International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 02(E); February 2019; Page No.17454-17458
DOI: http://dx.doi.org/10.24327/ijcar.2019.17458.3311

Research Article

INVISIBLES IN PLASTIC - A THREAT TO HUMAN HEALTH

Sonia Garg*, Naveenta Gupta, Meenal Batta, Shilekh Mittal and Kushdeep Arora

[1,2] Physiology, GGS Medical College, Faridkot, India
[3]Forensic Medicine, GGS Medical College, Faridkot, India
[4]Physiology, Dasmesh Dental Institute of Medical sciences and Research, Faridkot, India

A R T I C L E I N F O

Article History:
Received 6th November, 2018
Received in revised form 15th December, 2018
Accepted 12th January, 2019
Published online 28th February, 2019

Key words:
Plastics, Bisphenol A, Adverse Effects, Human Health.

A B S T R A C T

Just look around and you will find so many plastic items around you. Plastic has become a very important fixture in our everyday lives. Their beneficial impact on society is undeniable and can be best demonstrated by their medical uses and applications in public health. So slowly we are entering the "Age of Plastics." Everybody is being exposed to plastics to varying extents and are responsible for potentially dangerous human exposure to toxic chemicals released by them such as bisphenol A (BPA) and phthalates (DEHP) which are now finding their way into our body and the environment.We knew that this plastic is coming back to us through our food chain. So we are not only using, but we are eating, drinking and even breathing the plastics. The adverse effects of BPA on human health are widely disputed and has been recently associated with a wide variety of medical disorders. So here we will try to find

- Whether the rising prevalence of diabetes, thyroid disorders, infertility, cardiovascular diseases (CVD), obesity, breast carcinoma etc. are related to the plastics ?
- Do we have a possible way out?

INTRODUCTION

Every year approximately 100 million tons of plastics are produced and today, more than 20 different types of plastics are in use worldwide [APME,2006]. BPA is one of the highest production and consumption volume chemicals in the world [Sriphrapradang *et al*.,2013]. In medicine alone, the diversity of plastics' uses is incredible. Prosthetics, engineered tissues, and microneedle patches for drug delivery are all possible with polymers [Vert,2011;Prausnitz,2004]. In many sectors of society, plastics have replaced glass, wood, fibers, and m *et al* in various products, including dishware, clothing, food packaging [Andrady and Neal,2009]. Disposable products such as canned food, polycarbonate-bottled liquids have been a major application for plastics within the last century because plastics are inexpensive, easy to produce, lightweight and biocompatible [Holmgren,1974]. Associations were found between exposure to these compounds and destructive effects on health and reproduction. Studies from different countries and areas have demonstrated the presence of urinary BPA in more than 90% of their study populations, suggesting a common exposure to BPA worldwide [Wang *et al*.,2013;Wang *et al*.,2014;Calafat, 2008]. Exposure to BPA is prevalent among children and adolescents [Wang *et al*.,2014], who may be more sensitive to its adverse effects including the effect on thyroid function. The higher urinary BPA concentrations were found to be associated with obesity, diabetes, hypertension,[Shankar and Teppala,2012; Rancière *et al*.,2015] and coronary artery disease[Melzer *et al*.,2010] in adults[Shankar and Teppala,2012] and obesity, in children and adolescents.[Ejaredar *et al*.,2017] increased BPA exposure during pregnancy was linked to anxiety,depression, aggression, and hyperactivity in children[Trasande *et al*.,2012] autism spectrum disorder or attention deficit disorder in humans.[Stein *et al*.,2015]and also linked to fertility problems, breast cancer, and prostate cancer.[Diamanti *et al*., 2009] Thus, exposure to BPA seems to be an important risk factor with catastrophic biological consequences.

Influence of Bisphenol A on Type 2 Diabetes Mellitus

BPA has recently come under intense scrutiny as a potential endocrine disrupting compound with diabetogenic effects. Using NHANES data, Lang *et al*.,2008 analyzed the relationship between urinary BPA and diabetes and found higher levels of BPA in urine with a self-reported diagnosis of diabetes showing a significant positive association. Melzer *et al*., 2010 subsequently analyzed data from the NHANES and also found a significant association between the two.

Shankar and Teppala, 2011 collected samples from adult NHANES participants between 2003–2008. which were then diagnosed according to the American Diabetes Association

Corresponding author:* **Sonia Garg
Physiology, GGS Medical College, Faridkot, India

standards of fasting blood glucose and hemoglobin A1c levels. This study also found a positive correlation between the diagnosis of diabetes and increased urinary BPA levels .Similar findings were found by Silver *et al*.,2011 who also analyzed pooled data from the 2003–04, 2005–06, 2007–08 NHANES reporting periods. In this study, diabetes was diagnosed when hemoglobin A1c levels ≥ 6.5%. Wang *et al*.,2012 also found associations between urinary BPA and obesity and insulin resistance in a group of adults aged 40 years and above in China. BPA, mostly at low doses, may have a role in increasing type 2 diabetes mellitus developmental risk, directly acting on pancreatic cells, in which BPA induces the impairment of insulin and glucagon secretion, triggers inhibition of cell growth and apoptosis, and acts on muscle, hepatic, and adipose cell function, triggering an insulin-resistant state. Bisphenol-A (BPA) is a widespread endocrine disruptor that produces insulin resistance by alterations in pancreatic beta-cell function. A recent work shows the association between increasing urinary BPA levels and diabetes mellitus. A 12.8% of diabetic patients show high BPA levels in urine samples (4.20 ng/ml or 18 nM)[Nadal *et al*.,2009].

Association Between Urine Bpa Levels and Obesity

The emerging worldwide obesity epidemic has been linked to increased exposures to environmental endocrine disruptors, collectively called "environmental obesogens" [Newbold *et al*.,2008;Wang and Lobstein,2006;Newbold *et al*.,2007;Heindel, 2003;Heindel and vom Saal,2009]. One such important potential obesogen is bisphenol-A (BPA). Humans are widely exposed to BPA and animal studies have linked BPA to obesity [Rubin, 2011;Rubin and Soto, 2009;Rubin *et al*.2001;Somm *et al*.,2009;Newbold,2010; Golub *et al*.,2010].Exposure to BPA has been shown to suppress the release of adiponectin [Hugo *et al*.,2008; Ben-Jonathan *et al*.,2009;Kidani *et al*.,2012], an adipocyte-specific hormone that increases insulin sensitivity. Thus BPA exposure could lead to increased insulin resistance and increased susceptibility to obesity and metabolic syndromes. BPA was shown to be a more effective adiponectin suppressor than estradiol, at a low environmental exposure level (0.1 nM) [Hugo *et al*.,2008]. Many studies have reported an association between urine BPA level and obesity in *adult* populations (>18 years of age) [Carwile and Michels, 2011; Wang *et al*.,2012]and also among children and adolescents [Trasande *et al*.,2012] using U.S. NHANES data. Recent evidence mostly from animal studies has suggested that BPA exposure may be related to increased insulin resistance [Alonso *et al*.,2006] and therefore may have a role in weight gain and the development of obesity [Rubin *et al*.2001;Somm *et al*.,2009]. Also, BPA exposure has been shown to be associated with high lipid levels [Wada *et al*.,2007] and increased levels of serum markers of oxidative stress [Bindhumol *et al*.,2003] and inflammation [Ben-Jonathan *et al*.,2009] all of which are mechanisms that have been implicated in the development of obesity. Hence justifying the role of environmental exposure to BPA in the development of obesity. Elevated levels of urinary BPA are associated with measures of obesity independent of traditional risk factors. This association is consistently present across gender and race-ethnic groups.

Exposure to Bpa and Thyroid Disorders

There have been studies showing that BPA acts as a thyroid receptor antagonist [Zoeller *et al*., 2005] and can increase serum free T4 [Zoeller *et al*.,2013]. It is well established that estrogen enhances autoimmunity; BPA, by acting as a xenoestrogen, can influence autoimmunity similarly to estrogen [Yoshino *et al*.,2004]. BPA can affect autoimmunity both directly and indirectly [Kharrazian, 2014].

BPA was independently associated with markedly raised TPO antibodies, leading to

Hypothyroidism [Diamanti *et al*.,2009]in both men and women. The finding may suggest a role of BPA exposure in autoimmune thyroid disease such as Hashimoto's thyroiditis. The three most important antigens in autoimmune thyroid disease are thyroglobulin, thyroid peroxidase and TSH receptor [Chailurkit *et al*.,2016]. Recent epidemiological studies have suggested that Bisphenol A (BPA) disrupts thyroid function in adults [Meeker and Ferguson,2011; Meeker *et al*.,2010]. BPA can disturb thyroid hormone action by reducing T_3 binding to the nuclear TRs and recruited nuclear receptor corepressors (N-CoRs) to the TR, resulting in transcriptional inhibition [Moriyama *et al*.,2002].Another study also found a possible association of urinary BPA with thyroid health indicators such as in patients of hypothyroidism, low fT4 or high TSH levels along with increase BPA levels were seen [Andrianou *et al*.,2016].

Bpa Exposure and Breast Carcinoma

Breast cancer is a world-wide leading cancer of women. In addition, there are large geographical differences in incidence rates of breast cancer [Parkin *et al*.,2005; Stewart,2003]. Along with other endocrine disrupting chemicals (EDCs), bisphenol A (BPA) has been suspected as a potential risk factor for breast cancer.

BPA exposure may disrupt normal breast development and has been linked to early puberty in girls that predispose women for later life breast cancer [Yang *et al*.,2009]. BPA acts as a mammary gland carcinogen. It induces various neoplastic lesions and leads to the development of malignant tumors in mammary glands[Wang *et al*.,2017]. BPA, having estrogenic activity, interact with estrogen receptors α and β, leading to changes in cell proliferation, apoptosis, or migration and thereby, contributing to cancer development and progression. At the genetic level, BPA has been shown to be involved in multiple pathways, such as the STAT3, MAPK, and PI3K/AKT pathways [Gao *et al*.,2015]. Hence accounts for its role in accelerating carcinogenesis of breast cancer. The most recent study also showed the effect of low-dose BPA on the early differentiation of human embryonic stem cells into mammary epithelial cells [Yang *et al*.,2013].

Exposure to Bpa Leading to Infertility

Impact of BPA exposure has increased the percentage of infertile women upto 30% worldwide [Inhorn and Patrizio, 2013]. BPA can widely impact the female fertility through multiple pathways. BPA mimics the reproductive hormone 'estrogen', hence interfering with endocrine function of hypothalamic-pituitary- ovarian axis, such as by changing gonadotropin-releasing hormones (GnRH) secretion in hypothalamus and promoting pituitary proliferation. Such actions affect puberty, ovulation and may even result in

infertility[Huo *et al*.,2015]. Specifically, BPA may alter overall female reproductive capacity by affecting the morphology and function of the oviduct, uterus, ovary in different times of life cycle[Ziv-Gal and Flaws,2016]. Also, BPA may disrupt estrous cycle and process of implantation and plays a major role in impaired women health including endometrial hyperplasia, recurrent miscarriages, sterility, and polycystic ovarian syndrome [Warner *et al*., 2002; Rayner *et al*., 2004; Eskenazi *et al*., 2007].

Experimental evidences demonstrate that BPA affects reproduction-related gene expression closely related with infertility. The effects on reproduction may last lifelong and pass to other generations too [Ziv-Gal and Flaws,2016]. Evidences from previous publications suggest that BPA is a reproductive toxicant [Peretz *et al*., 2014; Vandenberg *et al*.,2013;Maffini *et al*.,2006]. With the potential to affect the fertility in men and women, health care providers should counsel patients to reduce exposure to BPA for those seeking infertility treatment [Cantonwine *et al*., 2013].

Impact of Bisphenol A on Cardiovascular System

Cardiovascular(CV) disease is a significant health problem worldwide and one of the major contributors to mortality and morbidity. Several epidemiological studies indicate that BPA exposure in adult populations is associated with increased risk for CV diseases, including coronary artery heart disease, angina, heart attack, hypertension, and peripheral artery disease [Gao and Wang,2014].

Lang *et al*.,2008 first reported an association between higher urinary BPA level and cardiovascular diseases based on the 2003–2004 NHANES data. It was found that mean urinary BPA levels adjusted for age and sex were higher in persons who were diagnosed with CVD and have statistically significant association. In 2012, Melzer *et al.* analyzed a longitudinal study and assessed the effects of BPAs on the development of coronary artery disease. He also demonstrated the higher urinary BPA concentrations in patients of coronary artery disease and hypertension The positive association was also found between urinary BPA levels and heart rate variability (HRV) in elderly populations of Korea [Bae *et al*.,2012] and results are consistent with the study by Shankar and Teppala, 2012], who also reported a positive association between higher urinary BPA concentrations and HRV as well as high blood pressure.

Experimental studies suggest that low dose BPA exposure could affect the physiological functioning of CVS and leads to abnormalities such as arrhythmias, atherosclerosis, and altered blood pressure. The underlying molecular mechanisms may involve alteration of cardiac Ca^{2+} handling by affecting the phosphorylation of proteins and also change in transcription [Melzer *et al*.,2012]. Recent findings also found another molecular mechanism linking BPA exposure to increased risk of CVD in exposed individuals. BPA by acting as agonist of human pregnane X receptor, activates it which shows pro-atherogenic effects upon activation [Sui *et al*.,2018]. Hence justifying that environmental exposure to BPA is a contributing risk factor for CVD and hypertension [Han *et al*.,2016].

THE ROAD AHEAD: What Can Be Done Now to Restrict Plastic Usage to Sustainable Levels?

It is better late than never. Here are a few general rules of thumb.The best way to avoid BPA is to minimize plastic use. Using glass or stainless steel cookwares are convenient and safe alternatives. Avoid the plastics marked with recycle codes 3 or 7 as they are more likely to contain BPA[Srivastava and Godara ,2013]. Also, avoid placing plastic containers into a microwave or storing in areas of extreme heat (e.g. inside a car), as this can increase the amount of BPA that leaches into food stored in the container. Since plastic is found widely in processed food packaging including canned foods and beverages, which typically have a plastic lining, modifying your diet to include primarily fresh, whole foods will have the added benefit of helping you cut down on exposure to plastic chemicals. You can't really shop your way out of the problem, and it's unfair to put all that responsibility on consumers. The change needs to happen at the policy level.

Answerable Organizations and Rules for Reducing Plastic Toxicity

Toxicity of plastic is a global concern. The government, law implementing agencies and health authorities of the country should take more steps and pay attention to sustainable production, use, and disposal of plastics. Hospitals may also help prevent exposures among vulnerable populations such as in neonatal intensive care units (NICU) by limiting the usage of BPA containing devices and supplies. Every company must take their responsibility in terms of the reduction of unnecessary plastic consumption. It should be mandatory for the manufacturers to label plastic codes in the triangle recycling labels or imprints on plastic containers. A full information about all existing chemicals in consumer products must be required so that people becomes aware to use of those products. The public should be made aware of hazards of BPA exposure to mankind.

CONCLUSIONS

Time to pull our heads from the sand. However, while humanity has realized its benefits, it has yet to realize the cost! Greener solutions, however, are becoming available. "BPA free" consumer goods are becoming more commonly available and replacing foods that come in plastic packages and cans with fresh alternatives may reduce exposure by more than 50%. So it can be concluded that application of proper rules and regulations for the production and use of plastics can reduce toxic effects of plastics on human health and environment.

Bibliography

Alonso-Magdalena, P., Morimoto, S., Ripoll, C., Fuentes, E.and Nadal, A.2006. The estrogenic effect of bisphenol a disrupts pancreatic *β*-cell function in vivo and induces insulin resistance. *Environmental Health Perspectives*.,114(1):106–112.

Andrady, A.L.and Neal,M.A.2009. Applications and soci*et al* benefits of plastics. Phil Trans R Soc B.,364(1526):1977–1984.

Andrianou, X.D., Gängler, S., Piciu, A., Charisiadis, P., Zira, C., Aristidou, K. *et al*.2016. Human Exposures to Bisphenol A, Bisphenol F and Chlorinated Bisphenol A Derivatives and Thyroid Function. PLoS ONE., 11(10): e0155237.

Assoc. Plast. Manuf. Eur. (APME)2006. An Analysis of Plastics Production, Demand and Recovery in Europe.

Bae, S., Kim, J.H., Lim, Y.H., Park, H.Y. and Hong Y.C.2012. Associations of bisphenol A exposure with heart rate variability and blood pressure. Hypertension., 60: 786–793.

Ben-Jonathan, N., Hugo, E.R., Brandebourg, T.D.2009. Effects of bisphenol A on adipokine release from human adipose tissue: Implications for the metabolic syndrome. Mol Cell Endocrinol.,304: 49–54.

Bindhumol, V., Chitra, K.C.and Mathur, P.P.2003. Bisphenol A induces reactive oxygen species generation in the liver of male rats. *Toxicology.,*188(2-3):117–124.

Calafat, A.M., Ye, X., Wong, L.Y., Reidy,J.A. and Needham, L.L.2008. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ Health Perspect.,116(1):39–44.

Cantonwine, D.E., Hauser, R.and Meeker, J.D.2013. Bisphenol A and Human Reproductive Health. Expert Rev Obstet Gynecol., 8(4): 10

Carwile, J.L. and Michels, K.B.2011. Urinary bisphenol A and obesity: NHANES 2003–2006. Environ Res.,111: 825–830.

Chailurkit, L., Aekplakorn, W.and Ongphiphadhanakul, B.2016. The Association of Serum Bisphenol A with Thyroid Autoimmunity. Int J Environ Res Public Health.,13(11): 1153.

Diamanti-Kandarakis, E., Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., *et al*.2009. Endocrine-disrupting chemicals: An endocrine society scientific statement. Endocr Rev.,30:293-342.

Ejaredar, M., Lee, Y., Roberts, D.J., Sauve, R.and Dewey, D.2017. Bisphenol A exposure and children's behavior: A systematic review. J Expo Sci Environ Epidemiol,27:175-83.

Eskenazi, B., Warner, M., Samuels, S., Young, J. and Gerthoux, P.M .2007. Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study. American Journal of Epidemiology., 166, 79–87.

Gao H, Yang BJ, Li N, Feng LM, Shi XY, Zhao WH, Liu SJ.2015. Bisphenol A and Hormone-Associated Cancers: Current Progress and Perspectives. Medicine (Baltimore)., 94(1): e211.

Gao, X. and Wang, H.S.2014. Impact of Bisphenol A on the Cardiovascular System — Epidemiological and Experimental Evidence and Molecular Mechanisms. Int J Environ Res Public Health.,11(8): 8399–8413.

Golub, M.S., Wu, K.L., Kaufman, F.L., Li, L.H., Moran-Messen, F., *et al*.2010. Bisphenol A: developmental toxicity from early prenatal exposure. Birth Defects Res B Dev Reprod Toxicol.,89: 441-466.

Han, C., Hong, Y.C.2016.Bisphenol A, Hypertension, and Cardiovascular Diseases: Epidemiological, Laboratory, and Clinical Trial Evidence. Curr Hypertens Rep.,18(2):11.

Heindel, J.J.2003. Endocrine disruptors and the obesity epidemic. Toxicol Sci.,76: 247–249.

Heindel, J.J.and Vom Saal, F.S.2009. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. Mol Cell Endocrinol.,304: 90–96.

Holmgren,J.H.1974. Advantages of disposables: safety, cost, convenience. Mod Hosp.,122(1):35.

Hugo, E.R., Brandebourg, T.D., Woo, J.G., Loftus, J., Alexander, J.W., *et al*.2008. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. Environ Health Perspect.,116: 1642–1647.

Huo, X., Chen, D., He, Y., Zhu, W., Zhou, W., and Zhang, J.2015.Bisphenol-A and Female Infertility: A Possible Role of Gene-Environment Interactions.Int J Environ Res Public Health. ,12(9): 11101–11116.

Inhorn, M.C.and Patrizio, P.2015. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update.,21:411–26.

Kharrazian, D.2014. The potential roles of Bisphenol A (BPA) pathogenesis in autoimmunity. Autoimmune Dis.,2014:743616.

Kidani, T., Kamei, S., Miyawaki, J., Aizawa, J., Sakayama, K., *et al*.2010. Bisphenol A downregulates Akt signaling and inhibits adiponectin production and secretion in 3T3-L1 adipocytes. J Atheroscler Thromb.,17: 834–843.

Lang, I.A., Galloway, T.S., Scarlett, A., *et al*.2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA : the journal of the American Medical Association., 300(11):1303–1310.

Maffini, M.V., Rubin, B.S., Sonnenschein, C.and Soto, A.M.2006. Endocrine disruptors and reproductive health: the case of bisphenol-A. Mol Cell Endocrinol., 254–255:179–86.

Meeker, J.D., Calafat, A.M.and Hauser, R.2010. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environ Sci Technol.,44(4):1458–63.

Meeker, J.D.and Ferguson K.K.2011. Relationship between urinary phthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES) 2007–2008. Environ. Health Perspect.,119:1396–1402.

Melzer, D., Osborne, N.J., Henley, W.E., Cipelli, R., Young, A., Money, C.,*et al*.2012. Urinary bisphenol a concentration and risk of future coronary artery disease in apparently healthy men and women. Circulation.,125:1482–1490.

Melzer,D., Rice, N.E., Lewis,C., Henley,W.E., Galloway, T.S.2010. Association of urinary bisphenol a concentration with heart disease: Evidence from NHANES 2003/06. PLoS One, 5:e8673.

Moriyama, K., Tagami, T., Akamizu, T., Usui, T., Saijo, M., Kanamoto, N.*et al*.2002. Thyroid Hormone Action Is Disrupted by Bisphenol A as an Antagonist. *The Journal of Clinical Endocrinology & Metabolism*., 87(11): 5185–5190.

Nadal, A., Alonso-Magdalena, P., Soriano, S., Quesada, I.and Ropero, A.B.2009. The pancreatic beta-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes. Mol Cell Endocrinol.,304:63-8.

Newbold, R.R., Padilla-Banks, E., Jefferson, W.N.and Heindel, J.J.2008. Effects of endocrine disruptors on obesity. Int J Androl., 31: 201–208.

Newbold, R.R., Padilla-Banks, E., Snyder, R.J., Phillips, T.M.and Jefferson, W.N.2007. Developmental exposure to endocrine disruptors and the obesity epidemic. Reprod Toxicol., 23: 290–296.

Newbold, R.R.2010. Impact of environmental endocrine disrupting chemicals on the development of obesity. Hormones (Athens)..,9: 206–217.

Parkin, D.M., Bray, F., Ferlay, J.and Pisani, P.2005. Global cancer statistics,2002. Ca Cancer J Clin., 55:74–108.

Peretz, J., Vrooman, L., Ricke, W.A., Hunt,P.A., Ehrlich, S., Hauser, R., *et al*.2014. Bisphenol a and reproductive health: update of experimental and human evidence, 2007–2013. Environ Health Perspect.,122:775–86.

Prausnitz, M.R.2004. Microneedles for transdermal drug delivery. Adv Drug Deliver Rev.,56(5):581–587.

Rancière,F., Lyons, J.G., Loh, V.H., Botton, J., Galloway, T., Wang, T., *et al*.2015. Bisphenol A and the risk of cardiometabolic disorders: A systematic review with meta-analysis of the epidemiological evidence. Environ Health,14:46.

Rayner, J.L., Wood, C. and Fenton, S.E.2004. Exposure parameters necessary for delayed puberty and mammary gland development in Long-Evans rats exposed in utero to atrazine. Toxicol. Appl. Phar-macol., 195, 23–34.

Rubin, B.S., Murray, M.K., Damassa, D.A., King, J.C.and Soto, A.M.2001. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. Environ Health Perspect.,109: 675–680.

Rubin, B.S., Soto, A.M.2009. Bisphenol A: Perinatal exposure and body weight. Mol Cell Endocrinol.,304: 55–62.

Rubin, B.S.2011. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. J Steroid Biochem Mol Biol.,127: 27–34.

Shankar, A. and Teppala, S.2011. Relationship between urinary bisphenol A levels and diabetes mellitus. The Journal of clinical endocrinology and metabolism., 96(12):3822–26.

Shankar, A.and Teppala, S.2012. Urinary bisphenol A and hypertension in a multiethnic sample of US adults. J Environ Public Health :481641.

Silver, M.K., O'Neill, M.S., Sowers, M.R.and Park, S.K.2011. Urinary bisphenol A and type-2 diabetes in U.S. adults: data from NHANES 2003–2008. PloS one., 6(10):e26868.

Somm, E., Schwitzgebel, V.M., Toulotte, A., Cederroth, C.R., Combescure, C., *et al*.2009. Perinatal exposure to bisphenol a alters early adipogenesis in the rat. Environ Health Perspect.,117: 1549–1555.

Sriphrapradang, C., Chailurkit, L.O., Aekplakorn,W. and Ongphiphadhanakul, B. 2013. Association between bisphenol A and abnormal free thyroxine level in men. Endocrine., 44(2):441–7.

Srivastava, R.K., Godara, S.2013. Use of polycarbonate plastic products and human health. Int J Basic Clin Pharmacol.,2:12-7.

Stein,T.P., Schluter, M.D., Steer, R.A., Guo, L.and Ming, X.2015. Bisphenol A exposure in children with autism spectrum disorders. Autism Res.,8:272-83.

Stewart, B.and Kleihaus, P. 2003. World Cancer Report. IARC press, Lyon

Sui, Y., Park, S., Helsley, R.N.and Zhou, C. Bisphenol A Increases Atherosclerosis Mediated by the Human Pregnane X Receptor . Arteriosclerosis, Thrombosis, and Vascular Biology.,34:A285

Trasande,L.,Attina,T.M.,Blustein,J.2012.Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. JAMA.,308:1113-21.

Vandenberg, L.N., Ehrlich, S., Belcher, S.M., Ben-Jonathan, N., Dolinoy, D.C., Hugo, E.R., *et al*.2013. Low dose effects of bisphenol A. Endocrine Disruptors.,1:e26490.

Vert, M.2011. Not any new functional polymer can be for medicine: what about artificial biopolymers? Macromol Biosci.,11(12):1653–1661.

Wada, K., Sakamoto, H., Nishikawa, K., *et al*.2007 Life style-related diseases of the digestive system: endocrine disruptors stimulate lipid accumulation in target cells related to metabolic syndrome. *Journal of Pharmacological Sciences*.,105(2):133–137.

Wang, T. ,Li, M. ,Chen, B., *et al*.2012. Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance . J Clin Endocrinol Metab .,97:E223–E227.10.

Wang, Y., Lobstein, T.2006. Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes.,1: 11–25.

Wang, Z., Liu, H.and Liu, S.2017. Low-Dose Bisphenol A Exposure: A Seemingly Instigating Carcinogenic Effect on Breast Cancer. Adv Sci (Weinh). 2017 Feb; 4(2): 1600248.

Wang,B., Wang, H., Zhou,W., He,Y., Zhou,Y., Chen,Y., *et al*.2014. Exposure to bisphenol A among school children in eastern China: A multicenter cross-sectional study. J Expo Sci Environ Epidemiol.,24(6):657-64.

Wang,T., Lu, J., Xu, M., Xu, Y., Li, M., Liu,Y., *et al*.2013. Urinary bisphenol a concentration and thyroid function in Chinese adults. Epidemiology,24(2):295–302.

Warner, M., Eskenazi, B., Mocarelli, P., Gerthoux, P.M. and Samuels, S.2002. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Environ. Health Perspect., 110, 625–28.

Yang, L., Luo, L., Ji, W., *et al*.2013. Effect of low dose bisphenol A on the early differentiation of human embryonic stem cells into mammary epithelial cells. *Toxicol Lett* ., 218:187–193.

Yang, M., Ryu, J.H., Jeon, R., Kang, D., Yoo, K.Y.2009. Genotoxicity and carcinogenicity. Arch Toxicol.,83:281–285.

Yoshino, S., Yamaki, K., Li, X., Sai, T., Yanagisawa, R., Takano, H., *et al*.2004.Prenatal exposure to bisphenol A up-regulates immune responses, including T helper 1 and T helper 2 responses, in mice. Immunology.,112:489–495.

Ziv-Gal, A.and Flaws, J.A.2016. Evidence for bisphenol A-induced female infertility - Review (2007–2016).Fertil Steril.,106(4): 827–856.

Zoeller, R.T., Bansal, R., Parris, C.2005. Bisphenol-A, an environmental contaminant that acts as a thyroid hormone receptor antagonist in vitro, increases serum thyroxine, and alters RC3/neurogranin expression in the developing rat brain. Endocrinology.,146:607–612.