Review

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Systematic Review on Safety of Bisphenol A: from Invention to the Present

Bensu KARAHALİL[1], Hananeh KORDBACHEH[2]

[1]Gazi University, Faculty of Pharmacy, Toxicology Department, Ankara, Turkey
[2]Eastern Meditarranean University, Kuzey Kıbrıs Türk Cumhuriyeti

Abstract

Bisphenol a (BPA) is an industrial chemical that use in the production of polycarbonate plastics and epoxy resins. Recently, BPA has been received increased attention because of its high production volume, widespread applications and possible health effects. General population are mainly exposed orally to BPA through consumption of food and water stored in containers with BPA. In contrast, in occupational settings workers are exposed to BPA through inhalation of BPA dust particles. This review discusses the controversial of the current findings according to in vitro, in vivo and epidemiological studies. BPA exposure is associated with multi-organ toxicity including reproductive, developmental, metabolic and cardiovascular disorders. In order to protect the environmental and human health, numerous scientific bodies and regulatory agencies developed to keep the BPA exposure within the safe level. The various adverse health effect of BPA lead to development of alternatives with less harmful effect. However, the safety of the alternatives is not fully verified. To conclude, the current restrictions and limitations on use of BPA has reduced potential exposure and consequently possible health effect. However, still there are several unanswered questions regarding to the exact toxic effects, metabolism and fate of BPA on human and environmental health.

Keywords: Bisphenol A, Industrial chemical, Toxicity, Safe level, Environmental health.

Introduction

2,2-bis (4-hydroxyphenyl) propane widely known by its commercial name, bisphenol A (BPA), was firstly synthetized by Russian chemist Aleksandr P. Dianin in 1891 via acid catalyzed condensation reaction of two phenol molecules with one molecule of acetone[1].

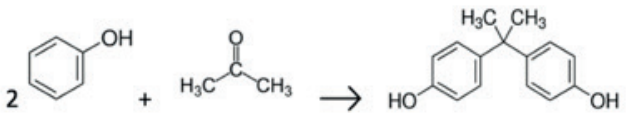

Figure 1: Synthesis of BPA

In 1953, the German scientist discovered that reaction of BPA with phosgene could produce a clear hard resin known as polycarbonate. In mid-twentieth century, BPA was patented under the brand name of "Makrolon" and "Lexan" in Germany and United States, respectively and marketing of BPA as an industrial chemical began[2]. Later on, the commercial production of BPA was rapidly expanded however, it never candidate as a drug and was not suitable as a pharmaceutical. As early as 1934, Edward Charles Dodds, a British biochemist, identified the weak estrogenic properties of BPA while he was looking for a synthetic estrogen by utilizing the rat test systems[3]. In 1993, a team of researcher at Stanford University accidentally found that BPA was leaching from polycarbonate dishes into flask content which interfered their experiment by estrogenic like activity with cells in culture[4]. BPA serves as a main ingredient of polycarbonate polymers and epoxy resins. Polycarbonate has high durability in a wide temperature ranges (-20 °C to 140°C) and resistance to many acids, oxidizing and reducing agents. Transparency and hardness of polycarbonate makes it ideal alternative to glass. In addition, polycarbonate is incredibly useful hard plastic with wide varieties of usage such as compact discs, food container, baby bottles, re-usable water bottles and medical equipment[5]. As polycarbonate, epoxy resins have wide range of consumer and industrial applications due to their toughness, robustness, resistance and adhesion properties. Epoxy resins are used as an inner coating on metal food and beverage containers as well as jar caps to protect food products from direct contact with metal[6]. This protective layer also minimizes the corrasion and leakage of any metal traces that could lead to possible

Corresponding Author: Bensu KARAHALİL **e-mail:** bensuka@gmail.com
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food-borne poisoning. In lesser extent, BPA is also used as photoactive dyes in the manufacturing of thermal paper that used in cash receipts. In 2010, a case-control study showed that urinary concentration of conjugated and unconjugated forms of BPA were significantly higher in cashier who had frequent contact with thermal paper by dermal exposure than control group[7]. BPA is one of the best-selling chemicals in the world, with total annual production of 7,082 metric tons in 2022 and is expected to reach 12,169 metric tons by 2032 as reported by total addressable market[8]. The release and distribution of BPA in the natural environment is widespread. Based on biomonitoring data, the human exposure to BPA is nearly ubiquitous. General population are mainly exposed to BPA through direct contact with materials containing BPA and consumption of contaminated food and water. It has been thought that BPA could be released from plastic materials over time and leaching is increased by the aging of material, alkaline condition and heating. BPA as a form of bisphenol A-glycidyl methacrylate is frequently used in dental composites, dental sealants and dental cement. Dental treatment is one of the sources of BPA exposure however the amount of BPA released from dental sealants is far below safe intake limits that set by government bodies. In 2015, European Food Safety Authority (EFSA) estimated the contribution from dental material is limited to 0.001% compared to total BPA exposure from all sources and potential adverse health effect is most likely negligible. Even though, chronic exposure to BPA released from dental material is still a concern[9].

Pharmacokınetıcs of BPA in Human

The absorption, distribution, metabolism and excretion of BPA have been investigated previously. The primary sources of BPA absorption are through ingestion, inhalation, maternofetal transmission and lesser extent through skin contact. Orally introduced BPA rapidly are absorbed through gastrointestinal tract and then metabolized by liver and intestine before reaching the target tissues including testes, fetus or uterus. Due to the presence of hydroxyl group, BPA is metabolized by phase II enzymes via glucuronidation and coupled by uridine 5'diphospho-glucuronosyltransferase (UGT) to BPA mono-glucuronide. Consequently, this biologically inactivated metabolite is excreted from hepatocytes into urine or feces within 24 hours after administration. Several laboratory animal experiments and epidemiological studies confirmed that BPA mono-glucuronide is the major metabolite in the plasma with lack of estrogenic like activity that is known as BPA detoxification process. Any abnormalities in functioning of glucuronosyltransferases enzymes lead to the elevation of unconjugated BPA concentration in the body. At higher doses of BPA treatment, the glucuronidation pathway becomes saturated and other metabolic pathways become activate10. The lesser extent, free BPA is metabolized through sulfotransferase (SULT) metabolizing enzyme. The sulfate conjugates, primarily BPA-sulfate, is minor metabolite that is considered biologically inactive and eliminated from body into the urine via glomerular filtration. 4-Methyl-2,4-bis(4-hydroxyphenyl) pent-1-ene (MBP) is a major active metabolite of BPA that possesses more potent estrogenic activity that BPA11. This metabolite is formed during direct hydroxylation of BPA ring by catalytic activity of microsomal enzymes. In 2011, a study has been found that cytochromes P450 (CYP) enzymes, mainly *CYP3A4* and *CYP3A5*, in the liver had ability to mediate the metabolism of BPA into isopropenyl phenyl (IPP) and hydroxycumul alcohol (HAC). Both metabolites are originated from carbocation intermediate and have high estrogen receptor binding properties[12].

BPA in both free and conjugated form could excreted in urine with a half-life of approximately 6 hours. Therefore, the urinary concentration of total BPA reflects recent, mostly within 24 h, exposure to the BPA. However, free form of BPA is biologically active and lipophilic in nature that has ability to accumulate in different human and animal compartments especially adipose tissue[10]. Various biological samples could be used for the biomonitoring of BPA, including blood, urine, amniotic fluid, hair and other tissues. Human biomonitoring studies have reported BPA can pass through placenta and influence fetal growth in uterus[13].

Toxicological Aspect of BPA

In 2017, the Member State of the European Chemicals Agency (ECHA) was classified BPA as a Substance of Very High Concern (SVHC) under category 1B, due to being toxic for reproduction and endocrine disruptor for both the human health and ecosystem14. BPA is considered to have an estrogenic-like and anti-androgenic properties that resulting in harmful impact on different systems and organs including

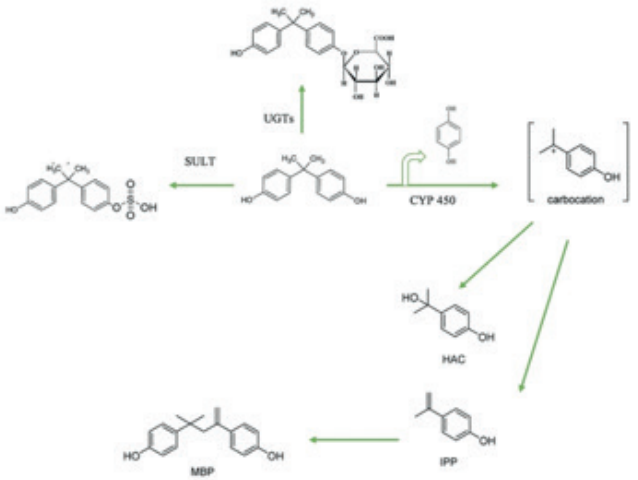

Figure 2: BPA and its four metabolites

developmental system, reproductive system immune system and metabolic disorders.

Reproductive System

Several studies documenting that BPA downregulates the activity of sex hormones and increases the incidence of infertility in both men and women. BPA is mimic estrogen hormone and binds to estrogen-related receptors such as ERα and ERβ, androgen receptors and aryl hydrocarbon receptors therefore interrupts activity and balance of sex hormones. The primary effects are elevated the concentration of hormones like progesterone, estradiol and luteinizing hormone and decreasing the concentration of cortisol[15]. It has been claimed that alterations of endometrial structure are associated with perturbation of sex hormone. Changes in ovarian morphology and ovulation as a result of BPA exposure have been well documented. Several studies have found aged-based relationship between BPA levels and changes of endometrial wall thickness. Scientists have found that exposure to BPA results in endometrial wall thickness in women less than 37 years old while women older than 37 years had a negative correlation with urinary BPA levels and thickness of endometrial wall[16]. BPA is also associated with increased incidence of cystic endometrial hyperplasia, stromal polyps, atypical hyperplasia and pregnancy problems such as miscarriage[17]. Experimental studies suggested a negative association between urinary BPA concentration and male reproductive system including decrease spermatogenesis, sperm motility, viability and abnormal sperm morphology ultimately decreasing male fertility and reproductive potential18. A study at reproductive center in Taiyuan evaluated the effect of chronic exposure to BPA on male sexual function. Among the participants, the primary effects were sexual dysfunction, reduced levels of libido following by reduced erection ability, reduced ejaculation intensity and premature ejaculation[19].

Developmental Systems

Accumulating evidence suggests that prenatal exposure to BPA altered the brain growth and behavior neural development such as hyperactivity disorder, depression, anxiety, prosocial behavior, learning-memory impairment and language development[20]. In addition to the change in growth and development of offspring during prenatal exposure, BPA exposure also cause precocious puberty in both girls and boys during the pubertal period. The underlying mechanisms of precocious puberty and premature thelarche caused by BPA exposure is related to its xeno-estrogenic activity[21]. Many studies have proven that BPA can disrupt hypothalamic-pituitary-gonadal axis causing to increase the concentration of gonadotropin releasing hormone and follicle stimulating hormone. A study in 2018 showed that, prenatal exposure to BPA might increase serum GnRH level and induced abnormal estrus cycle[22]. An occupational cohort study in China has proved a dose-response relationship between increased maternal exposure to BPA during pregnancy and greater magnitude of shortened anogenital distance (AGD) in male offspring[23]. A pregnancy cohort study concluded that, BPA concentration in first trimester maternal urine was associated with shortened AGD in newborn female. This study hypothesis that, BPA exposure during pregnancy alters typical gestational endocrine signaling pathway through estrogen receptor agonistic activity[24].

BPA Induced Metabolic Disorders

Several epidemiological data suggest that BPA negatively impacts on metabolic homeostasis. The relationship between urinary BPA concentration and risk of metabolic syndrome, diabetic mellitus and obesity development were extensively studied. One possible mechanism is mitochondrial dysfunction through increasing oxidative mediators and decreasing antioxidative enzymes. Besides that, BPA has been shown to alter synthesis and release of insulin by pancreatic B-cells and induces insulin resistance25. In 2010, Alonso-Magdalena et. al. have found that BPA exposure results to metabolic disorder through disrupting the glucose homoeostasis on animal model. The result showed that offspring had lower glucose tolerance, higher insulin resistance and higher plasma level of insulin, leptin, triglycerides and glycerol compare to control group26. Epidemiological studies and laboratory experiments showed that higher concentrations of BPA in urine were correlated with higher incidence of cardiovascular toxicity including peripheral arterial disease, coronary heart disease and higher blood pressure during pregnancy. Prenatal BPA exposure was reported to lead to multiple cardiac disorders in a sex specific manner. In female model BPA suppressed the migration of endothelial progenitor cells and high systolic blood pressure through mediate estrogen receptor α. In male model impaired vascular vasoresponsiveness and reduced cardiac remodeling were observed as well[27].

Other Health Effects Linked to BPA

In the study of Linillos-Pradillo et. al. the higher BPA concentration were associated with increased aspartate aminotransferase and alanine aminotransferase level in rat model compare to control group. This study concluded that both low and high dose of BPA can cause hepatic trauma through induces oxidative stress, mitochondria mediated apoptosis, genomic damage and alteration in liver enzyme levels[28]. In 2017 Kobroob et. al. found that BPA had negative impact on the kidney and leaded to deterioration of renal function including glomerular filtration and tubular function. BPA exposure resulted in azotemia, as indicated by increases in blood urea nitrogen and serum creatinine level[29]. In vivo and in vitro studies have suggested BPA with potential carcinogenic functions. BPA exposure

can significantly impact growth, proliferation, migration and apoptosis of cancer cells. Although, possible pro-carcinogenic effect of BPA is suggested by many studies, still there is inadequate epidemiological evidence to consider BPA as a human carcinogen and international agency for research on cancer (IARC) has not yet classified BPA as to its potential carcinogenicity30. Also, several published studies suggested that BPA could disrupt the normal respiratory function, immune function and increase risk of some neurodevelopmental diseases[15].

Safe Level of BPA Exposure

Due to the controversy over safety of BPA, numerous scientific studies and regulatory bodies expanded to assessed hazards and risk as result of dietary and non-dietary exposure to BPA. In 2002, the International Program for Chemical Safety (IPCS) of the World Health Organization (WHO) published that many endocrine disrupting chemicals such as BPA were not following common dose response rules[31]. Several mechanisms are involved in this phenomenon. The receptors may be stimulated by low doses and inhibited by overdoses because receptor-mediated responses saturate. In 2012, the National Institute of Environmental Health Science together with the National Toxicology Program (NTP) and Food and Drug Administration (FDA) developed the Consortium Linking Academic and Regulatory Insight on BPA toxicity (CLARITY-BPA). This program as name of CLARITY performed a regulatory-style study to assess the full range of potential health effects by using identical animal strains and experimental conditions to resolve uncertainties on BPA toxicity[22]. A recent study as a part of CLARITY-BPA addressed that BPA produce an unconventional dose-response curve typically known as non-monotonic dose response curve. BPA changed the believe that high doses produce more serious effects than low ones. A study assessed the dose response of BPA on female rat cardiac myocytes via evaluating multiple end points including development of arrhythmic activities, myocyte mechanics and calcium transient[32]. The result was in agreement with previous studies that low dose BPA rapidly stimulated the contraction of female myocytes while the effect declined at the higher concentration. The European Commission (EC) includes BPA in the list of chemicals in terms of its application in manufacturing of plastic materials that indented to come into contact with food. However, only a limited amount is allowed to leach from the material into food that known as specific migration limit (SML)[33]. In 2002, the EC established SML for BPA at 3 mg/kg of foodstuff and later on, EC re-evaluate the risks and introduced stricter limits on BPA in food contact materials, therefore, decreased the SML to 0.05 mg/kg of food on 2018[34]. Since 2011, different measures have been taken to limit population exposure to BPA. Infants and toddlers are more susceptible to hazardous chemicals such as BPA due to physiological differences, immature immune system and insufficient detoxification system. Infancy is the key period for mental and physical development and BPA could adversely affect the behavior, brain and prostate gland in fetus, infant and young children. Therefore, in 2012 the FDA banned the use of BPA in baby bottles and sippy cups. This change was followed in 2013 to disallow the use of BPA-based epoxy resins as a coating in packaging for infant formula[35]. Panel of food contact material and Enzymes and Processing Aids (CEP Panel) suggested the safe exposure limit, known as tolerable daily intake (TDI), for industrial chemicals such as BPA. This limit refers to the amount of a substance in air, food or drinking water that can be taken daily over a lifetime without appreciable health risk. In 2006, EFSA set an identical TDI for BPA at 50 µg/kg body weight/day based on available toxicological data. This value was calculated by diving no observed adverse effect level (NOAEL) of 5 mg/kg body weight /day that derived from animal experiment by a safety factor of 100 to account for interspecies variability of 10 and intraspecies variability of 10[36].

$$\text{ADI (human dose)} = \frac{\text{NOAEL (experimental dose)}}{\text{Safety Factor (100)}}$$

Figure 3: The equation uses to calculate ADI of BPA

The EFSA provided the risk assessment analysis based on identified two multi-generation reproductive toxicity studies in rodents. The effect of BPA on body and organ weight in adult and offspring rats as well as liver function in adult mice were observed. This study confirmed that a dose of 5 mg/kg b.w. of BPA was without any adverse effect on mice and their offspring. In 2015, EFSA performed new hazard characterization of BPA based on potential health effects, exposure estimates and evaluation the risks for human health37. EFSA lowered the TDI of BPA from 50 to 4 µg/kg body weight/day. This was based on applying a safety factor of 150 to the NOAEL of 609 µg/kg body weight/day. Several studies during the 2013 to 2018 revealed that BPA could adversely affect the immune system particularly via increasing in the proportion of certain cells called T-helper cells in mice. Eventually, in 2021, EFSA proposed to reduce the TDI 100 000 times lower to 0.04 ng/kg body weight /day. The current TDI value is safe and this value does not pose health risk to consumer therefore other that infant products, BPA below this level is eligible to be use as a part of food contact material[38].

Occupational Exposure to BPA

As the production and consumption of BPA is increasing, consequently the number of individuals that are occupationally exposed to this compound is increased dramatically. Therefore, there is an urgent need to understanding, characterizing and quantifying the workers

exposure to BPA in different occupational setting to provide a preventive and protective measures in work place. Threshold Limit Value (TLV) and Permissible Exposure Limits (PEL) are legal limits that referring to airborne concentrations of chemical substances and conditions where nearly all workers may be repeatedly exposed over a working lifetime without developing any adverse effects. In order to protect the workers and minimize worker's exposure to hazardous concentration. PEL is regulated by Occupation Safety and Health Administration (OSHA) whereas TLV set by American Conference of Governmental Industrial Hygienists (ACGIH)[39]. Yet there is neither specific TLV nor PEL for BPA in working place. However, the OSHA and ACGIH established an exposure limit for total dust that workers may be contact at 15 mg/m3 and 10 mg/m3 respectively40. Additionally, Europe has been established specific exposure limits for BPA at 3 mg/m3. Biological monitoring provides an important role to assess exposure and health risk to works in occupational settings. In 2013-2014, the National Institute for Occupational Safety and Health (NIOSH) conducted a biomonitoring study to examine the exposure of BPA at six US companies that are BPA manufacturers or make BPA-based materials. Over two consecutive days, series of urine samples of 77 workers were collected and analyzed. The result had shown that workers in the NIOSH study had BPA levels in their urine 70 times higher than general population in the U.S. However, more than 99% of detected BPA in urine was in conjugated form that were biologically inactivate. Unlike general populations, workers in this study were mainly exposed to BPA repeatedly through inhalation or dermal contact[41].

Alternatives to BPA

As mentioned above, the use of BPA in baby bottles were banded by Canada in 2008, in France in 2010 and in EU in 2011[42]. Such regulations and public health concerns has led to the removal of BPA from many commercial products and development of substitutes. Bisphenol S (BPS) and bisphenol F (BPF) are the most common alternatives of BPA that are used in the manufacturing of several consumer products including hard plastic items, food packaging and container as well as household products. These two analogs share close chemical structural similarities with BPA[43].

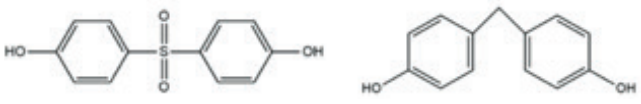

Figure 4: Chemical structure of BPS (left) and BPF (right)

The BPA replacement products are marketed under the labelled of "BPA free". In 2016, the use of BPA was restricted in thermal paper and by 2022, 61% of all thermal paper in the EU was replaced by BPS[44]. It is hypothesized that BPA alternatives are less likely to leach into food and beverage products and more resistant to heat. Although BPS and BPF are thought as safer alternatives to BPA, recent in vitro and in vivo studies revealed the anti-androgenic and estrogenic activities of these compounds in cell lines of different species. The safety and health risk of BPS is controversial. Some toxicological studies have concluded that BPS exposure impairs endocrine system as well as increases incidence of obesity and thyroid hormones[45]. For the first time in 2019, a study was designed to evaluate the maternofetal placental transfer rate of BPS and its main metabolite, BPS glucuronide, by using the human placental perfusion model. The results show that despite the structural similarities of bisphenols, BPS is a polar molecule with low lipid solubility therefore has lower rate of placenta diffusion compare to BPA. This study concluded that the blood placental barrier preventing fetus exposure to BPS and its metabolite[46]. In 2021, a study conducted by Kaptaner et. al., was showed that BPS exposure induced hepatocyte toxicity in rainbow trout fish via decreasing the activity of free radical scavenging enzymes including superoxide dismutase, glutathione and catalase as well as increasing oxidative stress and lipid peroxidation[47]. In contrast in 2021, Castellini et al. designed a study to investigate in vitro effect of BPS and BPF on human spermatozoa. This study concluded that BPS and BPF alone or in combination form had neutral effect on sperm viability, motility as well as sperm mitochondrial function. The results showed that these two analogs seem to be safer alternative to BPA for sperm biology48. However, information regarding to the biological activities of these two alternatives are still limited and toxicity as well as potential adverse effects for human health is not clear yet. To conclude, the utilization of BPS and BPF instead of BPA as safe alternative in consumer products should be carried out with caution and awareness.

Conclusion and Perspective

BPA has been received increased attention because of widespread usage, ubiquitous human exposure and possible health effect. Several studies showed estrogenic and antiandrogenic effect of BPA and target different organs. Regulatory agencies (FDA and EFSA) provide broad risk assessments to identify hazard associated with BPA exposure over years and extensively reviewed the available toxicological data to decide the safest level for BPA. EFSA has lowered the estimated safe level of BPA in order to minimize the possible risks to public health. Even though the level of BPA exposure is far below the established safe level, some precautionary measures should be taken to minimize the adverse health effect. These including limit the use of canned foods, avoid heat to plastic material, switch to BPA-free products and development of safer alternative to BPA. Figure 5 highlighted the scientific finding and major limitation of BPA from invention to the present. Although BPS and BPF are alternatives to BPA, they are not innocent

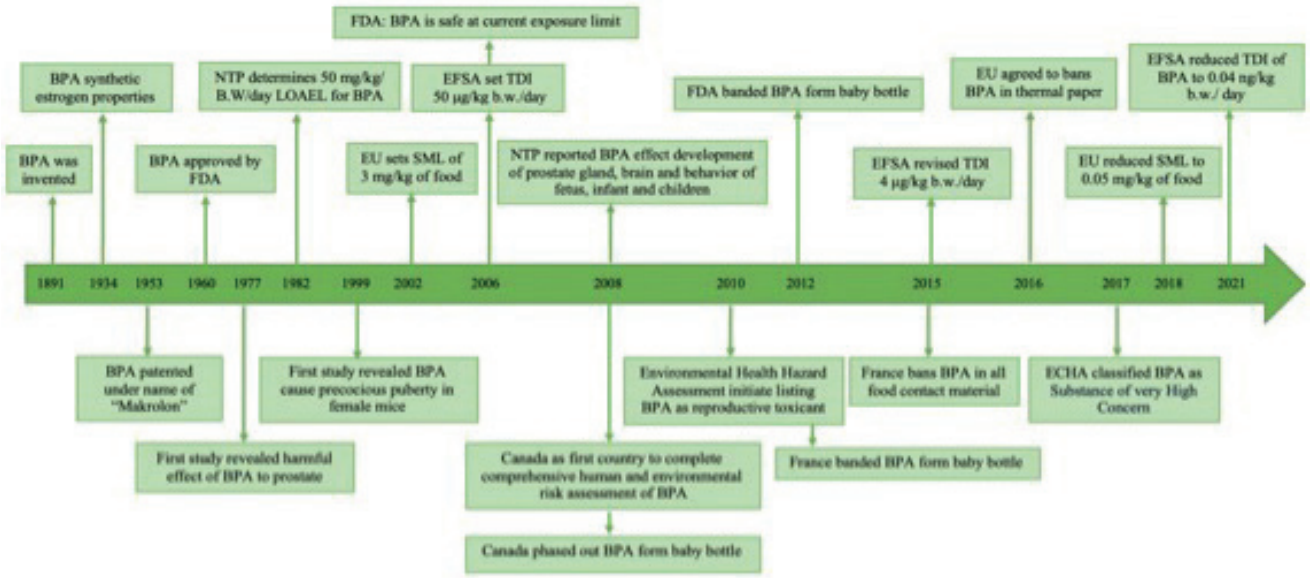

Figure 5: A timeline of the major scientific findings and limitations of BPA from invention to the present.
*NTP: national toxicology program, EU: European union, SML: specific migration limit, EFSA: European food safety authority, TDI: therapeutic daily intake, FDA: food and drug administration, ECHA: European chemicals agency

enough in terms of toxicity, but they are currently the only available alternatives to BPA. This work brings to light the need for further risk assessments, development of better alternatives, BPA free products and greater public awareness.

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