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Impact of bisphenol A exposure on fetal brain development and neurological health-a review

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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 a very large scale around the globe. As this compound has been classified as one of the EDCs, substantial evidence has demonstrated a 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, 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 the fetal stage to mature life. This review encompasses the literature available on 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.

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Environmental significance

Bisphenol A (BPA), a chemical that is widely used in plastics and resins and produced in high volumes, exposes people to its effects 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 that 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's interference with neuronal development.

1 Introduction

Endocrine disruptors (EDCs) are exogenous substances that imitate natural hormones. The World Health Organization (WHO) defines 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".[1] 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 indicates that they can penetrate the placental barrier. Exposure to EDCs, particularly during a critical embryonic phase like pregnancy, could have a significant impact on the peri- or postnatal cardiometabolic regulation.[2]

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Bisphenol A (BPA) is one of the most studied EDCs, particularly for its adverse effects on the endocrine and reproductive systems. BPA, also known as bisphenol A, is an extensively used chemical in the plastic polymer industry. This substance was first produced in 1891,[3] and its manufacturing has since increased to over 6 billion pounds, as reported by the study.[4] BPA has been used as a basic polymer in the milk packaging sector and as a coating and liner material for metallic cans (frequently used for food storage).[5] This substance is not restricted to epoxy resins and polycarbonate plastic; its alternatives are also utilized in dental materials, eyeglass lenses, *etc*.[6]

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 °C).[7] This potentially hazardous chemical acts as an endocrine disruptor, causing undesirable alterations in the human body's hormonal system, particularly affecting the secretion of thyroid hormones.[8]

In 1938, Dodds and Lawson studied the detrimental impact of BPA on estrogen (the female hormone) for the very first time,[9] and the permissible recommended limit *i.e.*, 0.2 ng kg^{-1} body weight (BW) per day was investigated by studies[10] demonstrating that the adverse consequences of BPA are not limited to a particular age group but influence all ages with a few variations.[11] Ilaria Cimmino, Francesca Fiory, and other contributors investigated numerous methods of BPA exposure and identified some of the most prominent probable BPA transmission mechanisms[12] as shown in Fig. 1.

Individuals' reproductive well-being could be harmed as a result of EDC exposure, potentially 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.[13] BPA exposure during pregnancy also affects the fetus. 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.[14]

The maternal route of BPA exposure to the fetus occurs during pregnancy when the mother consumes BPA-containing food. The dosage response of BPA is non-monotonic. Its lower concentrations may have some disruptive effects. Furthermore, due to the increased fetal exposure, the risk of harmful

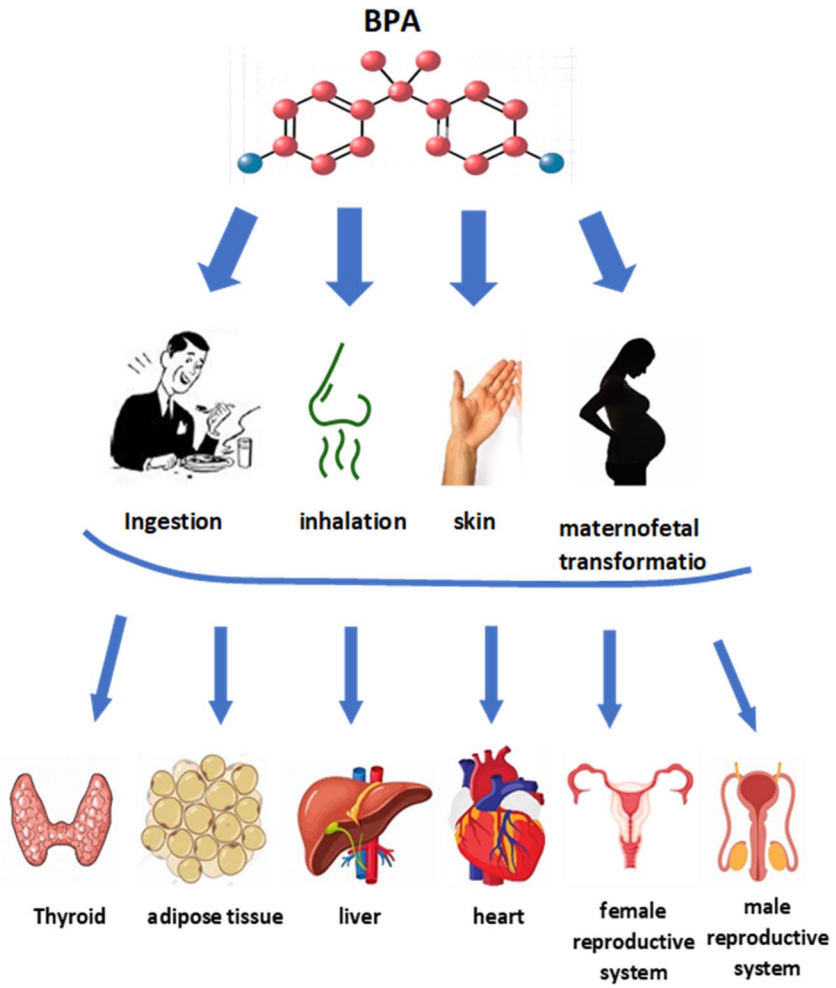

Fig. 1 Transfer of BPA and affected organs.

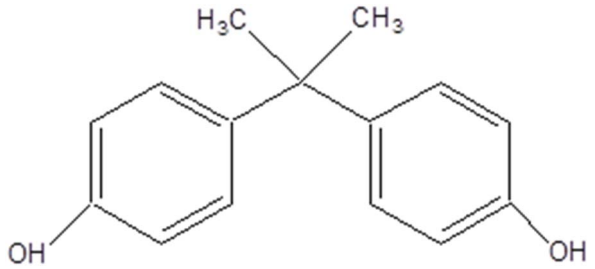

Fig. 2 Structural formula of bisphenol A.

consequences is significantly greater during development than at maturity, even at moderate dosages. One possible reason for the higher exposure is the embryonic 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 activity, regularly deconjugates into active estrogenic BPA in the fetal compartment.[15]

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.[16] There exist multiple studies that have evaluated BPA exposure and thyroid function in people as a result of its exposure in early life and fetal stages.[17]

BPA has the chemical formula $C_{15}H_{16}O_2$ (structural formula shown in Fig. 2) and is a white solid, soluble in organic solvents. Its presence has been detected in many dairy products.[18] BPA has also shown adverse effects on the estrogen receptors causing hormonal disturbances.[19] All the alternatives have a bisphenol ring attached to different substitutes.

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.[20] The placenta is considered a transitory organ that establishes a connection between the mother and the fetus.[21] The development of the fetus depends on the nutrition provided through the placenta from mother to fetus.[22,23] The placental formation in humans occurs at 10 days *i.e.* at 1.4 weeks of pregnancy. BPA can enter the maternal system through daily dietary intake. The anticipated pathway for BPA exposure in the female mouse fetus is shown in Fig. 3 based on research conducted by Miyu Nishikawa published in journal *Environmental Health Perspectives* that elaborates the BPA entry into the maternal system from BPA containing dietary supplements. It can alter the fetus's genotype through exposure to dietary supplements used by mothers during pregnancy.[24]

Several preclinical and experimental studies have found links between gestational EDC exposures and unfavorable newborn outcomes.[25,26] Although exposure to EDCs has a significant impact during gametogenesis and the initial stages of fetal development, some unfavorable outcomes as a result of fetal exposure to EDCs could go undetected until adulthood.[27]

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 the metabolome (177 serum metabolites and 44 urine metabolites), proteome, and methylome profiles proposed interactions between maternal exposures to fluctuating EDCs and omics layers that are linked to phenotypes, including fetal development, weight gain, insulin resistance, and metabolic and neuroendocrine issues.[28]

2.1 Neurodevelopment in the fetus

The nervous system is the primary target of EDCs, which cause developmental disturbances. EDC exposure during the fetal and/or newborn period, either through placental transport or lactation, affects early brain development, including neurogenesis, neuronal differentiation, and migration. BPA binds

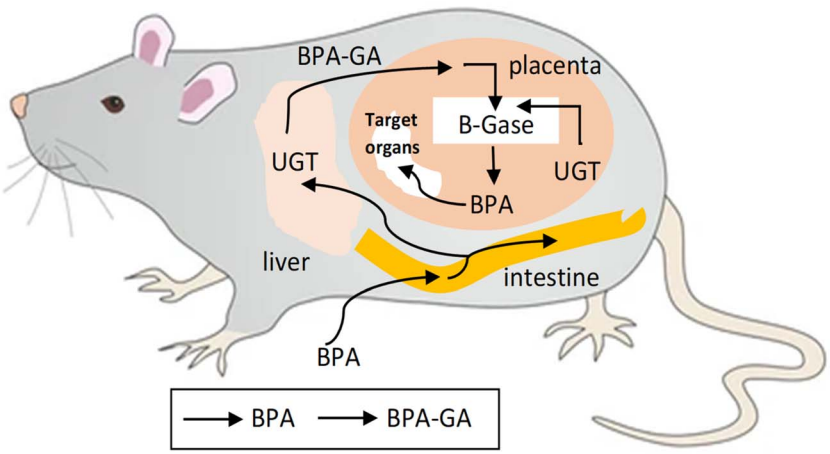

Fig. 3 Anticipated fetal BPA exposure pathway.

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.[29] ERβ is reported to have a significant function in neuronal differentiation.[30]

Thyroid hormones, among other hormones, have an important role in fetal neurodevelopment.[31] BPA is classified as an EDC (endocrine disrupting chemical), influencing TSH and thyroid hormone secretion.[32] Hypothyroxine can cause difficulties such as respiratory disorders, premature birth, and incorrect fetal brain development.[33]

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 increasing 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 exposure can result in hereditary alterations in an individual's brain profile.[34]

BPA exposure has been related to a variety of neurological problems[35,36] owing to oxidative stress induced by a decrease in reactive oxygen species (ROS). ROS is crucial for fetal development at various stages.[37] The free radicals produced by ROS are employed by the CNS to conduct several physiological functions.[38] Furthermore, many research studies have found that BPA exposure during neurodevelopment may lead to anxiety disorders.[39] Even low-dose exposure can cause the formation of chemicals that have harmful effects on the brain.[40] BPA exposure affects the form and morphology of the embryo.[41]

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 BPA exposure around 3 to 6 months of pregnancy can disrupt the white matter in the brain more than less virulent exposure.[42] 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 frequency and intensity of sexual urges, causing physical and emotional stress on the human mind and body.[43,44]

Billions of pounds of BPA are manufactured annually through industrial processes for use in business goods, making human exposure to BPA common. Concerns have 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, 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.[45] Studies have shown the effect of hyper sexuality disorder on society and crime rates. For example, in a study,[46] 60 males were examined with sexual cases filed against them, and the results showed that 33% of patients were hyper sexuality positive. Many *in vitro* studies have shown alterations in fetal neurodevelopment and behavior in connection to BPA exposure.[47] Low dose exposure of BPA also affects the fear stimulus as shown in an animal study conducted on mice.[48] *In vivo* studies also show the same kind of effect under BPA exposure. BPA analogues, like BPF, are also considered harmful to the fetus and their exposure also seems to affect the neurodevelopment of the brain. In a study,[49] the effect of BPA and BPF exposure on rat fetal neurodevelopment was studied using rat neuro stem cells (RNSCs). The applied concentration range was 0.05 μM to 100 μM. The results show an alteration in fetal neurodevelopment that directly depends on the exposure concentration of both BPA and BPF. This study concludes that not only BPA but its analogues like BPF are also harmful for neurodevelopment.

BPA is also linked with neurological diseases such as neurovascular disorders which include stroke and neurodegenerative diseases which include Alzheimer′s and Parkinson′s disease. In addition, epidemiological investigation also found that many neurological disorders such as anxiety, depression, cognitive developmental disorders, ADHD, and ASD in children are associated with neuro-destructive impacts of BPA on their developing brains. According to the 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. This 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 nervous system neurotoxicity by reducing synaptic plasticity, inhibiting the process of neurogenesis, inducing ROS levels, apoptosis and autophagy. Animal investigations show that exposure to BPA in the womb at low doses may affect the anatomy and electrical activity of the brain and, therefore, behavioral development. Epidemiological studies have documented an association between prenatal BPA exposure at various points in pregnancy and the incidence of neurobehavioral issues in children of varying ages. These effects are more pronounced among boys and are often linked with a higher risk of neurodevelopmental disorders.

Enhanced dopamine receptor activation in response to BPA exposure during organogenesis and lactation indicates two distinct periods of high BPA hazard. 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.[50]

BPA also influences oxytocin/vasopressin behaviors. Chronic low-dose BPA exposure during gestation, alters the neurotransmitter genes of mRNA expression in the offspring's brain, transgenerationally influencing social behavioral patterns, potentially through epigenetic mechanisms 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.[51,52] 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 the 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.[47]

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, and an increase in the level of anxiety-like behavior. Cognitive development is also impaired in learning and memory after 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 and AMPA receptor subunits, and other crucial pre/post-synaptic proteins.[53] Anxiety-like behaviors have been detected in offspring, although, 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 has 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.[53]

2.3 Mechanisms underlying brain development and involvement of BPA in 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 final 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 structures that facilitate neuronal migration.

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 numbers and connections, is the distinguishing feature of brain differentiation. The brain also changes after birth, growing in size and changing structurally in the gray and white matter regions until adulthood.[54]

Since the development and exposure to BPA alter the messenger RNA (mRNA) expression of certain 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.[55,56] 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*.[57] 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 the 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 basis for the adult brain's sex-specific responses to hormonal and environmental inputs, or "activation" effects.[58,59]

This hypothesis (summarized in Fig. 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 development of the 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).[60]

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 in the structure and functions of the brain. Few reports, nevertheless, have explicitly examined whether the molecular targets extend beyond 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 in sex steroid receptors and testosterone activating enzymes.[61,62]

Regarding the androgen–AR system, there is no information in the literature on how BPA affects the expression of the two 5α-reductases, and it appears that AR expression in the male hypothalamic SDN-POA increases only after exposure to adulthood.[63]

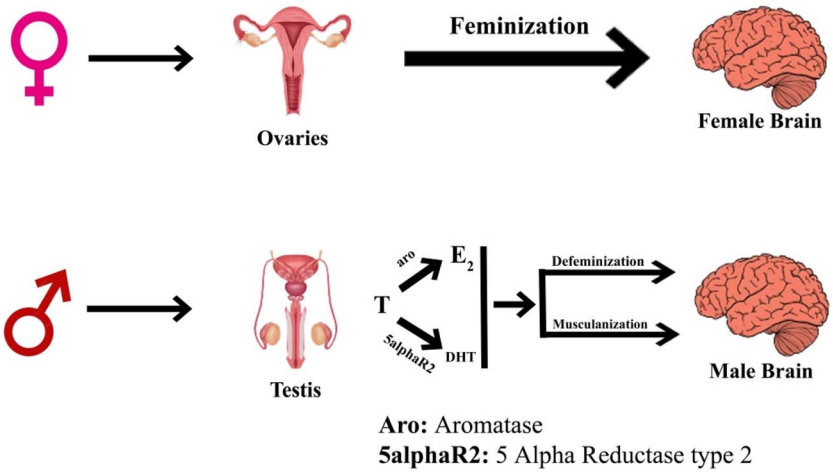

Fig. 4 The development of the testes or ovaries depends on the chromosomal sex of the embryo (sex chromosomes XX or XY).

2.4 Neuroendocrine targets

The human endocrine system comprises an intricate network of interactions, with the reproductive system being a quite complex component 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 of adult metabolic disorders as a result of changes occurring in the preconceptual, fetus and infant phases of an individual.[1]

Exposure to BPA leads to hormone nuclear receptors disruption and sexual disorders in addition to epigenetic modifications in fetus.[14] BPA exposure during pregnancy affects the neuroendocrine axis functions affecting the central (pituitary and/or hypothalamus) as well as peripheral (endocrine) axes. The 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.[64]

BPA is also known to mimic the effects 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.[65]

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 issues,[66] in addition to hypo- and 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.[67,68]

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 to the limbic system through glucocorticoid signaling and is able to respond to real and perceived threats by initiating and regulating the stress responses suitable for the situation. The disturbance in the HPA–limbic system connection may lead to continuous inhibition or continuous secretion of glucocorticoids, which may lead to the risk of developing severe psychiatric disorders.[69] 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, higher dosages of BPA (1.5 mg kg^{-1} day) during pregnancy change the locus coeruleus's sexual differentiation.[70]

Exposure to BPA during early developmental stages like the fetal stage may affect the signaling pathways involved in responding to the stress conditions. The recent studies involving the altered glutamatergic receptors like AMPA receptor subunits, 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 the limbic system by disturbing the GABAergic signaling. GABA synthesis involves the expression of GAD65 and GAD67, the critical enzymes involved in this process. The reduced expression of these enzymes has been reported to result from BPA exposure in the basolateral amygdala of the offspring. The basolateral amygdala sends the excitatory input to the HPA axis affecting dopaminergic and noradrenergic systems, hence leading to the inhibition of glutamatergic signaling exposure.[69]

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 gonadal hormone dysfunction and development but also with the 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 the EMT process in carcinogenesis, which is consistent with its effect on the migration of neurons during embryogenesis.[71–73]

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 (a 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.[74,75] 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.[76]

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.[77] According to several publications, BPA exposure during development has a significant impact on anxiety-related behaviors in mice. 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 increased anxiety displayed by exposed females in exploratory testing. All factors considered, these and other behavioral data suggest that BPA may influence anxiety by changing the HPA axis or interfering with estrogen-induced sexual differentiation in the brain.[78]

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.[28] The fetal brain also acquires various subtypes of interneurons that are present in adult stage.[79] The exposure of BPA alters the molecular structure of the brain by altering interneurons. The generation of interneurons in the fetus occurs from progenitor cells of the embryonic subpallium, from where they migrate to the pallium with the help of different stereotype streams.[80] The generation of interneurons is essential for the normal functioning and formation of the mammalian brain.[79] BPA affects the development of the brain by affecting the expression of Kcc2mRNA for the development of human cortical neurons.[81] Around 20% of cortical neurons are interneurons.[82]

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. BPA exposure also has an adverse effect on neural connectivity because it is also an EDC.[83] Neural connectivity actually refers to the link present between nerves that help in transmission of impulses.

Another important neurophysiological process involved in brain development is termed synaptic plasticity which is the ability of neurons strengthen their linking and communication abilities.[84,85] Many studies have shown that the synaptic plasticity in animals is greatly affected by exposure of BPA and other similar EDCs as an example. In zebra fish embryos BPA have been shown to induce strong brain specific aromatase expression even at 10 μM.[86] In a study,[87] 4 groups of pregnant rats were exposed to BPA at concentrations of 0.05, 0.5, 5 or 50 mg kg^{-1} body weight and results were collected and analyzed from the offspring. The results show that the exposure of BPA through the maternal route negatively affects offspring synaptic development and also widens the synaptic cleft. This study concluded that synaptic plasticity might be changed because of maternal BPA exposure causing memory and learning disorders. Further research is necessary in this field for deeper analysis and to completely deal with it.

3.1 Epigenetic effects

Epigenetic effects are genetic defects that are caused by environmental factors and instead of changing the gene sequence they affect the gene expression in organisms. Epigenetic effects may be influenced by a variety of environmental exposures.

Bisphenol A (BPA) is an environmental contaminant whose exposure, especially at critical developmental stages, can lead to epigenetic modifications. The long-term exposure of bisphenol A affects the genetic expression of a gene during development.[88] The effect of BPA on the thyroid hormone gene also affects the gene expression of the thyroid gland *i.e.* an epigenetic effect. However, only a little amount of data is available on this topic which is insufficient to reach any conclusion. The number of scholarly articles on BPA's effect on thyroid hormone genes are just 4 between 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 while maternal genes suppress the growth of the fetus.[89] If either the paternal or maternal gene does not express itself during fetal development it may lead to abnormalities throughout life. Even low dose BPA exposure during pregnancy in mice can affect epigenetic expression and epigenetic programming in the brain.[90] In a study published in 2017, the researchers showed the epigenetic changes in brain function and behavior related to prenatal BPA exposure.[78]

3.2 Transgenerational effect

The effect of BPA is not limited to a single generation; it can be transferred from one generation to another *i.e.*, from the parental P generation to F1, F2 and other generations. For example in one study,[4] the relationship of BPA exposure among the F1 and F3 generations is shown. Compared with the control group, the results show that the exposure to bisphenol A can cause transgenerational disorders.

Another study published in *Seminars in Cells and Developmental Biology*, Volume 43 suggests that EDCs have adverse transgenerational effects on metabolism, reproduction and the physical neurodevelopment (phenotype neurodevelopment).[91]

3.3 Effect on the pituitary gland

The pituitary gland is subdivided into three main portions: anterior lobe, middle lobe and posterior lobe. It secretes many hormones that are essential for homeostasis. The hormones secreted by the pituitary gland also affect and control the secretion of hormones from other glands located in different regions of the body.[92] BPA shows adverse estrogenic effects on the pituitary gland. Many studies have concluded the potential hazards of BPA exposure on the pituitary gland even at the embryonic stage especially in females not males. BPA exposure affects the POMC mRNA concentration, as shown in a study.[93] In this study the effect of low parental BPA exposure on mice was studied to understand its effect on sex and stress hormones in both genders. The results concluded that the BPA exposure did not greatly alter the concentration of POMC mRNA in the test group compared with the controlled group in both males and females at different post stress levels.

In another study,[94] published in the Journal *Biology of Reproduction*, teprenone mice were exposed to BPA at a concentration of 0.5 to 50 μg kg^{-1} day. The purpose of this study was to understand the effects of low dose BPA on pituitary proliferation and gonadotrophin hormones during the prenatal stage. The results concluded that the low-level exposure of BPA affects the gonadotrophin hormones. The level of gonadotrophin hormone mRNA increases at exposure level of 0.5 μg kg^{-1} day of BPA and decreases the level of mRNA at a concentration of 50 μg kg^{-1} day. However further studies are required to completely understand the effect of BPA exposure on the pituitary gland. Another study[95] published in the journal *Endocrinology* reported some interesting findings. In this study neonatal BPA exposure (0.05–50 μg kg^{-1} day) 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 were 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 stored in the brain for a brief amount of time like the dress you wore last week and where you parked your car yesterday. It can be described as the part of memory that is not considered very essential to the brain, so the human brain does not retain such information permanently. 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.[96]

Research studies on the hippocampus, the organ responsible for memory formation, have shown that the hippocampus estrogen receptor α is affected by BPA exposure in male offspring of mice,[97] hence affecting the estrogen signaling pathways in the brain. BPA exposure at the fetal stage in animals also shows adverse effects on the development of the hippocampus and dopamine related cells of the brain. A study on rhesus monkeys showed that the BPA exposure during the fetal stage decreased the number of dopamine related cells and hippocampus connections (which are essential for memory formation) but at the age of 14 to 18 months these cells were unaffected by BPA exposure.[98] This study concluded that the effects of exposure of BPA are age-dependent and the effect at the fetal stage is more harmful than in adulthood. However further studies are required to completely understand the effect of fetal BPA exposure on memory formation in adult humans.

3.5 Embryological morphological changes

Studies have shown that the structure of the developing embryo at fetal stages also depends on maternal hormones. Maternal hormones like glucocorticosteroids, progesterone, *etc.* play a significant role in fetal neurodevelopment.[99] BPA acts as an endocrine disruptor *i.e.* it has the ability to alter different hormonal secretions causing hormonal disturbances.[100] A study on rainbow trout fish showed significant changes during development when they were exposed to BPA.

It was observed that the shape of rainbow trout changes in a manner directly proportional to the concentration of BPA they

were exposed to. This suggests the potential danger that BPA exposure poses to embryonic or fetal development. Further studies are required in this field to explore the effects on developing embryos 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[101] by the activation of cell signaling cascades like SRC1-3, c-RAF, and HER3. In addition to this AKT is also affected by BPA exposure[102,103] while it has been observed that exposure to low-doses of BPA increases the production of reactive oxygen species chronically while elevating the inflammatory factor, NF-κB. During this process, the capacity of a cell to respond to genotoxic challenges is reduced due to suppressed expression of the genes that control the DNA repair mechanisms. 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.[101] 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 the cell cycle. According to this study and others, ambient BPA levels may affect cells' capacity to react to a second stressor by changing the same physiological functions but through distinct gene networks.[104]

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 (EREs). 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.[105,106] Moreover, BPA exposure leads to the growth of cancer by up-regulation of the mRNA for PCNA, which is in charge of cell division.[107] Based on a study conducted on the GC-1 cell line derived from mouse testes and 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 PKG pathways. This likely increased cell proliferation through a regulatory loop.[108]

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 form new cancer cell colonies and enter the bloodstream from the primary tumor. 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.[106,109,110]

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 induced EMT in ER+ human breast epithelial stem cells with HER2 overexpression, lead to tumor formation. Through the MAPK pathway, HER2 stimulates the production of COX-2 in 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.[111]

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.[105] Rat thymocytes that had been immortalized also showed similar effects. According to one study, BCL2L11 also 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.[112]

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.[113]

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 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.[114,115]

BPA promotes the expression of survival and anti-apoptotic proteins by enhancing the activity of these transporters, making

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.[116,117]

9 Risk mitigation

Mitigation is defined as the measures that are taken to handle a risk and to minimize its 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 improving your words or actions by being aware of their potential impact and making them more effective.[118]

10 Ban on the utilization of bisphenol A

Governments are taking important steps to manage BPA exposure as a human health risk. 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 items imported for sale in EU surpasses 0.1% by weight, importers and producers must notify the European Chemicals Agency (ECHA) through the "Substances of Concern" (SCIP database).[119] 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 per day.[120]

11 European Union

The 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^{-1} body weight (BW) per day.[10]

11.1 Canada

Canada was the first country to ban the use of BPA as a toxic substance in 2010.[121] Its use was prohibited in baby bottles, infant formula packaging, and plastic toys. The FDA banned the use of BPA in baby bottles and sippy cups in 2012.

11.2 Japan

In 2001, Japan banned the use of BPA in thermal receipt paper.[122] The use of BPA in other food contact materials is also restricted. To eliminate the risk factor of BPA France has almost banned its utilization in the production of all types of consumer products.[123] The development of BPA alternatives is an important step toward the elimination of BPA; however, current BPA alternatives have not reached a stage at which they are not considered EDCs. The basic alternatives of BPA are shown above. These alternatives also have endocrine activity and can alter the fetal development.

12 Methods

Estrogenic endocrine disruptors have the ability to affect both placental function and fetal growth *via* multiple mechanisms. This emphasizes the importance of minimizing exposure to these chemicals during pregnancy to protect the well-being and safety of the developing fetus.[124]

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 understand the broader 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 risks posed by BPA during important stages of development.[24]

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.[49]

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.[125] Molecular dynamics simulations are also utilized to investigate the interactions between BPA and nuclear receptors. Additionally, analytical techniques such as LC-MS are used to assess BPA levels in biological samples.[126]

The methodology of studies investigating the effects of BPA on neurodevelopment includes both *in vivo* and *in vitro* approaches to understand 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.[47]

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 were collected from web search engines "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". The search was limited to the articles published in English from January 2010 to date.

14 Conclusion

BPA and its substitutes including BPS, BPAF, and BPF are classified as endocrine disrupting chemicals (EDCs) which show strong estrogenic effects and the exposure of pregnant females to these EDCs has many adverse effects both on the mother and the fetus. The main impact is the abnormal development of the fetal brain. The main reason is that bisphenols disrupt 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 have banned the use of bisphenols in plastics and other packing materials while food regulatory authorities have passed regulations to ensure that food materials are free of bisphenols. Manufacturers of packing materials are required to ensure the absence of bisphenols and label their products as BPA free. However, in many developing counties including Pakistan, the regulations to ban the use of bisphenols are not so strict. This is why bisphenols could be a major threat to lives and it could be one among many other reasons contributing to the abnormal development in newborns. It is therefore suggested that strong compliance may be ensured with "BPA Free" certification, particularly for plastic packaging materials used in food.

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
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 mouse testis and 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
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

Author contributions

Jun Feng & Mansoor Elahi Mazari: writing – original draft, visualization. Samra Yasmin, Ammara Riaz, and Fatima Zohra Masood: final editing, visualization, revisions. Jalal Uddin: funding acquisition, final editing. Ghulam Mustafa Kamal, Jixin Zhong, and Abdullah Ijaz Hussain: supervision, formal analysis, final editing.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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