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Environmental Significance Statement

A chemical that is widely used in plastics and resins and has a high production volume, bisphenol A (BPA) exposes people to it and contaminates the environment. Because it can disrupt hormonal signalling pathways, especially during vulnerable developmental stages, its classification as an endocrine-disrupting compound (EDC) raises serious concerns. This review emphasizes how maternal BPA exposure has significant effects on fetal neurodevelopment, including changes in behaviour, brain structure, and long-term mental health. The known transgenerational and epigenetic impacts emphasize the long-lasting dangers BPA presents to human health. In order to inform regulatory policies and promote the reduction or replacement of BPA in consumer products—thereby safeguarding the environment and public health—it is imperative to comprehend the molecular mechanisms underlying BPA and its interference with neuronal development.

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Impact of Bisphenol-A Exposure on Fetal Brain Development and Neurological Health-A Review

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LIST OF ABBREVIATIONS

BPA	Bisphenol A
EDCs	Estrogenic Disrupting Chemicals
ROS	Reactive Oxygen Species
CNS	Central Nervous System
RNSCs	Rat Fetal Neural Stem Cells
SVHCs	Substances of Very High Concern
POMC	Pro-opiomelanocortin
GABA	Gamma-aminobutyric Acid
FDA	Food and Drug Administration
HPLC	High-Performance Liquid Chromatography
CH	Congenital Hypothyroidism
LCMS	Liquid Chromatography-Mass Spectrometry
QSAR	Quantitative Structure-Activity Relationship
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
UGT	Glucuronosyltransferase
HPA	Hypothalamic-Pituitary-Adrenal
GnRH	Gonadotropin releasing hormone
SDN-POA	sexually dimorphic nucleus-preoptic area
LH	Luteinizing hormone
AVPV	hypothalamic anteroventral periventricular nucleus
RHs	Releasing hormones
TRs	Thyroid hormone receptors
GRs	Glucocorticoid receptors
DNMTs	DNA methyltransferase
ERK	Extracellular signal-regulated kinases
AR	Androgen receptor
PKC	Protein kinase C

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BDNF	Brain-derived neurotrophic factor
CREB	cAMP response element binding protein
NMDA	N -methyl- D –aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
GN11	GnRH-secreting neuronal cell line
SRC1-3	Steroid receptor coactivators
c-RAF	Serine/threonine kinase protein
HER3	human epidermal growth factor receptor 3
AKT	protein kinase B
GPER	G-protein coupled estrogen receptor
BRCA1 and 2	Tumor suppressor genes
PKB	Protein kinase B
ROS	Reactive oxygen species
NF-κB	Nuclear Factor-κB
CtBP	Interacting protein
G2/M	Cell cycle checkpoint
PCNA	Proliferating cell nuclear antigen
GC-1 cells	Spg cells are an immortalized cell line derived from a mouse testis that are used to study the early stages of spermatogenesis
GPR30	G protein–coupled receptor for estrogen
EFGR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinases
ER-α	Estrogen receptor alpha
PKG	protein kinase G
E2	Bimolecular elimination
EMT	Epithelial-mesenchymal transition
MAPK	Mitogen-activated protein kinase
COX-2s	Cyclooxygenase-2
RL95-2 cells'	Human uterine epithelial
BCL2L11	Proapoptotic BH3 only protein Bcl-2-like protein 11

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p53	Tumor Suppressor gene
P21 and P27	Proteins that regulate the cell cycle and are involved in tumor growth and survival
mTOR	Mammalian target of rapamycin
ERK1/2	Proline-directed kinases
BCL-xl	B-cell lymphoma-extra large

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ABSTRACT

Bisphenol A (BPA), a ubiquitous industrial material, is widely employed as a starting material in preparing epoxy resins and polycarbonate plastics. This compound is utilized on very high scales around the globe. As this compound has been enlisted as one of the EDCs, substantial evidence has explored the positive correlation between BPA exposure and developmental disorders in the fetal central nervous system as well as fetal neurodevelopment. Its exposure also affects memory formation and the normal functioning of the pituitary gland. Bisphenol has adverse effects on thyroxine alternatively affecting fetal physical development. BPA also affects sexual behaviors and causes hypersexuality. In addition to that, these BPA exposure leads to certain epigenetic and transgenerational effects. The main aim of our review is to highlight the impact of BPA on fetal neurodevelopment and mental behavior. It is essential to completely understand the mechanism of action of BPA on the molecular structure of interneurons and other neurons during fetal development due to BPA exposure. This will help in the evaluation of interneuron linkage and other neural activities along with brain development from fetal to a mature state of life. This review encompasses the literature available about the abnormal impacts of BPA on fetal development due to maternal exposure to BPA. We have surveyed the relevant literature to disseminate the information obtained through research carried out to reveal these impacts.

Keywords: BPA; endocrine disruptor; hormonal disturbance; fetal exposure; estrogenic effects, BPA alternatives; reproductive system effects; neuroendocrine toxicity

1. INTRODUCTION

Endocrine disruptors (EDCs) are exogenous substances that imitate natural hormones. The World Health Organization (WHO) specifies an endocrine disruptor (ED) as "an invasive chemical or mixture that modifies the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, its progeny, or (sub)populations."(Hajjar et al. 2024). Humans are frequently exposed to EDCs through food packaging, personal care products, medications, and medical tubes. While several EDCs, such as parabens, phenols, and phthalates, have a short elimination half-life (less than 24 hours), research indicated they can penetrate the placental barrier. Exposure to EDCs, particularly during a critical embryonic phase like pregnancy, could

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have a significant impact on the peri- or post-natal cardiometabolic regulation (Puvvula, Song, Zalewska, Alexander, Manz, Braun, Pennell, DeFranco, Ho, Leung 2025)..

Bisphenol A (BPA) is one of the most studied EDCs, particularly for its adverse effects on the endocrine and reproductive systems. BPA, often known as Bisphenol A, is an extensively used chemical in the plastic polymer industry. This substance was first produced in 1891 (Tyl 2014), and its manufacturing has since increased to over 6 billion pounds, as reported by the study (Wolstenholme et al. 2013). BPA has been used as a basic polymer in the milk packaging sector, as a coating and liner material for metallic cans (frequently holding food) (Kamal et al. 2025). This substance is not only restricted to epoxy resins and polycarbonate plastic, but its alternatives are also utilized in dental materials, eyeglass lenses etc (Agarwal et al. 2025).

The mechanism of leaching of BPA begins with the packaging of food materials (polycarbonate plastic, epoxy resin and other BPA-containing packaging materials) and continues at room temperature. The process reaches hazardous proportions at extreme temperatures, both high and low (below - 4^0C) (Cooper et al. 2011). This potentially hazardous chemical molecule acts as an endocrine disruptor, causing undesirable alterations in the human body's hormonal system, particularly affecting the secretion of thyroid hormones (Pan et al. 2024) .

In 1938, Dodds and Lawsons studied the detrimental impact of BPA on estrogen (the female hormone) for the very first time (Mustieles et al. 2015), and the permissible recommended limits i.e., 0.2 ng/kg body weight (BW)/day was investigated by (Saal et al. 2024) demonstrating that the adverse consequences of BPA is not limited to a particular age group but influences all ages with a few variations (Cwiek-Ludwicka 2015). Ilaria Cimmino, Francesca fiori, and other contributors investigated the numerous methods of BPA exposure and identified some of among the most prominent probable BPA transmission mechanisms (Cimmino et al. 2020) as shown in **Error! Reference source not found.**.

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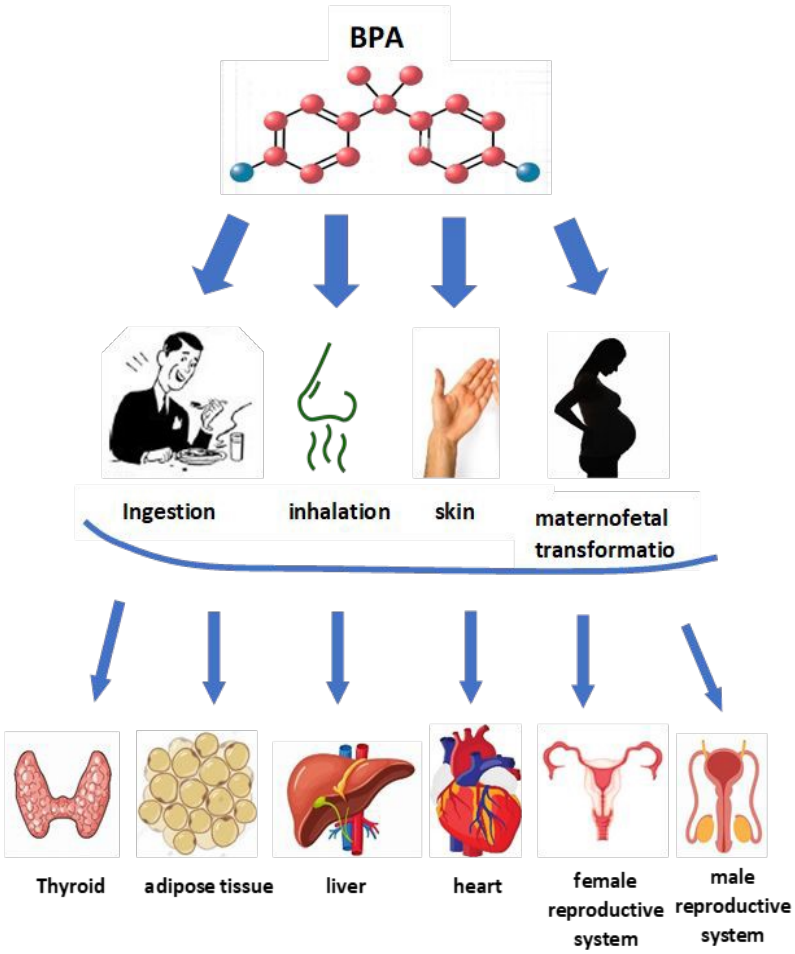

Figure 1. Transfer of BPA and affected organs

Individuals' reproductive well-being could be harmed as a result of EDC exposure, perhaps resulting in infertility. Multiple laboratory investigations have demonstrated the involvement of BPA as a reproductive toxicant. It mostly enters human tissues through saliva, blood, urine, amniotic fluid, ovarian follicular fluid, and placental tissues (Mahalingam et al. 2017). BPA exposure during pregnancy affects the fetus as well. BPA exposure at the fetal stage is also thought to induce infertility and sexual difficulties in males by altering their gonads, resulting in epigenetic abnormalities (Di Nisio and Foresta 2023).

The maternal route of exposure of BPA the fetus occurs during the pregnancy when the mother consumes BPA-containing food. The dosage response of BPA is non-monotonic. Its lower concentration may have some disruptive effects. Furthermore, due to the increased exposure of the fetus, the risk of harmful consequences is significantly greater during development than at maturity, even at moderate dosages. One possible reason for the higher exposure is the embryonic

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transfer of BPA and its glucuronide product, together with fetal UDP glucuronosyltransferase (UGT) enzyme deficiency. When these materials combine, BPA-glucuronide, which has zero estrogenic action, regularly deconjugates into active estrogenic BPA in the fetal compartment (Nishikawa et al., 2010).

This brief overview of neural development demonstrates that genetic/epigenetic and environmental factors interact throughout an individual's life to shape and influence the direction and activity of the developing neuronal network, while the environment provides proteins required for brain health and growth (Kunoh et al., 2024). There exist multiple studies that calculate BPA exposure throughout various stages of pregnancy (Braun et al. 2011). It also affects the neurological behavior and thyroid function of people as a result of its exposure in early ages and fetal life (Healy et al. 2015).

BPA has the chemical formula $C_{15}H_{16}O_2$ (structural formula shown in Figure 2) and is a white solid, soluble in organic solvents. Its presence has been noticed in many dairy products (Bommuraj et al. 2020). BPA have also shown an adverse effect on the estrogen receptors causing a hormonal disturbance (Le Fol et al. 2017). All the alternatives have bisphenol ring attached to different substitutes.

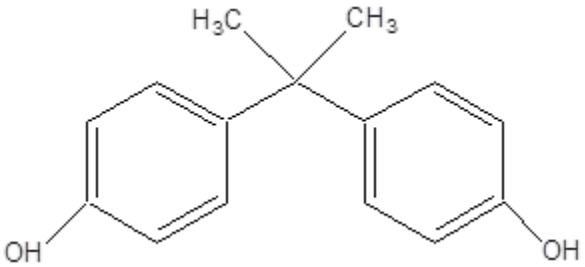

Figure 2. Bisphenol A structural formula

2. PATHWAY OF ENTRY INTO THE FETUS

Bisphenol A (BPA), an endocrine disrupting chemical (EDC), has a damaging effect on pregnancy. It influences placental formation, tissue shape, hormone production, and may raise the risk of pregnancy problems (Huifeng et al. 2025). Placenta is considered a transitory organ that establishes a connection between the mother and the fetus (Zha et al. 2024). The development of the fetus is depended upon the nutrition provided through the placenta by mother to fetus (Garnica and Chan 1996; James et al. 2007). The placental formation in humans occurs at 10 days i.e. at 1.4 weeks of pregnancy. The BPA can enter the mother's maternal system through the daily dietary intake. The anticipated pathway for BPA exposure in female mice fetus is shown in (Figure 3) by research

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conducted by Miyu Nishikawa published in journal Environmental Health Perspectives that elaborates the BPA entry in mother's maternal system from BPA containing dietary supplements. It can alter the fetus's genus through exposure to dietary supplements used by mothers during pregnancy (Dolinoy et al. 2007).

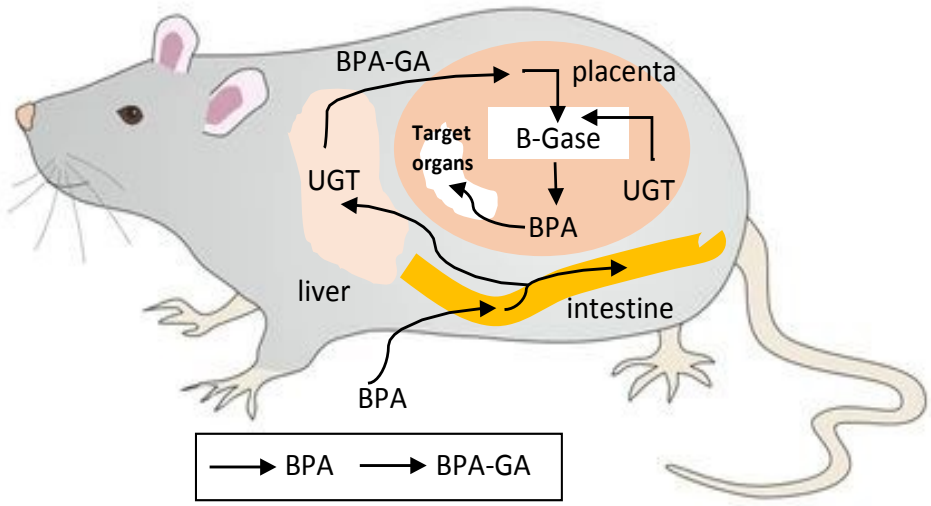

Figure 3 Anticipated fetal BPA exposure pathway

Several preclinical and experimental studies have found links involving gestational EDC exposures and unfavorable newborn outcomes (Diamanti-Kandarakis et al., 2009; Mnif et al., 2011). Although being exposed to EDCs has a significant impact during gametogenesis and the initial stage of fetal development, some unfavorable outcomes as a result of fetal exposure to EDCs could go undetected until adulthood (Mohajer and Culty 2025).

Several human observational studies have focused on biological monitoring of fluctuating EDCs, investigating their relationships with clinical endpoints in the context of prenatal exposures and maternal/newborn characteristics. Furthermore, a multi-omics investigation that considered metabolome (177 serum metabolites and 44 urine metabolites), proteome, and methylome profiles proposed interactions between mother's exposures to fluctuating EDCs and omics layers that are linked to phenotypes, including fetal development, weight gain, insulin resistance, and metabolic and neuroendocrine issues (Puvvula, Song, Zalewska, Alexander, Manz, Braun, Pennell, DeFranco, Ho, Leung, et al. 2025).

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2.1. NEURODEVELOPMENT IN FETUS

The nervous system is the focus of EDCs, which cause developmental disturbance. EDC exposure during the fetal and/or newborn period, either by placental transport or lactation, stimulated early brain development, including neurogenesis, neuronal differentiation, and migration. BPA binds mostly to estrogen receptors (ERs) like ERα and ERβ, making it a weak estrogen mimic with a 1000-10,000-fold lower affinity than natural estradiol (Archana et al. 2024). ERβ is reported to have a significant function in neuronal differentiation (MIYAZAKI ET AL. 2025).

Thyroid hormones, among other hormones, have an important role in fetal neurodevelopment (Williams 2008). BPA is classified as an EDC (endocrine disrupting chemical), influencing TSH and thyroid hormone secretion (Morreale de Escobar 2001). Hypothyroxine can cause difficulties such as respiratory disorders, premature birth, and incorrect fetal brain development (Sahay and Nagesh 2012).

BPA exposure during pregnancy has been identified as the primary cause of an increase in the risk of neurological abnormalities in children, as their neural systems are structured to respond to environmental changes during prenatal life. Recently, there has been an increased attention on the impacts of prenatal BPA exposure, which has been shown to change gene expression related to epigenetic mechanisms such as DNA methylation, histone modification, and microRNA expression. Evidence suggests that frequent contacts can result in hereditary alterations in an individual's brain profile (Nayan et al. 2024).

BPA exposure has been related to a variety of neurological problems (Chi et al. 2007; Chen et al. 2022) owing to oxidative stress induced by a decrease in reactive oxygen species (ROS). ROS is crucial for fetal development at various stages (Díaz-Hung and ME 2013). The free radicals produced by ROS are employed by the CNS to conduct several physiological functions (Hussain et al. 2021). Furthermore, many research have found that BPA exposure during neurodevelopment might lead to anxiety disorders (Li et al. 2023). Even low-dose exposure can cause the formation of a chemical that has a harmful effect on the brain (Fujiwara et al. 2018). BPA exposure affects the form and morphology of the embryo (Aluru et al. 2010).

2.2. EFFECT ON BRAIN DEVELOPMENT AND SEXUAL BEHAVIOR

BPA exposure in the fetus may happen through the maternal route, affecting brain development from the start. A study found that higher consumption of BPA around 3 to 6 months of pregnancy can disrupt the white matter in the brain more than less virulent exposure (Grohs et

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al. 2019). The abnormally developed brain from an early age has negative and significant repercussions on human life, generating retarded mental states. The negative effects of BPA on neurological growth also affect the hypothalamus. The impact on puberty might potentially lead to increased and intense sexual desires, leading to hypersexual illness in people. Hypersexual disorder is characterized by an increase in sexual urge frequency and intensity that causes physical and emotional stress on the human mind and body (Reid et al. 2012; Kingston 2018).

Billions of pounds of BPA are manufactured annually through industrial processes for use in business goods, making human exposure to BPA common. Fears have been increased about the potential negative health impacts of BPA, particularly in sensitive groups such as pregnant women and children. BPA is a chemical that disrupts the endocrine system and has been related to reproductive damage. We discuss BPA's history and present use, health and safety issues and laws and regulations, reasons for exposure, and evidence of male and female reproductive toxicity. Epidemiological and animal research show that both low and high levels of BPA (prenatal, postnatal, and adulthood exposure) can harm male and female fertility and reproductive organs (Cull and Winn 2025). Studies have shown the effect of hyper sexuality disorder on society and crime rate. For example, in a study (Krueger et al. 2009), 60 males were examined that have sexual cases filed on them the results have shown 33 % of patients were hyper sexuality positive. There are many in vitro studies that represent an alteration in neurodevelopment and behavior of fetus in contrast to BPA exposure (Rebolledo-Solleiro et al. 2020). The low dose exposure of BPA also affects fear stimulus as shown in an animal study conducted on mice (Negishi et al. 2004). In vivo studies also show same kind of effect under BPA exposure. BPA analogues like BPF is also consider being harmful for fetus and its exposure also seems to affect the neurodevelopment of brain. In a study conducted by (Gill and Kumara 2021), they studied the effect on neurodevelopment of rat fetal by exposure of BPA and BPF on rat neuro stem cells (RNSCs). The applied concentration range was 0.05μM to 100 μM. The result shows an alteration of neurodevelopment of fetus that directly depends upon the concentration of exposure by both BPA and BPF. This study concludes that not only BPA but its analogue like BPF is also harmful for neurodevelopment.

BPA is also linked with neurologic diseases such as neurovascular which include stroke, neurodegenerative diseases which include Alzheimer and Parkinson disease. In addition, epidemiological investigation also found that many neurological disorders such as anxiety,

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depression, cognitive developmental disorders, ADHD, and ASD in children were associated with neuro-destructive impacts of BPA on their developing brains. According to WHO, stroke, or brain attack, is estimated to be a leading global neurovascular disorder, the second most frequent cause of death globally, and the third factor for debilitating disability. It is because neurological diseases are fatal or can cause permanent disability and neurovascular diseases are one of them. Cerebrovascular disorders are disorders of the cerebral blood vessels and the spinal cord. BPA affects brain system neurotoxicity by reducing synaptic plasticity, inhibiting the process of neurogenesis, inducing ROS levels, apoptosis as well as autophagy. Animal investigations show that exposure to BPA in the womb at low doses may have affective the anatomy and electrical activity of the brain and, therefore, behavioral development, while epidemiological observations establish the iodine of maternal exposure to BPA at different times in pregnancy with neurobehavioral issues at different ages of childhood more telling in boys and often associated with neurodevelopmental disorders (Costa & Cairrao, 2024a)

Enhanced dopamine receptor activation in response to BPA exposure through organogenesis and lactation indicates two discrete times of high BPA hazardous potential. BPA is harmful to the brain in both high and low amounts. BPA administered during pregnancy may produce neurological deficits in the offspring, which may be related to interaction with mother thyroid or gonadal hormones (Costa & Cairrao, 2024b).

It also influences oxytocin/vasopressin behaviors: BPA. Chronic low-dose BPA exposure in gestation, alters the neurotransmitter genes of mRNA expression in offspring's brain trans generationally influencing social behavioral pattern it is assumed or influenced epigenetically through DNA methylation imprinting. This exposure leads to long-term sex-specific epigenetic modifications in the brain, which may later impact operations and behaviors in the brain. Neurodegeneration disorder is defined as the loss of structure or function of neurons including their death (Inadera, 2015a) (Ikhlas and Ahmad 2020). Infants with postnatal BPA exposure have been found to have reduced tyrosine hydroxylase immune reactivity in the midbrain and reduced gene expression of DAT. Significantly, prenatal and lactational exposure to BPA has been reported to enhance concentration of DA and its metabolite; 3,4-Dihydroxyphenylacetic acid in various brain areas, SN. This indicates that BPA alters the brain dopaminergic circuitry and can be linked to Parkinson 's disease (Rebolledo-Solleiro, 2021a).

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Various instinctual and voluntary movements of animals have also been associated with different behavioral pathologies of animals which include neuro development incidents such as ADHD, ASD, and Intellectual disability (ID). Among these abnormalities one may identify hyperactivity of the locomotor activity, cognitive impairment manifested by learning and memory dysfunction, as well as increase in the level of anxiety-like behavior. Cognitive development is also impaired through learning and memory after having been treated with early BPA exposure, research shows that there are negative effects on learning and memory in offspring. Such partial impairments may be mediated through changes in PKC/ERK and BDNF/CREB signaling pathways, NMDA receptor subunit, and AMPA receptor subunit, and of other crucial pre/post-synaptic proteins (Welch & Mulligan, 2022a). As for anxiety-like behaviors, these have been detected in offspring, though, in many cases, such phenotypes manifest depending on the sex of the offspring. Maternal exposure to BPA shifts the ratio of synexpressin I (excitatory) to synexpressin II (inhibitory), which have been implicated in the etiology of neuropsychiatric disorders, including ASD, ADHD, schizophrenia, and epilepsy. Because BPA can affect the ratio of excitation and inhibition, developmental exposure threatens the development of a plethora of mental illnesses (Welch & Mulligan, 2022b).

2.3. MECHANISMS UNDERLYING BRAIN DEVELOPMENT AND INVOLVEMENT OF BPA ON THESE PROCESSES

Beginning with the differentiation of neural progenitor cells, brain development during embryogenesis occurs during the late first month of gestation in humans. The creation and development of the two main brain cell lineages (glia and neurons) follow the key event of this initial phase, which is the proliferation of neural progenitors. After leaving the proliferative ventricular zone, these cells move to their ultimate locations, where neurons start to form and lengthen dendritic and axonal processes, as well as create neurotrophic factors and neurotransmitters. Specialized glial cells create scaffolding processes that allow cells to migrate in order to facilitate neuronal migration (Rajan & Fame, 2024a).

The major neural structures are formed by the end of embryogenesis, and the basic blueprint for the ultimate structure of the brain is established. Following the neonatal stage, neurons form synaptic connections with other neurons under the influence of their surroundings. It is now evident that the high ability for adaptation, which results from a constant modification of neuronal quantity and connections, is the distinguishing feature of brain differentiation. The brain

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also changes after birth, growing in size and changing structurally in the gray and white matter regions until adulthood (Rajan & Fame, 2024b; Stiles & Jernigan, 2010) .

Since the development and exposure to BPA alter the messenger RNA (mRNA) expression of certain of these genes, it is possible that the chemical, which modifies DNA methylation, directly affects the transcriptome. According to this theory, it has been shown in vitro that embryonic hypothalamus neurons may express different amounts of DNMTs following a brief exposure to micromolar levels of BPA (Cariati et al., 2020b; Negri-Cesi, 2015b). Additionally, changes in histone remodeling have been linked to neurodevelopmental abnormalities. Research has demonstrated that BPA alters histone marks in vivo as well as in vitro (Olsvik et al., 2019). Nevertheless, no assessment has ever been conducted on the compound's direct effects on the neuronal histone profile during embryogenesis.

It is commonly acknowledged that the growing brain has bipotentiality at birth, meaning it can equally develop into a male or female phenotype. The distinct hormonal environment that the brain is exposed to during a "critical sensitive window" of prenatal development is the determining variable. The hypothalamus and other nuclei undergo permanent changes in cell number and morphology during this time due to a complex series of "organizational" events. This results in the formation of particular neuronal networks that serve as the morpho-functional underpinnings of the adult brain's sex-specific response to hormonal and environmental inputs, or "activation" effects (Arnold, 2009; Negri-Cesi et al., 2008).

This hypothesis (summarized in Figure 4) states that the development of the testes or ovaries depends on the chromosomal sex of the embryo. When gonadal sex is established, brain feminization takes place when gonadal hormones are absent. In contrast, a prenatal testosterone peak from the fetal testes causes the developing male phenotype in boys. The brain experiences two different effects from testosterone: first, it organizes neurons to support a male-typical style of activity (a process known as masculinization); second, it suppresses the female-typical mode of action (a process known as defeminization) (McCarthy & Arnold, 2011a).

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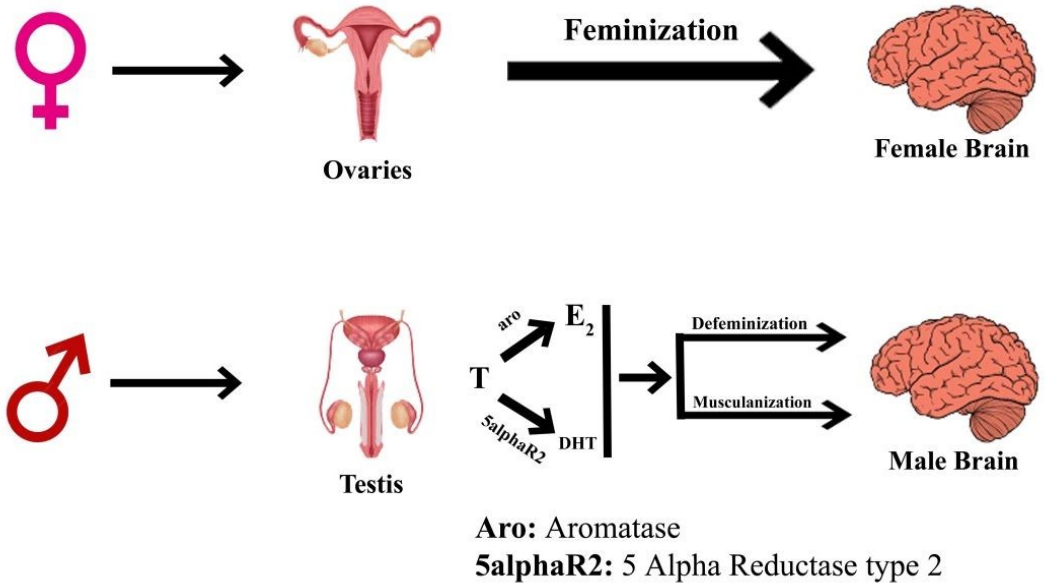

Figure 4. Showing the development of the testes or ovaries dependence on the chromosomal sex of the embryo (sex chromosomes XX or XY)

It is clear that disrupting the intricate regulation of this highly controlled dimorphic process within the critical developmental window may have long-term consequences, and that BPA, which functions as both an estrogen and an anti-androgen, may have a significant impact on the majority of these processes. Numerous studies show that embryonic exposure to low BPA disrupts the process of brain sex differentiation, resulting in long-lasting changes to the structure and functions of the brain. Few reports, nevertheless, explicitly examined whether the molecular targets were anything other than variations in ER and/or AR activity. In the hypothalamus and extra-hypothalamic brain regions, BPA affects the expression pattern of ERα and ERβ, influencing the factors which may be implicated on sex steroid receptors and testosterone activating enzymes (Marlatt et al., 2022; Schug et al., 2015).

About the androgen-AR system, there is no information in the literature about how BPA affects the expression of the two 5α-reductases, and it appears that AR expression in male hypothalamus SDN-POA increases only after exposure to adulthood (Sánchez et al., 2013).

2.4. NEUROENDOCRINE TARGETS

The human endocrine system comprises an intricate network of interactions, especially the reproductive system is a quite complex sort of entity in this network. This network can be disturbed by the interference from foreign agents like EDs ultimately leading to the dysregulation in its functioning. Dr. David Barker proposed a “Barker hypothesis” which elaborates the mechanism

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of adult metabolic disorders as a result of changes occurring in the preconceptual, fetus and infant phases of an individual (Hajjar et al. 2024).

Ion is and sexual disorders in addition to epigenetic modifications in fetus (Di Nisio and Foresta 2023). BPA exposure during pregnancy affects the neuroendocrine axes functions affecting the central (pituitary and/or hypothalamus) as well as peripheral (endocrine) axes. Endocrine hypothalamus is responsible for the regulation of primary homeostatic functions and may be considered as an interface between the human body and its surrounding environment. This gland activates the autonomic nervous system by secreting various releasing hormones (RHs) as well as neurohormones/neuropeptides. Hence, exposure to BPA may lead to homeostasis malfunctioning and memory loss. (Shahid et al. 2018).

BPA is also known to mimic the effect of vitamin D due to the similarity in its structural homology by binding with sex hormones like estradiol and testosterone, thereby disrupting the action of vitamin D. This toxic compound is also known to interact with steroid hormone receptors e.g., androgens and glucocorticoids (Gounden et al. 2024).

2.4.1. THYROID AXIS

Thyroid malfunctioning in the fetus during the first trimester of pregnancy may affect the individuals even in the adult stage leading to mental health issue. (Kolb and Fantie 2009) in addition to hypo- as well as hyperthyroidism. This is because the normal brain development depends on thyroid hormones, and adult brain functions are severely compromised when the thyroid axis is disrupted or inhibited during pregnancy. Some in vitro investigations showed that low BPA suppresses TR-mediated gene expression, increasing the recruitment of corepressors, despite the fact that BPA binds to thyroid hormone receptors (TRs) with low affinity, indicating that high doses are necessary to upset this axis. It appears that certain thyroid hormone-regulated developmental processes, like oligodendrocyte differentiation from precursor cells, are similarly impacted by the TR-antagonistic effect of BPA. The widely used elongated derivatives of BPA, on the other hand, have a greater effect on the thyroid axis and, depending on the kind of TR present, can operate as either TR agonists or antagonists (Bernal J. et al., 2022;Moog et al., 2017).

2.4.2. ADRENAL AXIS AND STRESS RESPONSE

Many neuroendocrine diseases and cognitive deficiencies have been connected to changes in the hypothalamic-pituitary-adrenal (HPA) axis during development. The HPA axis plays a crucial role in the neuroendocrine regulation of stress responses. This axis is intricately connected

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to the limbic system through glucocorticoid signaling and is able to respond to real as well as perceived threats by initiating and regulating the stress responses suitable for the situation. The disturbance in the HPA-limbic system connection may lead to a continuous inhibition or continuous secretion of glucocorticoids, which may lead to the risk of developing severe psychiatric disorders (Caudle 2016). . According to in vitro and in silico research, BPA has an affinity comparable to that of synthetic or natural glucocorticoids for binding to and activating glucocorticoid receptors (GRs). BPA may alter the action of sex hormones and directly disrupt this neuroendocrine system. Significantly, greater dosages of BPA (1.5 mg/kg/d) during pregnancy change the locus Coeruleus's sexual differentiation (Hinds & Sanchez, 2022; Sheng et al., 2021).

Exposure to BPA during the early developmental stages like fetal stage may affect the signaling pathways involved in responding the stress conditions. The recent studies involving the altered glutamatergic receptors like AMPA receptor subunit, NMDA receptor subunit NR1 and mGluR1 expression show that BPA exposure during the developmental stages significantly reduces the regulation of these molecules in the hippocampus and amygdala. In addition to the aforementioned molecules, multiple studies have concluded that BPA exposure may lead to abnormalities in limbic system by disturbing the GABAergic signaling. GABA synthesis involves the expression of GAD65 and GAD67, the critical enzymes involved in this process. The underlying mechanism behind the reduced expression of these enzymes has been reported to be the result of BPA exposure in basolateral amygdala of the offspring. The basolateral amygdala sends the excitatory input to HPA axis leading to dopaminergic and noradrenergic systems, hence leads to the inhibition of glutamatergic signaling exposure (Caudle 2016).

2.4.3. REPRODUCTIVE AXIS AND SEX BEHAVIOR

The idea that BPA negatively impacts on both sexes i.e., male and female reproductive functions, is supported by mounting data from various studies in vivo and human studies. These studies show that BPA interferes not only with gonad hormone dysfunction as well as development in addition to growth and activity of the GnRH neurons under the action of hypothalamus. The pure antagonist ICI 182 780 dramatically reduces the dose-dependent stimulation of GN11 migration that occurs in vitro when exposed to nanomolar concentrations of BPA, indicating the direct involvement of ER activation. BPA can promote EMT process in carcinogenesis, which is consistent with its effect on the migration of neurons during embryogenesis (Matuszczak et al., 2019; Molina-López et al., 2023; Shamhari et al., 2021).

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2.4.4. EFFECTS ON THE CONTROL OF FOOD INTAKE AND ENERGY EXPENDITURE UNDER THE HYPOTHALAMUS

A number of developmental cues strictly regulate each of these processes, and disruption of their function may be the root cause of serious reproductive problems like Kallmann syndrome. The pure antagonist ICI 182, 780 (Fulvestrant™ – the first estrogen receptor down-regulator) dramatically reduces the dose-dependent stimulation of GN11 (GnRH-secreting neuronal cell line) migration that occurs in vitro when exposed to nanomolar concentrations of BPA, indicating the direct involvement of endoplasmic reticulum activation (Meli et al., 2020; Santiago et al., 2024). Additionally, prenatal BPA exposure alters AVPV (hypothalamic anteroventral periventricular nucleus) shape, resulting in the demasculinization of the male nucleus and the masculinization of the female nucleus (reduction in size) in females. Specifically, BPA-treated males have a sustained, female-like luteinizing hormone surge when estrogen primed and have more Kiss-expressing cells in the AVPV(Cariati et al., 2020c).

2.4.5. IMPACT OF BPA ON OTHER BRAIN AREAS AND FUNCTIONS

BPA has an impact on a variety of nonreproductive dimorphic behaviors. Indeed, it has been shown that low doses administered to fetuses eliminate or reverse the dimorphism in adult animals' novelty response behavior and locomotor activity. This is accompanied by an estrogen-dependent alteration in the size of the brain region responsible for these behaviors (Ponzi et al., 2020a, 2020b). According to several publications, BPA exposure during development has a significant impact on mice' anxiety-related behaviors. It frequently blunts or reverses the typical dimorphic response in traditional anxiety tests like the elevated plus maze assay and the open-field exploration. Notably, elevated basal and stress-stimulated corticosterone levels correlate with the elevated anxiety displayed by exposed females in exploratory testing. All factors considered, these and other behavioral data suggest that BPA may influence anxiety through changing the HPA axis or interfering with the brain's estrogen-induced sexual differentiation (Kumar & Thakur, 2017; Rebuli et al., 2015).

3. FETAL MOLECULAR CHANGES DUE TO BPA EXPOSURE

The effect of EDCs extends beyond agonist or antagonist roles in endocrine pathways to include receptor expression, signal transduction, and hormone synthesis/transport/distribution/clearance. This interference can potentially disrupt the endocrine and/or metabolic pathways, consequently altering normal physiology (Puvvula, Song, Zalewska, Alexander, Manz, Braun, Pennell, DeFranco, Ho, Leung, et al. 2025). The fetal brain also acquires

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various subtypes of interneuron's that are present in adult stage (Yu et al. 2021). The exposure of BPA alters the molecular structure of brain by altering interneurons. The generation of interneurons in fetal occurs by progenitor cells of embryonic sub pallium from there they migrate to pallium with the help of different stereotype streams (Lim et al. 2018). The generation of interneurons is essential for the normal functioning and formation of mammalian brain (Yu et al. 2021). BPA affect the development of brain by affecting the expression of Kcc2mRNA for development of human cortical neurons (Yeo et al. 2013). Around 20 % of cortical neurons are interneuron's (Batista-Brito et al. 2020).

Alternation of neurotransmitters is also affected by the change in development of interneurons. The neurotransmitters are linked with interneurons. A neurotransmitter GABA is released in the human body which helps to regulate the neuronal activity and helps to form key nodes within neural circuitry in the brain. This neurotransmitter is also responsible for inhibiting the firing of other neurons. The BPA exposure also has adverse effect on neural connectivity because it is also an EDC (Ghassabian and Trasande 2018). Neural connectivity is actually the link present between nerves that help in transmission of impulses.

Another important neurophysiologic process involved in brain development is term as synoptic plasticity which is the power of neurons to develop strength of their linking and communicating abilities (Turrigiano and Nelson 2004; Stampanoni Bassi et al. 2019). There are many studies which represent that the synoptic plasticity of animal is greatly affected by exposure of BPA and other similar EDCs as an example. In zebra fish embryos the BPA consider to evoke strong brain specific aromatase even at 10 μM (Chung et al. 2011). In a study (Wang C et al. 2014), 4 groups of pregnant rats were exposed to BPA at concentration level 0.05, 0.5,5 or 50 mg/kg body weight and result is collected and analyzed from the offspring. The results show that the exposure of BPA through maternal route has negative affect on offspring synoptic development it also widens the synoptic cleft. This study concluded that the synoptic plasticity might change because of maternal BPA exposure causing memory and learning disorders. Further research is necessary in this field for further analysis and to completely deal with it.

3.1. EPIGENETIC EFFECTS

Epigenetic effects are the genetic defects that are caused due to environmental factor and instead of changing gene sequence it effects the gene expression in organism. Epigenetic effects occur through environmental factors BPA is also an environmental factor and its effect is more

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adverse at developmental stages that cause epigenetic effect alternation. The long-term exposure of Bisphenol A effects the genetic expression of a gene during development (Kundakovic and Champagne 2011).The effect of BPA on the thyroid hormone gene also effects gene expression of thyroid gland i.e. epigenetic effect. However, there is only a little amount of data available on this topic which is far less to reach any conclusion. The no of scholarly article on BPA effect on thyroid hormone genes are just 4 since 2011 to 2023.

The gene expression during fetal development is a critical event in the growth of an individual. Both the paternally and maternally expressed genes work together for the development of the fetus. Fetal growth is promoted by the paternal gene on the other hand the maternal genes suppress the growth of the fetus (Moore et al. 2015). If any parental or maternal gene does not express itself during fetal development it may lead to abnormality throughout life. Even low dose BPA exposure during pregnancy in mice can affect the epigenetic expression and epigenetic programming in brain (Kundakovic et al. 2013). In a study published in 2017 the researcher shows the epigenetic changes in brain function and behavior related to BPA exposure at prenatal state (Kumar and Thakur 2017).

3.2. TRANSGENERATIONAL EFFECT

The effect of BPA is not limited to a single generation it can transfer from one generation to other i.e., from parental P generation to F1, F2 and other generations also effected for example in a study conducted by (Wolstenholme et al. 2013). In this study the relation of BPA exposure among F1 and F3 generation are shown these when compared with control group show that the exposure to Bisphenol A can cause transgenerational disorders.

Another study published in seminars in cells and developmental biology volume 43 suggest that the EDCs has adverse transgenerational effects on metabolism, reproduction and the physical neurodevelopment (phenotype neurodevelopment) (Xin et al. 2015).

3.3. EFFECT ON PITUITARY GLAND

Pituitary gland is sub divided into three main portion anterior lobe, middle lobe and posterior lobe. It secretes many hormones that are essential for homeostasis. The hormone secreted by pituitary gland also affect and control the secretion of hormones from other glands situated at different region of body (Hiller-Sturmhöfel and Bartke 1998). BPA show adverse estrogenic effect on pituitary gland. There are many studies that concludes the potential hazards of BPA exposure on pituitary gland even at embryonic state especially in females not males. The BPA exposures

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affect the mRNA POMC concentration was shown in study (Panagiotidou et al. 2014). In this study the effect of low parental BPA exposure on mice was studied to understand its effect on sex and stress hormone of both genders. The results concluded that the BPA exposure did not greatly alter the concentration of POMC mRNA in test group as compared with controlled group in both males and females at different post stress level.

Another study conducted by (Brannick et al. 2012) published in journal biology of reproduction. In this study teprenone mice are exposed to BPA at concentration of 0.5 to 50 μg/kg/day. The purpose of this study is to understand the low dose BPA effect on pituitary proliferation and gonadotrophin hormones at prenatal state. The result concluded that the low-level exposure of BPA affects the gonadotrophin hormones. The level of mRNA gonadotrophin hormone increases at exposure level of 0.5μg/kg/day of BPA and decreases the level of mRNA at concentration level 50μg/kg/day of BPA. However further study is required to completely understand the effect of BPA exposure on pituitary gland. Another study (Eckstrum et al. 2018) published in journal endocrinology told some interesting findings. In this study neonatal BPA exposure (0.05-50 μg/kg/d) in mice caused sex-specific gene expression changes in pituitary development, reducing Pit1 and POMC mRNA expression in males, while POMC mRNA was reduced in both sexes. These effects were mediated by estrogen receptors and distinct from embryonic BPA exposure, highlighting sex-specific responses.

3.4. EFFECT ON MEMORY FORMATION

Short-term memory is defined as the memory and data store in brain not for a brief amount of time like the dress you wear last week and where you park your car yesterday. It can be described as the part of memory that seems not very essential to brain so human brain not keeps such incident permanently stored. Long term memory is defined as the memory stored permanently in your brain like your name, your work etc. Memory formation is an important cognitive function. The estrogen signaling pathways serve as the main point of cognitive processes like memory formation (Tecalco-Cruz et al. 2023).

The researches on hippocampus, the memory formation organ, have shown that the hippocampus estrogen receptor α is affected by BPA exposure in mice male's offspring's (Wu et al. 2020). Hence affecting the estrogen signaling pathways in brain. BPA exposure at fetal stage in animals also show adverse effect on the development of the hippocampus and dopamine related cells of brain. A study on rhesus monkey show that the BPA exposure during fetal state decreased

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no of dopamine related cells and hippocampus connections (which are essential for memory formation) but at the age of 14 to 18 months these cells are unaffected by BPA exposure (Elsworth et al. 2013).This study concludes that the effect of exposure of BPA is age-depended factor and the effect at fetal state is more harmful at adult state. However further study is required to completely understand the fetal exposure effect at memory formation at adult level in humans.

3.5. EMBRYOLOGICAL MORPHOLOGICAL CHANGES

Studies have shown that the structure of developing embryo at fetal stages is also depended upon maternal hormones. Maternal hormones like gluco carticosteroid, progesterone etc. plays a significant role in fetal neurodevelopment (Baud and Berkane 2019). BPA acts as endocrine disruptor i.e.it has the ability to alter different hormonal secretions causing hormonal disturbance (Lejonklou et al. 2016). A study on rainbow trout fish show significance changes during development when it they were exposed to BPA.

It is observed that the shape of rainbow trout changes which is directly proportional to the concentration of BPA given to them as shown in. It suggests the potential danger that the BPA exposure holdover embryo or fetal development. Further studies are required in this field to explore more effects on developmental embryo when exposed to BPA.

4. IMPACT OF BPA ON CARCINOGENESIS-RELATED CELL SIGNALING PATHWAYS

BPA exposure is associated with the elevated risks of carcinogenesis leading to the proliferative processes in all types of cells specifically thyroid or mammary epithelial cells (Porreca et al., 2016) by the activation of cell signaling cascades like SRC1-3, c-RAF,and HER3. In addition to that AKT is also affected by BPA exposure (Hu et al., 2021; Trivedi et al., 2023) while it has been observed that exposure to low-doses of BPA increased the production of reactive oxygen species chronically while leading to an elevation of inflammatory factor, NF-κB. During this process, the capacity of a cell to react against genotoxic challenges is demoted due to an observable suppression in expressing the genes that control the DNA repair mechanistic (Porreca et al., 2016). The p21-Tp53 axis is impaired in BPA-exposed cells, which ultimately increases the risk of cell death by distortion in the structure of DNA (Porreca et al., 2016).In human breast epithelial cells, it was demonstrated that BPA caused DNA methylation while disturbing the process of apoptosis and DNA repair by up-regulating CtBP resulting in the loss of control over the G2/M checkpoint in cell cycle. According to this study and others, ambient BPA levels may

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affect cells' capacity to react to a second stressor by changing the same physiological functions but through distinct gene networks (Fernandez, 2012).

5. IMPACT OF BPA ON CELL DIVISION AND CELL GROWTH

Estrogen is a female hormone responsible for developing the reproductive system and its related functions but when this category of hormones is exposed to the body via environmental routes, carcinogenesis takes place. There are two major forms of estrogen receptors (ER) in mammals namely; ER-α and ER-β which mediate the actions of oestradiol-17β (E2) by interacting with estrogen response elements (ERE). One well-known example of synthetic estrogen is BPA, which acts on the ERs both agonistically and antagonistically. It can obstruct the activation of numerous genes that are triggered by ERs and support the infinite multiplication of cancer cells (Murata & Kang, 2018; Park & Choi, 2014). Moreover, BPA exposure leads to the growth of cancer by up-regulation of the mRNA for PCNA, which is in charge of cell division (Ptak&Gregoraszczuk, 2012). Based on a study conducted on GC-1 cell line derived from a mouse testis that are used to study the early stages of spermatogenesis), exposure to a low dose of BPA induced the expression of GPR30 through the EFGR, ERK, c-Fos,ER-α, and PKGpathways. This likely increased cell proliferation through a regulatory loop (Sheng et al., 2013).

6. EFFECTS OF BPA ON CELLULAR TISSUE INVASION AND MIGRATION

The natural endogenous estrogen E2 (bimolecular elimination) triggers the epithelial-mesenchymal transition, which is a crucial mechanism for cancer cell migration in neoplasms that are estrogen-sensitive. EMT causes cancer metastases to grow new cancer cell nests and enter the bloodstream from the original cancer. By enhancing mesenchymal markers, lowering cell binding proteins, and stimulating protease activity, BPA accelerates the invasion and migration of cancer cells and increases the expression of the genes linked to this process (Kim et al., 2015; Park & Choi, 2014; Yang et al., 2023).

For instance, in ovarian cancer BG cells, E2 has been demonstrated to enhance snail expression through ER-α and ER-β, resulting in an EMT response. Another study found that E2 caused ER+ human breast epithelial stem cells with HER2 overexpression to undergo EMT and become tumors. Through the MAPK pathway, HER2 stimulates the production of COX-2sin breast epithelial cells. Through the MAPK pathway-dependent amplification of COX-2 expression, BPA has been demonstrated to enhance RL95-2 cells' capacity for invasion and cell migration (Wang et al., 2015).

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7. EFFECTS OF BPA ON APOPTOSIS

By deactivating pro-apoptotic proteins and triggering survival proteins and anti-apoptotic signals, BPA lowers apoptosis in cancer cells (Murata & Kang, 2018). Rat thymocytes that have been immortalized also showed similar effects. According to one study, BCL2L11also known as BIM can induce apoptosis in both neuronal and epithelial cells. The hypermethylation of this gene following BPA treatment implies that BPA exposure inhibits cell death. Another study demonstrated that BPA exposure inhibited apoptotic cell death by lowering the expression of pro-apoptotic p53 and its downstream pro-apoptotic Bax in both HRBECs and T47D ER-positive breast cancer cells (Dairkee et al., 2013).

According to a study by Bilancio et al. (2017), BPA treatment activated ERK and caused the 53 proteins to become phosphorylated and stabilized at ser15, which in turn reduced the expression of the cyclin D1 protein and increased the expression of P21 and P27. This, in turn, caused the cell cycle to stop (Bilancio et al., 2017).

8. IMPACT OF BPA ON RESISTANCE TO ANTICANCER DRUGS

Drug resistance can result from a number of reasons, such as alterations in the expression of ABC transporters and anti-apoptotic, pro-apoptotic, and/or pro-survival genes, which can help cancer cells evade the effects of anticancer medications. Multidomain integral membrane proteins known as ATP-binding cassette transporters move substances across cellular membranes by hydrolyzing ATP (Mansoori et al., 2017; Shahar&Larisch, 2020; Tufail et al., 2024).

BPA promotes the expression of survival and anti-apoptotic proteins by promoting the action of these transporters, which makes cancer cells more resistant to anticancer medications. By increasing the number of pumps by activating mTOR (mammalian target of rapamycin) in HRBECs, decreasing ERK1/2 (proline-directed kinases) activity in acute myeloid leukemia, and boosting BCL-xl (B-cell lymphoma extra-large) transcription in HT29 cells, it also causes tumor cells to become resistant to anti-cancer medications (Cree & Charlton, 2017; Shahar&Larisch, 2020).

9. RISK MITIGATION

Mitigation is defined as the prevention that are taken to handle a risk and to minimize it damage as much as possible like the precaution applied worldwide for controlling the widespread disease COVID-19. In scientific terms it can be defined as making your words or actions work

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better by being aware of how they might be perceived and making them more effective (Caffi 1999).

10. BAN ON THE UTILIZATION OF BISPHENOL A

The government is taking an important step in the management of BPA exposure as a risk factor to humans. BPA is banned in different countries because of the risk it poses. Different countries have taken steps to eliminate Bisphenol A from their society.

Regulation (EU) no. 10/2011 sets a 0.05 mg kg^{-1} migration limit for chemical compounds in food-contact plastics. If the content of BPA in EU for sale imported items surpasses 0.1% by weight, importers and producers must notify the European Chemicals Agency (ECHA) through the "Substances of Concern" (SCIP database) (Neri et al. 2024). In 2015, the EFSA Panel on Food Contact Materials and Aids lowered the BPA exposure threshold to 4 μg kg−1 body weight/day based on an updated assessment of its toxicity. In 2023, EFSA issued an opinion of scientists on the de novo evaluation of healthcare hazards connected to the amount of BPA in foods. The TDI threshold was decreased to 0.2 ng kg−1 body weight/day (Leist et al. 2024).

11.1. EUROPEAN UNION

European Union banned the use of BPA in the manufacture of food contact materials and its use in the manufacture of baby bottles was banned in 2011 (Commission, 2011). In 2016, the European Chemicals Agency added BPA to its candidate list of substances of very high concern (SVHCs) due to its endocrine-disrupting properties (European Chemicals Agency, 2016). Several other European countries, including France, Denmark, and Belgium, have also banned the use of Bisphenol A in food packaging. The European Food Safety Authority (EFSA) recommended lowering their estimated tolerable daily intake (TDI) for bisphenol A (BPA) 20,000-fold to 0.2 ng/kg body weight (BW)/day (Saal et al. 2024).

11.2. CANADA

Canada was the first country to ban the use of BPA as a toxic substance in 2010 (Aschberger et al. 2010) . Its use was prohibited in baby bottles, infant formula packaging, and plastic toys is prohibited. FDA banned the use of BPA in baby bottles and Sippy cups in 2012.

11.3. JAPAN

In 2001 the Japan ban use of BPA in thermal receipt paper (Konkel 2013). The use of BPA in other food contact materials is also restricted. To eliminate the risk factor of BPA France has almost banned it utilization in production of all type of consumer products (Metz 2016). The

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development of BPA alternatives are important steps toward the elimination of BPA; however, the current BPA alternatives has not reached the stage at which they are not considered as EDCs. The basic alternatives of BPA are shown above. These alternatives also has endocrine affect and can alter the development of fetus.

12. METHODS

The estrogenic endocrine disruptors have the ability to affect both placental function and fetal growth via multiple mechanisms. This emphasizes the importance to minimize the exposure to these chemicals during pregnancy to preserve the well-being and safety of the developing fetus (Kawa et al. 2021) .

The investigation of Bisphenol A (BPA) as a potential endocrine disruptor for the fetus is a comprehensive procedure that includes numerous scientific methods. Biomonitoring and placental cell analysis provide information about the degree of exposure and transfer mechanisms of BPA. Animal research and epidemiological investigations help to better grasp the larger implications of BPA on embryonic development and its adverse effects over time. In situ investigations and hormone assays are critical for determining BPA's cellular and molecular interactions, which provide a comprehensive picture of its endocrine-disrupting potential in the fetus. These methodologies establish a strong framework for analyzing the dangers posed by BPA during important stages of development (Dolinoy et al. 2007).

Previous studies subjected rat fetal neural stem cells (rNSCs) to varying doses of Bisphenol A (BPA) in differentiation media. The researchers next assessed the effects of these substances on cell proliferation, differentiation, and morphometric characteristics to better understand their role in neurodevelopment processes. BPA levels in the samples were most likely measured using analytical techniques such as HPLC and mass spectrometry (MS). The study used a monolayer-based system and Sholl analysis to evaluate the arborization and branching complexity of differentiated cells (Gill and Kumara 2021).

Bisphenol A (BPA) is commonly estimated as a possible endocrine disruptor using a combination of in silico, in vitro, and in vivo techniques. In silico approaches may include QSAR models that link chemical structure to biological activity, whereas in vitro testing may use cell lines to evaluate BPA's interaction with hormone receptors. In vivo research could include examining the impact of BPA on living organisms (Conroy-Ben et al. 2018). Molecular dynamics simulations are also utilized to investigate the interactions between BPA and nuclear receptors.

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Additionally, analytical techniques such as LC-MS are used to assess BPA levels in biological samples (Jondeau-Cabaton et al. 2013).

The methodology of a study studying the effects of BPA on neurodevelopment includes both in vivo and in vitro approaches to understanding its impact on the brain. In vivo, researchers expose embryonic individuals to BPA and study alterations in neocortical development, adult cortical architecture, and spatial learning ability. In vitro, BPA is put into cell cultures, such as embryonic rat hypothalamus cells, to determine its effect on protein expression linked to dendritic and synaptic development. Furthermore, the compound's impact on the proliferation and differentiation of hippocampus oligodendrocyte progenitor cells and neural stem cells is assessed. These approaches provide a complete picture of BPA's possible neurodevelopmental risks (Rebolledo-Solleiro et al. 2020).

13. LITERATURE REVIEW METHODOLOGY

The literature analysis method applied to screen the data was based on mapping the literature through narrative review. The data for this review was collected from web search engine “Google Scholar”, “JSTOR”, “Pub Med” and “Research Gate”. The key words used for searching were “Bisphenol A”, “BPA”, “Fetal Neurodevelopment”, “Neuro Disruptor” and “BPA Maternal Exposure”. All the search was limited to the articles published in English and time line filters applied from January 2010 to date.

CONCLUSION

BPA and its substitutes including BPS, BPAF, BPF are classified as endocrine disrupting chemicals (EDC’s) which severely show the estrogenic effects and the exposure of pregnant females to these EDC’s cause many adverse effects both on the mother and the fetus. The main impact results in the abnormal development of fetal brain. The main reason is that the bisphenols cause disruption in many important endocrine secretions including thyroxine and pituitary glands. This is the main cause of abnormal fetal neurodevelopment thus affecting the mental and physical health for life.

Most of the developed countries of the world have banned the use of bisphenols in plastics and other packing materials while food regulatory authorities have passed regulations to ensure the food materials being free of bisphenols. The packing materials manufacturers are bound to make sure the absence of bisphenols and stamp their products as BPA free. However, in many

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developing counties including Pakistan, the regulations to ban the use of bisphenols are not so strict. That's why bisphenols could be the major threat to the lives and it could be one among many other reasons of the abnormal development of the newborns. It is therefore suggested that a strong compliance may be ensured on the "BPA Free" certification in plastic packaging materials specially to be used in food materials.

CrediT authorship contribution statement

Jun Feng & Mansoor Elahi Mazari: Writing – original draft, Visualization. **Samra Yasmin, Ammara Riaz, Fatima Zohra Masood**: Final editing, Visualization, Revisions. **Jalal Uddin**: Funding acquisition, Final editing. **Ghulam Mustafa Kamal, Jixin Zhong, Abdullah Ijaz Hussain**: Supervision, Formal analysis, Final editing.

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Declaration of interest

The authors declare no conflicts of interest.

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Data Availability Statement

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All data has been provided in the manuscript.