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Review Article

Phthalates in Food Packaging-Impact on Human Health

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Abstract: Phthalates are esters of phthalic acid and aliphatic alcohols. It is widely used in everyday life, and can be used as a plasticizer, solvents and additives in many products, from food packaging to items of general use. Plastic materials are widely used in food industry and potentially can be source of phtalates in food. Phtalates can be present in food as a result of contamination of food. Phtalates in food, as a result of contamination of food or migration from packaging can jeopardiye human health. This work provides an overview of the presence of phthalates in food packaging, its migration into food, as well as the negative impact on human health by consuming and inhaling them.

Keywords: Phtalates, food, packaging, contamination, human health.

INTRODUCTION

Phthalates are esters of phthalic acid and aliphatic alcohols. It is widely used in everyday life, and can be used as a plasticizer, solvents and additives in many products, from food packaging to items of general use. High molecular weight phthalates, of which DEHP is the most common, are used as a plasticizer in food-grade plastic packaging material, while low molecular weight phthalates, as DEP and DnBP, are used as solvents and plasticizers in the production of items of general use.

The use of plastic materials is generally present in the food industry, so they are used as packaging material for packaging finished products, and in the process of processing and production. Since phthalates are not chemically bounded to the PVC polymer, they migrate very easily from the packaging material to the food product, but migration can occur during the technological process of food production and processing from plants in industrial facilities. Because of their lipophilic character, phthalates most often migrate to foods that are high in fat such as milk and dairy products, meat and meat products, fish, vegetable oils and fats.

Phthalates are, also, detected in food products that are not packed in packaging material containing phthalates, from which it can be concluded that the contamination of the product occurred due to environmental pollution such as water, air, soil as well as due to widespread use and its disposal to landfills.

Based on available scientific research, it has been proven that there is no bioaccumulation of phthalates and their esters in the human body. Because of the increasing use of phthalate, as well as its presence in the environment there is a justified concern for human health, especially because it leads to disorders in the reproductive and endocrine systems of human. Considering the high exposure of human to phthalates, the question of the justification of the use of phthalates arises, both in food packaging and in items of general use. This work provides an overview of the presence of phthalates in food packaging, its migration into food, as well as the negative impact on human health by consuming and inhaling them.

DIVISION, PROPERTIES AND METHABOLISM OF PHTHALATES

Phthalates are compounds of synthetic origin that are most often added to plastics to improve their mechanical properties, especially softness, flexibility and extensibility. As plasticizing additives, they are present in a number of items of general use, such as children's toys, cosmetics, solvents and insecticides, food packaging, medical devices, transfusion accessories and home improvement products, as well as in technological processes in the food and similar industries. (David and associates, 2003; ATDSR, 2001; ATDSR, 2002; Heudorf and associates, 2007). According to their chemical composition, phthalates are esters of phthalic acid and aliphatic alcohols (diesters of phthalic acid). These are volatile liquids that are added to plastic to increase its mobility.

Phthalates are obtained by esterification of phthalic anhydrides with long-chain alcohols (C7-C10) (Earls amd associates, 2003). If two ester groups are attached in the meta and para positions on the aromatic ring, they are called isophthalates or teraphthalates. In case the two ester groups are in the ortho position on the aromatic nucleus of 1,2-benzenedicarboxylic acid, they are called phthalic acid esters. The two alkaline groups may be similar or different; they may be branched or unbranched; may contain aromatic substitutes, for example butyl benyl phthalate (BBP) or other functional groups (Croatian Food Agency, 2014)

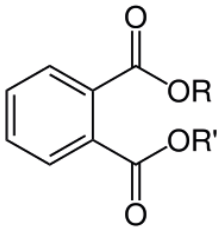

FIGURE 1: General chemical structural formula of phthalate

The proportion of phthalate in a plastic product can be up to 45% of its total weight, depending on the type and purpose of the plastic product (Peakall, 1975; Brooke and associates, 1991; WHO, 1997; Bouma and Schakel, 2002). The most common DEHP that adds to plastics to provide elasticity and softness (Croatian Food Agency, 2014). Every year, about a million tons of phthalate are produced in Western Europe, where the most common are: di- (2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP) and diisodecyl phthalate (DiDP) (Fierens and associates, 2012), di metli phthalate (DMP), di ethyl phthalate (DEP), di n butyl phthalate (DBP), butyl benzyl phthalate (BBP) and polyethylene ether phthalate (PET) which in addition to being used as an intermolecular lubricant tend to be excreted from the medium (Karen and Wright, 2006).

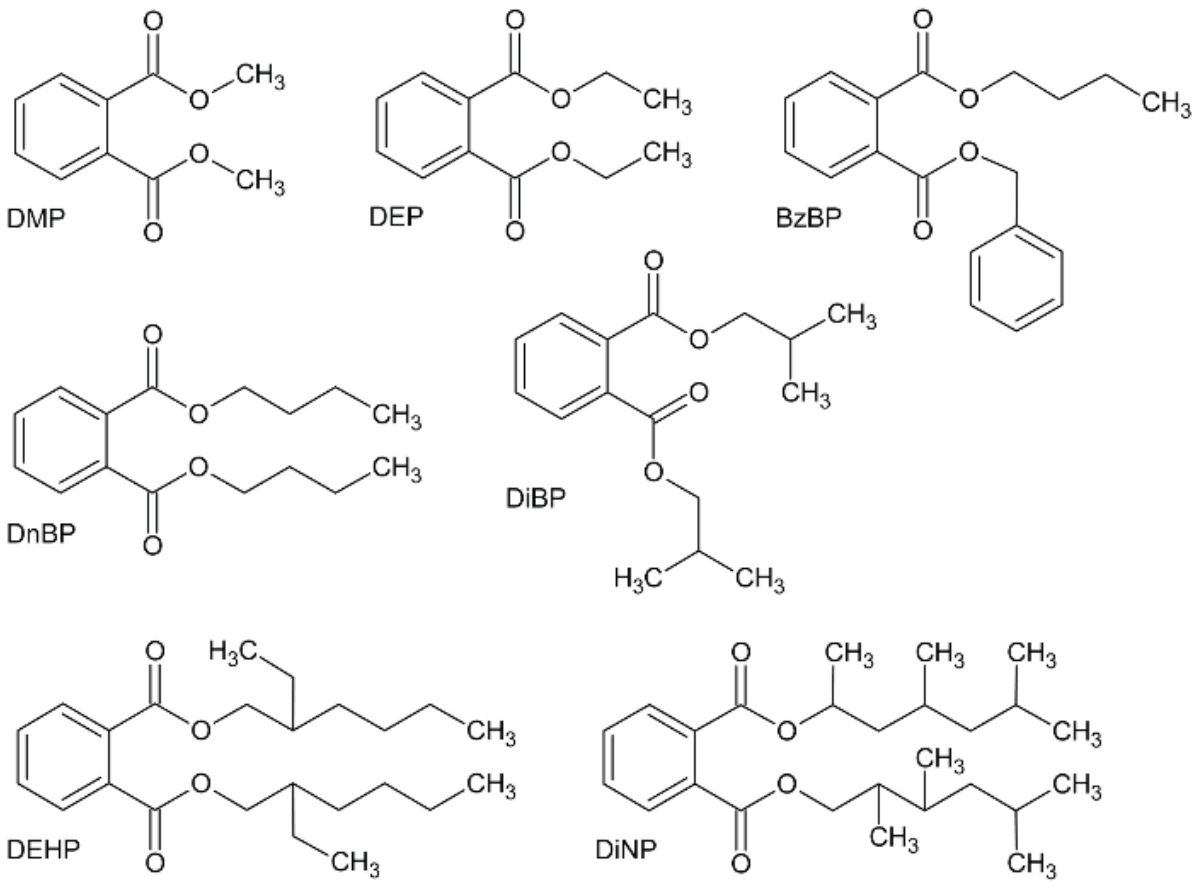

FIGURE 2: Structural formulas of phthalates (Frederiksen and associates, 2007)

Phthalates which have slightly short alkyl groups in their structure, such as methyl and butyl groups, have the feature of solubility in water, and phthalates with long alkyl chains or aromatic structures on the end chains are poorly soluble in water. High molecular weight phthalates, such as DEHP, are mainly used as a plasticizer in the production of PVC polyvinyl chloride, which is used in consumer products, such as food packaging (plastic packaging film), medical devices, vinyl foils (ATSDR , 2002). Lower molecular weight phthalates, such as DEP and DnBP, are used as solvents and plasticizers for cellulose acetate, in the manufacture of varnishes, personal care products (e.g. perfumes, lotions), as well as medicine packaging (ATSDR, 1995, 2001) such as prolonged-release medications (Hauser and associates, 2004).

Because of its lipophilicity, the largest amount of phthalates is found in fatty foods, such as milk and dairy products, fish, meat, and vegetable oils (David and associates, 2003). If short alkyl groups such as e.g. methyl or ethyl group, are at the end of chains, the volatility of phthalates is stronger, so it is possible that we will inhale phthalates without even being aware of it, so in the cosmetics industry these compounds are used in the production of perfumes and fragrances.

Phthalates are not chemically bound to polymers, so they can migrate freely from packaging as well as during the production process into food, beverages and drinking water (Serôdio and Nogueira, 2006). Phthalate migration is accelerated by aging and cracking of plastic packaging or plastic parts used in the food and beverage production process (Harris and Sumpter, 2001).

Since they are not chemically bound to plastic material, phthalates are easily washed away, evaporate quickly into the air and easily migrate into food, beverages and drinking water, most often from pack-

aging material, but other sources of food contamination with phthalates are also possible, e.g. from parts of the technological process of food production (European Chemical Bureau, 2008; European Union Council, 2001; Balafas and associates, 1999; Chou and Wright, 2006). Thanks to this, phthalates contaminate the environment and the food chain and are now one of the ubiquitous environmental contaminants. As a result, the general population is extensively and continuously exposed to phthalates (Sioen and associates, 2012). Since its first use as a plasticizer in 1930, phthalates have become one of the most widespread contaminants in the modern world. Unlike persistent organic pollutants such as organochlorine pesticides e.g. DDT, phthalates and its metabolites do not accumulate in the environment and have a short half-life in living organisms. Thus, monoester metabolites were detected in 90–100% of urine samples of men and women of the general population (Duty and associates, 2005a; Hoppin and associates, 2002; Kato and associates , 2005; Swan and associates, 2005).

One of the essential properties of phthalates, which determines their application, is the molecular weight. High molecular weight phthalates DEHP, DINP and DIDP are mainly used to soften PVC. Low molecular weight phthalates DEP, DBP and BBP have solvent function in consumer items (Cao XuL, 2010). They are mostly used in the cosmetic and pharmaceutical industries. DEP is used as an odor fixative or carrier in the production of fragrances, perfumes and in prolonged-release medications. Among other low molecular weight phthalates, dimethyl phthalate (DMP) should be mentioned. DMP is most commonly used to stabilize and dilute organic peroxides during transport and storage (Clark and associates, 2011).

Table 1: Properties of phthalates (Cao XuL, 2010)

Phthalates	CAS number	Formula	Density (g/ml)	Boiling point (°C)	Melting point (°C)	Water solubility (mg/l) at 25°C
DEHP (di-2-ethylhexyl phthalate)	117-81-7	C24H38O4	0,985	384	-47	0,195
DBP (di-n-butyl phthalate)	84-74-2	C16H22O4	1,043	340	-35	9,9
BBP (benzyl butyl phthalate)	85-68-7	C16H22O4	1,119	370	-35	3,8
DINP (di-iso-nonyl phthalate)	68515-48-0; 28553-12-0	C26H42O4	0,972	370	-50	3,08 x 10-4
DIDP (di-iso-decyl phthalate)	68515-49-1; 26761-40-0	C28H46O4	0,966	400	-50	3,81 x 10-5
DNOP (di-n-octyl phthalate)	117-84-0	C24H30O4	0,985	390	-25	2,49 x 10-3
DEP (diethyl phthalate)	84-66-2	C12H14O4	1,232	295	-40,5	591

PHTHALATES IN FOOD PRODUCTS

Progress in the science of packaging materials in recent decades have led to the widespread and diverse use of plastics to provide cheaper, lighter, stronger, safer, more durable and versatile products and consumer goods that serve to improve quality of life. Plastics can be designed to keep food fresher for longer, and can provide therapeutic benefits through time-release medications and other medical applications (Andrady and Neal. 2009; Thompson and associates, 2009 a, b).

The presence of phthalates in food can be the result of their migration from packaging materials and objects in direct contact with food, and food contamination from the environment or food contamination caused during the production or processing process. The most commonly observed phthalate in food

is DEHP, which is not surprising given the fact that 50% of total annual phthalate production is DEHP (Wenzl, 2009). Phthalates identified in food are mainly higher molecular weight phthalates such as DIDP, BBP and DIBP. The amount of phthalates that will migrate into food, and especially into fatty foods, will be greatly influenced by their initial concentration in the material, lipophilic character, temperature, storage and storage conditions, and the fat content in the food. Phthalates are not covalently bound within the PVC molecule, in principle similarly dissolve similarly, small amounts of fatty foods or oils are sufficient for complete extraction of lipophilic softeners into food. As the release of phthalates from PVC is mainly related to direct contact with fatty foods, manufacturers of packaging materials have changed the recipes. Diisononyl adipate (DINA) and di-2-ethylhexyl adipate (DEHA), which until recently were used as a substitute for DEHP (Cao XuL, 2010), are slowly being replaced by citrates. The most commonly used citrate as a softener for PVC but also for other types of packaging materials in contact with fatty and non-fatty foods is acetyl tributyl citrate (ATBC). Except ATBC, there are a significant number of other substitute softeners for phthalates, but there is insufficient scientific evidence of their adverse effects on human health. Phthalates are most often present in multilayer packaging, while in smaller quantities they are found in varnishes and printing inks. Phthalates can be present in the coatings of dishes, utensils and food preparation equipment from which they can be released into food during thermal food preparation (Fierens and associates, 2012). Choosing the type of packaging in which a particular type of food will be packaged can reduce or increase the specific migration of phthalates.

Food products are contaminated with phthalates by unintended migration during the technological process of production, processing and packaging of finished products through packaging materials in which the finished products are packed. Fresh agricultural products contain minimal concentrations of phthalates. The total concentration of phthalate in fresh meat (muscle) and raw milk is 120 - 280 micrograms / kg, rarely exceeding 500 micrograms / kg (Casajuana and Lacorte, 2004; Rhind and associates., 2005; Sharman and associates, 1994). Elevated phthalate values up to 53000 micrograms / kg have been detected in finished food products that are considered to be most likely contaminated during processing or in the packaging process (Castle and associates, 1989). Studies have shown an increase in DEHP from 80 micrograms / kg in fresh chicken meat to 13100 micrograms / kg after frying in a Teflon-lined pan, and 16100 micrograms / kg after packaging (Tsumura and associates, 2001a).

Hot fats and food products packed in PVC packaging, significantly raise the level of phthalates. High temperatures and fatty hot food in contact with PVC products can cause high levels of phthalate contamination. Many of us buy and store cooking oil in plastic bottles, eat butter, margarine, cheese spreads from plastic containers and it never occurs to us to take in some foreign substances that "dissolve from plastic". Phthalates are released especially quickly from plastic bottles that contain mineral water and carbonated drinks. Contamination of the land with phthalates near the waste recycling site was also observed. So waste recycling places have become a threat to human health. The main pollutants found in the soil are DEHP and DnBP.

The plastic film used in greenhouses has become another source of phthalate in food, with an elevated concentration of phthalate in vegetables ranging from 790 ± 630 to 3010 ± 2130 mg / kg on Nanjing agricultural land where vegetables are grown. Ma and associates, 2015).

EFSA (2005) reported a tolerant daily intake (TDI) of 50 μg / kg body weight for DEHP and 10 μg / kg body weight for DnBP. A regulation issued by EFSA to prevent food contamination by phthalates considers that phthalate concentrations in food greater than or equal to a specific migration limit (SML) of 300 μg / kg are high (Petersen and Jensen, 2010). Concentrations in food between 0 and 50 μg / kg were considered low, because in the opinion of EFSE, the migration in these concentrations reflects the low exposure potential. Concentrations between 50 and 300 μg / kg are marked as mean (Engel and associates,

2012). Thus, when classifying food, it is necessary to apply the criteria for average, and not for maximum measurements, so as not to misclassify food as food with a high phthalate concentration. To protect human health, the European Food Safety Authority (EFSA) has established a total daily intake (TDI) for some of these food-contaminating substances, in particular for DBP 0.01 mg / kg body weight, for BBP 0.5 mg / kg body weight, for DiNP and DiDP 0.15 mg / kg body weight, for DEHP 0.05 mg / kg body weight (EFSA, 2005a, b, c, d, e). Due to toxicity and widespread use, European Regulation no. 10/2011 established a specific migration limit (SML) for DEHP of 1.5 mg / kg.

Serrano and associates (2014) in their study compared the association of a group of foods with high (≥300 μg / kg) and low (<50 μg / kg) phthalate concentrations, as well as their relationship with the load they represent for the human body. Based on the data obtained in the study, they found high concentrations of DEHP in poultry meat, roasting oil and cream-based dairy products (≥300 μg / kg). Also, the presence of DEP in small concentrations in all food groups was determined. According to the data of this research, epidemiological studies have shown a positive connection between the consumption of meat, fat, dairy products and DEHP. The estimated DEHP exposure based on typical diet was 5.7; 8.1 and 42.1 μg / kg per day for women of reproductive age, adolescents and newborns, with dairy products as the largest source of exposure. A diet rich in meat and milk resulted in a twofold increase in exposure. Estimates for infants based on a typical diet exceeded the Environmental Protection Agency's reference values of 20 μg / kg per day, while a diet rich in milk and meat in adolescents also exceeded this threshold.

Fierens and associates (2012) investigated the effect of cooking (cooking, steaming, frying or grilling) at home on the level of phthalates in different types of food (starch products, vegetables, meat and fish). In general, phthalate concentrations in food were reduced after cooking, except in vegetables, where there were almost no changes. DEHP, which was present in all raw foods, decreased to 65.4% after cooking. Sioen and associates (2012) in their study, found cooked food in kindergartens and primary schools has a higher concentration of DEHP and DBP after packaging in aluminum-lined polyethylene containers and stored in warm electric isothermal serving carts compared to before, which implies migration from packaging (Cirrilo and associates, 2011). The influence of cooking and heating in phthalate-containing containers must be taken into account when calculating the exposure assessment in order to determine the exact phthalate content in food directly consumed. Also, it is necessary to determine the difference between food products when calculating daily intakes (milk, meat, cereals), and take into account which of the products are most exposed to phthalates, this is especially important when making dietary recommendations for foods with high phthalate exposure that should be avoided.

PLASTIC WRAPPING

Today's way of life is difficult to imagine without the use of plastic products, which, as such, accompany a person throughout his life, starting from birth (Brooke and associates, 1991; WHO, 1997; Peterson and Breindahl, 2000).

Food packaging is very important for storing food at different temperatures, prolongs the shelf life of the food product itself, and also protects foods from natural agents such as air, which can reduce or change the quality of the product itself. In practice, plastic is used as a safe and suitable packaging for primary food packaging. There are several different types of plastics, each of thoose has unique properties and applications in the food sector, e.g. polycarbonate, high and low density polyethylene, styrene, polypropylene. Plastic packaging is made of various polymers, and additives are used to improve elasticity, flexibility, color, resistance, durability, etc. Both plastics and additives can migrate over time from packaging to food or beverages as a result of increased product temperatures or mechanical stress.

According to Cao (2010) research, phthalates can migrate into foods made from PVC materials, such as pipes commonly used in the milking process, lid seals, food packaging foils, gloves used in food preparation, and conveyor belts. Phthalals are also found in printing inks and adhesives on food wrappers, as well as container coatings used in food packaging (NTP-CERHR, 2003; Indirect food additives, 2014). In the United States, phthalates are approved by the Food and Drug Administration (FDA) as plasticizers in food packaging and food contact materials used during processing and storage, while the European Commission and Chinese authorities have restricted phthalates in contact with food (Petersen and Jensen, 2008). There may be large variability in phthalate concentrations in food groups depending on the food production process, processing process, presence and type of packaging, and lipid content (Wittassek and associates, 2011; Schecter and associates, 2013). The assessment of phthalate exposure in food has become a topic of great interest given the importance of the dietary pathway and the health impacts associated with specific phthalate species found in food.

Increased phthalate content has been reported in drinking water packaged in polyethylene bottles (Criado and associates, 2005). The results of the research (Bošnir and associates, 2007) show that the values of phthalate migration from plastic packaging into soft drinks are many times higher (5 to 40 times) than the migration of phthalate from the same packaging into mineral water. As one of the possible reasons, the authors state a difference in pH value that is less than 3 in soft drinks and greater than 5 in all mineral waters (Jurica and associates, 2013). The World Health Organization has defined the maximum permissible concentration of the most used phthalate DEHP in drinking water and it is 8 micrograms / l (WHO, 2011).

Polyvinyl chloride (PVC) polymer without the addition of softener would be very heavy, brittle and practically useless for technical application, so that with the addition of softener it becomes flexible and elastic. Softeners are mostly added to polymers used in the food industry. These are foils for wrapping food and the like. Contamination of food with softeners can occur. The best known softeners to be added are high molecular weight phthalates, such as butylbenzyl phthalate (BBzP), di-2-ethylhexyl phthalate (DEHP) and di-n-octyl phthalate (DnOP) used as plasticizers in PVC materials, such as are food packaging and medical products. In recent years, di-nonyl phthalate (DiNP) and di-decyl phthalate (DiDP) have increasingly replaced DEHP in these products (Zotta and associates, 2014). Due to non-covalent bonds between phthalates and their parent substances, there can be significant migration of phthalates not only into the food product but also into the environment which can lead to environmental pollution and thus ubiquitous exposure in the population.

Castle and associates (1988a) proposed two ways to reduce the migration of phthalates from PVC food films:

- production of thinner films with a reduced level of DEHA that is normally present in PVC films
- partial or complete replacement of DEHA with higher molecular weight plasticizers.

The migration of plasticizers from DEHA-coated PVC packaging films increases with prolonged contact time between the food product and the PVC packaging film (Down and Gilbert, 1977). It was observed that when using thinner PVC films containing 13.3% DEHA compared to conventional PVC film with 18.30% there was a decrease in the level of DEHA migration from 41% to 53%. The migration level of plasticizer from PVC foil with 23% plasticizer was 3 to 21 times lower than the level of DEHA migrating from conventional PVC film with 18% DEHA. Also, DEP was detected in baked food products, which were packed in cardboard boxes with cellulose-acetate openings plasticized with 16 to 17% DEP, where DEP is present in the product in the range of 1.7 to 4.5 mg / kg. From which it can be concluded that DEP evaporated, and thus DEP migrated into food, although there was no direct contact of DEP with food.

Tsumura and associates (2001b) investigated the contamination of food with phthalates derived

from PVC gloves in retail outlets serving ready-to-eat foods. PVC gloves used in food preparation contain up to 41% DEHP, 60.2% DEHA, 74.8% DiNO, 27.9% BBzP. They came to the conclusion that the level of phthalates in ready meals (in contact with PVC gloves) was increased in relation to the raw materials from which the finished dish was prepared (not yet in contact with PVC gloves). The authors also noted lower phthalate levels in ready meals in which PVC gloves were not used in the preparation.

Different plasticizers such as epoxidized soybean oil (ESBO), phthalates, adipates, etc. can be used as PVC sealants in different countries. In order to reduce the migration of plasticizers from PVC lid sealants into foods, especially fatty foods, the use of polyadipates as high molecular weight plasticizers was investigated (Biedermannand associates, 2008). Although polyadipates have been used successfully as PVC interrogators, they are not easy to work with because they create a viscous plastisol that makes it difficult to place a uniform ring in the lid, so viscose plastisol needs to be diluted with less viscous plasticizers (Castle and associates, 1988a). The results of the research showed that the migration of polyladipates was below the legal limits in 11 foods that were stored for two years in packaging containing polyadipates. Thus, di (2-ethylhexyl) terephthalate (DEHT) is used as a new plasticizer in Canada, as a substitute for DEHP in PVC sealants used to close beverage bottles (Parent, 2009), indicating a declining trend in the use of DEHP in packaging materials in food products in North America.

Polystyrene (PS) is a styrene polymer that in its pure state is a hard, colorless plastic with limited flexibility. It can be poured into molds with fine details and thus used for packaging yogurt and dairy products. The packaging for the yoghurt packaging contained traces of DMP, but also high amounts of DEHA. These compounds can migrate into fatty foods at high temperatures during production. On the other hand, expanded polystyrene can be used as a base for packaging meat, fish, cheese, fruit and the like. Polystyrene substrates can release some compounds such as DMP, DEHP, OP, NP and DEHA (Fasano and associates, 2012).

PET is a product formed by the reaction of terephthalic acid and ethylene glycol. Because of the properties such as strength and clarity, this polymer is used for the production of PET bottles for water packaging, soft drinks and other food products. Comonomers such as isophthalic acid and dimethyl terephthalate can be used to produce polymers that provide thicker-walled PET bottles, which allows them to be used for packaging large-volume liquids (Park and associates, 2008). Due to incomplete reaction, residues of monomers (terephthalic acid, ethylene glycol, isophthalic acid, dimethyl terephthalate) in the polymer can migrate from PET packaging to food. PET degradation products (e.g., terephthalate) and polymeric additives such as Tinuvin P or Tinuvin 234 can migrate into food (Monteiro and associates, 1999; Begley and associates, 2004; Choodum and associates, 2007). Due to the name "phthalate" in the name of the polymer, it gives the wrong impression that phthalates and DEHA can be migrated from PET packaging to food (Biscard and associates, 2003; Farhoodi and associates, 2008; Montuori and associates, 2008). It should be emphasized that PET polymers have no chemical or physical bonds with phthalates, even their chemical structures are different. Phthalates are esters of orthophthalic acid, while paraphthalic acid (terephthalic acid) or metaphthalic acid (isophthalic acid) is used to produce PET polymers. Unlike PVC packaging, which needs to be plasticized with phthalates in order to be more flexible, PET packaging should be as strong and rigid as possible, for that reason it is important to emphasize that phthalates are not used in the production of PET polymers.

Plasticizers, such as DBP, DCHP and DEHP are ingredients in printing inks (2-8%) for food packaging, and are used to improve the adhesion of paint to the packaging surface, flexibility and resistance to crease formation (Castle and associates, 1988). Regardless of the fact that the ink is on the outside of food packaging (film, cardboard), it can be one of the sources of phthalates in food. The ink used to print declarations on confectionery and snack products is one source of phthalate contamination of these products

(Castle and associates, 1989). Confectionery and snack products were stored for 90 to 180 days at 20 ℃ in polypropylene packaging with printing ink. Considering propylene itself does not contain plasticizers, the migration of plasticizers into food came from the printing ink on the packaging. Castle and co-workers found in their research that there was an increase in DBP migration from 0.2 to 6.7 mg / kg over a period of 180 days. The presence of one or more plasticizers has been observed in a number of confectionery and snack products packaged in printed polypropylene packaging. Balafas and associates (1999) discovered the presence of phthalates and adipates in food products packaged in printed PE materials, which led to the conclusion that printing inks are the ultimate source of food contamination. To solve these problems, new technologies are being introduced where packaging material manufacturers are focusing on minimizing the use of ink and introducing new ink curing techniques such as fast UV systems that reduce ink evaporation. Phthalates were also detected in food packaged in paper and cardboard packaging, e.g., the level of DiBP and DBP in sugar packaged in paper packaging (packaging contains 95 - 98 mg / kg DiBP and 56 - 64 mg / kg DBP) after storage at room temperature after 4 months it was 2.2 - 2.6 mg / kg DiBP, or 0.50 - 1.00 mg / kg. The main source of phthalates in paper and cardboard packaging was from printing inks and adhesives. Also, if recycled materials are used to make paper and cardboard packaging, phthalates may be transferred from the ink and glue if the ink and glue have not been completely removed during the recycling process.

PVC pipes are commonly used in the process of milking and transferring milk between tanks and reservoirs in dairy farms and milk processing plants. Phthalates are used as plasticizers that give PVC pipes flexibility, of which DEHP is used the most with as much as 40% in pipes (Ruuska and associates, 1987; Tsumura and associates, 2002a). Because they are not chemically bound to the polymer, plasticizers can migrate from PVC pipes to milk, especially at higher temperatures during the milking process. In dairy products, more than 80% of the total phthalate concentration, found in an amount of 50 to 200 micrograms / kg, may come from milking equipment (Casajuana and Lacorte, 2004; Castle and associates, 1990). Additional processing, packaging, and condensation can lead to a 5 to 100-fold increase in DEHP concentration in dairy products, such as cheese and cream (Casajuana and Lacorte, 2004; Mortensen and associates, 2005; Petersen, 1991; Sharman and associates , 1994). Due to concern for human health, some countries have banned the use of DEHP in the production of PVC pipes for milking, e.g. Denmark banned the use of DEHP in the production of milking tubes in 1989, while in Norway DEHP is replaced by other plasticizers in the production of milking tubes (Petersen, 1991). The UK uses plasticizer-free pipes, except in the center of gravity between tankers and tanks where DiDP-coated PVC pipes are used rather than DEHP (Castle and associates, 1990). In their study, Feng and associates (2005) found that the level of DEHP in cow's milk collected using PVC tubes plasticized with 28% DEHP ranged from 111.7 to 282.9 ng / g, which is on average 15 times more than milk hand-collected without the use of PVC pipes (8.4 to 23.7 ng / g), indicating that migration from PVC pipes could be a major source of DEHP in milk and dairy products . The increase in the concentration of DEHP to 11000 micrograms / kg in food products can also be attributed to rinsing from PVC gloves used during food preparation (Tsumura and associates, 2001a; Tsumura and associates, 2001b).

Food that is prepared by heating in microwave ovens can be contaminated with phthalates, so that heating facilitates the migration of phthalates from the packaging material in which the food is packaged to the food product. In the case of food products packed in cardboard boxes with cellulose acetate windows plasticized with 16 - 17% DEP, the presence of DEP in the range of 1.70 to 4.5 mg / kg was detected during heating. It is concluded that there is a possibility that DEP has evaporated from the film to the food without direct contact of the food packaging (Cao, 2010).

HEALTH IMPACT

Phthalates, in addition to affecting the organoleptic properties of food (Wagner and Oehlmann, 2009), are considered by many to be endocrine distortions (EDs), and affect the human reproductive system and may have a carcinogenic effect on the human body. In the public, phthalates have been associated with adverse health effects, particularly with regard to early life exposure (Serranoand associates, 2014).

The main source of exposure of the human body to phthalates is the consumption of food that is contaminated during production, processing and packaging. Other important sources of exposure include inhalation of contaminated air, unintentional inhalation of dust, and the use of general use items such as personal care products and cosmetics (Koo and Lee, 2004; Kavlock and associates, 2006). So we can conclude that human exposure to phthalates can be oral (by consuming food and water), inhalation (by inhaling dust particles) and dermal (using cosmetic products and personal hygiene products). Exposure of the human body to phthalates through food is mainly possible through the accumulation of phthalates in the food chain and the use of PVC in food packaging (Chai and associates, 2008; Li and associates, 2012; Spillmann and associates, 2009; Wormuth and associates, 2006).

Because DEHP is a lipophilic molecule, it dissolves immediately in whole blood, plasma, platelet concentrate, lipid-containing infusion solutions, parenteral solutions, or other substances that dissolve intravenous drugs. This is the reason for phthalate exposure to medical procedures such as: hemodialysis, whole blood, platelet or plasma transfusion, extracorporeal membrane oxygenation, cardiopulmonary bypass, intravenous infusion solutions, enteral and parenteral nutrition (Vidić, 2008).

In humans, phthalates e.g. DEHP, are intensively hydrolyzed to monoesters, then further metabolized by enzymatic oxidation of the alkyl chain to more hydrophilic metabolites (MEHP), which are further oxidized to mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP, 5OH-MEHP) and mono- 2-ethyl-5-oxohexyl phthalate (MEOHP). In contrast, monoethyl phthalate (MEP), the DEP hydrolysis monoester, is mainly excreted in its free form (Gomez and Gallart, 2018).

The major metabolite of DEHP, mono-2-ethylhexyl phthalate, is excreted in the urine along with urine and faeces, unchanged or conjugated as glucuronide (Itoh and associates, 2005) but has been detected in breast serum and breast milk (Ghisari and Bonefeld-Jorgensen , 2009; Albro and Lavenhar, 1989; Koch and associates, 2005; Frederiksen and associates, 2007; Gomez and Gallart, 2018). After exposure, phthalates are rapidly metabolized and excreted in urine and feces (ATSDR 1995, 2001, 2002).

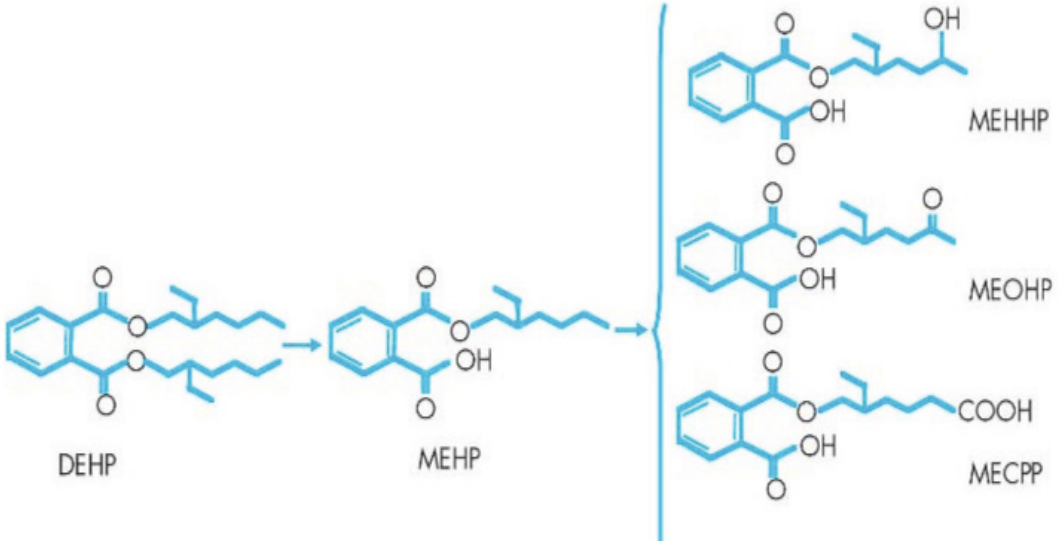

FIGURE 3: DEHP metabolism in the human body (Hauser R., Calafat A.M., 2005)

The most common approach to researching human exposure to phthalates is to measure urinary concentrations (biomarkers) of phthalate metabolites such as mono-ethyl phthalate (MEP), mono-2-ethylhexyl phthalate (MEHP), mono-butyl phthalate (MBP) and mono-benzyl phthalate. (MBzP). Two oxidative metabolites of DEHP, mono- (2-ethyl-5-hydroxylhexyl) phthalate (MEHHP) and mono- (2-ethyl-5-oxohexyl) phthalate (MEOHP) were present in most subjects at urinary concentrations higher than those in MEHP , which is a hydrolytic metabolite of DEHP (CDC 2005).

The metabolites DMP, DEP, DiBP, DnBP, BBzp, DEHP, DiNP, and DiDP have been identified as biomarkers of current human exposure to phthalates (Latini and associates, 2005).

TABLE 2: Phthalates and their metabolites (Serrano and associates, 2014)

NAME OF PHTHALATE	CODE	URINARY METABOTYL	CODE
Dimethyl phthalate	DMP	Mono-n-methyl phthalate	MmMP
Diethyl phthalate	DEP	Mono-ethyl phthalate	MEP
Di-isobutyl phthalate	DiBP	Mono-isobutyl phthalate	MiBP
Di-n-butyl phthalate	DnBP	Mono-n-butyl phthalate	MnBP
Di-n-octyl phthalate	DnOP	Mono- (3-carboxypropyl) phthalate	MCPP
Di-n-isononyl phthalate	DiNP	Mono-carboxyoctyl phthalate	MCOP
Di-n-isodecyl phthalate	DiDP	Mono-carboxynonyl phthalate	MCNP
Benzylbutyl phthalate	BzBP	Mono-benzyl phthalate	MBzP
Di-2-ethylhexyl phthalate	DEHP	Mono-2-etilheksil ftalat	MEHP
		Mono- (2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
		Mono- (2-ethyl-5-oxyhexyl) phthalate	MEOHP
		Mono-(2-etil-5-karboksipentil) ftalat	MECPP

Koch and associates (2013) monitored urinary phthalate excretion in individuals who fasted for 48 hours, found that diet was the most important route of DEHP, DiNP, and DiDP exposure, while DMP, DEP, DiBP, DnBP, and BBzP were primarily associated with exposure to other items of general use and surroundings.

Phthalates have also been identified in the placenta, and their presence has also been found in breast milk. From which it can be concluded that fetal exposure is directly related to maternal exposure to phthalates (Latini and associates, 2003; Lin and associates, 2008). Increased concentration of metabolites DEP, DiBP, DnBP, DEHP in the mother also affects the shortening of anogenital gap (AGD) in male newborns, a marker of andorgenization (Swan and associates , 2005; Swan, 2008). Prenatal exposure to phthalates has been associated with changes in labor time, neonatal hormone levels, and mental behavior in children and infants (Sathyanarayana, 2008).

In the adult population, various epidemiological studies support an association between phthalate exposure and testicular markers in men, particularly with reduced semen quality (Joensen and associates, 2012). Some phthalates act as antiandrogens and can seriously disrupt the development of the male reproductive system, although details of the mechanism are still incomplete. Toxicity of some phthalates to testes and ovaries, including DEHP, is due in part to interference with follicle-stimulating hormone (FSH) function at the level of sertoli cells in the testis and granulosa cells in the ovary. Some phthalates are weak estrogens, as evidenced by binding to estrogen receptors (WHO, 2012). Phthalates are considered endocrine

distortions due to their complex effects on several hormonal systems, including the estrogenic androgenic system. Some phthalates, including BBP and DBP, act as weak estrogens in cell culture systems. They can bind to estrogen receptors, elicit estrogen-appropriate cellular responses, and act as an adjunct to natural estrogen, estradiol, in altering these systems (Joblind and associates, 1995; Kang and associates, 2005). Phthalates also bind less to androgen receptors, disrupting cellular activities that are otherwise initiated by androgens (Borch and associates, 2006). DBP, DiBP, and BBP bind most strongly to androgen receptors, and could therefore be expected to act most extensively through this cellular pathway (Fang and associates, 2003). In addition to their direct effects prescribed through interactions with steroid hormone receptors, phthalates can also cause proliferation, malignant invasions, and breast tumor formation in carcinogenic cell cultures that have low hormone deficiency or deficiency, indicating that at least some effects of these compounds are independent of their direct estrogenic or androgenic effects (Hsieh and associates, 2012).

Stahlhut and associates (2007) link endometriosis in women with high levels of phthalate metabolites. Cobellis and associates (2003) published a study examining the association between DEHP levels in plasma, peritoneal fluid, and endometriosis. Plasma samples were obtained the day before surgery or immediately before anesthesia for laparoscopy. Peritoneal fluid was obtained during laparoscopy. Concentrations of DEHP and MEHP in plasma and peritoneal fluid were measured using HPLC-UV. The results showed that women with endometriosis show higher plasma DEHP concentrations. An association between plasma DEHP concentration and endometriosis was observed, suggesting a possible role of phthalate esters in disease development.

Duty and associates (2005) examined the relationship between urinary phthalate levels, sperm quality and phthalate exposure, as well as reproductive hormone levels in adult men using LC-MS / MS analysis. They found that some phthalate monoesters were associated with lower sperm concentration, lower motility, and increased sperm percentage with abnormal morphology in humans. In particular, an association between monobutyl phthalate (MBP), a metabolite of DBP, with motility and sperm concentration was observed.

CONCLUSION

Many chemicals, including phthalates, which are in commercial use, can damage human health. The presence of phthalates in the human body can cause endocrine distortions that can negatively affect the human reproductive system, and cause carcinogenic effects in the human body. Recently, the rate of patients with endocrine-related cancers and the number of people with genital malformations, as well as complications during pregnancy, have increased. Thus, it is concluded that genetic factors can not be the only ones responsible, other factors must be taken into account, such as diet, lifestyle, environment with chemicals, and the influence of the external environment.

Since phthalates enter the human body mostly from packaging material, the aim of this work is to point out its harmfulness, as well as to point out the need to find packaging material that is not harmful to the human body. Research into the effects caused by phthalates in the human body is very important to provide evidence that would help in the adoption of adequate legislation in this area, and thus reduce the risk of diseases that may arise from the possible use of these materials.

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