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Chapter- 21

Insights into the Adverse Effects of Bisphenol A on the Environment and Human Health

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Abstract:

Plastic, an integral part of our daily lives, is present in various items such as carry bags, packaging materials, and medical supplies like syringes. Despite contributing to scientific advancements, the non-biodegradable nature of certain plastic polymers poses environmental concerns. Bisphenol A (BPA), widely used in plastic manufacturing, has been banned due to its harmful impact on both the environment and human health. Its replacement, bisphenol F (BPF), is now employed. This study investigates the toxicity of BPA, BPF, and their combination on primary producers, specifically eukaryotic green algae. The escalating global plastic consumption, compounded by the persistent presence of BPA in aquatic environments, necessitates attention to prevent plastic pollution from affecting future generations. Plastic and nanoplastic materials are pervasive in soil and the environment, posing health risks to humans through air, water, and soil pathways. Plastic particles enter the food chain via small fish in lakes and seas. Crucially, interactions between BPA and natural substances or environmental stressors can yield both positive and negative effects, as evidenced by in vitro and in vivo studies. It is imperative to consider these interactions when assessing BPA exposures and their health implications, as they significantly influence endpoint measurements and cellular responses. This article emphasizes the adverse effects of plastic pollution on the environment and human health, while also exploring emerging remedies to mitigate BPA's impact.

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Introduction:

Industrial chemicals, including epoxy resin, polycarbonate plastics, and various polymer compounds, are frequently synthesized using bisphenol A (BPA) (Ma et al., 2019). BPA is ubiquitous in the environment due to its large-scale production and diverse applications (Abraham & Chakraborty, 2020). Research has extensively investigated BPA incidences, human exposure, and toxicity (Rochester, 2013). To comply with stringent regulations governing BPA use, numerous bisphenol analogues, such as bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF), are being developed as substitutes (Chen et al., 2016). This review consolidates current knowledge on the presence of bisphenol analogues (excluding BPA) in consumer goods, food, human exposure, biomonitoring, and the environment (Sonavane & Gassman, 2019; Rochester & Bolden, 2015). Recent attention has focused on BPA and its substitutes, such as BPS, BPF, and BPAF, due to their widespread use and presence in the environment, raising concerns about human health (García-Recio et al., 2022; Khan et al., 2023; Valentino et al., 2016). Research indicates that BPS, like BPA, functions as an endocrine-disrupting chemical (EDC) (Catenza et al., 2021; Minatoya & Kishi, 2021). Epoxy resins containing BPA are prevalent in consumer products like food containers, dental sealants, PVC pipe coatings, baby bottles, and canned goods. BPA, as an environmental contaminant, can potentially leach into food and water, warranting investigation (Di Donato et al., 2017; Huo et al., 2015). Despite the abundance of BPA research, limited information exists about BPS (Wu et al., 2018). This study examines literature on BPS, primarily published between 2010 and 2023, alongside information on human exposure, toxicities, and environmental dispersion (Abdulhameed et al., 2022). The findings reveal the widespread distribution of BPS in the environment, albeit often at lower concentrations than BPA in various media, such as water, sewage waste, household dust, air, consumer goods, and human urine (Guo et al., 2023). Various entry points, including digestive, respiratory, and cutaneous tracts, expose individuals to BPA. Endocrine disruptors like BPA adversely affect tissues and organs, including the immune, reproductive, and neuroendocrine systems, acting as estrogen substitutes and anti-androgens (Longnecker, 2009). This review aims to gather recent research on BPA, providing a comprehensive overview of its exposure status and associated health impacts on the liver, kidneys, reproductive system, metabolism, immunological system, and neurobehavioral development (Liu et al., 2021).

Physical and Chemical Properties of BPA:

Bisphenol A (BPA) is an organosynthetic molecule with the molecular formula $(CH_3)_2C(C_6H_4OH)_2$, having a molecular weight of 228 Da. The scientific designation for Bisphenol A is 4,4'-dihydroxy-2,2-diphenylpropane, with CAS number 80-05-7, in accordance with the International Union of Pure and Applied Chemistry (IUPAC) (Figure 1). With two hydroxyphenyl groups, Bisphenol A (BPA) belongs to the class of bisphenols and diphenylmethane derivatives. The two methyl groups replace the methyl hydrogen in the carbon tetrahedral bond (Li et al., 2015). First synthesized by Russian chemist Aleksandr P. Dianin in 1891 through the combination of phenol and acetone with an acid catalyst, BPA gained prominence in the 1950s for its reaction with phosgene, yielding polycarbonate—a transparent, rigid resin widely used in thermal paper, dental compounds, safety and medical equipment, and food and drink packaging (Eladak et al., 2015). While less soluble in water, BPA exhibits greater solubility in acetic acid, diethyl ether, and ethanol. Despite its short half-life of less than a day in the air, BPA persists for around 4.5 days in water and soil. Although not meeting the criteria for classification as a persistent organic pollutant (POP) due to its brief half-life, BPA is frequently listed in POP categories due to its accumulation in human tissues and organs and its involvement in various disorders (Delfosse et al., 2012).

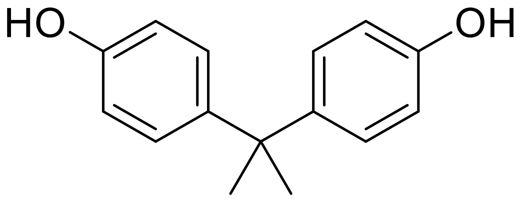

Figure 1. Structure of Bisphenol A (BPA).

BPA manufacturing:

BPA is a significant industrial chemical primarily employed as a raw ingredient for epoxy resin and polycarbonate, which, being clear and durable, is extensively used in everyday consumer products. BPA-containing epoxy resins play a crucial role in the production of thermal paper used in sales receipts, as well as in lining water pipes and the interiors of many food and beverage cans (Konieczna et al., 2015). The conventional commercial-scale production of BPA typically involves the use of a potent mineral acid catalyst, such as hydrochloric acid. Due to the highly corrosive nature of hydrochloric acid, industries must employ corrosion-resistant materials. Consequently, cation exchange resin has emerged as an alternative catalyst currently in use, effectively reducing corrosion in equipment. The reaction occurs in a fixed-bed column reactor filled with cation exchange resin, where two moles of phenol and one mole of acetone undergo the reaction process (Konieczna et al., 2015).

Moreover, a sophisticated wastewater treatment facility is necessary for the mineral acid-catalyzed process. The wastewater produced in this process requires treatment involving calcium precipitation, lime neutralization, and subsequent biotreatment due to the presence of hydrochloric acid. Certain components containing thiol groups can enhance both the yield and rate of BPA production. As the reaction advances, the proton from the acidic catalyst electrophilically attacks the acetone molecule. During this stage, the acetone-acetone reaction, also referred to as dimerization, may generate undesired by-products, potentially altering the reaction mechanism. Consequently, the formation of Mesityl oxide leads to an increase in impurities, triggering additional phenolic reactions and complicating the process (Figure 2). It is therefore expected that phenolic impacts will exert further effects on human health (Ćwiek-Ludwicka et al., 2015).

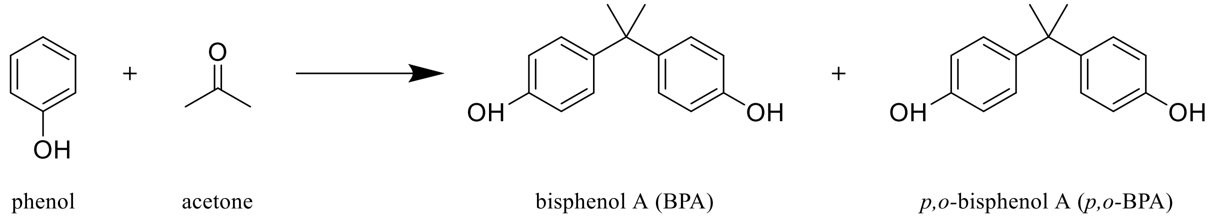

Figure 2. Chemical reaction for preparation of Bisphenol A (Adapted from Ćwiek-Ludwicka et al., 2015).

Bioconcentration and Bio-accumulation:

Persistent organic pollutants (POPs), which are organic substances resistant to degradation and prone to bioaccumulation in the environment, exert adverse effects on human health. Despite their harmful nature, POPs are still employed in the production of pesticides, medications, and fertilizers, leading to soil, water, and air contamination. Elevated levels of POPs have been identified in human and animal tissues and blood. Among these pollutants, Bisphenol A (BPA) stands out. BPA can be released into the environment either directly or indirectly throughout the various stages of a product's life cycle, including manufacturing, usage, and disposal (Cimmino et al., 2020). The entry of BPA into the human body occurs through ingestion, inhalation, and integumentary contact (skin and eye), highlighting multiple pathways of exposure.

BPA, existing in powder or crystal form, can be released into foods and beverages from plastic items, particularly under acidic or basic conditions. The accelerated entry of BPA into the human body occurs at elevated temperatures, such as when heating stored food in plastic packages and baby bottles. Additionally, high concentrations of vegetable oils and interaction with basic or acidic substances promote BPA release from polymeric materials (Vandenberg et al., 2007). BPA, with the ability to traverse the placental barrier, has been detected in fetal and maternal serum, as well as in placenta (Ziv-Gal et al., 2016). The substance can permeate the fluids and tissues of the human womb and can be ingested through touch or inhalation. Thermal paper, as in receipts, releases BPA upon skin contact, leading to elevated plasma and urine BPA levels in individuals with frequent thermal paper exposure, such as cashiers (Hormann et al., 2014). Other sources of exposure include the burning of household garbage, releases from municipal wastewater treatment facilities, and the degradation of plastic products. Recent studies on metabolism and toxic kinetics reveal that BPA is rapidly absorbed through the mouth and subsequently conjugated with glucuronic acid in the liver (Andra et al., 2016). Accumulating in various animal and human tissues, BPA disrupts physiological processes, raising concerns about its bioaccumulation in the modern world (Valentino et al., 2016).

Types of plastics and their application:

In contrast to the tens of atomic mass units commonly present in other chemical compounds, the size of these molecules is exceptional, ranging in the hundreds or even millions of atomic mass units, as detailed in the chemistry of industrial polymers. The primary factors contributing to the unique qualities associated with plastics, such as their capacity to be molded and shaped, are the size of the molecules, their physical state, and the structures they assume (Rhodes, 2018). There are primarily six types of plastics (Figure 3).

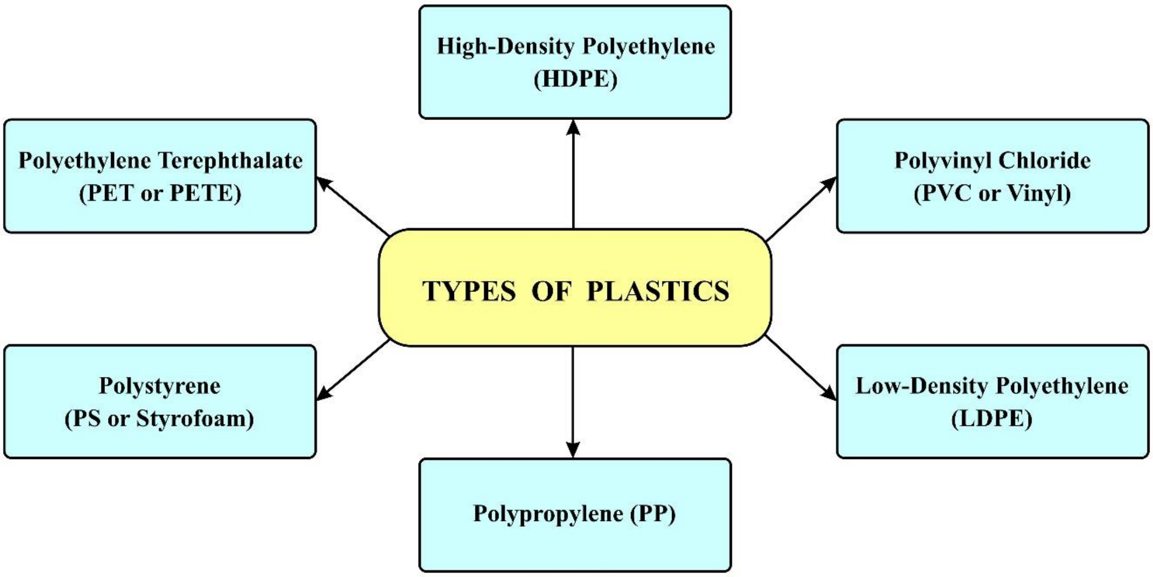

Figure 3. Shown above 6 different types of plastics these include: Polyethylene Terephthalate, Polypropylene, Polystyrene (PS) or polystyrene, high-density polyethylene, Vinyl or Polyvinyl Chloride (PVC).

Polyethylene Terephthalate (PET or PETE), one of the most commonly used plastics, is utilized in various applications. It is employed in food packaging and textiles, particularly in the production of polyester. PET is known for its robustness, lightweight nature, and general transparency. Examples of its use include beverage bottles, food containers (such as salad dressing, peanut butter, honey, etc.), and polyester clothes or rope (Ganesan et al., 2022).

Polypropylene (PP), known for its strength and durability, surpasses other plastic varieties in heat resistance, making it ideal for food packing and storage containers designed for heat applications. Highly flexible, it maintains its strength and shape over an extended period. Examples include straws, bottle caps, prescription bottles, containers for hot meals, packing tape, disposable diapers, and DVD/CD boxes (Hubai et al., 2022).

Polystyrene (PS), commonly known as Styrofoam, is an inexpensive and efficient insulating material extensively utilized in the construction, food, and packaging industries. Similar to PVC, polystyrene is considered a hazardous substance capable of releasing toxic pollutants such as the neurotoxic styrene. These pollutants can be readily absorbed by food items and, subsequently, consumed by individuals. Applications of polystyrene include cups, takeaway containers, product packaging for transportation and delivery, egg cartons, cutlery, and building insulation (Edwards et al., 2022).

High-density polyethylene (HDPE), one of the three main forms of polyethylene alongside low-density and linear low-density, constitutes a significant portion of global plastic usage. Its robustness and resistance to moisture and chemicals make it ideal for applications such as pipelines, cartons, and other construction materials. Examples encompass rigid pipes, toys, buckets, park chairs, detergent bottles, cereal box liners, and milk cartons (Schwarz et al., 2019).

Vinyl, or Polyvinyl Chloride (PVC), is a robust and rigid plastic widely utilized in building and construction due to its resistance to chemicals and elements. It finds applications in high-tech fields such as cables, benefiting from its non-conductive nature (Deng et al., 2022). Its immunity to germs, ease of cleaning, and suitability for single-use applications make it prevalent in medical settings to prevent infections (Deng et al., 2022). However, it is crucial to acknowledge that PVC, throughout its lifecycle, releases harmful pollutants such as lead, dioxins, and vinyl chloride, rendering it the most threatening plastic to human health (Thakur et al., 2023). Various everyday items, including credit cards, oxygen masks, rain gutters, toys for both humans and animals, plumbing pipes, teething rings, and IV fluid bags, fall under this category (Roosen et al., 2022).

LDPE, or low-density polyethylene, is an HDPE variant that is softer, clearer, and more malleable. It is often utilized in corrosion-resistant work surfaces, among other items, and beverage carton liners. Examples include drinking cups, bubble wrap, sandwich and bread bags, plastic wrap, waste bags, and cling wrap (Mortula et al., 2021).

Plastics that do not fall into any of the other six categories or are combinations of various types are collectively classified in this category. We incorporate them because comprehending the significance of the #7 recycling code, encountered occasionally, is essential. The critical aspect in this context is the frequent non-recyclability of these polymers. Illustrative items encompass translucent plastic flatware, infant and sports bottles, gadgets, CDs, DVDs, and lighting fixtures (Endres, 2019).

Plastic waste disposal and its management:

Plastic trash, commonly referred to as plastic pollution, is defined as "the accumulation of microplastic particles (e.g., plastic bottles, grocery bags, food wrappers, and others) in the natural ecosystem, negatively impacting animals, wildlife habitat, and humans." This term also encompasses the substantial amount of plastic that remains unrecycled, often ending up in landfills or, in developing countries, deposited in unregulated disposal sites (Hoang, 2022). Halting the influx of plastic waste into the ecosystem necessitates systemic reform. Globally, less than 10% of the seven billion tons of plastic waste generated has been recycled (Samal et al., 2017; Ayeleru et al., 2020; Mondal et al., 2022). Enormous quantities of plastic waste are released into the environment or transported over long distances for disposal or incineration.

The most prevalent type of plastic debris in the environment is cigarette butts, which contain small plastic fibers in their filters (Akan et al., 2021).

To manage plastic waste globally, various techniques have been attempted to decompose or convert it into more manageable forms. Incineration, involving the ignition of plastic waste, produces harmful fumes. Recycling, illustrated in Figure 4, transforms plastic waste into valuable forms; however, this process incurs energy loss, leaving the plastic essentially unchanged. Landfilling, another disposal method, fails to achieve anticipated plastic degradation due to a lack of oxygen for bacterial breakdown. Constructing infrastructure by combining plastic with bitumen and producing gasoline from plastic emerge as potentially superior approaches to plastic waste management. Among these technologies, biodegradation, as cited by Sarkar et al. (2022), is considered the most environmentally benign and cost-effective method of plastic deterioration.

The majority of plastic water bottles, which can take thousands of years to disintegrate, are discarded, contributing to the pervasive issue of "plastic fog" in the world's oceans. This phenomenon encompasses 171 trillion microplastics, potentially weighing almost 2.3 metric tonnes if retrieved. Degradation of plastic bottles in the atmosphere results in the formation of microplastics, infiltrating our food and water and posing a significant health risk. Additionally, plastic releases toxic compounds, adversely affecting animals and disrupting both human and animal food chains. Widespread disposal habits, such as drinking half a bottle and discarding it, contribute to the ubiquitous presence of plastic bottles in cities. Packaged in plastic for accessibility and hygiene, these bottles are consumed at a staggering rate, with an individual using 4-6 plastic water bottles daily, totaling significant environmental impact. Recognizing that plastic is derived from petroleum, the production of a billion plastic bottles requires 24 million gallons of oil, and plastic takes nearly 700 years to decompose. Despite these environmental concerns, 80% of plastic bottles are not recycled, emphasizing the urgent need for sustainable practices. Recycling one ton of plastic saves 5.74 cubic meters of landfill space and reduces recycling and disposal costs. The entire life cycle of plastic bottles, from production to disposal, contributes substantially to pollution, encompassing litter, environmental degradation, and carbon emissions. A recommended alternative is filtered water from an under-sink reverse osmosis system (Jung et al., 2022). Implementing circular principles in manufacturing and waste management can minimize the release of harmful substances, promote sustainable practices, and contribute to the overall well-being of ecosystems and human populations (Saha, 2023).

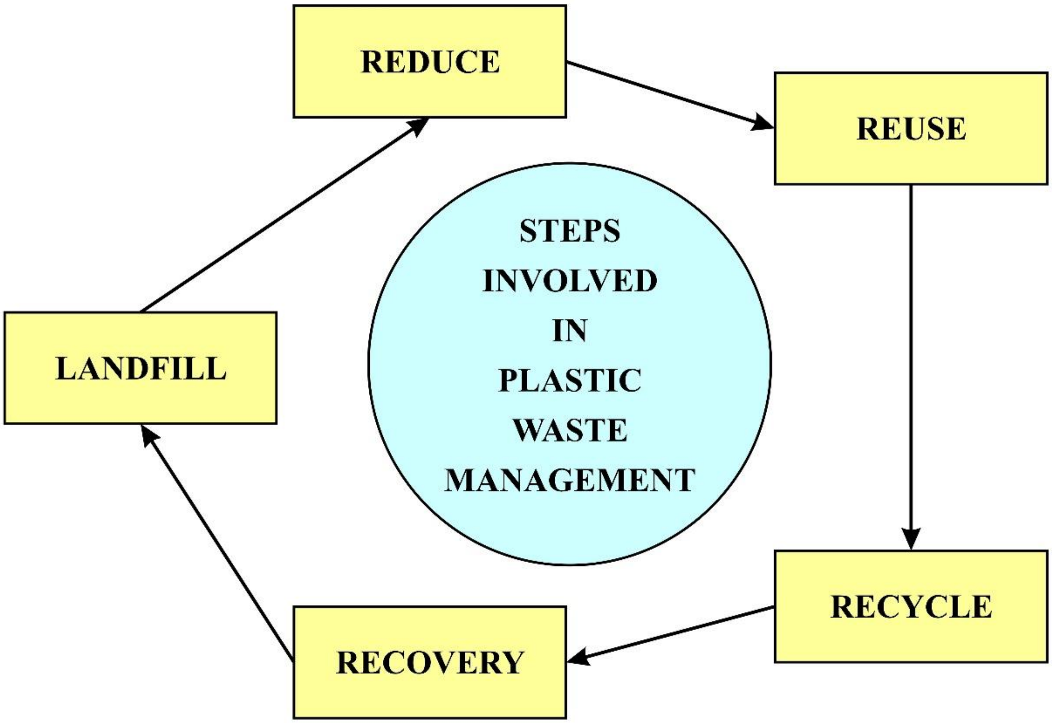

Figure 4. Processes that are involved in plastic waste management.

Biodegradation:

Biodegradation by Fungi:

Fungi, as natural decomposers, exhibit a remarkable ability to break down diverse organic compounds, including Bisphenol A (BPA). Research demonstrates that specific fungal species can efficiently biodegrade BPA under suitable conditions, providing a natural and eco-friendly alternative to chemical-intensive methods. White-rot fungi, known for their broad pollutant-degrading capacity, show promise in addressing the adverse effects of BPA on human health and the environment. Noteworthy studies highlight the effectiveness of white-rot fungi species, such as *Stereum hirsutum* and *Heterobasidium* spp., in degrading BPA, with significant resistance observed at a concentration of 100 ppm. Degradation to approximately 99% occurred within 7 to 14 days. Another investigation focused on the treatment of BPA using manganese peroxidase (MnP) and laccase from lignin-degrading fungi, revealing MnP's rapid elimination of BPA within an hour. Laccase, when combined with HBT, eradicated estrogenic activities within 6 hours. The sustained absence of estrogenic activities after 48 hours demonstrated the efficacy of ligninolytic enzymes in mitigating BPA's adverse effects (Lee et al., 2005).

Utilizing white-rot fungi for BPA biodegradation offers advantages over alternative methods, presenting a natural and sustainable approach applicable directly to contaminated environments. However, challenges, including environmental factors like pH and temperature, as well as the presence of other contaminants, must be considered. Despite potential impediments such as cultivation cost and time, white-rot fungi employ enzymes like lignin peroxidase (LiP), MnP, and laccase to transform BPA into simpler, less harmful compounds. LiP oxidizes and cleaves BPA's aromatic rings, forming intermediates like benzoquinones, while MnP oxidizes BPA to BPA-quinones. Laccase also plays a role in this transformation process (Tsutsumi et al., 2001). Previous research has demonstrated that *Trametes hirsuta*, through intracellular and extracellular enzymes such as laccase and cytochrome P-450 monooxygenase, can convert BPA into various metabolites. This enzymatic process involves polymerization, hydroxylation, dehydration, and bond cleavage, producing intermediate products that are either harmless or less hazardous, suggesting the potential for bioremediation (Li et al., 2023).

Biodegradation by immobilized enzyme:

An effective strategy demonstrating potential involves utilizing immobilized enzymes for BPA degradation. These enzymes, affixed to solid substrates such as polymers or matrices, allow for repeated use, enhancing both stability and catalytic efficiency through techniques like covalent bonding, adsorption, encapsulation, and cross-linking. Covalent bonding, though providing robust immobilization suitable for highly stable applications, can be laborious and costly (Zdarta et al., 2018). Adsorption offers another method for enzyme immobilization, relying on weak electrostatic or hydrophobic interactions to bind enzymes to the support material; however, this approach may lead to unstable immobilization and reduced activity due to weak attachment (Dong et al., 2012). Encapsulation involves trapping enzymes within microspheres or capsules, providing a protective shield against external factors, potentially enhancing stability but possibly limiting substrate diffusion and causing decreased activity.In industrial and environmental biotechnology, recent research highlighted challenges associated with laccase enzyme stability and reusability. In comparison to its free form, laccase covalently bound onto SiO2 supports exhibited better stability and endurance, with relative activity above 80% after 30 successive reaction cycles. Complete BPA degradation was achieved within 5 hours of incubation, attributed to the immobilized laccase's enhanced efficiency, particularly in the presence of TX-100 (Zdarta et al., 2018).

These results underscore the viability of enzyme immobilization to enhance laccase's stability, reusability, and effectiveness across diverse applications (Chang et al., 2019). Another study illustrated the effectiveness of *Trametes versicolor* laccase immobilized on Ba-alginate beads in degrading bisphenol A (BPA) under optimal conditions: 40°C, 2 mg/L BPA concentration, and 50 minutes. Both Box-Behnken design (BBD) and artificial neural network (ANN) accurately predicted degradation efficiency, with BBD achieving 83.48% and ANN achieving 84.33%. Statistical analysis confirmed the reliability of both models (R2: 0.98 for BBD, 0.97 for ANN; MSE: 9.88 for BBD, 38.25 for ANN). Immobilized laccase displayed superior storage stability, retaining 68.64% and 44.62% of activity compared to free laccase (Abdul Latif et al., 2022).

Biodegradation by bacterial strains:

The investigation into bisphenol A (BPA) biodegradation involved isolating bacterial strains from deserts and arid soils in southern Tunisia. Ten bacterial strains, including *Pseudomonas putida*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella* sp. and *Pantoea* sp., exhibited high BPA removal potential in mineral salt medium (MSM) containing 1 mM BPA, with removal rates ranging from 36% to 97%. Strain G320 (*P. putida*) demonstrated exceptional efficiency, achieving a 97% removal rate within a 4-day incubation period at 30^0C. With a concentration increase to three millimoles per liter, strain G320 exhibited a half-life of two days and complete degradation within eight days. GC–MS analysis verified BPA biodegradation compounds and an algal toxicity test evaluated their toxicity. The detoxification process was validated by analyzing the effects of BPA biodegradation metabolites on *Tetraselmis* sp. strain V2 algae in terms of dry weight, cellular structure, and chlorophyll levels, emphasizing the potential of desert soil bacteria for BPA detoxification and the utility of algal species in toxicity assessment (Fawcett et al., 2021).

Predicted environmental distribution of BPA:

The anticipated environmental distribution of Bisphenol A (BPA) revolves around various ecological compartments due to its widespread use and potential environmental persistence. BPA, a synthetic compound commonly found in plastics, epoxy resins, and other consumer products, can enter the environment through multiple pathways when disposed of or leaked. In aquatic environments, BPA can infiltrate water bodies through industrial effluents, urban runoff, or improper disposal of plastic waste, potentially contaminating and adversely affecting aquatic life forms such as fish, invertebrates, and algae. Studies have suggested bioaccumulation of BPA in aquatic organisms, potentially causing disruptions in endocrine systems and reproductive functions (Mora Lagares & Vračko, 2023). Furthermore, BPA can leach into soil from landfill sites, agricultural activities (e.g., through the use of plastic mulches), and the decomposition of plastic materials, influencing microbial communities and potentially impacting plant growth. Soil-water interactions may also allow BPA to enter groundwater, posing risks to drinking water sources. Airborne BPA particles may result from various sources, including industrial emissions, thermal degradation of plastics, or volatilization from products containing BPA, depositing onto soil and water bodies and contributing to the overall environmental load (Bandopadhyay et al., 2018). Understanding the predicted environmental distribution of BPA involves assessing its mobility and transformation in different ecosystems, considering factors such as temperature, pH, and the presence of other pollutants that can influence its fate and behavior in various environmental matrices. Moreover, the persistence of BPA in different compartments varies, with some studies suggesting potential degradation by microorganisms or environmental factors like sunlight (Dueñas-Moreno et al., 2022). Predicting the environmental fate of BPA involves complex modeling that considers its movement across various environmental compartments, potential transformation pathways, and interactions with biotic and abiotic factors. This predictive analysis helps in comprehending the potential risks associated with BPA exposure and in formulating strategies for its mitigation and management in natural ecosystems (Im & Löffler, 2016).

Toxicity of BPA:

Aquatic toxicity through BPA:

Not all nations have implemented regulations to limit the use of bisphenol A (BPA) in plastics that come into contact with food industry products because some people are still unaware of the risks that BPA can pose to the human endocrine system. The usage of bisphenol A in the manufacturing of plastics that come into contact with food is not currently subject to any legislation, necessitating thoughtful consideration. Notably, developed countries like Japan and significant developing nations such as India, Nigeria, Indonesia, Bangladesh, Pakistan, Egypt, and Mexico lack such rules. Forty nations have taken some action to limit the manufacturing of these plastics or, at the very least, the amount of BPA they contain, aiming to prevent BPA from entering the plastics (Thoene et al., 2018). Multiple studies conducted in India have demonstrated the presence of BPA in various water sources, indicating its potential danger to aquatic organisms. For instance, research carried out in rivers, lakes, and coastlines has revealed detectable levels of BPA contamination, focusing on diverse water bodies, including the Ganges River and its tributaries. Internationally, research from different countries has underscored the pervasive nature of BPA contamination in aquatic environments. Studies conducted in the United States, Canada, China, and European nations have consistently found BPA residues in water bodies, showcasing the global prevalence of this chemical and its threat to aquatic ecosystems. These studies often assess BPA levels, persistence, and resultant toxicity on various aquatic species, emphasizing widespread concerns about its impact on biodiversity and ecosystem health (Kumkar et al., 2023). Regarding the actual impact on aquatic life, studies have shown adverse effects on organisms due to BPA exposure. Fish, in particular, have been extensively studied, with research demonstrating disruptions in their reproductive systems, altered hormone levels, reduced fertility, and developmental abnormalities resulting from exposure to BPA-contaminated water. Moreover, BPA's ability to bioaccumulate in aquatic organisms raises concerns about its potential transfer through the food chain, posing risks to higher trophic levels, including organisms consumed by humans. Efforts to mitigate BPA's impact on aquatic environments have involved stricter regulations, improved wastewater treatment processes, and exploration of eco-friendly remediation methods (Canesi & Fabbri, 2015). Furthermore, research into alternative materials and chemicals to replace BPA in various industries aims to reduce its environmental footprint and mitigate its adverse effects on aquatic ecosystems. Understanding the global and local implications of BPA contamination in aquatic environments is crucial for implementing effective policies, conducting further research, and adopting sustainable practices to safeguard the health of aquatic ecosystems and the species reliant upon them (Abu Hasan et al., 2023).

Toxicity of BPA on human:

An essential industrial chemical, bisphenol A (BPA), extensively utilized in polycarbonate and other polymer manufacturing, has raised global concerns due to its estrogenic properties, acting as an endocrine disruptor upon entering biological systems. Linked to human cancer (Ni et al., 2022) and potential harm to brain tissues, thyroid glands, and reproductive systems, BPA prompts a critical examination of its impacts. This review delves into the emerging field of BPA biodegradation in natural environments, shedding light on recent studies extracting BPA-degrading microbes from diverse sources, including water bodies receiving industrial waste and landfills (Karabulut & Gulay, 2022). Amidst the BPA controversy, bridging the knowledge gap between research assessing BPA's harm and studies utilizing naturally occurring microorganisms for effective BPA elimination becomes paramount. Closing this gap is instrumental in devising strategies to employ BPA in plastics production without environmental accumulation (Babu et al., 2013).

Effects on human endocrine system:

In humans, one of the most intricate and coordinated systems is the endocrine system. BPA, a detrimental endocrine-disrupting chemical (EDC), inhibits or modifies the production, secretion, discharge, and transportation of various hormones and enzymes, impairing the system's efficacy by substituting transportation proteins along with indigenous hormones (Oriakpono & Nduonofit, 2021). This modification alters the quantities of associated as well as free hormones in plasma. Furthermore, BPA disrupts the physiological processes of organs by affecting the function of neuroendocrine cells. Research has indicated that bisphenol A (BPA) can lead to increased blood levels of estradiol in females and decreased testosterone in males, impacting mental health and causing sex-specific behavioral abnormalities and mental disability (Greca et al., 2019). In males, the neuroactive hormone Dehydroepiandrosterone (DHEA) is lowered, potentially contributing to the depressive-like phenotype and the emergence of unsettled and depressed inclinations. A compilation of earlier research on the endocrine disruption caused by BPA is used to evaluate its powerful consequences (Rybczyńska-Tkaczyk et al., 2023).

Effects on human reproductive system:

Several theories propose various ways in which BPA harms the reproductive system, drawing evidence from both in vitro and in vivo investigations (Meli et al., 2020). Specifically, BPA is widely believed to possess estrogenic and antiandrogenic properties that can interfere with the hypothalamic-pituitary-gonadal axis and modify usual epigenetic motifs, potentially causing adverse effects on the reproductive system. BPA's activity can impact the mechanisms of gonadotropin-releasing hormone (GnRH) discharge, gonadotropin release, and signaling stimuli for the development of spermatogonia cells in the Sertoli cell line. Changes in gonadotropin levels, particularly a decrease in the serum concentration of LH, lead to Leydig cells producing less testosterone (Gerona et al., 2013). Typically, testosterone is converted into DHT, responsible for spermatogenesis, spermatozoa transportation, and retention before ejaculation via the male reproductive tract. Moreover, Sertoli's cells continue to operate when testosterone is transformed by aromatase to estradiol. As demonstrated in young rats exposed to high estrogen doses, low testosterone levels and altered estradiol catabolism result in elevated estradiol levels, impairing sperm production (Divakaran et al., 2014).

Leydig cells are believed to express estrogen receptors (ERα), while Sertoli cells, pachytene spermatocytes, and circular spermatids in the mature rat and male testis possess ERβ receptors. Molecular research indicates that Bisphenol A (BPA) acts as a specific ER modulator, functioning as either an agonist or antagonist of estrogen hormones depending on the tissue (Xing et al. 2022). In vitro studies demonstrate that BPA's interaction with estrogen receptors alters their ability to recruit tissue-specific co-activators, crucial for eliciting tissue-dependent responses (Desai et al. 2022). Additionally, BPA has been shown to exhibit an affinity for the membrane-associated G protein-coupled estrogen receptor (GPER), akin to estradiol's primary affinity. This chemical interaction with the GPER receptor, expressed in the pituitary and hypothalamus, can induce rapid, non-genomic effects (Desai & Jagtap, 2022).

Instead, recent research has revealed that BPA functions as an antagonist of the androgen receptor, blocking the control of androgen-dependent transcription by endogenous androgens and suppressing the growth of Sertoli cells. These processes are performed by inhibiting the amino- and carboxyl-terminal sections (AR N/C) of AR and strengthening its interactions with nuclear receptor co-repressor (NCoR) and whispering mediator for the thyroid hormone receptors (SMRT) (Michałowicz et al., 2014).

Other harmful effects:

There is a notable increase in the prevalence of many cancer types, which appears to be associated with BPA, including testicular, ovarian, uterine, prostatic, and breast cancer. According to the findings of several in vivo investigations, the elevated estrogenic function demonstrates the carcinogenic mechanism resulting from the action of BPA. Ongoing studies focus on the triggering of carcinogenesis and the formation of malignant cells by BPA. Despite their low affinity for each other, BPA adheres to ER and triggers cellular reactions. The receptor loses the capacity to bind and retain co-repressors. The type and expression levels of ER-regulated targets determine the tissue and cellular specificity of the BPA response because the BPA–ER complex regulates co-regulators in a manner inconsistent with BPA's affinity for ER. BPA can induce genomic reactions at concentrations below those where it is anticipated to attach to nuclear ERs (Freire et al., 2019).

Research studies have demonstrated a direct correlation between BPA exposure and oxidative damage, immunological response, and inflammation. The relationship between BPA and the activation of apoptosis in the cell, along with the destruction of mitochondria, led to a methodical breakdown, altering the numbers of immune cells and the functioning of both adaptive and innate immune systems due to prenatal exposure to BPA. This exposure also elevated pro- and anti-inflammatory cytokines as well as chemokines while decreasing T regulatory (Treg) cells. Exposure to BPA may induce an increase and deterioration in the development of both male and female T1D (Mortensen et al., 2014).

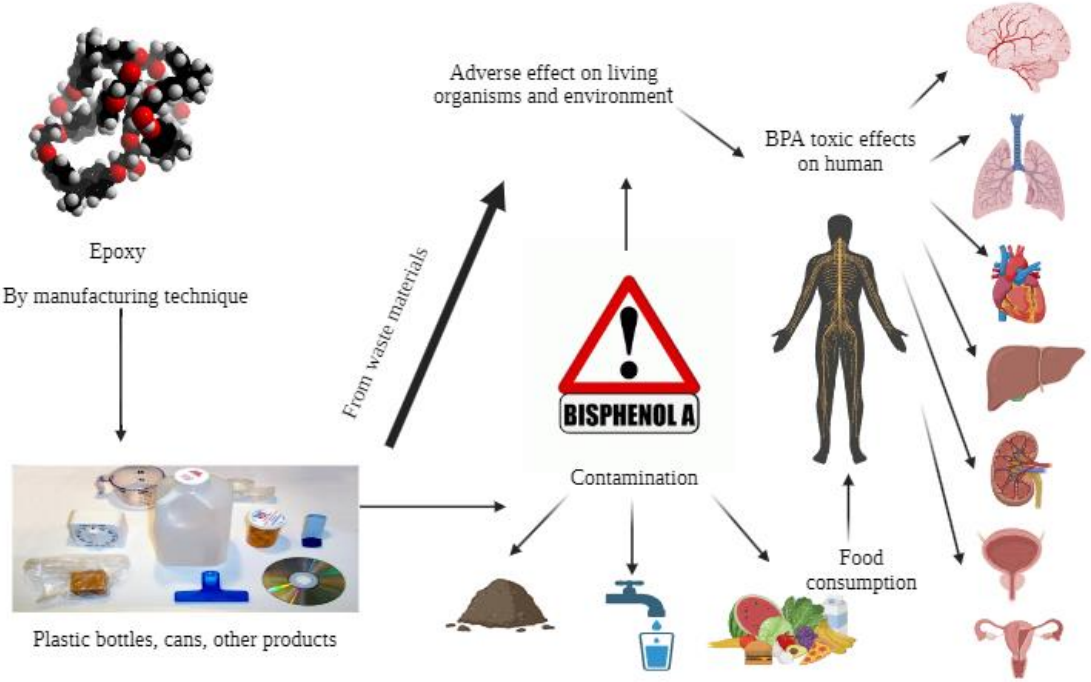

Figure 5. Illustration depicting the intricate interplay of Bisphenol A on the environment and human health, revealing nuanced insights.

BPA biomonitoring and guidelines:

According to biomonitoring research, 93% of analyzed urine samples had detectable amounts of BPA, indicating common exposure in the US. The rapid metabolism of BPA in the body suggests frequent exposures among Americans, as evidenced by its elevated detection rate. Younger children and individuals under six have higher BPA exposures than older adults and children (VomSaal et al., 2014). Epidemiological information worldwide on BPA's impact is lacking. In studies on the US general population, those with recent BPA exposure (measured by urinary BPA levels) are more likely to develop hepatic enzyme anomalies, cardiovascular disease, type 2 diabetes, and immunological conflict (Saha et al., 2022a; Saha et al., 2022b). Although the mechanisms by which BPA negatively affects health are not well understood, some connections are believed to be related to non-estrogenic effects. Exposure to BPA during pregnancy is linked to lower birthweights. The two indicators use the most extensive nationwide representation of urine BPA levels over time for children and women of reproductive age. Indicator B11 displays the median and 95th percentile of total BPA levels in the urine of women aged 16 to 49. For adolescents aged 6 to 17, Indicator B12 shows the median and 95th percentiles of BPA amounts in urine (Woudenberg et al., 2014).

The general public's primary exposure to BPA occurs through food consumption. The recommended BPA dose by the US Environmental Protection Agency (EPA) is 50 µg/kg BW/day. In 2015, the EFSA revised the TDI from 50 µg/kg BW/day to 4 µg/kg BW/day due to its adverse health effects (Teeguarden et al., 2015). BPA usage faced restrictions globally as its worsening health impacts emerged. In 2008, the US Food and Drug Administration considered a No Observed Adverse Effect Level (NOAEL) of 5,000 ng/kg body weight/day through food intake. Several EU member states prohibited its use in food containers for children under three, with some extending the ban to other products. Denmark banned BPA in food-related packaging, including cups and bottles, in 2010. EU Commission Directive No. 8/2011 banned BPA in baby bottles from March 1, 2011 (Manzoor et al., 2022).

Conclusion & Future directions:

The industrial component, BPA, finds extensive use in the production of epoxy resin, polycarbonate plastics, and various polymer-based materials, making it omnipresent in the environment due to its widespread applications. This study emphasizes dietary intake as the primary route of BPA exposure for individuals, with minimal impact from personal care product usage. Further investigations are warranted to assess BPA and its metabolites' presence in the human body, along with establishing recommended exposure levels. Biomonitoring studies indicate rapid and continuous BPA exposure in both humans and animals.

In-depth research is essential to comprehend the fate of these substances, particularly in economically disadvantaged countries, and to elucidate the long-term negative health effects of BPA exposure. A comprehensive analysis of existing data reveals a concerning, albeit not entirely clear, association between Endocrine-Disrupting Chemicals (EDCs) and human cancers. BPA, acting as an estrogen mimic under various circumstances, influences ovarian morphology, leading to cystic ovaries and heightened proliferative lesions that may signify an increased risk of ovarian cancers. Evidence suggests that early exposure to BPA during mammary development is associated with an elevated risk of breast cancer.

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