A comprehensive review on Bisphenol A (BPA) toxicity updates: Controversy is not over yet

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ABSTRACT

Bisphenol A (BPA) is a commonly used industrial chemical in plastics production. It is present in different types of plastics as polycarbonate and epoxy resin. Plastics that contain BPA are used for various purposes as food containers, medical equipment, and toys. So, BPA exposure is almost universal among humans. Food and water have been recognized as significant BPA exposure sources. Other sources include waste smoke, thermal paper, and dental materials. Since it was created, concerns regarding BPA safety and health hazards have been raised. Research over a decade showed multiple health hazards of BPA in humans. Bisphenol A is known to be a hormonal disruptor interfering with regular hormonal activity in the body. In addition, it has a cytotoxic effect by increasing free radicals. Bisphenol A is linked to many diseases affecting the reproductive, endocrine, nervous, and immune systems and different types of cancer. The FDA and other health-related institutions have regulated the use of BPA plastics. However, a debate is unsolved as regards the safe dose of BPA for daily human exposure. This article explores the toxic aspects of BPA and discusses the different regulations relating to BPA use.

Introduction

Bisphenol A (BPA) is a commonly used industrial chemical in plastics production. BPA has been continuously manufactured since its first synthetic form was created in the 1900s (Hoepner et al., 2016). 4'4-iso-propylidenediphenol, also known as BPA, has the chemical formula C15H16O2 with a molecular weight of 228.29 g/mol. One part acetone and two parts phenol are combined and compressed during the production of BPA (Staples et al., 1998). Bisphenol A is often a white, colorless, crystalline substance with a faint phenolic smell (Muhamad et al., 2016).

Polycarbonate plastics (PC) and epoxy resins contain BPA. Polycarbonate plastics are present in Optical materials and electronic equipment (Arnich et al., 2011). Additionally, it is utilized in products that come into contact with food, such as microwave-safe dishes, feeding bottles, plates, cups, goblets, and storage containers (EFSA, 2015).

Epoxy resins provide outstanding corrosion-fighting capabilities as well as mechanical and thermal stability. Epoxy resins are utilized in the food sector to store drinking water, the inner lining of metal food and beverage cans, and other applications (Vandenberg et al., 2010).

Bisphenol A has uses outside of food, such as in toys, thermal paper, and medical equipment. Probably due to migration from packages, BPA is also discovered in cosmetics. Due to the widespread use of BPA, various items may expose the general public to it (Hormann et al., 2014).

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Bisphenol A exposure raises concerns due to potential health impacts on various bodily organs, particularly in youngsters. Nevertheless, according to the Food and Drug Administration (FDA), BPA is safe at low concentrations in some foods. This article outlines the primary toxicological issues with BPA consumption.

Sources of exposure:

Epidemiological studies showed that exposure to BPA is practically widespread in humans. Bisphenol A is detectable in the urine of nearly all adults and children tested and in the serum of pregnant women, breast milk, follicular and amniotic fluid, cord blood and placental tissue, and human fetal livers (Rochester 2013).

Food and water have been identified as substantial sources of BPA exposure (Huang et al., 2017). It's estimated that more than 90 percent of total BPA comes from food sources. Bisphenol A in food is the outcome of BPA exposure to raw plant materials and animals. Due to their high consumption, fruits and vegetables were found to contribute the most to total dietary BPA intake (9.92 g/kg). After that comes meat, followed by fish, water, grain, milk, and dairy products (Martínez et al., 2017). Also, food containers and cans can release BPA in contained food (Lorber et al., 2015).

The lungs are the next important route of exposure to BPA. The estimated indoor BPA exposure is 9.62104 g/kg/day, which accounts for 78% of non-dietary BPA exposure (Martínez et al., 2018). Bisphenol A can move into the atmosphere during manufacturing (Liao et al., 2012). In addition, research showed that BPA could be released from burning plastic garbage into the environment in developing countries (Abraham and Chakraborty, 2020).

Thermal paper is frequently employed on cash receipts and cinema tickets. Bisphenol A was used as a color developer in the creation of thermal paper. Thermal paper has been identified as a substantial source of BPA for specific occupations (Bernier and Vandenberg, 2017).

Almost all published research showed that dental materials share little to the total BPA exposure, and its adverse effects can be ignored. Still, the possible impacts may be considerable if talking about exposure for a long time (Lee et al., 2017).

Pharmacokinetics:

Nearly 95% of orally administered BPA is swiftly and efficiently absorbed from the gastrointestinal tract in rats, primates, and humans (Kurebayashi et al., 2002).

Bisphenol A undergoes substantial first-pass metabolism in the gut wall and liver following oral absorption (Inoue et al., 2003; Pritchett et al., 2002). Biotransformation of BPA occurs mainly via BPA-glucuronide (Völkel et al., 2002). Thus, BPA-glucuronide is an adequate, unique, and stable biomarker for determining BPA exposure (Kuester and Sipes, 2007). It is rapidly removed from the blood by the kidneys and eliminated with urine after oral ingestion in humans, having a terminal half-life of fewer than 6 hours (Tsukioka et al., 2003). Bisphenol A-sulfate has been detected in human urine samples at concentrations significantly lower than BPA-glucuronide (about 10%) (Ye et al., 2005). Only trace amounts of unconjugated or free BPA were detected in urine and serum samples (Pastor-Belda et al., 2016).

Bisphenol A has been detected in amniotic fluid and fetal plasma during pregnancy, indicating transit across the placenta. Moreover, it was discovered to be secreted in breast milk and passed to infants and newborns (Reddivari et al., 2017).

The excellent biotransformation of BPA and the quick renal elimination does not indicate a potential for bioaccumulation (Völkel et al., 2005). However, research on monkey and rodent fetuses and newborns suggests that the liver has a limited capacity to process BPA, providing the potential for BPA to be harmful at crucial developmental phases (Doerge et al., 2011).

Mechanism of toxicity

Interference of BPA with endogenous hormones is responsible for its most profound impacts on the human body. It disturbs hormonal functions via estrogenic, anti-androgenic, and anti-thyroid actions (Rahman et al., 2017). Based on the existing research, BPA has a relatively low affinity for binding to specific hormone receptors. For example, the binding affinity of BPA to estrogen receptors is 1,000 to 10,000 times less than that of natural estrogen (diethylstilbestrol) (Lemmen et al., 2004). Normal endocrine signaling does not significantly impact overall hormone levels. However, even little changes in hormone action might profoundly affect biological activity (Saltzman and Ziegler, 2014). Initially, BPA was utilized as a booster to enhance the growth of animals in meat production before its toxicity was established (Erler and Novak, 2010).

Another toxic mechanism is BPA's detrimental effects on cells and tissues, which are mediated by increased oxidative stress. Bisphenol A increases the generation of dangerous free radicals (Rahman et al., 2020). High quantities of free radicals, namely reactive oxygen species (ROS), cause oxidative damage to cellular structural macromolecules such as protein, lipid, carbohydrate, DNA, and RNA, hence predisposing the cell to pathology (Valko et al., 2006; Heldring et al., 2007).

Toxic effects of BPA

A substantial amount of data (over 300 published studies) linked BPA to deleterious health effects in laboratory, wildlife, and in vitro models of mammals and nonmammals. Although these studies support the claim that environmental exposure to bisphenol A (BPA) may be harmful to human health (Martínez et al., 2018), there is less research on the effects of BPA on humans due to ethical concerns (Rochester, 2013).

1. Reproductive toxicity

Because BPA mimics estrogen, it is believed to be harmful to the female reproductive system. Numerous researches on animals demonstrate that BPA, as a toxicant, has adverse effects on fertility, delays the onset of female puberty, and influences the estrous cycle. In cross-sectional investigations, it was discovered that urine BPA levels were positively correlated with a variety of female reproductive problems and virility (Matuszczak et al., 2019).

Animal and human research indicated a possible association between BPA levels and the development of reproductive illnesses, such as polycystic ovary syndrome (PCOS), endometriosis, and increased endometrial thickness in women (Wang et al., 2022).

Additionally, miscarriage and premature birth were commonly associated with varying amounts of BPA (Shen et al., 2015). Similarly, exposure to BPA impacts early in vitro reproductive treatment outcomes. It was discovered that a higher BPA level was related to a lower implantation rate and metaphase II (MII) oocyte count (Radwan et al., 2020).

In several ways, BPA is said to impair men's reproductive capacity. Increased BPA levels in males were associated with decreased sperm concentration and motility (Ji et al., 2018). Also detected in BPA-exposed

individuals were erectile dysfunction, ejaculatory difficulties, and loss of sexual desire (Li et al., 2010). Boys born to BPA-exposed mothers are more likely to be born with congenital abnormalities of the reproductive system than those born to non-exposed mothers (Matuszczak et al., 2019).

2. Endocrine toxicity

Bisphenol A has been proven to affect the estrogenic system and the androgenic, prolactin, insulin, and thyroid hormone systems (Fenichel et al., 2013).

Researchers discovered a correlation between BPA exposure and changed thyroid hormones. An elevated BPA level in urine was observed to be correlated with increased free triiodothyronine and decreased TSH concentration (Wang et al., 2013).

The potential effects on insulin or glucose homeostasis have aroused concerns that BPA exposure may contribute to type 2 diabetes. According to experimental investigations, BPA exposure causes insulin resistance and decreased glucose metabolism in mice (Moon et al., 2015). Human studies have demonstrated a strong connection between urine BPA levels and type 2 diabetes in addition to the established risk factors of diabetes (Rancière et al., 2019).

3. Neurobehavioral toxicity

Several animal and human researches have determined that prenatal exposure to BPA impacts brain development and behavior. Bisphenol A exposure can result in anxiety, an increased risk of autistic traits, poor learning and memory, and alterations in social behavior patterns (Jones and Watson, 2012).

The effect of BPA on neurobehavioral functioning in children may vary by gender. An experimental study in mice showed that maternal exposure to BPA significantly reduced anxiety and depression in male offspring in their adult life. While in the adult female offspring, it increased anxiety behaviors, enhanced new object recognition, and impaired contextual fear conditioning memory development (Gong et al., 2022).

4. Immunotoxicity

Exposure of pregnant mice to BPA affected the number and function of innate and adaptive immune cells in the offspring, including a decrease in regulatory T cells, anti-inflammatory cytokines, and chemokines and an increase in pro-inflammatory cytokines (Xu et al., 2013 and Jain et al., 2022).

The distribution of CD8+ and CD4+ T cells in the spleen and ileal Peyer's patches is altered by BPA exposure. Immunological cell and cytokine dysregulation can lead to autoimmune disorders and immune deficiencies (Ozaydın et al., 2018).

5. Other organ toxicity

The liver plays a unique function in the metabolism of most substances, so it is likely to be a target of toxicity. Multiple studies have demonstrated that BPA negatively affects the structure and function of both human and animal livers. Human hepatic steatosis has been associated with BPA (Martella et al., 2016), enhanced insulin resistance in HepG2 cells, changed liver morphology (Geng et al., 2017), and elevated serum levels of hepatic enzymes (Mahdavinia et al., 2019).

Bisphenol A decreases RBC count and Hb level. It is believed that a decrease in erythropoietin synthesis results from either the estrogenic activity of BPA, a decrease in serum testosterone levels, or an increase in red blood cell death (Abid and Hassan, 2016).

It has been stated that prenatal exposure to BPA retards child development. It primarily impacts the growth of height,

weight, and the nervous system. A shorter anogenital distance (AGD) was observed in both males and females (Sun et al., 2018).

Bisphenol A and cancer

The endocrine-disrupting qualities of BPA suggest it may influence developmental plasticity in early life, predisposing humans to cancer at dosage under the oral reference dose (RfD). In vivo literature investigating the carcinogenic characteristics of BPA in rodents showed considerable evidence that early-life BPA doses below the RfD enhance susceptibility to breast, prostate, and other cancers (Seachrist et al., 2016).

The correlation between BPA content in the urine and BPA concentration in breast adipose tissue samples of breast cancer patients was investigated. Cancer patients were found to have a higher concentration of BPA in their urine and breast adipose tissue samples than the control group. The conclusion is that BPA may raise the risk of developing breast cancer (Keshavarz-Maleki et al., 2021).

Another study aimed to examine the potential connection between serum BPA concentrations and breast and prostate cancer incidence in the Spanish European Prospective Investigation of Cancer and Nutrition (EPIC) subcohort. The results detected a similar rate of BPA detection among cases and sub-cohorts from the sample, and no connection was seen with breast cancer risk. Though, an increased risk of prostate cancer when serum BPA levels rose was noticed (Salamanca-Fernández et al., 2021).

Bisphenol A exposure and interaction with genetic variations are claimed to be associated with colorectal cancer (CRC) incidence, and this association may be partially mediated by oxidative stress. This association was assessed by evaluating urine BPA and indicators of oxidative stress in diseased and control groups. There was a substantial positive correlation between BPA and CRC risk (Deng et al., 2021).

In silico analysis of a group of genes found to be dysregulated in ovarian cancer cell lines in the presence of BPA hypothesized a link between BPA exposure and ovarian cancer. Scientific and clinical research should confirm the correlation between BPA levels, gene deregulation, and cancer formation (Zahra et al., 2021).

Bisphenol A is primarily eliminated via the urinary system. Continuous bladder exposure to BPA is assumed to be connected with the advancement of cancer. The average levels of BPA in urine were assessed regards their affection on the metabolic process of bladder fibroblasts and cancer-associated fibroblasts (CAF). The results imply continuous exposure to BPA may increase cancer growth by altering stromal cells' metabolism (Pellerin et al., 2021).

Safety and regulations

As the use of BPA became increasingly widespread, regulators and the general public expressed safety concerns. Scientists are tasked with proving the connection between BPA and purported health risks, particularly at levels below those permitted.

A consortium-based research program was formed by the National Toxicology Program (NTP), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Food and Drug Administration (FDA). The Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) program was designed to investigate the spectrum of potential health problems associated with BPA exposure (NIEHS, 2022).

Current FDA and Environmental Protection Agency (EPA) lowest observed adverse effect level (LOAEL) is 50,000

µg/kg/day. The acceptable daily intake (ADI) dose is now determined at 50 µg/kg/day. This safety limit is calculated built on the fact that a 1000-fold dose lower than the LOAEL should have no adverse effect on daily oral exposure (Vom Saal and Vandenberg, 2021).

The FDA's last report on BPA use was in 2018, and the agency has not yet banned its use. Experts from the FDA in relevant domains assessed scientific studies. The FDA review determined that there was no evidence in the analyzed studies to warrant a reevaluation of the safety of BPA in food packaging. Notably, the FDA prohibited using BPA in baby bottles and sippy cups in 2012 and coatings for infant formula containers in 2013. This prohibition was not predicated on safety but on desertion. Regulatory approval is no longer required for the specific use of the food additive because that usage has been abandoned permanently (FDA, 2018).

Members of the Endocrine Society criticized the FDA because their assumptions contravene fundamental endocrinology principles. They said that FDA decisions are based on false premises. Based on evidence from human investigations, it was concluded that low doses of BPA change hormone-sensitive organs and are associated with a broad spectrum of human disorders; the human results are confirmed by multiple findings from animal tests and in vitro mechanistic studies (Vom Saal and Vandenberg, 2021).

Regards the European Food Safety Authority (EFSA), in 2006, finished its first thorough risk assessment of BPA. In January 2015, EFSA issued a comprehensive re-evaluation of BPA exposure and toxicity and decreased the tolerated daily intake (TDI) from 50 to 4 µg/kg/day. The fall in the TDI resulted from uncertainties about the dangers of low-dose BPA. In their December 2021 draught reevaluation of BPA, EFSA's scientists determined a TDI of 0.04 ng/kg/day. The decrease in the TDI derives from evaluating studies published from 2013 to 2018 (EFSA, 2022).

Diverse global legislative frameworks and regulatory norms govern the distribution and use of BPA. In Japan, the observed BPA amounts do not show any hazard to the population, so no restrictions are needed. In Latin America, Africa, and some countries in Asia, however, it is crucial to set up legal rules on the use of BPA as much research has proved the occurrence of BPA toxicity from food and water sources (Tarafdar et al., 2022).

Remediation

Due to the recognition of BPA as a dangerous contaminant, numerous studies were conducted to mitigate its influence on health. Bisphenol A degradation procedures using biological methods have been utilized to limit its contamination alongside other methods, such as membrane separation, adsorption, and oxidative and thermal degradation (Tarafdar et al., 2022).

Bisphenol A can be remedied enzymatically by naturally occurring microbes or enzymes such as the laccase enzyme. Biosurfactants such as rhamnolipid (RL) increase the rate and extent of enzymatic BPA degradation (Onaizi and Alshabib, 2021).

One more method for BPA elimination is membrane separation. This is possible using reverse osmosis and nanofiltration membranes. The most recent is the β-cyclodextrin (β-CD) modified graphene oxide (CDGO) membrane, which is more efficient than the previous ones (Chen et al., 2020).

Because of its low cost, excellent efficiency, and ease of operation, adsorption is an up-and-coming candidate for BPA removal. Numerous adsorbents, including biosorbents, minerals, metal-organic frameworks, graphene, and carbonaceous materials, have been intensively studied. Due to their abundant

availability and controllable physiochemical properties, activated carbons are highly desirable for practical applications (Sun et al., 2020).

Oxidative degradation is another BPA remediation technique. Photocatalytic and photoelectrocatalytic oxidation is a practical and environmentally benign method for removing BPA from marine ecosystems. Despite their rapid breakdown, these reactions may generate very hazardous intermediates. Numerous researchers have created technologies that break down BPA and oxidize its hazardous intermediates to the lowest amounts feasible (Lin et al., 2020).

Conclusion and recommendations

According to prior research, BPA poses a significant health risk. The use of BPA is controlled as a result of its widespread occurrence and the substantial evidence indicating its danger to human health. Nevertheless, there are still many unsolved uncertainties surrounding the toxicity of BPA. To keep the proper dose level without adverse health effects up-to-date, it is necessary to continually review new scientific research. Egypt and other emerging nations should impose strict rules on using BPA in food containers, considering the worldwide stance toward its prohibition.

Conflict of interest

All authors declare that they have no conflicts of interest.

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مراجعة شاملة لتحديثات سمية Bisphenol A (BPA) :الجدل لم ينته بعد

اية مجدى القاضى[1] ، رشا الحداد على موسى[1] ، مى مصطفى عبد القادر[1] ، هند جمال عارف[1] ، عزة عمر حسن[1]

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تستخدم ماده بيسفينول أ بشكل شائع في الصناعات البلاستيكية. ويستخدم البلاستيك الذي يحتوي علي هذه المادة في العديد من الاغراض إذ أنه يوجد في أوعية الطعام البلاستيكيه، الأجهزه الطبيه واللعب، هذا يعني ان تعرض الانسان لهذه الماده واسع المدي. ولقد تم اعتبار الماء والغذاء أحد مصادر التعرض لماده بيسفينول أ، بالإضافه الي الأوراق الحراريه والأدوات المستخدمه في طب الاسنان، وهناك العديد من الأبحاث التي أجريت لتوضح مدي أمان إستخدام ماده بيسفينول أ و الآثار الجانبية لها علي صحه الانسان، حيث وجد أنها تؤثر علي الهرمونات وتتعارض مع نشاطها داخل الجسم، واكتشفت بعض الاثار السميه علي الخلايا وذلك من خلال زياده نسبه الشوارد الحرة التي تضر الخليه، لذلك تسببت هذه المادة في العديد من الأمراض التي تؤثر علي الإنجاب والغدد الصماء و الأعصاب والمناعه وحدوث أنواع كثيرة من السرطانات. ولقد قامت منظمه الغذاء والدواء وبعض المنظمات الاخري التي تهتم بالصحة بتنظيم إستخدام البلاستيك الذي يحتوي علي بيسفينول أ. ولكن لم يتم الإستقرار علي الجرعه الامنه التي يمكن أن يتعرض لها الانسان بشكل يومي. وسوف يوضح هذا المقال الاثار السميه لماده بيسفينول أ و ويناقش التنظيمات المختلفه المتعلقه بإستخدام هذه المادة