Multifaceted and Controversial Bisphenol: A (Review)

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ABSTRACT: Bisphenol A (BPA) is commonly used for the manufacturing of plastic wares and epoxy resins, which both play vital roles in our daily life. The discovery of BPA has a tremendous beneficial effect, however, it has been discovered that BPA is a potent environmental endocrine disruptor to which persistent exposure has a negative impact on the metabolic, reproductive, and developmental processes which ultimately leads to diseases in humans and other organisms. Though, the numerous health issues associated with exposure to BPA are multifaceted and contentious. However, as humans rely heavily on plastics for day-to-day needs there are huge worries about the environmentally friendly nature of these plastics and the long-term consequence on human health. Exposure to BPA is a worldwide challenge and it has been detected in both the urine and serum of humans. The negative effects associated with exposure to BPA can be short-term or long-term. The focus is on scientists to do their research thoroughly to provide solutions and suggestions on how to prevent or minimize the life-threatening effect of BPA. The review aims to focus on the usage, incidence, and negative effects of BPA in humans and animals using available information within the last 10 years and to recommend steps to take toward minimizing exposure.

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Bisphenol A (BPA; 2,2-Bis-(4-hydroxyphenyl)-propane, \((\text{CH}_3)\text{C(\text{C}}_6\text{H}_4\text{OH})_2\)) is an organic compound which has been established as an endocrine disruptor with a chemical structure similar to the natural hormone estradiol (Gadamsetty et al., 2019). It is produced in high volume worldwide for the production of polycarbonate plastics, epoxy resins and other speciality chemicals (Gear and Scott, 2017). As a result of its high volume production and extensive usage, the likelihood of polluting the environment with BPA is quite high. The degradation of BPA-based product, sewage treatment effluent and landfill leachates are some of the routes through which BPA is being released into the environment and these leads to negative effects interfering with animal physiology and development (Messinetti et al., 2018). The consumption of monomeric BPA contaminants in groceries and drinks accounts for the majority of human contact, other routes of exposure include inhalation, diet, and dermal contact (Chung et al., 2017). Due to its excellent mechanical properties, the low adsorption of moisture, and the fact that synthetic polymers made from BPA have good thermal stability, several everyday consumer products contain BPA as part of the ingredients these include plastics, polyvinyl chloride, medical products, digital media (such as Compact Discs and Digital Versatile Discs), sunglasses, paper coatings, adhesives, flame retardants, thermal receipts, food and beverage packaging, dental sealants, electronics, water bottles and baby bottles, toys, water pipes (Chung et al., 2017; Abrahm and Chakraborty, 2020; Siddique et al., 2020). BPA is easily degraded when assessed with other persistent environmental contaminants, therefore the widespread incidence of BPA can be correlated with the extensive use of products.
containing BPA rather than its persistence in the environment (Zuccarello et al., 2018; Ramakrishna et al., 2022).

Fig 1. Chemical structure of bisphenol a (Li et al., 2015).

Several studies on BPA have led to the conclusion that it is an endocrine disruptor (EDC) (Corrales et al., 2015; Im and Loffler, 2016; Ma et al., 2019). EDCs are chemicals that imitate, modify, and impede endogenous hormonal actions (Salvaggio et al., 2019; Asenuga and Olagunju, 2023). Following the exposure of humans and animals to EDCs, there is an alteration in hormone concentrations, activities, or receptors which leads to disruption in structure and function within the body (Ullah, 2019; Asenuga and Olagunju, 2023). There is convincing evidence about the estrogen-mimicking activities of BPA and the ability of BPA to attach to the androgen receptor, these activities will modify the physiological effects of estrogen and androgen within the body (Vijayalakshmi et al., 2018; Ullah, 2019).

Literature Search Procedure: This review was accomplished by searching relevant published research and review papers and books with other online materials. Around 200 journals were referred and 43 journals were cited after due consideration. The material used was primarily gathered from Google Scholar and PubMed searches of literature. For this study, we focus on papers published within 2013-2023 using search keywords such as bisphenol A, sources, environmental contaminant, endocrine disruptor and health impacts of BPA. Using the search keyword Bisphenol A provided the highest number of papers used for this review. The published papers were analysed manually and further sorted using the title, abstract and paper contents.

What Is BPA: BPA is a man-made compound containing carbon, oxygen and hydrogen, it is made up of two phenolic rings linked through a bridging carbon or other chemical structure, and it is a white crystalline solid substance that easily dissolves in organic solvent with a molecular weight of 228.29 g /cm³. It also has a melting point of 156 °C and a boiling point of 220 °C (Ma et al., 2019). BPA has been categorized as an endocrine-disrupting chemical in which early life exposure can have severe effects on fetal development (Ullah, 2019). The detection of BPA in food, soil, water (drinking, surface, and ground), municipal and industrial waste, sediment, indoor air, and dust may be attributed to the high volume produced yearly (Guergana et al., 2014; Chakraborty et al., 2019).

The production of BPA started in 1891 but its use wasn’t rampant until 1930 when BPA was added to plastic to manufacture polycarbonate plastic (Ma et al., 2019; Ramakrishna et al., 2022). Research done in the late 1990s and early 2000s using animals showed that some diseases can be triggered following exposure to BPA, this led to the concerns raised by the Food and drug administration (FDA) about the safety of BPA in 2008 (Ramakrishna et al., 2022). Numerous health challenges such as alteration of the mammary gland and reproductive organ development, breast, nipple and prostate cancer, male and female infertility, precocious puberty in girls, and illness like diabetes and obesity are associated with exposure to BPA (Leung et al., 2017; Ullah, 2019; Salvaggio et al., 2019; Ramakrishna et al., 2022).

Sources and Route of Exposure to BPA: Based on the environmental sources of BPA it can be categorized as a preconsumer and postconsumer products. Preconsumer sources include accidental and effluent release during the production, transportation and processing of BPA and BPA-containing products (Guergana et al., 2014; Hahladakis et al., 2018, Ma et al., 2019). While Postconsumer sources can be linked to BPA disposal or waste management and these include effluent release from community wastewater treatment plants (WWTP), leaching from landfills, burning of household waste, and biodegradation of plastics in the environment (Corrales et al., 2015; Ma et al., 2019; Abrahlan and Chakraborty, 2020).

There are several routes through which BPA can enter the body these include through the digestive tract, respiratory tract and dermal absorption, with the digestive tract route being the largest source of absorption (EFSA, 2015). Martinez et al., (2018) estimated that 0.048–0.050 μg/kg bw/day for 3–17 year children and adolescents, from 0.034 to 0.035 μg/kg bw/day for adults and from 0.047 to 0.049 μg/kg bw/day for pregnant women are the mean dietary intake of BPA. In widespread populations, the dietary route can be said to be the main route of BPA exposure when compared to the non-dietary route (Ma et al., 2019). Several scientific papers have documented that the principal route through which human digestive tracts become exposed to BPA is via continuous consumption of canned food (Corrales et al., 2015; Siddique et al., 2020). The heating process involved
with the sterilization, microwaving and the acidic nature of foods stored in packages containing BPA determines the rate of leaching of BPA into the food and contaminating it (Michałowicz, 2014; Abraham and Chakraborty, 2020).

Transdermal absorption and inhalation of dust with BPA can be regarded as a secondary route of exposure in humans (Michałowicz, 2014; Li and Suh, 2019). The volatility of BPA is very low but it is capable of sticking to particulate matter such as dust, dirt, soot or smoke (Graziani et al., 2019). The fact that epoxy resins containing BPA can resist heat, electricity and chemical, makes them vital for electronic production and this exposes humans to inhalation of indoor dust containing BPA ((Michałowicz, 2014). In addition, some medical devices also contain BPA such as incubators and kidney dialysis machines products, this might be responsible for the presence of BPA in patients undergoing dialysis treatment and in newborn intensive care units (Ivana et al., 2018; Abraham and Chakraborty, 2020).

Detection: The presence of BPA has also been detected in the abiotic environment such as in the air, water, soil, sediment, food and biota like human beings, wildlife, and aquatic organisms in variable concentrations (Michałowicz, 2014; Abraham and Chakraborty, 2020). Also, the presence of BPA in several body fluids including the blood, urine, breast milk and tissues is a fact (Pinney et al., 2017; Abraham and Chakraborty, 2020). BPA is poorly soluble in water and is therefore most effectively detected in urine. Therefore, urine is the sample of choice for evaluating BPA exposure irrespective of its source (Siddique et al., 2020). The quantification of nanogram (ng) or picogram (pg) levels of BPA in the environment, food and body fluids have been done using several analytical procedures and instruments, the instrument includes high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS), solid phase microextraction (SPME)-gas chromatography-mass spectrometry (SPME-GC-MS), with SPME-GC-MS being a faster and highly sensitive method for analysing BPA (Ghazali and Johari, 2015; Abraham and Chakraborty, 2020).

Possible Mechanism of Action of BPA in the Body: BPA is structurally similar to endogenous 17β-oestradiols, the exact mechanisms through which BPA elicit its action at the cellular level are not completely understood (Farrugia et al., 2021). However, one possible mechanism of action of BPA is it is binding to estrogen receptors (ERs) to elicit its estrogenic and antagonistic activity on ERs due to its similarity in structure to estradiol though BPA has a low binding affinity for ERα and ERβ (Yang et al., 2017; Abraham and Chakraborty, 2020). The role of ERs in the human body cannot be underestimated, they play vital roles for both genomic and non-genomic signal transduction (Guergana et al., 2014). Genomic signal transduction is essential for gene expression while the modification of regulatory proteins is attributed to non-genomic signal transduction (Guergana et al., 2014). Mechanisms independent of the ERs have also been implicated with the effect of BPA. BPA at a lower concentration can bind and activate numerous other targets inside the nucleus and on the cell membrane (Canesi and Fabbri, 2015; Ma et al., 2019). One such mechanism includes acting as an androgen antagonist. Another mechanism is the antagonist or agonist effect of BPA on thyroid hormones which will eventually leads to the disruption of the thyroid system, this is due to the structural similarities between BPA and thyroid hormone (Canesi and Fabbri, 2015; Ramakrishna et al., 2022). In addition, the roles of orphan nuclear estrogen-related receptor y (ERRy) in mediating the estrogenic activity of BPA are also established (Tohmé et al., 2014). Moreso, BPA is capable of activating several genes that can modulate female cancers such as PI3K/AKT, STAT3 and MAPK (Ramakrishna et al., 2022).

Metabolism: In humans and other primates, the metabolism of BPA takes place in the liver where it is been conjugated with glucuronide to form bisphenol A-glucuronide, which is a highly soluble metabolite eliminated rapidly through the urine. The glucuronidation process is catalysed by UDP-glucuronosyltransferase (UGT) which has several isoforms in different species and the genetic polymorphism of this enzyme influences the toxicity of the metabolites produced after BPA metabolism (Siddique et al., 2020). There are suggestions that since no hormonal activity can be found in bisphenol A-glucuronide, the metabolism of BPA ingested through the oral route might neutralize the estrogenic activity of BPA with only little unconjugated BPA to bind to estrogen receptors (ERs) (Guergana et al., 2014). However, the production of xenoestrogen compounds which can be more potent than BPA has been observed following the metabolism of BPA in medaka, O. latipes (Canesi and Fabbri, 2015). In addition, repeated enterohepatic recirculation has been observed in rodents which can be attributed to slow elimination of BPA by rodents and placed them at the risk of longer exposure to unbound BPA before elimination (Farrugia et al., 2021). In fish, the use of the liver to metabolize BPA is not as efficient compared to other animal species because the main
route of exposure is through inhalation with the gills resulting in a more marked estrogenic effect of BPA in fish and related specie (Salvaggio et al., 2019). Appropriate precautions should also be taken when extrapolating result from scientific research using animal studies because there is wide variation in metabolic kinetics concerning route of administration, dose, sex and also age (Siddique et al., 2020; Farrugia et al., 2021).

**Effect of BPA on the Body:** The endocrine-disrupting activity of BPA can result in profound health effects in humans and animals even at very low concentrations (Abraham and Chakraborty, 2020). In Vertebrate, the teratogenic effect of BPA has been observed at high concentration (1-10 mg/L range) while low concentration (within the mg/L range) is associated with endocrine and pleiotropic effects (Canesi and Fabbri, 2015). Previous findings suggest that exposure to BPA during early pregnancy can result in fetoplacental and uterine growth restriction (Geetharathana et al., 2016). In the US, Pre and postnatal exposure to BPA can lead to nervousness, depression, rule-breaking and aggressive behaviour, as well as hyperactivity in children, these behavioural problems are more pronounced in females than in males (Staples et al., 2018; Ramakrishna et al., 2022).

The dramatic increase in human obesity and other metabolic disorder is alarming over the past decades and this has been attributed to exposure to diverse chemicals including BPA, it has been established in some studies that BPA has obesogenic effects (Siddique et al., 2020; Ramakrishna et al., 2022). This obesity is associated with the activation of some nuclear transcription factors at the molecular level such as peroxisome proliferator-activated receptor (PPAR alpha, delta, gamma) and some steroid hormone receptors that are involved in controlling the proliferation of the adipocytes and also regulating their differentiation. This alters lipid metabolism and eventually affects the composition of our body (Ramakrishna et al., 2022). Skin allergies and irritation have been documented in some workers in industries dealing with BPA or its products (Abraham and Chakraborty, 2020).

The concentrations of BPA found in the environment are capable of inducing oxidative stress and inflammatory genes such as Tumour necrosis factor (TNF-α), Interleukin (IL-6) and 1β in the body (Ferguson et al., 2016; Cho et al., 2018). Oxidative stress is the imbalance between the endogenous and exogenous generation of reactive oxygen species (ROS, free radicals) and the amount of antioxidants in the body (Ilaria et al., 2017). Unconjugated BPA in the body can enzymatically or non-enzymatically stimulate the generation of phenoxy radicals which then react with NADPH or intracellular glutathione (GSH), leading to ROS formation (Ivana et al., 2018) which harms the human and animal body. The genotoxic effects attributed to BPA have been known to cause meiotic arrest, induce meiotic aneuploidy and chromosome aberrations, and prevent meiotic double-strand breaks (DSBs) repair (Klara et al., 2019). BPA affects hormone concentrations and the male reproductve system in rodents and humans (Oliveira et al., 2017; Ullah, 2019). Gadamsetty et al., 2019 also documented the ability of BPA to damage the nephrons, this will eventually affect the renal capacity leading to reduced renal efficiency in rats and this has also been observed in humans (Ramakrishna et al., 2022). Inhalation of BPA through the gills is the principal route of exposure in fish and not the diet. The estrogenic effect of BPA in fish is more pronounced as a result of inefficient metabolism via the inhalation route when compared with the liver (Canesi and Fabbri, 2015). Some of the pleiotropic effects observed in fish exposed to BPA include abnormal sex ratios with more female fish seen, reduced tail length, increased production of vitellogenin in males or sexually immature females, reduced circulating levels of testosterone, decreased expression of genes associated with oocyte growth, cholesterol uptake, and several matrix metalloproteinases that are essential for ovulation, reduced hatching success rate, increased expression of gene related to steroid biosynthesis, and high prevalence of intersexuality (Canesi and Fabbri, 2015; Akram et al., 2020).

**Environmental Impact and Bioaccumulation:** The natural occurrence of BPA does not exist, the widespread existence of BPA can be attributed to its high demand in the manufacturing industry necessitating its high production (Corrales et al., 2015; Ramakrishna et al., 2022). Currently, the lowest-observable-adverse-effect level (LOAEL) of BPA is 50 mg/kg body weight per day, though recently in response to the advanced safety evaluation of BPA and its undesirable health effects, the European Food Safety Authority (EFSA) reduced the tolerable daily intake (TDI) to 4 μg/kg bw/day (EFSA, 2015; Siddique et al., 2021). The transmission of the aberrant effects of BPA in aquatic animals to humans through biomagnification is also been considered (Ramakrishna et al., 2022). Due to the low octanol-water partition coefficient (log Kow = 3.64) and bioconcentration factor (BCF = 196), the bioaccumulating potential of BPA is low (Abraham and Chakraborty, 2020). However, it is trapped in the soil due to the high value of the soil-water partition coefficient of 314 to 1524. However, the biodegradation of BPA in oxygen-abundant soil

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conditions helps to mitigate the bioaccumulating potential in the soil (Ramakrishna et al., 2022).

Conclusion: The widespread use of products containing BPA infers that basically, everyone comes into contact with the BPA one way or the other. BPA is an established endocrine disruptor to which exposure in humans and animals should be reduced to the barest minimum. Generally, there are convincing facts that BPA alters physiological homeostasis in humans and animals leading to various disease conditions. The possibility of using plants and microorganisms to transform BPA into compounds with lower toxicity and estrogenicity should be explored.

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