BISPHENOL-A: AN ENVIRONMENTAL TOXICANT

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ABSTRACT

There is a great concern that exposure to man-made substances that mimic endogenous hormones may adversely affect mammalian reproduction. Bisphenol-A (BPA) is one of them and the most common compound used in industry for the manufacture of epoxy resins and polycarbonate plastics. Several studies reported BPA migrates from can surface coatings or plastics into food and with repeated use of such products; it has been detected in the biological samples of general population. For these purposes, different approaches have been employed, from in vivo studies on female rodents to in vitro experimental procedures. Based on the review published, BPA exposure leads to negative health problems such as neurotoxic, immunotoxic, carcinogenic, genotoxic, metabolic problems, effects on social behavior, effect on fertility and reproductive tract, transgenerational inheritance and other problems.

Key words: Endogenous hormones, BPA, transgenerational inheritance.

INTRODUCTION

Bisphenol A (CAS No: 80–05–7) is a high production chemical used primarily in the manufacture of polycarbonate plastics and epoxy resins. It exists at room temperature as a white solid and has a mild phenolic odor. Polycarbonate plastics are used in certain food and drink packaging, eg, infant and water bottles, impact-resistant safety equipment, compact discs and medical devices. Polycarbonate plastics are marked with “7”, the recycle symbol or may contain the letters “PC” near the recycle symbol. Polycarbonate plastic can also be mixed with other materials to create molded parts for use in household items, mobile phone housings and automobiles. Epoxy resins are used to coat metal products such as food cans, bottle ops, and water supply pipes. Bisphenol A-derived materials are used in dental sealants or composites. BPA is almost everywhere around us in form of our daily usable goods.

Bisphenol A is an endocrine disruptor that interferes with the production, secretion, transport, action, function and elimination of natural hormones. BPA can imitate our body's own hormones in a way that could be harmful for health. More specifically, bisphenol A closely resembles the structure and function of the estradiol hormone and has the ability to bind and to activate the
same estrogen receptor as the natural hormone and may lead to sensitive adverse effects on infants and young children. In 2010 Food and Drug Administration (FDA) of United States banned use of BPA in baby bottles. In September 2010 Canada’s environment science department declared BPA to be a ‘toxic substance’.

Bisphenol A shows potential acute, chronic, and sub chronic toxicity. Many evidences indicated that BPA exhibits developmental toxicity in the reproductive organs considering the epididymis and epididymal sperm, seminal vesicles and prostate and inhibitory effects on testosterone synthesis. Low sperm count, abnormal sperm morphology and poor semen quality are reported. Some of the studies revealed that BPA has different effects on the ovary depending on the time of exposure. Maternal exposure affects the earliest stages of oogenesis in the developing fetal ovary. The resulting meiotic defects increase the likelihood that embryos produced by the exposed females in adulthood will be chromosomally abnormal. In particular, the utero exposure of mice as well as rhesus monkeys stated disturbances during the prophase events of meiosis and an increase in multiple oocyte follicles (MOFs). In vitro and in vivo studies have revealed links between BPA exposure and its hormone related cancers, including breast, ovarian cancers and endometrial carcinoma and prostate. Many evidences demonstrate that fetal exposure to low doses of BPA alters cell proliferation and apoptosis.

**Exposure**

The prime source of exposure to bisphenol A for most people is through the diet. While dust, air and water (skin contact at the time of bathing and swimming) are other possible sources of exposure, daily exposure of bisphenol A is mainly through food and beverages. Exposure of BPA can also occur by certain dental sealants made with bisphenol A-derived material such as bisphenol A dimethacrylate (bis-DMA), in processing of PVC plastic and thermal paper, the type of paper used in some purchase receipts, self adhesive labels, and fax paper. Bisphenol A can also be found as a residue in paper and cardboard food packaging materials. Workers may be exposed by inhalation or skin contact during the manufacture of bisphenol A and bisphenol A-containing products, eg, polycarbonate and polyvinyl plastics, thermal paper, epoxy or epoxy-based paints and lacquers and tetrabrominated flame retardants.

Bisphenol A can migrate into food from food and beverage containers with internal epoxy resin coatings and from consumer products made of polycarbonate plastic such as baby bottles, food containers, tableware and water bottles. The rate at which bisphenol A leaches from polycarbonate containers into liquid appears to depend more on the temperature of the liquid than the age of the container, i.e., more migration with higher temperatures.

Estimating the concentration of BPA in human exposure can be measured in human blood, urine, breast milk, and other fluids or tissues. Daily intake was estimated by human is given in table I. However, because of the continuous and widespread human exposure, BPA has been identified in a variety of human samples at much higher levels than would be expected based on the assumption that Bisphenol A is rapidly metabolized and ingested only infrequently. The elimination rate of BPA (excreted > 90%) as metabolites is within 24 hours.
Table I. Summary of Ranges of Estimated Daily Intakes in People Based on Sources of Exposure

<table>
<thead>
<tr>
<th>Population</th>
<th>Bisphenol A µg/kg bw/day</th>
<th>Sources of exposure</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant 0–6 months (Formula-fed)</td>
<td>1–11</td>
<td>Canned formula fed and polycarbonated bottles + formula fed (liquid/powder)</td>
<td>Chapin et al., 2008; EFSA, 2006; European Commission, 2002; European-Union, 2003</td>
</tr>
<tr>
<td>Infant (Breast-fed)</td>
<td>0.2–1</td>
<td>Exclusively breast fed</td>
<td>EFSA, 2006; Chapin et al., 2008</td>
</tr>
<tr>
<td>Infants 6–12 months</td>
<td>1.63–13</td>
<td>Breastfed and canned formula fed and polycarbonated bottles + formula fed</td>
<td>FDA, 1996; EFSA, 2006; European Commission, 2002; European-Union, 2003</td>
</tr>
<tr>
<td>Child 15–6 years</td>
<td>0.043–14.7</td>
<td>Indoor and outdoor air, dust, soil, and liquid and solid food from daycare and home</td>
<td>Wilson et al., 2003; Miyamoto and Kotake, 2006; EFSA, 2006; European Commission, 2002; European-Union, 2003; Wilson et al., 2007</td>
</tr>
<tr>
<td>Adult (general population)</td>
<td>0.008–1.5</td>
<td>Canned food + bottled food and polycarbonate, tableware</td>
<td>FDA, 1996; EFSA, 2006; European Commission, 2002; European-Union, 2003; Miyamoto and Kotake, 2006; Thomson and Grounds, 2005</td>
</tr>
<tr>
<td>Adult (occupational)</td>
<td>0.043–100</td>
<td>Powder paint workers</td>
<td>European-Union, 2003; Chapin et al., 2008; USEPA, 1988</td>
</tr>
</tbody>
</table>

BPA and Human Health

Human health is also affected by the use of BPA under various doses. Major affects are seen during experiments. In this review, effects of BPA on health with emphasis on reproductive health are highlighted.

Reproductive Toxicity

Male-mediated effects of developmental exposure to BPA on adult fertility or reproductive outcome were evaluated. There is extensive evidence that BPA affects the reproductive system in male rats and mice. The evidence supports an effect on the testes, with following changes in testosterone secretion and sperm production. Effects of BPA on other reproductive structures have been reported in many studies, including the epididymis and epididymal sperm, prostate,
and seminal vesicles. These discoveries are steady with impacts of low dosages of positive control chemicals. Exposures of BPA on male reproductive system are studied comprehensively, indicating morphological changes in seminiferous cords, Sertoli cells and Leydig cells. Another study reports significant decline in testis, epididymis, prostate and seminal vesicle weights and the testicular daily sperm production in Wistar rats.

Many studies have been found significant effects of BPA on the female reproductive system. Perinatal exposure to low-doses of bisphenol A (BPA) in mice results in alterations in the ovary, uterus, and mammary glands and in a sexually dimorphic locale of the brain known to be important for estrous cyclicity. Exposure to environmental endocrine disruptors during fetal development has been suggested to contribute to declining conception rates and inclined incidence of female reproductive disorders such as oocyte aneuploidy, polycystic ovarian syndrome, and altered cyclicity, furthermore endometriosis, uterine fibroids, fetal growth retardation, and pregnancy loss and it is due to effects of sex hormones levels. Perinatal exposure of BPA has resulted in early opening of vagina and altered estrous cyclicity, over expression of ERα and progesterone receptor in the endometrium, and an elevated number of ovarian antral follicles in mice. In rodents, perinatal exposure to environmentally relevant doses of BPA (ranging between 2µg/kg and 250µg/kg body weight) has been shown to advance puberty and reproductive deterioration with age, alter estrous cyclicity, disrupt ovarian and mammary gland development and has been correlated with an increased incidence of mammary tumors. Neonatal exposure to high doses of BPA (500 µg/50 mL) has been reported to alter ovarian structure, increasing the number of cysts and creating a polycystic ovarian syndrome phenotype in female animals. For instance, prenatal BPA treated sheep (BPA 5 mg/kg/day in cotton seed oil from day 30 to 90 of gestation) showed a significant decrease in GnRH mRNA expression prior to the expected onset of preovulatory LH surge.

The effect of BPA on the oviduct is progressive proliferative lesions (PPL) when neonatal mice treated with BPA (10, 100 or 1000 µg/kg/day) and found that all groups had PPL in the oviduct. In another study, gestational mice were exposed relevant doses to BPA at 0.1, 1, 10, 100, or 1000 µg/kg/day. PPL was observed in all groups. Experimental studies suggested that BPA exposure could impair the uterine receptivity, which is important for successful embryo implantation. A study showed that exposure of BPA (0, 0.025, 0.5, 10, 40, and 100 mg/kg/day) to pregnant mice during gestation days, 0.5 to 3.5 doses resulted in defective uterine receptivity in the 100 mg/kg/day BPA-treated group. Female mice exposure to BPA (6.75 and 10.125 mg/animal) on days 1–4 of gestation altered uterine morphology and significantly reduced the number of implantation sites. However, a very recent human epidemiological study did not support these results. Minguez-Alarcon and his colleagues found no relation between urinary BPA concentrations and in vitro fertilization (IVF) outcomes, including endometrial wall thickness, fertilization rates, implantation and embryo quality. Yamasaki and fellows examined the time-course changes of uterine weight in the immature rat uterotrophic assay using milligram (mg) amounts of BPA. Immature Crj:CD (SD) rats were injected subcutaneously (s.c.) with BPA, or BPA was administered orally via stomach tubes for 3 days beginning on postnatal day (PND) 18. This study demonstrated that rats given 0, 8, 40, and 160 mg BPA/kg/day s.c. or 0, 40, 160, and 800 mg BPA/kg/day of BPA orally show evidence of an endocrine-disrupting effect, and that uterotrophic activity was more sensitive to s.c. injection than oral administration.
Another study reported that BPA reduced rat ovarian weights and follicle numbers, and restrains with the constituent ratio of follicles. With increasing doses of BPA, the expression of factor in the germ line alpha (FIGLA) and oocyte-specific histone H1 variant (H1FOO) genes decreased, and anti-mullerian hormone (AMH) genes expression increased, indicating that BPA exposure during the pre-pubertal period may impede the development of ovaries, and follicle development-related genes may play certain roles in this process. \(^{39}\)

**Behavioral Activity**

Social behaviors, such as communication, sexual partner choice, pair bonding, social inquisitiveness and recognition, play behavior, copulation, social grooming, and animosity, are compromised in animal models exposed to BPA, phthalates, and other endocrine disruptor chemicals (EDCs). Early contact to these chemicals is likewise associated with maladaptive social behaviors in children. These behavioral altering influences the fetal or adult gonadal production of testosterone or estrogen, expression of ESR1, ESR2, and AR in the brain regions control these behaviors, neuropeptide/protein hormone (oxytocin, vasopressin, and prolactin) and their related neural receptors, and/or through epimutations. \(^{40}\) BPA resulted in an increment in defensive aggression in male Sprague-Dawley rat offspring prenatally exposed to BPA (administered orally to mothers during gestation) at a dose of 40 μg/kg/day; no effect was found in the offspring of mothers treated during lactation. \(^{41}\) Prenatal and lactational oral exposure of Sprague-Dawley rats to 40 μg/kg/day improved adult play and other socio-sexual practices in both males and females. \(^{42}\) Maternal consumption of low levels of dietary BPA contributes male offspring at a disadvantage for mating, not only because of poorer spatial route and greater nervousness-like behavior but also because they are less attractive to female conspecifics. \(^{43}\) Thus, early exposure of animal and humans to widely prevalent chemical bpa may lead to insidious behavioral effect, reduce the reproductive capacity and cause infertility.

**Carcinogenicity**

BPA also increases sensitivity to oncogene-induced tumorigenesis will be essential for examining whether the increase in susceptibility is confined to a DNA damaging agent or whether other tumorigenic events are also facilitated by the BPA-induced molecular changes. In males, BPA induces prostate cancer cells migration via a modulation of the ion channel protein expression intricately in calcium entry and in cancer cell migration. \(^{12}\) In females, exposure to oestrogens or synthetic compounds, malignancies of the reproductive tract occurs. \(^{44}\) Neonatal/prepubertal rats to BPA via lactation from nursing dams treated orally with 0, 25, and 250 μg BPA/kg body weight/day at 50 days of age, increased cell proliferation and decreased apoptosis playing a role in mammary cancer susceptibility. \(^{45}\) Another study related BPA exposure with breast cancer, pre-pubertal BPA exposure resulted in increased cell division in mammary glands of rats, a process associated with increased risk of tumor development in a chemically-persuaded mammary cancer. \(^{13}\) One of the study showed that pubertal low dose BPA exposure recapitulated the morphogenic changes associated with perinatal low dose BPA exposure in mice or rats; resulted in increased luminal progenitors in primary adult glands; and stably altered mammary stem cells (MaSC) function leading to early neoplasia in the regenerated glands. \(^{36}\)
Immunotoxicity

The immune system, and its function, is under complex and integrated control and its disruption can be triggered by multiple factors. BPA indicates that deleterious immunologic changes, including increased propensity to develop wheeze, hypersensitivity, and asthma after dietary and inhalation exposure to these chemicals, may be occurring. The study stated that prenatal exposure to BPA and high-molecular-weight phthalates might increase the risk of hypersensitivity symptoms and respiratory tract infections all through childhood. BPA has been reported to modify immune function at doses between 2.5 - 30 µg/kg/day, including patterns of cytokine and immunoglobulin production, response to infection, and autoimmune disease progression. Exposure to BPA has also been cognized with modulation of innate immune system cell function. In addition, the impacts of BPA work on the immune functions of lymphocytes and macrophages in Carassiusauratus (fish). The effects of BPA were compared with those of two natural steroid hormones, estradiol and hydrocortisone. Results demonstrated that BPA (0.054-5.4 mg/L), estradiol (0.0002-2.0 mg/L) and hydrocortisone (5-50 mg/L) significantly actuated Carassiusauratus lymphocyte proliferation while higher doses of hydrocortisone (500-5000 mg/L) appeared to be inhibitory. BPA (0.005-50 mg/L), estradiol (0.005-800 mg/L) and hydrocortisone (0.005-500 mg/L) markedly enhanced macrophage division, whereas higher doses of BPA (500-1000 mg/L) appeared to inhibit cell proliferation. Furthermore, higher dosage of BPA (50 mg/L) and hydrocortisone (50 and 500 mg/L) stifled the macrophages respiratory burst while estradiol is responsive all the doses tested (0.05-500 mg/L).

Neuroendocrine Effects

Nervous system is very important for all mental, sensory and motor activities, and regulates homeostasis through interaction with the endocrine system. Pollutant such as bisphenol A, can lead to severe and widespread neuroendocrine disruptions in discrete brain regions, including the hippocampus, amygdala, and hypothalamus, resulting in behavioral changes in a wide range of species. BPA-induced changes in function of the hypothalamus pituitary-gonad axis have been observed in both males and females. In males, effects on LH, prolactin, and brain aromatase activity have been noticed. Exposure of weanling males to 2.4 µg/kg/day BPA for 15 days resulted in decreased serum LH and testosterone levels due to variation in LH synthesis and secretion at the pituitary level. One of the study stated that BPA leads to alterations in some behaviors and neuronal morphology that endure into adulthood. Male and female, adolescent rats received BPA, 40 µg/kg/body weight for a week and were tested for anxiety and spatial memory, locomotor activity, non-spatial visual memory, and sucrose preference. In addition, stress-induced serum corticosterone levels were measured. BPA-treated males, but not females, had declined arm visits on the elevated plus maze, but there was no effect on anxiety. Non-spatial memory, object recognition, was also declined in BPA treated males, but not in females. BPA exposure did not alter spatial memory, object placement, but decreased observation during the tasks in both sexes. No significant group differences in sucrose preference or serum
corticosterone levels in response to a stress challenge were found\textsuperscript{57}. In another study, BPA doses produced significant declines in Esr1 expression in the juvenile female rat anteroventral periventricular nucleus (AVPV) of the hypothalamus and significant declines in Esr2 expression in the adult female rat AVPV and medial preoptic area (MPOA), relative to vehicle controls\textsuperscript{58}.

**Metabolic Effects**

Bisphenol A (BPA) has been reported to disrupt glucose homeostasis. On a normal diet, perinatal exposure to 50μg/kg/day BPA inferred in increased body weight, elevated serum insulin, and impaired glucose tolerance in adult offspring. On a high-fat diet, such injurious effects were accelerated and exacerbated. Furthermore, severe metabolic syndrome, including obesity, hyper leptinemia, hyperglycemia, hyper insulinemia, dyslipidemia, and glucose intolerance were observed in rats\textsuperscript{59}. BPA is lipophilic, and it can accumulate in fat stores to increase the number and size of adipocytes, therefore resulting in weight gain as adipocytes also express endrogen receptors (ERs) to which BPA bind\textsuperscript{60}. Subsequent oral dosing in humans, BPA was rapidly conjugated and excreted in urine due to the absence of enterohepatic circulation\textsuperscript{61}. In the same way, BPA given orally or intravenously was also mainly excreted in urine from cynomolgus monkeys\textsuperscript{62}. In contrast, in rats, the major excretion route was feces when BPA orally or intravenously administration\textsuperscript{63}, suggesting that BPA is mainly metabolized to BPA-glucuronide and excreted into feces through the bile and subject to enterohepatic circulation in rats, irrespective of dose and administration route\textsuperscript{64}. However, the renal elimination and potential exposure of BPA during dialysis, health risks of BPA for end-stage renal disease patients are evaluated\textsuperscript{65}. Bisphenol A (BPA) has been reported to possess hepatic toxicity. BPA below the NOAEL induce mitochondrial dysfunction in the liver and this is related with an increase in oxidative stress and inflammation\textsuperscript{66}.

Longer exposure to BPA in adults hindered hepatic glucokinase activity and function\textsuperscript{67}, meanwhile chronic BPA administration during a period of 8 months induced increased adipose tissue, glucose intolerance, higher levels of cholesterol, and over expression of key genes involved in cholesterol biosynthesis\textsuperscript{68}. One of the data suggests that BPA introduction amid pregnancy could be considered a new risk factor for the deterioration of maternal glucose metabolism and the increased occurrence of diabetes\textsuperscript{69}.

**Oxidative Effects**

Several studies have been reported the occurrence of oxidative toxicity after BPA exposure in rats and mice. It was suggested that BPA triggered tissue injury in the liver, kidney, brain and other organs by the formation of reactive oxygen species (ROS). Moreover, the study revealed that low doses of BPA generate ROS by decreasing the activities of antioxidant enzymes and increasing lipid peroxidation therefore cause oxidative stress in liver of rats\textsuperscript{70}. The various doses of BPA exposure caused a significant increase in intracellular ROS and a significant reduction in the level of glutathione (GSH). N-Acetyl cysteine, an inhibitor of intracellular ROS formation, can significantly decline the generation of intracellular reactive oxygen\textsuperscript{71}. BPA exposure may impact the DNA damage response and repair, the effect of BPA exposure on base excision repair of oxidatively induced DNA damage, cells compromised in double-stranded break repair were treated with BPA alone or co-exposed with either potassium bromate (KBrO3) or laser irradiation, ie, oxidative damaging agents and noted that KBrO3 with BPA increased guanine base lesions in genomic DNA. With laser irradiation-induced DNA damage, treatment with
BPA suppressed DNA repair as revealed by several indicators. BPA causes long-term adverse effects on the liver, leads to deleterious effects in the liver of female rat offspring.

Genotoxicity

Studies reveal the potential of BPA to induce mutations, chromosomal aberrations, sister chromatid exchange and transformation in human. The potential genotoxicity of bisphenol was determined in the human hepatoma cell line (HepG2) at non-cytotoxic concentrations (0.1 μmol L-1 to 10 μmol L-1) after 4-hour and 24-hour exposure and found that BPA induced significant DNA damage only after the 24-hour exposure, while no DNA strand breaks observed after the 4-hour exposure.

Disruption in the progression of meiosis I and the persistence of meiotic DNA strand breaks in pachytene spermatocytes, and the ataxia–telangiectasia-mutated and checkpoint kinase 2 signal pathway was also activated when BPA is given at 0, 2, 20 or 200 μg/kg body weight (bw)/day for 60 consecutive days in adult rats. BPA exposure can cause a significant increase in the DNA damage of spermatocytes of male rats via oxidative stress and can alter the relative proportions of germ cells at various developmental stages.

Altered DNA methylation at various CpG sites was related with exposure to mercury, lead or BPA, in woman candidates and may reflect an independently associated predictor (e.g. socioeconomic status, genetic variants, diet, altered blood cell composition). Low-dose exposure to bisphenol A in female mouse is sufficient to elicit the meiotic abnormalities this estrogen imitate disrupts chromosome behavior in the mammalian oocyte and causes a specific meiotic phenotype at metaphase (congression failure) and an increased risk of non-disjunction at anaphase by disturbances of spindle fibers. In the fetal period, female mice exposed to low dose of BPA (400 ng/day) had adverse effects on oogenesis by disrupting meiosis, resulting in synaptic defects and an increased rate of recombination. The perturbations produced chromosomally abnormal eggs and embryos when these fetuses reached adulthood.

Similar defects were noted in adult female rhesus macaques in that intrauterine exposure to BPA interrupted the meiotic prophase events by increasing the levels of recombination and centromeric associations between non homologous chromosomes. An in vitro study of human fetal oocytes demonstrated that BPA was identified with the disruption of meiotic maturation, spindle organization and chromosome alignment, and an increase in the rates of oocyte degeneration in which, human oocytes discarded by patients undergoing IVF/ICSI cycles were cultured in vitro with BPA (20, 200 ng/mL or 20 μg/mL).

Developmental Effects

Results from developmental toxicity studies in mice and rats show adverse effects on pup survival and growth following maternal exposure to dose levels of bisphenol A defined by the NTP as “high” (>5mg/kg bw/day). In rats, a~20–36% decrease in the number of pups per litter is reported following maternal dosing with ≥500mg/kg bw/day. Increases in fetal death and post-implantation loss are seen in rats treated with 1000mg/kg bw/day during pregnancy. Reductions in fetal weight or growth during postnatal life occur at oral dose levels of ≥300mg/kg bw/day in rats. In mice, developmental toxicity is generally reported at higher oral doses in the form of fetal death, decreased number of live pups, reduced fetal or pup body weight at ≥
875mg/kg bw/day,\(^{83,84}\), and reductions in body weight during postnatal life in the F1 generation at 600mg/kg bw/day.\(^{85}\). Fetal death in mice has also been observed in a recent study that reported embryo lethality following subcutaneous dosing with 10mg/kg bw/day bisphenol A to pregnant mice.\(^{86}\). Occasionally, decreases in pup survival have been reported at much lower oral dose levels, such as 0.0024mg/kg bw/day in mice.\(^{87}\). However, this effect is not typically reported at oral doses in this range even in studies from the same laboratory using a similar dosing regimen and the same source of mice.\(^{88}\).

Delayed onset of puberty (assessed by day of vaginal opening) has been reported in the female offspring of rats orally treated with bisphenol A at 50mg/kg bw/day during gestation\(^89\) or 500mg/kg bw/day during gestation and lactation\(^3\). However, decreased body weight was not observed in females at the dose where delayed vaginal opening was reported by Tinwell and fellows.\(^89\) This high dose effect of delayed vaginal opening is not the predicted effect of exposure to an estrogenic compound. It is worth noting that Tinwell et al did not detect any difference in onset of puberty in female rats when age at first estrus assessed by vaginal smear was used as the marker of puberty. Other “high” dose studies report no effect on onset of puberty in female rats exposed during gestation and lactation at maternal oral doses ranging from 32 to ~1000mg/kg bw/day.\(^90\). Delayed puberty in male rats treated during development has also been reported at oral doses of ≥50mg/kg bw/day.\(^91\). This effect was associated with decreased body weight in the study by Tyl et al\(^3\), but not in the study by Tan et al. A delay in puberty of 18 days has also been reported in male mice at 600mg/kg bw/day in a 2-generation reproductive toxicity study.\(^85\).

The reproductive and developmental effects on low dose exposure cause permanent changes to genital tract, lower bodyweight, increase of anogenital distance in both genders,\(^92\), disrupts ovarian development.\(^27\).

**CONCLUSION**

Data demonstrate that bisphenol-A functions as a xenoestrogen (synthetic estrogen) and change the expression of the endocrine receptor by binding with them. Prenatal and neonatal phases are critical periods during this time. BPA exposure affects many tissue, organ and biological pathways. It appears to be species and strain specific in the sensitivity of particular outcomes. Results from studies show that may reflect the estrogenic effect of BPA, could be related to an inhibitory effect on spermatogenesis, oogenesis and infertility. BPA exposure at work place as seen in cohort study also gives evidence that it has an adverse effect on male and female sexual dysfunction and shows dose response relationship of BPA exposure. Vertical transmissions of BPA exposure at different dose level need to be confirmed by additional studies. Nevertheless, the extensive use of BPA in consumer products to which humans are chronically exposed, these findings increase the need to examine the health effect of BPA in both occupationally and environmentally exposed population at relevant dose level.

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