in vivo at the environmental PCB metabolite concentrations that were in place at the time. Moreover, it was discovered that DEHP (5 mM) and TCDD (10 nM) increased AhR expression in a PPAR-dependent manner while inhibiting FSH-induced estradiol production (Thompson & Nelson, 2001). The stimulatory effect of transfected SF-1 on aromatase mRNA expression and activity in KGN cells was found to be improved by the addition of atrazine and simazine at 10 mM in another investigation (Krishnan & Stark, 2007). In recent studies, it was discovered that pregnant mice treated with 5-500mg/kg of the pesticide simazine had shorter anogenital distances

and lighter whole-body, ovarian, and uterine weights in their progeny (Barr, 2002). The vitality and proliferation of KGN granulosa cells were reduced by simazine at a dose of 1 nM.

The catalytic activity of aromatase in human placental microsomes has been demonstrated to be inhibited by a number of azole-containing substances used in both agriculture (fungicides) and medicine (antifungals) (Ayub and Levell, 1988; Mason et al., 1987; Vinggaard et al., 2000). The antifungal medications ketoconazole and nimorazole were less potent (IC50 values of 7.3 and 66lM, respectively), whereas the inhibitory potencies for econazole, tioconazole, bifoconazole, miconazole, isoconazole, and clotrimazole were observed in the upper nanomolar range (Ayub and Levell, 1988). Several antifungal medications have been found to reversibly (but not always competitively) suppress the activity of aromatase in human placental microsomes (Ayub and Levell, 1988).

### 2.2.2 *Varying Levels of Estrogen in Humans and its Effects*

Reduced sex desire, excess fat around the belly, bone loss, osteoporosis, fatigue, anxiety, irritability, depression, forgetfulness, oversleeping or sleeping too much, and water retention are all signs of low oestrogen in people assigned male at birth (AMAB) (White, W.J.,2019, Cauley, 2015). Males with cardiovascular illness had lower oestrogen levels, according to researchers. It can be caused by hypogonadism, a disorder that causes a decrease in sex hormones. Although oestrogen is necessary for the male body to operate properly, having too much of it can be unhealthy. It's one of the hormones that helps the body make sperm. Infertility is caused by high oestrogen levels, which slow down sperm production and make it more difficult to develop healthy sperm. Increased oestrogen can lead to the development of more breast tissue than is typical, condition termed as gynecomastia (Hess et al., 1997). Increased oestrogen levels can also disrupt the hormone balance required to achieve and maintain an erection, resulting in erectile dysfunction (ED). In boys, too much oestrogen can cause small height or delayed puberty. Epiphyseal closure is a common occurrence in teenagers with high oestrogen levels, resulting in short height in guys (Cooke et al., 2017). Possible symptoms of too much oestrogen include decreased sex drive, decreased sperm concentration, fatigue, body hair loss, decreased muscle mass, lower penis and testicular growth, loss of bone density (osteoporosis), heat flushes, and difficulty concentrating.

Low oestrogen levels may impede transgender women or nonbinary people with penises from having the physical look they desire. Feminizing hormone therapy may be an option if this

is the case. Taking oestrogen to produce secondary sex traits such as softer facial features, less body hair, breasts, and hips is part of this treatment (Tangpricha & den Heijer, 2017).

Low oestrogen levels in young women can be brought on by excessive exercise, eating disorders like anorexia, a low-functioning pituitary gland, premature ovarian failure, toxins, or an autoimmune condition, turner syndrome, chronic kidney disease, pregnancy failure, and polycystic ovarian syndrome (PCOS) (Clegg, 2012, Rosenfield & Ehrmann, 2016, Cena et al., 2020). Low oestrogen levels in women over 40 years old can signal the start of menopause. Perimenopause is the term for this period of transition. The ovaries continue to produce oestrogen during perimenopause. Until menopause, production will continue to decline (Clegg, 2012).

When the oestrogen and testosterone levels in the body are out of balance, certain symptoms might arise. Women may experience symptoms such as breast bloating, swelling, and tenderness, fibrocystic lumps, decreased sex drive, irregular menstrual cycles, increased premenstrual syndrome (PMS) symptoms, mood swings, headaches, anxiety, and panic attacks, weight gain, hair loss, cold hands or feet, difficulty falling or staying asleep, sleepiness or fatigue, and memory issues. High oestrogen levels can put you at risk for a variety of additional problems (Almeida et al., 2017). For instance, increased oestrogen levels are associated with an increased risk of breast and ovarian cancer. According to the American Cancer Society (ACS), oestrogen dominance may raise your chance of developing endometrial cancer. High levels of oestrogen may make blood clots and strokes more likely. Oestrogen dominance can also cause thyroid issues. This might cause symptoms such as exhaustion and weight gain (Almeida et al., 2017). High oestrogen levels can occur naturally, but they can also occur as a side effect of some drugs. For example, oestrogen replacement therapy, a common treatment for menopause symptoms, may cause oestrogen levels to rise to dangerous levels (Clegg, 2012).

Certain antibiotics, herbs or other natural medicines, such as gingko or ginseng, and phenothiazines, among others, might cause oestrogen levels to rise (a medication used for mental health conditions). High oestrogen levels can also be handed down the generations. Stress, weight gain or obesity, certain cancers, liver disorders, and problems that impact hormone balances, such as hypogonadism, are all examples of health factors that might boost oestrogen levels (de Ronde & de Jong, 2011).

## 2.3 BIOSYNTHESIS OF PROGESTERONE

The hormone progesterone, which is generated by the female reproductive system, controls the condition of the uterus' inner lining (endometrium). Progesterone is produced by

the ovaries, placenta, and adrenal glands. It is secreted by the corpus luteum of the ovaries throughout the first ten weeks of pregnancy, and the placenta follows the later stages which is responsible for stimulating the uterus to prepare for pregnancy (Cable & Grider, 2020). Cholesterol is the precursor molecule for all the steroid hormone synthesis; It is converted into an intermediate molecule prognolone by the cleavage of a side chain of cholesterol in the presence of cholesterol side-chain cleavage enzyme. This prognolone is converted into progesterone in presence of the enzyme 3-b-Hydroxysteroid dehydrogenase (3b-HSD) (Christenson & Devoto, 2003). The uterine wall is made ready by progesterone so that a fertilised egg can be implanted and grow inside the lining. Additionally, it avoids uterine muscular spasms, which could lead to the uterine wall rejecting the connected egg. When a fertilised egg is deposited in the uterus, a placenta develops. Progesterone induces the endometrium to produce certain proteins throughout the second half of the menstrual cycle, preparing it to accept and nourish an implanted fertilised egg. Oestrogen and progesterone levels falls and the uterine wall stops growing in the absence of implantation, the endometrium disintegrates, and menstruation starts (Cable & Grider, 2020).

A molecule with a chain of 21 carbon atoms, progesterone is generated from cholesterol. It has four linked cyclic hydrocarbons, ketone, and oxygenated functional groups in addition to two methyl branches and two methyl branches. It has a hydrophobic disposition. An unsaturated C (4)-C steroid hormone, progesterone possesses oxo substituents at positions 3 and 20 in its pregnane structure. It is a C21-steroid hormone that also includes 20-oxo and 3-oxo-Delta steroids. It originates from a pregnane's hydride. Chemically, it is also called as Pregn-4-ene-3,20-dione. Progesterone and synthetic steroid hormones like the progestogen levonorgestrel that exhibit progesterone-like properties are collectively referred to as progestins.

Progesterone has a 500-million-year history, which is widely regarded as the length of its existence. However, the discovery of progesterone molecules in walnut trees in 2010 has pushed back the age of its origins. The hormone could be an old bio-regulator that evolved billions of years before modern plants and animals appeared, according to the researchers. The novel discovery has the potential to alter our understanding of progesterone's evolution and function in living beings. Professor Willard Allen, an organic chemist who later studied medicine, was the first to discover and isolate progesterone in the modern era. They identified a chemical in the corpus lutuem that prolonged pregnancy while working in Professor George Corner's embryology lab. Willard Allen, PhD, published the first study on extracting progesterone from the corpus luteum on 1929. Pure progesterone exists in two crystalline forms, one of which

melts at 128 degrees Celsius (alpha progesterone) and the other at 121 degrees Celsius (beta progesterone) (beta progesterone) (Corner G.W,1941).

### 2.3.1 *Effects of Xenobiotic Compounds in Production of Progesterone*

Human adrenocortical cancer cell line H295R was used to examine the potential to obstruct the manufacture of steroid hormones. All three of the triazole fungicides, propiconazole, tebuconazole, and epoxiconazole, increased progesterone production while lowering that of testosterone and estradiol, similar to prochloraz. Inhibition of progesterone to testosterone conversion enzymes is indicated by this (Knazicka et al., 2021).

Human granulosa cells exposed to genistein (1-50 $\mu$M) have lower progesterone levels (Whitehead et al., 2002). Moreover, human granulosa cells exposed to genistein at 50 and 100 $\mu$M levels produced less progesterone from pregnenolone (Whitehead et al., 2002). (Lacey et al., 2005). In one investigation, exposure to genistein (0.5–50 $\mu$M) decreased basal progesterone levels and FSH-induced progesterone (10 $\mu$M) levels (Whitehead & Lacey, 2000). Another study revealed that high doses of genistein (30-100 $\mu$M) lowered FSH-induced progesterone levels while low doses of genistein (0.1-3 $\mu$M) boosted them (Haynes-Johnson et al., 1999).

TCDD has been demonstrated to result in a concentration-dependent reduction in estradiol synthesis in human luteinized granulosa cells (hLGCs) in the 0.1–10 nM range (Enan et al., 1996; Heimler et al., 1998). In these trials, progesterone secretion was unaffected, and the synthesis of estradiol was no longer impacted by the administration of androgen substrate (Heimler et al., 1998). These results showed that TCDD had no effect on CYP11A inhibition or cholesterol mobilisation, but they did raise the possibility that TCDD might interfere with progesterone's biosynthesis-related steps in the steroidogenesis pathway.

However, very few research have examined the biological consequences of o,p'-DDT at concentrations comparable to or lower than the levels at which humans are now exposed. o,p'-DDT has been shown to suppress estrodial (E2) and progesterone synthesis in ovarian granulosa cells at a dose of 4 ng/ml (Wójtowicz et al., 2004).

### 2.3.2 *Varying Levels of Progesterone in Humans and its E ffects*

7 weeks after the gestation, the degeneration of the corpus luteum takes place while the placentally produced progesterone will maintain the remainder of the pregnancy. Progesterone has several functions that includes menstruation, implantation (Halasz et al., 2013) and parturition (Mesiano, 2001). Premenstrual syndrome (PMS) can also be correlated to the levels

of progesterone symptoms such as breast tenderness, bloating, and mood swings. Blood progesterone level rise after gradually after ovulation and fall right before menstruation. PMS is caused because of low levels of blood progesterone (Reed & Carr, 2018).

Low levels of progesterone in woman are known to cause irregular due to abnormal levels of progesterone. Induction of pregnancy can also be difficult in females as the hormone can no longer prepare the uterine wall to receive the embryo. Pregnant women with low levels of progesterone can have an ectopic pregnancy, miscarriage or an early labour. Normal level of progesterone produced during various phases of ovulation is given in table 3. Low levels of progesterone in non-pregnant females can lead to mood swings, headaches, migraines, anxiety, depression, weight gain and irregular periods which can even lead to a syndrome/disease which is commonly known as PCOD (Polycystic Ovarian Disease) (Reid, 2017). Low levels can also increase the estrogen levels in blood leading to a decreased sex drive, weight gain and may cause gallbladder problems (Endocrine Society, 2022).

High levels of progesterone in woman can be naturally seen during pregnancy, but it can also be associated with a condition called the congenital adrenal hyperplasia (CAH) (Hughes 1988). It can also be observed in cases of ovarian cysts, molar pregnancies (non-viable pregnancies), an ovarian cancer subtype, and adrenal cancer (Hughes, 1988). Progesterone in males is used to produce the male hormone testosterone. It helps in building the bone mass, regulate blood sugar, and maintain brain activity. It also assists the process of converting fat to energy and thyroid hormone production.

Males with low levels of progesterone experience symptoms such as decreased sex drive, hair loss, weight gain, depression, gynecomastia, erectile dysfunction, and loss of muscle and bone mass in addition to the aforementioned effects. It can also result in serious conditions like osteoporosis, arthritis, and prostate cancer. High levels of progesterone in males maybe caused due to high dose of pregnenolone supplementation or testicular cancer leading to increase in the estrogen level which causes symptoms like depression, fatigue, and development of cardiovascular conditions.

### 2.4 BIOSYNTHESIS OF TESTOSTERONE

In addition to the small amounts produced by the adrenal glands in both sexes, testosterone is created by the gonads and Leydig cells in the testes and ovaries of men and women. Dihydrotestosterone, an androgen, is routinely created from testosterone to have these effects. In women, testosterone is produced by the adrenal glands and the ovaries. The majority of the

TABLE 3

Normal levels of Progesterone in adult male and female Source: (Seladi-Schulman, 2020)

| **Progesterone** | **Normal Range** |
|---|---|
| **Adult Female** | |
| Pre-ovulation | <0.89 ng/mL |
| During ovulation | $\leq$ 12 ng/mL |
| Post-ovulation | 1.8-24 ng/mL |
| Frist trimester | 11-44 ng/mL |
| Second trimester | 25-83 ng/mL |
| Third trimester | 58-214 ng/mL |
| **Adult Male** | < 0.20 ng/mL |

testosterone produced in the ovary is transformed into estradiol, which is the main hormone used for female sex (Nassar et al., 2020). The pituitary and hypothalamus are key players in controlling the amount of testosterone produced by the testes. Gonadotrophin-releasing hormone from the brain causes the pituitary gland to release luteinizing hormone, which travels through the bloodstream to the gonads and stimulates testosterone production and release (Nedresky & Singh, 2022). Androgens are hormones that are necessary for the development and functioning of the male reproductive organs, one of the most prominent and abundantly found androgen is testosterone. Normal levels of testosterone produced in male and female is provided in table 4. The Leydig cells are present in the testicular interstitium and are the main sources of circulating testosterone (about 95%). Around 6-7mg of testosterone is produced by the testis on a daily basis. Dihydrotestosterone and estradiol can also be produced by further metabolizing testosterone (Schonfeld, 1943). A key regulator of steroidogenesis and Leydig cell cholesterol homeostasis is luteinizing hormone (LH). LH, a dimeric glycoprotein that is a member of the G protein receptor family and has both an alpha and a beta component that have been glycosylated, is bonded together covalently. The primary function of LH is to bind to its receptor in the Leydig cells, increase testosterone production, and release it (Wein, 2013). Androstenedione and di-hydro epi androsterone are the precursors of testosterone. In the presence of the enzymes 17-$\beta$-HSD, they are converted into testosterone and androstenediol respectively. The androstenediol can be converted into testosterone by 3- $\beta$ -HSD (Badawy et al., 2021).

Estrogen can either function antagonistically or synergistically with testosterone to affect its effects. Under the control of the 5 alpha-reductase enzyme found in microsomes, testosterone is converted to DHT in the endoplasmic reticulum. Both of them attach to the same intracellular

androgen receptor, which controls the tissue's gene expression. Testosterone is a steroid from the androstane class which contains a ketone and hydroxyl group at the 3rd and the 17th positions respectively. Chemically, testosterone is 17-beta-hydroxy-4-androstene-3-one(Wein, 2013).

**TABLE 4**

Normal levels of testosterone in adult male and female Source: (Severson, 2018,Patrick,2018)

| Testosterone | Normal Range |
|---|---|
| Adult males | 270-1070 ng/dL |
| Adult females | 15-70 ng/dL |

The hypothalamic-pituitary-gonadal axis is essential for the control of gonadal and testosterone function during puberty. While travelling along the hypothalamohypophyseal portal system, the hypothalamus secretes GnRH, which stimulates the anterior pituitary gland to release LH and follicular-stimulating hormone. The regulation of circulating testosterone takes place through a negative feedback loop where increasing levels of testosterone suppresses the GnRH and affect the anterior pituitary making it less responsive to GnRH.

Through the whole of males' reproductive life, the hypothalamus releases GnRH is pulses of every 1-3 hours. The plasma levels of LH and FSH increases during the beginning of puberty and decreases gradually during the third decade of life. Onset of puberty results in the changes in neuronal input to the hypothalamus and brain activity causing a sudden increase in the GnRH secretion and thereby increasing the testosterone levels (Janes, 2016).

### 2.4.1 *Effects of Xenobiotic Compounds in Production of Testosterone*

Most of the xenobiotic effects studies, particularly those on endocrine disrupters have concentrated on long-term developmental effects on the testis and male reproductive tract, with abnormalities of the reproductive tract and semen quality frequently being degraded. However, a recent study by Adeoya-Osiguwa et al. in 2003 demonstrated that very low concentrations of a number of xenobiotics, all of which were found to be weakly estrogenic, have partial, but biologically highly relevant, acute and direct effects on the function of mature spermatozoa by significantly speeding up the acrosome reaction and capacitation.

The idea that EDC exposure causes to lower semen quality and hence increased male infertility has been supported by rising EDC levels. For instance, over the past 30 years, the use of polybrominated diphenyl ethers (PBDE), dichlorodiphenyltrichloroethane (DDT), and dichlorodiphenylethane (DDE) has increased globally; numerous EDCs, including alkylphenols,

bisphenol A (BPA), triclosan, and pentachlorophenol (PCP), have increased in the environment due to manufacturing and their inclusion in common consumer products (Aneck-Hahn et al., 2006). The reduction in male reproductive function over the recent decades may be caused by both hereditary and environmental causes, according to associations between rising EDC levels and declining male fertility (Rehman et al., 2018).

BPA has been linked to a higher risk of cryptorchidism and worse quality semen (Vilela et al., 2013). Even after treatment, bilateral cryptorchidism is linked to lower paternal fertility rates, worse semen quality, an increased risk of TC, and an increased risk of azoospermia (Virtanen et al., 2007). The advancement of prostate cancer has also been linked to increased BPA exposure. By producing prostatic fluid, the prostate gland plays a critical role in sperm motility (Rehman et al., 2018). (Tarapore et al., 2014). In North America, prostate cancer is considered to be the second most frequent male malignancy (Tarapore et al., 2014). BPA levels have been shown to be greater in individuals with prostate cancer than in persons without the disease.

### 2.4.2 *Varying Levels of Testosterone in Humans and its Effects*

Low levels of testosterone are male is termed as male hypogonadism. This condition is normally seen in men who have crossed the age of 30, where there is a gradual 1% decrease per year in the production of the male steroid hormone (Dudek et al., 2017). The symptoms leading up to the deficiency can be of two types, pre-pubertal and post-pubertal. Small testes (less than 20 mL in volume), a small phallus, fewer secondary sex traits (such as facial or axillary hair), gynecomastia, trouble growing muscle mass, eunuchoid proportions, poor sperm count, and low energy/libido are all signs of pre-pubertal development. Apart from phallus size and eunuchoid proportions, post-pubertal characteristics also include osteoporosis, hot flashes, and severe hypogonadism. LH and FSH plasma levels can be tested with testosterone, low levels with normal setting of FSH and LH is a sign of secondary hypogonadism. Low levels of testosterone with elevated levels of FSH and LH is a sign of primary hypogonadism (Abadilla & Dobs, 2012). Ageing, as testosterone production declines with age, medicines, chemotherapy, diseases of the hypothalamus-pituitary axis, cryptorchidism, orchitis, and hereditary conditions including Klinefelter and Kallmann syndrome are some of the reasons of male hypogonadism. Premature decrease in production can be caused due to any sort of physical injury to the organ itself, internal infection of the testis, presence of tumor on the pituitary gland, certain metabolic disorders like hemochromatosis, alcohol diseases, HIV/AIDS, and many more (Dudek et al., 2017). In Klinefelter's syndrome, there is a dysgenesis of seminiferous tubules and loss of sperm

nursing cells called the Sertoli cells which leads to decreased inhibin levels and increased FSH levels which in-turn increases aromatase levels which elevates the conversion of androgens to estrogens. Kallman syndrome deals with the failure of migration of GnRH-producing neurons leading to the decreased levels of GnRH, which in-turn reduces LH and FSH, testosterone and the sperm count. A deficiency in the enzyme 5-alpha reductase can also cause hypogonadism. It is an enzyme required for the conversion of testosterone to dihydrotestosterone, hence these patients have normal testosterone and LH levels, but have low DHT levels and an increased testosterone-to-DHT ratio (Bhasin et al., 2000).

High levels of testosterone in males is termed as hyperandrogenism. Hyperandrogenic prepubescent boys may exhibit virilization. Penile enlargement, excessive hair growth in androgen-dependent areas, and voice deepening are all signs of virilization. The symptoms in adult males depends on the source of the testosterone, whether it naturally produced by the androgens or if it administered from an exogeneous source. Some males have a genetic predisposition of developing high levels of testosterone. In adults, high levels of testosterone can lead to aggressive behaviour, oil skin, sleep apnea, congenital adrenal hyperplasia, testosterone supplement abuse (Janes, 2016). It can develop from exogenous steroid use, Cushing syndrome, testicular tumours, adrenal virilization/tumors, and adrenal tumours. Impaired testosterone metabolism is caused mainly due to congenital adrenal hyperplasia. Classical CAH cases is caused due to a dramatic increase in the enzyme 17-hydroxyprogesterone which is diverted towards adrenal androgen synthesis and causes hyperandrogenism. Additionally, this disease reduces the hypothalamic sensitivity to progesterone, which causes a rapid increase in GnRH production and consequently higher levels of LH and FSH. The generation of gonadal steroids is boosted when LH and FSH levels are elevated (17-hydroxyprogesterone, DHEA, testosterone, LH, and FSH). The adrenocorticotropic hormone stimulation test, which exhibits an excessive 17-hydroxyprogesterone response, is used to make the diagnosis (Bhasin et al., 2000).

The main cause of low levels of testosterone in females is the natural decline with age. But the hormone levels do not fall after the menopausal period, procedures like hysterectomy, and chemical oophorectomy leads to low levels of testosterone. The symptoms of this condition include reduced libido, irregular menstrual cycle, fertility problems, weight gain, less bone mass and muscle weakness.

Prepubescent girls with high testosterone levels may develop clitoromegaly, acne, and hirsutism. The ovaries produce testosterone in females and high levels in adult females causes acne, voice change, reduced size of breast, excess hair growth, irregular menstrual cycle, infertility, male-pattern baldness, or virilization. The causes of this condition include polycystic ovarian

syndrome (PCOS), ovarian cancer and Cushing syndrome. GnRH secretion is aberrant in PCOS, which causes an increase in LH secretion. LH increases androgen production by ovarian theca cells, which causes hirsutism, masculine escutcheon, acne, and androgenic alopecia in PCOS patients. In ovarian or adrenal tumours, if the testosterone level is elevated and DHEAS level is normal, then it most likely to be an ovarian tumour and the vice-versa condition is an adrenal tumour (Faghfoori et al., 2017).

## 3 CONCLUSION

A largely unknown domain of endocrine toxicology is how xenobiotics might impair steroidogenesis and the processes by which these substances affect the activity of steroidogenic enzymes. This review has demonstrated that chemical groups with substantially diverse structural properties can impair steroidogenesis and have endocrine-disrupting effects. It is obvious that some substances, including the systemically administered antifungal medications and azole fungicides, interact directly with steroidogenesis by acting as powerful inhibitors of steroidogenic enzymes and are known to disturb the endocrine system primarily through this route. Although they are widely known endocrine-disrupting substances that interfere with steroidogenesis to some extent, other families of compounds, for example, the TCDD-like chemicals, exhibit less consistent effects on steroidogenic enzymes and hormone production.

The endocrine system will be affected by a variety of chemicals because they may act as steroid receptor antagonists, agonists, inducers or inhibitors of steroidogenic enzymes, and through other, unexplored mechanisms. As a result, it is to be anticipated that many mechanisms will be at play for many endocrine-disrupting substances, eventually leading to complicated dose-response relationships for a wide range of endocrine parameters. More work has to be put into determining how minor endocrine disturbances in isolated in vitro systems relate to the circumstances in complete organisms. The characterization of the toxicological risk of various endocrine disrupting substances for people and wildlife requires the development of biologically relevant bioassays and the selection of ecologically realistic dosage ranges. Endocrine toxicity research also needs to take larger tissue and species variations in the expression of steroidogenic enzymes into account and conduct more fundamental studies.

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