

A REVIEW ON TOXICOLOGICAL CONSEQUENCES OF BISPHENOL-A ON THE DIVERSE INTERNAL ORGAN SYSTEM

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Abstract

A xenoestrogen Bisphenol-A (BPA) is an endocrine disruptor usually present in our surrounding environment which has been primarily used as an intermediate for the production of polycarbonate plastics, epoxy resin based products and other polymer materials. The widespread use of BPA in diverse products has increased its global demand at 6%-10% for each year. BPA considered to induce endocrine disrupting effects include cardiovascular disease, diabetes, obesity, oncogenesis, abnormal immune system response, reproductive disorders, hepatocytic diseases, DNA damage, insulin resistance, hyperinsulinemia, and hypertension. In this review aimed to briefly summarize an impact of BPA in both *in vitro* as well as *in vivo* studies on various organs of human and animal models (Rat, mice, and mouse).

Keywords: BisphenolA (BPA); Xenoestrogen; Toxicity; Organ system; Human; Animals

I. Introduction

Endocrine-disrupting chemicals (EDC) are the natural or synthetic exogenous chemical that alters the endocrine functions and therefore cause antagonistic health effects in an intact organism which can either mimic or block natural hormones by disrupting the synthesis, release, transport, metabolism, binding, activity or removal of animals and human bodies responsible for the upkeep of homeostasis, behavior, reproduction, and development (EFSA Scientific Committee 2013; Kavlock *et al.*, 1996). Many endocrine disruptors are present in the environment such as fungicide, vinclozolin, halogenated aromatic hydrocarbons including dioxin, bisphenol A (BPA), PCBs, phthalates, herbicides such as atrazine (Maffini *et al.*, 2006). A monomer of BPA (2,2-bis[4 hydroxyphenyl] propane) was first synthesized by A. P. Dianin in 1891 that has been utilized for more than 50 years (Ben-Jonathan and Steinmetz, 1998). The maximum volume of BPA has produced every year that could be the combination of 1 mol acetone with 2 mol of phenol in the presence of an acid catalyst (Staples *et al.*, 1998). BPA is commonly found in our surrounding environment, air, drinking water, wastewater, and surface water (Susiarjo *et al.*, 2007; Vom Saal & Welshons, 2014). Over 6 billion pounds of BPA are manufactured annually and 100 tons are delivered into the air per annum. 65% BPA is utilized to produce polycarbonate plastic such as baby bottles, cell phones, carbonless paper, computers, spectacles, and optical lenses, reusable water bottles, dashboards, bumper, kettles, refrigerators, mixers, food and microwave containers, beverage cans, hairdryers, electric shavers, helmets, eye-protective glasses, medical equipment (incubators for newborn babies, machines which are utilized in dialysis, oxygenators, inhalators used for respiration purposes), glass-making, road signs, ski lifts, roof lights, roofing, protective panels are materials for the construction industry, paints, coatings CDs, DVDs, fax machines and 35% of BPA polymerized to form epoxy resins based products include water pipes and coating inside the cans (Vandenberg *et al.*, 2009; Vandenberg *et al.*, 2012; Liao & Kannan, 2014). BPA act as a significant intermediate for the assembly of flame retardants as well as it has the potential to act as a synthetic estrogen (Dodds & Lawson, 1936).

BPA has enormous unique chemical and physical properties including MW is 228.29 g/mol, white color with crystal or flake form, mild phenolic odor, 220^oC at 4 mm Hg and 150-155^oC are boiling and melting point of BPA also highly soluble in corn oil but partially soluble in water due to their hydrophobic nature (Staples *et al.*, 1998). Reactivity of BPA determined by their hydroxyl group may undergo nitration, sulphonation, and alkylation and also be capable of changing into salts, esters, ethers

(Flint *et al.*, 2012). As an endocrine disruptor, each BPA ($\text{HO-C}_6\text{H}_4\text{-C(CH}_3)_2\text{-C}_6\text{H}_4\text{-OH}$) is polymerized and connected by an ester linkage to make polycarbonate plastics and epoxy resins. Because of an expanded pace of temperature BPA interact with acidic and basic compounds and leached out from their sources by hydrolysis of an ester bond between BPA molecules. Temperature influences the relocation of BPA from metal jars and proceeds with utilization or continued washing of polycarbonate items also a reason for releasing BPA from their sources (Vandenberg *et al.*, 2009).

II. Diverse range of BPA

The environmentally safe reference dosage of BPA is $50\mu\text{g/kg/day}$ set up by the U.S. Environmental Protection Agency. Studied atmospheric BPA in the coastal area of sea is $1\text{-}32\text{ pg/m}^3$, polar region is $1\text{-}17\text{ pg/m}^3$, and Urban areas of USA, New Zealand, China. Previously studies revealed that diverse variety of BPA levels in residue particles, drinking water system, and several types of food, effluents, and tap water $0.099\text{ - }0.317\mu\text{g/dm}^3$ (Asia, North America) bottled water (France) $0.07\text{-}4.21\mu\text{g/dm}^3$ (Vom Saal *et al.*, 2007; Colin *et al.*, 2014). Loganathan & Kannan (2011) stated that BPA levels going from $0.5\text{-}10.2\text{ mg/kg}$ in dust particles from various homes of Eastern USA. This determined significant BPA concentrations from $0.01\text{-}44.63\text{ }\mu\text{g/dm}^3$ and $28.7\text{-}98.4\text{ }\mu\text{g/dm}^3$ in-stream water tests gathered from Taiwan, Portugal (Lee *et al.*, 2013). Various investigations on BPA uncovered from different canned food sources include cereals ($1\text{ - }3.8\text{ }\mu\text{g/kg}$), seafood ($1\text{ - }99.9\text{ }\mu\text{g/kg}$), milk ($1.32\text{ - }176\text{ }\mu\text{g/kg}$), vegetables and natural product like fruits ($3.7\text{ - }265.6\text{ }\mu\text{g/kg}$) (Cunha & Fernandes, 2013). Also, BPA levels are additionally recognized in breast milk, urine samples, amniotic fluid, neonatal blood, placenta, cord blood, and human serum (Apelberg *et al.*, 2007).

III. Metabolism of BPA

The liver is a primary organ for the metabolism of synthetic estrogen BPA. After the admission of BPA from their sources into circulation, it directly moves via the gastrointestinal tract and conjugates with glucuronic acid to form BPA - glucuronide carried out by hepatic enzymes a process called glucuronidation and also increases the solubility in water. A biologically active form of free BPA is often named unmetabolized BPA that is primarily converted into bisphenol - A sulfate. The metabolic rate of BPA is faster with a half-life of $< 6\text{ hrs}$ within the body (Snyder *et al.*, 2000; Chapin *et al.*, 2008).

IV. Receptor-mediated BPA action

Several EDC has mimicked the activity of E2 an endogenous sex hormone. One amongst endocrine disruptors of BPA has structurally similar to E2 which binds with both estrogenic receptors $\text{ER}\alpha$ and $\text{ER}\beta$ (Colborn *et al.*, 1993; Bolli *et al.*, 2008). Baker & Chandsawangbhuwana (2012) reported that the structure of BPA & E2 (Fig. 1) and (Fig. 2). However, the binding affinity of BPA for ERs is over 2000 to 10000 fold lower than E2 (Bolli *et al.*, 2008; Bolli *et al.*, 2010). Estrogen-related receptors α ($\text{ERR}\alpha$), Estrogen-related receptors β ($\text{ERR}\beta$), Estrogen-related receptors γ ($\text{ERR}\gamma$) are a subfamily of orphan nuclear receptor that is allied to $\text{ER}\alpha$ and $\text{ER}\beta$. ligand-binding domain (LBD) and DNA binding domain of ERR has homology with ER. Along with ERs, progesterone receptors (PRs), androgen receptors (ARs), thyroid receptors (TRs), and retinoid receptors (RXR) are also nuclear hormone receptors. EDCs bind to those receptors and apply their actions that may lead to metabolic diseases (Diamanti-Kandarakis *et al.*, 2009; Ben-Jonathan *et al.*, 2009).

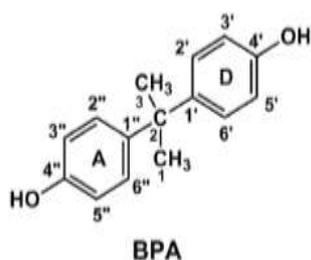


Figure. 1 Structure of BPA

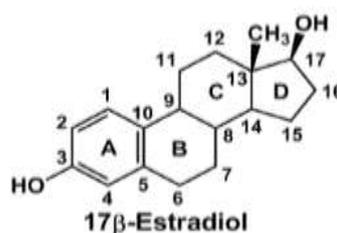
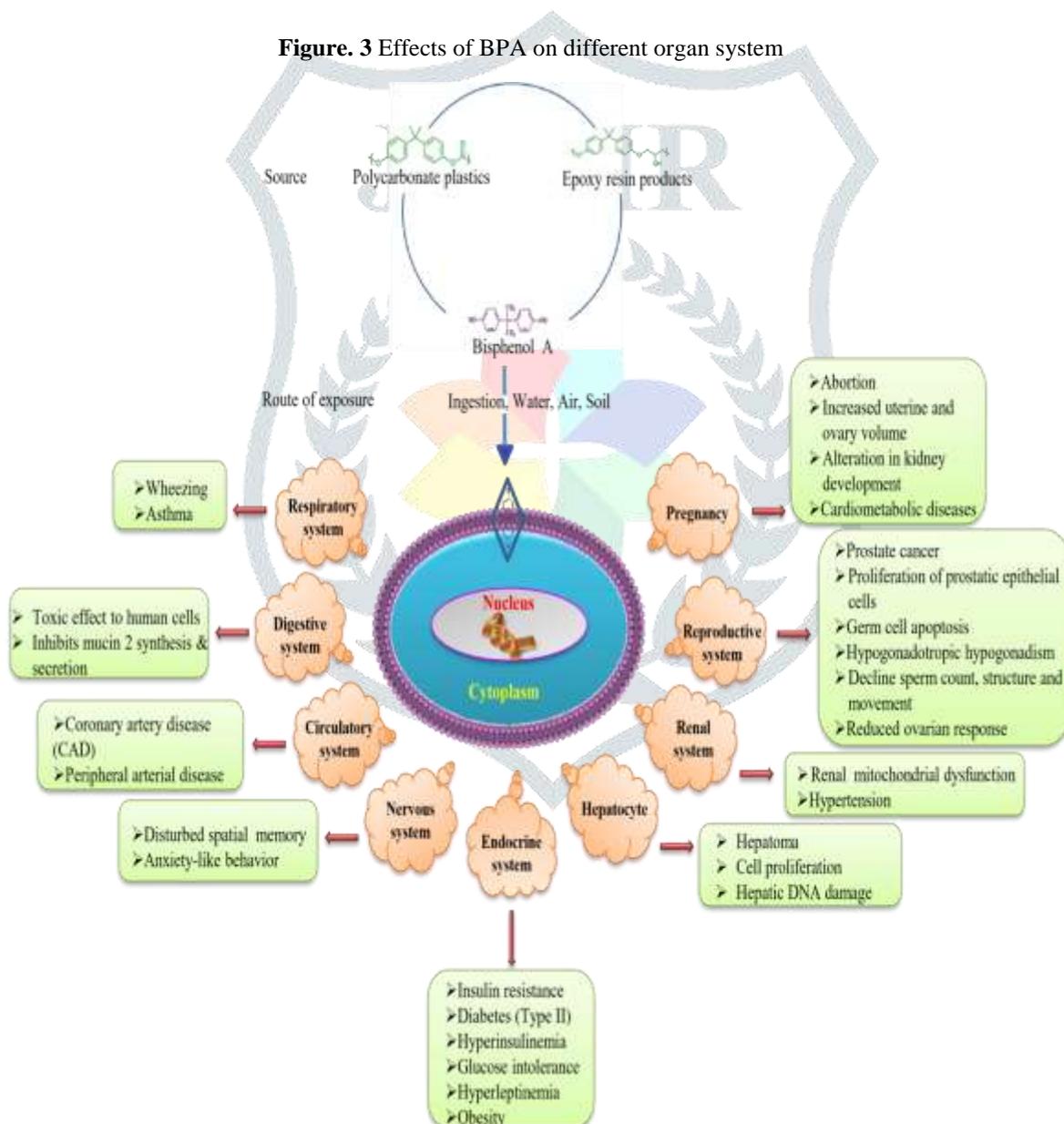


Figure. 2 Structure of E2

V. Health associated consequences of BPA

At present, numerous *in vivo* and *in vitro* experiments indicated that BPA has tremendous health impacts in humans similar to in animal models (Fig. 3). Preceding investigations found that BPA influences reproductive function, cognitive function, development of mammary gland, metabolism, estrous cycle (negative effect), ovarian cycle by disrupts the ovarian follicle activity, hypothalamic kisspeptin / GnRH system and estrous cyclicity, insulin synthesis, and release, insulin-related signaling, increased the incidence rate of type-2 diabetes (Pouzaud *et al.*, 2018; Beausoleil *et al.*, 2018). Besides the above-mentioned reports, some previous evidence suggested that BPA impaired behavior and spine density (Xu *et al.*, 2015; Inagaki *et al.*, 2012), abnormal mammary gland development as well as BPA induces diabetogenic and obesogenic effects, glucose intolerance, insulin resistance, hyperleptinemia, and hyperinsulinemia (Elsworth *et al.*, 2015; Pouzaud *et al.*, 2018). Earlier researchers are reported that a low dose of BPA has a serious effect on pituitary, breast, islets, and endothelium via non-genomic regulation and multiple diseases including meiotic aneuploidy in female mouse and prostate cancer (Alonso-Magdalena *et al.*, 2005; Calafat *et al.*, 2009). There are studies concerned with male children from BPA-exposed mothers has shorter AGDs and lower birth weight than unexposed mothers (Miao *et al.*, 2011; Miao *et al.*, 2011).

Figure. 3 Effects of BPA on different organ system



5.1 Impact of BPA on Reproductive System

The examination explored the high dosage (250,000 $\mu\text{g}/\text{kg}/\text{d}$) of BPA modulates body, testes, and epididymis in NCTR Sprague Dawley rat dams (Dere *et al.*, 2018). Huang *et al.* (2017) observed that various doses (0.01, 0.1, 1, 10, 100, and 1000nM) of BPA directly promote the proliferation of prostatic

epithelial cells through upregulating the expression of ER α and ER β , downregulating the expression of AR of the cells and diminishing apoptosis-induced cell demise in Male SD rats. Wisniewski *et al.* (2015) studied that the GC-2 cells (a mouse spermatocyte-derived cell line) were received BPA at dosages of 0, 20, 40, and 80 μ M concentrations at 48h. The outcomes indicated an induced immoderate gamete programmed cell death through IFN β (Interferon-beta) -mediated up-regulation of pro-apoptosis molecule XAF1 (X-linked inhibitor of apoptosis-associated factor); suppressed XIAP (X-linked inhibitor of apoptosis protein) expression and therefore the antiapoptotic activity. Additionally, BPA compromises sperm production, acrosome and plasma membrane integrity, reduction in a mitochondrial activity that disrupts the hypothalamic-pituitary-gonadal axis were results in hypogonadotropic-hypogonadism in adult Wistar rats. Exposure to BPA also resulted in apoptosis of immortalized mouse pachytene spermatocyte derived GC-2spd (ts) (GC-2) cell line, that is partially mediated via perturbation in Ca²⁺-calmodulin-Ca²⁺-calmodulin-dependent protein kinase IIs (Ca²⁺/CaM/CaMKII) signaling and also the mitochondrial apoptotic pathway (Qian *et al.*, 2015). Moreover, organelles such as mitochondria and ER were damaged and respond to oxidative stress induced by BPA. However, cellular apoptosis has been regulated by the accumulated ROS trigger PERK/EIF2 α /Chop pathway revealing a crucial role in BPA induced toxicity in the male reproductive system (Yin *et al.*, 2017), and testis harmfulness has also been assessed (Jiang *et al.*, 2018). The utero exposure report to BPA had multigenerational impacts on the ovaries by diminishing the number of preantral follicles, altering mRNA levels of cytochrome P450, and, female reproductive hormone E2 levels in the F1 generation, whereas the F2 generation Inbred FVB mice have harmful effects on steroidogenesis due to decreased male reproductive hormone testosterone levels, and changes mRNA levels of various steroidogenic factors (Mahalingam *et al.*, 2017). Studied the perinatal administration of BPA changed the expression of tight junction proteins such as claudin-1, claudin-3, claudin-4, claudin-7, ZO-1 within the female internal reproductive organ of epithelial uterine tissue and reduced the rate of implantation rate in adult pregnant feminine Wistar rats (Martínez-Peña *et al.*, 2017). In this study, increased serum BPA levels related to higher volumes uterine, ovarian and also frequent abortions were observed in women on a dose-dependent basis and male infants decreased their birth weight and lower gestational age dimensions (Zheng *et al.*, 2012; Chou *et al.*, 2011). Rajakumar *et al.* (2015) have reported that BPA disrupts gene expression in human placental trophoblast cells by increased 11 β -HSD2 activity, protein and mRNA levels; augmented aromatase, GLUT-1, CRH, hCG mRNA levels, and reduced leptin mRNA. An elevated level of serum BPA is associated with higher LDL and HDL cholesterol (Olsen *et al.*, 2012). Very recently, Ma *et al.* (2020) found that maternal BPA exposure during pregnancy indicated that decreased sperm counts, interstitial-cell stimulating hormone (ICSH), and testosterone levels as well as damage to testicular tissue structure at the sexual maturity stage (PND56). Also, completely different miRNA expressions include miR-361-5p, miR-203a-3p, and miR-19b-2-5p at fetal stage (GD20) in male offsprings. Earlier authors have documented that low-dose of BPA caused c-Myc-dependent DNA damage and mitogenic effects on ER α -negative mammary cells as well as DNA damage occur in MCF-7 (ER-positive) cells but not in HEK293 (ER-negative) cells in human (Pfeifer *et al.*, 2015; Yin *et al.*, 2014).

5.2 Influence of BPA on Urogenitalis apparatus

Evaluated the continuous use of polycarbonate-based bottles result in increased concentration of BPA in urine (Carwile *et al.*, 2009). Despite there are several reports exhibited that higher urinary BPA levels additionally related to reduced heart rate variability, the enhanced incidence of hypertension, an expanded predominance of the peripheral arterial disease, insulin resistance, increased BMI and waist circumference, abdominal obesity, obesity in children, higher T3 and lower TSH, negatively associated with CMV antibody titer in children and positively associated in adult, augmented type-2 diabetes, wheezing and asthma (Shankar & Teppala, 2012; Wang *et al.*, 2013; Donohue *et al.*, 2013). Besides, an enormous range of studies have shown that higher levels of urinary BPA associated with type-2 diabetes, coronary artery disease (CAD), elevated levels of sex hormone-binding globulin (SHBG), higher BMI and waist size in premenopausal women, reduction in sperm count, alterations in structure, movement and DNA damage in men in diverse populations (Kim & Park, 2013; Wang *et al.*, 2012; Silver *et al.*, 2011; Meeker *et al.*, 2010) and along with this increased maternal urinary concentrations (2.0-4.1 μ g/L and 2.0-3.9 μ g/L) of BPA associated with depression, anxious, aggressive behavior, emotional disturbances (Braun *et al.*, 2011; Perera *et al.*, 2012). Past examinations revealed that higher urinary concentration of BPA results in reduced ovarian response and an elevated rate of implantation failure in women under IVF (Mok-Lin *et al.*, 2010; Ehrlich *et al.*, 2012) and also lesser sexual function

in occupationally BPA exposed workers. The urine samples from 0 to a half-year-old infant showing a flood of steroid after leaving the maternal uterine steroidogenic environment may be affected by BPA that disrupts the premature reproductive gland function at some vital biological process windows (Wang *et al.*, 2017). Ecologically pertinent dosages of BPA altered kidney development in a gender-dependent manner during embryonic development of pregnant mice that increased the danger of developing cardiometabolic diseases later in life in pregnant OF1 mice (Nuñez *et al.*, 2018). Kobroob *et al.* (2018) evaluated that BPA elicited renal mitochondrial dysfunction in an exceedingly dose-dependent manner and protecting the kidney against nephrotoxicity by melatonin in male Wistar rats.

5.3 Influence of BPA on Endocrine system

Formerly, (Fernandez *et al.*, 2018) expressed that *in vivo* and *in vitro* exposure of BPA to female Sprague-Dawley rats results in modification on the hypothalamic-pituitary-thyroid axis. During pregnancy, the thyroid-stimulating hormone (TSH) was reciprocally related to urinary BPA that had a foremost impact on fetal development and interfere with normal childbirth in pregnant women (Aung *et al.*, 2017). Hao *et al.* (2011) investigated the occupationally, BPA exposed women has higher prolactin and lower progesterone levels. Studies from the recent year confirmed that treatment with BPA in male Wistar rats and Mature Sprague Dawley male rats testes lower the testosterone levels in blood serum, downregulates steroidogenic genes (StAR, CYP17a, 3 β -HSD), up-regulates CYP19, LHR genes, reduce sperm cell production and Leydig cells. Also, BPA induces calcium influx independent of classical ERs, via K⁺, TRPV1, and Cl⁻ ionic channels modulation, as well BPA activates IP₃-receptor/Ca²⁺ channels, PKA, PKC and inhibit SERCA at ER thereby change intracellular calcium storage which activates MEK and p38 MAPK mediated genomic response (Marghani *et al.*, 2018; Gonçalves *et al.*, 2018). This study indicated that BPA affects the viability and function of β cells; mitochondrial defects and mitochondria-dependent apoptotic signals have expanded the pace of apoptosis in Rat insulinoma (INS-1) cells (Lin *et al.*, 2013). Impaired testicular functions were due to administration of BPA results in decreased insulin, insulin receptor (IR), insulin receptor substrate-1 (IRS-1), phosphoinositide 3-kinase (PI-3 kinase), GLUT-2, antioxidant enzymes, 3- β -hydroxysteroid dehydrogenase (3 β -HSD), 17- β -hydroxysteroid dehydrogenase (17 β -HSD), Steroidogenic Acute Regulatory Protein (StAR) and also male reproductive hormone testosterone in rat testis. BPA has a greater binding affinity with E₂, cytochalasin B, and glucose with GLUT-2 and GLUT-8 identified by molecular docking (D'Cruz *et al.*, 2012). Furthermore, BPA has also effects on skeletal muscle, cardiac and hepatic insulin signaling molecules, and glucose oxidation of rats (Jayashree *et al.*, 2013; Indumathi *et al.*, 2013; Sivashanmugam *et al.*, 2017).

5.4 Influence of BPA on Nervous system

Chen *et al.* (2018) studied that the spatial memory of male juvenile Sprague-Dawley (SD) rats was disturbed by BPA exposure due to down-regulation of spine density and glutamate receptor (NR) levels in neurons of the hippocampus based on dose-dependent manner. Along with this excitatory receptor, levels were decreased in V1 which alter visual inputs. Warita *et al.* (2014) demonstrate that higher dosages of BPA induce alterations in NGF-based neuron development and suppress cell death by changing *Ngf* gene expression, decreased mRNA levels of *Casp3* and *Trp73* that are necessary for mice brain development. Kumar & Thakur, (2017) evaluated that perinatal BPA exposure has related to a reduced synaptic density as evident from a decrease in synaptophysin expression and the ratio of excitatory (PSD95) to inhibitory (gephyrin) synaptic protein in cerebral cortex and hippocampus regions of postnatal 3 weeks and 8 weeks male mouse brain thereby induce anxiety-like behavior. A recent study, Szymanska & Gonkowski, (2019) have demonstrated the BPA induced changes in neurochemical characterization of the enteric neurons located within porcine jejunum leads to the primary sign of subclinical BPA intoxication due to changes in neurons immunoreactive to substance P, vasoactive enteral polypeptide, galanin, vesicular acetylcholine transporter, and cocaine and amphetamine-regulated transcript peptide as well as fluctuations in intensity.

5.5 Influence of BPA on Digestive system

Lately, assessed the BPA induced cytotoxicity at doses of 0.01 μ g/mL, 0.1 μ g/mL, 1 μ g/mL, 5 μ g/mL, 10 μ g/mL, 50 μ g/mL, and 100 μ g/mL in three completely distinctive cell lines such as 3T3-L1 (mouse fibroblasts), MCF-7 (breast cancer cells), PC3 (prostate cancer cells). The outcomes indicated ingestion of BPA contained food has harmful to human cells observed by slightly lower IC₅₀ of MCF7 than PC3 and 3T3-L1 (Hernández-Hernández *et al.*, 2019). The study by (Zhao *et al.*, 2019) reported that BPA inhibits mucin 2 synthesis and secretion in human colonic goblet cell line LS174 T through

mitochondrial dysfunction by disrupting the mitochondrial membrane potential, decreased mitochondrial respiratory chain complexes I, III, IV, and V activity, reduced ATP production. Besides, BPA evokes elevated mitochondrial and intracellular ROS production, increased oxidative stress products (MDA and H₂O₂), and reduced the antioxidant indices (SOD and T-AOC), and also increased DNA fragmentation, caspase 3, 8, 9, 10 mRNA expression, and enzyme activity. In a previous study, ROS generation to play a most important role in the submicromolar concentrations of BPA induced cell proliferation and DNA damage in human liver cell lines due to the histone H2AX activation, a sensitive marker for DNA damage (Kim *et al.*, 2018). Hepatic DNA damage occurred due to elevated production of free radicals and disrupted ROS elimination. Moreover, BPA induces chronic inflammation in female rat offspring (Eid *et al.*, 2015). Hassani *et al.* (2018) recently examined that a low dosage of BPA has shown the same phenomenon in liver tissues of juvenile rats that might be a risk factor for liver cancer in humans and Sprague-Dawley/CD rats. Expanded oxidative pressures and altered proteome and phosphoproteome of the liver might contribute to the pathophysiology of liver diseases in male Wistar rats.

5.6 Influence of BPA on Circulatory system

A few examinations have recorded in humans, BPA exposure causes chromosomal aberrations in both ER-dependent and independent pathways, cancer cell progression by up-regulation of Akt, COX-2, HIF-1 α , and VEGF (Vascular endothelial growth factor) protein expression that involved in the pro-inflammatory and pro-angiogenesis pathway. The exposure of BPA at low (0nM and 1nM) concentration affect cell proliferation, increased expression of glucocorticoid 11- β -hydroxysteroid dehydrogenase2 mRNA and protein, decreased expression of angiogenic growth factors; impaired basal and VEGF stimulated tube formation; alteration in DNA methylation-related with metabolic stress response in human first-trimester trophoblast cells, HTR8/SVneo and human endothelial cells (Menon & Dev, 2018; Basak *et al.*, 2018). (Geetharathan & Peera, (2018) noted the experimental study, exposure to BPA ventricular tissue degeneration and changes in their functions by significantly decreased antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase, and catalase activity and also increased lipid peroxidation along with up-regulation of pro-apoptotic protein caspase 3. Bae *et al.* (2012) highlighted the evidence on the effects of BPA exposure on cardiovascular diseases associated with minimized heart rate variability (HRV) and increased blood pressure in noninstitutionalized elderly citizens.

VI. Conclusion

We have explored and incorporated an immense toxic effect of synthetic estrogen BPA on animal and human health in many kinds of literature. In our daily life, we are exposed to BPA from various BPA-based products and environments that induce a massive effect on normal body metabolism, function, reproduction, etc. at the cellular and molecular level in various global populations. Although BPA is one of the most effective studied EDC, currently we need further research to minimize or reduce the toxicity of BPA on the animal and human systems.

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