Impact of Xenoestrogens on Reproductive Health

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Abstract

Xenoestrogens such as phthalates, parabens, bisphenol A, dichlorodiphenyltrichloroethane, and dioxins are compounds found in ordinary substances such as detergents, cosmetics, plastics, pesticides and herbicides (Sonnenschein & Soto, 1998). Estrogen is a vital component in the development of the male and female reproductive system. However, xenoestrogens mimic endogenous estrogenic signaling and exhibit endocrine disrupting properties that may cause long-lasting repercussions on human reproductive health. Xenoestrogen bind to both intracellular and membrane-bound estrogen receptors resulting in an inappropriate activation of tissue-specific estrogenic responses, leading to low sperm count in males and precocious puberty and polycystic ovarian syndrome in females (Shanle & Xu, 2011). Although the pathways of many xenoestrogens mechanism are unknown, the detrimental outcomes on reproductive health are evident.

Impact of Xenoestrogens on Reproductive Health

Introduction

Xenoestrogens are endocrine disrupting chemicals that mimic estrogen in the human body. Exposure to xenoestrogens have far reaching repercussions on human reproductive health. Exposure to endocrine disrupting xenoestrogens alter the homeostasis of the reproductive system. This paper will discuss the predominant mechanisms of endocrine disruptors, the origins of xenoestrogens, the biological effects of xenoestrogens on the human reproductive system, and methods to minimize xenoestrogen exposure. Although a portion of the data incorporated in this paper will be collected from primary research articles with non-human subjects, the chief conclusions of this review will pertain to the human reproductive system (Takeuchi, Tsutsumi, Ikezuki, Takai, & Taketani, 2004).

17β–estradiol (E2) is the chief endogenous estrogen hormone. Estrogens such as E2 are steroid hormones involved in a plethora of biological pathways such as the formation of androstenedione which consequently regulate the physiology of many tissue and organ functions including the development of both male and female reproductive organs. (Yasar, Ayaz, User, Gupur, & Muyan, 2016). The effects of estrogens are mediated through binding to the two estrogen receptors, estrogen receptor α (ERα) and estrogen receptor β (ERβ). Estrogen receptors largely behave as ligand specific transcription factors. Xenoestrogens such as phthalates, bisphenol A (BPA), dioxins, dichlorodiphenyltrichloroethane (DDT), and parabens mimic endogenous estrogen by binding to ERα and ERβ. Like estrogen, xenoestrogens induce both genomic and non-

genomic biological pathways. Repercussions of increased estrogen signaling through the presence of xenoestrogens compounds on human reproductive health include an increased frequency of precocious puberty and polycystic ovarian syndrome in females (PCOS) and decreased sperm count in males.

Background and Significance

Further research regarding the effects of xenoestrogens is crucial due to a direct correlation between the increased exposure to endocrine disrupting chemicals, the declined sperm count in males, and the increased frequency of precocious puberty and PCOS in females. Although general trends of the impact of xenoestrogens on reproductive health are manifest, the understanding of the xenoestrogen mechanism is insufficient (Jeung & Choi, 2010). Although there is a correlation between xenoestrogens and carcinogenesis this will be excluded for purpose of clear focus in this paper.

Origins and Overview of Xenoestrogens

Estrogenic mimicking compounds are found in daily products such as pesticides, industrial chemicals, cleaning products, and cosmetics (Sonnenschein & Soto, 1998). Endocrine disrupting chemicals are defined as environmental and or dietary compounds that interfere with endogenous hormone signaling, metabolism or synthesis (Shanle & Xu, 2011). Xenoestrogens that bind to ERs by exhibiting estrogenic structural similarities behave as endocrine disrupting compounds. Xenoestrogens alter biological functions through the following predominant methods: mimicking endogenous estrogen, disrupting synthesis and metabolism of endogenous estrogen and hormone receptors, and inhibiting the binding of endogenous estrogen (Sonnenschein & Soto, 1998).

Endocrine disrupting chemicals such as phthalate esters are frequently found in plastics, detergents, solid waste disposal sites, and paints. Phthalates were first created in 1920, serving as an alternative plasticizer for camphor. In 1970, phthalates were banned; however, their lasting effects are still prevalent (Wang et al., 2016). Studies have confirmed that phthalates such as dibutyl phthalate, di-2-ethylhexyl phthalate, dimethyl phthalate, monoethyl phthalate, mono-2-ethylhexyl phthalate, mono-benzyl phthalate, and monobutyl phthalate have direct correlation to the decrease in sperm concentration, motility, morphology, and DNA damage in humans (Wang et al., 2016).

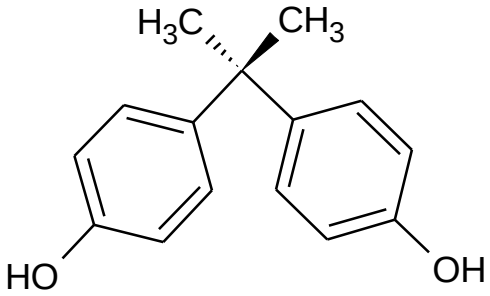
Parabens such as methylparaben, ethylparaben, propylparaben, butylparaben, and isobutylparaben are compounds commonly found in beauty and personal care products such as shampoos, moisturizers, and face makeup. Parabens have anti-fungal and anti-bacterial properties and serve as common preservatives. Parabens were first commercialized in the 1950's and have continued to serve as preservatives in personal care products throughout the years (Scientific American, 2014).

BPA was first synthesized in 1891 by German chemists. In 1950, during the technology revolution, BPA production flourished alongside the growing plastic industry. In 1953, polycarbonate resins from BPA were invented by Dr. Hermann Schnell. Polycarbonate resins revolutionized the world of plastics, serving as a pliable yet durable compound. Polycarbonates served as plastic components of electronic applications, plastic bottles, and linings for metal-based cans. In the 1960's the U.S. Food and Drug Administration (FDA) approved polycarbonate resins for packaging of food (Caliendo, 2012).

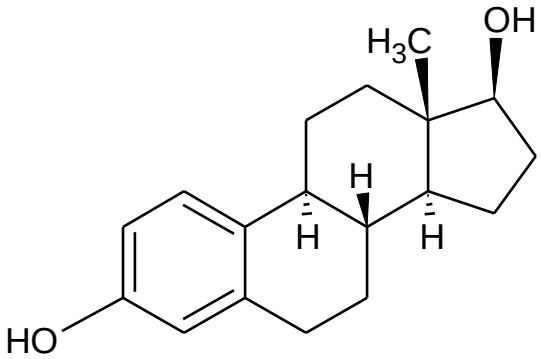
The estrogenic properties of BPA were not discovered until 1992 by Dr. David Feldman. The discovery arose while autoclaving containers formed from polycarbonates synthesized with BPA. The BPA leaching from the containers yielded estrogenic activity (Rissman, 2016).

The structure of BPA provides the ability to bind to both the ERα and ERβ receptor. As shown in Figure 1, the two (4,4')-OH groups on the benzene rings allow BPA to bind to the ER. BPA is classified as an endocrine disrupting compound that binds to membrane-bound estrogen receptor inducing rapid non-genomic estrogenic signaling (Shanle & Xu, 2011). Since its commercialization, BPA serves as a model for xenoestrogen endocrine disrupting compounds. Industrially, BPA has been used as a monomer in the production of epoxy resins and polycarbonates. These compounds are common components of everyday products such as medical and dental devices, plastic water bottles, and thermal paper. Humans can absorb BPA through external or internal exposure. The highest exposure to BPA is attributed to food, resulting in part from plastic irrigation apparatuses (Acconcia, Pallottini, & Marino, 2015).

The estrogen receptor affinity of BPA is notably lower than estradiol as shown in Figure 2. However, the circulating concentrations of BPA can match, or exceed, the circulating concentrations of estradiol. Humans can maintain an average of 1-2 ng/mL of BPA circulating in serum and such concentrations are elevated enough to classify as a biologically active level (Nagel & Bromfield, 2013). Such levels of circulating BPA have been linked to a variety of reproductive-targeted pathologies such as infertility and recurrent pregnancy loss (Acconcia et al., 2015).



Bisphenol A



17 β-estradiol

Figure 1. Chemical structure comparison between 17 β-estradiol and Bisphenol A. The ability of BPA to mimic estradiol derives structural similarities between the two phenol groups of BPA and E2 (Steinmetz, Brown, Allen, Bigsby, & Ben-Jonathan, 1997). BPA surpasses the minimum chemical structural requirements for estrogenic activity of a 4-OH group on the A-phenyl ring and a hydrophobic side group on the 2-position of the propane. The two (4,4')-OH groups on the benzene rings allows BPA to bind to the ER. Adapted from ACD/Structure Elucidator, C40E41, Advanced Chemistry Development, Inc., 2017. Used by permission.

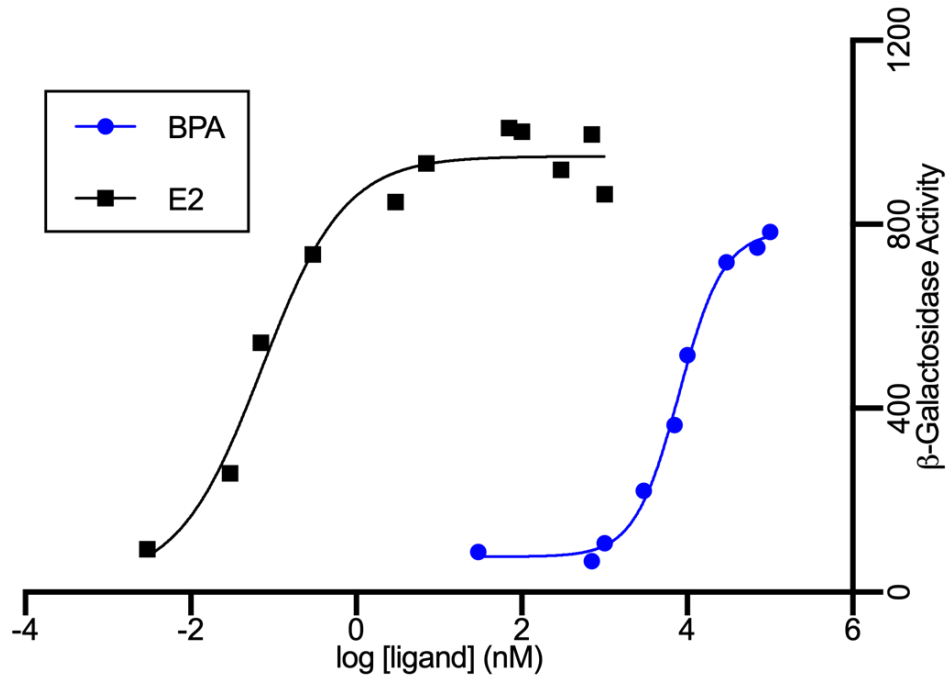


Figure 2. Dose response curve of BPA versus E2. This dose response curve depicts BPA eliciting an estrogenic response at high concentrations. This graph displays the comparable binding trends of BPA to estrogen, supporting the estrogenic properties of BPA. Used by permission from Dr. Cameron Q. Sheeler, Liberty University.

BPA disrupts the endocrine balance in the following three ways: estrogen mimicking, antiandrogen behavior, and steroid hormone synthesis alteration. First, BPA behaves as a xenoestrogen and binds to estrogen receptors causing estrogen-like behaviors. Additionally, BPA behaves as an antiandrogen; blocking the standard action of androgens. Through scientific studies of Acconcia, Pallottini and Marino (2015) evaluating the antiandrogen behavior of BPA through transcriptional activation and androgen receptor redistribution assay, it is known that BPA binds to androgen receptors,

blocking nuclear translocation. BPA binds to androgen receptors in a manner that inhibits the efficient transfer of the androgen receptor into the nucleus. When BPA is present, a higher concentration of androgen receptors is required and or require a longer amount of time for the translocation process to occur. Consequently, in the presence of BPA, androgen receptor translocation is drastically delayed. Lastly, BPA has ability to alter the synthesis of steroid hormones (Acconcia et al., 2015). BPA alters progesterone and estradiol synthesis in vitro and reduces mRNA and protein expression levels of three genes encoding steroidogenesis enzymes.

Dichlorodiphenyltrichloroethane (DDT) was once employed as a pesticide in agricultural communities. DDT was first created in the United States during the 1940's. It quickly dominated the insecticide community due to its ability to combat insect-borne human diseases such as malaria and typhus. In 1972, the use of DDT was banned in the United States due to its adverse environmental effects (United States Environmental Protection Agency, 2017).

DDT functions as an endocrine disrupting chemical through the following two mechanisms: competing with endogenous estrogen for receptor binding sites and stimulating the release of gonadotropin-releasing hormone (GnRH). Both functions cause a notable disturbance to the homeostatic status of the human endocrine system. Due to the stimulation of GnRH release, the presence of DDT can induce premature female puberty. While DDT has not been shown to affect the male puberty process, exposure to DDT post-puberty is linked to low semen quality (Nabi, Muhammad, Khan, & Ali, 2015).

Dioxin behaves as another endocrine disrupting compound. Dioxins were first produced in Germany in the 1800's. In the early 1900's dioxins were widely used in electrical transformer cooling fluids, lubricants, and plastics. Due to the toxic properties of dioxins, the United States Congress banned the use of dioxins in 1978. However, dioxins are deemed a persistent environmental pollutant. Although widespread throughout the environment, dioxins are commonly found in the food chain, specifically the fatty tissue of animals. These harmful chemicals are both byproducts of a variety of industrial processes such as chlorine bleaching and pesticide synthesis as well as natural processes such as forest fires and volcanic eruptions ("Dioxins and Their Effect," 2016). Exposure to low concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin is associated with the premature maturation of the genitals, gonads, and hypothalamic-pituitary axis (Nabi et al., 2015).

Mechanism of Endocrine Disruptors

Xenoestrogens are classified as endocrine disrupting chemicals. The presence of xenoestrogens may cause dysregulation of the estrogen receptor dependent transcriptional pathways resulting in the false induction of tissue-specific estrogenic responses (Ozen & Darcan, 2011). The inappropriate signaling resulting from xenoestrogen-estrogen receptor binding can lead to the overall degradation of reproductive health, consequently altering fertility (Shanle & Xu, 2011).

ERα and ERβ serve as the two subtypes of nuclear estrogen receptors in humans that mediate the effects of normal estrogen signaling in both reproductive and non-reproductive tissue (Shanle & Xu, 2011). Estrogen receptor subtype expressions show

specificity to tissue types. In females, ERα is highly expressed in reproductive tissues such as the ovaries, uterus, and mammary glands. ERβ is minimally expressed in the mammary glands while significantly expressed in the ovaries. In males, ERβ is highly expressed in the prostate, epididymis, and germinal cells (Lecomte, Demay, Ferriere, & Pakdel, 2017).

ERα and ERβ function as ligand-dependent transcriptional factors; however, ERα and ERβ exhibit differing ligand specificities and transcriptional activities (Hess et al., 1997). The function of ERβ and ERα is dependent on cofactor availability and cellular context (Shanle & Xu, 2011).

ERα and ERβ are located respectively on chromosome 6 *ESR1* and chromosome 14 *ESR2* (Rochira et al., 2016). As denoted in Figure 3, ERα is comprised of 595 amino acids and includes eight exons, resulting in a total length of 66kDa proteins. The genomic segment of ERα spans approximately 300kb. ERβ is comprised of eight exons and 530 amino acids, spanning 254kb. The central domain of the estrogen receptors contains a conserved zinc finger DNA-binding domain (Yasar et al., 2016). The ligand-independent transactivation function is located on the N-terminal domain of the estrogen receptor while the ligand-dependent transactivation function is located on the C-terminal domain (Lecomte et al., 2017). The DNA binding domains exhibit a 97% similarity between both ERα and ERβ while the N-terminal and C-terminal exhibits a 17% and 56% similarity, respectively (Yasar et al., 2016).

Xenoestrogens with endocrine disrupting activities must bind to intracellular or membrane-bound estrogen receptors, activating a hormonal transduction system

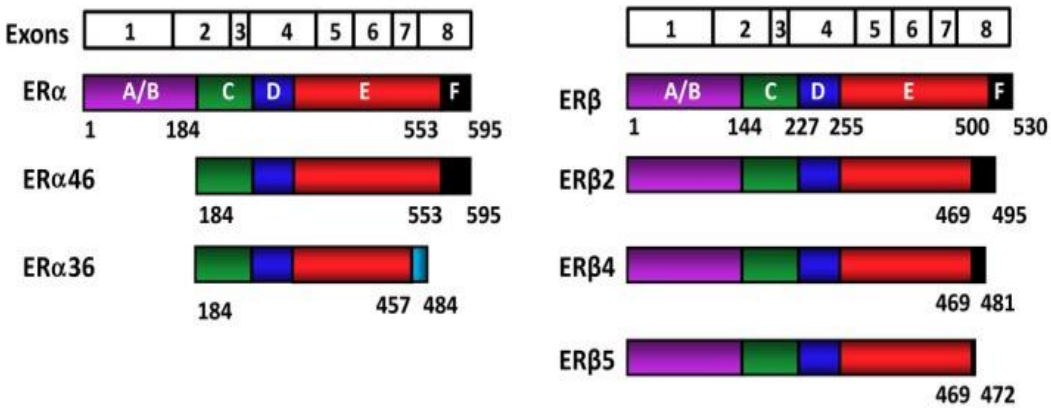


Figure 3. ERα and ERβ are composed of 595 and 530 amino acids, respectively. Both ERα and ERβ are comprised of 8 exons. The N-terminal of ERα and ERβ share an amino acid similarity of 17% while the DNA binding region of central C exhibit a shared identity of 97% of amino acids. Upon binding of E2, ERα and ERβ dimerizes which causes a conformational change resulting in a functionally active estrogen receptor. Adapted from "Molecular mechanism of estrogen-estrogen receptor signaling." By P. Yasar, G. Ayaz, S. D. User, G. Gupur, and M. Muyan, 2017, *Reproductive Medicine and Biology, 16,* p. 5. Copyright 2016 by Reproductive Medicine and Biology. Used by permission.

(Welshons et al., 2003). Typically, xenoestrogens bind to intracellular estrogen receptors acting on the genomic level. However, ER targeting xenoestrogens exhibit the potential to alter both genomic and non-genomic estrogen receptor activity. Genomic altering xenoestrogens include phytoestrogens, bisphenols, and organochlorine pesticides (Shanle & Xu, 2011).

As shown in Figures 4 and 5, genomic signaling results from ligands binding to intracellular ER causing dimerization. Sequentially, ER dimers coupled with other transcriptional factors directly bind to DNA, initiating a genomic transcription. The intracellular ligand-dependent receptor process is contrasted with the non-genomic process. The non-genomic process results from a ligand binding to membrane-bound ERs, triggering a cellular cascade (Nadal et al., 2000). When ligands bind to membrane bound ERs a rapid response to estrogenic exposure occurs (Shanle & Xu, 2011). As depicted in Figure 5, the activity of membrane bound ERs is mediated through a G-protein coupled receptor. This G-coupled protein receptor, known as GPR30, activates MAPK or P13 kinase signaling cascade.

Another method of endocrine disrupting chemicals is through binding site competition. Ligands bind to receptor sites through the amino acid side groups that provide hydrophilic interactions or hydrogen bonding between ligand and receptor. ERα and ERβ contain large binding sites which allow the binding of a variety of small molecules. The presence of high concentrations of endocrine disrupting chemicals with affinity for ERα and ERβ ligand binding sites minimizes the chance of the proper binding of endogenous estrogen. An inappropriate activation of estrogen receptors results through the binding of endocrine disrupting chemicals such as BPA (Shanle & Xu, 2011).

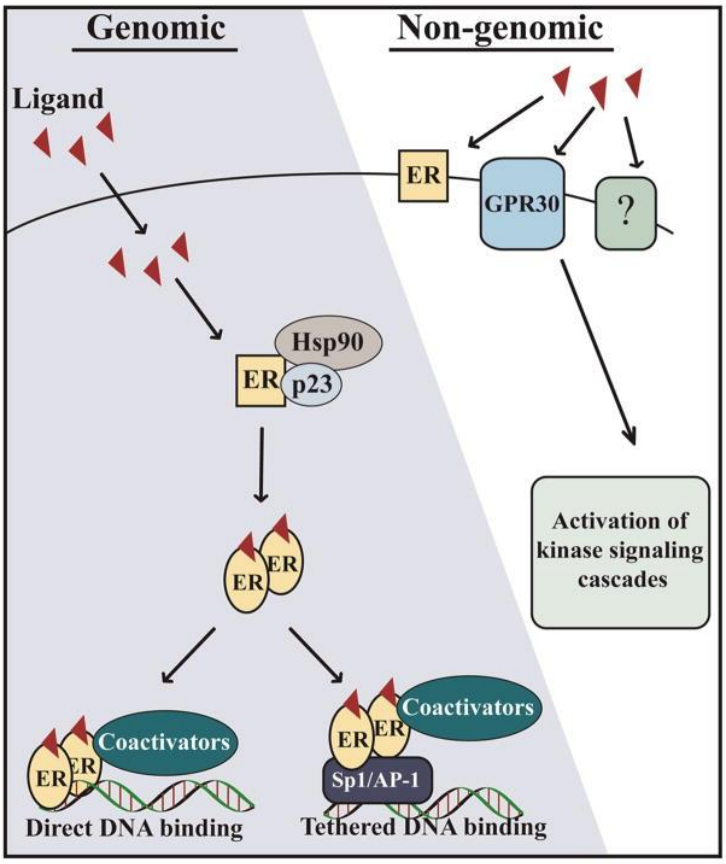


Figure 4. Genomic versus non-genomic estrogen receptor signaling pathway. Genomic signaling occurs when ligands, including xenoestrogens, diffuse across the cellular phospholipid bilayer binding directly to the intracellular ER causing ER dimerization. Dimerized ERs bind directly to the estrogen response element. Non-genomic signaling occurs when ligands bind membrane-bound estrogen receptors resulting in activation of kinase signaling cascade. Adapted from "Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action." By E. K. Shanle, and W. Xu, 2011, *Chemical Research in Toxicology, 14,* p. 27. Used by permission.

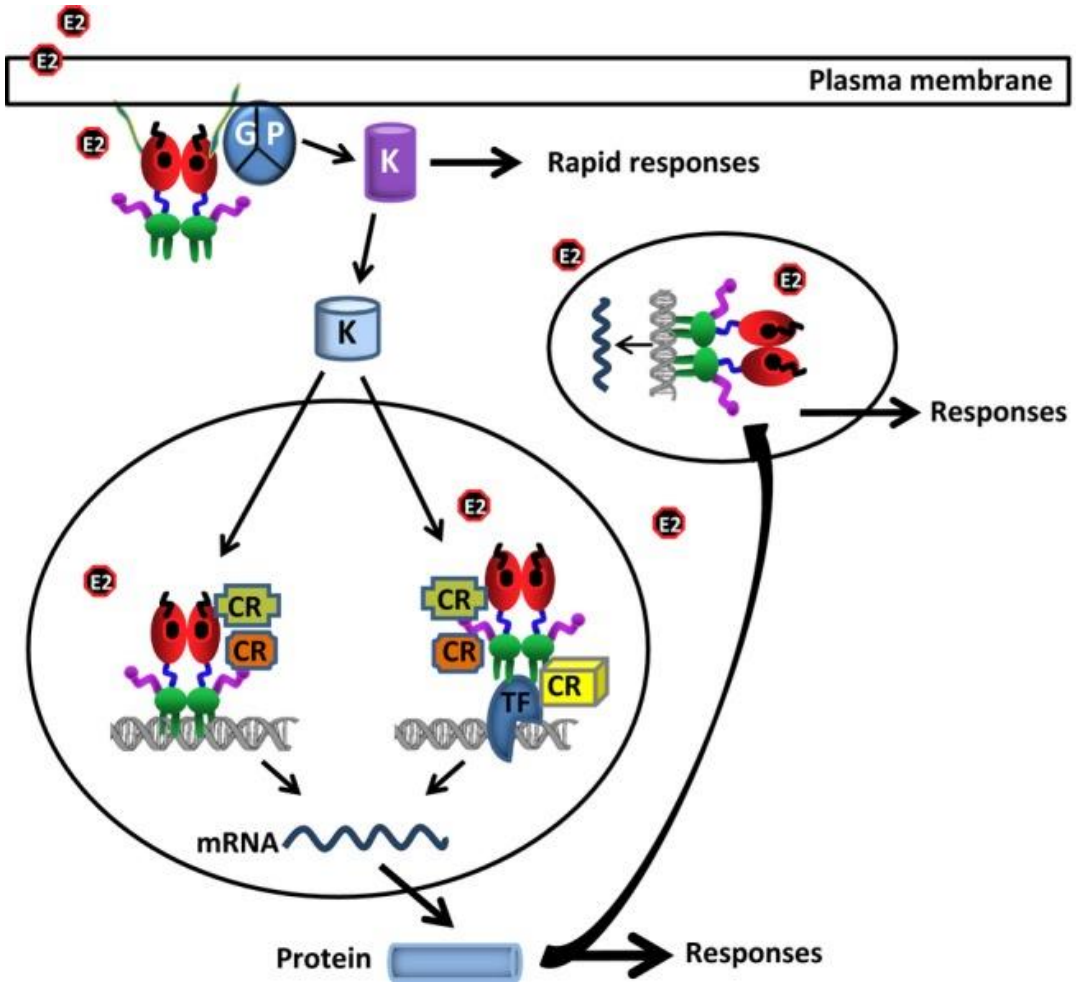


Figure 5. Integrated model of the activation of the kinase cascade leading to the cellular response. The ER bound with E2 interacts with the G protein that activates kinases. The kinases then phosphorylate regulatory proteins and transcriptional proteins leading to alterations in gene expression. Adapted from "Molecular mechanism of estrogen-estrogen receptor signaling." By P. Yasar, G. Ayaz, S. D. User, G. Gupur, and M. Muyan, 2017, *Reproductive Medicine and Biology, 16,* p. 9. Copyright 2016 by Reproductive Medicine and Biology. Used by permission.

Function of Endogenous Estrogen in the Female Reproductive System

Estrogen is an endogenous hormone that is vital in both males and females. Estrogen regulates the development of secondary sexual characteristics such as the regulation of menstrual cycle, stimulation of endometrium growth, and breast development. In males, estrogen functions as a component in sperm maturation. Estrogen serves as a feminizing factor during fetal development.

In female humans, endogenous estrogen is chiefly produced in the ovaries, placenta, and adrenal glands. Through the action of androgenase, androgen, the estrogen precursor, is converted to estrogen. The ovaries serve as the main site of estrogen synthesis due to their high content of aromatase (Knudtson & McLaughlin, n.d.).

Estrogen is a primary regulator in the growth and development of the mammary glands, vagina, fallopian tubes, uterus, egg follicle, and endometrial lining. Estrogen circulates the bloodstream, targeting organs such as the breasts, vagina, and uterus. As shown in Figure 6, puberty is initiated through the elevation of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. This occurs as a result of the release of GnRH by the hypothalamus. The increased release of GnRH results in LH and FSH secretion. These high levels of LH and FSH promote the production of estrogen. Elevated estrogen levels then result in the development of secondary sexual characteristics (Knudtson & McLaughlin, n.d.)

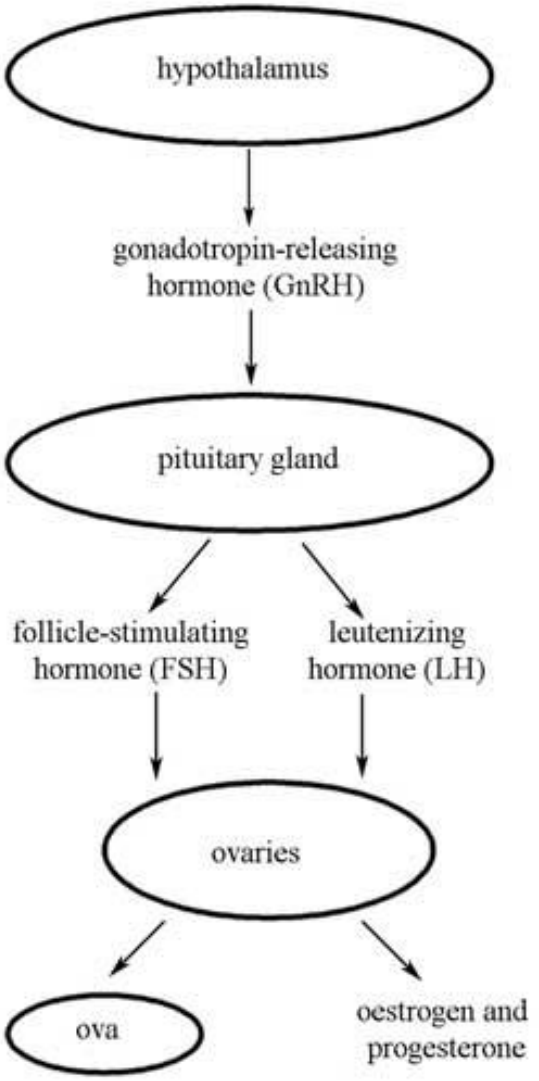


Figure 6. Endocrinology of female reproductive system development. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) which regulates the release of the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. The ovaries are stimulated by LH and FSH and estrogen is synthesized. Adapted from, "Hormonal Regulation of the Female Reproductive System." 2017. *Open University.* Used by permission.

Effects of Xenoestrogens on the Female Reproductive System

Estrogen stimulates the generation of secondary female sexual characteristics such as endometrial growth, menstrual cycle regulation, and breast development. Puberty is characterized by the maturation of the hypothalamic pituitary gonadal axis in addition to the development of secondary sexual features. The age at which puberty occurs in females is growing progressively younger (Ozen & Darcan, 2001). Negative health implications such as a predisposition to polycystic ovarian syndrome arises from precocious puberty. The onset of puberty is regulated by the endocrine system and exposure to xenoestrogens may have a dysregulating impact upon the hypothalamic-pituitary-gonadal system (Massart et al., 2006).

Endocrine disruptors such as phytoestrogens and phthalates have been identified as possible environmental factors influencing the onset of female puberty (Nabi et al., 2015). Xenoestrogens directly influence the gonadotropin-releasing hormone resulting in an increased endogenous estrogen production. Studies show that some xenoestrogens cause premature puberty due to an activation of increased GnRH production. The release of the GnRH from the hypothalamus causes the secretion of the follicle stimulating hormone and luteinizing hormone which cause the progression of puberty. The modification of normal GnRH release through the interference with xenoestrogens directly impacts the progress of puberty (Ozen & Darcan, 2011).

These endocrine disrupting chemicals exert their estrogenic characteristics through direct binding to intracellular or extracellular estrogen receptors or increasing aromatase activity. Aromatase is an enzyme catalyst that increases the conversion of

testosterone into estrogen. These behaviors increase the total amount of estrogen-behaving compounds present (Ozen & Darcan, 2011).

The female gonad exhibits heightened sensitivity to exposure to BPA. Endocrine disrupting compounds such as BPA interfere with ovarian morphology, steroidogenesis, and folliculogenesis. BPA, commonly found in ovarian follicular fluid, exhibits a stimulatory role in ovarian theca-interstitial cells. These cells are responsible for the production of androgens through the direct regulation of 17β-hydroxylase. This hydroxylase is a vital enzyme in androgen synthesis. Consequently, the presence of BPA stimulates the production of androgen synthesis. Heightened androgen synthesis is a characteristic of polycystic ovarian syndrome (Barrett & Sobolewski, 2014).

There is a strong correlation between polycystic ovarian syndrome (PCOS) and BPA exposure. PCOS is defined by anovulation and hyperandrogenemia (Barrett & Sobolewski, 2014). PCOS is responsible for 80% of anovulatory infertility cases (Melo, Ferriani & Navarro, 2015). Scientific studies evaluating the BPA-serum levels of women suffering from PCOS exhibited high levels of BPA compared to non-hyperandrogenemia women (Takeuchi et al., 2004).

Effects of Estrogen on Male Reproductive Development

While testosterone serves as the hormone responsible for the development of secondary male sexual characteristics, estrogen is a vital component of sperm maturation and vitality. Blood-estrogen concentration in males is low; however, estrogen content in semen and rete teste fluid is extraordinarily high, reaching up to 250 pg ml^{-1} (Ruz et al., 2006). The two primary estrogen receptors, ERβ and ERα, are present in the testes

(Joseph et al., 2011). ERβ is expressed in fetal testes, suggesting a role of estrogen in the maturation of testes (Rochira et al., 2016). Secondly, ERα is expressed in the efferent ductules regulating fluid reabsorption (Joseph et al., 2011).

Appropriate fluid regulation is an essential component in the male reproductive system. The efferent ductules located in the testes serve as the primary site of fluid reabsorption. ERα serves as a fluid reabsorption regulator in the efferent ductules. Fluid regulation includes the dictation of ion transport and water reabsorption (Joseph et al., 2011).

Effects of Xenoestrogens on the Male Reproductive System

The detrimental effect of xenoestrogens on the male reproductive system is chiefly via the manifestation of embryonic exposure to xenoestrogens. Such exposures impact specific structures of the male reproductive system; ultimately, negatively influencing future fertility (Rochira et al., 2016). Sperm counts in Western countries have declined 50% since 1966. Sperm counts are also reported to have decreased from 113 million/mL to 66.5 million/mL from 1940 to 1990 (Giwercman, Carlsen, Keiding, & Skakkebaek, 1993). This trend in decreasing sperm count has been partially credited to the increase of endocrine disrupting xenoestrogens (Wang et al., 2016).

The impact of xenoestrogens on male fertility was first observed in wild animals including fish, amphibians, mammals, reptiles, and birds that had exposure to estrogenic chemicals in their natural environment. Alterations in male reproductive habits and the general feminization in reproductive behavior have been noted in such wild animals (Delbes, Levacher, & Habert, 2006).

Neonatal tests have proven to be highly sensitive to xenoestrogens. High exposure to xenoestrogens correlates with the inactivation of ERα and ERβ (Delbes et al., 2006). Inactivation of ERα and ERβ poses a serious threat to male fertility. Decreased fluid reabsorption results in a backflow of fluid from the efferent ductules into the testes; causing decreased sperm concentration and motility (Ruz et al., 2006). In addition to the backflow of fluid into the testes, disruption of fluid levels results in diluted sperm entering the epididymis decreasing sperm count in semen and ultimately decreasing fertility (Hess et al., 1997). The ERα role in fluid reabsorption has been tested through mice with an ERα knockout gene. Mice deficient of the estrogen receptor ERα were sterile due to the elevated fluid retention in the efferent ductules (Hess et al., 1997).

The absence, or diminished, levels of ERα are also linked to long-term teste atrophy. Decreased fluid reabsorption stems from the lack of an epithelial cell component responsible for the uptake of fluids. Such structures are the endocytic vesicles and PAS+ lysosomal granules of the epithelial cell. The backpressure resulting from luminal fluids causes long-term atrophy of the testes (Hess et al., 1997).

Minimizing Xenoestrogen Exposure

The presence of endocrine disrupting chemicals in everyday household products should not be minimized or dismissed. Xenoestrogens such as phthalates, BPA, and parabens are found in perfumes, plastic containers, and cosmetics, respectively. Measures can be taken to minimize the presence of xenoestrogen in one's environment. Plastic containers such as reusable plastic water bottles and food storage containers commonly contain BPA products. Reheating food in plastic containers allows for heightened

amounts of xenoestrogens to leach out and penetrate food. Avoiding consuming products stored in plastics can be accomplished through drinking water from stainless steel water bottles and alternatively using glass containers as a replacement for plasticware.

Cosmetic products and perfumes commonly contain endocrine disrupting compounds such as phthalates. Phthalates can be found in personal care products items including soaps, perfumes, nail polish removal, diaper cream, wet wipes, face paint, baby powder, glitter gel, and baby oil (U.S. Food & Drug Administration [FDA], 2013). The most predominant phthalate compounds historically found in personal care products are dibutylpthalate, dimethlpthalate, and diethylphthalate. Today, diethylphthalate is the primary phthalate still found in cosmetics (FDA, 2013). Exposure to phthalates can be accomplished through the following mechanisms: ingestion, inhalation, integumentary absorption, and intravenous injection. Industries use phthalates for solvent and fixative properties of the compounds (Al-Saleh & Elkhatib, 2016). The FDA (2013) advises the primary method of avoiding phthalates exposure from personal care products is to consciously seek and buy non-phthalate containing products.

Parabens are compounds found in a wide variety of cosmetics such as shampoos, moisturizers, shaving products, and deodorants. Parabens serve as anti-bacterial compounds that prevent unwanted bacterial presence in personal care products. Despite the beneficial presence of parabens regarding limiting bacterial growth, parabens exhibit endocrine disrupting qualities. Exposure to parabens through personal care products can be circumvented by prudently reading product labels. If a product contains parabens, the

ingredient list would contain compound names such as methylparaben, propylparaben, butylparaben, or ethylparaben (FDA, 2018).

Conclusion

Xenoestrogens are endocrine disrupting chemicals that mimic endogenous estrogen in the human body. Chemicals such as PBA, parabens, phthalates, dioxins, and dichlorodiphenyltrichloroethane are compounds found in pesticides, plastic containers, and personal care products (Sonnenschein & Soto, 1998). Through mimicking estrogen, xenoestrogens inappropriately trigger estrogen receptors. Xenoestrogens exhibit the capabilities to trigger both genomic and non-genomic pathways through binding to intracellular estrogen receptors and membrane-bound receptors, respectively.

Xenoestrogens alter biological functions through mimicking endogenous estrogens, disrupting synthesis and metabolism of endogenous estrogen and hormone receptors, and inhibiting the binding of endogenous estrogen (Sonnenschein & Soto, 1998). Exposure to such compounds have far reaching repercussions on human reproductive health such as decreased sperm count, precocious puberty, and polycystic ovarian syndrome. Xenoestrogen exposure can be minimized through implementing lifestyle changes such as avoiding heating food in reusable plasticware and switching to paraben-free health and beauty products.

References

Acconcia, F., Pallottini, V., & Marino, M. (2015). Molecular mechanisms and action of BPA. *Dose Response, 13*(4), 1-9. doi: 10.1177/1559325815610582

ACD/Structure Elucidator, C40E41, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2017

Al-Saleh, I., & Elkhatib, R. (2016). Screening of phthalate esters in 47 branded perfumes. *Environmental Sciences and Pollution Research, 23*(1), 455-468. doi: 10.1007/s11356-015-5267-z.

Barrett, E. S., & Sobolewski, M. (2014). Polycystic ovary syndrome: do endocrine disrupting chemicals play a role? *Seminars in Reproductive Medicine, 32*(3), 166-176. doi: 10.1055/s-0034-1371088

Caliendo, H. (2012). History of BPA. Retrieved from https://www.packagingdigest.com/food-safety/history-bpa

Doss Response Curve of BPA versus E2. Used with permission from Dr. Cameron Q. Sheeler, Liberty University, 2019.

Delbes, G., Levacher, C., & Habert, R. (2006). Estrogen effects on fetal and neonatal testicular development. *Society for Reproduction and Fertility, 132*(4), 527-538. doi: https://doi.org/10.1530/rep.1,01231

Dioxins and their effect on human health (2016). *World Health Organization.* Retrieved from https://www.who.int/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health

Giwercman, A., Carlsen, E., Keiding, N., & Skakkebaek, N. (1993). Evidence for increasing incidence of abnormalities of the human testis: a review. *Environmental Health Perspectives, 101*(2), 65-71. Retrieved from https://ehp.niehs.nih.gov/cms/attachment/14d7f1d7-64e4-4da2-90b1-0eeb81573936/ehp.93101s265.pdf

Green, J. M., Langue, A., Scott, A., Tznadel, M., Wai, H. A., Takesono, A., … Tyler, C. R. (2018). Early life exposure to ethinylestradiol enhances subsequent responses to environmental estrogens measured in a novel transgenic zebrafish. *Scientific Report, 8*(2699). Retrieved from https://www.nature.com/articles/s41598-018-20922-z

Hormonal regulation of the female reproductive system (2017). *Open University.* Retrieved from https://www.open.edu/openlearncreate/mod/oucontent/view.php?id=34&printable=1&extra=thumbnailfigure_idm1329008

Hess, R., Bunick, D., Lee, K., Bahr, J., Taylor, J., Korach, K., & Lubahn, B. (1997). A role for oestrogens in the male reproductive system. *Nature, 390*(6659). 506-512. doi: 10.1038/37352

Jeung B., & Choi, K. (2010). Toxicological mechanism of endocrine disrupting chemicals: is estrogen receptor involved? *Toxicological Research, 26*(4), 237-243. doi: 10.5487/TR.2010.26.4.237

Joseph, A., Shur, B., & Hess, R. (2011). Estrogen, Efferent Ductules, and the Epididymis. *Biology of Reproduction, 84*(4), 207-217. doi: 10.1095/biolreprod.110.087353

Knudtson, J., & McLaughlin, J. (n.d.). Female reproductive endocrinology. *Merck Manual.* Retrieved from https://www.merckmanuals.com/professional/gynecology-andobstetrics/female-reproductive-endocrinology/female-reproductive-endocrinology

Lecomte, S., Demay, F., Ferriere, F., & Pakdel, F. (2017). Phytochemicals targeting estrogen receptors: beneficial rather than adverse effects? *International Journal of Molecular Sciences, 18*(7). doi: 10.3390/ijms18071381.

Lee, H., Jeung, E., Cho, M., Kim, T., Leung, P. C., & Choi, K. (2013). Molecular mechanism(s) of endocrine-disrupting chemicals and their potent oestrogenicity in diverse cells and tissues that express oestrogen receptors. *Journal of Cellular and Molecular Medicine, 17*(1), 1-11. Retrieved from 10.1111/j.1582-4934.2012.01649.x

Massart, F., Parrino, R., Seppia, P., Frederico, G., & Saggese, G. (2006). How do environmental estrogen disruptors induce precocious puberty? *Edizioni Minerva Medica, 58*(3), 247-254. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16832329

Melo, A. S., Ferriani, R. A., & Navarro, P. A. (2015). Treatment of infertility in women with polycystic ovary syndrome: approach to clinic practice. *Clinics 70*(11), 765-769. doi: 10.6061/clinics/2015(11)09

Nabi, G., Muhammad, H., Khan, A., & Ali, S. (2015). Environmental pollutants can cause precocious puberty. *Journal of Zoology, 10*(2), 130-135. doi: 10.5829/idosi.wjz.2015.10.2.94111

Nadal, A., Ropero, A., Laribi, O., Maillet, M., Fuentes, E., & Soria, B. (2000). Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor α and estrogen receptor β. *Proceedings of the National Academy of Sciences of the United States of America, 97*(21), 11603-11608. doi:10.1073/pnas.97.21.11603

Nagel, S., & Bromfield, J. (2013) Bisphenol A: a model of endocrine disrupting chemical with a new potential mechanism of action. *Endocrinology Society, 154*(6), 1962-1964. doi: 10.1210/en.2013-1370

Ozen, S., & Darcan, S. (2001). Effects of environmental endocrine disruptors on pubertal development. *Journal of Clinical Research in Pediatric Endocrinology, 3*(1), 1-6. doi: 10.4274/jcrpe.v3i1.01

Rissman, E. F. (2016). The endocrine society centennial: no longer a surprise: estrogen chemicals in a multitude of places. *Endocrinology, 157*(8). doi: https://doi.org/10.1210/en.2016-1445

Rochira, V., Madeo, B., Diazzi, C., Zirilli, L., Daniele, S., & Carani, C. (2016). *Estrogens and male reproduction*. South Dartmouth, MA: Endotext

Ruz, R., Gregory, M., Smith, C., Cyr, D., Lubahn, D., Hess, R., & Hermo, L. (2006). Expression of aquaporins in the efferent ductules, sperm counts, and sperm motility in estrogen receptor-α deficient mice fed lab chow versus casein. *Molecular Reproduction and Development, 73*(2), 226-237. doi: 10.1002/mrd.20390

Scientific American. (2014). Should people be concerned about parabens in beauty products? Retrieved from https://www.scientificamerican.com/article/should-people-be-concerned-about-parabens-in-beauty-products/

Shanle, E., & Xu, W. (2011). Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanism of action. *Chemical Research in Toxicology, 24*(1), 6-19. doi: 10.1021/tx100231n

Sonnenschein, C., & Soto, A. (1998). An updated review of environmental estrogens and androgen mimics and antagonists. *The Journal of Steroid Biochemistry and Molecular Biology, 65*(1-6), 143-150. doi: https://doi.org/10.1016/S0960-0760(98)00027-2

Steinmetz, R., Brown, N. G., Allen, D. L., Bigsby, R. M., & Ben-Jonathan, N. (1997). The environmental estrogen Bisphenol A stimulates prolactin release in vitro and in vivo 1. *Endocrinology, 185*(5), 1780-1786. doi: 10.1210/en.138.5.1780

Takeuchi, T., Tsutsumi, O., Ikezuki, Y., Takai, Y., & Taketani, Y. (2004). Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. *Endocrine Journal, 51*(2), 165-169. doi: https://doi.org/10.1507/endocrj.51.165

U.S. Food & Drug Administration. (2013). *Phthalates.* Retrieved from http://wayback.archiveit.org/7993/20170110234455/http://www.fda.gov/AboutFDA/Transparency/Basics/ucm2 62353.htm

U.S. Food & Drug Administration. (2018). *Parabens in Cosmetics.* Retrieved from https://www.fda.gov/cosmetics/cosmetic-ingredients/parabens-cosmetics#products

United States Environmental Protection Agency. (2017). *DDT-a brief history and status.* Retrieved from https://www.epa.gov/ingredients-used-pesticide-products/ddt-brief-history-and-status

Wang, C., Yang, L., Wang, S., Zhang, Z., Yu, Y., Wang, M., … Wang, S. (2016). The classic EDCs, phthalate esters and organochlorines, in relation to abnormal sperm quality: a systematic review with meta-analysis. *Scientific Reports, 6,* 19982. doi: 10.1038/srep19982

Welshons, W.V., Thayer, K. A., Judy, B. M., Taylor, J. A., Curran, E. M., & vom Saal, F. S. (2003). Large effects from small exposures. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. *Environmental Health Perspectives, 111*(8), 994-1006. doi: 10.1289/ehp.5494

Yasar, P., Ayaz, G., User, S. D., Gupur, G., & Muyan, M. (2016). Molecular mechanism of estrogen-estrogen receptor signaling. *Reproductive Medicine and Biology, 16*(1), 4-20. doi: 10.1002/rmb2.1200 10.1002/rmb2.120066.