PRINT ISSN 1119-8362
Electronic ISSN 2659-1502

Full-text Available Online at
https://www.ajol.info/index.php/jasem
http://www.bioline.org.br/ja

J. Appl. Sci. Environ. Manage.
Vol. 27 (8) 1665-1671 August 2023

Multifaceted and Controversial Bisphenol: A (Review)

***ASENUGA, ER; ADEOYE, BO**

*[1]Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Benin, Nigeria
[2]Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Ibadan, Nigeria

*Corresponding Author Email: ebunoluwa.olowu@uniben.edu
Co-Author Email: Adeoyebisi2014@gmail.com

ABSTRACT: Bisphenol A (BPA) is commonly used for the manufacturing of plastic wares and epoxy resins, which both play vital roles in our daily life. The discovery of BPA has a tremendous beneficial effect, however, it has been discovered that BPA is a potent environmental endocrine disruptor to which persistent exposure has a negative impact on the metabolic, reproductive, and developmental processes which ultimately leads to diseases in humans and other organisms. Though, the numerous health issues associated with exposure to BPA are multifaceted and contentious. However, as humans rely heavily on plastics for day-to-day needs there are huge worries about the environmentally friendly nature of these plastics and the long-term consequence on human health. Exposure to BPA is a worldwide challenge and it has been detected in both the urine and serum of humans. The negative effects associated with exposure to BPA can be short-term or long-term. The focus is on scientists to do their research thoroughly to provide solutions and suggestions on how to prevent or minimize the life-threatening effect of BPA. The review aims to focus on the usage, incidence, and negative effects of BPA in humans and animals using available information within the last 10 years and to recommend steps to take toward minimizing exposure.

DOI: https://dx.doi.org/10.4314/jasem.v27i8.8

Cite this paper as: ASENUGA, E. R; ADEOYE, B. O. (2023). Multifaceted and Controversial Bisphenol-A (Review). *J. Appl. Sci. Environ. Manage.* 27 (8) 1665-1671

Dates: Received: 10 July 2023; Revised: 25 July 2023; Accepted: 14 August 2023 Published: 30 August 2023

Keywords: Bisphenol A; Endocrine Disruptors; Plastics; Epoxy resins; Environmental Pollutant.

Bisphenol A (BPA; 2,2-Bis-(4-hydroxyphenyl)-propane, $(CH3)2C(C6H4OH)_2$) is an organic compound which has been established as an endocrine disruptor with a chemical structure similar to the natural hormone estradiol (Gadamsetty *et al*., 2019). It is produced in high volume worldwide for the production of polycarbonate plastics, epoxy resins and other speciality chemicals (Gear and Scott, 2017). As a result of its high volume production and extensive usage, the likelihood of polluting the environment with BPA is quite high. The degradation of BPA-based product, sewage treatment effluent and landfill leachates are some of the routes through which BPA is being released into the environment and these leads to negative effects interfering with animal physiology and development (Messinetti *et al*., 2018). The consumption of monomeric BPA contaminants in groceries and drinks accounts for the majority of human contact, other routes of exposure include inhalation, diet, and dermal contact (Chung *et al*., 2017). Due to its excellent mechanical properties, the low adsorption of moisture, and the fact that synthetic polymers made from BPA have good thermal stability, several everyday consumer products contain BPA as part of the ingredients these include plastics, polyvinyl chloride, medical products, digital media (such as Compact Discs and Digital Versatile Discs), sunglasses, paper coatings, adhesives, flame retardants, thermal receipts, food and beverage packaging, dental sealants, electronics, water bottles and baby bottles, toys, water pipes (Chung *et al*., 2017; Abraham and Chakraborty, 2020; Siddique *et al*.,2020). BPA is easily degraded when assessed with other persistent environmental contaminants, therefore the widespread incidence of BPA can be correlated with the extensive use of products

containing BPA rather than its persistence in the environment (Zuccarello *et al*., 2018; Ramakrishna *et al*., 2022).

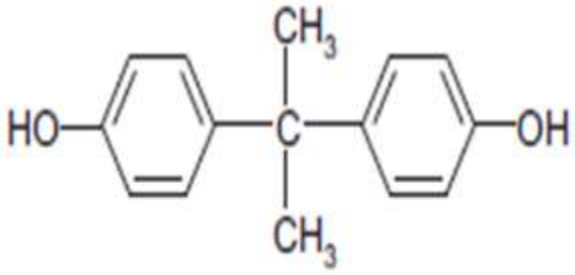

Fig 1. Chemical structure of bisphenol a (li *et al.,* 2015).

Several studies on BPA have led to the conclusion that it is an endocrine disruptor (EDC) (Corrales *et al*., 2015; Im and Loffler, 2016; Ma *et al*., 2019). EDCs are chemicals that imitate, modify, and impede endogenous hormonal actions (Salvaggio *et al*., 2019; Asenuga and Olagunju, 2023). Following the exposure of humans and animals to EDCs, there is an alteration in hormone concentrations, activities, or receptors which leads to disruption in structure and function within the body (Ullah, 2019; Asenuga and Olagunju, 2023). There is convincing evidence about the estrogen-mimicking activities of BPA and the ability of BPA to attach to the androgenic receptor, these activities will modify the physiological effects of estrogen and androgen within the body (Vijayalakshmi *et al*., 2018; Ullah, 2019).

Literature Search Procedure: This review was accomplished by searching relevant published research and review papers and books with other online materials. Around 200 journals were referred and 43 journals were cited after due consideration. The material used was primarily gathered from Google Scholar and PubMed searches of literature. For this study, we focus on papers published within 2013-2023 using search keywords such as bisphenol A, sources, environmental contaminant, endocrine disruptor and health impacts of BPA. Using the search keyword Bisphenol A provided the highest number of papers used for this review. The published papers were analysed manually and further sorted using the title, abstract and paper contents.

What Is BPA: BPA is a man-made compound containing carbon, oxygen and hydrogen, it is made up of two phenolic rings linked through a bridging carbon or other chemical structure, and it is a white crystalline solid substance that easily dissolves in organic solvent with a molecular weight of 228.29 g /cm3. It also has a melting point of 156 ◦C and a boiling point of 220 ◦C (Ma *et al*., 2019). BPA has been categorized as an endocrine-disrupting chemical in which early life exposure can have severe effects on fetal development (Ullah, 2019). The detection of BPA in food, soil, water (drinking, surface, and ground), municipal and industrial waste, sediment, indoor air, and dust may be attributed to the high volume produced yearly (Guergana *et al*., 2014; Chakraborty *et al*., 2019).

The production of BPA started in 1891 but its use wasn't rampant until 1930 when BPA was added to plastic to manufacture polycarbonate plastic (Ma *et al*., 2019; Ramakrishna *et al*., 2022). Research done in the late 1990s and early 2000s using animals showed that some diseases can be triggered following exposure to BPA, this led to the concerns raised by the Food and drug administration (FDA) about the safety of BPA in 2008 (Ramakrishna *et al*., 2022). Numerous health challenges such as alteration of the mammary gland and reproductive organ development, breast, nipple and prostate cancer, male and female infertility, precarious puberty in girls, and illness like diabetes and obesity are associated with exposure to BPA (Leung *et al.,* 2017; Ullah, 2019; Salvaggio *et al*., 2019; Ramakrishna *et al*., 2022).

Sources and Route of Exposure to BPA: Based on the environmental sources of BPA it can be categorized as a preconsumer and postconsumer products. Preconsumer sources include accidental and effluent release during the production, transportation and processing of BPA and BPA-containing products (Guergana *et al*., 2014; Hahladakis *et al*., 2018, Ma *et al*., 2019). While Postconsumer sources can be linked to BPA disposal or waste management and these include effluent release from community wastewater treatment plants (WWTP), leaching from landfills, burning of household waste, and biodegradation of plastics in the environment (Corrales *et al*., 2015; Ma *et al*., 2019; Abraham and Chakraborty, 2020).
There are several routes through which BPA can enter the body these include through the digestive tract, respiratory tract and dermal absorption, with the digestive tract route being the largest source of absorption (EFSA, 2015). Martinez *et al.,* (2018) estimated that 0.048–0.050 µg/kg bw/day for 3–17 year children and adolescents, from 0.034 to 0.035 µg/kg bw/day for adults and from 0.047 to 0.049 µg/kg bw/day for pregnant women are the mean dietary intake of BPA. In widespread populations, the dietary route can be said to be the main route of BPA exposure when compared to the non-dietary route (Ma *et al*., 2019). Several scientific papers have documented that the principal route through which human digestive tracts become exposed to BPA is via continuous consumption of canned food (Corrales *et al*., 2015; Siddique *et al*., 2020). The heating process involved

with the sterilization, microwaving and the acidic nature of foods stored in packages containing BPA determines the rate of leaching of BPA into the food and contaminating it (Michałowicz, 2014; Abraham and Chakraborty, 2020).

Transdermal absorption and inhalation of dust with BPA can be regarded as a secondary route of exposure in humans (Michałowicz, 2014; Li and Suh, 2019). The volatility of BPA is very low but it is capable of sticking to particulate matter such as dust, dirt, soot or smoke (Graziani *et al*., 2019). The fact that epoxy resins containing BPA can resist heat, electricity and chemical, makes them vital for electronic production and this exposes humans to inhalation of indoor dust containing BPA ((Michałowicz, 2014). In addition, some medical devices also contain BPA such as incubators and kidney dialysis machines products, this might be responsible for the presence of BPA in patients undergoing dialysis treatment and in newborn intensive care units (Ivana *et al*., 2018; Abraham and Chakraborty, 2020).

Detection: The presence of BPA has also been detected in the abiotic environment such as in the air, water, soil, sediment, food and biota like human beings, wildlife, and aquatic organisms in variable concentrations (Michałowicz, 2014; Abraham and Chakraborty, 2020). Also, the presence of BPA in several body fluids including the blood, urine, breast milk and tissues is a fact (Pinney *et al*., 2017; Abraham and Chakraborty, 2020). BPA is poorly soluble in water and is therefore most effectively detected in urine. Therefore, urine is the sample of choice for evaluating BPA exposure irrespective of its source (Siddique *et al*., 2020). The quantification of nanogram (ng) or picogram (pg) levels of BPA in the environment, food and body fluids have been done using several analytical procedures and instruments, the instrument includes high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS), solid phase microextraction (SPME)-gas chromatography-mass spectrometry (SPME-GC-MS), with SPME-GC-MS being a faster and highly sensitive method for analysing BPA (Ghazali and Johari, 2015; Abraham and Chakraborty, 2020).

*Possible Mechanism of Action of BPA in the Body***:** BPA is structurally similar to endogenous 17β-oestradiols, the exact mechanisms through which BPA elicit its action at the cellular level are not completely understood (Farrugia *et al*., 2021). However, one possible mechanism of action of BPA is it is binding to estrogen receptors (ERs) to elicit its estrogenic and antagonistic activity on ERs due to its similarity in structure to estradiol though BPA has a low binding affinity for ERα and ERβ (Yang *et al*., 2017; Abraham and Chakraborty, 2020). The role of ERs in the human body cannot be underestimated, they play vital roles for both genomic and non-genomic signal transduction (Guergana *et al*., 2014). Genomic signal transduction is essential for gene expression while the modification of regulatory proteins is attributed to non-genomic signal transduction (Guergana *et al*., 2014). Mechanisms independent of the ERs have also been implicated with the effect of BPA. BPA at a lower concentration can bind and activate numerous other targets inside the nucleus and on the cell membrane (Canesi and Fabbri, 2015; Ma *et al*., 2019). One such mechanism includes acting as an androgen antagonist. Another mechanism is the antagonist or agonist effect of BPA on thyroid hormones which will eventually leads to the disruption of the thyroid system, this is due to the structural similarities between BPA and thyroid hormone (Canesi and Fabbri, 2015; Ramakrishna *et al*., 2022). In addition, the roles of orphan nuclear estrogen-related receptor y (ERRy) in mediating the estrogenic activity of BPA are also established (Tohm´e *et al*., 2014). Moreso, BPA is capable of activating several genes that can modulate female cancers such as PI3K/AKT, STAT3 and MAPK (Ramakrishna *et al*., 2022).

Metabolism: In humans and other primates, the metabolism of BPA takes place in the liver where it is been conjugated with glucuronide to form bisphenol A-glucuronide, which is a highly soluble metabolite eliminated rapidly through the urine. The glucuronidation process is catalysed by UDP-glucuronosyltransferase (UGT) which has several isoforms in different species and the genetic polymorphism of this enzyme influences the toxicity of the metabolites produced after BPA metabolism (Siddique *et al*., 2020). There are suggestions that since no hormonal activity can be found in bisphenol A-glucuronide, the metabolism of BPA ingested through the oral route might neutralize the estrogenic activity of BPA with only little unconjugated BPA to bind to estrogen receptors (ERs) (Guergana *et al*., 2014). However, the production of xenoestrogen compounds which can be more potent than BPA has been observed following the metabolism of BPA in medaka, O. latipes (Canesi and Fabbri, 2015). In addition, repeated enterohepatic recirculation has been observed in rodents which can be attributed to slow elimination of BPA by rodents and placed them at the risk of longer exposure to unbound BPA before elimination (Farrugia *et al*., 2021). In fish, the use of the liver to metabolize BPA is not as efficient compared to other animal species because the main

route of exposure is through inhalation with the gills resulting in a more marked estrogenic effect of BPA in fish and related specie (Salvaggio *et al*., 2019). Appropriate precautions should also be taken when extrapolating result from scientific research using animal studies because there is wide variation in metabolic kinetics concerning route of administration, dose, sex and also age (Siddique *et al*., 2020; Farrugia *et al*., 2021).

Effect of BPA on the Body: The endocrine-disrupting activity of BPA can result in profound health effects in humans and animals even at very low concentrations (Abraham and Chakraborty, 2020). In Vertebrate, the teratogenic effect of BPA has been observed at high concentration (1-10 mg/L range) while low concentration (within the mg/L range) is associated with endocrine and pleiotropic effects (Canesi and Fabbri, 2015). Previous findings suggest that exposure to BPA during early pregnancy can result in fetoplacental and uterine growth restriction (Geetharathan *et al*., 2016). In the US, Pre and postnatal exposure to BPA can lead to nervousness, depression, rule-breaking and aggressive behaviour, as well as hyperactivity in children, these behavioural problems are more pronounced in females than in males (Staples *et al*., 2018; Ramakrishna *et al*., 2022).

The dramatic increase in human obesity and other metabolic disorder is alarming over the past decades and this has been attributed to exposure to diverse chemicals including BPA, it has been established in some studies that BPA has obesogenic effects (Siddique *et al*., 2020; Ramakrishna *et al*., 2022). This obesity is associated with the activation of some nuclear transcription factors at the molecular level such as peroxisome proliferator-activated receptor (PPAR alpha, delta, gamma) and some steroid hormone receptors that are involved in controlling the proliferation of the adipocytes and also regulating their differentiation. This alters lipid metabolism and eventually affects the composition of our body (Ramakrishna *et al*., 2022). Skin allergies and irritation have been documented in some workers in industries dealing with BPA or its products (Abraham and Chakraborty, 2020).

The concentrations of BPA found in the environment are capable of inducing oxidative stress and inflammatory genes such as Tumour necrosis factor (TNF-α), Interleukin (IL-6) and 1β in the body (Ferguson *et al*., 2016; Cho *et al*., 2018). Oxidative stress is the imbalance between the endogenous and exogenous generation of reactive oxygen species (ROS, free radicals) and the amount of antioxidants in the body (Ilaria *et al*., 2017). Unconjugated BPA in the body can enzymatically or non-enzymatically stimulate the generation of phenoxy radicals which then react with NADPH or intracellular glutathione (GSH), leading to ROS formation (Ivana *et al*., 2018) which harms the human and animal body. The genotoxic effects attributed to BPA have been known to cause meiotic arrest, induce meiotic aneuploidy and chromosome aberrations, and prevent meiotic double-strand breaks (DSBs) repair (Klara *et al*., 2019). BPA affects hormone concentrations and the male reproductive system in rodents and humans (Oliveira *et al*., 2017; Ullah, 2019). Gadamsetty *et al*., 2019 also documented the ability of BPA to damage the nephrons, this will eventually affect the renal capacity leading to reduced renal efficiency in rats and this has also been observed in humans (Ramakrishna *et al*., 2022). Inhalation of BPA through the gills is the principal route of exposure in fish and not the diet. The estrogenic effect of BPA in fish is more pronounced as a result of inefficient metabolism via the inhalation route when compared with the liver (Canesi and Fabbri, 2015). Some of the pleiotropic effects observed in fish exposed to BPA include abnormal sex ratios with more female fish seen, reduced tail length, increased production of vitellogenin in males or sexually immature females, reduced circulating levels of testosterone, decreased expression of genes associated with oocyte growth, cholesterol uptake, and several matrix metalloproteinases that are essential for ovulation, reduced hatching success rate, increased expression of gene related to steroid biosynthesis, and high prevalence of intersexuality (Canesi and Fabbri, 2015; Akram *et al*., 2020).

Environmental Impact and Bioaccumulation: The natural occurrence of BPA does not exist, the widespread existence of BPA can be attributed to its high demand in the manufacturing industry necessitating its high production (Corrales *et al*., 2015; Ramakrishna *et al*., 2022). Currently, the lowest-observable-adverse-effect level (LOAEL) of BPA is 50 mg/kg body weight per day, though recently in response to the advanced safety evaluation of BPA and its undesirable health effects, the European Food Safety Authority (EFSA) reduced the tolerable daily intake (TDI) to 4 μg/kg bw/day (EFSA, 2015; Siddique *et al*., 2021). The transmission of the aberrant effects of BPA in aquatic animals to humans through biomagnification is also been considered (Ramakrishna *et al*., 2022). Due to the low octanol-water partition coefficient (log Kow = 3.64) and bioconcentration factor (BCF = 196), the bioaccumulating potential of BPA is low (Abraham and Chakraborty, 2020). However, it is trapped in the soil due to the high value of the soil-water partition coefficient of 314 to 1524. However, the biodegradation of BPA in oxygen-abundant soil

conditions helps to mitigate the bioaccumulating potential in the soil (Ramakrishna *et al*., 2022).

Conclusion: The widespread use of products containing BPA infers that basically, everyone comes into contact with the BPA one way or the other. BPA is an established endocrine disruptor to which exposure in humans and animals should be reduced to the barest minimum. Generally, there are convincing facts that BPA alters physiological homeostasis in humans and animals leading to various disease conditions. The possibility of using plants and microorganisms to transform BPA into compounds with lower toxicity and estrogenicity should be explored.

REFERENCE

Abraham, A; Chakraborty, P (2020). A review on sources and health impacts of bisphenol A. *Rev Environ Health.* 35(2): 201-210.

Akram, R; Iqba, R; Hussain, R (2020). Evaluation of Oxidative stress, antioxidant enzymes and genotoxic potential of bisphenol A in fresh water bighead carp (Aristichthys nobils) fish at low concentrations. *Environ. Pollut.* 1; 268(Pt A):115896.

Asenuga, ER; Olagunju, AS (2023). Exposure and Associated Health Risk of Endocrine Disruption compounds. *AJHSE*. 4(1): 57-66.

Canesi, L; Fabbri, E (2015). Environmental Effects of BPA: Focus on Aquatic Species. *Dose-Response.* 13(3): 1-14.

Chakraborty, P; Sampath, S; Mukhopadhyay, M (2019). Baseline investigation on platicizers, bisphenol A, polycyclic aromatic hydrocarbons and heavy metals in the surface soil of the informal electronic waste recycling workshops and nearby open dumpsites in Indian metropolitan cities. *Environ Pollut.* 248: 1036–1045.

Cho, YJ; Seung, BP; Jung, WP; So, RO; Myoungseok, H (2018). Bisphenol A modulates inflammation and proliferation pathway in human endometrial stromal cells by inducing oxidative stress. *Reprod. Toxicol.* 81: 41–49.

Chung, YH; Han, JH; Lee, SB; Lee, YH (2017). Inhalation Toxicity of Bisphenol A and Its Effect on Estrous Cycle, Spatial Learning, and Memory in Rats upon Whole-Body Exposure. *Toxicol Res.* 33(2):165-171.

Corrales, J; Kristofco, LA; Steele, WB; Yates, BS; Breed, CS; Williams, ES; Brooks, BW (2015). Global assessment of bisphenol A in the environment: review and analysis of its occurrence and bioaccumulation. *Dose-Response.* 13(3): 1559325815598308.

EFSA Panel on Food Contact Materials & Aids (2015). Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. Pp 13

Farrugia, F; Aquilina, A; Vassallo, J; Pace, NP (2021). Bisphenol A and Type 2 Diabetes Mellitus: A Review of Epidemiologic, Functional, and Early Life Factors. *Int. J. Environ. Res. Public Health.* 18: 716.

Ferguson, KK; Meeker, JD; Cantonwine, DE; Chen, YH; Mukherjee, B; McElrath, TF (2016). Urinary phthalate metabolite and bisphenol A associations with ultrasound and delivery indices of fetal growth. *Environ Int.* 94: 531-537.

Gadamsetty, J; Alekhya, S; Motati G; Gadiparthi, S; Murali, K; Kokkiligadda, RS; Mounika, S; Kandru, N; Mukkamulla, N; Gopala, KC; Anurag, M; Nagaraja, S (2019). Protective Role of Luteolin Against Bisphenol A-Induced Renal Toxicity Through Suppressing Oxidative Stress, Inflammation, and Upregulating Nrf2/ARE/HO-1 Pathway. *IUBMB life*. 71(7): 1041–1047.

Gear, RB; Scott, MB (2017). Impacts of Bisphenol A and Ethinyl Estradiol on Male and Female CD-1 Mouse Spleen. *Sci Rep.* 7(1): 856

Geetharathan, T; Josthna, P (2016). Effect of BPA on Protein, Lipid Profile and Immuno-Histo Chemical Changes in Placenta and Uterine Tissues of Albino Rat. *Int. J. Pharm. Clin. Res.* 8(4): 260-268.

Ghazali, FM; Johari, WL (2015). The occurrence and analysis of bisphenol A (BPA) in environmental samples – a review. *J Biochem Microbiol Biotechnol.* 3(2): 30–38.

Graziani, NS; Carreras, H; Wannaz, E (2019). Atmospheric levels of BPA associated with particulate matter in an urban environment. *Heliyon*. 5(4): 01419.

Guergana, M; Stephanie, LB; Anne, TM; Catherine, B (2014). Review Bisphenol-A: Epigenetic Reprogramming and Effects on Reproduction and Behavior. *IJERPH.* 11: 7537-7561.

Hahladakis, JN; Velis, CA; Weber, R; Iacovidou, E; Purnell, P (2018). An overview of chemical additives present in plastics: migration, release, fate and environmental impact during their use, disposal and recycling. *J. Hazard Mater.* 344: 179–199.

Ilaria, M; Fabio, A; Ilaria P (2017). Review Article. Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans. *Oxid Med Cell Longev*. 2017: 6501046

Im, J; Loffler, FE (2016). Fate of bisphenol A in terrestrial and aquatic environments. *Environ Sci Technol.* 50: 8403–8416.

Ivana, D; Jana, S; Marek, P; Eliska, G; Andrea, S (2018). Bisphenol A as an environmental pollutant with dual genotoxic and DNA-protective effects. *Neuro endocrinol. Lett.* 39(4): 294–298.

Klara, H; Sara, M; Metka F; Marija, S; Lidija, K; Bojana, Ž (2019). Genotoxic activity of bisphenol A and its analogues bisphenol S, bisphenol F and bisphenol AF and their mixtures in human hepatocellular carcinoma (HepG2) cells. *Sci. Total Environ.* 687: 267–276.

Leung, YK; Govindarajah, V; Cheong, A; Veevers, J; Song, D; Gear, R (2017). Gestational high-fat diet and bisphenol A exposure heightens mammary cancer risk. *Endocr. Relat. Cancer.* 24 (7): 365–378.

Li, D; Suh, S (2019). Health risks of chemicals in consumer products : a review. *Environ Int.* 123: 580–587.

Li, L; Wang, Q; Zhang Y; Niu, Y; Yao, X; Liu, H (2015). The Molecular Mechanism of Bisphenol A (BPA) as an Endocrine Disruptor by Interacting with Nuclear Receptors: Insights from Molecular Dynamics (MD) Simulations. *PLoS ONE.* 10(3): 0120330.

Ma, Y; Liu, H; Wu, J; Yuan, L., Wang, Y., Du, X. (2019). The adverse health effects of bisphenol A and related toxicity mechanisms. *Environ. Res.* 176: 108575.

Martinez, MA; Rovira, J; Prasad, S; Nadal, M; Schuhmacher, M; Kumarm V (2018). Comparing dietary and non-dietary source contribution of BPA and DEHP to prenatal exposure: A Catalonia (Spain) case study. *Environ. Res.* 166: 25–34.

Messinetti, S; Mercurio, S; Pennati, R (2018). Bisphenol A affects neural development of the ascidian Ciona robusta. *J Exp Zool A Ecol Integr Physiol*. 331(1): 5-16.

Michałowicz, J (2014). Bisphenol A – Sources, toxicity and biotransformation. *Environ. Toxicol. pharmacol.* 37: 738–758.

Oliveira, IM; Romano, RM; de Campos, P; Cavallin, MD; Oliveira, CA; Romano, MA (2017). Delayed onset of puberty in male offspring from bisphenol A-treated dams is followed by the modulation of gene expression in the hypothalamic–pituitary–testis axis in adulthood. *Reprod. Fertil. Dev.* 29: 2496–25.

Pinney, SE; Mesaros, C.A; Snyder, NW; Busch, CM; Xiao, R; Aijaz, S (2017). Second trimester amniotic fluid bisphenol A concentration is associated with decreased birth weight in term infants. *Reprod. Toxicol.* 67: 1–9.

Ramakrishna, MG; Agnishwar, G; Swati C; Koyeli; G (2022). Bisphenol A-an Overview on its Effect on Health and Environment. *Biointerface research in applied chemistry.* 12(1): 105-119.

Salvaggio, A; Tiralongo, F; Krasakopoulou, E; Marmara, D; Giovos, I; Crupi, R; Messina, G; Lombardo, BM; Marzullo ,A; Pecoraro, R; Scalisi, EM; Copat, C; Zuccarello, P; Ferrante, M; Brundo, MV (2019). Biomarkers of Exposure to Chemical Contamination in the Commercial Fish Species. *Toxicol. Res*. 33(2): 165-17

Siddique, S; Gong, Z; Cariton, K (2020). Exposure to bisphenol A and risk of developing type 2 diabetes: A mini review. *Emerging Contaminants.* 6: 274-282

Siddique, MA; Harrison, SM; Monahan, FJ; Cummins, E; Brunton, NP (2021). Bisphenol A and metabolites in meat and meat products: occurrence, toxicity, and recent development in analytical methods. *Foods*. 10: 714

Staples, C; van der Hoeven, N; Clark, K; Mihaich, E; Woelz, J; Hentges, S (2018). Distributions of concentrations of bisphenol A in North American and European surface waters and sediments determined from 19 years of monitoring data. *Chemosphere.* 201: 448–458

Tohm´e, M; Prud'homme, SM; Boulahtouf, A; Samarut, E; Brunet, F; Bernard, L; Bourguet, W; Gibert, Y; Balaguer, P; Laudet, V (2014). Estrogen-related receptor g is an in vivo receptor of bisphenol A. *FASEB J.* 28: 3124-3133.

Ullah, A; Pirzada, M; Jasan, S; Ullah, H; Turi, N; Ullah, W; Siddiqui, MF; Zakria, M; Lodhi, KZ; Kham, MM (2019). Impact of low-dose chronic exposure to bisphenol A and its analogue bisphenol B, bisphenol F and bisphenol S on hypothalamo-pituitary-testicular activities in adult rats: a focus on the possible hormonal mode of action. *Food Chem. Toxicol.* 121: 24-36.

Vijayalakshmi, V; Senthilkumar, P; Mophin-Kani, K; Sivamani, S; Sivarajasekar, N; Vasantharaj, S (2018). Bio-degradation of Bisphenol A by Pseudomonas aeruginosa PAb1 isolated from effluent of thermal paper industry: Kinetic modeling and process optimization. *J. Radiat. Res. Appl. Sci.* 11: 56-65.

Yang, Q; Yang, X; Liu J; Ren, W; Chen, Y; Shen, S (2017). Exposure to bisphenol B disrupts steroid hormone homeostasis and gene expression in the hypothalamic–pituitary–gonadal axis of zebrafish. *Water, Air, Soil Pollut.* 228: 112.

Zuccarello, P; Oliveri, CG; Cavallaro, F; Copat, C; Cristaldi, A; Fiore, M (2018). Implication of dietary phthalates in breast cancer. A systematic review. *Food Chem. Toxicol*. 118: 667–674.