Plastic Packaging Materials as Possible Source of Hazardous Chemicals to Food and human health: A Review

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ABSTRACT

Plastic packaging has been implicated as a source of food packaging material (FPM) borne compounds transfer into food. These chemical migrants from packaging materials to food products are associated with human health risks. However, opinions on plastic packaging safety differ greatly and scientific agreement on product safety is still indefinable. The present review intends to explore and present the state of science about the safety of plastics, the potential for consumer exposure and discuss the major issues with respect to associated health risks safety.

Key words: Plastic packaging, chemical migrants, plastic packaging safety, health risk, consumer exposure

INTRODUCTION

Food packaging has become a modern civilization culture due to the importance and functional roles of packaging materials; as such nearly all food stuff available on market are packaged. There are numerous packaging materials but each of which provides different advantages, however, of interest in the present write up is plastic packaging materials (PPM). Plastic packages constitute the largest fraction of food packaging materials due to their flexibility, portability (light weight), inert nature, durability, versatility, their potential for diverse applications (Proshad *et al.*, 2018) and other advantages over other packaging materials. It is indicated that the number of plastics produced globally in the first decade of the present century is comparable to the total world production in the century earlier (Mathur *et al.*, 2014). According to GEF (2018) the making of plastics increased by more than twenty-fold between 1964 and 2015, with yearly output of 322 million metric tonnes (Mt), and is projected to double by 2035, and almost quadruple by 2050. By definition, plastics are polymer chains of molecules (usually made of

carbon, hydrogen, oxygen, and/or silicon) which are hooked or joined together. The raw materials for making polymers include petroleum-based products and other products, which are heated together under pre-determined conditions (Halden, 2010). Monomers are the building units of polymers and determinant of their polymeric properties. Different combinations of monomers produce plastic resins with different characteristics, such as strength or molding capability (Halden, 2010).

Plastic materials used in packaging are greatly varied in their chemical structure, offering dissimilar properties based on the processing, incorporated additives and combination with other polymers (Tatiane *et al.*, 2018). Several categories of additives, such as antioxidants, stabilizers, lubricants, anti-static, anti-blocking agents etc., have been produced to advance the performance of polymeric packaging materials (Al-Dayel *et al.*, 2012). Additive materials enrich plastics with such properties like elasticity, flexibility and resistance to breakage and transparency to light (Al-Dayel *et al.*, 2012). The addition of plasticizers, antioxidants, fillers, flare retardants, and colorings to plastic polymers imparts preferred functionalities and generates hundreds of different assortments of plastic materials of deviating properties (Halden 2010). It is also indicated that such additives like antioxidants, ultraviolet (UV) stabilizers or plasticizers (softeners) are compulsory to (i) safeguard packaging material from UV power-driven or oxidative deterioration, (ii) increase softness and (iii) enhance the general appearance or quality of the plastic package. Nonetheless, additives are non-covalently bound to the polymer and are consequently vulnerable to migration when subjected to heat or during long-term storage (Mathur *et al.*, 2014). Several contributions in the literature (Tatiane *et al.*, 2018) illustrate that there is likelihood of migration of components from the packaging to the product.

Key findings documented by FSANZ (2014) on chemical migration from packaging into food (CMPF) indicate availability of evidences on the migration of chemical into food from packaging. They concluded that unintentional leaching of certain chemicals from packaging could pose a health risk to community but there is a high degree of doubt about the exact nature of the problem. It is also reported by Mathur *et al.* (2014) that though plastic polymers are not regarded as toxic, there could be toxic residual remnant chemicals, chemical additives and decomposition products in the plastic products that can leach out since are not bound to

the plastic polymer. Halden (2010) associated human health risks with plastics monomeric building units notably bisphenol A (BPA), their additives e.g., plasticizers and a blend of the two e.g., antimicrobial polycarbonate. As such, the present review intended to examine the potential health risks associated with chemical migration into food from plastic packaging.

METHODOLOGY

The current work employed a narrative review to provide an insight on health implications that are associated with PPM under the following methodological review approach:

(a) Brief description of different types of plastic packaging including their categorization based on assigned number codes, highlighting the composition, uses and safety implication.
(b) Discussion on the monomeric building units and/ or additives (e.g. BPA, phthalates, etc.) with great potential for adverse human health risks.
(c) Explanation of the ways through which human exposure to chemicals migrating from plastic packages can occur and factors affecting their migration.
(d) Description of the underlined potential health risks due to plastic packaging chemical migrations into foods.
(e) Description of the established main observations from the revisited literature.

The data collection was achieved through searching a variety of relevant literatures from different electronic sources of scientific literature (PubMed, Google Scholar) and "grey" literature (government publications, trade body and industrial collections). Several keywords were used during search, either individually or in combinations; under which the articles were sought and finally selected. Examples of key words include plastic packaging, plasticisers, additives, chemical migration, health risks of plastic package and bisphenol A.

FINDINGS AND DISCUSSION

Types of Plastic Packaging

Plastics can be divided into two major categories namely (i) thermoset or thermosetting plastic and (ii) thermoplastics.

(i) Thermoset or Thermosetting Plastics

Thermoset are materials which stay in a stable solid state after being cured once. Polymers inside the material cross-link in the course of curing process to make an unbreakable, irreversible bond. This implies that thermosets won't melt even when exposed to exceedingly high temperatures **(**ROMEORIM, undated**).** Thermoset are valuable due to their hardness, strength and durability. They are used mostly for aircraft parts, auto parts, tires and constructions applications (Halden, 2010). Additional uses include adhesives, inks, and coatings (Halden, 2010). Examples include silicone, epoxy, phenolic and polyurethane. In addition, some materials such as polyester can occur in both thermoplastic and thermoset versions **(**ROMEORIM, undated).

(ii) Thermoplastics

A thermoplastic is any plastic material which melts into a soft, flexible form beyond a certain temperature and hardens upon cooling. In contrast to thermoset, thermoplastics can be re-melted and re-shaped several times **(**ROMEORIM, undated)**.** Thermoplastic molecules are held together by weak bonds, making plastics soften upon heating and return to their original form at room temperature (Halden, 2010). They can be easily moulded, shaped and extruded into films, fibers, packaging and products such as milk jugs, floor coverings, credit cards, and carpet fibers (Freudenrich, 2007; Halden, 2010). Examples include polypropylene (PP), polyethylene (PE), and polyvinyl chloride (PVC) (Freudenrich, 2007).

Classification of Plastics based on Number Code

Plastics are categorized in seven main categories based on the classification system established by the Society of the Plastic Industry (SPI) namely SPI or number code. The SPI code ranges from 1 – 7 and

the SPI code on each plastic product is commonly molded into the bottom (Yadav, undated). However, from personal observation sometimes the SPI code is placed on the label of the plastic packaging. The description of each of this category is given below.

Polyethylene Terephthalate (PET) – Type 1

Polyethylene terephthalate is usually abbreviated PET. It is the most common thermoplastic polymer resin of the polyester clan (Mepex Consult AS, 2017). An alternative abbreviation PETE originates from Polyethylene Terephthalate Ethylene (Schuler, 2008). PET is biodegradable and semi-crystalline. PET is a clear tough plastic with good gas and moisture barrier properties and in some instances, there is little need for additional barriers (Mepex Consult AS, 2017). It exhibits some exceptional characteristics superior to other types such as distinctive appearance, food grade i.e., non-toxic, chemical resistance, good creep resistance, impact resistance, unbreakable and recyclability. PET is frequently used in making disposable containers or bottles for liquids, soft drinks and foods such as water, various types of juice, butter, salad dressing, vegetable oil, mouthwash, detergents, cleaner, cosmetics, etc. (Schuler, 2008; Proshad *et al.,* 2018), jars and tubs, thermoformed trays and bags and snack wrappers because it is strong, heat resistant and resistant to gases and acidic foods (Mathur *et al.*, 2014) and it is manufactured for single use only (Proshad *et al.*, 2018). It can be either transparent or opaque (Mathur *et al.,* 2014).

High-Density Polyethylene (HDPE) – Type 2

Polyethylene is the most used plastic in the world. HDPE is a harder plastic with a higher melting point than low density polyethylene (LDPE) (Freudenrich, 2007), (see Type 4) and it is stiff and strong (Mathur *et al.*, 2014). It is made from petroleum product, giving rise to a heat-resistant plastic (Proshad *et al.,* 2018). It has a clear and even surface and has some good barrier characteristics; nonetheless it is not a good barrier to oxygen. However, if enriched with polyamide (nylon) – (PA) or other additives, HDPE becomes a good barrier against gases. It is similarly durable against shocks and heat (Mepex Consult AS, 2017).

According to Proshad *et al.* (2018) HDPE does not contain harmful BPA or phthalates and is presumed to have no identified health risk for food use. Compared to PET, HDPE made container is regarded safer for food

and drink (Proshad *et al.,* 2018). HDPE is used in making opaque plastic milk, juice and water bottles and jugs, bottles for bleach, detergent (household cleaner containers) and shampoo, some plastic bags (Schuler, 2008), cereal box liners and several other types of bottles and tubs (Mepex Consult AS, 2017). Furthermore, HDPE is used in making toys, various types of plastic grocery, rubbish and retail bags (Mathur *et al.,* 2014; Proshad *et al.,* 2018). Nevertheless, HDPE is heat sensitive as it melts at a relatively low temperature (Mathur *et al.,* 2014).

Polyvinyl Chloride (PVC or V) – Type 3

PVC is a thermoplastic that is made by polymerization of vinyl chloride (Freudenrich, 2007). It's however, fragile as such it requires additives and stabilizers to make it useable (Freudenrich, 2007; Schuler, 2008). Usually, phthalates or adipates are used as plasticizers to make PVC flexible and mouldable (Mathur *et al.,* 2014). However, phthalates are harmful to human upon exposure. Plasticized PVC pipes contain phthalates and many other toxic chemical substances including BPA, lead, dioxin and cadmium (Proshad *et al.,* 2018). While plasticizers are added for softening and creating flexibility, lead is often added for strength. These toxic additives contribute to pollution and human exposure (Schuler, 2008). PVC are used for making containers for fruit juice and cooking oil (Proshad *et al.,* 2018), peanut butter containers, cling wrap, and bottles for plastic squeeze, detergent and window cleaners (Schuler, 2008), making pipes and plumbing (Freudenrich, 2007), as well as commercial-grade cling films for over-wrap of trays in supermarkets and filled rolls at delicatessens (Mathur *et al.* 2014).

Low Density Polyethylene (LDPE) – Type 4

LDPE is a thermoplastic made from the monomer ethylene. It is the most common polymer in plastics. In LDPE, the polymer strands are interlinked and loosely organized, so it is soft and flexible (Freudenrich, 2007). It is a 'heat-resistant' polymer, which can be both clear and opaque (Proshad *et al.,* 2018). It is used in making grocery store bags, zip-lock bags, most plastic wraps, bottles (Schuler, 2008), films of various sorts (including domestic/ household cling film) (Mathur *et al.,* 2014), disposable gloves, garbage bags (Freudenrich, 2007), freezer bags, juices

and milk cartons (Proshad *et al.,* 2018), bread bags, flexible lids and squeezable food bottles (Mathur *et al.,* 2014). It is presumed that LDPE do not contain any harmful components and are therefore safe for food and beverages uses (Proshad *et al.,* 2018).

Polypropylene (PP) – Type 5

Polypropylene is a type of plastic polymer, which is prepared from propylene monomers (Freudenrich, 2007). PP is usually harder, strong, hydrophobic, more heat resistant, denser and more transparent than polyethylene (Mathur *et al*., 2014; Proshad *et al.,* 2018) and has a high melting point (Mepex Consult AS, 2017). The different forms of polypropylene have dissimilar melting points and hardness (Freudenrich, 2007). PP has low oxygen barrier quality and is thus frequently used in packaging that does not need a specific oxygen barrier (Mepex Consult AS, 2017). It is typically used for packing yogurt, beverage, ketchup, medicine (Proshad *et al.,* 2018), soup, syrup containers, straws and for making baby bottles (Schuler, 2008), car trim, battery cases, bottles, tubes, filaments and bags (Freudenrich, 2017) microwavable packaging and sauce and salad dressing bottles (Mathur *et al.*, 2014). It is a good material for storing acids, bases and other solvents (Mepex Consult AS, 2017). Like LDPE, PP containers are considered safe since no harmful substances are found in food or water and beverages from PP plastic (Proshad *et al.,* 2018).

Polystyrene (PS) - Type 6

Polystyrene is made of styrene molecules (Freudenrich, 2007). According to Proshad *et al.* (2018) styrene is very risky for health. The International Agency for Research on Cancer (IARC) has acknowledged that styrene is human carcinogen (Proshad *et al.* 2018). PS is used in several applications, though its use is declining. It is used for production of containers such as pots, clamshells, bottles, lids, food trays and opaque disposable cutleries. PS is regularly found in compact disc cases, egg cartons, meat trays, carry-out containers, and disposable plates, bowls and cups (Mepex Consult AS, 2017; Schuler, 2008). It is also extensively used in producing packaging and insulating materials (Proshad *et al*., 2018). PP can make hard impact-resistant plastics for cabinets (for computer monitors and TVs), furniture, glasses and utensils. Once polystyrene is heated and air blown through the mixture, stryfoam is formed, which is used in making styrofoam based items (Schuler, 2008). Styrofoam is lightweight, moldable and an excellent insulator

(Freudenrich, 2007) that has a good stability for heat, though it is not flame retardant (Mepex Consult AS, 2017).

Polycarbonate (PC) – Type 7

With exception of the types already mentioned, all the remaining plastics are labelled as Type 7 plastics. Polycarbonate container is made of BPA, which can leach out into beverage or food stored in them. Owing to the BPA's health risk reflected in multiple studies, the use of type 7 or polycarbonate plastic materials has of late declined greatly (Proshad *et al.,* 2018). Polycarbonate is essentially used for packaging consumer goods (Proshad *et al.,* 2018). It is clear, durable and heat resistant and normally used as a replacement for glass in objects like refillable water bottles, sterilisable baby bottles (Mathur *et al.,* 2014), "sippy" cups, baby food jars, plastic dinnerware and clear plastic cutlery (Schuler, 2008). PC is also at times used in epoxy-based lacquers on the inner part of food and drink cans to inhibit the contents reacting with the metal of the can (Mathur *et al.*, 2014). The assigned number codes are used internationally as described in Table 1. The code number provides a guide to consumers and recyclers to identify and verify each plastic product (Yadav, undated).

Table 1: Different types of plastics and their classification

SPI Code	Name and Abbreviation	Density	Properties	Usage area
	Polyethylene terephthalate (PET)	1.34 – 1.39	• Clear & smooth surface • Barrier against air & water • Durable against shocks & heat	Widely used for drink & detergent bottles bottles, but also as packaging for other products including trays & cups
	High Density Polyethylene (HDPE)	0.91 – 0.94	• Rigid & tough materials • Good properties in terms of solvents • Stretchable	Widely used for bottles, also for chemical products. Heavily used in building materials & in car parts

	Polyvinylchloride (PVC)	1.16 – 1.30	• Resistant against fats and oils • Very strong material	Mainly used within construction for pipes, flooring, but also for garden furniture, shower curtains & toys. Found in rigid & soft products
	Low Density Polyethylene (LDPE)	0.90 – 0.92	• Soft, flexible, waxy surface, scratches easily, translucent	Garbage bags, squeeze bottles, black irrigation tube, silage & much films, rubbish bins, shrink wrap, food packaging
	Poly propylene (PP)	0.90 – 0.92	• Good container for acids, alkalis & solvents • A strong material with high melting point	Moulded products for buildings & cars. Flexible and rigid packaging products, straws, lunch boxes, compost bins
	Polystyrene (PS)	1.04 – 1.09	• Good protection against liquids that have a short life time • Rigid & foam shaped • Poor transporter of heat • Low melting temperature	Other used for food packaging and for drinks e.g., water cups, safety helmets, brittle toys
	Acrylonitrile butadiene styrene, (ABS) Polyamide (PA) Polymethyl methacrylate	Other plastic[181] types and laminates 1.13 – 1.15	• A range of different types of plastics with varying properties	Products that are based on other types of plastic or a combination of plastics, for instance laminated plastics used for packaging

Source: **(**Schuler, 2008; Plastic New Zealand, 2009; Grigore, 2017)

Safer Choices of Plastics for Food and Beverage

According to Schuler (2008) and Proshad *et al.* (2018) safer plastics for food and beverage include PETE (Type 1), HDPE (Type 2), LDPE (Type 4) and PP (Type 5), whereas plastics to be avoided include PVC (Type 3), PS (Type 6) and PC (Type 7). This implies that the basic knowledge about plastic classification based on SPI or number code is important to the consumers from the food safety perspective.

Monomeric with Potential Health Risks

As indicated earlier, plastics play a great role in almost every phase of food production and preparation. Food is processed on plastic equipment, and packed and dispatched in plastic containers or plastic-lined boxes and cans. Similarly, at household level, foods are stored in and leftovers reheated in plastic containers (Mathur *et al.,* 2014) whose building slabs are monomers. It is accepted that plastic polymers on their own are non-toxic since are unreactive and their big size restricts transport through biological membranes (Mathur *et al.,* 2014). According to Proshad *et al.* (2018) human health risks due to plastics can originate from their monomeric building units (e.g., Bisphenol A), their additives (e.g., phthalates) or from a combination of the two (e.g., antimicrobial polycarbonate). Among the numerous toxic materials generated by plastics, constituents and additives of principal concern are Bisphenol A (BPA) and phthalates which is the focus of the present review.

Bisphenol A (BPA)

As presented before, BPA is among the Food Contact Materials (FCMs), implying that it is used in the preparation of plastics for the production of materials that have direct interaction with food (Konieczna *et al.,* 2015). It is a building block of polycarbonate plastics and a common additive of PVC (Halden, 2010). In the course of polymerization, BPA tends to leave some unbound monomers, which can be released from packages into food and drinks over time. When plastics degrade, they can release BPA through normal use and/ or due to high temperature and exposure to alkaline or acidic solutions foods and beverage products (Halden, 2010; Lee *et al.,* 2016). Repeated washing of packages similarly accelerates leaching (Halden, 2010). Food and drinks stored in such containers

including the ubiquitous clear water bottles can have a trace amount of BPA (Proshad *et al.,* 2018). According to Lee *et al.* (2016) the daily human intake of BPA is ~ 1 µg/kg/bw.

Phthalates

Phthalates is an assemblage of organic lipophilic chemicals fundamentally used as plasticizers. Phthalate plasticizers (PAE's) are defined as benzene-di-carboxylic acid esters with dissimilar degrees of toxic results particularly endocrine disrupting changes (Saad *et al.,* 2015). Phthalates are extensively used as plasticizers in PVC products. Phthalates are non-covalently bonded with PVC; thus, they are free to migrate and are released into the surroundings by direct release, evaporation, migration, leakage and abrasion (Lee *et al.,* 2016). As a result, phthalates are capable of transferring into food, drink, skin, and the environment. The daily human intake is ~ 0.1-2 µg/kg/bw (Lee *et al.,* 2016).

Chemicals Migrating from Plastic Packages

People may be exposed to Food Package Material (FPM) migrating chemicals e.g., phthalates and others (Table 2) through different routes such as ingestion, inhalation, and absorption through the skin, that is, dermal exposure (Saad *et al.,* 2015) or parenteral administration (Mathur *et al.,* 2014). Both dermal exposure and inhalation are normal to short chain phthalates such as dimethyl and diethyl phthalates (DMP and DEP) owing to the day-to-day usage of soap, shampoo, conditioner and other personal care products. Oral exposure is largely due to consumption of phthalate-contaminated food with the long chain phthalates like di-ethylhexyl and di-*n*-octyl phthalates (DEHP and DOP).

However, human exposure to phthalate esters mostly arises through dietary intake, particularly plastic packaged foods owing to the weak covalent bond between phthalates and their parent materials (polymer) which cause release and bioaccumulation of phthalate esters into the packaged foods (Saad *et al.,* 2015). Direct interaction with food for primary packaging has been recognized as the major way in which chemical migration occurs. The migration of additives or contaminants from polymeric food packaging to food could be through three different, but inter-related, phases namely (i) diffusion within the polymer, (ii) solvation (association) at the polymer food interface, and (ii) dispersion

into bulk food. The migration has been demonstrated to increase with increasing food fat content and storage temperature (Al-Dayel *et al.*, 2012). Table 2 presents substances likely to migrate from food packaging materials to food.

Table 2: Overview of substances migrating from FPM

Type	Class of substance	Substance	FPM/ Use
IAS	Plastic monomers	Vinyl chloride	PVC
		Acrylamide	Polyacrylamide
		caprolactam	Polyamide
		6-aminohexanoic acid	polyamides
		p-hydroxybenzoic acid	Polyesters
		2-hydroxy-6-naphthoic acid	Polyesters
	Metals	Aluminum	Aluminum foil
	Plastifiers, monomers etc.		Plastic polymers, coated aluminum cans, coated paper / cardboard
	Dyes		Paper / cardboard
	Antioxidants		Plastic polymers
	Plastifiers	Bisphenol A, phthalates	Plastic polymers
	Photo-initiators	2-isopropylthioxanthone	Paper / cardboard
	Water / fat repellents	Perfluorinated acids etc.	Paper / cardboard
NIAS	Mineral oils	MOSH / MOAH	Recycled paper / cardboard

Source: Schrenk, D (2014); IAS - Intentionally Added Substances, NIAS - No-intentionally Added Substances (NIAS)

Factors affecting Chemical Migration into Food

The migration of chemicals from packaging materials into food and drink is a complex phenomenon that is influenced by several factors (Almeida *et al.*, 2018). The size of migrating chemical is among the determining factors. Chemical molecules or ions with small or less than 1000 Daltons are likely to leach into food (FSANZ, 2014). Ever since the non-

polymeric compounds mostly are of low molecular weight and are either delicately bound or not bound completely to the polymeric macro-molecules, they or their degradation products, can be detached from the plastic product to other contact media e.g., food, water and beverages (Mathur *et al.*, 2014).

The incompleteness of the polymerization process enables BPA monomer residues to migrate into food in the course of storage and processing at high temperatures in bottles or other containers (Almeida *et al.*, 2018). Chemical composition of food also affects the migration rate of the contaminants. For example, polarity and functional properties of the food packaging material like crystallinity and permeability may alter the migration of the additive or plasticizer into the food. Furthermore, the amount of fat in the food is vital in determining the rate of migration since most packaging chemicals are lipophilic (that is, dissolve readily in fat); thus, can freely migrate into fat foods at superior rates and levels (FSANZ, 2014). Chemical migration is also influenced by product filling conditions, storage environments, shelf life and food product: pack ratio. Impairment to the food product packaging might potentially lead to greater chemical migration through alterations in ambient oxygen, moisture, light and temperature (FSANZ, 2014). Almeida *et al.* (2018) further highlights other influencing factors to include the specific interaction between packaging material and food (direct or indirect contact), interaction time (since the concentration of the migratory chemical element in food is directly proportional to the square root of the interaction time), temperature during contact (higher temperatures appear to be associated with a higher migration rate due to increased diffusion rate), type of packaging / food contact material (finer packages are associated with higher migration rates) and the nature and amount of the compound migrating into food and drink (Almeida *et al*., 2018). The transfer of BPA from food contact materials to food is amplified by heating, contact with alkaline or acidic substances, excessive use, and exposure to microwaves (Almeida *et al.*, 2018). Chemical migration from a variety of plastic packages into food products have been demonstrated by several researchers (Zugravu and Cilincă, 2009; Tatiane *et al.*, 2018). This generally implies that though other factors can hardly be controlled, others can be controlled to minimize the rate of chemical migration and hence human exposure through ingestion.

Potential Health Risks due BPA and Phthalates Migration to Food

The functional role of food and beverage packaging as a source of pollutants has caused many concerns due to their extensive use. These pollutants originate from Food Packaging Material (FPM) constituents (monomers and other raw materials, additives, residues) which migrate from the packaging into the food (Al-Dayel *et al.,* 2012). It has also been indicated that some additives comprise of heavy metals (lead, cobalt, nickel, copper, etc.), highly toxic phthalates (Dibutyl phtalate or DBP) and other non-intentionally added substances (Lahimer *et al.,* 2013). However, the ingredients on which most health concerns have been placed to are BPA, which is applied in tough polycarbonate products and epoxy resins which line tin cans and a group of plastic softeners termed phthalates (Mathur *et al.,* 2014). Their health risks to human have attracted many investigations which have led to the accumulation of literatures in connection with human exposure to these compounds.

Bisphenol A (BPA)

BPA is regarded an endocrine disruptor and there is a relationship between exposure to BPA and the appearance of adverse health effects (Almeida *et al.,* 2018), such as cancer, infertility, diabetes, and obesity, among others. BPA has been shown to interact with estrogen receptors and act as agonist or antagonist through endocrine receptor (ER) dependent signaling pathways due to its phenolic structure. Lee *et al.* (2016) have also documented that BPA displays hormone like properties which might interrupt endocrine system function, obesity, cancer, heart disease, neurological effects, reproductive and sexual development deviation.

According to Warner and Flaws (2018) more hormones in the body can be interrupted by imitators in addition to estrogen. For instance, BPA can bind to androgen, estrogen, thyroid, estrogen-related, and peroxisome proliferator-activated receptors. More evidences have been documented by the European Parliament (2019) which implicates BPA to interact with a good number of nuclear receptors, including oestrogen receptors. Even though the intensity of the binding of BPA with the oestrogen receptor is

much weaker than that of natural (endogenous) oestrogen, this multiplicity of the receptors (some binding to BPA with strong affinity) and indicating pathways that may be activated or influenced by BPA could describe the great number of biological and health parameters likely to be influenced by BPA at very low doses. According to Konieczna *et al.* (2015), BPA play a role in the development of several endocrine disorders including female and male infertility, precocious puberty, hormone dependent tumours such as breast and prostate cancer and several metabolic disorders including polycystic ovary syndrome (PCOS). Elevated levels of urinary BPA concentration were correlated with a decreased number of sperm in the ejaculate, as well as its decreased motility and viability.

Studies experimented in men with prostate cancer revealed a much higher concentration of BPA in the urine of those patients in comparison with the control group (Konieczna *et al.*, 2015). Furthermore, BPA has been associated with obesity. Results from animal studies have been correlated with prenatal exposure to endocrine disrupting chemicals, BPA inclusive, and the incidences of obesity, impaired glucose tolerance and lipid metabolism in mice. Mice subjected to 10 mg BPA/kg body weight per day had greater concentrations of plasma triglycerides, and elevated body weight in four months of age as compared to the control group (Konieczna *et al.*, 2015). The relationship between obesity and plasma triglyceride concentrations has been demonstrated elsewhere (Després *et al.*, 1989). Their results documented significantly higher plasma levels of very low-density lipoprotein triglyceride (VLDL-TG), low density lipoprotein-cholesterol (LDL-CHOL), LDL-TG, LDL-apolipoprotein (apo) B and reduced high density lipoprotein-cholesterol (HDL-CHOL) levels in obese women compared to non-obese controls. As per Almeida *et al.* (2018), BPA being lipophilic, it can accumulate in adipose tissue which could also explain the levels of plasma triglycerides. According to Kelly *et al.* (2015) since BPA can be detoxified by the body and does not normally accumulate, it is debatable whether or not its serum concentrations can be high enough to affect the normal estrogen related functions. However, Calafat *et al.* (2005) in evaluating urinary concentration of BPA reported the detection of BPA in 95% of the samples studied at concentrations ≥0.1 μg/L urine; the geometric mean and median concentrations were 1.33 μg/L (1.36 μg/g creatinine) and 1.28 μg/L (1.32 μg/g creatinine), respectively; the 95th percentile concentration was 5.18 μg/L (7.95 μg/gcreatinine). On the other hand, Teeguarden *at al.* (2013) demonstrated the convergence of robust methods for measuring or

calculating BPA serum concentration from several published research outcomes.

They reported that characteristic serum BPA concentrations are in orders of magnitude lower than levels quantifiable by modern analytical techniques and below concentrations desired to occupy more than 0.0009% of Type II Estrogen Binding Sites, GPR30, ERα or ERβ receptors. Their results illustrated inadequate or no potential for estrogenicity in humans which in turn poses questions to reports of quantifiable BPA in human serum. Moreover, according to FSANZ (2014) migration of chemical from packaging to food are characteristically too little to cause acute adverse health effects. But, repeated dietary exposure to migrating chemicals over a long period could results to chronic exposure (FSANZ, 2014). It can thus be presumed that regardless of the low levels of migrating contaminants, the total exposure and health risks will depend on their overall accumulation overtime and toxicity level. Such accumulations of chemicals have been demonstrated in earlier studies (Almeida *et al.*, 2018). Moreover, according to Warner and Flaws (2018) the prototype of "the dose makes the poison" does not apply to BPA, phthalates, and other endocrine disrupting chemicals. The unique properties of BPA and phthalates, including low-dose effects, non-monotonic dose response curves (NMDRCs), and rapid metabolism, break up traditional principles of toxicology. On the other hand, FSANZ (2014) reported that allegations about a causal relation between BPA and a variety of public health effects are unproven. However, as reported by the European Parliament (2019) several studies have recorded effects of BPA at doses believed safe by regulatory thresholds operative in the EU.

Cases in point include the hypothalamic and hippocampal outcomes on gene transcription in rats, *in vitro* work on mouse and human pancreas demonstrating environmentally applicable levels (exposures in the 1-20 μg/kg body weight/day range) to modify insulin signals and other organ systems. Furthermore, according to Gerona *et al.* (2020), CLARITY data (i.e. data extracted from the Clarity database which is a large subset of data that comes from the PennChart (Epic) application) offer proof of significant adverse effects at the lowest dose studied (2·5 μg/kg per day), far lower than the lowermost discovered adverse effect level (5000 μg/kg per day) applied to establish the tolerable daily intake for BPA. Nevertheless, based on the hypothesis that human exposure to BPA is

negligible, the US Food and Drug Administration (FDA) has not taken into account the adverse low dose effects in CLARITY data and many other studies (Gerona *et al*., 2020). These data suggest disagreements in threshold value which could even undermine the exposure toxicity. It is well appreciated that knowledge about the amount of BPA that go into the human body is vital for risk assessment. Nevertheless, quick metabolism of orally ingested BPA means accurate evaluation in humans needs not only measurement of BPA but also of its major conjugated metabolites (the primary metabolite, BPA glucuronide, and secondary metabolite, BPA sulfate) which are however excreted in urine. As such (Gerona *et al.*, 2020) biomonitoring of urine over time offers the best understanding to human exposure to BPA. Differences in BPA measurement techniques have also been associated with discrepancies in BPA threshold value. According to Gerona *et al.* (2020) indirect techniques used in BPA exposure estimation underestimates actual human levels of BPA. The evidence established from the comparative analysis of urine samples using both indirect and direct methods demonstrated that the geometric mean established using indirect method was nearly 19 times lower than the direct method.

These inconsistence in BPA estimation and difficulties in its direct health effects characterization in human is due to BPA great changeability in the body over time (European Parliament, 2019), owing to a short half-life. Furthermore, the inconsistence could be linked with repeated exposures during the course of the day and dependence on a single bio-specimen collected in each subject, which is a design used so far in most epidemiological cohorts. They indicated that (European Parliament, 2019) this strong time-based variability will, on average, lead to a strong under-estimation of the slope of dose-response functions and a reduction in the ability of studies to demonstrate any effect of the compound. This observation suggests that even though direct methods can provide an estimation that could be more or less reflective of the actual exposure this could certainly be achieved if several bi-specimen are sampled over time for estimation of the mean exposure. Fisher *et al.* (2015) on the other hand reported low reproducibility and sensitivity of BPA and all phthalate metabolites all the way through pregnancy and into the postpartum period but much higher replicability within a day. The time of a day when the urine was amassed was a significant predictor of specific gravity adjusted exposure levels. This led to the conclusion that, if the intention is in average exposures across gestation, maternal/fetal exposure, approximation may be more accurate if multiple measurements, gathered

across the course of the entire pregnancy, rather than a single spot measure, are implemented. Available data indicate that estimates of human exposure have been based nearly fully on data from indirect methods, which implies underestimation of human exposure to BPA and proposes higher exposure than has been presumed formerly.

These different standings in threshold value suggest the need for extra studies to reconcile the differences. However, apart from the demonstrated disagreements among researchers in the currently available literature particularly with respect to the dose–effect relationship and threshold value of the migrating chemicals, overwhelming evidence still illustrate adverse effects associated with BPA and phthalates. Evidences of chemical migration are undisputable and the limits set by the EU have been demonstrated to be attained. Fasano *et al.* (2012) assessed the migration of BPA and phthalates (DMP, DBP, BBP, DEHP, OP, NP, and DEHA) from a variety of common food packaging and correlated their levels with the limits developed by the EU and compared the migration potential of plasticizers and additives from plastic wine tops at an incubation temperature of 40°C (Extreme Conditions) and ultrasonic extraction. The results indicated comparable levels of phthalates (NP, OP, BPA and DEHA) with EU maximum levels, all samples displayed chemical migration lower than specific migration limit (SML) and overall migration limit (OML) established (Reg 10/2011). Plastic wine tops exhibited the uppermost level of migration even though wine tops are not in contact with the wine but in the headspace of the bottle on the other hand, available reports indicate the potential role of BPA in the pathogenesis of breast cancer (Konieczna *et al.*, 2015) which could be among the factors that contribute to the development of prostate cancer as well. Evidence from animal studies documented by European Parliament (2019) strongly suggest effects of BPA on fat weight/obesity, metabolic disorders leading to type-2 diabetes, neuro development and behaviour such as hyperactivity, reproductive processes and memory performance.

Presently, BPA is prohibited from food contact materials intended for children under three years old in the EU but not for food contact materials in general (European Parliament, 2019). BPA is also linked with breast and prostate cancer due to its tumor enhancing properties (European Parliament, 2019). Determination of systemic levels of BPA in patients with type 2 diabetes mellitus (T2DM) was done (Soundararajan *et al.*,

2019) and compared to individuals with normal glucose tolerance ($n = 30$ each) signifies the European Parliament (2019) report on diabetes. Their results demonstrated significantly higher serum levels of BPA in patients with T2DM compared to control individuals and established a significant association of elevated BPA levels with cellular senescence, pro-inflammation, poor glycemic control, insulin resistance, and shortened telomeres (chromosome ends) in patients with T2DM. Such evidences suggest the role of BPA in the development of T2DM. In another investigation in which Comparative Toxicogenomics Database (CTD) was used (Hassan *et al.,* 2020), it was revealed that BPA has 1932 interactions with genes/proteins and few often used phthalates (DEHP, MEHP, DBP, BBP, and MBP) indicated 484 gene/protein interactions. Analogous toxicogenomics and adversative effects of BPA and phthalates on human healthiness are associated with their 89 common interacting genes / proteins (Hassan *et al.,* 2020). Such genes interactions are likely to affect the genetic pattern which provides evidence of the contaminant effects. The effects of BPA exposure in inducing abnormal DNA methylation of specific genes related to childhood asthma is also reported (Yang *et al.,* 2020).

The result showed that MAPK1 protein methylation was minor in children with asthma than in children without asthma. Mediation analysis proposed that MAPK1 methylation works as a mediation variable between BPA exposure and asthma. In view of the results, it was concluded that the mechanism of BPA exposure on childhood asthma could, therefore, be through the alteration of MAPK1 methylation. A more or less similar study (Miura *et al.,* 2019) examined the relationship of prenatal BPA exposure with genome-wide DNA methylation modifications in cord blood in 277 mother-child pairs. It was witnessed that a big share of BPA-associated differentially methylated CpGs was characterized with a decrease in epigenetic methylation in DNA (hypo-methylation) among all new-born (91%) and female infants (98%), as opposed to an increase in epigenetic methylation in DNA (88%) among males (hyper-methylation). They also found 27 and 16 CpGs with a False Discovery Rate (FDR) < 0.05 in the analytical study for both male and female, respectively. They concluded that epigenome-wide analysis of cord blood DNA methylation proposes potential sex specific epigenome reactions to BPA exposure (Miura *et al.,* 2019). This implies that similar exposure may have different outcomes based on an individual's sex. According to Almeida *et al.* (2018) age, gender, liver function, and physiological status are other factors that influence BPA metabolism.

Associations of urinary BPA levels (exposure) with sperm parameters including sperm movement characteristics among fertile men have been recognized (Honglei *et al.,* 2018). The available data indicate that exposure to BPA would reduce both sperm concentration and sperm swing characteristics [amplitude of lateral head (ALH) and mean angular displacement (MAD)], and raise sperm velocity ratios [linearity (LIN), straightness (STR) and wobbler (WOB)], which might facilitate additional effects on impaired male fertility.

Weakened spermatogenesis and sperm movement could illuminate some light on male subfertility resulting from exposure to BPA. The adverse effects of BPA on spermatogenesis have been associated with its interaction with Sertoli cells (somatic cell of the testis) and block the meiotic progression of germ cells (Honglei *et al.,* 2018). It is further documented that BPA can interact with steroid receptors, reduce steroidogenic enzymes, and generate reactive oxygen species (ROS), which might affect spermatogenesis. Rodent studies of both low- and high-dose BPA exposure have reported declines of sperm count and testosterone concentration, damage of sperm motility and sperm DNA impairment (Honglei *et al.,* 2018). The observation suggests the effect in spermatogenesis can occur at a wide range of BPA exposure doses. Earlier animal studies (NRDC, 2008) have also associated BPA with reproductive deformities such as lower sperm counts, hormonal changes, enlarged prostate glands, anomalies in the number of chromosomes in eggs, and pre-cancerous alterations in the breast and prostate. It has likewise been linked with obesity and insulin resistance, an ailment that usually precedes the development of diabetes. Similarly, it is documented that BPA offers a good illustration of complex receptor interactions (Cwiek-Ludwicka and Ludwicki, 2014). This is demonstrated by *in vitro* studies which show it to be both an oestrogenic receptor agonist and an androgenic receptor antagonist. In vivo studies also observed lots of different responses signifying a potential endocrine effect that was nonetheless expressed above its threshold value, that is, 5 mg/kg body weight (bw) per day. Toxicological studies on BPA permitted the No Observed Adverse Effect Level (NOAEL) to be established as 5 mg/kg bw/day, and as a result a Tolerably Daily Intake (TDI) level established to be 0.05 mg/kg bw/day (Cwiek-Ludwicka and Ludwicki, 2014).

An earlier review (Posnack, 2014) based on in vitro, in vivo and epidemiological studies indicate adverse effects of BPA on cardiac function, the cardiac electrical conduction effect being concentration-dependent. However, according to Warner and Flaws (2018) the prototype of "the dose makes the poison" does not apply to BPA, phthalates, and other endocrine disrupting chemicals. Data from mammalian model (Posnack, 2014) demonstrated modification in cardiac structure and function in mice. Other observations included sex-specific variances after BPA exposure, comprising of concentric remodelling (male), raised systolic and diastolic blood pressure (female) and altered calcium handling protein expression (male & female). These documented results generally indicate that while other adverse effects are sex linked others are sex independent. Epidemiological results indicate association between higher BPA urine levels and intensified risk of coronary artery disease, hypertension, carotid atherosclerosis, angina (inflammatory infection of the throat) and myocardial infarction (heart attack), and declined heart rate inconsistency. Higher BPA urinary levels have also been associated with LDL and HDL cholesterol levels, and the echogenicity of vascular plaques. Experimental data also advocate that BPA can affect a diversity of endocrine signaling pathways, taking account of those mediated by oestrogens, androgens, progestins, and thyroid hormone (Gerona *et al*., 2020). Exposure during pregnancy has been associated with changes in a wide array of developing tissues, with corresponding postnatal effects on behaviour, fertility, growth, metabolism and cancer risk.

Phthalates

Though the epigenetic effects of phthalates have not been entirely clarified, but gathering evidence proposes that they may be connected with adverse health effects, some of which may be heritable (Bowman and Choudhury, 2016). Phthalate migration into a variety of milk product have been illustrated and the levels of migration established. Saad *et al.* (2015) examined. the migration of the six most common phthalates of di-ethyl phthalate (DEP), di-methyl phthalate (DMP), benzylbrobyl phthalate (BBP), di-brobyl phthalate (DBP), di-ethylhexyl phthalate (DEHP) and dsi-n-octylphthalate (DOP) in samples of pasteurized milk, fermented milk "Rayeb" and Domuatti cheese packaged in plastic bottles and containers. Nonetheless, the results indicated that none of the 6 phthalates of DMP, DEP, DBP, BBP, DEHP and DOP were detected in any sample of milk, Rayeb and Domuatti cheese examined during the first

month of production in both bottle and container sizes. Similarly, none of the four phthalates namely DMP, DEP, DBP and/ or BBP were discovered in the three examined products up to the last month of expiry. Only 2 and 3, each out of 24 and 2 out of 18 samples of milk, Rayeb and Domuatti cheese, respectively displayed low levels of contamination with DEHP or DOP. The determined residues of DEHP or DOP phthalates ranged from 30 - 88 ng/ml. It is shown that adverse health risks among consumers depend on the type, nature and levels of chemical contamination which indicates consumer exposure. This could explain the variation in migration phenomenon of the six phthalates. The results further indicate that the total concentration of the contaminant (e.g., phthalate in this case) might not be reflective of the toxicity since not all types of phthalate might contribute to the contamination and hence toxicity.

Available data indicates that phthalates, which exist in more than 10 congeners in business and uncountable metabolites, can similarly interact with multiple hormone systems. Endocrine disrupting action might or might not be receptor driven and might be agonistic, antagonistic, or a mixture of both (Warner and Flaws, 2018). Even though the clinical consequence of phthalate exposure has been tough to assess with epidemiologic studies, the evidence that physiological variations occur due to exposure to phthalates is increasing and points toward the need for more examination at a molecular, specifically epigenetic level (Bowman and Choudhury, 2016). Phthalates, as is the case with BPA, are normally believed to disrupt endocrine function and badly affect sex and thyroid hormones, reproduction, and neuro development. Several in-vitro and in-vivo investigations have revealed that phthalates have functions analogous to the thyroid hormone and the capacity to bind thyroid receptors and, consequently, affect thyroid homeostasis (Kuo *et al.*, 2015). In a study of the relationship of phthalates exposure with thyroid function in pregnant women and their newborns (Kuo *et al.,* 2015) observed that the greater the urinary mono-benzyl phthalate (MBzP) level in pregnant mothers, the lesser the Thyroid Stimulating Hormone (TSH) level in cord blood serum. It was concluded that maternal urinary MBzP may affect TSH activity in newborns. The modification of thyroid homeostasis by certain phthalates in the initial life, which is a critical period for neurodevelopment, is a pressing concern. Among the phthalates, dibutyl phthalate (DBP) and bis(2-ethylhexyl) phthalate (DEHP) have a common mode of action, but different active metabolites

(monobutyl phthalate (MBP) versus mono-(2-ethylhexyl) phthalate (MEHP)) and are thought to have the biggest effect on development of metabolic disorders (Baralić *et al.,* 2020). Examination of the association between phthalate exposure and central precocious puberty (CPP) in girls (Jung *et al.,* 2019) demonstrated no significant difference in the five urinary phthalate levels between the CPP and pubertal control groups.

Furthermore, phthalate metabolites were significantly lesser in the CPP group than in the pre-pubertal control group. Earlier studies also reported conflicting results on CPP and phthalate concentration. Whereas Chen *et al.* (2013) indicated significantly higher levels of seven urinary phthalates [(1) MMP, (2) mono-ethyl phthalate (MEP), (3) MBP, (4) mono-benzyl phthalate (MBzP),and (5) MEHP; and two oxidized metabolites:(6) mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and (7) mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)] in the CPP group than in pre-pubertal controls, Lomenick *et al.* (2010) revealed no difference in nine urinary phthalates [DBP (Di-n-butyl phthalate), DEHP (Di-(2-ethylhexyl) phthalate), MBP (Mono-n-butyl phthalate), MBzP (Monobenzyl phthalate), MCPP (Mono-3-carboxypropyl phthalate), MECPP (Mono (2-ethyl-5-carboxypentyl) phthalate), MEHP (Mono (2-ethylhexyl) phthalate), MEHPP (Mono (2-ethyl-5-hydroxyhexyl) phthalate), MEOHP (Mono (2-ethyl-5-oxohexyl) phthalate)] between girls with CPP and pre-pubertal controls, proposing that phthalate exposure is not linked with CPP. Several studies (as reviewed by Posnack, 2014) have similarly documented toxic effects of Di-(2-ethylhexyl) phthalate (DEHP) and its byproducts based on in vitro, in vivo and epidemiological studies.

The documented toxicity includes cardiac toxicity leading to termination of contractile function in chick embryonic cardiomyocytes, reduction in systolic and diastolic blood pressures in male offspring after in utero exposure to DEHP and a rise in blood pressure in rat offspring after maternal exposure to DEHP. Epidemiology data on the other hand indicated a direct relationship between elevated urinary phthalate levels and both increased blood pressure in adolescent population and increased coronary risk in the elderly people. Posnack (2014) also documented significant relationship between elevated MEHP (Mono (2-ethylhexyl) phthalate) urinary levels and Low Density Lipolipid (LDL) cholesterol levels and the echogenicity of vascular plaques, but not blood pressure. Echogenicity of vascular plaques is an indicator of lipid infiltration and a foreteller of future cardiovascular demise.

Synergistic Effects of Phthalates and Bisphenol A

Though several studies which have been conducted so far are based on single endocrine disrupting chemical (EDC), that is, (phthalate or BPA) recent data conflicts such documented observation on the basis of combined effects. Baralić *et al.* (2020) compared the subacute toxic effects of low doses of single compounds (bis (2 –ethylhexyl) phthalate (DEHP), di-butyl phthalate (DBP), and bisphenol A (BPA)) with the effects of their mixture through different biochemical, hormonal, and hematological parameters in-vitro using rats. It was observed that a blend of low doses of DEHP, DBP and BPA caused significant alterations in body weight gain, water and food consumption, thyroid hormone and testosterone levels, lipid profile, liver-related biochemical parameters, and the glucose level as opposed to single substance doses on compared parameters. It was concluded that more noticeable effects witnessed at certain parameters with mixture exposure are due to the elevated total exposure amount, suggestive of the dose addition.

The results of the study challenge the results of toxicity studies of single chemicals and further contribute to the understanding of the health effects triggered by exposure to chemical mixtures. The results imply that exposure effects estimated based on single endocrine disrupting chemical (EDC) might have underestimated the overall effects of its blend. Reproductive toxicity of phthalates and BPA was examined (Baralić *et al.*, 2020) in binary and multicomponent blends, commonly targeting male reproductive tract disorders, mostly after the perinatal exposure. It was shown that prenatal exposure to the blend of DBP and DEHP changes fetal testosterone production and insl3 gene manifestation in a manner that resulted in cumulative dose-additive escalations in reproductive tract malformations (Baralić *et al.*, 2020). Manikkam *et al.* (2013) also examined the effect of mixed EDCs bisphenol-A (BPA) and phthalates [bis (2-ethylhexyl) phthalate (DEHP) and di-butyl phthalate (DBP)] at two dissimilar doses in promoting epigenetic transgenerational inheritance of adult-onset disease and associated DNA methylation epimutations in sperm. The results showed significant increases in the prevalence of total disease / abnormalities in F1 and F3 generation male and female animals from plastics lineages. Pubertal anomalies, testis disease, obesity, and ovarian disease (primary ovarian inadequacy and polycystic ovaries) were increased in the F3 generation animals. Prostate and kidney disease were only witnessed in the direct fatally exposed F1

generation plastic lineage animals. Examination of the plastics lineage F3 generation sperm epigenome earlier identified 197 differential DNA methylation regions (DMR) in gene promoters, termed epimutations. The results show that a blend of plastic derived compounds, BPA and phthalates, can boost epigenetic transgenerational inheritance of adult-onset disease. The sperm DMR provide potential epigenetic biomarkers for transgenerational disease and/or ancestral environmental exposures.

This observation further justifies the need for consideration of the synergistic effect of the plastic derived EDCs in particular BPA and phthalate. Another study (Pednekar *et al.,* 2018) evaluated the exposure of BPA and phthalates in plasma samples of fertile and infertile women. BPA and four phthalate monoester metabolites [namely mono-benzyl phthalate (MBzP), mono-methyl phthalate (MMP), mono-2-ethylhexyl phthalate (MEHP) and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)] were quantified in human plasma. BPA was evident in 77% of plasma samples of infertile women and 29% of fertile women. All the four phthalate metabolites were identified in plasma samples of both fertile and infertile women. The infertile women indicated significantly higher plasma levels of MBzP, BPA and MEHHP as compared to fertile women.

The concentrations of MMP and MEHP did not vary significantly between the two groups. The results generally suggest the likely association of BPA, MBzP and MEHHP with infertility implying their combined infertility effect. Furthermore, the observation implies that some phthalates (MMP and MEHP) have insignificant effects on women infertility. This could on the other hand suggest that the total concentration of a particular plastic monomer (phthalate in this case) might not be indicative of the reflective dose effect for a particular health risk.

CONCLUSION

Available literature provides evidences which demonstrate that chemical migration from plastics packaging is an unquestionable reality. Though several chemicals are migrating from plastic packages, however, the chemicals of great health concerns are BPA and phthalates. There is accumulated evidence of the human health risks associated with BPA and phthalate leakage into packaged food with dietary intake being the major

root for human exposure. The health effects due to migrating chemicals is demonstrated to be through their interactivity with multiple hormone systems, implying a wider range of effects that can occur depending on the number of affected hormonal receptors. Although disagreements among researchers are still demonstrated in available literature particularly with respect to the dose-effect relationship and the threshold value of the migrating chemicals, however, overwhelming evidence still illustrate several adverse effects associated with BPA and phthalates which can hardly be undermined. Such effects include adverse effects on spermatogenesis, obesity, type two diabetes mellitus, raised systolic and diastolic blood pressure (female) and altered calcium handling protein expression (male & female), coronary artery disease, hypertension, carotid atherosclerosis, cancer risks, angina etc. Even though several studies have been done for a single chemical (BPA or phthalates) the comparative results indicate a cumulative dose-additive amplification when a mixture of the two is examined which implies the need for further reexamination of the synergistic effect of the plastic derived EDCs in particular BPA and phthalate.

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