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SYSTEMATIC REVIEW: IMPACT OF BISPHENOL-A (BPA) EXPOSURE ON HUMAN HEALTH

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Abstract

Introduction: *One chemical substance used in producing epoxy resins and polycarbonate (PC) is called bisphenol-A (BPA). Three million tons of the chemical compound bisphenol-A are still produced annually. The amount of BPA produced in 2015 was 7.7 million tons; by 2022, 10.8 million tons are anticipated to be made. This study aimed to ascertain the effects of bisphenol-A exposure on human health.* ***Discussion:*** *This study used a systematic review method by collecting articles through online databases with a publication range of 2018 - 2024. The article search used the PRISMA flow diagram. The findings of 30 articles all examined the impact of BPA exposure on health. The level of exposure to bisphenol-A can have an impact on health due to the nature of BPA EDC (Endocrine Disrupting Hormone) which can inhibit the activity of natural hormones in the body.* ***Conclusion:*** *The impact on human health due to exposure to bisphenol-A such as cancer, obesity, disruption of reproductive health, hypertension, disrupting child development, and also behavioral changes in children. Bisphenol-A enters the body not only through food packaging but also through air and dust contaminated with BPA. The length of exposure and concentration of BPA affect its effects on the human body.*

INTRODUCTION

In this modern era, people prioritize a practical lifestyle, especially when it comes to food or beverage packaging. Food packaging aims to protect food from physical, chemical, and biological damage so that the shelf life of food can be extended. Plastic has emerged as a preferred material for packaging because it is flexible, affordable, and easy to find anywhere. Plastic is still an important part of everyday life. The practical, cheap, and easy-to-obtain features of plastic make most humans rely on plastic in their daily activities. According to *Making Oceans Plastic Free* data, Indonesia alone consumes 182.7 billion plastic bags annually. Plastic packaging is very dominant in Indonesia's food industry. The largest use of plastic, at 60%, accounts for 60% of this plastic usage, especially in food and beverage packaging. Indonesia is a developing country with an increasing plastic consumption rate. Plastics with recycling symbols "3" and "7" usually contain BPA (1). Plastic packaging is commonly used in hot food packaging, such as meatballs, fried foods, and noodles. In addition to food packaging, plastic is used to make household appliances such as cups, baby bottles, toothbrushes, plates, and spoons. The use of plastic in food packaging also plays a role in BPA exposure. Most plastic and canned food packaging contains BPA. Chemicals in packaging, including BPA, can be dissolved in food and beverages, particularly at high temperatures (2). A chemical compound utilized in epoxy resin and polycarbonate (PC) is called bisphenol-A (BPA). Bisphenol-A (BPA) is a synthetic chemical commonly used in industry, composed of phenol and acetone molecules with a melting point of 156°C and a boiling point of 220°C. In the 1940s, manufacturing companies began using BPA as a monomer in products such as epoxy resins, polycarbonates, and polysulfones. Additionally, BPA is used as an antioxidant and a polymerization inhibitor. Polycarbonate is a strong material that is transparent to

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visible light but opaque to ultraviolet light. Epoxy resin is used as a protective coating for food packaging and beverage cans.

Transparent, durable, and lightweight plastic called polycarbonate is used to make food containers, drink bottles, and other household items. Food and drink items have been found to be contaminated by polycarbonate, a plasticizer. This occurs due to BPA's tendency to move into warm or hot foods and beverages. Three million tons of the chemical compound bisphenol-A are still produced annually. BPA's hard, light, and transparent properties make it an excellent choice for use as an additive. The output of BPA was 7.7 million tons in 2015, and it was anticipated to reach 10.8 million tons by 2022. BPA exposure poses significant risks to health, is hazardous if inhaled, and can cause respiratory tract irritation. It is dangerous if ingested, can cause skin irritation if absorbed through the skin, and can injure the eyes if it comes into contact with them. According to Dodds and Wilfred Lawson, BPA exhibits properties similar to the sex hormone estrogen found in the human body, raising concerns that it could disrupt the endocrine system if present in the human body (3).

Studies conducted in the United States revealed BPA concentrations above the normal limit in more than 90% of urine samples (4). Furthermore, studies in Asian nations found that 94.3% of samples had values between <0.1 and 30.1 ng/mL (5). BPA contamination was also discovered in some animal and human canned food packaging. However, the amount of BPA in animal canned food was less than in canned food consumed by humans (6).

Moreover, epoxy resins are produced using bisphenol-A. Water supply pipes, bottle caps, and food cans are among the metal products used as varnishes to coat epoxy resins. This keeps the metallic goods fresh and free of contaminants while preventing the metal from rusting. Manufacturing electrical and electronic components is another frequent application of epoxy resin. These products are frequently seen in a wide range of gadgets, including cell phones, laptops, and game consoles, as well as cars, airplanes, and housing materials (3).

According to EFSA (European Food Safety Authority), exposure to BPA in food can be considered tolerable for adult humans if it does not exceed 4µg/kg body weight per day. Meanwhile, according to BPOM No. 20 of 2019, the threshold of BPA that the body can accept is 0.6 mg/kg per day. Research shows that using BPA can be detrimental because it can cause health issues in the human body (7). BPA is an endocrine system disruptor that can emulate the body's hormones and can cause negative impacts on health, such as the occurrence of hypertension, obesity, behavioral changes, impaired reproductive development, cancer, diabetes, and cardiovascular effects (4).

The results of a study conducted in Korea on 560 elderly participants aged more than 60 years revealed a relationship between bisphenol-A exposure and the occurrence of hypertension. The concentration of bisphenol-A increased after consuming canned drinks, leading to an increase in systolic blood pressure by 4.5 mmHg (8). In addition, other studies have also shown that bisphenol-A exposure can potentially contribute to ovarian cancer due to stimulation of proliferation, increased aerobic glycolysis in cancer cells, and increased production of ATP, pyruvate, and lactate from OVCAR-3 cells (9).

The use of plastic is still widely practiced, even for hot food packaging during "food delivery," which allows the migration of bisphenol-A into the human body when consuming food or drinking in plastic packaging containing BPA. The use of plastic materials containing bisphenol-A can be very dangerous to health and may cause the occurrence of cancer, diabetes, hypertension, obesity, reproductive system abnormalities, and behavioral changes. Therefore, the problem formulation was obtained as follows: "what is the impact of bisphenol-A exposure on human health?" To collect, evaluate, and identify scientific evidence, researchers used the systematic literature review method to answer this question and gain a deeper understanding by collecting and analyzing data from various studies on the impact of bisphenol-A on human health.

DISCUSSION

This research adopts a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) method (10). This study's secondary data were sourced from online media accredited and published on national and international sites such as Google Scholar, Pubmed, ScienceDirect, Garuda, Scopus, SpringerLink, EBSCOhost, and Researchgate. The articles selected focus only on the impact of bisphenol-A exposure on human health-causing diseases like prostate cancer, breast cancer, ovarian cancer, diabetes, reproductive system abnormalities, and behavioral changes. The following keywords were used by researchers in the literature review (Table 1).

Table 1. Keywords

Keywords
Bishpenol - A AND Human
Bisphenol-A and Impact
Food packaging AND impact
Food packing AND (cancer OR Prostate OR Breast OR Diabetes OR Obesity)
Bishpenol - A AND (cancer OR Prostate OR Breast OR Diabetes OR Obesity)
Bishpenol - An AND Reproduction System
Bishpenol - A AND (Exposure OR Metabolism OR Migration)
BPA AND Food Packaging
Bishpenol - A AND (Health OR Impact)
Bishpenol - A AND Cancer (Prostate OR ovarian OR breast)

The search for journal articles initially yielded 11,789 articles, including national sources like 692 from Google Scholar, 27 from Garuda, as well as international journals such as 5,673 from the Pubmed database, 3,540 from ScienceDirect, 3,849 from Scopus, and 3,681 from SpringerLink. The selection of articles begins with identification, followed by sorting. Subsequently, screening was performed by checking for duplication with the Mendeley application using the 'Check for Duplicates' feature. After the duplicate articles were removed, 10,027 unique articles were finally received. Then, the articles were reviewed based on the title and abstract's suitability to the research topic. A total of 115 articles were chosen, and 9,912 articles were excluded due to the lack of titles and abstracts matching the research topic. The 115 selected articles were reviewed in full text to see the suitability of the research methodology (cross-sectional, case-control, and cohort). Then, we observed and excluded 63 articles with inappropriate methodology, lacking alignment with the research focus, and finally obtained 52 articles that were assessed for eligibility. In the last stage, the articles to be included in the study for further analysis were selected. Of the 52 articles, 22 articles were found to be ineligible based on the inclusion criteria. The inclusion criteria in this study are: 1) Research articles published during 2018–2023 in English or Indonesian; 2) The dependent variable in the research article is bisphenol-A; 3) Independent variables of plastics containing bisphenol-A, packaged food; 4) Research articles with access to full texts; 5) Articles with cross-sectional research designs, including case-control, cohort, and experimental studies; 6) Articles from the Undip subscribed database accessed through SSO. Ultimately, 30 articles were obtained and included in the systematic review research (36). Below is a detailed process diagram of sorting articles, depicting the complete workflow from searching for articles from several journal databases until articles that match the research topics and criteria are obtained (Figure 1).

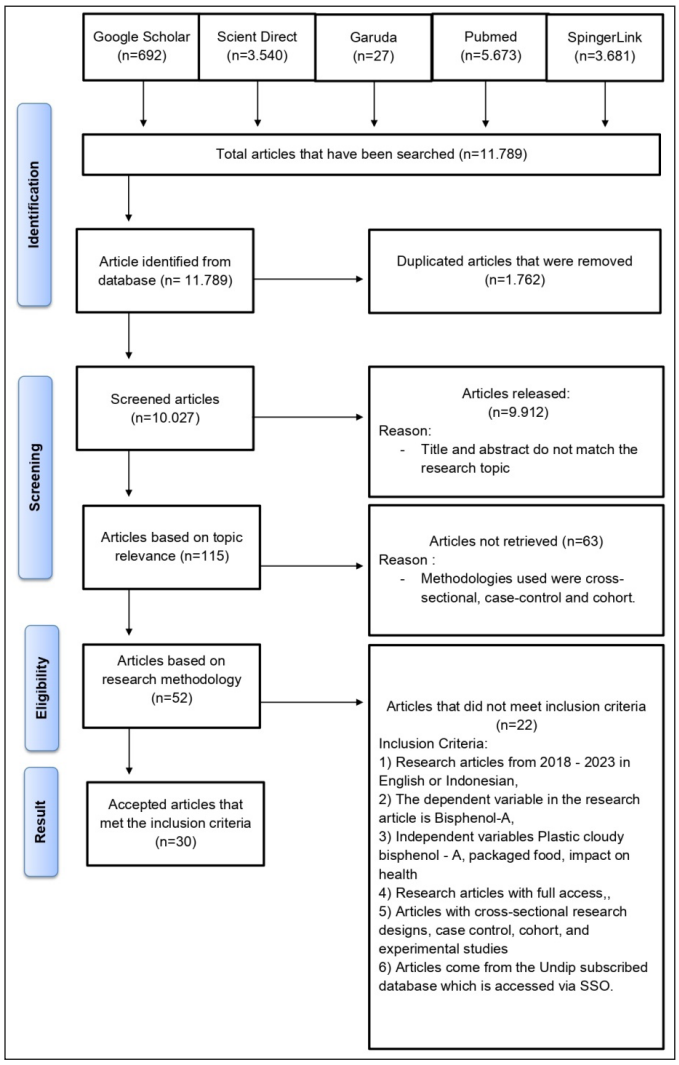

Figure 1. Flow Chart of Article Screening

The 30 articles discussed the impact of BPA exposure on health. The articles reviewed adopted cross-sectional (43%), case-control (27%), and cohort (30%) research designs (Table 2).

There were 11 articles discussing the risk of cancer (11-12,21-22,13-20), with 5 articles discussing reproductive health disorders (13,23–26), 4 articles discussing the risk of hypertension (27–30), 3 articles discussing obesity (31–33), and behavioral changes (34-35), and 2 articles discussing diabetes (33, 36) and developmental disorders in children (37–38). Of the total, 14 studies were conducted in China (13, 14, 36–39, 17–18, 20, 23, 28, 30, 32, 34), 3 in Spain (26–27, 31), 3 in Italy (19, 24, 31), 3 in the United States (16, 21–22), 2 in Korea (29–33), and 1 each in Japan (35), Mexico (15), Denmark (25), and Iran (11). Among the selected articles, 26 articles showed an association between bisphenol-A exposure and health (11–12, 23–24, 26–33,13, 34–35, 37–40,14–20), while 4 articles found no significant association between bisphenol-A exposure and health (21–22, 25, 36).

Table 2. Data Extraction

Research Title	Research Objectives	Study Design, Sample	Study Design, Sample	Research Results, Conlusion
Urinary bisphenol A concentrations are associated with reproductive parameters in young men (China)(26)	This study aimed to evaluate the relationship between urinary BPA levels and semen quality, as well as reproductive hormone levels.	Cross-sectional **Sample** students aged 18-23 years, a total of 215	Independent variable: bisphenol-A Dependent variable: male reproductive health	1. BPA detected in 95.3% 2. A p value of <0.01 was obtained, meaning that exposure to BPA can reduce sperm quality and increase Luteinizing hormone (LH) levels in men. 3. BPA adversely affects young men's endocrine function **Conclusion:** No significant associations were found between BPA and other semen parameters or reproductive hormone levels
Maternal exposure to bisphenol A and anogenital distance throughout infancy: A longitudinal study from Shanghai, China (China)(23)	In this study, we aimed to investigate the impact of maternal BPA exposure on the anogenital distance (AGD) of offspring in a longitudinal birth cohort from birth to one year of age.	Cohort **Sample** Women with a gestational age of 12 - 16 weeks, a total of 982	Independent variable: bisphenol-A Dependent variable: reproductive health	1. BPA was detected in 77.90% of urine samples 2. Women with detectable BPA give birth to LBW 3. Boys with BPA-detected mothers had decreased AGD at 12 months of age **Conclusions:** Maternal exposure to BPA was associated with shortened AGDap and AGDas in boys at age 12 months but not in girls, which suggests a gender specificeffect of BPA exposure on offspring's development
Bisphenol A is not associated with a 5-year incidence of type 2 diabetes: a prospective nested case-control study (China)(36)	This study aims to investigate whether serum BPA level could predict the 5-year incidence of type 2 diabetes (T2D).	Case-control **Sample** Individuals aged 20 - 80 years, with 232 cases and 232 controls	Independent variable: bisphenol-A Dependent variable: incidence of diabetes	1. No association of BPA levels with insulin resistance **Conlusion:** BPA is not associated with a 5-year T2D incidence. These data do not support previous cross-sectional study that BPA exerted a detrimental effect on glucose metabolism.
Relationship between bisphenol A exposure and attention-deficit/ hyperactivity disorder: A case-control study for primary school children in Guangzhou, China (China)(34)	To investigate the possible association between environ-mental BPA exposure and the altered behavior of children.	Case - control **Sample** Children aged 6 - 12 years, 468 in total with 253 controls and 215 cases	Independent variable: bisphenol-A Dependent variable: behavior change in children	1. BPA detected in 90% of urine samples 2. A p value of <0.001 was obtained, which means that there is a significant relationship between BPA exposure and behavioral changes in children. 3. BPA exposure can increase the incidence of ADHD higher in boys than girls with OR = 4.58 (95% CI: 2.84 - 7.37). **Conlusion:** Our findings provide direct evidence that childhood BPA exposure may be related to ADHD and 8-OHdG concentrations for children. Moreover, BPA exposure could increase the higher occurrence of ADHD for boy than for girls.
Association between prenatal bisphenol A and phthalate exposures and fetal metabolic related biomarkers: The Hokkaido study on Environment and Children's Health (Japan)(35)	This study aimed to assess the association between prenatal exposure to bisphenol A and phthalates, and cord blood metabolic-related biomarkers.	Cohort **Sample** 20,926 pregnant women	Independent variable: bisphenol-A Dependent variable: child health	1. BPA detected in 99.1% of pregnant women 2. The results of the study BPA was positively associated with adiponectin levels with (β=0.03, 95% CI: 0.00 - 0.06) which means prenatal exposure to BPA can alter fetal adiponectin and leptin levels **Conlusion:** The present study provided some evidence that prenatal exposure to bisphenol A and certain phthalates may modify fetal adiponectin and leptin levels
Human exposure to bisphenol AF and diethylhexylphthalate increases susceptibility to develop differentiated thyroid cancer in patients with thyroid nodules (Italy)(12)	This study aims at investigating the role of fifteen multiclass organic pollutants, assumed as markers of environmental pollution, most ofwhich exerting endocrine-disrupting activity, in thyroid cancer development.	Cross-sectional **Sample** A total of 95 thyroid nodule patients	Independent variable: bisphenol-A Dependent variable: thyroid cancer	1. There is an association of BPA exposure to the risk of DTC in patients with thyroid nodules with a p value <0.001. **Conlusion:** A significant relationship was found between malignancy and the detection in the serum of both bisphenol AF and DEHP.
Bisphenol A and adiposity measures in peripubertal boys from the INMA-Granada cohort (Spain)(31)	To assess associations between urinary BPA concentrations and several adiposity measures in peri- pubertal boys from the Environment and Childhood (INMA).	Cohort **Sample** A total of 298 obese boys aged 9 - 11 years old	Independent variable: bisphenol-A Dependent variable: obesity	1. Urinary BPA concentration was associated with higher BMI z-scores (β=0.22; 95%CI=0.03 - 0.41) 2. Increased odds of being overweight/obese with OR=1.46 (95%CI=1.05 - 2.05) 3. BPA may exert obesogenic effects in peripubertal children, potentially increasing the risk of overweight/obesity, especially abdominal obesity. **Conlusion:** BPA may exert an obesogenic effect in peripubertal boys, potentially increasing the risk of over- weight/obesity, especially abdominal obesity. However, these results should be interpreted with caution given the modest sample size and the possibilities of reverse causality and residual confounding by diet and lifestyle patterns

Research Title	Research Objectives	Study Design, Sample	Study Design, Sample	Research Results, Conlusion
Endometrial Carcinoma and Bisphenol A: A Pilot Case-Control Study (Italy)(19)	Endometrial cancer evolves from a hyperestrogenic pattern. Bisphenol A (BPA) can act as estrogen-mimetic at low doses. The aim of this pilot observational case-control study is to evaluate the possible hormone-dependent effects of BPA in endometrial cancer.	Case-Control **Sample** 17 women with endometrial cancer and 7 controls with benign cancer.	Independent variable: bisphenol-A Dependent variable: cancer	1. Higher BPA concentration was found in the case group (0.59±0.19 Vs 0.54±0.12) with p value <0.001. 2. BPA may induce abnormal cell proliferation indirectly at the uterine level. It may act as a central trigger of hyperestrogenic **Conlusion:** Evaluating our results in the perspective of the literature, we hypothesized that BPA could induce an indirect abnormal cell proliferation at the uterine level. It probably acts as an hyperestrogenic central trigger, through a possible exacerbation of the action of the well-known risk factors. More studies are necessary to understand the mechanisms at the bases of the described process.
Association Between Bisphenol A Exposure and Risk of All-Cause and Cause-Specific Mortality in US Adults (American)(16)	To examine the association of BPA exposure with all-cause mortality and cause-specific mortality among adults in the United States.	Cohort **Sample** 3,883 adults over the age of 20.	Independent variable: bisphenol-A Dependent variable: cancer and cardiovascular	1. Participants with the highest urinary BPA levels had a 51% higher risk of all-cause mortality OR =1.51 (95% CI: 1.07-2.13) 2. Higher exposure to BPA was significantly associated with an increased risk of all-cause mortality. **Conlusion:** In this nationally representative cohort of US adults, higher BPA exposure was significantly associated with an increased risk of all-cause mortality. Further studies are needed to replicate these findings in other populations and determine the underlying mechanisms
MicroRNA expression in response to bisphenol A is associated with high blood pressure (Korea)(29)	Evaluated associations among BPA exposure, microRNA (miRNA) expression, and BP in a randomized crossover trial with 45 non-smoking females over 60 years of age.	Cohort **Sample** A total of 45 non-smoking women aged over 60 years.	Independent variable: bisphenol-A Dependent variable: hypertension	1. Urinary BPA levels differed significantly depending on the amount of canned beverages consumed p value <0.0001 2. This study shows BPA exposure increases blood pressure through miRNA involvement Epigenetic biomarkers such as miRNAs can have a major impact in preventing the development of various diseases including hypertension. **Conlusion:** Our results suggest that epigenetic biomarkers for BPA exposure and hypertension provide mechanistic data to explain hypertension exacerbation as well as key in- formation for predicting the health effects of BPA exposure.
Cross sectional study on exposure to BPA and phthalates and semen parameters in men attending a fertility center (Italy) (24)	This study evaluated the possible association between chemical exposure and the quality of the seminal fluid of 105 subjects in a fertility clinic.	Cross-sectional **Sample** A total of 105 men	Independent variable: bisphenol-A Dependent variable: male reproductive health	1. There is a significant correlation p value = 0.005 between canned food consumption and BPA levels. 2. There is a relationship between BPA exposure and decreased sperm quality in men with a p value <0.023. **Conlusion:** No further statistically significant associations were found, even considering the working activity.
Association of bisphenol A and its alternatives bisphenol S and F exposure with hypertension and blood pressure: A cross-sectional study in China (China)(30)	to explore the association and dose-response relationship of bisphenols exposure with hyper- tension risk and blood pressure levels.	Cross-sectional **Sample** A total of 1437 without hypertension	Independent variable: bisphenol-A Dependent variable: hypertension	1. Individuals with high BPA exposure had a risk of hypertension with OR=1.30 (95% CI: 0.95 - 1.78) and OR=1.40 (95% CI: 1.03 - 1.91). 2. There was 0.576 mg/L BPA in patients with hypertension **Conclusion:** No significant associations of BPF exposure with hypertension risk or blood pressure levels were found
Quantification of bisphenol A in urine samples from children studying in public schools from the Brazilian Capital (Brazil)(40)	this work aimed to employ an analytical method to quantify BPA (free + deconjugated) based on the use of deuterated surrogate standardization, coupled to liquid-liquid microextraction, matrix-matched calibration and HR-MS measurements.	Cross-sectional **Sample** There were 343 children aged 6 to 8 years.	Independent variable: bisphenol-A Dependent variable: child development	1. BPA was found in 89.5% of the samples 2. Exposure during childhood affects the developing endocrine system which is highly sensitive to EDCs **Conclusion:** To the best of our knowledge, this is the second study in Latin America to quantify urinary BPA in human samples highlighting the continuing importance of re- search institutions in providing scientific knowledge in less-favored countries
Prenatal exposure to bisphenol A and its alternatives and child neurodevelopment at 2 years (China)(38)	We aimed to evaluate the relationships of repeated measurements of bisphenol exposure during pregnancy with child neurodevelopment.	Cross-sectional **Sample** A total of 456 mother-child pairs	Independent variable: bisphenol-A Dependent variable: child development	1. Population exposed to BPA by 76% 2. Prenatal exposure to BPA may affect a child's neurodevelopment **Conclusion:** However, prenatal BPF exposure was not significantly associated with child neuro- development. We provide evidence that prenatal exposure to BPA and BPS may affect child neurodevelopment

Research Title	Research Objectives	Study Design, Sample	Study Design, Sample	Research Results, Conlusion
Bisphenol A exposure and risk of ischemic heart disease in the Spanish European Prospective Investigation into cancer and nutrition study Nerea Larra n (Spain)(27)	The aim of this study was to assess the potential association of serum BPA concentrations and the risk of incident IHD in a sub-cohort of the Spanish European Prospective Investigation into Cancer and Nutrition (EPIC).	Cohort **Sample** There were 41,446 participants aged 26-29 years.	Independent variable: bisphenol-A Dependent variable: Ischemic heart disease	1. 70% of participants were exposed to BPA 2. No significant association between BPA concentration and the occurrence of ischemic heart disease. **Conclusion:** Cox regression models showed no significant association of BPA serum levels and IHD, acute myocardial infarction or angina pectoris risk.
Urinary bisphenol A and its interaction with ESR1 genetic polymorphism associated with non-small cell lung cancer: findings from a case-control study in Chinese population (China)(20)	Preliminarily discussed the interaction between BPA exposure and ER related genetic polymorphism on NSCLC.	Case Control **Sample** Patients with lung cancer were 615 and controls were 615.	Independent variable: bisphenol-A Dependent variable: lung cancer	1. BPA was detected in 97.2% of cases and 98.4% of controls. 2. In controls there is a p value of 0.001 while for cases the p value is <0.001 which means higher urinary BPA levels in lung cancer patients compared to healthy individuals. **Conclusion:** In conclusion, exposure to high levels BPA may be associated with NSCLC and the relationship may be modified by genetic polymorphism in ESR1
Exposure to bisphenol A and breast cancer risk in northern Mexican women (Mexico)(15)	To evaluate the association between BC and urinary concentrations of free-bisphenol A (BPA-F), the biological form of BPA, among women residing in Northern Mexic.	Case Control **Sample** Female population A total of 394 cases and 404 controls	Independent variable: bisphenol-A Dependent variable: breast cancer	1. Results showed that urinary BPA-F was significantly positively associated with breast cancer with OR=2.31 (95% CI: 1.43-3.74). **Conclusion:** BPA-F may be an environmental cofactor of BC. Since this is the first report on BPA-F association with BC, our results need to be replicated.
Bisphenol A exposure, interaction with genetic variants and colorectal cancer via mediating oxidative stress biomarkers (China)(14)	the potentially biological mechanism of the association between BPA and CRC and expand the understanding of the harm of BPA exposure to the human body at the same time.	Case Control **Sample** Population A total of 275 case patients and 538 controls	Independent variable: bisphenol-A Dependent variable: colorectal cancer	1. BPA was associated with colorectal cancer risk and a positive association of BPA with colorectal cancer risk with a p value <0.05. 2. Oxidative stress is also an influence of BPA on colorectal cancer risk **Conclusion:** In summary, our study explored the relationship between BPA and the risk of CRC, suggesting that BPA might be a risk factor affecting the risk of CRC
Bisphenol -A in biological samples of breast cancer mastectomy and mammoplasty patients and correlation with levels measured in urine and tissue (Iran) (11)	The aim of this research was to evaluate BPA concentration in both the urine and breast adipose tissue samples of breast cancer mastectomy and mammoplasty patients and study correlations of BPA levels in breast adipose tissue with urine samples in the both groups.	Case Control **Sample** human urine and breast adipose tissue samples of 41 and controls of 11	Independent variable: bisphenol-A Dependent variable: breast cancer	1. Urinary BPA concentrations were significantly higher in cancer patients (2.12 ± 1.48 ng/ml; with p value < 0.01 2. Urinary BPA concentration was positively correlated with breast adipose tissue BPA in the case group with a p value <0.001. 3. Urinary BPA concentrations were positively correlated with BPA concentrations in breast adipose tissue proving that BPA can accumulate in breast adipose tissue due to its lipophilic and bioaccumulation properties. **Conclusion:** Showed that BPA was present in urine and breast adipose tissue samples of the studied populations. With regard to higher BPA mean concentration in cancerous patients than non-cancerous individuals in this study, BPA might increase the risk of breast cancer incidence
Bisphenol A, S, and F exposure, ESR1/2, CAT, and eNOS genetic polymorphisms, and the risk of hypertension (China) (28)	Herein, we designed a case-control study to explore the association of BPA and its alternatives BPS and BPF exposure with hypertension risk, and to investigate whether the association can be modified by genetic polymorphisms in ESR1/2, CAT, and eNOS.	Case Control **Sample** A total of 439 cases and 439 controls	Independent variable: bisphenol-A Dependent variable: hypertension	1. The OR for hypertension in the highest BPA tertile was OR= 2.02 (95% CI: 1.39 - 2.94), with a significant linear trend p<0.001. 2. The relationship between total bisphenol (BPS) exposure and hypertension risk is similar to that of BPA exposure 3. BPA exposure linked to increased risk of hypertension **Conclusion:** Individuals with specific genotypes in ESR1/2, CAT, and eNOS might be more susceptible to the hypertensive effects of BPA
Risk of breast cancer and prediagnostic urinary excretion of bisphenol A, triclosan and parabens: The Multiethnic Cohort Study (America)(22)	This nested case-control study investigated endocrine-disrupting chemicals (EDCs) and breast cancer risk within the Multiethnic Cohort (MEC).	Cohort **Sample** Consists of 118,441 women aged 45 - 75 years old	Independent variable: bisphenol-A Dependent variable: breast cancer	1. Breast cancer risk is not associated with BPA exposure. **Conclusion:** In summary, breast cancer risk in a multiethnic population was unrelated to BPA and was weakly inversely associated with triclosan and paraben exposures. Studies with multiple urine samples collected before breast cancer diagnosis are needed to further investigate these EDCs and breast cancer risk

Research Title	Research Objectives	Study Design, Sample	Study Design, Sample	Research Results, Conlusion
Urinary Bisphenol A, F and S Levels and Semen Quality in Young Adult Danish Men (Denmark)(25)	In this cross–sectional study, we investigated the associations between exposure to BPA, BPF, and BPS and semen quality.	Cohort **Sample** Urine samples from 556 men aged 18 - 20 years old	Independent variable: bisphenol-A Dependent variable: reproductive health	1. BPA detected in 95% of urine samples 2. No association was observed between urinary BPA concentration on ejaculate volume, sperm concentration, total sperm count or sperm morphology 3. This study provides no evidence that BPA exposure is associated with semen characteristics **Conclusion:** We found no associations between urinary bisphenol of semen quality in a sample of young men from the general Danish population
Associations of urinary concentrations of phthalate metabolites, bisphenol A, and parabens with obesity and diabetes mellitus in a Korean adult population: Korean National Environmental Health Survey (KoNEHS) 2015 - 2017 (Korea) (33)	assessed the associations between urinary biomarkers of phthalate, BPA, and paraben exposure with obesity and DM.	Cross-sectional **Sample** 339 adults aged 19 years and over	Independent variable: bisphenol-A Dependent variable: obesity and diabetes mellitus	1. There is a positive relationship between BPA and weight gain with a p value of <0.001. 2. Significant association between BPA and DM with OR = 1.65 (95% CI: 1.06 - 2.59) 3. High urinary concentrations of BPA are associated with obesity and DM. **Conclusion:** the highest quartiles of BPA, methyl paraben (MeP), and ethyl paraben (EtP) showed a significantly higher risk of DM than those in the lowest quartiles
Environmental endocrine disruptor Bisphenol A induces metabolic derailment and obesity via upregulating IL-17A in adipocytes (China) (32)	This study is designed to explore the toxicological pathogenesis of chronic inflammation in BPA exposure during obesity.	Cross-sectional **Sample** 289 participants aged above 16 and below 65 years old	Independent variable: bisphenol-A Dependent variable: metabolic disorders and obesity	1. Urinary BPA levels in obese patients were significantly increased to a mean concentration of 4.33 (IQR: 1.65, 7.78) with a p value of <0.01. 2. The association between BPA exposure and the occurrence of obesity was significantly associated with OR = 4.72 (95%CI: 3.18 - 11.18) with p value <0.01). **Conclusion:** Our findings identified and demonstrated from human study to animal experiment that IL-17A of deficiency could alleviate AT inflammation and IR exacerbated by BPA exposure during obesity exerted potential mediation roles in associating BPA and obesity risk
Enhancing de novo ceramide synthesis induced by bisphenol A exposure aggravates metabolic derangement during obesity (China)(39)	investigated the effects of BPA exposure on ceramide de novo synthesis and whether increased ceramides aggravate adipose tissue (AT) inflammation and obesity-related IR.	Case Control **Sample** There were 200 obese patients aged 18 years and164 controls.	Independent variable: bisphenol-A Dependent variable: metabolic disorders and obesity	1. Obese patients had higher urinary BPA levels compared to controls with a p=0.001 value. 2. There was a positive association between BPA exposure and obesity risk with OR = 2.34 (95%CI: 1.40-3.92). 3. Higher levels of BPA in obese individuals were significantly associated with **Conclusion:** These findings indicate that BPA aggravates obesity-induced IR, which is partly via increased de novo synthesis of ceramides and subsequent promotion of AT inflammation. Ceramide synthesis could be a potential target for the prevention of environmental BPA exposure- related metabolic disease

Impact of Bisphenol-A Exposure on Cancer Incidence

Microplastics, which are plastic particles less than 5 mm in size, can adsorb BPA. When microplastics enter the human body through food, drink, water, soil, and air, they pose health risks. BPA-containing microplastics migrate into the body and enter the bloodstream, circulating to various organs and tissues, potentially causing diseases and disrupting endocrine function (41).

Low-dose BPA exposure in fetuses can lead to altered cell proliferation, apoptosis, and mammary gland development, culminating in mammary gland carcinogenesis. According to epidemiological studies, BPA can increase estrogen density and sensitivity. Research indicates that BPA can stimulate the expression of WNT-4 and the receptor activator of nuclear factor kappa-B ligand (RANKL), which regulates mammary cell proliferation and carcinogenesis. During BPA exposure, the HOXB9 gene, which can increase the risk of breast cancer, is upregulated. Additionally, BPA can disrupt the hypothalamic-pituitary-gonadal axis, potentially causing malignant breast tissue development. BPA also acts as a cytotoxic antagonist, reducing the effectiveness of therapeutic interventions (42).

BPA has been shown to alter cell proliferation, increasing cancer incidence. A study indicates a significant relationship between bisphenol-A exposure and breast cancer risk in women (11, 15, 18). These studies found higher levels of BPA in the urine of breast

cancer patients compared to those without cancer. The presence of BPA in adipose tissue contributes to cancer development as it disrupts hormone-dependent cancer pathogenesis, mimicking the structure of synthetic estrogen diethylstilbestrol (DES), which affects health adversely, causing breast cancer (41). A study found that urinary BPA concentrations were significantly higher in cancer patients ($p < 0.01$), with positive correlations between BPA in urine and breast adipose tissue ($p < 0.001$) (11). Another study in Mexico showed a significant positive relationship between urinary BPA-F and breast cancer (OR = 2.31, 95% CI: 1.43-3.74) (15). A study also found a positive relationship between BPA exposure and breast cancer risk (OR = 2.49, 95% CI: 1.52-4.13), with higher urinary BPA levels in breast cancer patients ($p < 0.001$) (18). Animal studies support these findings, showing that prenatal or prepubertal BPA exposure alters mammary gland morphology and increases breast cancer risk. In contrast, chronic exposure in adulthood enhances carcinogenesis and metastasis in transgenic mice (43). In vivo studies demonstrate that BPA exposure increases breast cancer risk in mice through molecular alterations and estrogen-dependent tumor cell proliferation (15).

Beyond breast cancer, women also face increased risks of endometrial cancer. BPA was found in serum, follicular fluid, fetal serum, and amniotic fluid. During the prenatal period, BPA disrupted ovarian steroidogenesis by altering steroidogenic enzymes. Prenatal BPA exposure also causes various ovarian developmental abnormalities, such as endometriosis (9).

Excess BPA circulating at hypothalamic and pituitary levels may disrupt gonadotropin secretion feedback. BPA acts as an antiestrogen factor, enhancing GnRH and LH secretion and stimulating ovarian steroid hyperproliferation. A research found significantly higher BPA concentrations in endometrial cancer patients ($p < 0.001$), with BPA inducing abnormal cell proliferation in the uterus (19). Studies on ovariectomized monkeys exposed to BPA showed increased endometrial proliferation, suggesting that BPA, along with estrogen, disrupts hormonal balance and enhances estrogenic response, potentially leading to endometrial tumorigenesis in humans (44). However, case-control study in America found no significant relationship between BPA and endometrial cancer (OR = 1.82, 95% CI: 0.81-4.10) due to single-time urine measurements (21). The effects of BPA exposure were similar to those of estrogen on ovarian cells because estrogen provided a hormonal environment that fostered tumor progression by directly regulating ovarian cell proliferation and apoptosis. BPA exposure controlled the expression of several tissues in the ovary associated with oncogenic signaling (ovarian cancer development) and activated luteinized granulosa cells to express matrix metalloproteinase-9 (MMP-9), an extracellular matrix protein linked to ovarian cancer progression (9).

Research indicates that BPA can increase colorectal cancer because BPA can cause oxidative stress, resulting in changes in lipid metabolism. In vitro tests established that BPA can cause oxidative stress in animals. A 2021 study found a positive relationship between BPA exposure and the risk of colorectal cancer ($p < 0.05$), noting that colorectal cancer is influenced by genetic and environmental factors (14). Another study detected BPA in 88.5% of colorectal cancer patients ($p < 0.05$), linking BPA exposure to colorectal cancer via lipid metabolism changes (17). BPA significantly increases the occurrence of colorectal cancer processes in tumor tissue due to lipid metabolites. In vitro studies on snails showed that nanomolar BPA concentrations enhanced colorectal cancer migration, invasion, and epithelial-to-mesenchymal transition (45). Colorectal cancer can also be caused due to other factors like diet and nutritional deficiencies (46).

BPA may also elevate thyroid cancer risk by increasing TSH levels in patients with thyroid nodules (12). Research on zebrafish (p-value <0.001) revealed that BPA can cause thyroid disorders and directly damage cells, supported by the findings of in vitro research that BPA can cause genotoxic effects. The occurrence of thyroid cancer can also be caused by chemicals in the environment (47).

A study found higher urinary BPA levels in lung cancer patients than in healthy individuals, indicating a significant relationship between BPA and lung cancer ($p < 0.001$). However, the study could not conclude a causal relationship due to single-time BPA exposure measurements (20). BPA, along with genetic polymorphisms in estrogen, might influence lung cancer risk. In vivo studies in mice show that low BPA doses increase tumor risk, while high doses enhance cell proliferation and apoptosis. BPA's stimulation of cell migration can cause oxidative stress (48).

Impact of Bisphenol-A Exposure on Reproductive Health

When exceeding normal levels, BPA in the body disrupts growth and development, particularly regarding weight, height, and nerve growth. The increase in BPA affects puberty in both males and females. BPA causes a decrease in hormone activity and worsens infertility in both men and women. Due to BPA toxicity, cortisol

concentration in the blood serum is reduced, and progesterone, estradiol, and luteinizing hormone levels are enhanced. In the human body, BPA competes with estradiol to become an estrogen receptor (49).

Research shows that bisphenol-A exposure affects male fertility and adversely affects the male endocrine system. A study detected BPA in 95.3% of samples ($p < 0.001$), which led to decreased sperm quality in men aged 18-23 and impaired their endocrine function (26). In men from infertile couples, urinary and virgin plasma BPA concentrations were inversely related to testosterone levels and positively correlated with serum estradiol or FSH levels in fertile men; higher LH showed a tendency to decrease testosterone (49). Meanwhile, another research revealed a relationship between BPA exposure and decreased sperm quality in men with a p-value of <0.023. Most of the men whose urine samples detected BPA often consume canned food, so in this study, a positive correlation was also found between canned food consumption and BPA levels with a p-value = 0.005. BPA is referred to as an EDC (Endocrine Disrupting Hormone), which can inhibit the activity of natural hormones in the body, especially estrogen (24). BPA can reduce sperm quality and increase luteinizing hormone (LH) levels. The results of experimental studies on BPA demonstrated estrogenic and antiandrogenic effects, changing gonadotropin levels that can lower testosterone production from LH and inhibit the activity of androgen biosynthetic enzymes and antiandrogenic metabolic activity (50). However, study in 2021 did not find any relationship between urinary BPA concentrations and ejaculation volume, sperm concentration, total sperm count, or sperm morphology, even though BPA was detected in 95% of urine samples. These differing results can be attributed to variations in exposure levels and sample sizes (25).

Additionally, BPA impacts female reproduction also, which can cause PCOS in women, especially in overweight or obese women. BPA has a positive correlation with testosterone (T) with a value of $p < 0.05$. Women with PCOS show significantly higher levels of LH and T than FSH levels (13). In women with ovarian dysfunction, serum BPA was positively correlated with testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEA-S) (51). Another study indicated that the association between bisphenol analogs and PCOS was stronger in overweight and obese women than in those with normal weight (13).

Research suggested that PCOS could lead to low birth weight (LBW) at delivery, and maternal BPA exposure could reduce the anogenital gap (AGD) in boys at 12 months of age. However, no definitive results were found for girls (23). BPA exposure is linked to decreased testosterone levels in newborn boys due to its anti-androgen effects. Testosterone plays a crucial role in sex differentiation and development during the perinatal and postnatal periods (52). Maternal BPA exposure specifically affects male offspring, potentially impacting adrenarche and pubarche without altering steroid hormone levels (50).

Impact of Bisphenol-A Exposure on Hypertension Risk

Bisphenol-A affects the human body through its mechanisms related to estrogen. Estrogen receptors play a crucial role in controlling blood pressure and repairing blood vessels in the cardiovascular system. The mechanism involving estrogen receptors in the cardiovascular system was complex. Bisphenol-A could directly affect the cardiovascular system by impacting blood pressure. The mechanism of action of bisphenol-A influenced ion channel activity, reactive oxygen production, and contractile proteins, potentially disrupting the cardiovascular system (4).

BPA exposure increases blood pressure through the involvement of miRNAs. According to research in 2020, specific miRNAs can serve as biomarkers for detecting blood pressure changes caused by BPA exposure. In samples that consumed canned drinks, BPA was detected with a p-value of <0.0001. Besides this study, another study involving 1437 participants, in which 30.1% were diagnosed with hypertension with OR = 1.30 (95% CI: 0.95 - 1.78) (29). The hypertension group had higher BPA levels compared to non-hypertensive people; hypertensive patients demonstrated BPA levels of 0.576 mg/L. Another study in 2021 found a significant relationship between bisphenol-A exposure and the incidence of hypertension with a p-value <0.001. Hypertension was more prevalent among drinkers, smokers, and passive smokers. Hypertensive individuals also had a higher BMI, serum uric acid, and fasting glucose level. Estrogen benefits the cardiovascular system by regulating vasodilation, repairing endothelial cells and blood pressure, inhibiting cell proliferation and migration, and reducing insulin resistance, lipid peroxidation, and inflammation. In a randomized crossover trial, BPA was shown to cause hypertension. Participants who drank canned soy milk had 16 times higher BPA levels than those who drank soy milk from a glass and thus suffered from increased blood pressure. BPA can cause high blood pressure in cases of acute BPA intake. BPA exposure is also linked to insulin resistance, adiponectin release, oxidative stress, inflammatory responses, endothelial dysfunction, autonomic nervous system disorders, and

liver, kidney, and thyroid dysfunction, all contributing to hypertensive effects (53).

The development of epigenetic biomarkers, such as miRNAs, is crucial for preventing diseases like hypertension. Environmental exposure to BPA may elevate the risk of hypertension and increase blood pressure levels. BPA, found in various foods and environmental media, can enter the human body through food and beverage consumption, inhalation, and skin contact (28).

Impact of Bisphenol-A Exposure on Risk of Obesity and Diabetes

Obesity corresponds to the accumulation of fat due to an imbalance between energy intake and energy expenditure over a prolonged period. Obesity is characterized by a Body Mass Index (BMI) of more than 25. Bisphenol-A exposure, which causes obesity, often occurs in children and adolescents (54).

Obesity is associated with an increased risk of various chronic diseases, and its etiology can largely be explained by genetic factors and lifestyle choices, including diet. A study found that urinary BPA levels in obese patients increased significantly ($p < 0.01$). The study also established a significant relationship between BPA exposure and obesity ($p < 0.01$), indicating that environmental BPA exposure might be a crucial risk factor for obesity (32). This impact is not limited to adults. According to another research, BPA exposure can have an obesogenic effect on prepubertal boys, increasing the risk of overweight and abdominal obesity (OR = 1.46, 95% CI: 1.05-2.05) (31). Obesity leads to chronic systemic inflammation, which impairs glucose tolerance and decreases insulin sensitivity (55). In studies with mice, BPA was found to exacerbate adipose tissue inflammation and promote macrophage polarization towards pro-inflammatory isoforms. Perinatal BPA exposure can cause systemic immune imbalance by decreasing cell frequency (56). BPA in the body can reduce the production or secretion of adiponectin, an insulin-sensitive adipocytokine derived from adipocytes, leading to obesity (57). This was confirmed in another research, which found a positive relationship between BPA and weight gain ($p < 0.001$) (33). BPA can also affect pancreatic cell function and increase insulin resistance, raising the risk of diabetes (33). However, research in 2018 did not find a significant association between BPA exposure and insulin resistance (36). BPA exposure contributed to several chronic diabetes complications, including diabetic nephropathy, diabetic cognitive dysfunction, diabetic retinopathy, and diabetic cardiomyopathy. BPA is estrogenic or estrogen-like, allowing it to bind to and activate estrogen receptors specifically. Chronic exposure to BPA could cause hyperinsulinemia, worsen glucose tolerance, and decrease insulin sensitivity (58).

Impact of Bisphenol-A Exposure on Child Development

BPA can bind to estrogen receptors and affect thyroid and gonadal hormone signals, influencing normal brain development and behavioral patterns. A research found that tetrabromobisphenol-A was linked to a decrease in Ln-transformed sound velocity (SOS) of 0.007 m/s. In girls, higher bisphenol-A concentrations were associated with a risk of decreased bone mineral density (OR = 0.413, 95% CI: 0.215-0.721) (37). In vitro studies have found that bisphenol-A can alter bone growth trajectories by altering the differentiation, maturation, and proliferation capacity of human bone (59). Animal studies have shown that exposure to BPA during pregnancy adversely affects bone growth and bone mass accumulation in rat offspring (60). Bone mineral density is a measure of bone strength that correlates with bone mass. Bone density in childhood is an important predictor of bone mass, and low bone density in the early years produces long-term effects on peak bone mass and lifelong bone health. Prenatal exposure to BPA correlates with decreased bone density. The effects of maternal bisphenol-A exposure on bone health are sex-specific and dose-dependent (60).

A study found that 76% of the 456 samples were exposed to BPA (32). BPA exposure in children often begins in the womb. Animal studies indicate that BPA can cause neurobehavioral disorders, as shown in zebrafish, where BPA induces hypothalamic neurogenesis and disrupts early brain development. Rodent studies revealed that BPA exposure significantly altered offspring behavior, leading to increased anxiety and depression. This evidence suggests that BPA can interfere with children's neurodevelopment (60).

Impact of Bisphenol-A Exposure on Child Behavior

BPA exposure has become one of the factors influencing children's behavior. Prenatal BPA exposure causes behavioral disorders in children aged 0-12 years. High levels of BPA exposure led to externalizing problems such as aggression, hyperactivity, and attention issues, as well as internalizing problems such as anxiety, depression, and somatization. During childhood, BPA exposure needs special attention because, at this stage, the endocrine system is very sensitive to chemical exposure and can be disrupted by high levels of BPA. Bisphenol-A during childhood development disrupts

attention deficit/hyperactivity disorder (ADHD) (61).

BPA is an endocrine-disrupting compound commonly found in plastic bottles or containers used for feeding children. Even low to moderate doses of BPA can be harmful, particularly for infants during the neonatal period, as it can affect metabolism. Childhood exposure impacts the developing endocrine system, which is highly sensitive to endocrine-disrupting chemicals (EDCs). Research detected BPA in 90% of urine samples from 468 children aged 6-12 years. This study found a significant relationship between BPA exposure and behavioral changes in children ($p < 0.001$). High BPA exposure was associated with externalizing problems such as aggression and hypersensitivity, as well as internalizing problems like anxiety, depression, and somatization (34). BPA can disrupt the endocrine system and increase DNA oxidative damage upon entering the human body. In addition to endocrine disruption, in vivo studies have shown that pre- and postnatal BPA exposure is neurotoxic in rats, leading to behavioral changes, including depression, anxiety, and hyperactivity due to impaired neurotransmission processes (55).

BPA exposure may also increase the incidence of ADHD, particularly in boys. High BPA exposure during pregnancy or the prenatal period has been linked to behavioral changes in school-age children (55). Research show BPA was detected in 99.1% of pregnant women, with findings suggesting that prenatal BPA exposure can alter fetal adiponectin and leptin levels (35). A study conducted in 2020 found that 90% of urine samples in 343 children were detected with BPA. Exposure during childhood affects the developing endocrine system, which is very sensitive to EDCs. Most of the children who had BPA detected in their urine samples frequently consumed canned foods. Childhood BPA exposure can impair development and increase the risk of metabolic diseases (40).

AUTHORS' CONTRIBUTION

The author takes full responsibility for the entire research and writing process, from conceptualization, data collection, and analysis to drafting the final version. Specifically, the author's contributions outlined as follow. SLS and YHD : Conceptualization and Methodology, the author designed this research framework and methodology. OKTI, SLS, YHD : Data Collection and Analysis, the author conducted data collection, whether through surveys, experiments, or literature studies, and performed data analysis to derive research findings. OKTI and SLS : Writing and Revision**,** the author wrote all parts of the thesis, from the introduction to the conclusion, and made revisions based on the academic advisor's feedback. OKTI and YHD : Visualization and Presentation, the author created data visualizations and prepared the presentation for the thesis defense.

All steps in this process were carried out independently by the author, with guidance and direction from the academic advisor.

CONCLUSIONS

Bisphenol-A (BPA) is a chemical compound used to produce polycarbonate (PC) and epoxy resin. Polycarbonate is a hard, transparent plastic commonly used in water bottles, food containers, and household products. It is known for its strength and transparency to light while being opaque to ultraviolet rays. Polycarbonate is frequently used in manufacturing packaging materials and food containers, including household appliances, drinking water bottles, baby milk bottles, and food utensils. Epoxy resin, on the other hand, is used as a protective coating for packaged food and beverage cans.

BPA exposure can have significant health impacts, including cancer, obesity, reproductive health issues, hypertension, disrupted child development, and behavioral changes in children. BPA can enter the body not only through food packaging but also through contaminated air and dust. The duration and concentration of BPA exposure influence its effects on the human body. BPA exposure sources include food, air, water, and dust. The health impact of BPA is linked to its function as an endocrine-disrupting chemical (EDC), which can interfere with the activation of natural hormones in the body.

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