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Review Article

THE COMPREHENSIVE EVALUATION OF BISPHENOL A BY BIBLIOMETRIC ANALYSIS

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ABSTRACT

In recent years, there has been a trend towards healthy and safe food. However, people can be exposed to chemical compounds in a number of ways. The negative effects of these chemical compounds on public health are gradually increasing. Bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl) propane), one of the endocrine disrupting compounds, is used in many fields. It is also known that BPA is a synthetic compound with high toxicity used in many areas such as water, soil, air, food, electrical and electronic equipment, devices, thermal paper and socks. In this review study, the areas of application, the legal limit values, the chemical structure, the different analogues, the migration with food and the health effects of bisphenol A were analysed.

1.Introduction

Today, the increasing world population, urbanization and industrial developments constantly increase the production of chemical compounds (Tokula et al., 2023). People can be directly or indirectly exposed to chemical compounds. There are many chemical compounds such as heterocyclic and polycyclic compounds, dichloro-diphenyl-trichloroethane (DDT), chlorpyrifos, mycotoxins, atrazine, tributyltin dioxins, parabens, pesticides, nonylphenol, vinyl chloride, diethylhydroxylamine (DEHA), styrene, 1,3 butadiene, formaldehyde, melamine, di-2-ethylhexyl phthalate (DEHP), lead, phthalates, cadmium, acrylamide, and bisphenol A that people can be exposed to in various ways. These chemical compounds can cause various diseases in humans (Ozdemir et al., 2019; Fendoğlu et al., 2019; Savaş et al., 2021; Oz et al., 2021; Savaş & Oz, 2021; Aoudeh et al., 2022; Oz et al., 2021 Savaş et al., 2023; Kılıç et al., 2023; Ekiz et al.,2023; Elbir et al., 2023).

BPA is a synthetic monomer used in the production of polycarbonate plastics and epoxy resins. BPA is one of the endocrine disrupting chemical compounds that people are exposed to in many areas (Wetherill et al., 2007; Eledak et al., 2015; Seachrist et al., 2016; Tokula et al., 2023). It is known that the amount of production

and use of BPA, especially plastic, cosmetics, electronic equipment and health equipment (dental materials, optical lenses), is increasing (Mohapatra et al., 2010; Huelsmann et al., 2020). The number of studies on bisphenol A and its analogues, which are among the endocrine disrupting compounds, is increasing. However, it is thought that the number of studies on analogues used instead of BPA is quite low. In this study, up-to-date information on bisphenol A in the last ten-year period has been compiled.

2. Literature data of BPA research

The VOSviewer software is a powerful visual analysis tool designed to explore multidimensional, temporal and dynamic aspects of scientific literature. In this study, the Web of Science (WOS) database was used as the primary source of information. The VOSviewer analysis tool was used to determine the current situation and identify the main points related to bisphenol A. Here, I used the WOS database as the access platform and conducted a literature search using "Bisphenol A", "food" and "migration" as keywords. The search covered articles published between 2014 and 2024. After the screening process, a total of 487 articles on food and migration of BPA were obtained. Selected literature was exported and saved for further analysis. VOSviewer software was used to review and cluster authors and keywords. To gain a deeper insight into the research field of BPA, I used both the WOS platform and the VOSviewer analysis platform. These platforms were used to investigate and analyse collaborations and the number of published documents in the field of BPA research.

3. Data on annual article numbers

The number of publications per year gives an insight into the popularity and interest level of the topic studied. Figure 1 presents the available and analysed data of BPA research from 2014 to 2024 showing the number of publications focused on food and migration. Between 2014 and 2024, it can be seen that interest in BPA has increased and more studies have been conducted. It is thought that people's orientation towards healthy, safe and more functional foods has an important effect on this increase. In this context, it is understood from Figure 1 that more studies have been conducted on food and migration of BPA and that it is a very popular topic. On the other hand, the top three countries with the highest number of studies on food and migration of BPA are China, USA and Spain, respectively (Figure 2). It is thought that the level of development of the countries conducting the current researches is quite effective. In addition, the findings of the study shed light on the current status and future outlook of BPA research.

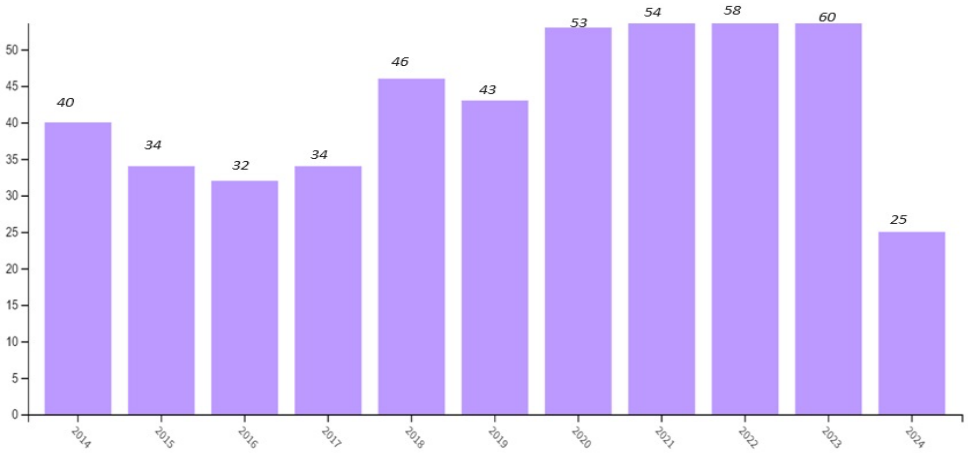
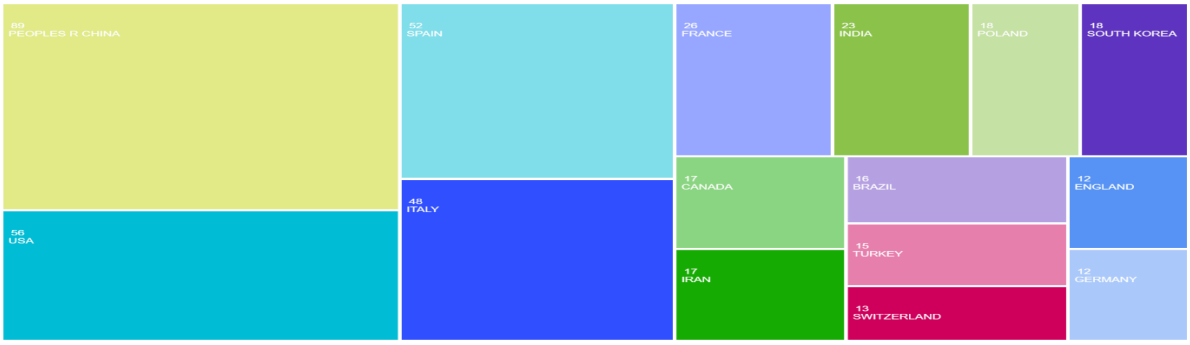


Figure. 1. Annual document analysis in the WOS database

a)



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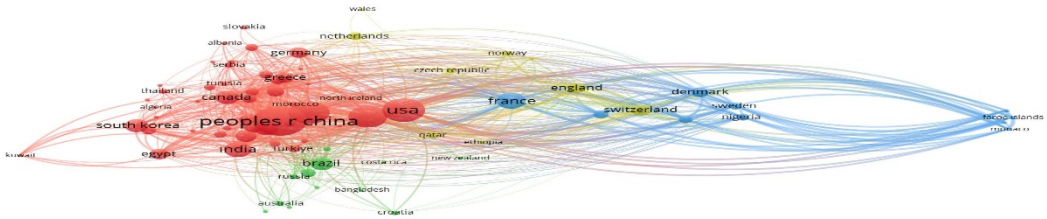


VOSviewer

Figure 2. National distribution of studies on BPA through the WOS database and VOSviewer software

4. Analysis of published journals

The field distribution of articles published on the relationship between food and migration of BPA is presented in Figure 3. The data obtained from the WOS database shows that the research direction is mainly in the fields of food science and technology, environmental science and toxicology. In particular, the fact that most of the research conducted in the emergence of this distribution is in the field of food is thought to be due to the migration of BPA to humans with more food.

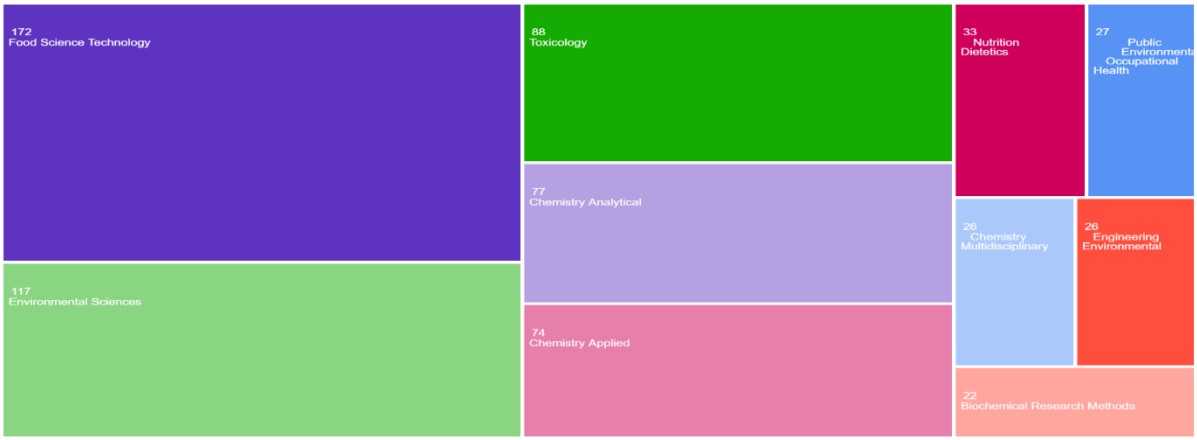
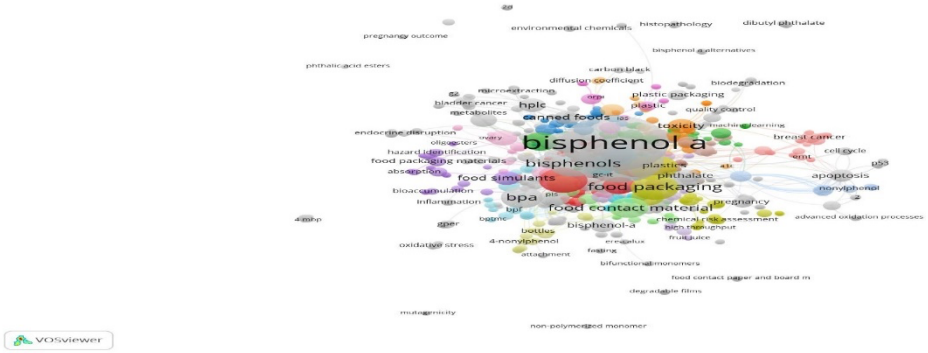


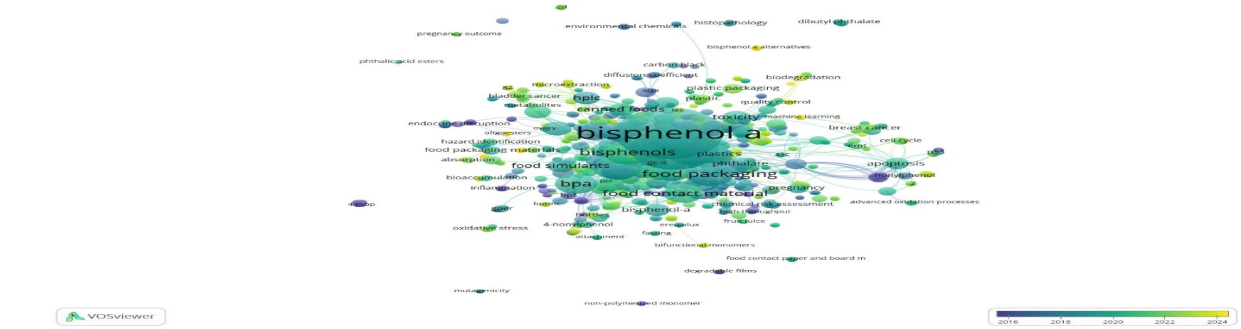
Figure 3. Analysis of global journal publications on the relationship of BPA to food and migration from 2014 to 2024

5. Evaluation Data

This section provides a visual summary of the studies on BPA. This visual summary is created by using different keywords. The visualisation of these keywords is presented in Figure 4. In addition to the keywords "Bisphenol A", the keywords used for BPA are "food" and "migration".



a)



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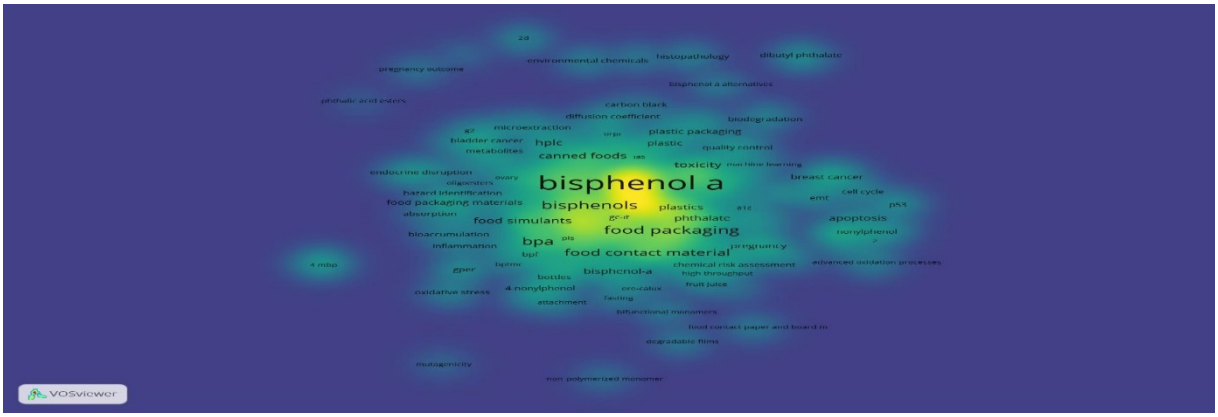

c)

Figure 4. Network visualisation (a), overlay visualisation (b) and density visualisation (c) of bisphenol A

Especially food and migration are important parameters affecting human health. Moreover, the relationship between these parameters and BPA is considered to be one of the most important issues to be considered and emphasised in future research. Figure 4 shows network visualisation (A), overlay visualisation (B) and density visualisation (C). As can be seen from the figures, it is determined that BPA is more focused on food packaging materials, health risks, canned foods, bisphenol derivatives, migration and toxicity. In addition, 63 different clusters were revealed by Vosviewer software (Figure 4A).

6. Usage Areas and Legal Limits of BPA

BPA is a widely used synthetic compound. It is known to be used in many areas such as plastics, food packages, canned vegetables and drinks, CD, DVD, sports equipment, baby foods, coatings, dental materials, thermal papers, cigarette filters, auto parts, dinner sets, socks, electronic and electrical equipment (Biles et al., 1997; Yoshida et al., 2001; Imanaka et al., 2001; Milić et al., 2015; Freire et al., 2019; Akash et al., 2020; Huelsmann et al., 2020; Banaderakhshan et al., 2022). There are many studies in the literature in which different levels of BPA are detected (Kang et al., 2006; Esteban et al., 2014; Seyyar & Oz, 2016; Savaş et al., 2021; Czarny-Krzymińska et al., 2023). It is stated by Huelsmann et al. that bisphenol A is produced approximately 10 million tons/year in 2022. There are legal restrictions for BPA, which is known to significantly affect human health. Initially, BPA was banned for use in baby bottles (EC, 2011) and later restricted to use in thermal papers (EC, 2011; EC, 2018; Serra et al., 2019; Czarny-Krzymińska et al., 2023). In addition, Commission Directive 2002/72/(EC), European framework regulation (EC) 1935/2004, Commission Directive (2011/8/EU), Regulation (EU) 10/2011, Commission Regulation (EU) 2018/213 and European Food Various regulations regarding BPA have been made by the Safety Authority (EFSA) (in 2006, 2008, 2010, 2013 and 2015). Eventually this change, which reduced it from 60 to 50 µg BPA per kilogram of food, was published (Almeida et al., 2018; Siddique et al., 2021).

Pursuant to Commission Regulation 10/2011/EU on plastic materials and articles intended to come into contact with foodstuffs, the use of BPA in plastic food contact materials is subject to a specific migration limit of 0.6 mg/kg (EFSA, 2015; Banaderakhshan et al., 2022). The European Food Safety Authority (EFSA) set a temporary Tolerable Daily Intake (t-TDI) for BPA at 4 µg/kg body weight/day in 2015 (EFSA, 2015; Banaderakhshan et al., 2022). BPA is not used in the production of polycarbonate substances and materials used for the consumer group defined as infants and young children in the Turkish Food Codex Communique on Infant Formulas and Follow-Up Formulas (Communique No: 2019/14). In addition, the specific migration limit is specified as 0.05 mg/kg. (Anonymous, 2019).

7. BPA Chemical Structure, Types and Alternatives

BPA, 2,2-bis(4-hydroxyphenyl) propane, is an organic compound consisting of two phenol rings (Kang et al., 2006; Ginter-Kramarczyk et al., 2023). BPA, which was first synthesized by condensation of phenol and acetone in the presence of acid; is solid, phenolic odor, cream-white color and crystal structure. It is stated that BPA gives plastics important properties such as hardness, transparency, durability and compatibility with other polymers (Staples *et al.* 1998; Cousins *et al.* 2002; Skledar & Mašič, 2016; Eker et al., 2021). Some physical and chemical properties of BPA are compiled in Figure 5 (Cao, 2010).

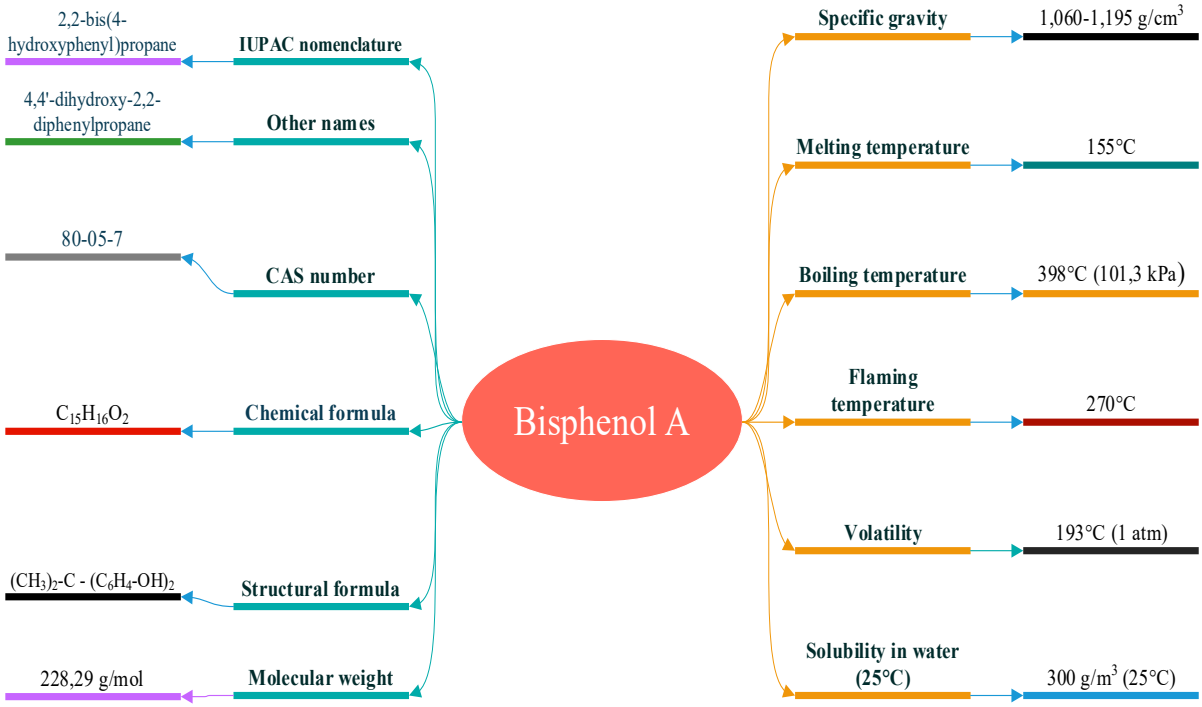

Figure 5. Some physical and chemical properties of BPA

Table 1. Chemical structural of various bisphenols

Compound name	Chemical formula	CAS number	Molecular weight
Bisphenol A	$C_{15}H_{16}O_2$	80-05-7	228.29
Bisphenol AF	$(CF_3)_2C(C_6H_4OH)_2$	1478-61-1	336.23
Bisphenol AP	$C_{20}H_{18}O_2$	1571-75-1	290.36
Bisphenol B	$C_{16}H_{18}O_2$	77-40-7	242.31
Bisphenol BP	$C_{25}H_{20}O_2$	1844-01-5	352.43
Bisphenol C	$(CH_3)_2C[C_6H_3(CH_3)OH]_2$	79-97-0	256.34
Bisphenol E	$CH_3CH(C_6H_4OH)_2$	2081-08-5	214.26

Bisphenol F	$CH_2(C_6H_4OH)_2$	620-92-8	200.23
Bisphenol FL	$C_{25}H_{18}O_2$	3236-71-3	350.41
Bisphenol G	$C_{21}H_{28}O_2$	127-54-8	312.45
Bisphenol M	$C_6H_4[C(CH_3)_2C_6H_4OH]_2$	13595-25-0	346.46
Bisphenol P	$C_{24}H_{26}O_2$	2167-51-3	346.46
Bisphenol PH	$C_{27}H_{24}O_2$	24038-68-4	380.48
Bisphenol S	$O_2S(C_6H_4OH)_2$	80-09-1	250.27
Bisphenol SIP	$C_{14}H_{15}O_4S$	95235-30-6	279.34
Bisphenol Z	$C_6H_{10}(C_6H_4OH)_2$	843-55-0	268.35
Bisphenol A diglycidyl ether	$C_{21}H_{24}O_4$	1675-54-3	340.4

Reproduced from: Niu et al. 2017; Czarny-Krzymińska et al., 2023.

On the other hand, it is stated that there are many types of BPA and it is used in many areas as an alternative to BPA (Yamada et al., 2010; Banaderakhshan et al., 2022; Zhang et al., 2023). It is used as a substitute for BPA, especially for BPB, BPE, BPS, BPP, BPF and BPAF. However, these used bisphenol types were also determined at different levels in indoor dust, surface waters and sediment, rivers, soil and human serum samples (Liao et al., 2012; Song et al., 2012; Jin & Zhu, 2016; Si et al., 2019; Gao et al., 2021). In Table 1, the chemical structures of various bisphenols are given. BPA analogs used as a substitute for BPA; It is stated to be used as a monomer for the production of phenolic resins, as a monomer for the production of polycarbonate plastics and epoxy resins, as a reagent and colorant for coatings, adhesives, tank linings, flooring, filament winding, casting, pultrusion, oxidizing agents and high performance polymer research (Mohapatra et al., 2010).

8. BPA and Health Relationship

Bisphenol A is widely available in various fields such as air, soil, sediment, water and foods (Abraham & Chakraborty, 2020). Determined in many areas, as well as BPA is an important compound that threatens human health, is a known endocrine disruptor (EDC). EDCs are defined as a group of exogenous organic substances that interfere with the endocrine system and the physiological role of hormones. The European Union has defined approximately

900 chemicals or accepted them as EDCs. These substances can cause various health problems in humans and animals. EDCs can show their effects with various receptors or enzymatic reactions (Eker et al., 2021). Human exposure to BPA, one of the important EDCs, can occur in various ways. There is a migration especially through food, the skin or respiratory route (Vandenberg et al., 2012; Rochester, 2013; Esteban et al., 2014; Siracusa et al., 2018; Plattard et al., 2021; Banaderakhshan et al., 2022; Czarny-Krzymińska et al., 2023). The United States Environmental Protection Agency (EPA) states that more than 1 million pounds of BPA has leaked into the environment (Seachrist et al., 2016). In addition to environmental leakage, people can be exposed to BPA in different ways. As a matter of fact, studies show that people are exposed to high levels of BPA. Lee et al. (2008) determined that the BPA level in pregnant women and their fetuses varied between nd-66.48 μg/L. Again, Kuruto-Niwa et al. (2007), Ye et al. (2015), Rocha et al. (2018) and Gys et al. (2021) found different levels of BPA and its derivatives in their study on urine samples. It is stated that BPA has estrogenic effects besides being endocrine disruptor (Viñas et al., 2012). BPA, which is in the xenoestrogen group, binds to estrogen receptor α (ER α) and estrogen receptor β (ER β). However, it is stated that the affinity of BPA to ER β is 10 times higher than that of ER α (Gould et al., 1998; Eker et al., 2021). In addition, BPA exposure is associated with many diseases (diabetes, obesity, cardiovascular, chronic respiratory and kidney diseases, breast cancer, behavioral problems, dental development disorders and reproductive disorders) (Rochester, 2013; Eladak et al., 2015; Skledar and Mašič, 2016). According to Caserta et al. (2013) determined that infertile women had higher BPA levels than fertile women. Li et al. (2014) stated in their study on female rats that low-dose BPA exposure decreased ovarian weights and follicle number and showed that it interfered with the component ratio of follicles. So the European Food Safety Authority has reduced the tolerable daily BPA intake from 50 μg/kg body weight/day to 4 μg/kg body weight/day (Cwiek-Ludwicka et al., 2015; Skledar and Mašič, 2016).

A few recent studies in the literature are presented below. Davis et al. (2024) reported that there is a relationship between BPA content and male fertility parameters and that BPA may affect male reproductive ability. Varma et al. (2024) reported that exposure to BPA and BPS during pregnancy impairs bone mineralisation of the offspring, while Jiang et al. (2024) reported that oral exposure of the mother to low doses of BPA may lead to accelerated onset of puberty in female offspring.

9. Migration and levels of BPA into foods

Food plays an important role in the continuity of human life functions. However, besides containing rich macro and micro compounds, our foods can also be exposed to various chemicals. One of these chemical compounds, which bisphenol A, is a synthetic compound that threatens human health. BPA, which can affect human health, can migrate to humans in various ways. Especially foods play an important role in this transition. There are many parameters affecting the migration of BPA into foods. Temperature, pH, composition of foods, level of contact with packaging, contact time, storage time and type of packaging are among these parameters. (Munguia-Lopez and Soto-Valdez, 2001; Almeida et al., 2018). It is stated that BPA in food can cause many diseases in humans (Almeida et al., 2018). Table 3 summarises BPA studies conducted on different foods in the last decade. Table 3 shows the BPA levels detected in various food products and breast milk. As can be seen, while it is determined that there is a difference between the BPA levels determined (Table 2), it is observed that the highest BPA level is determined in canned products.

On the other hand, there are studies that investigating BPA and its derivatives in different food products and breast milk. And it is stated that in these studies, varying levels of BPA and its derivatives were detected (Inoue et

al., 2003; Česen et al., 2016; Chi et al., 2024; Zheng et al., 2024).

Table 2.BPA amounts determined at different levels

Author	**Materials**	**Level of determination**
Grumetto et al. 2013	Milk	nd-521 ng/ml
Liao and Kannan 2013	Beverages, dairy products, fats and oils, fish and seafood, grain products, meat and meat products, canned fruits and vegetables	0.235-8.99 ng/g
Bemrah et al. 2014	Milk and products	0.045-6.103 µg/L
Sakhi et al. 2014	37 different food samples	nd-8.7 µg/kg
Sungur et al. 2014	Cannes foods and beverages	nd- 1858.71 µg/kg
Yang et al. 2014	Carp bile and algae	16-1020 ng/g
Kawamura et al. 2014	Cannes foods	3.4-390 ng/g
Liao and Kannan 2014	Milk, baby food, cheese, yoghurt	nd-10.8 µg/L
Zimmers et al. 2014	Breast milk	<0.22–10.8 ng/ml
Lorber et al. 2015	Vegetables and fruits, meat, fish, fruit/vegetable juice	0.24-149 ng/g
Niu et al. 2017	Milk	Nd-0.548 µg/L
Tzatzarakis et al. 2017	Oil	<2 ng/ml
Konieczna et al. 2018	Canned tuna	1.07 ng/g
Santonicola et al. 2018	Raw milk	nd-2.34 µg/L
Santonicola et al. 2019	Raw milk	0.035-2.776 µg/L
Adeyi and Babalola, 2019	Beveraga	0.4–10.2 ng/ml
Oz and Seyyar, 2016	Fish	4.93-27.11 ng/g
Česen et al. 2016	Honey	<LOD-107 ng/g
Cao et al. 2019	Whole or partially canned foods	5.3-41 ng/g
Dualde et al. 2019	Breast milk	<LOQ–41 ng/ml
Sayıcı et al. 2019	Breast milk	0.03–0.59 ng/ml
Jin et al. 2020	Breast milk	< LOD–15 ng/mL
Gonzalez et al. 2020	23 different canned and uncanned foods	<0.17-88.66 µg/kg
Savaş et al. 2021	Chicken legs and breasts	nd-63.78 ng/g
Makowska et al. 2022	Pork loin meat	13.77-49.86 ng/g
Cohen et al. 2023	Various school meals	nd
Wang et al. 2023	Various meat products (steak, fresh meat etc.)	1.4-13.8 µg/kg
Zheng et al. 2024	Breast milk Infant formula Complementary food	<LOQ-0.27 ng/ml <LOQ-2.16 ng/g <LOQ-13.5 ng/g

10. Determination of BPA and Analytical Methods Used

The number of studies on BPA has been increasing in recent years. Different methods and devices are used to determine the BPA level. Especially in the determination of BPA, the most appropriate method should be determined first. In general extractions such as QuEChERS, SUPRAS-based microextraction, Sol-gel immunoaffinity chromatography, soxhlet extraction, microwaveassisted extraction, accelerated solvent extraction, supercritical fluid extraction, continuous liquid-liquid extraction, column replacement technique, liquid-liquid extraction, sonication and solid-phase extraction methods are used. In addition, chromatographic methods are mainly used in the determination of BPA. On the other hand, it is seen that devices such as UPLC/MS-MS, HPLC-UV, HPLC-FLD, HPLC-MS, LC-MS/MS, GC-MS, ELISA and LC-MS-MS are used in the determination of BPA (Rudel et al., 1998; Kolpin et al., 2002; Meesters and Schröder, 2002; Braunrath et al., 2005; Gang et al., 2005; Watabe et al., 2005; Gatidou et al., 2007; Hu et al., 2007; Grumetto et al., 2008; Cao et al., 2011; Sungur et al., 2014; Babu et al., 2015; Seyyar & Oz, 2016; Kawamura et al., 2014; Alabi et al., 2014; Cao et al., 2019; Adeyi and Babalola, 2019; Cunha et al., 2020; Savaş et al., 2021; Siddique et al., 2021; Shaaban et al., 2022). Also, for sensitivity, Mohapatra et al. (2010) listed the devices as LC–MS/MS> GC–MS/MS> LC–MS.

11.Detoxification of bisphenol A and future approaches

BPA is an organic pollutant with a multitude of applications. The use of BPA in a multitude of products has given rise to significant concerns pertaining to human health, largely due to its pervasive presence in the environment and the potential ecotoxicological consequences of its use (Ahammed et al., 2020; Zhu and Wei, 2022).

A further significant issue is the detoxification of BPA. In particular, it is stated that BPA attracts considerable attention due to its biodegradation by microorganisms, its environmental compatibility and its low operating costs. There are studies in the literature in which BPA is detoxified by different biological pathways (Buhari et al., 2023).

The effects of bisphenol A are reported to be detrimental not only to humans but also to a multitude of living organisms. Ahammed et al. (2020) in their study on cucumber, reported that 21 days exposure to BPA (20 mg L^{-1}) caused a decrease in the length and dry weight of shoots and roots. Furthermore, the study revealed that the treatment led to a notable reduction in growth and biomass accumulation, accompanied by a decline in chlorophyll content, cell viability, and root activity. Additionally, the accumulation of reactive oxygen species (ROS), electrolyte leakage, and malondialdehyde (MDA) was observed to have increased significantly. Furthermore, the researchers applied dopamine to detoxify BPA and reported that dopamine has a positive role against BPA phytotoxicity. They also suggested that it may reduce the risks associated with dietary intake of BPA through vegetable consumption.

Zhu and Wei (2022) have developed a novel biocatalyst by genetically immobilising the Bacillus megaterium tyrosinase enzyme on the surface of polyhydroxyalkanoate (PHA) biopolymer beads. They have also demonstrated the in vivo production of the biocatalyst for the efficient degradation and detoxification of various bisphenol analogues in one pot. In particular, it was reported that the degradation of bisphenol by PHA-BmTyr can significantly reduce or even eliminate the estrogenic activity of pollutants. Furthermore, the detoxification of BPA via green chemical methods is a viable approach. In a study conducted by Thiounn et al. (2023), the DMBPA (*O,O′*-dimethyl bisphenol A) compound, produced by recycling BPA-derived plastics with low-temperature application, was observed to react with elemental sulfur at temperatures between 310 and 325 degrees Celsius. This resulted in the conversion of over 95% of the DMBPA into monoaryl species, ultimately yielding the BC90

composite material. Furthermore, the researchers indicated that the adverse endocrine-disrupting effects of BPA could be effectively mitigated through the utilisation of environmentally benign chemical techniques.

Furthermore, research is being conducted on the detoxification of BPA with novel approaches. In a recent study, Chen et al. (2024) demonstrated that soil can effectively activate peroxymonosulfate for the removal of BPA from water and slurry.

In general, bisphenol A (BPA) and its derivatives are endocrine-disrupting compounds that affect human health in a number of ways. In particular, a significant number of countries have implemented substantial restrictions on the utilisation of BPA. Nevertheless, its extensive utilisation represents a considerable hazard to human health. In this context, there is a body of literature examining the detoxification of BPA. Given the indications from these studies that BPA is detoxified at different rates, It would appear that further research is required in the area of BPA and its derivatives, with a particular focus on detoxification processes. There is currently a notable gap in this field of study. It is therefore considered that further research in this field, with regard to both public health and the continuity of the ecological environment, would be of significant value to relevant researchers.

12. Conclusion

BPA is one of the widely used chemical compounds in many materials. Due to its widespread use, many studies have been carried out on bisphenol A and its analogues in recent years. BPA exposure poses a major concern as it affects human health in various ways. As a matter of fact, many countries have limited the use of BPA in various products. In this review study, besides the general characteristics of BPA, information about the migration limits to foods for the last 10 years, legal regulations, effects on health and analytical methods used for analysis are presented. It is also thought that more research should be done on analogs of BPA.

13. References

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