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BPA AND NEUROTOXICITY: IMPLICATIONS FOR MENTAL HEALTH AND BEHAVIOR

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ABSTRACT

The environmental endocrine disruptor bisphenol A (BPA) is pervasive and causes serious health concerns to people, especially when it comes to neurotoxicity. By attaching to estrogen receptors and interfering with thyroid hormone transmission, BPA mimics estrogen and disrupts neurodevelopmental processes such synaptogenesis, neurogenesis, and myelination. Additionally, it damages mitochondrial function, triggers oxidative stress by producing reactive oxygen species (ROS), and triggers neuroinflammation by activating microglia and releasing pro-inflammatory cytokines. These molecular abnormalities affect learning, memory, and behavior, and they may be a contributing factor to neurodevelopmental disorders including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Long-lasting behavioral impairments are also brought on by epigenetic alterations brought on by BPA exposure, including as DNA methylation and histone modification, which alter gene expression and neuron function. The brain is more susceptible to neurotoxic compounds as a result of BPA exposure's weakening of the blood-brain barrier (BBB), which may hasten neurodegenerative processes and cognitive decline. In addition to highlighting the need for further study to fully comprehend the long-term consequences of BPA exposure on cognitive and emotional health across generations, this review also addresses the molecular pathways behind BPA-induced neurotoxicity and its implications for mental health.

KEYWORDS: Bisphenol A (BPA); Neurotoxicity; Endocrine Disruptors; Cognitive Impairment; Oxidative Stress; Environmental Toxicology.

ABBREVIATIONS

- **BPA** - Bisphenol A
- **ERα** - Estrogen Receptor Alpha
- **ERβ** - Estrogen Receptor Beta
- **BDNF** - Brain-Derived Neurotrophic Factor
- **T4** - Thyroxine (a thyroid hormone)
- **T3** - Triiodothyronine (a thyroid hormone)
- **ROS** - Reactive Oxygen Species
- **NF-κB** - Nuclear Factor Kappa B
- **TLR** - Toll-Like Receptor
- **TNF-α** - Tumor Necrosis Factor Alpha
- **IL-1β** - Interleukin 1 Beta
- **IL-6** - Interleukin 6
- **CNS** - Central Nervous System
- **IL-1β** - Interleukin 1 Beta
- **NO** - Nitric Oxide
- **LTP** - Long-Term Potentiation
- **PSD-95** - Postsynaptic Density Protein 95
- **BBB** - Blood-Brain Barrier
- **ZO-1** - Zonula Occludens-1 (a tight junction protein)
- **ADHD** - Attention Deficit Hyperactivity Disorder
- **ASD** - Autism Spectrum Disorder
- **ROS** - Reactive Oxygen Species

Molecular Mechanisms Underlying Bisphenol A (BPA)-Induced Neurotoxicity: Bisphenol A (BPA) is a widely used industrial chemical found in plastics, food containers, and water bottles. Its structural similarity to estrogen allows it to act as an endocrine disruptor, interfering with various physiological processes, including neurodevelopment and neural function. BPA-induced neurotoxicity is a major phenomenon involving hormonal disruption, oxidative stress, mitochondrial dysfunction, neuroinflammation, and epigenetic alterations. This comprehensive review explores the mechanisms through which BPA impairs brain health, contributing to cognitive and behavioral deficits.

1. Hormonal Disruption and Neurodevelopment: BPA exerts neurotoxic effects primarily by mimicking estrogen, binding to estrogen receptors (ERα and ERβ), and disrupting hormonal signaling pathways. Estrogen plays a major role in brain development, particularly in synaptogenesis, neurogenesis, and myelination.[1] BPA's interaction with these receptors alters the transcriptional regulation of genes critical for neuronal function, such as BDNF (brain-derived neurotrophic factor) and synaptic proteins like PSD-95.

Mechanism: BPA competes with endogenous estrogen for receptor binding, leading to altered activation of estrogen response elements (EREs) in the genome. This can result in inappropriate upregulation or downregulation of key genes. For example[2], studies show that BPA exposure during prenatal development decreases hippocampal BDNF expression, impairing learning and memory in adulthood.

Impact on thyroid hormones: Thyroid hormones are vital for brain development, especially during fetal and early postnatal stages. BPA interferes with thyroid receptor binding and reduces serum levels of thyroxine (T4) and triiodothyronine (T3). Reduced thyroid hormone signaling leads to impaired neuronal differentiation and synaptic plasticity, as demonstrated in rodent studies.[3]

2. Oxidative Stress and Mitochondrial Dysfunction: Oxidative stress is a hallmark of BPA-induced neurotoxicity, resulting from excessive production of reactive oxygen species (ROS) and impaired antioxidant defenses. Neurons, with their high metabolic demands, are particularly susceptible to oxidative damage.[4]

ROS generation: BPA activates NADPH oxidase and inhibits mitochondrial respiratory chain complexes, increasing ROS production.[5] Elevated ROS levels damage cellular structures, including lipids, proteins, and DNA.

Mitochondrial dysfunction: BPA exposure disrupts mitochondrial integrity by depolarizing the mitochondrial membrane, impairing ATP production, and inducing cytochrome c release, leading to apoptosis. For instance, Costa et al.[6] demonstrated that BPA reduces mitochondrial membrane potential in hippocampal neurons, correlating with decreased neuronal viability.

3. Neuroinflammation and Immune Dysregulation: Chronic neuroinflammation is a significant contributor to BPA-induced cognitive and behavioral impairments. Microglial cells, the brain's resident immune cells, are activated in response to BPA exposure, releasing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).

Microglial activation: BPA binds to toll-like receptors (TLRs) on microglia, triggering nuclear factor-kappa B (NF-κB) signaling and the production of inflammatory mediators.

Consequences: Persistent neuroinflammation disrupts synaptic function and exacerbates neuronal apoptosis. Additionally, inflammatory cytokines impair the blood-brain barrier, allowing further neurotoxic agents to penetrate brain tissue. Zhang et al. (2023) reported that BPA-induced microglial activation correlates with anxiety-like behaviors and reduced spatial memory in rodent models.

4. Epigenetic Alterations in Neural Pathways: BPA-induced neurotoxicity also involves epigenetic changes, including DNA methylation, histone modifications, and non-coding RNA expression. These alterations modify the transcriptional landscape of neurons, leading to long-lasting effects on brain function and behavior.[7] BPA exposure reduces global DNA methylation levels while hypermethylating promoters of specific genes, such as ERα and BDNF.

Histone modifications: BPA alters histone acetylation patterns, disrupting chromatin structure and gene expression. For example, decreased acetylation of histone H3 at the BDNF promoter suppresses its transcription.[8]

5. Behavioral and Cognitive Implications: BPA-induced molecular and cellular changes translate into measurable behavioral and cognitive deficits. Studies[9] link prenatal and early-life BPA exposure to increased risks of attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and anxiety. Moreover, BPA exposure impairs spatial learning, memory, and social interaction in animal models.Disrupted synaptic plasticity, impaired neurogenesis, and chronic inflammation collectively contribute to these behavioral abnormalities.[10]

Neuroinflammation and Immune Dysregulation in BPA-Induced Neurotoxicity

Mechanistic Insights into Neuroinflammation

Neuroinflammation is a critical response in the brain to a variety of insults, including exposure to environmental toxins like Bisphenol A (BPA). BPA has been shown to trigger neuroinflammatory pathways that result in long-lasting effects on the central nervous system (CNS), contributing to cognitive deficits, mood disorders, and neurodevelopmental abnormalities. Neuroinflammation, in essence, refers to the activation of the brain's immune cells—primarily microglia, astrocytes, and endothelial cells—triggered by stressors such as BPA exposure.[11]

Microglia, the resident immune cells of the brain, act as the first line of defense against harmful stimuli. In a healthy state, microglia are involved in homeostatic functions like synaptic pruning, modulating neural connections, and responding to injury. However, BPA exposure activates microglia, causing them to shift to a pro-inflammatory phenotype. This shift involves an upregulation of various pro-inflammatory molecules, such as cytokines (TNF-α, IL-6, IL-1β), chemokines, and oxidative agents, which ultimately disrupt normal neuronal functions.[12]

Key Pathways in BPA-Induced Neuroinflammation

1. Activation of Microglia through TLRs: One of the primary mechanisms by which BPA induces neuroinflammation is through the activation of Toll-like receptors (TLRs), especially TLR4, present on microglia.[13] BPA interacts with these receptors, initiating a cascade of signaling events that activate the NF-κB pathway. NF-κB, a well-known transcription factor, plays a central role in regulating immune responses. Once activated, NF-κB promotes the expression of pro-inflammatory cytokines like IL-6 and TNF-α. This inflammatory cascade leads to neuronal damage and synaptic dysfunction, which underlie the cognitive and behavioral effects observed in BPA-exposed individuals.[14]

Cytokine and Chemokine Dysregulation: BPA-induced activation of microglia leads to an excessive release of inflammatory cytokines. For instance, studies[15] have shown that elevated levels of IL-1β and TNF-α contribute to an environment that not only disrupts neuronal signaling but also impairs synaptic plasticity, a crucial mechanism for learning and memory. IL-6, another cytokine released upon microglial activation, has been linked to neurodegenerative conditions such as Alzheimer's disease, making it a key player in BPA-induced neurotoxicity.

Oxidative Stress and Mitochondrial Dysfunction: As part of the inflammatory response, microglial activation also leads to the production of reactive oxygen species (ROS) and nitric oxide (NO). These molecules can cause direct damage to neuronal structures by inducing lipid peroxidation, protein oxidation, and DNA damage. Additionally, excessive ROS production leads to mitochondrial dysfunction, further exacerbating cellular injury and promoting apoptotic pathways. The combined effects of inflammatory cytokines[16] and oxidative stress significantly compromise neuronal integrity, leading to cognitive dysfunction and behavior changes in BPA-exposed animals.[17,18]

2. Effects on the Blood-Brain Barrier (BBB): The blood-brain barrier (BBB) is a crucial structure that regulates the exchange of substances between the bloodstream and the brain, maintaining CNS homeostasis. Under normal conditions, the BBB prevents harmful substances, including pathogens, toxins, and immune cells, from entering the brain. However, BPA exposure has been shown to compromise the integrity of the BBB, making the brain more susceptible to a variety of neurotoxic insults.[19]

BPA and Tight Junction Disruption: BPA induces the breakdown of tight junction proteins, which are critical components in maintaining the BBB's selective permeability. Proteins such as claudins, occluding, and zonula occludens-1 (ZO-1) are normally involved in sealing the tight junctions between endothelial cells. BPA exposure reduces the expression of these proteins, leading to increased BBB permeability.[20] This increased permeability allows the infiltration of peripheral immune cells and toxins into the brain, further exacerbating the inflammatory response and causing neuronal damage. In rodent models, BPA exposure has been shown to reduce the expression of tight junction proteins by up to 40%, correlating with memory deficits and increased anxiety-like behaviors.[21]

Neurodegenerative Implications: The breach of the BBB allows the infiltration of neurotoxic substances, including inflammatory cytokines and amyloid-beta plaques, which are closely associated with neurodegenerative diseases such as Alzheimer's. This mechanism has been suggested as a pathway through which BPA accelerates the onset of neurodegenerative diseases. Elevated levels of IL-6 and TNF-α have been observed in the hippocampus and cortex of BPA-exposed animals, which are regions critical for memory and emotional regulation.[22]

3. Sustained Inflammation and Neuronal Damage: Sustained neuroinflammation in the context of BPA exposure leads to chronic neuronal damage, which significantly contributes to long-term cognitive and behavioral impairments. The release of pro-inflammatory cytokines, ROS, and NO by activated microglia results in a vicious cycle of inflammation and neuronal injury.[23] Over time, these chronic inflammatory signals can alter neuronal function and structure, leading to synaptic dysfunction and apoptosis.

Impaired Synaptic Plasticity and Memory Deficits: One of the most profound effects of sustained neuroinflammation is the impairment of synaptic plasticity, which is crucial for learning and memory. BPA-induced inflammation disrupts long-term potentiation (LTP), a cellular process that strengthens synaptic connections and is associated with memory formation.[24] Studies[25] have demonstrated that BPA exposure reduces synaptic density and impairs the function of synaptic proteins such as synaptophysin and postsynaptic density protein 95 (PSD-95), which are essential for synaptic transmission and plasticity. These changes are most prominent in the hippocampus and prefrontal cortex, regions that are critically involved in memory and cognitive function.

Neurobehavioral Consequences: The impact of sustained neuroinflammation on neuronal function is mirrored in the behavioral abnormalities observed in BPA-exposed animals. Increased levels of pro-inflammatory cytokines like IL-6 and TNF-α are closely associated with heightened anxiety, depression-like behaviors, and impaired social interactions.[26] These behaviors are often seen in animal models of neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). In particular, BPA exposure has been linked to altered social behavior, heightened anxiety, and impaired cognitive abilities in both rodents and primates.[2]

4. Implications for Mental Health: Cognitive Impairments and Mood Disorders: Cognitive Impairments: Learning and Memory Deficits Linked to Prenatal BPA Exposure Prenatal exposure to BPA (bisphenol A) poses significant risks to cognitive development by interfering with hormonal regulation during critical brain development stages. BPA's estrogen-mimicking properties alter hippocampal function, particularly by reducing the production of brain-derived neurotrophic factor (BDNF), a protein critical for neuronal growth, synaptic plasticity, and memory formation. This disruption leads to compromised long-term potentiation (LTP) in the hippocampus, which is the foundation of learning and memory processes.

Animal studies[27,28] have demonstrated that prenatal exposure to BPA results in observable learning deficits, such as difficulty in maze navigation and impaired spatial memory. These deficits correlate with oxidative damage caused by BPA-induced reactive oxygen species (ROS), which interfere with neuronal signaling and structural integrity. For instance, a study[29] found that rats exposed to BPA prenatally exhibited lower glutamate receptor activity in the hippocampus, essential for memory processing.[30]

Human studies[31], substantiate these findings, revealing that elevated maternal BPA levels during pregnancy correlate with reduced cognitive function and academic performance in offspring. A cohort study[32] linked prenatal BPA exposure with lower IQ scores and delayed cognitive milestones in young children. Such findings emphasize that BPA's neurotoxic effects are not only transient but also have long-lasting implications for mental development.[33]

Mood Disorders: Anxiety and Depression-like Behaviors: BPA's neurotoxicity significantly impacts mood regulation by disrupting the hypothalamic-pituitary-adrenal (HPA) axis and neurotransmitter systems. Its interference with the HPA axis results in altered corticosterone release, a stress hormone, leading to heightened anxiety-like behaviors in animal models. Studies[34], have demonstrated that prenatal BPA exposure in mice and rats induces depressive behaviors, characterized by decreased exploratory activity and altered social interactions.[35,36]

BPA also alters the serotonergic and dopaminergic systems in the brain. Reduced serotonin availability in key regions, such as the prefrontal cortex and hippocampus, has been linked to depressive symptoms, while disrupted dopamine signaling affects motivation and reward pathways, contributing to anhedonia. In human populations, higher prenatal BPA levels have been associated with increased risks of emotional dysregulation, anxiety, and depression in children.[37] Longitudinal studies[38] highlight that these effects often emerge during early childhood and may persist into adolescence.[39]

Furthermore, BPA's ability to impair GABAergic activity, which plays a crucial role in inhibiting neural excitability, contributes to heightened emotional reactivity and vulnerability to mood disorders. Neuroinflammation, another consequence of BPA exposure, exacerbates these effects by altering cytokine levels and microglial activation in the brain.[40]

Mental Health Consequences: Mood Disorders and Cognitive Impairments

1. Cognitive Impairments: Cognition and Learning Problems Associated with Prenatal BPA Inhalation: It disrupts hormone balance throughout crucial phases of brain development, prenatal exposure to bisphenol A (BPA) presents serious dangers to cognitive function. By decreasing the synthesis of brain-derived neurotrophic factor (BDNF), a protein essential for neuronal development, synaptic plasticity, and memory formation, BPA's estrogen-mimicking characteristics modify hippocampus functioning. The hippocampal long-term potentiation (LTP), which is the basis of learning and memory functions, is weakened as a result of this disturbance.[39]

Studies[41], on animals have shown that prenatal exposure to BPA causes noticeable cognitive disabilities, including difficulty navigating mazes and poor spatial memory. Such deficiencies are associated with oxidative damage brought on by reactive oxygen species (ROS) generated by BPA, which disrupt structural integrity and neural function. Rats exposed to BPA during pregnancy, for example, showed reduced glutamate receptor activation in the hippocampus, which is crucial for memory processing.[42]

Human research supports these conclusions by showing that higher maternal BPA levels during pregnancy are associated with worse child scholastic achievement and cognitive function. According to a cohort study,[32] young children who were exposed to BPA during pregnancy had lower IQs and delayed cognitive milestones. These results highlight the fact that BPA's neurotoxic effects are not only temporary but also have long-term impacts on mental development.[43,44]

2. Mood Disorders: Symptoms of Depression and Anxiety: By interfering with the neurotransmitter and hypothalamic-pituitary-adrenal (HPA) axis, BPA's neurotoxicity has a substantial effect on mood regulation. In animal studies, its disruption of the HPA axis causes a change in the release of the stress hormone corticosterone, which intensifies anxiety-like behaviors. Prenatal BPA exposure in mice and rats has been shown to cause depressed behaviors, including altered social interactions and reduced exploratory activity.[45]

Additionally, BPA modifies the brain's dopaminergic and serotonergic circuits. Depressive symptoms have been associated with decreased serotonin availability in important areas, including the hippocampus and prefrontal cortex, whereas anhedonia is a result of disturbed dopamine transmission that impacts reward and motivation pathways. greater prenatal BPA levels have been linked in human populations to a greater risk of emotional dysregulation, anxiety, and depression in offspring.[46] According to longitudinal research[47], these effects often manifest in early infancy and may continue throughout adolescence.

Moreover, increased emotional reactivity and susceptibility to mood disorders are caused by BPA's capacity to disrupt GABAergic function, which is essential for reducing brain excitability. Another result of BPA exposure is neuroinflammation, which intensifies these effects by changing the brain's cytokine levels and microglial activation.[48]

A thorough examination of BPA exposure and regulatory environments

1. Exposure at Low and High Doses: Low-Dose Exposure: A Hidden Danger Because bisphenol A (BPA) disrupts hormones by binding to estrogen receptors (ERα and ERβ), it may have significant toxicological consequences even at low doses. Due to the important hormone dependence of developmental processes, the low-dose effects are especially problematic for vulnerable groups, such as pregnant women, fetuses, and neonates. According to research, neurodevelopmental problems and metabolic dysfunctions may result from doses as low as 0.05 mg/kg body weight/day, which falls within the range of typical human ambient exposure (Wetherill et al., 2021; Richter et al., 2020). These results are further supported by animal models, which show that low-dose BPA exposure impairs synaptic plasticity, a crucial process controlling memory and learning.[49]

Low-dose BPA exposure has also been connected in human epidemiological studies to minor but noteworthy endocrine changes. Reduced birth weight, atypical pubertal start, and heightened vulnerability to cognitive impairments, such as attention-deficit disorders and decreased IQ, are all linked to prenatal exposure. This suggests that BPA affects gene expression during crucial developmental windows by epigenetic modification, which is different from its direct receptor binding.[50,51]

2. Excessive Exposure: Immediate and Long-Term Harm: In contrast to the effects of low doses, acute cellular toxicity and systemic organ damage are linked to large doses of BPA (>50 mg/kg body weight/day). According to studies[52], high-dose exposure causes inflammation, increased reactive oxygen species (ROS) generation, and mitochondrial dysfunction, which ultimately results in organ damage, especially to the liver and kidneys. According to Tewarson et al. (2022), mice exposed to high levels of BPA had histological signs of nephropathy, fatty liver, and smaller reproductive organs. The interruption of steroidogenesis, a vital route in hormone synthesis, mediates these effects.[53,54]

The chronic consequences of high-dose BPA exposure also include insulin resistance and metabolic syndrome. High levels of BPA change insulin receptor signaling and glucose absorption via pathways controlled by oxidative stress, raising the risk of diabetes and cardiovascular disease.[55,56]

Knowing NMDR in the context of BPA toxicity: The biological effects of BPA are not proportionate to the dosage, indicating a non-monotonic dose-response relationship. The effects of low and high dosages might be quite different or even antagonistic. For instance, BPA at low concentrations promotes cell proliferation by binding to estrogen receptors and causing estrogenic action. However, because of receptor desensitization or the activation of other toxicological pathways, greater dosages may block the same pathways (Vandenberg et al., 2021).

When it comes to endocrine disruption, BPA's non-monotonicity is very significant. BP'A stimulates estrogen receptor-mediated transcription by imitating estradiol at low concentrations. By competing with natural ligands or causing receptor degradation, BPA, on the other hand, impairs receptor function at large concentrations. Neurotoxicity studies similarly show this tendency, with low dosages affecting synaptic transmission and large doses triggering apoptotic pathways (Song et al., 2023; vom Saal et al., 2022).

Difficulties with Risk Assessment

Conventional toxicological frameworks, which depend on linear dose-response assumptions, are called into question by NMDR curves. The low-dose effects of endocrine disruptors like BPA are often missed by regulatory criteria. Because of the significant ramifications of NMDR, new methods to toxicity assessment, including sophisticated omics techniques and in vitro high-throughput screening, are required in order to better anticipate the dose-specific effects of BPA (Zoeller et al., 2022).

Regulatory Standards and Safe Limits: Because toxicological research is interpreted differently in different countries, BPA's regulatory restrictions vary significantly. Citing new data on immunotoxicity and endocrine effects at low levels, the European Food Safety Authority (EFSA) significantly reduced the tolerated daily intake (TDI) for BPA from 4 µg/kg body weight/day to 0.04 ng/kg body weight/day in its 2023 evaluation (EFSA Scientific Committee, 2023). By acknowledging non-monotonic dose-response patterns as crucial, this signaled a paradigm change in risk assessment.[57,58]

1. Food and Drug Administration (FDA) of the United States: However, because to its reliance on outdated linear dose-response models, the FDA's current threshold of 50µg/kg body weight/day has remained mostly unaltered. But new studies calling for more stringent restrictions are forcing the FDA to review its standards (FDA Report, 2023).[59,60]

2. Regulations Specific to Life Stages: The goal of several regulations is to safeguard vulnerable groups. Recognizing the increased susceptibility of developing systems to low-dose BPA effects, Canada and Japan have enacted restrictions on BPA in newborn items, including baby bottles and sippy cups (Health Canada, 2023).[61,62,63]

3. International Regulatory Structures: Risk modeling and thorough toxicological investigations are required to define BPA levels. In order to establish acceptable exposure limits, EFSA and the FDA consider both in vitro and in vivo evidence, taking into consideration variables such as human exposure patterns and interspecies heterogeneity.

The 2023 EFSA Reevaluation Process: This required adding developmental toxicity endpoints and non-monotonic response data to its evaluation methodology. Cumulative exposure hazards are highlighted in the updated TDI, particularly during pregnancy and infancy.[22,64]

FDA Guidelines: The FDA is progressively investigating alternate testing approaches, including as computational models and endocrine-specific tests, to revise its criteria, even if it continues to be cautious in its revisions (FDA Report, 2023).[65,66]

Regional Trends: By outright prohibiting BPA in all food-contact materials, nations such as France have established precedents, underscoring the widening gap in international regulatory approaches.[67]

Possible Strategies for Mitigation

a. **Nutritional Measures:** One important tactic to lessen the consequences of BPA exposure is dietary modification. Research has shown that the endocrine-disrupting effects of BPA may be mitigated by diets high in phytonutrients and bioactive substances. For example, by binding BPA in the gastrointestinal system and restricting absorption, eating foods rich in fiber may lower its bioavailability (Wetherill et al., 2021). Additionally, it is shown that omega-3 fatty acids, which are present in fish and flaxseeds, reduce oxidative stress brought on by BPA, protecting cellular health.[68]

By strengthening detoxification pathways, glucosinolate-rich vegetables like broccoli and cauliflower provide protection against BPA-mediated toxicity.[55] Exposure may be considerably decreased by limiting the use of food packaging that contains BPA and switching to a diet high in whole, unprocessed foods.[69]

b. Antioxidants' Function: In order to combat the oxidative stress brought on by BPA, antioxidants are essential. Folic acid has been identified as a protective factor against BPA-induced genetic damage and is an essential vitamin for DNA repair and methylation.[70] Similar to this, lipid-soluble antioxidant vitamin E prevents lipid peroxidation and preserves cellular integrity by neutralizing reactive oxygen species produced by BPA.[71,72]

Well-known for strengthening the immune system, vitamin C also lessens the neurotoxicity caused by BPA by maintaining neuronal viability and lowering inflammation. According to recent studies, using these antioxidant supplements may greatly reduce the dangers of BPA exposure.[73] Berries and green tea contain polyphenols, which are also strong inhibitors of BPA-induced oxidative damage and promoters of cellular repair processes.

c. Other Resources: A key tactic for lowering exposure is to swap out BPA-containing goods with safer ones. In manufacturing, biocompatible polymers like polylactic acid (PLA) have become popular as environmentally acceptable substitutes (Tewarson et al., 2022). These materials are non-toxic and sustainable since they come from renewable resources like maize starch.

Stainless steel and glass, which have long been used to store food, are becoming more popular as BPA-free alternatives. Packaging innovations, such the use of silicon-based materials, provide safe and long-lasting options for storing food and beverages (FDA, 2023). Making the switch to these substitutes not only protects public health but also supports international environmental objectives.

d. Biocompatible Polymers and BPA-Free Plastics: Consumer safety has been transformed by the creation of BPA-free plastics. These substances are designed to replicate the useful qualities of polymers containing BPA without the dangers involved. BPA-free bottles and containers are often made from polypropylene and polyethylene terephthalate (PET) (EFSA Scientific Committee, 2023).

Because of their safety and biodegradability, biocompatible polymers like polyglycolic acid (PGA) and polyhydroxyalkanoates (PHA) are becoming more and more well-liked. In medical applications where biocompatibility is crucial, including drug delivery systems, these materials are especially advantageous (Richter et al., 2020). Exposure levels in susceptible groups have been greatly decreased by the use of biocompatible and BPA-free substitutes.

e. Policies for Public Health: Reducing exposure to BPA has been made possible in large part by policy initiatives. To control the use of BPA in consumer goods, governments throughout the globe have put strict regulations into place. For instance, the European Union established a precedent for worldwide policy improvements in 2011 when it outlawed BPA in infant bottles (EFSA, 2023). Canada has imposed stringent limits on the use of BPA after being one of the first nations to pronounce it harmful (Health Canada, 2023).

Campaigns to raise public knowledge of the dangers of BPA have also been very important. People are now more equipped to make educated decisions because to campaigns encouraging the use of BPA-free items and calling for stronger labeling regulations (Vandenberg et al., 2022).

f. Prohibiting the use of BPA in infant bottles and food containers: An important turning point in public health campaigning has been reached with the ban on BPA in infant bottles and food containers. According to studies, because of their growing endocrine systems, babies and young children are more susceptible to BPA exposure (Peretz et al., 2022). In order to limit exposure during crucial developmental phases, regulatory agencies such as the FDA and EFSA have implemented limits on BPA in items intended for newborns (FDA, 2023).

Furthermore, exposure hazards have been further reduced by the food industry's use of non-toxic substitutes, such as can liners devoid of BPA. These actions demonstrate how crucial regulatory supervision is to reducing the pervasive use of BPA and guaranteeing consumer safety.

Prospects for the Future

New Research

The deeper effects of BPA on the environment and human health are the main focus of ongoing research. The study of epigenetic alterations, in which exposure to BPA modifies gene expression without altering the underlying DNA sequence, is one important field. It has been discovered that BPA alters DNA methylation patterns and histones, which has long-term effects on gene regulation.[74] Because these effects are transgenerational—that is, BPA-induced alterations may be passed on to subsequent generations—they are very worrisome. Research using animal models, such that conducted by Wetherill et al. (2021), has shown that exposure to BPA by mothers affects the reproductive and neurological systems of their children up to the third generation.[75] For instance, after prenatal BPA exposure, several genes essential in neural development, such as brain-derived neurotrophic factor (BDNF), show lasting epigenetic changes.[76]

Additionally, current research is looking at BPA substitutes that could similarly be harmful to the epigenetic system. BPA-free items that include bisphenol-S (BPS) or bisphenol-F (BPF) are not risk-free and may also cause epigenetic modifications, according to Vandenberg et al. (2022).[77] These results highlight how urgently safer substitutes and thorough testing of novel materials are needed. The impact of BPA on microRNAs—small RNA molecules that control gene expression and are implicated in neurodevelopmental and neurodegenerative diseases—is another area of current investigation.[78]

Unanswered Questions

Even after decades of research, there are still a number of important uncertainties about BPA. The link between BPA exposure and neurodegenerative diseases like Parkinson's and Alzheimer's is one important area of uncertainty. Although BPA's capacity to penetrate the blood-brain barrier and cause oxidative stress is well known, it is still unclear how directly it contributes to the development of these disorders. According to animal models, BPA may worsen the development of amyloid-beta plaque, which is a defining feature of Alzheimer's disease.[79] According to Tewarson et al. (2022), exposure to BPA may also disrupt dopamine pathways, which might exacerbate Parkinson's disease. There is currently insufficient evidence, nevertheless, to connect long-term, low-dose exposure to the development or progression of these illnesses in people.

The vulnerability of individuals to BPA poisoning is another outstanding issue. How people metabolize and are impacted by BPA depends on a variety of factors, including genetic predispositions, variances in metabolic pathways, and changes in the gut flora. According to Zoeller et al. (2022), variations in detoxification enzymes, such glutathione-S-transferases, have a major impact on BPA metabolism and the ensuing health consequences. Furthermore, nothing is known about how BPA and other endocrine-disrupting chemicals interact over time. In order to evaluate risks in the actual world, future research must take a more comprehensive approach and look at these relationships.[78,80]

Innovative Therapeutic Strategies

Researchers are looking for preventive substances that can lessen the harm caused by BPA because of its neurotoxic properties. Following BPA exposure, antioxidants such N-acetylcysteine (NAC) have shown promise in lowering oxidative stress and maintaining neural function (Richter et al., 2020). Similarly, by reducing BPA-induced mitochondrial dysfunction, resveratrol, a polyphenol present in grapes, has shown neuroprotective properties.[81,82]

Another interesting strategy is to target the signaling pathways that BPA disrupts. For instance, medications that increase the Nrf2 pathway's activity—a crucial regulator of cellular defense mechanisms—are being researched as possible treatments.[83] Furthermore, measures to improve the health of the gut microbiota may lessen the systemic toxicity and bioavailability of BPA. In animal models, probiotics such strains of Lactobacillus and Bifidobacterium have been shown to break down BPA and lessen its negative effects on neurodevelopment (Peretz et al., 2022).

Additionally, cutting-edge biomaterials are being created to function as BPA scavengers, eliminating the chemical before it has a chance to do any damage. According to Tewarson et al. (2022), advances in nanotechnology are being made with the goal of developing water purification system filters that can eliminate BPA at trace levels. These devices reduce environmental pollution in addition to addressing health issues.[84] Table 1 explains the Bpa- induced Neurotoxicityand its important mechanisms of action.

Table 1: Summary of BPA-Induced Neurotoxicity and Its Mechanisms.

Category	Key Points	Molecular Mechanisms	Implications for Mental Health and Behavior
Hormonal Disruption & Neurodevelopment	- BPA mimics estrogen and binds to estrogen receptors (ERα and ERβ) - Alters brain development processes like synaptogenesis, neurogenesis, and myelination	- BPA competes with endogenous estrogen for receptor binding, leading to altered gene expression (e.g., BDNF, synaptic proteins like PSD-95). - Affects thyroid hormone signaling.	- Impaired learning and memory due to decreased BDNF expression. - Disrupted neurodevelopment can lead to cognitive and behavioral deficits.
Oxidative Stress & Mitochondrial Dysfunction	- BPA generates reactive oxygen species (ROS), leading to oxidative stress. - Disrupts mitochondrial function, causing ATP depletion and apoptosis.	- BPA activates NADPH oxidase and inhibits mitochondrial complexes. - Depolarizes mitochondrial membrane and induces cytochrome c release.	- Increased neuronal damage and apoptosis. - Cognitive deficits and behavioral changes due to mitochondrial dysfunction and ROS-induced injury.
Neuroinflammation & Immune Dysregulation	- BPA induces activation of microglial cells, leading to chronic neuroinflammation. - Release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6).	- BPA interacts with toll-like receptors (TLRs), triggering NF-κB signaling. - Microglial activation leads to the release of inflammatory cytokines and oxidative stress.	- Anxiety-like behaviors, reduced memory, and impaired social interactions. - Neurodevelopmental issues like ADHD, ASD.
Epigenetic Alterations	- BPA exposure causes changes in DNA methylation, histone modifications, and non-coding RNA expression.	- Reduced global DNA methylation, hypermethylation of promoters like ERα and BDNF. - Histone acetylation changes affecting gene expression.	- Long-lasting effects on gene regulation and neuronal function. - Cognitive and behavioral abnormalities.
Neurodegenerative Implications	- BPA weakens blood-brain barrier (BBB) integrity. - Increased BBB permeability allows harmful substances to enter the brain.	- Disruption of tight junction proteins (claudins, occludins, ZO-1) leading to BBB breakdown.	- Increased vulnerability to neurotoxic substances and accelerated neurodegeneration (e.g., Alzheimer's). - Impaired memory and emotional regulation due to hippocampal and cortical damage.
Cognitive Impairments	- BPA exposure impairs spatial learning and memory. - Decreased hippocampal function and synaptic plasticity.	- BPA exposure reduces synaptic density and impairs synaptic proteins like synaptophysin and PSD-95. - Disrupts long-term potentiation (LTP) in the hippocampus.	- Long-term memory deficits. - Difficulty with tasks requiring learning and memory, as observed in rodent models and human studies (lower IQ scores, delayed cognitive milestones).
Mood Disorders	- BPA exposure is linked to anxiety and depression-like behaviors. - Alters hypothalamic-pituitary-adrenal (HPA) axis and neurotransmitter systems.	- Disrupts serotonin and dopamine systems, affecting mood regulation. - Alters corticosterone release, heightening anxiety.	- Increased risks of anxiety, depression, and emotional dysregulation, especially in children exposed to BPA prenatally. - Long-lasting mental health issues, including mood disorders and emotional difficulties.

CONCLUSION

Implications of BPA Neurotoxicity for Public Health

The growing body of research on Bisphenol A (BPA) has illuminated its significant impact on human health, especially regarding neurotoxicity and its effects on mental and behavioral development. BPA, a widely used industrial chemical found in plastics, is increasingly recognized for its potential to disrupt endocrine and neural functions, particularly when exposure occurs during critical developmental periods such as pregnancy and early childhood. Recent studies[85,86] have provided conclusive evidence linking prenatal BPA exposure to cognitive impairments, learning and memory deficits, and neurobehavioral disorders. These findings highlight the need for urgent public health measures to address the risks posed by BPA exposure.[87]

Key Findings: One of the central findings from recent research is that BPA, even at low doses, can have detrimental effects on brain development. It disrupts the endocrine system by mimicking estrogen, which is crucial for the development of the central nervous system (CNS). This interference results in changes in neural signaling pathways, affecting cognitive processes such as learning, memory, and attention. Animal studies have demonstrated significant impairments in these cognitive functions following prenatal exposure to BPA, which have also been observed in human populations. Moreover, BPA exposure has been linked to mood disorders, such as anxiety and depression, which are increasingly recognized as key consequences of neurotoxicants like BPA.[88,89]

Additionally, the neurobehavioral effects of BPA exposure are becoming clearer. Studies have found a correlation between BPA exposure and increased hyperactivity, impulsivity, and aggression, particularly in children. These behaviors are commonly associated with developmental disorders such as ADHD, a connection that is still being explored in greater depth.[90] These neurobehavioral dysfunctions are not only a consequence of direct exposure but also an outcome of the long-term disruption of hormonal signaling pathways, especially during critical windows of brain development (Peretz et al., 2022; Richter et al., 2020).

Importance of Addressing BPA Neurotoxicity for Public Health: Given the widespread use of BPA in everyday products, such as food containers, baby bottles, and water bottles, the potential for widespread exposure is a significant concern. The implications for public health are far-reaching, as BPA exposure can affect not only individuals but also entire populations, especially vulnerable groups like pregnant women, infants, and children. Addressing BPA neurotoxicity is critical for preventing the onset of developmental disorders, learning disabilities, and behavioral issues that can affect individuals throughout their lives.

Public health strategies must focus on reducing BPA exposure at all levels. Regulatory measures such as banning BPA from baby bottles and food containers, as well as introducing alternatives like BPA-free plastics and biocompatible polymers, are vital steps toward mitigating this risk. Moreover, educating the public about BPA and its potential risks, as well as promoting research into safer alternatives, should be prioritized. The role of antioxidants and dietary interventions in mitigating BPA's effects also needs further exploration, as they may offer potential preventive measures.

The long-term societal and economic costs associated with untreated neurodevelopmental and neurobehavioral disorders stemming from BPA exposure are substantial. Investing in research to fully understand BPA's mechanisms of action and to develop effective therapeutic and preventative measures will be critical in mitigating these risks. Furthermore, global cooperation among regulatory bodies like the FDA and EFSA is essential to establish consistent safety standards for BPA exposure and to ensure that preventive measures are implemented universally.

As future research continues to uncover the complex interactions between BPA, the endocrine system, and the nervous system, a comprehensive approach to public health, regulatory policy, and consumer behavior change is essential. This approach will help protect future generations from the harmful effects of BPA and other endocrine-disrupting chemicals, ultimately contributing to the well-being of populations worldwide.

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