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A META-ANALYSIS OF BISPHENOL A'S DEVELOPMENTAL EFFECTS ON THE FEMALE REPRODUCTIVE SYSTEM

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ABSTRACT

Bisphenol A (BPA), a monomer that is polymerized to manufacture polycarbonate plastic products and resins that are used in every day products, has raised alarm in the public health community. Research has shown that BPA may cause detrimental developmental effects in the female reproductive system. This review examines the current literature and presents the effects of BPA in rodent models. The wealth of data shows that there is convincing evidence that BPA acts as an estrogen-disrupting compound by binding to the estrogen receptor (ERα and ERβ) in different tissues in the female reproductive tract. Most often this results in disruption of the neuroendocrine axis, which de-synchronizes the production of hormones and steroids that are essential for normal reproductive function. The de-regulation of the neuroendocrine axis causes degradation of the genetic quality of gametes, deprivation of healthy and mature antral follicles, acceleration of the onset of puberty, and morphological changes to the reproductive tissues resulting in cancers and low fecundity/fertility. It is of vital importance to elucidate the harms of small dose and persistent exposure to this pervasive chemical in our environment. Public health practitioners must work to reduce the amount of BPA circulating in the environment to ensure that the current population, as well as future generations, does not exhibit adverse reproductive alterations.

INTRODUCTION

In recent decades, there has been an increased usage of bisphenol A (BPA) globally. BPA is a monomer polymerized to manufacture polycarbonate plastic products and resins, a component of many consumer products.[1] In 2015, the worldwide population will consume beyond 5.4 million tons of BPA[2], with a constant 6-10% growth in demand each year1; the United States is the only non-Pacific Asian country to head the list of the top 5 BPA producers worldwide.[2] A brief, minute exposure to BPA can produce long-term trans-generational effects. This literature review will expand on the mechanisms and effects BPA causes on the development of the female reproductive system.

Physical and Chemical Properties

BPA (2,2-(4,4-dihydroxydiphenol) propane) is an organic monomer composed of two phenol rings connected by a methylated bridge.[3] The monomers are polymerized through ester linkages to create plastic products. Heat and either acidic or basic conditions can accelerate the hydrolysis of the ester bond, resulting in the release of monomers into the environment.[1]

Endocrine Disruption

There is extensive evidence that BPA acts as an endocrine-disrupting chemical. The presence of the phenol rings in the BPA monomer is structurally analogous to endogenous estrogen. As such, BPA acts as a selective-estrogen receptor modulator (SERM), and functions as an agonist or antagonist depending on the estrogen receptor it binds on a specific tissue.[1] *In vitro* assays establish that BPA is a considered a "weak estrogen," with a 10,000-fold lower binding affinity to the estrogen receptor (ERα and ERβ) than that of estradiol. BPA exposure *in vivo* shows that the estrogenic effects of BPA are much more amplified.[4]

In most instances, BPA exerts its effects by modulating the estrogen receptor mRNA expression and activity. Following BPA exposure, estrogen receptor-alpha (ERα) and -beta (ERβ) protein expression levels increase in the medial basal hypothalamus of female rats.[4,5] The hypothalamus is a critical component of the neuroendocrine axis, and helps mediate feedback and levels of endogenous estrogen expression. This feedback mechanism may not be fully mature in the developing young.[6] Thus, an increase in ERα and ERβ can cause a difference in hormone pulse frequency. This de-synchronization triggers a delay in the onset of puberty and subsequent estrous/menstruation cycles.[7,8]

In addition to increasing the number of receptors on the surface of the epithelium, BPA causes disruptions in how the ER receptors dimerize and interact with transcription factors. ERα is specifically up-regulated in the uterine epithelium, and induces epithelial morphogenesis, cyto-differentiation, and secretory activity. ERβ is found in the uterine epithelium; however, in the presence of BPA, it modulates the effects of ERα, and tends to favor anti-proliferation. Thus, ERβ represses ERα transcriptional activity by forming a heterodimer with ERα to block its activity. RT-PCR analysis of uterine tissue following prenatal BPA exposure has shown that BPA down-regulates ERβ. The absence of ERβ in the tissues provides the opportunity for ERα to prompt proliferation of the uterine epithelia.[9] Over-proliferation leads to an array of morphologies that will be discussed later. RT-PCR further establishes that BPA varies the mRNA expression of the transcription factors involved in nuclear estrogen-dependent signaling. When rodents are exposed to 2 μg/(kg day) of BPA *in utero*, there is a reduction in the retinoic acid receptor alpha (RAR) and retinoid receptor alpha (RXR) mRNA expression in the gonads of female embryos. Dimerization of these transcription factors plays a crucial role in the growth of embryos. The reduction in the transcription factors causes toxic effects during embryogenesis that can continue throughout the life of the offspring.[10]

In addition to modulating the estrogen receptors, BPA also influences enzyme activity and the metabolism of hormones in regions that require sex steroid hormone production.[1] BPA exposure decreases steroidogenesis by reducing the expression of important enzymes, like StAR, 3β-HSD, and Cyp17α, which are all involved in sex steroidogenesis in theca and granulosa cells. The decline of these enzymes results in the reduction of steroid production by granulosa cells. This causes disruptions in the communication between theca and granulosa cells, inhibiting the follicles ability to mature to an antral state. Thus, it cannot ovulate and release the oocyte.[11] Microscopic analysis of BPA-exposed granulosa cells show that they display a degenerated morphology as indicated by their dark and rounded up appearance. This demented structure can prevent the adequate communication between the cells during ovulation.[12]

Non-monotonic Dose-Response Relationship

Typically, toxicology tests assume a monotonic relationship. However, BPA, and many hormones, adopt a non-monotonic relationship that does not follow a linear dose response. For instance, estradiol follows an inverted U-shape dose-response curve. At low and high levels, the effects of estradiol are down-regulated. However, at intermediate levels, the true effects of estradiol are observed.[13] To exemplify a similar non-monotonic response in BPA, murine pups were treated with either 1 nM or 100 μM of BPA during the pre-implantation period. These extreme dosages gave the most drastic changes in birth weight. Body weight increased 39% with 1 nM BPA exposure and 34% with

100 µM BPA exposure, when compared to the intermediate dosages.[14] In another study, the pups that were exposed to 0.1 mg/(kg/day) BPA or 1.2 mg/(kg/day) BPA both experienced an increase in body weight compared to control females. However, by post-natal day 87, the low-dose BPA females retained higher body weights than both the control and high-dose females. This indicates that even a low-dose of BPA exposure can expound greater effects to offspring than high, persistent exposure. Although the low-dose BPA-exposed animals experience greater body weights, the high-dose BPA-exposed animals experienced abnormal vaginal cytology and defects in the pattern of estrus cyclicity.[15] Thus, timing of exposure and dosage can have different effects on distinct regions or functions of the reproductive system.

Pregnant mice injected with 2 µg/(kg/day) or 20 µg/(kg/day) of BPA experienced pubertal onset, measured by vaginal opening, at an earlier time point when compared to the control females. Further, the body weight at vaginal opening was lower in all exposed females compared to the control females. This reveals that even the lowest doses of BPA exposure can result in abnormal development.[16] Vaginal and uterine morphological changes occurred following exposure to 0.1 mg/(kg/day) BPA or 50 mg/(kg/day) BPA. The thickness of the total epithelia was reduced following exposure to 0.1 mg/(kg/day) BPA when compared to the control group. The 50 mg/(kg/day) BPA dose also showed a reduction in the epithelial thickness. However, it was much less pronounced than the rodents exposed to less BPA.[17] Thus, reduced usage of BPA may not be enough; only its complete eradication may yield significant health changes.

While BPA typically follows a U-shaped dose response, several experiments have noticed other non-monotonic dose response curves depending on the dose, the animal, and the age at which the animal was exposed to BPA. Conclusively, this review will elucidate that exposure to BPA will exert the most extreme damage to the reproductive system in a non-monotonic manner.

Prevalence and Seriousness in Fetal Development

Though BPA has been found to affect both men and women at every stage of life, the most vulnerable stage is during fetal development because rapid and crucial modeling of the reproductive system (and other organ systems) occurs. When female mice are exposed to BPA during their pregnancy, appreciable levels of BPA in the fetus and amniotic fluid are observed. These fetal concentrations are higher than the levels observed in the maternal serum. This reveals that BPA crosses the placenta and reaches fetal organs where it maintains an enhanced bioavailability.[18] Normally, unexposed fetuses express fetal α-fetoprotein. This protein crosses the placental border and binds to estrogen, prohibiting its entry into the fetus. This aids in minimizing estrogenic activity and diverting the estrogen to be degraded in the maternal liver.[19] In exposed fetuses, BPA binds to fetal α-fetoprotein. This thwarts fetus' innate protection against excess endogenous estrogen exposure.[18,20]

BPA acts on the ovary and disturbs the cells that assist in the development of oocytes. Females are born with all of the oocytes that they will ever have. Thus, any damage incurred to the ovary will result in long-term and trans-generational effects that can be carried through several generations.[18]

MEIOSIS DIRECTLY INFLUENCES THE GENETIC QUALITY OF GAMETES

Meiosis is a two-stage process that divides genetic information to create gametes.[21] Evidence has shown that BPA can disturb this essential process by arresting the cell, causing alterations during recombination synapse, and also disturbing the meiotic spindle structures. These defects lead to congression failure, or chromosomal misalignment on the metaphase plate, and eventually, meiotic arrest, or aneuploidy.[22]

Prophase

The preliminary steps during prophase I in fetal development set the cell up for recombination and division, and consume approximately 90% of the meiotic process.[23]

A female fetus is more susceptible to distress occurring in prophase because a female's oocytes are arrested in this stage until just prior to ovulation during puberty. This causes the "grand-maternal effect," the phenomenon in which exposure to BPA during pregnancy disturbs oocyte development in unborn female fetuses. When these female fetuses reach adulthood, the perturbations that occurred in the oocyte are translated into chromosomally abnormal eggs and embryos. Thus, a mother who is exposed to BPA during pregnancy will transduce these maladies onto her offspring. The offspring will have abnormal oocytes that will result in a difficulty or inability to reproduce once she reaches reproductive age.[23]

Congression Failure

During prophase I in fetal development, chromosomal pairing and recombination are two of the most important processes. Microscopic analysis shows BPA exposure causes incomplete synapsis and increases end-to-end association between non-homologous sister chromosomes. This reflects a failure in pairing and movement of the chromosomes. To determine differences in recombination, researchers look at MLH1 foci in homologous chromosomes; the MLH1 foci are common components indicative of DNA breakage, which occurs when chromosomes synapse and recombine. Typically, the cell controls recombination through crossover interference. This ensures that at least one exchange per chromosome pair occurs (one MLH1 foci). Crossover interference places restrictions on the proximity of recombination—crossover points should be comfortably spaced along the synapse. However, BPA exposure disrupts this crossover interference mechanism. Analysis of the chromosomes in these exposed oocytes during prophase show that there are far greater MLH1 foci. These multiple foci sites lie in close proximity to one another.[23,24]

Spindle Formation

Following chromosome pairing and recombination during prophase I in fetal development, spindle formation ensures that chromosomes are aligned on the metaphase plate for even separation during anaphase. Exposure of oocytes to BPA causes a time and dose-dependent delay in cell cycle progression. BPA interferes with the pericentriolar material (PCM), which leads to the formation of abnormal spindles, and eventually, chromosome non-disjunction. BPA blocks the pericentrin from localizing to the poles and induces notable microtubule polymerization.[21,25] Further, when polymerization occurs, microscopic analysis of the spindle apparatus shows loose and elongated meiotic spindles originating from unfocused bipolar spindles. Non-focused or non-bipolar spindles are major stressors in meiosis—they incapacitate the spindle and its ability to segregate the chromosomes.[22]

Progression from Meiosis 1 (M-1) to Meiosis 2 (M-2)

The transition from M-1 to M-2 starts at puberty and occurs during every menstrual cycle, and the oocyte's arrest from prophase is unsuspended. Exposure to BPA delays the meiotic progression from M-1 to M-2 in a dose dependent manner. At lower BPA exposure, approximately 75% of cells complete meiotic division; at higher BPA doses, far fewer cells reach this stage. An even longer exposure to BPA retards the oocytes so that they may not progress from M-1 to M-2.[12,21,22,26] To determine if this mechanism is reversible, a BPH wash was performed. Interestingly, it restored the centrosomal protein function from BPA exposure *in vitro*. However, microtubule polymerization and attachment to chromosomes could not adequately be reorganized following a BPA wash. Thus, the defects imposed by BPA on meiosis are functionally irreversible.[21] The oocytes undergo maturation arrest in which their development has been interrupted before cytokinesis is reached.[22]

Aneuploidy

The defects in meiotic spindle assembly lead to chromosome disjunction, or aneuploidy, a cellular condition that has an abnormal number of chromosomes. It is estimated that 10-25% of all fertilized human oocytes are aneuploid, which is the leading cause of miscarriage, congenital defects, and mental retardation. Post-meiotic examination of mice exposed to damaged cages leaching BPA into the environment[27] showed that none, or very few chromosomes, were found in polar bodies following exposure to BPA. These cells, when analyzed earlier during the prophase stage, contained altered synaptic and recombination profiles. Thus, the early meiotic defects from exposure to BPA lead to the formation of aneuploid species.[21,23] Interestingly, the same constellation of meiotic defects were seen in mice with a homozygous ERβ knockout.[23]

OVARIAN ANTRAL FOLLICLES

Antral follicles are the mature ovarian follicles that progress to the ovulation stage. A low antral follicle count (AFC) is a predictor of natural menopause and low fertility/fecundity. Analysis of AFC will show how follicles respond to BPA exposure.[12] Follicle degeneration is directly linked to the health of granulosa cell vitality. The proliferation of granulosa cells causes secretion of specific hormones that help follicle maturation so that at least one reaches the antral state to ovulate following the LH surge. Then the follicle will reorganize into a corpus luteum, which secretes mostly progesterone, which will function to promote the reproductive cycle.[28]

BPA exposure prevents steroidogenesis by disrupting the estradiol biosynthesis pathway.[11] Reports from rodents exposed to BPA indicate a low number of corpora lutea and cyst-like antral follicles.[12,29,30] A reduction or degeneration of these follicles leads to a decline in estradiol, estrone, testosterone, androstenedione and progesterone. First, BPA exposure affects granulosa and theca cells by down-regulating steroidogenic acute regulatory protein (StAR) and cholesterol side chain cleavage enzyme (P450scc). Reduction of StAR expression prevents cholesterol from importing into the mitochondria. Reduction of P450scc mRNA expression inhibits the conversion of cholesterol to androstenedione. Later, BPA thwarts androstenedione from diffusing from the theca cells to the granulosa cells where it is aromatized to estrogen.[11]

The absence of the steroidogenic enzymes prohibits the growth of a mature antral follicle. In several large antral follicles exposed to BPA, there were small oocytes that seemed to be trapped in the granulosa cell layer.[24] If the oocyte cannot escape the granulosa cell encapsulation, it will not be able to be fertilized. When ovulation did happen in BPA exposed rodents, the oocytes were severely degenerated.[22] Severely degenerated oocytes will have difficulty being fertilized by sperm or will experience issues during development.

ACCELERATED ONSET OF PUBERTY

Menstruation is the first notable sign of adrenarche in females. While humans and high-order primates undergo monthly menstruation, all other female mammals undergo the estrus cycle.

There are four stages to the estrus cycle: proestrus, estrus, metestrus, and diestrus. Proestrus and estrus are similar to the follicular stage in the menstrual cycle. During the follicular stage, high estradiol levels invoke the endometrium to proliferate. During proestrus, the corpus luteum regresses as progesterone concentrations decline. Meanwhile, the concentrations of estradiol/estrogen increase, which causes the preovulatory follicle to grow to its antral state. Ovulation occurs during the estrus stage. During this time, the vaginal epithelia become cornified. Cornified cells are a good indicator for the onset of estrus. Metestrus and diestrus are stages similar to the luteal stage, at which time estradiol stimulates the synthesis of receptors for progesterone. This enhances the growth of the corpus luteum.[31]

Despite the differences between the menstrual and estrus cycles, animal models can still be used to study humans. For the most part, mammals have the same reproductive system that is regulated by the hypothalamic-pituitary-gonadal (HPG) neuroendocrine axis.[31]

BPA results in an excess of *in utero* "estrogen" exposures, an increased body weight, and an earlier vaginal opening and first estrus/menstruation.

In Utero Exposures

The intrauterine position of fetuses plays a role in fetal hormone levels. Endogenous sex steroids can diffuse across the membrane via the amniotic fluid from one fetus to another.[32] Appropriately, a fetus positioned between two females (0M) has higher concentrations of estradiol than does a fetus of the same sex positioned between either one (1M) or two (2M) males.[33] BPA has a similar mechanism, in which the 0M position results in higher BPA concentrations and developmental defects. The combination of a 0M intrauterine position and BPA exposure results in increased postnatal growth and accelerated age of first vaginal estrus.[1] These two responses seem to be related to each other, and will be explored further in subsequent sections in this review.

Body Weight

Over the last century, changing patterns in the onset of puberty have been noticed. These pubertal patterns correlate with increasing body weights in females. Girls who have earlier menses are exposed to greater amounts of estrogen, which amplifies the risk of breast and uterine cancers. BPA in the environment has been hypothesized to earlier menses and fat deposition. Effects observed in body weight gain following BPA exposure to rodents do not cease following removal of BPA from the environment. Among groups of female mice with the same birth body weight and ingesting normal chow, exposure to BPA substantially increased their weight gain.1[4,15,33] Howdeshell *et al.* examined the effects of BPA exposure in combination with intrauterine position in female pups with similar body weights at birth. In this report, the weight of 0M females increased the most (22%), while the weight of 1M females increased less (9%), due to 50% less diffusion of BPA and estrogens a proximal female sibling. 2M females were unaffected in comparison to the other groups as they were not directly near female siblings and did not gain an excess of endogenous estradiol and BPA exposure.[33] The females had more weight gain and serum BPA concentrations than their male counterparts.

Vaginal Opening and First Estrus

As noted above, the effects of BPA are thought to be primarily through the mimicking of estrogen, which disturbs the estradiol-negative feedback loop of the neuroendocrine axis. Studies show varied results in the vaginal opening and first estrus; however, research groups agree that exposure to BPA causes vaginal opening and first estrus to be off of what is expected. These variances in precocious or delayed puberty may have been due to the difference in the animals that were exposed to the BPA, as well as the timing of their exposure.

A delay in the onset of puberty is observed in ewes exposed to BPA. When the ewes are treated prenatally with BPA, there is an early increase in postnatal LH secretion. Early secretion advances the neuroendocrine pubertal development, resulting in large secretions of estradiol. However, this results in a quick shutdown of the system through negative feedback in the HPG axis.[6,35] Thus, the ewes experience a delayed puberty until they can escape the repression of the negative feedback response.

In other studies, however, the age at vaginal opening is significantly earlier in BPA-exposed females, and this observation is confirmed by the presence of completely cornified cells. The total days of cornified cells in a vaginal smear assay are greater in the BPA-exposed groups.[16,35] Serum analysis from Sprague-Dawley rats exposed to BPA during gestation and lactation exhibit increased LH levels, resulting in

delayed, prolonged estrus.[1,9] Similarly, the ewes exposed to BPA have longer estrus cycles, which is potentially indicative of the reduced sensitivity to negative feedback to estradiol.[35]

MORPHOLOGICAL ALTERATIONS TO THE REPRODUCTIVE TRACT

BPA causes morphological changes in the vagina, ovary, and mammary glands that result in tumors/lesions, and cancers of the uterus and breast tissues.

Vagina

In addition to increased ERα protein expression and decreased ERβ protein expression following BPA exposure, the vagina experiences a large reduction in the thickness of the epithelial layer.[1,9] Mice exposed to BPA levels150 μg/(kg/day)—0.1 mg/(kg/day) see a reduction in the stratification of vaginal epithelia.[9,17,20] Vaginal atrophy causes a dryness, itching, burning, soreness, pressure, malodorous discharge, and painful sexual intercourse followed by vaginal bleeding.[36]

Ovary

The ovaries exhibit far greater alterations due to BPA exposure. They tend to be smaller with decreased volume of the endometrial lamina propria, despite having increased protein expression of ERα and progesterone receptor (PR) in the luminal epithelium and subepithelial stroma and decreased ERβ expression during estrus.[1,9,29] Decreased uterine epithelia create issues with the implantation of a fertilized embryo and support during its development.

Polycystic ovarian syndrome (PCOS) is a common endocrine abnormality that is characterized by elevated serum LH and testosterone, low/normal levels of follicle stimulating hormone (FSH), and abnormal estrogen secretion.[29] Animal studies have shown that BPA exposure up-regulates the activity of the GnRH pulse generator.[37] These faulty levels cause a disruption of the normal pulsatile secretions that coordinate the ovarian and uterine cycle. The lack of secretion harmony results in immature eggs that cannot ovulate, and instead, remain as cysts. This can lead to a greater incidence of miscarriage, pregnancy-induced high blood pressure, and premature delivery.[38]

Tumors/Lesions

Prenatal BPA exposure is considered to be associated with increased tumor incidence of reproductive tissues.[39] Following exposure to high BPA doses, analysis of murine vaginal tissue show up-regulation of several oncogenes and growth factor genes. BPA induces tumor proliferation via amplification of DNA synthesis and increased *c-fos* (proto-oncogene) expression. While estradiol can also have these effects in a cell, BPA induces a longer sustained peak and blocks control mechanisms that turn the expression off.[20] Additionally, BPA can cause certain cells to proliferate during puberty by up-regulating the ER-positive cells. Because the tissues of the ovary and breast tend to already have an increased number of ER present on their cells, these tissues are most prone to respond to BPA by proliferating to a greater extent.[1,18,39]

Ovarian Cancer

In addition to modifications through DNA, BPA's effect on the deregulation of the neuroendocrine system can cause the growth of ovarian cysts, which may progress to ovarian cancer. Mice given BPA injections have a significant increase in the presence and number of cystic ovaries, cystic endometrial hyperplasia (CEH), and progressive proliferative lesions (PPL) of the oviduct and cystic mesospheric duct remnants.[40] Ovarian carcinoma cells exposed to BPA also showed an increase in proliferation. Proliferation is mediated by an up-regulation of cell cycle promoting-genes such as cyclin, cyclin dependent kinase (CDK), E2F1/E2F3 (activating transcription factors), and proliferating cell nuclear antigen (PCNA), while down-regulating the expression of p21WAF1/CIP1, Weel-1, and GADD45α, genes typically responsible for the inhibition of proliferation.[41] BPA down-regulates pro-apoptotic genes while up-regulating pro-survival genes and pathways, like MAPK, a common mitogenic pathway.[39]

Mammary Glands

Though mammary glands are not associated with the genital tract, these secondary sex tissues are still relevant to reproduction and hormone signaling. Very low maternal doses of BPA lead to an increase in the number of ducts, terminal ducts, terminal end buds, and alveolar buds in female offspring. In addition to these tissue growths, the exposed mice also have increased secretory product within the alveoli and a greater, but altered, localization of fat pads. These phenotypes observed prior to puberty are similar to that of non-exposed pregnant dams, further exemplifying advanced and rapid growth in BPA-exposed rodents.[1,18] At puberty, exposed mice show an increased mammary gland proliferation/apoptosis ratio. With greater proliferation, BPA exposed animals have numerous hyperplastic ducts with desmoplasia. These changes have the potential to proliferate into cancer.[42]

Breast Cancer

Early puberty and the increased percentage of hyperplastic ducts are the precursors to the development of breast cancer. BPA has shown to cause MCF-10F human breast cancer cells to transform when cultured in a 3D collagen matrix. Typically, the cells are tubule-like; exposure to BPA transforms the cells into spherical masses. The transformation is caused by the promotion of DNA adducts and reactive oxygen species (ROS), which disrupt the genomic information as well as the proper division of cells.[39] BPA induces pathways that stimulate proliferation while blocking apoptosis of the cell with an unregulated or disrupted cell cycle. Proliferation and inhibition of apoptosis are controlled by the regulation of specific cell-cycle genes, especially those cell-cycle checkpoint genes under the regulation of ERα.[43]

PUBLIC HEALTH IMPLICATIONS

BPA imposes cell- and organ-specific effects that disrupt the development of the female reproductive system. These changes lead to significant issues that are raising concerns in the global public health scene.

The United States is currently stricken by an obesity epidemic. A higher adipose index can alter specific hormones, that can cause an adverse alteration in the neuroendocrine axis.[8] When the neuroendocrine axis is not properly signaling and secreting the proper hormones, disorders such as polycystic ovarian syndrome (PCOS) and cancers can develop.[30,39] Further, because the log[octanol/water partition coefficient] (K_{ow}) value for BPA is 3.4, BPA may exert greater effects on people with higher BMIs, as it can accumulate within the adipose tissue for extended periods of time.[3]

BPA has shown to have a more direct effect on the occurrence of uterine and breast cancers. By up-regulating the activation of ERα and ERβ, BPA induces the cells in these reproductive tissues to proliferate uncontrollably. This proliferation leads to an overgrowth of ducts and lesions that may metastasize if not diagnosed and treated promptly.[39]

With all of the adverse alterations to the reproductive tract, BPA has created barriers to fertility. 95% of random urine or ovarian follicular fluid samples of adult women have detectable levels of BPA.[11] This induces all of the changes, from the molecular level of gamete quality control, to implantation of a fetus in the deformed uterine tissue, that make it difficult to support a successful pregnancy. When blood serum samples were collected, 72.9% of BPA containing samples came from infertile women, while a smaller subset (23.1%) belonged to fertile women.[5] Mice exposed perinatally to BPA have significant declines in both the number of pregnancies and the total number of litter per dam.[44] Fertility effects were examined in females exposed to leached components from a resin-based composite that included 25 or 100 μg/(kg/day) BPA. There was a 54.5% reduction in the number of preg-

nancies when both groups of BPA-exposed females were mated with unexposed males.[45]

CONCLUSION

Bisphenol A is classified as an endocrine-disrupting compound and modulate the functions of estrogen by turning on/off genes that are controlled by ERα and ERβ, and their coactivators.[1] A disruption of normal endogenous estradiol disturbs the neuroendocrine axis, thereby disrupting the secretion and pulsatility of specific hormones that dictate the development and proper functioning of the female reproductive tract.[7,8] These hormonal disruptions may lead to aneuploidy, gamete degeneration, and declines in fertility or fecundity. Additionally, excess ERα and ERβ stimulation can lead to morphological alterations in the vagina, uterus, and mammary tissues, causing cancers that drive up the mortality rate.

Industry remains the largest source of environmental BPA. The public must be educated on the harms associated with this prevalent monomer, and begin to reduce BPA production. Additionally, it is important to control the BPA that is already in use by consumers. Proper recycling of plastics and filtration of industry waste-water can help eradicate BPA in our environment.[3]

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