

Toxicological Evaluation of Bisphenol A and Its Analogs

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Abstract:

Bisphenol A(BPA) is known as one of the oldest sentetic compounds with endocrine activity. BPA is commonly used in production of epoxy resins, polycarbonates, dental fillings, food storage containers, baby bottles and mineral water containers. BPA is associated with various health problems such as diabetes, obesity, cardiovascular diseases, chronic respiratory diseases, renal diseases, breast cancer, behaviour disorders, teeth development disorders and reproductive diorders. Increasing health concerns led the endustry to seek alternatives for BPA, as BPA has begun to be excluded from the products, the use of alternative bisphenols has been increased. However the chemicals used as a replacement of BPA are also bisphenols and may have similar physiological effects on organisms. According to the researches, it is demonstrated that BPA analogs may result in similar or higher toxic effects compared to BPA.

Key Words: Bisphenols, BPA, endocrine disruptor, BPS, BPF

Bisfenol A ve Analoglarının Toksik Etkilerinin Deđerlendirilmesi

Özet:

Bisfenol A (BFA) endokrin aktiviteye sahip bilinen en eski bileşiklerden biridir. BFA epoksi reçinelerin, polikarbonatların, dental dolguların, yemek saklama kaplarının, bebek biberonlarının ve mineral su konteynırlarının üretiminde yaygın olarak kullanılmaktadır. BFA diabet, obezite, kardiyovasküler hastalıklar, kronik solunum hastalıkları, renal hastalıklar, meme kanseri, davranış bozuklukları, diş gelişimi bozuklukları ve üreme bozuklukları gibi çeşitli sağlık problemleriyle ilişkilendirilmiştir. Artan sağlık endişeleri endüstriyi BFA alternatifleri aramaya yönlendirmiştir, BFA ürünlerden çıkarılmaya başlandııkça alternatif bisfenollerin kullanımı artmıştır. Ancak BFA yerine kullanılan kimyasallarda bisfenoldür ve organizmalar üzerinde benzer

fizyolojik etkileri olabilmektedir. Araştırmalara göre BFA analoglarında BFA'ya kıyasla benzer veya daha yüksek toksik etkiler oluşturabileceği gösterilmektedir.

Anahtar kelimeler: Bisfenoller, BFA, endokrin bozucular, BFS, BFF

Introduction:

Endocrine disruptors, such as pesticides and BPA, can be defined as exogenous substances that cause different levels of changes in evolution and function of endocrine system.¹

Bisphenols are a class of chemicals known as diphenylmethanes. They contain two benzene rings separated by a central carbon atom and mostly have 4-OH substituent on both benzene rings. Some bisphenols may have a sulfone group or a sulfide instead of central carbon atom.²

Regulations and increasing concerns of communities led the industry to seek alternatives for BPA, as BPA has begun to be excluded from the products due to the consumers concern use of alternative bisphenols has increased and BPA has begun to be replaced by its chemical analogs.^{3,4,5,6}

The chemicals used to replace BPA are also bisphenols and may have similar physiological effects on organisms.⁵ According to the researches, it is demonstrated that BPA analogs may result in similar or higher toxic effects compared to BPA.⁴

Bisphenol (BPA):

The chemical nomenclature of BPA is [2,2-bis(4-hydroxyphenyl)propane] with a molecular weight of 228.29 g/mol.^{4,7,8} If physical properties are examined it is seen that it has water solubility of approximately 120-130 ppm, low volatility, low air emission and fast photooxidation half life(<7 hours).^{1,8}

BPA is known as one of the oldest synthetic compounds with endocrine activity and was first discovered by Dianin in 1891.^{1,9} BPA is one of the mostly produced chemicals in the world estimated to have 5-6.8 million tones of production per year

and is used in a wide range of areas. ^{1,4,10} %70 of the BPA produced is used in production of polycarbonate plastics while %25 is used in production of epoxy resins.¹⁰

BPA is commonly used in production of epoxy resins, polycarbonates, dental fillings, food storage containers, baby bottles and mineral water containers.^{2,8} Also BPA is seen in thermographic and pressure sensitive papers, cash, receipts and toys.^{3,6,8} In addition it is used in medical devices and health care services such as eye lenses, newborn incubators, nebulizers.¹

The main source of BPA exposure is food.⁴ BPA contamination on foods usually happens as a result of migration from the containers including BPA.¹⁰ Exposure is caused by consuming food and beverage in recycled bottles, cans covered with epoxy resins and polycarbonate containers that BPA has leaked in.¹ Environmental factors such as temperature, heat, acidity increases the hydrolysis of ester bounds that bound BPA molecules with epoxy resins and polycarbonates. BPA leakage in polycarbonates happens more often to the solutions with low pH values whereas in epoxy resins higher temperature increases the BPA leakage.¹ When exposure concentrations are examined it is seen that average exposure concentrations range from 10 $\mu\text{g kg}^{-1}$ to 70 $\mu\text{g kg}^{-1}$ in solid canned food whereas it ranges from 1 $\mu\text{g L}^{-1}$ to 23 $\mu\text{g L}^{-1}$ in liquid canned food.² Fish, dairy, meat, canned vegetables and baby food are examples of goods that may contain BPA.¹⁰ Specific migration limit of BPA is determined as 0,6 mg/kg in 2002/72/EC commission directive and in Turkish Food Codex.¹⁰

In addition to the source of exposure mentioned above, dust may also cause a significant exposure by inhalation of indoor dust and thermal papers may cause transdermal exposure from the skin.^{4,9,11,12} Dental composite resins may also cause BPA to leak into saliva.¹ Other than these, sources such as water sources in nature, tap water, air, medical devices can be examples of sources of exposure.^{1,11} BPA being used in epoxy based floor materials, adhesives, paints, electronic devices is also another source of exposure.¹ BPA is detected in blood, urine and sweat in humans.¹¹

Generally it is suggested that, BPA is bioactivated by oxidation reactions catalysed by cytochrome P450 and detoxified by glucuronidation reactions and sulfatation reactions. It is shown that the toxic effects of BPA decreases in the presence of ADH, ALDH2 and SULT1E1 while increases in presence of CYP2E1.¹³

The main mechanism of toxic effects induced by BPA is that it is an endocrine disruptor. This property may cause both developmental and reproductive disorders.² BPA is associated with diabetes, obesity, cardiovascular diseases, chronic respiratory diseases, renal diseases, breast cancer, behaviour disorders, teeth development disorders and reproductive disorders.^{9,14}

It is shown in literature that low dose of BPA has negative effects on endocrine system and it is effective in primer endocrine disorder.^{1,10} It effects cell signaling pathways.¹³ It is claimed to be effective on central nervous system, immune system, cardiovascular system, respiratory system and renal system.^{1,10} It may be associated with thyroid hormone function disorders.¹⁰ Due to the exposure birth defects may be seen.¹ Pregnants and fetus are very sensitive to pathologies induced by BPA due to its penetration from placent barrier.¹³ In researches it is shown that BPA can pass to fetus from the mother and can cause behaviour changes and anomalies in reproductive organs of the fetus.¹⁰ In addition to the effects mentioned above, it is suggested that BPA has mutagenic and genotoxic potentials.³

BPA can both bind to $Er\alpha$ and $Er\beta$ receptors and effect them by either activating or suppressing their expressions.^{1,7} It's relative binding affinity is predicted to be 1000-10000 times lower than estradiol and it is qualified as a weak environmental eustrogen.⁷

BPA can act as a potential antagonist of endocrine receptors in some cases.⁸ Infertility in men and women, early puberty, polycystic over syndrome can be given as examples to the endocrine disorders in which BPA plays a pathogen role.⁸ In addition it is reported to be associated with low sperm count and motility, spontaneous abortus and metabolic changes.¹³ When it's effects on reproduction system is examined it is seen that the main target is ovarian granulosa cells. The

disruption of these cells by BPA can play an important role on fertility.¹² According to its effect on androgen receptor, it is seen that BPA is a known antagonist. It slows the nuclear transport and forms non-functional foci in the nucleus.¹⁵

The chemical structure of BPA and thyroid hormone has similarities. BPA has a property of binding to thyroid receptors competitively with thyroid hormone. It is seen to disrupt gene expression by thyroid receptors *in vivo* and *in vitro*.¹⁴

In addition to mentioned effects, it is observed that BPA activates PXR from the nuclear receptors, induces CYP3A4 and environmental exposure to BPA can change 25-hydroxy vitamin D level in circulation in adults and there is a negative correlation between BPA and 25(OH)D.¹⁶

In a previous research, it is reported that BPA induces DNA strand breaks in ER-positive MCF-7 cells and its genotoxicity is ER-dependent. It is observed that it induces micronucleus formation and chromosomal aberrations in rat bone marrow, causes DNA damage in lymphocytes. In a different study it is suggested that oxidative stress occurs by observing an increase in 8-hydroxyguanosine plasma levels, an increase in lipid peroxidation, a decrease in glutathione activity in liver.²

There are controversial results about the genotoxicity of BPA. Even though it is found to be negative according to basic genotoxicity tests, researches show that it induces chromosomal aberrations and morphological changes in SHE cells, achromatic lesions and c-mitotic effects in mice bone marrow, its metabolites bind to DNA in SHE cells and rodents, it causes DNA strand breaks in ER-positive MCF-7.² Another study revealed that BPA causes ER-dependent DNA damage by inducing strand breaks in ER-positive MCF-7 cells.⁴

Hassani et al.,⁷ showed that protein and phosphoprotein levels taking part in biological processes associated with hepatotoxicity, fatty liver and carcinoma are affected by BPA exposure. Also it is observed that BPA induces oxidative stress, an increase in MDA and a decrease in GSH occurs.⁷

In 2008 worries about the effects of current BPA exposure of fetus, adults and children on brain, behaviour and reproduction are declared in the report of National Toxicology Programme and in 2010 FDA reported that they share the same worries.¹

BPA is banned in Japan, Canada and in most of US. In 2011 EU forbidded the production, marketing and ithlalat of baby bottles containing BPA.²In our country baby bottles and other food containers with BPA are collected by the Ministry of Agriculture in 2011.¹

Bisphenol S (BPS):

BPS is an important analog of BPA in industrial applications and an increasingly used alternative.⁶ The chemical nomenclature of BPS is bis[4-hydroxyphenyl]sulfone and it has a molecular weight of 250.27 g/mol.^{3,16} BPS is a heat resistant structural analog of BPA.¹⁶It has high thermal stability and it is resistant to sunlight.^{16,17}

As a member of large and diverse group of bisphenols, BPS is commonly used in numerous consumer products as a replacement of BPA. As being the most commonly used alternative of BPA, BPS is frequently used in production of plastics and thermal papers.^{3,17}

BPS is used as improver in thermal papers, stabilizer in canned soft drinks and canned food.^{6,16} In addition BPS is used as fastening agent in cleaning products, electroplating solvent, a constituent of epoxy resins in various industrial applications.⁵ As a commonly used analog of BPA in production, the presence of BPS in nature and food is demonstrated in numerous researches.⁴ According to data of National Health and Nutrition Examination Survey (NHANES) Significant concentrations of BPS was detected in canned food especially in canned vegetables and mushrooms.⁴ In addition literature findings has shown that a significant exposure occurs by dust.⁴ Also presence of BPS is detected in mud, water, tap water, sewage.^{5,6,11} In a previous study, BPS was detected in dust samples from various microenvironments and many products produced from thermal paper.¹¹ BPS was detected in human tissues too.⁶BPS was found in human urine in concentration and frequencies comparable to BPA.⁵ Especially after its detection in human urine, concerns about it's safety was brought out.¹⁶

In addition to exposures mentioned above BPS was detected in many daily products. These products include personal care products, paper products and food such as hair products, toothpaste, currency, mailing envelopes, dairy products, canned food, cereals.⁵

Skledar et al.,¹⁷ showed that glucuronidation is the most important pathway for metabolism and detoxification of BPS and UGT1A9 plays an important role in this process.¹⁷

Cumulative evidences suggest that BPS is toxic to organisms because of its similar chemical structure to BPA. Recently it is reported that similar to BPA, BPS promotes eustrogenic activity, proarithmetic effects and hypothalamic neurogenesis in cell lines in vitro and in animals in vivo. When the eustrogenic effects of BPA and BPS are compared, in a study it is shown that genomic eustrogenic activity of 40 μ M BPS is 15 times lower than BPA. It has toxic effects in rats endocrine system, adult zebrafish, breast cancer cells and over ectomized mice.⁶

BPS is claimed to have toxic effects on endocrine system similar to BPA in literature data.⁴ In a previous research it is reported that isopropilation of 4-hydroxy group decreases the eustrogenic activity.¹⁷ BPS is also defined as a weak antiandrogenic compound.¹⁶

BPS exposure in zebrafish larvae suggests that oxidative stress and interference of immune response is induced.⁶ In other researches it is demonstrated that BPS inhibits pepsin activity, increases ROS levels in rats, induces lipid peroxidation and decreases antioxidant enzyme activity.¹¹

Also a recent study suggested that there might be a link between BPS exposure and obesity and steaosis. An in vivo study showed that BPS may alter brain functions in mammals.¹⁷

In addition to the effects mentioned above when its genotoxic potential is examined, a research had results on BPS exposure and genotoxicity including double strand breaks however it is seen that BPS has weaker genotoxic potential compared to BPA.^{3,4} In a study in HepG2 cells it is seen that BPA and BPS cause a significant increase in DNA strand breaks.² Also BPS was effective on hepatic cells, bound to serum albumines and caused DNA damage.⁵

When association between BPS and thyroid hormone receptors are examined, it is seen that similarly to BPA, it binds to thyroid hormone receptors. BPS can both bind to TR α and TR β but its affinity to TR β is higher.¹⁴ In a research, in zebrafish embryos that are exposed to BPS at concentrations of 10 ve 100 μ g/l for 75 days, triiodothyronine and thyroxine plasma levels were decreased.¹⁶

BPS exposure caused acute toxicity in *Daphna Magnia*, induced uterine growth in rats, in zebrafish it decreased weight of gonads, altered plasma estrogen and testosterone and caused reproductive disorders, also it increased the female ratio over males, decreased the body length, caused changes in testosterone, estradiol and vitellogenine concentrations and reproductive disorders.⁵ In non-genomic signal researches BPS has a similar potency to BPA. From femtomolar to picomolar concentrations, BPS induced E α modulated pathways and activities such as membrane MAPK signal, cell proliferation and caspase 8 activation. These fast, non-genomic pathways have an important role in optimal cell function, modulation of proliferation and apoptosis beside activities such as pancreatic cell function and estrogen-modulated brain function.⁵

Bisphenol F (BPF):

As one of the important and increasingly used analogs of BPA, the chemical nomenclature of BPF is [1,1-bis(4-hydroxyphenyl)ethane] and has a molecular weight of 200.23 g/mol.^{3,4,6} BPF is used in production of polycarbonate resin.² Beside that BPF is used especially in systems that require increasing thickness and durability, epoxy resins and coating.⁶

Storage and pipe coatings, industrial floors, road and bridge deck toppings, structural adhesives, grouts, coatings, and electrical varnishes are examples of these systems. In addition for several consumer products such as lacquers, varnishes, liners, adhesives, plastics, water pipes, dental sealants, and food packaging BPF epoxy resins are used.⁵

Even though it is more biodegradable under aerobic and anaerobic circumstances compared to BPA, BPF has turned into an ubiquitously present environmental contaminant.^{2,4} BPF has been detected in nature and food.⁴ The presence of BPF is reported in mud, tap water, indoor dust, water, sewage and human tissues.^{6,11} In a recent study it was detected in dust samples from various microenvironments and many products from thermal paper.¹¹

A study that has been recently done showed that this compound accumulates in human urine.⁴ BPF is also detected in personal care products such as lotions and toothpaste, paper products such as tickets, envelopes; foods such as canned food and cereals.⁵ Active BPF distributed to many tissues including uterus, placenta, amniotic fluid and fetus. Primary elimination form of BPF is seen to be sulfate conjugate.⁵

So far evidences suggest that just like BPS, because of its similar chemical structure BPF is toxic to organisms as BPA. In studies BPF is reported to cause mild to moderate acute toxicity and weak estrogenic activity.⁶ In in vivo studies it is demonstrated to be estrogenic, androgenic and thyroidogenic, in in vitro studies state that it is estrogenic, androgenic and other physiological/biochemical effects. There are studies showing that BPF exposure induces uterine growth in rats and points estrogenic activity.⁵ Studies show that BPF causes a more potent estrogenicity compared to BPA.⁴

BPF exposure causes an increase in thyroid weight and changes in thyroid hormone concentrations.⁵ According to a study BPF can bind to both TR α and TR β , its affinity to TR β is higher.¹⁴

Besides it causes changes in hemathological parameters and enzyme expression. Also BPF has shown other in vitro effects such as cytotoxicity, cellular disfunction, DNA damage and chromosomal aberrations and decreased in vitro adinopectine production and release.⁵

BPF is reported to promote eustrogenic activity comparable to BPA, proarithmetic effects and hypothalamic neurogenesis in cell lines in vitro and in animals in vivo. In addition as a result of BPF exposure concentration dependent increase of ROS content, T-AOC activity, SOD levels, LPO levels, NO and iNOS production, cytokine and chemokine expression in zebrafish larvae suggests that oxidative stress and immune response in fish are induced.⁶

BPF is claimed to cause a genotoxic damage that might interfere with DNA replication. In a previous study it is seen that BPF has weaker genotoxic potential compared to BPA.³ When genotoxic effects of BPF is examined it is reported that BPF induces DNA strand breaks but no micronuclei in HepG2 cells. A recent study suggested that genotoxicity of BPF depends on metabolic capacity of the cell.²

Bisphenol AF (BPAF):

The chemical nomenclature of BPAF is [2,2-bis(4-hydroxyphenyl)hexafluoropropane] and its molecular weight is 336.23 g/mol.^{3,4} It is used in production of polycarbonate resin and also a component of certain plasters and is used as a rubber bridging material.²

BPAF is detected in environment, tap water, bottled water and canned food.^{4,11} Also in a recent study it is shown that it accumulates in human urine.⁴

When the effects of BPAF is examined, it is reported that BPAF causes more potent toxicity in cells including blood cells. In addition in literature findings it is demonstrated that BPAF binds stronger to eustrogen receptor and has more effects in gene expression compared to BPA. Also it is shown that BPAF presents neurotoxic and genotoxic potential.⁴

In their study Mokra et al.,⁴ stated that BPA and BPAF have the highest genotoxic potential in incubated cells and previously reported that BPA and BPAF induced the formation of ROS in peripheral mononuclear blood cells more potently and only BPAF caused a significant increase of OH levels in these cells.⁴ In other studies it is demonstrated that BPAF in high concentrations causes more potent DNA damage in MCF-7 cells compared to BPA. Besides it is reported to form micronuclei in V79 cells, induce aneuploidy in SHE cells.^{2,4} Also while causing metaphase arrest in V79 cells, it also causes morphological changes in SHE cells along with aneuploidy.²

In mammal cells BPAF didn't induce chromosomal aberration and gene mutation. Since toxicity data is insufficient and it has a similar structure to BPA, BPAF has been nominated for a comprehensive toxicological characterisation by the US National Institute of Environmental Health Sciences.²

Bisphenol Z (BPZ):

The chemical nomenclature of BPZ is (1,1-bis(4-hydroxyphenyl)cyclohexane. Bisphenol compounds including BPZ have been detected in numerous human and environmental samples. It is reported in different researches that concentrations of BPs in sewage sludge, municipal waste water influents and effluents, sediments and surface water are elevated.¹⁸

BPZ is used in the synthesis of anaesthetic phencyclidine.¹⁹ Also another area of use of BPZ is to cure highly heat resistant plastic materials and in electrical insulation. Several analogues of BPA, including BPF, BPS, or BPZ, are being used in personal care products, paper products and food packaging materials.²⁰

Schmidt et al.,¹⁹ showed that BPZ was biotransformed in HLM in a manner similar to the case of BPAF. According to their research based on the peak areas, hydroxylated BPZ was the main in vitro metabolite in HLM in the presence of NADPH and GSH.¹⁹

In their study, J.Lee et al.,²¹ reported that BPZ exposure caused a decrease of T3 and T4 levels, but the change was not monotonous.²¹ Kovacic et al.,¹⁸ showed that

UV exposure is an effective way of removing BPF, BPS and BPZ from water, showing the fastest degradation rate in case of the photo-Fenton reaction.¹⁸

OTHER BISPHENOLS:

The chemical nomenclature of Bisphenol C is 2,2-Bis(4-hydroxy-3-methylphenyl) propane; of Bisphenol M is 4,4'-(1,3-phenylenediisopropylidene) bisphenol; of Bisphenol AP is 4,4'-(1-phenylethylidene) bisphenol; of Bisphenol P 4,4'-(1,4-phenylenediisopropylidene) bisphenol; of Bisphenol 1 is (sulphonylbis(4,1-phenylene))bis(oxy)dimethanol.^{2,3} The molecular weight of BPAP is 290.36 g/mol, of BPC is 256.34 g/mol, of BPM is 346.46 g/mol and of BPP is 346.46 g/mol.³

According to the study of Lee et al.³ some bisphenols including BPAP, BPM, BPP showed greater genotoxic potential compared to BPA. BPP is reported to have the greatest genotoxic potency and suggested to have an association with double strand breaks.³

BP-1 is reported to be a component of polymer bottles. Polybutyleneterephthalat modified by BP-1 is seen to improve glass transition temperature and thermal stability.²

In their research Fic et al.,² demonstrated that BPA, BPAF, BPF, BPS, BPZ, BP-1, BP-2, DMBPA and DMBPS are not mutagenic in Ames test however DMBPA, BP-2, BPZ ve BPAF have toxic effects on *S. Typhimurium*.²

Risk Assessment

The current lowest-observable-adverse-effect level (LOAEL) of BPA is determined as 50 mg/kg bodyweight per day by U.S.EPA.²² In hazard assessment protocol by EFSA it is indicated that the current temporary Tolerable Daily Intake (t-TDI) for BPA is 4 µg/kg bw per day.²³ Mikolajewska et al.,²⁴ showed that dietary BPA exposure of children is 1.088-4.492 µg/day, exposure to BPA of 3-month infants fed from polycarbonate bottles is 4-11 µg/kg b.w./day, dietary exposure (Canned food and beverages) in adults is 1.56–10.453 µg/day, daily exposure to BPA through inhalation 0.008–0.014 µg/person/day, exposure to BPA from thermal paper is 71

µg/day (exposure by 10 h/day), exposure from paper currencies is 0.0001–1.41 ng/day.²⁴ These data suggest that both children and adults may be exposed to BPA higher than t-TDI mainly by dietary exposure and might be affected by toxic health outcomes. Although a t-TDI was not found for bisphenol analogs, Wu et al.²⁵ reported that bisphenol analogs in foodstuffs are found as bps <0.01 ng/g bpa 0.125 ng/g bpf <0.05 ng/g bpp <0.025 ng/g bpaf <0.01 ng/g In U.S. between 2008-2012 which seem to be lower than BPA.²⁵

Conclusion:

BPA is a widely produced and commonly used chemical. Due to its endocrine disrupting nature, it is associated with many diseases and disorders such as diabetes, obesity, cardiovascular diseases, chronic respiratory diseases, renal diseases, breast cancer, behaviour disorders, thyroid hormone function disorders, teeth development disorders and reproductive disorders. central nervous system, immune system, cardiovascular system, respiratory system and renal system are shown to be effected by BPA. It is also suggested that BPA has mutagenic and genotoxic potentials. Due to its toxic health effects, the use of alternative bisphenols has been increased and BPA has been replaced by its chemical analogs such as BPS, BPF, BPAF, BPZ. However these replacing analogs are also bisphenols and it is suggested that they may pose similar or higher health risks for living organisms. In researches BPS is reported to promote eustrogenic activity, antiandrogenic activity, proarithmetic effects and hypothalamic neurogenesis in cell lines and posses a potential of endocrine disruption similar to BPA. BPF is demonstrated to be eustrogenic, androgenic and tiroidogenic. BPAF is reported to be causing more potent toxicity in cells, binding stronger to eustrogen receptor and more effective in gene expression compared to BPA, in addition to its neurotoxic and genotoxic potential. BPZ and other bisphenols also have similar structure to BPA and may show similar toxic effects. Therefore it is important to examine the toxicological profile of these compounds and focus on risk assesment of BPA analogs to estimate the relationship between exposure and toxic outcomes. Further studies especially in humans are needed to enlighten the risk of BPA analogs.

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Uncorrected proof