

Waste materials that released in to the environment

[Business](#), [Manufacturing](#)



A large number of waste materials are released in to the environment including the domestic waste products, industrial pollutants and chemical pesticides etc. As a result of the dumping of these pollutants in to the environment paves the way for pollution of both soil as well as marine pollution. As a result of the exploration by humans, the marine ecosystem and water bodies are become a pool of micro pollutants such as the pesticides, industrial effluents, and other potential domestic waste matters. The major sources of most of these pollutants came from waste water effluents and discharges (Loos et al., 2009). Domestic waste products are mainly constituted by plastic products. Thompson et al (2009) reported that from poles to the equator the marine environment is polluting by the man made debris. Glass, metals, paper and plastic products and organic and inorganic pollutants mainly constitutes the marine debris. Among them plastic products mainly comprises the major portion of the marine debris and these marine debris, a wide range of endocrine disrupting compounds (EDCs), were released in to the environment (Hatef et al., 2012).

More than 700 emerging contaminants are categorized into 20 classes are listed in the European aquatic environment (Norman et al., 2013). The major estrogenic compounds detected in the environment includes:

ethynylestradiol, octylphenolbisphenol A (BPA), tetrabromobisphenol A (TBBPA) , pesticides, surfactants and organo halogens (Metzler et al., 2001).

Xenoestrogens having widely variant structures have been identified in in vitro studies (Solo et al., 1994). Among these EDCs, bisphenols possess a major role as an endocrine disrupting compound. It is one of the major production chemical worldwide with over six billion pounds produced over

year (Vandenberg et al., 2009). The study report by Clyton et al (2011) stated that, these endocrine disrupting compounds were considered safer from toxicological side effects but later studies revealed that it has negative health impacts on the hormonal regulation of humans as well as other living beings especially on marine population. According to the US Environmental Protection Agency, endocrine disrupting chemicals (EDCs) are defined as “ exogenous agent(s) that interferes in secretion, synthesis, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes” (Diamanti-Kandarakis et al. 2009). EDCs disrupt the endocrine system work either by receptor mediated or receptor independent mechanisms (Denslow et al., 2008).

Bisphenols are the major endocrine disrupting compounds found in plastic products. Thus they are widely used in various consumer products. Different bisphenol compounds include bisphenol A (BPA), bisphenol S / BPS, and BPF. These various bisphenol compounds comprise a total worldwide production rate over 8 billion pounds per year (Liao et al., 2012). These bisphenols are mainly used in the manufacturing of polycarbonate plastics and epoxy resins. Among these various bisphenol compounds; BPA has been frequently used in numerous commercial applications (Liao et al., 2012). Vandenberg et al (2012) reported that these endocrine disrupting chemicals mimic the natural hormones and bind to their receptors and block the action of the natural hormones. Many of these endocrine disrupting compounds interact with thyroid system, androgen and estrogen hormone receptors (Khetan et

al., 2014). The EDCs binds with the endocrine receptors and thereby controlling the immune system and fat development (Zoeller et al., 2013).

Bisphenol A is an organic compound having two phenol moieties. It was the common name for 2, 2 - (4, 4'-dihydroxydiphenyl) propane , 4, 4'-isopropylidenediphenol, chemical formula C₁₅H₁₆O₂, Its important properties include low vapor pressure, moderate water solubility, and low volatility transparency, high mechanical strength, low moisture absorption and good thermal stability. It is a solid at room temperature (Tsai, 2006).

BPA has been used for more than 50 years and it is an industrial monomer chemical used to produce poly carbonate plastics which are widely used in many household items such as plastic bottles and baby bottles (Ying et al., 2010), tableware (plates, mugs, plastic utensils (Bignardi et al., 2015). The epoxy resins which are used for the production of lacquer coatings of food and beverage cans (Goodson et al., 2002), dental fillings (Manabe et al., 2000), sealants (Ashby et al., 1997), medical devices (Shintani et al., 2003), and sports equipments (Prinz et al., 2016) also contain BPA. Another widespread usage of BPA was in the production of thermal receipts (Mendun et al., 2010).

BPA can act as a weak estrogen receptor agonist and it is associated with a variety of adverse health effects on reproduction and development of humans and other laboratory animals (Huang et al., 2012; Vandenberg et al., 2012). BPA is widely used in the manufacturing of resins such as epoxy resins, phenol resins, polycarbonates, polyacrylates, poly esters and lacquer coatings on food cans (Staples et al., 1998). Studies have reported that BPA

from these food and beverage cans and packages tends to leach out in to the surroundings. Studies by Goodson et al in 2002 revealed that foods and beverages are being contaminated by the leaching of BPA in to the surrounding food materials and beverages. BPA has been shown to migrate from cans and cap sealing resins (Horie et al., 1999), and has been detected in drinks (Kawamura et al., 2001), vegetables (Yoshida et al., 2001), fruits (Noonan et al., 2011) and honey (Inoue et al., 2003). The main factors influencing the migration of BPA includes the time used in heating and temperatures used in the manufacturing process during plastic production (Kang et al., 2003; Goodson et al., 2004).

Previous studies (Yamada et al., 1999; Behnisch et al 2001) reported that high levels of BPA were identified in the leachates of waste landfills. Yamamoto et al (2001) reported that BPA levels in the leachates of waste landfills of hazardous materials showed a range of 1.3 to 17,200 ng/ml. BPA leaching from plastic waste in to the water were also reported. In addition BPA was also been found in indoor air (Nakazawa et al., 2006) and in river water (Kawaguchi et al., 2004). Levels of BPA have been suspected in biological samples such as human urine (Casa et al., 2013) and also in blood serum (Gonzalez et al., 2015). The levels of BPA are also found within the reproductive system such as in testicle tissue and in seminal plasma (Manfo et al in 2014). The presence of BPA in ovarian follicular fluid (Ikezuki et al., 2002). The presence of BPA in mother's milk and in fetal plasma (Shonefelder et al., 2002) and in amniotic fluid were reported (Yamada et al., 2002; Cao et al., 2012).

BPA was also found to be identified in human saliva in the work done by Yang et al in 2007. It was found that half-life of the BPA within human body is 6 hrs and most of it is excreted in to urine as glucuronic acid conjugates (Volkela et al., 2005). Traphoff et al (2013) explained the non-genomic as well as genomic effect of BPA that results in the altered regulation of transcription. Moreover, BPA has been identified as an androgen receptor antagonist (Kitamura et al., 2005). BPA disrupts the function of androgen receptors by inhibiting their effective nuclear translocation (Teng et al., 2013). BPA also reported to induce alterations of DNA methylation (Dolinoy et al., 2007; Susiarjo et al., 2013). BPA promotes the formation of malignant and benign tumors in rat models (Rodriguez et al., 2011)

In 2014, Mirmira and his team reported that BPA was found to be leached out from baby bottles. Another study by Richter et al (2007) revealed that BPA had leached from beverage cans also. With reference to these above study reports, and on the basis of potential effects on human health, endocrine system and mainly on reproduction, various government agencies in US including: the United State's Food and Drug Administration (FDA), United States (the US Environmental Protection Agency, USEPA), Canada (Health Canada), and in Europe (the European Food Safety Authority, EFSA) had established a tolerable daily intake level of BPA ranging from 25 to 50 $\mu\text{g} / \text{kg}$ of body weight (Rochester et al., 2013). In 2010, the Canadian government had prohibited the sale, import and advertisement of BPA containing feeding bottles declared BPA to be a toxic substance and added it to the schedule 1 of the Canadian Environmental Protection Act 1999 (' Order adding a toxic

substance to schedule 1 of Canadian Environmental Protection Act 1999). In 2012, FDA (Food and Drug Administration) had declared a complete prohibition of the use of BPA in baby bottles and in sippy cups. Finally in 2015, the endocrine society had discussed the importance of the regulation of the compound and its potential health effects on living beings.

Bisphenol S (BPS) is introduced as a safe alternative to BPA. BPS is an organic compound having the chemical formula $(\text{HOC}_6\text{H}_4)_2\text{SO}_2$. It contains two phenol functional groups on either side of a sulfonyl group. It is commonly used in curing fast-drying epoxy resin adhesives. It is close analog of bisphenol A (BPA) in which the dimethylmethylen group $(\text{C}(\text{CH}_3)_2)$ is replaced with a sulfone group (SO_2) . Grignard et al (2012) reported that for producing BPA - free plastic consumer products manufacturers who were in need of BPA alternative were in seek of BPS. BPS is chemically more stable and it is less biodegradable than BPA (Ike et al., 2006; Danz et al 2009). BPS is more liable to dermal penetration than BPA (Liao et al., 2012). In 2014, Helius - Toussaint et al, concluded that the outstanding properties of BPS over BPA makes it more body burden or bioavailable in living system.

The presence of BPS is widely seen in the consumer products in which BPA is initially used including the use of BPS as a constituent of phenolic resins, as a wash fastening agent in clearing products, and its use as a electroplating solvent (Rochester and Bolden, 2015). BPS is used as developer in thermal paper receipts paper, money, flyers, tickets, airplane boarding passes, mailing envelopes, and mainly in paper products labelling " BPA free paper "(Liao et al., 2012) . BPA has been detected in everyday personal care

products including toothpaste , hair care products , body wash and lotions makeup cosmetics (Kannan and Liao, 2013). The findings of the study carried out by Vinas et al (2010) showed that the presence of BPS is detected in tinned food stuffs also. The work reports of Vinas Watson et al in 2013 reported that BPS seems to have control over non genomic signaling pathways. The studies of Chen et al in 2002 on *Daphnia magna* showed the acute effects of BPS. BPS reported to cause estrogenicity rather than mutagenicity in *Daphnia magna*. Another study reported that, induction of uterine growth in rats is mediated by low doses of BPS and found to bind to the estrogen receptor (Yamasaki et al., 2004). Estrogen levels were found to be increased in both the males and females and testosterone levels were decreased in males. Also gonads of several genes of hypothalamic- pituitary and gene expression in brain were also altered by low concentration of BPS. The works of Naderi et al in 2014 reported that BPS exposure for a period of 4-6 months in *Danio rerio* showed a decrease in egg production.

Previous experimental results found out that high doses of bisphenols (bpa, bps) at micro and milli molar levels had induced DNA damage through the production of ROS in hepatocellular carcinoma (HepG2) , neuronal cells (Neuro 2a) and mesenchymal cells (Audebert et al ., 2011; Naka et al., 2011; Leem et al., 2017). Similar studies have done by Gassman et al (2015), reported that DNA strand breaks was observed as a result of exposure of BPA at very low nano and molar concentration in zebra fish, but it is found to be non-cytotoxic. The enzymatic processing of BPA by CytP450 induce the formation of ROS and it also generates quinone form of BPA which is DNA

reactive (Rogan and Cavalieri, 2010). This occurs by a mechanism which is similar to the pathway in which natural estrogen are metabolized in to their respective quinones. Another study reports (Roy et al., 1995; Izzottii et al., 2009) establishes that BPA-DNA adduct formation is observed in in vitro and in vivo condition on exposure of BPA at a very high dose. Moreover, many previous experimental results discussed the alterations in chromatin structure and DNA damage by BPA (Fernandez et al., 2012, Porredca et al in 2016). Lots of studies had been carried out in focusing the interaction and effect of several xenoestrogens like bisphenols on maraine crustaceans as they are consumed by the humans and makes an essential part of diet. The reported the detection of BPA in crabs and shrimps at a concentration level ranging from 17- 602ng/g (Yoshida et al., 2001). The works of Laufer et al (2013) reported the effect of BPA on lobster larvae. The work establishes that BPA disrupt the sell hardening by suppressing the crosslinking of tyrosine derivatives as they have similar structure to them. Lobster showed toxic effect of BPA on third and fourth larval stages (Biggers et al., 2004).

The antioxidant system of maraine organism includes the various antioxidant enzymes low molecular weight scavengers and they interact in a regulated pathway. This regulated pathway is disrupted by the action of chemical xenoestrogens. Interaction of these chemicals results in the generation of ROS and induction of the antioxidant system which is further modulated by the changes in the levels of various cellular signaling pathways and transcription factors (Klotz et al., 2010). A broad spectrum of xenobiotic compounds comes in contact with various receptors involved in important

signaling pathways in biological system (Kehrer et al., 2015). Thus, the exposure of cells to xenobiotics results in the activation of nuclear receptor xenosensors such as the CAR (Constitutive Androstane Receptor), PXR (Pregnane X Receptor), AhR (Aryl Hydrocarbon Receptor), and Nrf2 (Nuclear Factor (erythroid- derived 2)- like -2) receptor. The binding of the xenobiotics with the receptors is accompanied by the generation of reactive oxygen species (ROS) resulting in DNA damage and xenosensor activities (Klotz et al., 2017).

Nrf2 is a transcription factor belonging to the leucine zipper family (CNC-bZIP) and the stimulation of nrf2 receptor occurs by the suppression of its negative regulator Keap-1 (Kelch-like ECH-associated protein 1) (Tebay et al., 2015). Thiol and phenol containing xenobiotic compounds usually stimulate the keap1-nrf2 interaction and finally leading to nrf2 activation (Flohe et al., 2011).

The reactive oxygen species (ROS) formed as a result of this interaction stimulates the formation of cellular electrophiles and lipid peroxidation products such as 4-hydroxynonenal (HNE) (Long et al., 2017) . The works of Chen et al in 2005 reported that nrf2 transcriptional activity is stimulated in PC12 cells on exposure to HNE. Then observed a cellular resistance mechanism against the stress condition by the increased expression of the phase 2 enzymes and the proteins involved in the antioxidant defence such as NQO1 (Quinone oxidoreductase 1) and GCS1 (γ -Glutamylcysteinesynthetase 1). The works of Hayes et al in 2015 showed that PI3K/Akt pathway was also involved and stimulated in response to HNE

exposure. The study of Penning et al in 2005 illustrated the coordinated link between nrf2, Akt and tyrosine kinase dependent signaling through the inhibitory phosphorylation of Glycogen Synthase Kinase (GSK).

The FOXO -3 stimulates the transcription of Keap-1 gene in tumor cell lines (Guang et al., 2013). In the study done by Hu et al (2006) on murine ovaries reported that the xenobiotic induced formation of FOXO-3 factor is enhanced by Nrf2. A similar study was done in *C. elegans* (*caenorhabditiselegans*) which are exposed to diethyl maleate (DEM) at higher concentration lowered their life span and development. These studies establishes that xenobiotic induced FOXO formation requires Nrf2. BPA induces the activation of T3 mediated gene expression through the inhibition of TR α and β receptors by binding to them (Moriyama et al ., 2002). BPA induces an inhibitory effect on T4 induced metamorphosis by the reduction in TR β mRNA levels (Iwamuro et al., 2003; Yang et al., 2005). BPA at a lower concentration of 100 μ M induces a suppression of RXR γ gene expression and found to be accelerated by a concentration of 0. 025- 0. 4 μ M in the presence of T3 (Iwamuro et al., 2006). BPA also had an affinity to bind with the inhibition site of (γ - amino butyric acid) (GABA) receptor in *Xenopus oocytes* (Aoshima et al ., 2001).