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Plastic Packaging - Possible Source of Food Contamination

Bachelor Thesis

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Nutrition and Foodstuffs

Declaration

I hereby declare that this Bachelor thesis titled "Plastic Packaging - Possible Source of Food Contamination" is my own work completed with the expert guidance of my thesis supervisor and all the literature sources I used in the Bachelor thesis are properly cited in Publication Bibliography.

In Prague, 07.04.2021 Signature: _____

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Plastové obaly - možný zdroj kontaminace potravin

Souhrn

S rozvojem potravinářského průmyslu a výroby plastů se staly plastové obaly velmi populárními a nahradily z velké části jiné obalové materiály potravin. Do plastových obalů jsou však přidávána aditiva, sloužící k vylepšení vlastností plastového materiálu a umožnění jeho vhodnosti pro daný účel. Nejznámější z nich jsou především ftaláty a bisfenol A s jeho analogy. Nejhojněji používaným ftalátem je di-(2-ethylhexyl) ftalát, známý hlavně jako DEHP. Tato aditiva jsou hojně využívána v potravinářském průmyslu, ale i jiných odvětvích, mohou se však snadno uvolňovat z plastových obalů kvůli slabým vazbám s polymerem a migrovat tak do balené potraviny nebo nápoje. Migraci ftalátů a bisfenolů ovlivňují různé faktory, patří mezi ně teplota, pH, UV záření, charakter balené potraviny a doba skladování. Obecně platí, že čím vyšší teplota a čím delší doba skladování, tím více ftaláty a bisfenoly z obalu do obsahu migrují. Značný je také vliv charakteru potraviny, kde v případě vysokého obsahu lipidů migrují aditiva z plastů do potraviny ve vyšším množství než v případě převažujícího obsahu vody. Vyskytovat se však nemusí jen v potravinách. Ftaláty a bisfenol A jsou takřka všudypřítomné a byly detekovány v moči více než 90 % populace. Jsou také spojovány s různými zdravotními riziky. Hlavním negativním vlivem ftalátů a bisfenolů je endokrinní disrupce, kterou mohou v jisté míře způsobovat i jejich nižší koncentrace. Endokrinní disruptory mají podobnou chemickou strukturu jako hormony, váží se na receptory určené pro hormony a narušují tak hormonální působení. Ftaláty a bisfenoly se podobají především sexuálním hormonům a působí jako slabé estrogeny. U mužů toto může vést ke zhoršení kvality spermatu, denně přijímané dávky nad 25 mg BPA/kg tělesné hmotnosti způsobily například u myší zhoršení spermatogeneze, pohyblivosti spermií a snížení jejich počtu. U žen může dojít ke zhoršení plodnosti. Dalším z následků vyšších koncentrací ftalátů a BPA je vyšší prevalence obezity a diabetu II. typu. BPA ovlivňuje také metabolismus kostí a může vést ke vzniku osteoporózy, což souvisí také s jeho vlivem na metabolismus vitaminu D_3. Vysoké koncentrace BPA (nad 50 mg/kg tělesné hmotnosti denně) způsobily u myší snížení množství aktivní formy vitaminu D_3 a zvýšily jeho vylučování.

Klíčová slova: Bisfenol A, Ftaláty, DEHP, Zdravotní rizika, Migrace obal-potravina

Plastic Packaging - a Possible Source of Food Contamination

Abstract

With the development of the food industry and the manufacturing of plastic materials, plastic packaging became very popular and has replaced many of food packaging materials. However, additives that improve the traits of plastic either during or after the production are added to the plastic materials. Phthalates and Bisphenol A with its analogues are the most common ones. The most used phthalate is di-(2-ethylhexyl) phthalate also known as DEHP. These additives are plentifully used in food industry as well as in other industrial branches and can easily release from the plastic packaging due to the weak bonds with the polymer and therefore they can migrate to the packed foodstuff or beverage. There are several factors which influence the intensity of migration of phthalates and bisphenols such as temperature, pH, UV irradiation, the character of the food matrix and the time span. In general, the higher the temperature is and the longer the time span or length of storage is, the more phthalates and bisphenols migrate from the plastic package to food inside it. Significant is the impact of the character of the food matrix as well. In case of high fat content in the foodstuff, the migration of additives is accelerated and considerably higher than in foods with a high percentage of water. Furthermore, phthalates and bisphenols may not only be present in foodstuffs but are considered as ubiquitous. They have been detected in the urine of over 90% of the population and are linked to various health risks. The main negative impact of both phthalates and bishenols is the ability to cause endocrine disruption which already happens at low concentrations. Endocrine disruptors have a similar structure to hormones so that they bind to the receptors meant for hormones and they interfere in their function. Phthalates and bisphenols are similar to sex hormones and act as weak estrogens. This may lead to worse sperm quality in males. In rodents, the daily dose of 25 mg BPA/kg of body weight resulted in lower spermatogenesis, worse sperm motility and lower sperm counts. In addition, high concentrations of phthalates and bisphenol A were linked to higher obesity incidence and type ll diabetes. Bisphenol A influences bone metabolism as well which can contribute to osteoporosis. This is related to the metabolism of vitamin D_3. Daily exposure to bisphenol A concentrations which exceed 50 mg/kg of body weight caused a decrease of the active form of vitamin D_3 and increased its excretion in rodents.

Keywords: Bisphenol A, DEHP, Phthalates, Health risks, Migration package-food

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1. Introduction

Plastic packaging has become a part of everyday life. Nowadays, a need to find alternative ways and reduce the use of plastics goes along with its negative impact on the environment and health. Plastic has won popularity because of its versatility and flexibility and is widely being used by the packaging industry for food and beverage containers. Various shapes can be formed out of plastics according to the needs of the producer and the form can easily be adjusted to the shape of packed foodstuffs. Using plastic as a packaging material brings many advantages such as cheap manufacturing which allows offering a low price to the customer, extended shelf life of the packed product due to very low gas permeability, versatility and good protection against environmental contamination. These traits make plastic widely utilized all around the world and many other materials such as wood, metal or paper were replaced by plastic. Furthermore, it is a very light material in comparison with other packaging materials which facilitates transport and saves transportation costs.

With the growing use of plastic materials for a purpose of food packaging, there are concerns about their possible impact on human health. Additives in plastic represent the biggest problem. They are added to the virgin plastic material to improve its properties. Such substances may migrate from the package to the foodstuff inside and become a potential threat to human health. The migration of the potentially toxic compounds in plastic packages can be influenced by many factors. These include very high or low temperatures, sudden changes of temperature, the time span of exposure and storage time, UV irradiation, microwave radiation and the character of the food matrix.

Among the most famous contaminants, phthalates and bisphenols are the most concerning additives. Both belong to the group of endocrine disruptors which resemble the structure of hormones, can bind to the receptors meant for them and interfere in normal hormonal processes in the organism. In the last several dozens of years, since it was found out about migration and possible toxicity of additives in plastic materials, various studies have been carried out examining the number of additives that may migrate, the impact of above-mentioned factors which may influence the intensity of migration and the impact of these substances on both human health and human development.

The limits and regulations for particular additives were set by authorities all around the world based on data that emerged from the epidemiological studies and most importantly, studies on animals. In Europe, the European Food Safety Authority (EFSA) is responsible for this task. In addition, all the chemicals which come in contact with food must be authorized by the European regulations. EFSA set tolerable daily intakes and specific migration limits to regulate the amount of food contact chemicals present in food and reduce the health risks connected to such chemicals.

The aim of the Bachelor thesis is with the use the available scientific literature:

1) to make an overview about important contaminants in foodstuffs and beverages which come from plastic packages

2) to characterize the main factors which influence the migration of undesirable chemical compounds from plastic packaging into foodstuffs and beverages

3) to describe the impact of the mentioned contaminants on human health

2. Plastic materials and packaging

In the past, various different natural means of preservation, transportation and packaging were used. The early civilization used animal skins or plant materials for the purpose of food preservation and transportation. Some of these materials still exist in the modern world and are utilized in some parts of the world (Ayamba et al. 2020, p. 2). At the beginning of the 20th century the history of plastic production started when the very first synthetic plastic was made in 1907 by a Belgian-American chemist Leo Baekeland. He created after him named Bakelite which soon became mass-produced. Over the years plastic industry has been evolving and the production of plastics has been growing rapidly. New plastic materials were developed with a vast range of desirable properties (Plastics Europe, 2020). With an increase of consumption of snacks and street food the packaging material has become very important and has led to growth and expansion of packaging market and different forms and designs started to be used (Ayamba et al. 2020, p. 2).

The term "plastic" describes types of materials made of either synthetic or natural polymers that may be molded under the exposure of heat or pressure. Thanks to their versatility and ability to increase the product´s shelf life, they can be used for many purposes and also the food packaging industry takes advantage of them and utilizes them in a large amount (Guerreiro et al. 2018, p. 320). Furthermore, plastics provide a good protection against microbial, physical and chemical contamination (Traistaru et al. 2013, p. 180). Plastics used for food containers have a diverse chemical structure which enables them to offer a wide range of properties which can be altered by the incorporation of additives and combination with other polymers (Guerreiro et al. 2018, p. 320). Importantly, plastic packages are supposed to encase or coat the food in a cost-effective way which satisfies the requirements of both the industry and the customer, keep the food safe and preserve its quality (Ayamba et al. 2020, p. 2). More than one third of packaging materials are made of plastics and there are commonly multiple adhesive layers of different polymers stuck to each other creating an ideal package for particular foodstuffs (Martínez-Bueno et al. 2019, p. 191).

There are hundreds of plastics, but only few of them are used in food packaging industry. Polyolefins, for instance, including low- and high-density polyethylene and polypropylene are some of the most used plastic packaging materials. Also, vinyl plastics are widely utilized in the food industry, among these is polyvinyl chloride the most important one (Bhunia et al. 2013, p. 525). Globally, 360 million tonnes of plastics were produced, nearly 62 million tonnes out of that amount in the European Union representing about 17% of the world production. The highest number of plastics produced has Asia where 51% of the world production take place (Plastics-the Facts 2019 2019, pp. 14–15). Plastic materials are divided into two main groups based on the way they are manufactured and the way they can or can not be remade after that (Plastics Europe, 2020). However, the increasing use of plastics, especially as food and beverage packaging resulted in production and accumulation of plastic waste which

represent a huge problem because of its nonbiodegradability and high volume (Bošnir et al. 2007, p. 92).

Small monomers containing atoms of hydrogen and carbon (e.g. ethylene, propylene) are the basic materials for forming plastic polymers that are manufactured either using polymerization or polycondensation. (Bhunia et al. 2013, p. 525).

Thermosets are made in a different way than thermoplastics. After they are formed they can not be reformed and they never soften once they were molded. Epoxide, Polyurethane and Unsaturated polyester resins, as well as epoxy resins, vinyl esters and silicone, come under this group (Plastics Europe, 2020; Plastics-the Facts 2019, 2019, p. 13).

Thermoplastics are a group of flexible plastic materials which can be reheated, reshaped and frozen repeatedly. Under exposure to high temperature, they can be formed whereas after cooling down they become hard. Flexible and mostly versatile plastic packages are made of thermoplastics which are molded in the shape of a product size. A typical example is the vacuum packaging of meat (Guerreiro et al. 2018, p. 320). Materials that belong to thermoplastics are Polyethylene terephthalate (PET), Polyvinyl chloride (PVC), Polyethylene (PE), Polypropylene (PP), Polystyrene (PS), Polyamide (PA), High-density polyethylene (HDPE) and Low-density polyethylene (LDPE) (Plastics Europe, 2020). PP, HDPE and LDPE belong to the group of polyolefins that are produced from ethylene or propylene. The density of HDPE is relatively high, from 941 to 965 kg/m^3 whereas the density of LDPE I usually between 910 and 940 kg/m^3. PP and HDPE have a higher softening point which enables them to withstand high temperatures (Bhunia et al. 2013, pp. 525–526). PP is a saturated linear polymer, light, heat and chemical resistant material of a relatively low price, ideal for food packaging (Alp and Yerlikaya 2020, p. 428). The chemical structure of some polymers commonly used as food contact material and for packaging are in figure 1.

Polyamides (PAs) are formed by condensation of amine monomers and carboxylic acid and because of the presence of the polar amine group in the polymeric structure, PAs are highly permeable to water vapor and absorb water quite good as well which enables the plasticizing effect of the material (Bhunia et al. 2013, p. 528).

Polycarbonates (PCs) are linear polyesters produced by the reaction of carbonyl chloride with bisphenol A and are utilized in food and beverage containers exposed to high temperature during hot filling or hot processing after filling. PCs are also suitable for boil-in-bag packs and microwave cookware as well as for reusable food containers or trays for frozen food and prepared meals (Bhunia et al. 2013, p. 528). Apart from the packaging industry, PCs are utilized for fabricating eyeglass lenses, toys, impact-resistant safety equipment, compact discs and automobile components (Pelch et al. 2019, p. 2).

Polyesters (PEs) are formed during condensation-polymerization of carbonyl groups when carbon-oxygen-carbon links are made. In food packaging, the most important polyester is polyethylene terephthalate. PET is impermeable to gases, has a little resistance to water vapor, it has a light weight and it is transparent (Bhunia et al. 2013, pp. 527–528). PET can

be manufactured in two ways. Either from esterification of the terephthalic acid with ethylene glycol or alternatively, using transesterification of dimethyl terephthalate with ethylene glycol. In both cases, the process of polymerization follows and after that, the final product becomes hard and rather brittle. It is used to make containers used especially for the beverage industry (Erythropel et al. 2014, p. 9968).

PVC is the second most widely used polymere for food packaging and it is produced through the polymerization of the vinyl chloride monomer. The major advantage is its lower gas permeability. On the other hand, PVC has higher water vapor permeability than polyolefins (Bhunia et al. 2013, pp. 526–527). PVC is a popular material in plastic packaging due to its versatility, low price and resistance to chemicals. Moreover, PVC is easy to process and it can have antimicrobial traits (antimicrobial PVC). Plasticizers represent about 30% of the overall weight of PVC (Alp and Yerlikaya 2020, p. 428).

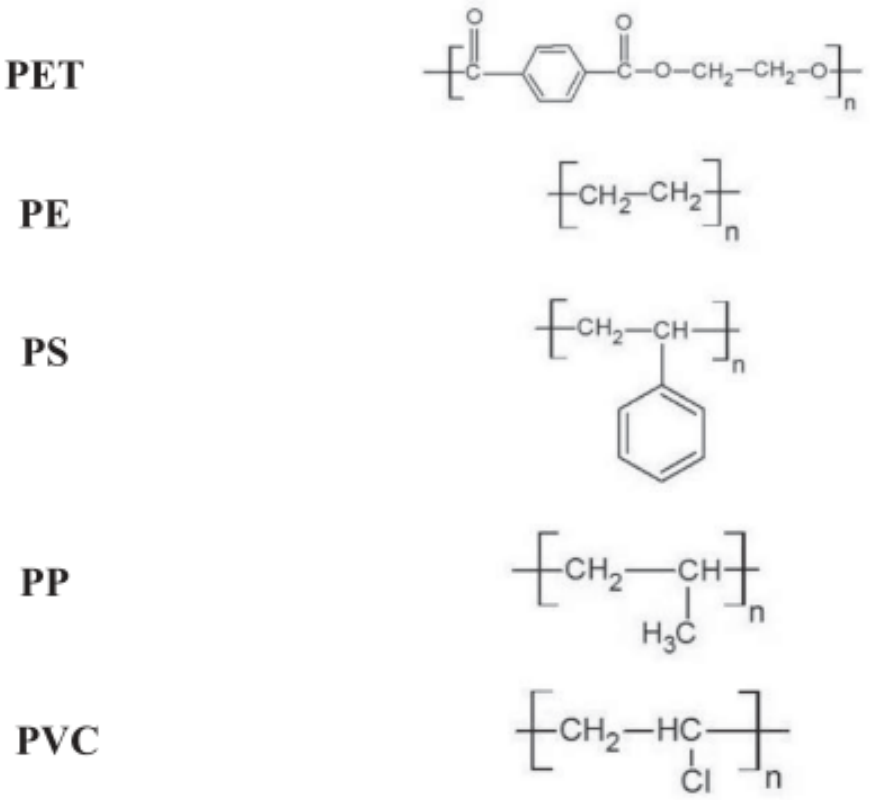


Figure 1: Chemical structure of some polymers used as food contact materials (Bhunia et al. 2013, p. 526)

3. Additives in plastic materials

Additives are widely utilized in basic polymers to improve their properties and performance, both during and after production. Because of high technical requirements for the final applications in packaging, layers of polymeric materials have to be combined with additives to form a structure with desirable properties to meet the requirements for the performance needed. Thus, mixing additives with a polymer base is a common practice (Guerreiro et al. 2018, p. 320). Additives have many functions as a part of the polymer. For example, they help to ease the shaping of polymer, improve functionality, flexibility or ageing properties of it (Hahladakis et al. 2018, p. 184). In addition, they provide plastic material with softness and pliability, they may act as flame-retardants and protect against UV irradiation. Additives are mostly added during the manufacturing of plastics and constitute about 20% of the overall weight of the material (Stöven et al. 2015, p. 246). They can be added during the shaping of the polymer, through injection moulding, extrusion blow or vacuum moulding (Hahladakis et al. 2018, p. 184). Among the additives in polymer plastic packaging, plasticizers, heat stabilizers, antioxidants and slip agents are the most commonly utilized in packaging materials. In addition, light stabilizers, lubricants and antistatic agents are also widely used (Bhunia et al. 2013, p. 528).

Slip agents are utilized to significantly lower the coefficient of friction on the surface of the polymer. They provide lubrication and impart lower surface resistivity. Furthermore, they render reduced melt viscosity and anti-sticking properties to the plastic material. Commonly used slip agents are fatty acid amides, fatty acid esters and waxes (Hahladakis et al. 2018, p. 187; Bhunia et al. 2013, p. 530).

Other commonly used additives are heat and light stabilizers. Heat stabilizers are responsible for preventing the degradation of polymers during exposure to increasing temperature. Some polymers such as PVC require the addition of a heat stabilizer to maintain their functionality. On the other hand, certain polymers such as LDPE or PEs can keep their stability under severe heat conditions without any heat stabilizer (Hahladakis et al. 2018, pp. 186–187). Light stabilizers protect plastics against degradation caused by the sun and weather. Polyolefins are susceptible to UV light, moisture and the presence of oxygen (Hahladakis et al. 2018, p. 192) and their exposure to light causes polymer brittleness, colour change, surface crazing and may cause product failure. Often utilized are hindered amine light stabilizers such as Tinuvin 622 or Chimasorb 944 (Bhunia et al. 2013, p. 537).

In the next two chapters plasticizers including phthalates and antioxidants including bisphenol A and its analogues are closely introduced.

3.1 Phthalates – the most common plasticizers

For a purpose of improving flexibility, workability and stretchability of plastic, plasticizers are added. They also improve impact resistance in the final product (Hahladakis et al. 2018, p. 186). For the purpose of fabrication, plasticizers are selected depending on various parameters. Compatibility with other components in the plastic matrix, low volatility or the lack of coloration are some of these parameters (Bhunia et al. 2013, p. 528). Plasticizers can constitute a large part of the polymer and represent up to 40% of the polymer weight (Erythropel et al. 2014, p. 9967). Thanks to the relatively low molecular weight of plasticizers (300-600 g/mol) in comparison with polymers, they can potentially migrate to packed food and become indirect food additives this way (Hahladakis et al. 2018, p. 190). Widely used and the most important class of plasticizers are phthalate diesters which are closely discussed in chapter 3.1.1. (Erythropel et al. 2014, p. 9967).

The functional effect of plasticizers is called plasticization and it is a result of various interactions between the polymer and the small plasticizer. In a common plasticizer di-(2-ethylhexyl) phthalate (DEHP) there are polar interactions between the polar carbonyl functionalities in DEHP with the polar carbon chloride bonds in the PVC chain, but there is also a lack of interactions between the nonpolar parts in DEHP. This results in more flexible and malleable material because the PVC chains interact less with each other when the plasticizer is present (Erythropel et al. 2014, p. 9970).

Phthalates are diesters of 1,2-benzenedicarboxylic acid (phthalic acid) and represent a wide range of chemical compounds. The structure of the phthalic acid is shown in figure 2. During the synthesis of phthalates, the phthalic acid is esterified with various alcohols and during this synthesis two carbonyl groups are in orthoposition to one another which means that they are positioned on the neighboring carbon atoms in the aromatic ring (Erythropel et al. 2014, p. 9970). Phthalic acid reacts with various alcohols with a different chain length starting from methanol and ethanol up to iso-decanol. They can have a straight chain or some branching (Giuliani et al. 2020, p. 4). For example, the esterification of phthalic acid with 2-ethyl hexanol leads to formation of liquid DEHP (Erythropel et al. 2014, p. 9970). Furthermore, phthalates

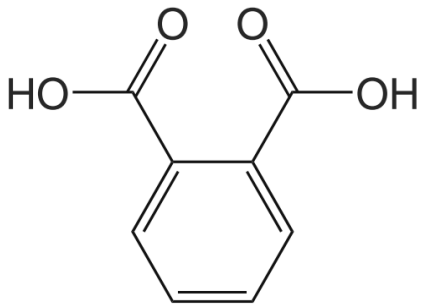


Figure 2: Structure of the phthalic acid (Erythropel et al. 2014, p. 9968)

differ in their use patterns and are incorporated to different food contact materials and other polymeric goods (Silano et al. 2019, 33).

Phthalates are man-made chemicals, widely used in different industrial branches. Thanks to their various physical-chemical properties they have a wide range of potential uses. Phthalates are almost colourless and odourless at room temperature and depending on the length of their chain the fat solubility increases (Giuliani et al. 2020, p. 4). They are additives commonly used to transform hard polyvinyl chloride raisins into pliable plastics which can be shaped and formed easily (Luo et al. 2018, p. 363). This is what makes phthalates plasticizers and therefore suitable for manufacturing of a wide range of products such as wall and floor coverings, wire cable jacketing, medical devices, blood bags and food contact materials (Meeker et al. 2009, p. 2098). Phthalates represent a wide group of chemical compounds (Luo et al. 2018, p. 365) and according to the length of their side chain and to its related molecular weight, there are two groups of phthalates, with a different way of metabolizing in the human body and different use in the plastic industry (Hauser and Calafat 2005, p. 806; Braun et al. 2013, p. 2; Giuliani et al. 2020, p. 4).

3.1.1 Low- and high-molecular weight phthalates

The group of low-molecular-weight phthalates includes di-methyl phthalate (DMP), di-butyl phthalate (DBP) and di-ethyl phthalate (DEP). They are added to various products as aerosol delivery agents and emollients. They also impart flexibility in nail polishes and preserve scent in scented products (Braun et al. 2013, p. 2). The carbon chain of the low-molecular weight phthalates contains one to four carbon atoms (Praveena et al. 2018, p. 11333). They are primarily utilized in personal care products as solvents, fixatives and adhesives (Serrano et al. 2014, p. 1) and they can also be used in children´s toys, pharmaceuticals, waxes, medical devices and inks (Praveena et al. 2018, p. 11333). Specifically, DBP is used in cellulose acetate plastics, as a solvent for oil-soluble dyes, in varnishes, coatings, nail polishes and cosmetics. DEP is utilized in dyes, cosmetics, pesticides and costings. In figure 3 the chemical structure of DEP and DBP is shown (Giuliani et al. 2020, pp. 2–3).

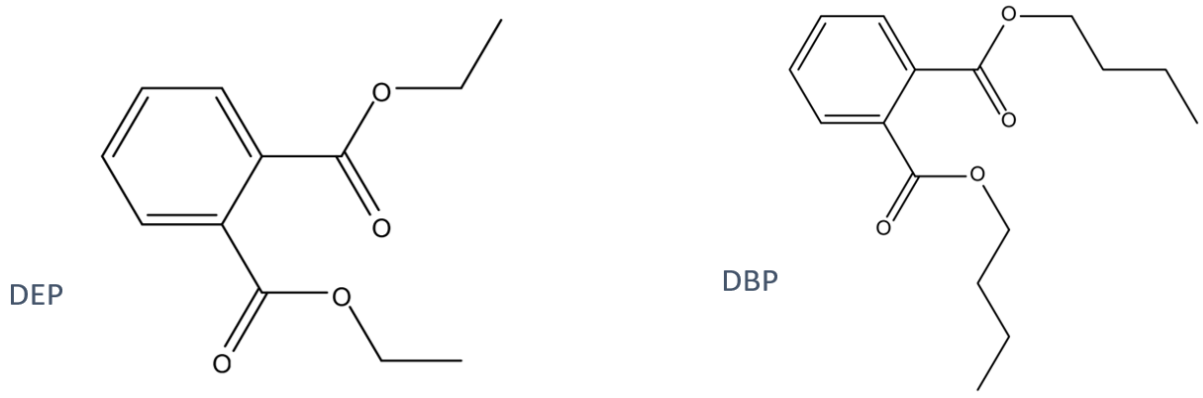


Figure 3: The chemical structure of two widely used low-molecular weight phthalates DEP and DBP (Giuliani et al. 2020, pp. 2–3)

High-molecular weight phthalates are commonly utilized in polyvinyl chloride plastics as plasticizers. They are used in adhesives, food packaging, rainwear and other PVC products. The group includes di-2-ethylhexyl phthalate (DEHP), benzyl butyl phthalate (BBP), di-isonoyl phthalate (DINP), di-isodecyl phthalate (DiDP) (Braun et al. 2013, p. 2). DEHP is used PVC plastics, perfumes, food packaging, medical devices and blood storage bags. DINP is added to rubbers, inks, adhesives, lacquers and sealants and BBP is typically in food packaging, synthetic leather, automotive products, vynil floors, solvents and glues (Giuliani et al. 2020, p. 2). The carbon chain of the above mentioned phthalates contains eight to ten carbon atoms (Praveena et al. 2018, p. 11333). Out of them, DEHP is the most commonly found phthalate in foodstuffs and a potential human carcinogene (Alp and Yerlikaya 2020, p. 431). The structure of DEHP, DINP and BBP is pictured in figure 4. High molecular weight phthalates represent about 80% of overall phthalate volume used in plasticized products in Europe (Giuliani et al. 2020, p. 5). Over time, they can leach from the product because of non covalent bonds with plastic (Braun et al. 2013, p. 2). Phthalates such as DBP, DEHP and DINP are usually contained in PP and PVC materials (Alp and Yerlikaya 2020, p. 428).

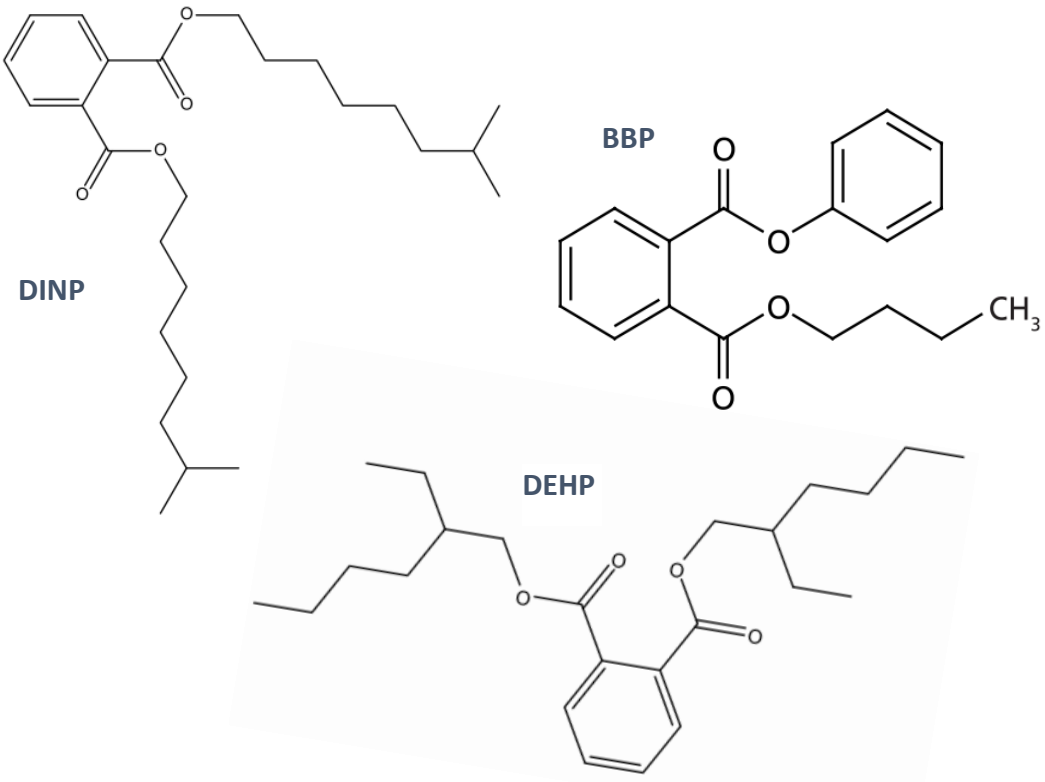


Figure 4: Chemical structure of DINP, BBP and DEHP (Giuliani et al. 2020, p. 2; Leitz and Lachenmeier 2010, p. 531)

3.1.2 Metabolism of phthalates

Ingestion is considered to be the main pathway through which phthalates enter the human body whereas inhalation contributes less to the overall amount of migrated phthalates. Another way of phthalates entering the human body is the dermal way from personal care

products which includes cosmetics and lotions. The main pathway of high-molecular weight phthalates is the ingestion route whereas the low-molecular weight phthalates enters the body rather via the dermal route from cosmetics or through inhalation (Praveena et al. 2018, p. 11334). In general, phthalate diesters are quickly metabolized to their monoesters, their active metabolites (Meeker et al. 2009, p. 2098). They can undergo two stages of metabolism in the human body. During the first stage which is the first biotransformation which takes place in the body, they undergo hydrolysis and oxidation, during the second biotransformation they undergo conjugation. The second stage of metabolism takes place only in case of some metabolites of high molecular weight phthalates. Thus, there are differences in metabolism of the two groups of phthalates though (Praveena et al. 2018, p. 11334).

The low-molecular weight phthalates are metabolized into their hydrolytic monoesters and the hydrolysis of one of the ester bonds takes place (Hauser and Calafat 2005, p. 806). After this biotransformation in the human body, low-molecular weight phthalates become hydrolytic monoesters metabolites which are then catalysed in the intestine and parenchyma by esterases and lipases and later excreted in form of urine or faeces (Praveena et al. 2018, p. 11334). The metabolism of low-molecular weight phthalates ends with hydrolytic monoesters while in case of high-molecular weight phthalates the metabolism continues with the transformation of the hydrolytic monoester to oxidative products. Thus, the way of metabolizing of high-molecular weight phthalates is more complex and includes more metabolites (Hauser and Calafat 2005, pp. 806–807). High-molecular weight phthalates also undergo the first phase of biotransformation which includes an enzymatic oxidation of the long alkyl chains (Praveena et al. 2018, p. 11334). Thus, hydrolytic monoesters of corresponding high-molecular weight phthalates are created. These monoesters are more hydrophilic than the original phthalates and can be either straight excreted through urine and faeces or undergo another transformation leading to the production of glucuronide conjugates which are even better soluble in water and therefore, the excretion through urine increases (Hauser and Calafat 2005, p. 806). The hydrolysis of the dialkyl phthalate to the corresponding monoester is performed by esterases which are present in the digestive tract. After this reaction, the alkyl chain in form of alcohol is released. The monoesters undergo oxidation of the alkyl chain which takes place either on the terminal or on subterminal carbon and this reaction is catalyzed by cytochrome P450 enzymes (Silano et al. 2019, 40). Glucuronidation both facilitates urinary excretion of phthalate metabolites and may reduce their potential biological activity (Hauser and Calafat 2005, p. 806). The percentage of free monoester excretion depends on aqueous solubility (Hauser and Calafat 2005, p. 806).

For example, DEHP is at first transformed into its primary monoester metabolite mono-(2-ethyl-5-oxohexyl) phthalate (MEHP). After that, further biotrasformation catalyzed by cytochrome P450 takes place and during a multi step oxidative pathway of the side chain products such as mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and Mono2-(2-hydroxyethylhexyl)-phthalate (MHEHP) are created. In addition, further

metabolism follows and hydroxy-, oxo- and carboxy- biotransformation products are created. Mostly, the conjugation of these metabolites follows. The final metabolites Mono(2-ethyl-5-oxohexyl)-phthalate (MEOHP), Mono(2-carboxymethylhexyl)-phthalate (MCMHP) and Mono(2-ethyl-5-carboxypentyl)-phthalate (MECPP) are produced and eliminated in urine (Silano et al. 2019, p. 40). Already within 24 hours, 65 to 70% of the ingested DEHP is secreted from the body (Erythropel et al. 2014, p. 9975). The whole metabolic pathways of DEHP are closely shown in figure 5 (Silano et al. 2019, p. 40). Thus, the metabolites of DEHP such as its oxidative metabolites MEOHP and MEHHP, for instance and its hydrolytic monoester MEHP are excreted glucurinated whereas monoethyl phthalate (MEP), the hydrolytic monoester of a low-molecular weight phthalate DEP is excreted in its free form (Hauser and Calafat 2005, p. 806).

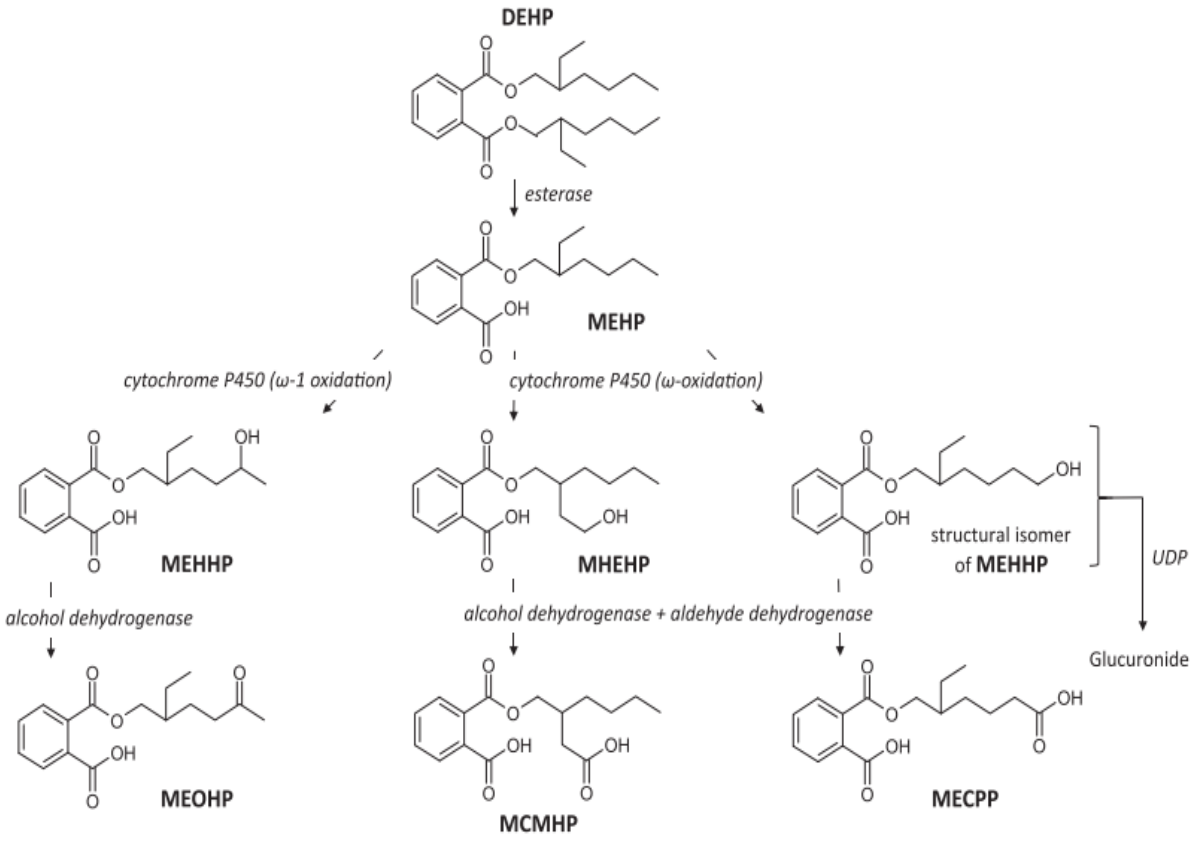


Figure 5: Metabolic pathways of DEHP in human body (Silano et al. 2019, p. 41)

The urinary levels of phthalates are used as a biomarker for monitoring the exposure to phthalates in humans (Praveena et al. 2018, p. 11336). Ingestion and dermal absorption can result in large amounts of bioavailable hydrolytic monoesters. Bioavailability is an ability of a pollutant to enter into the biological receptors and depends on the pollutant matrix, exposure time and the way of entry. The way in which pollutants such as phthalates are processed in the body is influenced by the environment in the gastrointestinal tract.

The variation of pH value in the gastrointestinal tract has an impact on the solubility of the pollutant as well as its bioavailability and absorption and the low pH value plays a role in releasing the pollutants from the matrix (Praveena et al. 2018, p. 11334).

3.1.3 DEHP

Di-(2-ethylhexyl) phthalate is the most common high-molecular weight phthalate (Hahladakis et al. 2018, p. 186). To form the liquid DEHP, the phthalic acid is esterified with 2-ethyl hexanol. About 95% of the world production of DEHP is used as plasticizers (Erythropel et al. 2014, p. 9970), out of that amount 80% represents the DEHP used in PVC production (Hahladakis et al. 2018, p. 186).

DEHP has come under scrutiny due to the suspicion of being harmful to health and environment and its breakdown products are believed to cause endocrine disruption (Erythropel et al. 2014, p. 9967). In the research, the biggest focus is on DEHP and its metabolites meaning that these compounds are the most studied ones (Robinson and Miller 2015, p. 382). DEHP and its metabolites are also classified as ubiquitous contaminants in the environment and human daily exposure was estimated in micrograms per kilogram of body weight. In case of patients in hospitals, DEHP leaches into liquids that flow through PVC tubes and other PVC medical equipment. This way of exposure takes place at even higher levels than exposure through food and bottled water and may put the patients with chronic diseases at risk (Erythropel et al. 2014, p. 9967).

The amounts of exposure from food and water do not usually exceed the tolerable daily intake which was set 0.05 mg/kg for DEHP (Erythropel et al. 2014, p. 9967; Silano et al. 2019, 13). Commonly used medical equipments are infusion bags, tubings, PVC blood bags and PVC storage bags. The concentrations in these equipments are considerably higher than those reported in food or water. The levels detected in medical equipment are three or six orders of magnitude higher than levels measured in food and water. In blood from blood bags the DEHP concentrations of 50 000 to 70 000 µg/L have been detected which is a level that significantly exceeds the tolerable daily intake (Erythropel et al. 2014, p. 9974). The detection of DEHP in bottled water is surprising because water bottles are mostly made of PET, which does not contain any DEHP and no DEHP is added during the manufacturing of the water bottles. This is why the material of the bottle is not as significant as the source of water which can already be contaminated. The levels of DEHP found in bottled water were mostly in the range between 0 and 1 µg/L (Erythropel et al. 2014, p. 9971).

The metabolism of DEHP should be taken into consideration because its metabolites seem to be more toxic than DEHP itself. During the breakdown of DEHP, various metabolites are produced. One of them is mono(2-ethylhexyl)phthalate (MEHP) wich is a monoester of DEHP and its structure is shown in figure 3. MEHP is considered to be an endocrine disruptor and is associated with antiandrogenic activities in the human body (Erythropel et al. 2014, p. 9971).

3.1.4 Food contamination with phthalates

According to seventeen studies performed in North America, Europe and Asia between 1990 and 2013 which were monitoring phthalate content in different types of food, amounts of some phthalates are commonly present in various foodstuffs. Di-isobutyl phthalate (DIBP), di-n-butyl phthalate, benzylbutyl phthalate (BBP) and DEHP were primarily detected in more than 50% of the samples by more than half of the studies. On the other hand, DEP, DINP and DMP occurred rarely. There were also differences between the occurrence and amount of particular phthalates among countries. In the United States, for instance, the leading phthalates, most often detected phthalates were DEP and DEHP, whereas in China dominated DMP and DEP. In some foods such as meat, cheese, oils and fats high phthalate concentrations were detected frequently. In most of the cases, DEHP was present in high amounts with more than half of the cases exceeding 300 μg/kg which is a specific migration limit and all values equal to or higher than 300 μg/kg were considered high. Other phthalates were generally reported in low concentrations. In oils and fats, all species of the above-mentioned phthalates were reported. Other foodstuffs including yoghurt, milk, eggs, grains (pasta, noodles, rice), fruit and vegetable have generally low concentrations of phthalates, mostly lower than 50 μg/kg (Serrano et al. 2014, p. 4). In case of seafood, spices, bread and cereals concentrations were varying significantly and both low concentrations under 10 μg/kg and high concentrations reaching the threshold of 300 μg/kg were measured (Serrano et al. 2014, p. 5). Although the contamination of bottled water was the main concern, packaged food contained higher amounts of DEHP in comparison with bottled water (Erythropel et al. 2014, p. 9967). Mostly the concentrations of DEHP in water do not exceed 1 μg/L whereas the concentrations in various foodstuff are mostly higher as mentioned above (Erythropel et al. 2014, p. 9971).

Alcoholic beverages are also susceptible to phthalate contamination due to their ethanol content. Average concentrations of DEHP, BBP and DBP in commercial white wines measured in tetra pak boxes were 16 μg/L, 1 μg/L and 10 μg/L respectively. Nevertheless, there were concentrations of phthalates detected in bottled wine packed in the glass as well which is a consequence of contact with phthalates during winemaking. The transportation and storage include equipment such as pumps and hoses and materials such as fining agents and filtration (Giuliani et al. 2020, pp. 16–17). In comparison, the average concentration of DEHP and DBP was 0.196 μg/L and 0.046 μg/L, respectively (Giuliani et al. 2020, p. 20).

3.1.5 Maximum daily intake and legislation

All food contact materials including kitchen utensils and food processing equipment must be compliant with the overall migration level in Europe stated by EU regulations after the assessment of these values (Traistaru et al. 2013, p. 180). Thus, phthalates that can come in contact with food are in Europe listed and authorized in the legislation of the EU under various restrictions and specifications. Phthalates such as DBP, BBP, DEHP, DINP and DIDP are on the list of authorised chemicals intended to come into contact with food. This is specified

in Regulation (EU) No. 10/20119 on plastic materials and articles (Silano et al. 2019, 15). In Europe, there is a specific migration limit (SML) for each of the phthalates mentioned above in this chapter. For DEHP the SML was set at 1.5 mg/kg of food simulant, for DBP and BBP, the SML is 0.3 mg/kg and 30 mg/kg of food stimulant, respectively. These three phthalates are authorized with individual specific migration limits. For DINP and DIDP there is a total specific migration limit (SMLT) of 9 mg/kg of food simulant. Furthermore, these five phthalates with another similar substances fall under Group Restriction No. 32 whereby a SMLT of 60 mg/kg was established for the whole group of the mentioned phthalates and other similar phthalates in general (Silano et al. 2019, pp. 15-16). In studies in which migration of plastic additives into foodstuffs is investigated, food stimulants that stimulate a particular environment are often used and they are closely discussed in chapter 4 (Xu et al. 2010, p. 11312; Bhunia et al. 2013, p. 530). The European Food Safety Authority set up maximum tolerance daily intake for an average person by 3 mg/kg per day for DEHP (Alp and Yerlikaya 2020, p. 431).

In addition, EFSA established a Total Daily Intake (TDI) for particular phthalates (Yuan et al. 2020, p. 136). TDI defines a quantity of a chemical compound that can be ingested daily without representing significant health risk (Russo et al. 2019, p. 2). The values of TDI were established according to the results of experiments on animals, mostly rodents. No Observed Adverse Effect Level (NOAEL) was determined and an uncertainty factor of 100 was considered to set all the TDIs for particular phthalates. The reproductive and developmental toxicity of BBP was considered as the most sensitive toxicological endpoint for this phthalate. In a multi-generation study on rodents, the NOAEL of 50 mg BBP/kg of body weight per day was identified and TDI was set at 0.5 mg/kg of body weight. A similar process applies to DEHP which affected fertility and reproduction of both males and females in rodents and had an effect on the development of the offspring. In this case, NOAEL of 5 mg/kg/day was identified and TDI was set at 0.05 mg/kg of body weight. In case of DINP hepatic changes were taken as its main toxicological effect. NOAEL of 15 mg/kg/day identified and the TDI was set at 0.15 mg/kg of body weight. Similarly, impact on liver, reproduction and development were the key factors for the evaluation of DiDP. NOAEL of 15 mg/kg/day was identified based on liver effects observed in dogs and the TDI value was set to be 0.15 mg/kg of body weight (Silano et al. 2019, pp. 12–13).

In the study carried out by Heinemeyer et al. (2013) the tolerable daily intake of 50 µg/kg of body weight was not exceeded in most cases. The daily intake in the German population was estimated based on data obtained from measurements from food monitoring of products sold on the German market, 37 groups of food were investigated and a special focus was given to foods which are consumed in high amounts such as bread and other bakery products, dressings and mayonnaise, vegetables and butter. The results derived from mathematic methods, the median of estimated exposure was 3.6 µg/kg/day. Less than 1% of the German adults may be exposed to values over the tolerable daily intake (Heinemeyer et al. 2013, pp. 473–477).

3.2 Bisphenol A – the most common antioxidant

Antioxidants are a part of various polymer resins added in order to delay the oxidative degradation of plastics when the material is exposed to the reactive free radicals that can be generated by heat or radiation (Bhunia et al. 2013, p. 528; Hahladakis et al. 2018, p. 186). However, antioxidants and their products of degradation can migrate from the plastic material both during processing and storage of the product. The process of oxidation is increased and accelerated during the exposure to heat including also a contact with hot foods and exposure to microwave and infrared heating. The most commonly utilized antioxidants are arylamines, phenolics and organophosphites. The two latter groups are utilized to reduce hydroperoxides created during oxidation to alcohols. The group of phenolics includes bisphenol A, butylated hydroxytoluene or tetrakismethylene-(3,5-di-t-butyl-4-hydroxyhydrocinnamate) methane known as Irganox 1010. The most common used organophophites are tris-nonylphenyl phosphite and 2,4-di-tert-butylphenyl which is also known as Irgafos 168 (Bhunia et al. 2013, p. 531; Hahladakis et al. 2018, pp. 185–187).

A commonly used and well-known chemical worldwide used in plastics for food packaging is 2,2-Bis (4-hydroxyphenyl)propane) (BPA). For the first time, it was synthesized by a Russian chemist Aleksandr Dianin in 1891. In 1953 the ability of BPA to polymerize with phosgene to polycarbonate was discovered. After that, in 1957 in the USA and in 1958 in Europe the industrial production of BPA began and BPA started to apply in the manufacture of polycarbonate (Vilarinho et al. 2019, p. 34). For more than 50 years, BPA has been used as a key monomer of epoxy resins in polycarbonate plastics. Thanks to its resilience, flexibility and durability it has become a very popular chemical compound used in many different fields. In the food industry, BPA represents the main component of protective coatings in long-term containers for food and beverages (Castellini et al. 2020, p. 1). Currently, it is estimated that there are 5 to 6.8 million tons produced per year and out of this amount 70% of BPA is used for the production of polycarbonate plastics and 25% for the production of epoxy resins (İyigündoğdu et al. 2020, pp. 457–458).

BPA results from the condensation of two molecules of phenol with one molecule of acetone in presence of an acid catalyst. Its molecular weight is 228.29 g/mol. The chemical formula of PA is shown in figure 6. Similar to other phenols, it can be converted into ethers, esters and salts and it also undergoes electrophilic substitution such as nitration, sulfonation or alkylation (Vilarinho et al. 2019, p. 34). Every year, around 700 million tones of BPA are produced (Robinson and Miller 2015, p. 380).

Production of plastics, thermal paper and dental materials are the main fields for which BPA has found a use (Wyżga et al. 2020, p. 2). For the purpose of fabricating the thermal paper, BPA is used as a developer because of its effectiveness, availability and affordability. Thermal paper is a common paper which has been covered with a thermal reactive or thermal sensitive layer. It is used mainly for conventional receipts (Vilarinho et al. 2019, p. 36). In case of plastics, BPA is contained in PCs, epoxy resins and is used in the production of PVC.

These plastic materials are used for food and beverage containers (Robinson and Miller 2015, p. 380). Epoxy resins are made in a reaction of BPA with epichlorohydrin and they are utilized for thermosetting polymers with good mechanical properties. The range of application is wide, such polymers are present in soda and beer cans, canned foods like fish, fruits and vegetables (Vilarinho et al. 2019, p. 35). They are also used in protective linings for food beverage cans and vats (EFSA 2015, p. 4).

Bisphenol A is an environmental contaminant which can be found in soil, water environments, drinking water, food, dental sealants and indoor dust (Russo et al. 2019, p. 1). It does not occur in the environment naturally but it is formed during manufacturing and leaches from the products which contain it (Haq et al. 2020, p. 1). In the environment, BPA can be found in wastewater from factories, in seawater and water in rivers. It also leaches from waste landfills that are together with domestic and industrial waste the main sources of soil contamination by BPA. In seawater, BPA is more persistent than in rivers which means that it stays longer in seawater without any degradation which takes approximately 30 days. This is why the marine organisms have relatively high BPA content and it can play an important role in human exposure because of the intake of BPA from marine organisms (Thent et al. 2018, p. 2).

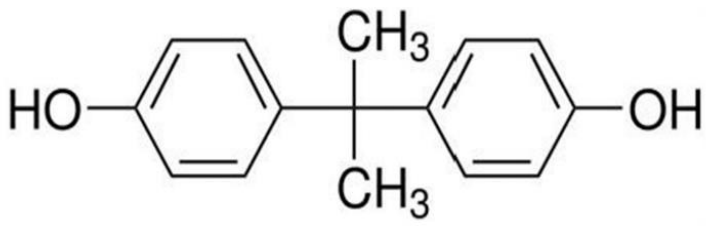


Figure 6: formula of Bisphenol A (Thent Chemical et al. 2018, p. 2).

3.2.1 Food contamination with BPA

BPA migrates to liquid foodstuffs through the diffusion of its residues contained in PC after the hydrolysis of the polymer during manufacturing (Vilarinho et al. 2019, p. 34). The dietary exposure is predominantly a result of the consumption of foodstuffs packed in polycarbonate food containers and the use of epoxy resins in canned food production. Thus, dietary exposure is the most concerning, since it may impact a great number of people (Vilarinho et al. 2019, p. 46).

Significant differences in concentrations of BPA between canned and non-canned foodstuffs were observed in the majority of food groups, higher concentrations were found in canned food where seven out of seventeen revised canned food categories reached the average BPA concentrations over 30 µg/kg of the particular foodstuff whereas in non-canned food the average in the meat and seafood which were two categories with the highest values,

the average concentration of BPA was 9.4 µg/kg and 7.4 µg/kg of the foodstuff, respectively (EFSA 2015, p. 8).

Milk is one of the most consumed food along with dairy products and provides one-third of daily protein intake. Nowadays, milk and dairy products are usually packed in plastic materials which can be in combination with paper or thermed cartoons. These materials are mostly made of PET or HDPE which do not contain BPA and BPA can not be released from them. Nevertheless, BPA was found in such products, even though the chemical composition does not allow its release. This can be caused by contamination during the production, through the supply chain and contact with the equipment during processing. Bisphenols (BPs) contamination of milk could also be caused through animal feeding. In Europe, the lowest concentration of BPA was found in milk sold on the Norwegian market in cardboard package which contained 0.02 µg/kg of BPA. On the contrary, the highest amount was measured in skimmed milk from the Spanish market which contained 800 µg/kg (Russo et al. 2019, p. 4).

In the EU, the consumption of canned seafood is very popular. Fish may contain significant levels of Endocrine disruptors (EDCs) because of the sea pollution and among these BPA and its analogues are present and they are constantly detected in aquatic ecosystems (Russo et al. 2019, p. 6). EDCs concentrations were detected in both muscle and liver in fresh fish since they pass through the liver after the ingestion and reach muscles later. Thus, some amount of BPA may already be present in fresh fish tissue and seafood and to this amount already present in fish adds the amount coming from the migration from plastic materials (Russo et al. 2019, p. 7).

3.2.2 Metabolism of BPA

The dietary route represents the main way of human exposure to BPA (Castellini et al. 2020, p. 2). When bisphenol A enters the body via an oral route through ingestion of contaminated foods and beverages it is absorbed in the gastrointestinal tract and continues to the liver where its metabolism takes place (Robinson and Miller 2015, p. 380). It is quickly bound to glucuronic acid by diphosphonate glucuronosyl transferase and it is turned into BPA glucuronide. This rapid process makes bisphenol A more soluble in water and enables its half-life elimination through urine within about six hours after ingestion (Castellini et al. 2020, p. 2). Other metabolites of BPA are BPA monosulfate and BPA disulfate which are also produced during oxidation and hydrolysis of BPA. These metabolites undergo a conjugation after which they are excreted in urine and faeces (Robinson and Miller 2015, p. 380; Russo et al. 2019, p. 2). In case of ingesting an amount of 50-100 µg/kg of body weight which is at and above the tolerable daily intake (50 µg/kg of body weight), the complete elimination of BPA takes essentially 24 hours with some amount of free BPA which is less than 1% of the overall amount (Castellini et al. 2020, p. 2).

3.2.3 Exposure to BPA

As a consequence of the extensive use of BPA, the exposure to the population is widespread (Pelch et al. 2019, p. 2). More than 90% of the world population including infants have traces of BPA in blood and urine. The concentration values are in a range from 0.11 mg/L to 946 mg/L. Even at low concentrations below 1 ng/L, BPA may exert an estrogenic activity (Russo et al. 2019, p. 2).

Both dietary and non-dietary exposure to BPA were assessed by EFSA. In the first case, the information on BPA occurrence in food and the corresponding consumption levels were used to estimate the dietary exposure in different groups of the population. An average exposure was estimated based on the average concentration and average consumption data. In addition, a high exposure was estimated after consideration of an average concentration and high consumption data. These values were obtained from different studies and measurements after EFSA´s call for data. The data in various food categories did not show many differences and therefore were used in the calculations. There were significant differences between canned and non-canned foodstuffs. The highest levels of BPA exceeding the level of 30 µg/kg occurred in the following canned food categories: “Grain and grain-based products”, “Legumes, nuts and oilseeds”, “Meat and meat products”, “Fish and other seafood”, “Herbs, spices and condiments”, “Composite food”, and “Snacks, desserts, and other foods”. On the contrary, the lowest levels occurred in canned beverages in which the average concentration of BPA was 3 µg/kg. Water, alcoholic and non-alcoholic beverages, fruit and vegetable juices were included in this group. In non-canned foodstuffs, the highest concentrations occurred in two groups. In meat products, an average BPA concentration was 9.4 µg/kg and in fish and other seafood the average concentration was 7.4 µg/kg (EFSA 2015, p. 8). In colostrum an average BPA concentration of 3 µg/L and a high concentration of 5.8 µg/L were used for the exposure assessment. For the mature human milk, these concentrations were 1.1 µg/L and 4.0 µg/L, respectively. Food contact articles were also taken into consideration and the BPA migration from different PC articles into the water was used. In particular, water coolers (0.8 µg/L), water kettles (0.11 µg/L), filters (0.04 µg/L), tableware (0.09 µg/L) and cookware (0.29 µg/L) made of PC were included (EFSA 2015, p. 9). Dietary exposure for infants aged 0-6 months was divided into three groups. For infants in their first five days, the estimated average dietary exposure was 225 ng/kg of body weight and high dietary exposure 435 ng/kg of body weight. For infants from three days to three months of age, the average dietary exposure estimation was 165 ng/kg of body weight and the high dietary exposure estimation was 600 ng/kg of body weight. For infants aged four to six months estimated average dietary exposure was 145 ng/kg of body weight and high dietary exposure 528 ng/kg of body weight. With a specific migration limit set by the EU for BPA at 0.6 mg/kg of food, none of these values exceed the limit by far (EFSA 2015, p. 4). Among the population aged six and more months, the estimated average was the highest which can be caused due to the relatively higher consumption of foods and beverages per kg of body weight (EFSA 2015, p. 10). Thus, related to their body weight, children carry

significantly higher concentrations of BPA. Furthermore, because of lower cytochrome P450 levels in early life, exposure in this life stage is more dangerous because cytochrome P450 plays a role in the metabolism of environmental chemicals including BPA (Kim et al. 2019, p. 2). In adolescents, adults and elderly people, the average exposure ranged from 116 to 159 ng/kg and the high estimated exposure ranged from 335 to 388 ng/kg. Estimated exposure of BPA coming from PC kettles was in the range of 2 to 3.2 ng/kg, the higher amounts were observed in adults and elderly people who consume a lot of tea and coffee (EFSA 2015, p. 10).

3.2.4 Doses of BPA and legislation

Since the involvement of BPA in the industry and production of food containers, the acceptable doses of BPA which enters the human body needed to be established. In the United States a refence doses of 0.05 mg BPA/kg of body weight was set in 1988 by the United States Environmental Protection Agency. In Japan, a migration limit of 2.5 mg/kg of food was set. In Europe, the migration limit of 3 mg BPA/kg of body weight set in 1990 was reconsidered to 0.6 mg BPA/kg of body weight in 2004 (Thent et al. 2018, p. 2).

The dietary route represents the main route of human exposure to BPA. As a result, tolerable daily intake has been established based on studies on rodents where the harmful effects of BPA were caused at significantly higher doses. BPA is allowed to be used as a monomer in plastic food contact materials in accordance with the Commission Regulation No 10/2011/EU which involves plastic materials and compounds intended to come into contact with foodstuffs. The TDI for BPA was set in the amount of 50 µg/kg of body weight and EFSA stated that the current levels of exposure do not exceed this amount and therefore they should not be a threat to consumers at any age. The amount of 50 µg/kg per day was set based on multi-generation rodent studies (EFSA 2015, p. 4). Also, the short half-life elimination of BPA which occurs after the rapid first-pass liver metabolism was considered (Castellini et al. 2020, p. 2).

In 2017, EFSA established a temporary tolerable daily intake 4 µg/kg of body weight (Gundert-Remy et al. 2017, p. 8). The use of BPA is a subject to specific migration limit which was set at 0.6 mg/kg of food simulant. Furthermore, there is a restriction for manufacturing polycarbonate infant feeding bottles (EFSA 2015, p. 4). In plastic materials which are designed to come in contact with infants and toddlers, BPA migration is not allowed in the EU at all (Russo et al. 2019, p. 10).

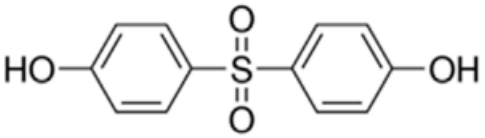
3.2.5 Bisphenol A analogues

Bisphenols in general are also known as diphenylmethanes. They contain two benzene rings which are separated by a central carbon atom and have various substitutes on benzene rings. There are mostly –OH substitutes but some bisphenols contain sulfone and sulfide group instead (İyigündoğdu et al. 2020, p. 457). Strong toxicity of Bisphenol A resulted in replacing this chemical by its analogues. The most frequent ones are Bisphenol S (BPS), Bisphenol F (BPF), Bisphenol AF (BPAF) and Bisphenol Z (BPZ) and are used as analogues of BPA with similar

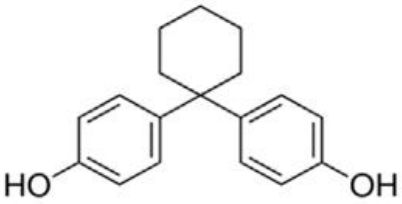
properties. The chemical formula of them is shown in figure 7 (Wyżga et al. 2020, p. 1; İyigündoğdu et al. 2020, p. 460).

The use of BPA analogues has increased in the past several years. The whole chemical name of BPS is bis(4-hydroxyphenyl) sulfone and it has a molecular weight of 250.27 g/mol. BPS is resistant to heat and sunlight used in the production of plastics and thermal paper. It is used in canned soft drinks and canned foods and as a constituent of epoxy resins (İyigündoğdu et al. 2020, p. 459). BPS is chemically more stable than BPA which may reduce its emission but its biodegradability is lower and it can penetrate quicker through the skin in comparison with BPA (Wyżga et al. 2020, p. 2). BPF is chemically 1,1-bis (4-hydroxyphenyl) methane and is used for the production of polycarbonate resins. It has been detected in nature and food and in comparison with BPA, it has higher biodegradability. Another bisphenol A analogue used for polycarbonate resins and also as a part of certain plasters is BPAF. The chemical nomenclature of BPAF is 2,2-bis (4-hydroxyphenyl) hexafluoropropane and it has a relatively high molecular weight of 336.23 g/mol, compared to other bisphenols. BPZ is 1,1-bis (4-hydroxyphenyl) cyclohexane and is used in electrical insulation and for the production of highly heat-resistant plastic materials (İyigündoğdu et al. 2020, pp. 459–460). The presence of BPA resembling chemicals has been reported as widespread. They have been detected in foodstuffs, house dust, personal care products, thermal paper and even human biological tissues (Pelch et al. 2019, p. 2).

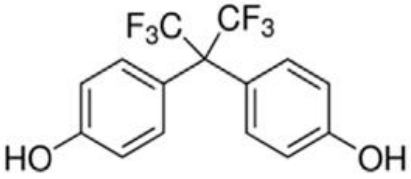
Bisphenol S



Bisphenol Z



Bisphenol AF



Bisphenol F

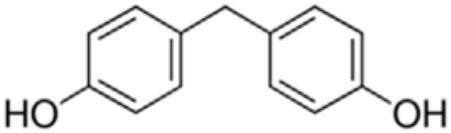


Figure 7: The chemical structure of some of the bisphenol A analogues (Liang et al. 2020, p. 2).

4. Migration of chemical compounds from package to food

Using plastics as a packaging material brings many advantages which can not be replaced by any other material so far. Plastic has a low weight and volume, low permeability, high flexibility and it has the desired transparency. However, plastic polymers are rarely used alone, usually, the polymer resins and some additives need to be mixed in to improve the performance of the packaging material. Plasticizers to render flexibility and elasticity, silica and carbon to strengthen the plastic material or thermal stabilizers are used. Some of the added chemicals can be toxic and have an impact on the function of the human body or formation of various illnesses (Rastkari et al. 2018, p. 29).

All types of food packaging materials and food contact materials must be registered and approved after examining the absence of organoleptic changes to packaged food and toxic effects to the consumer (Guerreiro et al. 2018, p. 321). There are standardized tests set by the EU regulations for analyzing the substances that can migrate from food contact materials. The identification of such substances is very complex though. Because of many existing chemical classes, low concentration levels, not sufficient amount of information about the ingredients used in plastic production and a lack of analytical standards for some of the compounds. In addition, there are still substances that are not included in chemical or spectral databases (Martínez-Bueno et al. 2019, p. 192).

Migration is a process of interaction between food packaging material and foodstuff inside (Xu et al. 2010, p. 11311). It is a transfer of chemical substances from the packaging material into foodstuffs and it takes place on the food contact materials which contain food contact chemicals (FCCs) (Traistaru et al. 2013, p. 180). These can migrate from the package to the foodstuff under the influence of various environmental factors or the factor of time. Not only food package and beverage bottles are considered to be food contact materials but also food processing equipment and kitchen- and tableware (Muncke et al. 2020, p. 2). Foodstuffs may be contaminated during manufacturing and processing as well. Significant food contact materials can be tubing used for milking, lid gaskets or gloves used for food preparation for instance. Around 12,000 different chemicals worldwide can be used as food contact materials and FCCs, 8030 substances out of it are on the list of regulations in the European Union. In the United States, 10,787 substances are permitted to be utilized as both direct and indirect food additives, nearly half of that amount being FCCs (Muncke et al. 2020, p. 3). The interaction of the packaging material with food might change the properties of the mechanical barrier as well as the safety of the foodstuff inside. Potentially dangerous food contact chemicals are mostly above mentioned additives (Traistaru et al. 2013, p. 180).

The process of migration can be divided into four main steps. Firstly, the diffusion of chemical compounds through polymers, secondly the desorption of the diffused molecules from the polymer surface, followed by the sorption of the compounds at the plastic-food interface

and eventually desorption of the compounds in the food (Bhunia et al. 2013, p. 523). There have been many studies investigating number of plasticizers and other additives migrating to foodstuffs. Some traces of plasticizers, however, may come from different sources such as water contamination during production or background contamination in the laboratory (Luo et al. 2018, p. 366). Nevertheless, concentrations in the environment are usually very low (Hauser and Calafat 2005, p. 807). In general, additives used for improving traits of plastic material are usually small molecules when compared to the long polymer structures (Erythropel et al. 2014, p. 9967).

Since the 1950s this phenomenon of migration has been studied. In every package material, some amount of migrating chemical compounds can occur but there are significant differences in their levels (Muncke et al. 2020, p. 2). There are several factors that may influence the intensity of migration. Most of the studies carried out to find out about the amounts of migrating compounds are performed on food simulants (Bhunia et al. 2013, p. 530). For example, oil is used to simulate fatty foods and water is used to represent aqueous foods. In the regulations stated by the EU, foods are basically divided into water foods, alcohol foods, acidic foods and fatty foods (Xu et al. 2010, p. 11313). Food simulants are suitable for that purpose due to the difficulties of analyzing a wide spectrum of food matrices under the actual storage conditions (Guerreiro et al. 2018, p. 323). Testing on food simulants simplifies the analytic procedures and they must represent the extreme situation in food processing (Yuan et al. 2020, p. 136). Nevertheless, the use of food simulants may lead to underestimation of real migration into food and the migration rate of contaminants needs to be assessed over time as well (Xu et al. 2010, p. 11312). Thus, migration data can be obtained either from testing on food simulants or monitoring of the chemical substances in food in contact with plastic materials (Vilarinho et al. 2019, p. 46).

The factors which may possibly influence migration between plastic package and food are the duration of storage, heat exposure, the thickness of the food contact layer, packaging size, contact time, UV irradiation, microwave radiation and lipophilic character of food matrix (Luo et al. 2018, p. 366; Muncke et al. 2020, p. 3). The desorption of particular additives is affected by the type, size and age of plastic material as well as by the environment in and out of the package (Stöven et al. 2015, p. 246). Some concentrations may already be present in the ingredients before they enter the production and also, the composition of the production line can contribute to phthalate migration (Leitz and Lachenmeier 2010, p. 531). The overall migration depends not only on one of the mentioned factors, but it is a result of the effect of several factors. Basically, high temperature and storage time accelerate migration, especially in case of phthalates (Luo et al. 2018, p. 366). Phthalates are generally very likely to migrate due to their weak non-covalent bonds which bind them to the parental plastic material. Therefore, they leach in the environment easily and may become ubiquitous (Serrano et al. 2014, p. 1).

4.1 Impact of temperature

Temperature is the main factor influencing the migration of food contaminants from plastic packaging into food. Both high and low temperatures have an impact on the rate of migration and the structure of the polymer. Structural changes may happen under the melting point also in the course of a short time exposure (Lopes et al. 2019, p. 2). As a result of increasing temperature, the diffusion of monomers, polymers and other compounds increases, which can lead to a higher migration rate. The intensity of diffusion also grows when packages are exposed to the fluctuation of temperature. This occurs when some frozen food is cooked and so put from very low temperatures into high temperatures (Bhunia et al. 2013, p. 530). The structural changes of polymer occur already at the temperature below melting point during the heating (Lopes et al. 2019, p. 2). In case of BPA, it was found out that the temperature is a key factor influencing its migration rate. With rising temperature the level of migration increases and after reaching 80 °C, the increase is even greater due to the hydrolysis of carbonate linkage which starts at that temperature (Vilarinho et al. 2019, p. 35).

Ayamba et al. (2020) performed a study in which besides other things the impact of temperature on phthalate migration from PET packaging material into aqueous food simulant (water) and fatty food simulant (oil) was investigated. A linear correlation was determined between the increasing temperature and migrated phthalate concentration. In the figure 8 the relation between increasing temperature and an amount of migrating phthalates can be seen. The concentration of DEHP and DBP was growing gradually with an increasing temperature. In case of DEHP the average concentration of 0.76 µg/kg was detected at 5 °C growing to 1.04 µg/kg at 20 °C, 1.28 µg/kg at 40 °C reaching 1.68 µg/kg at 80 °C. The average concentrations of DBP were 0.13 µg/kg at 5 °C, 0.24 µg/kg at 20 °C, 0.32 µg/kg at 40 °C and 0.50 µg/kg at 80 °C. BBP was not detected at any temperature after 4 hours of exposure. The high amounts of DEHP in comparison with DBP may be caused by the different molecular structure. Because of its long chain, DEHP is weakly bonded to the packaging material and may migrate easily when exposed to heat (Ayamba et al. 2020, pp. 6–7).

In case of the migration of phthalates from plastic bottles into the water, there are positive correlations suggesting that the higher the temperature is the more intensive the migration is. For 10 mg/L DEHP at 40°C, it takes 165 days of storage to migrate but at 4-8 °C the same amount of DEPH migrates in 368 days. The migration of phthalates can be decreased by the low storage temperature (Luo et al. 2018, p. 368).

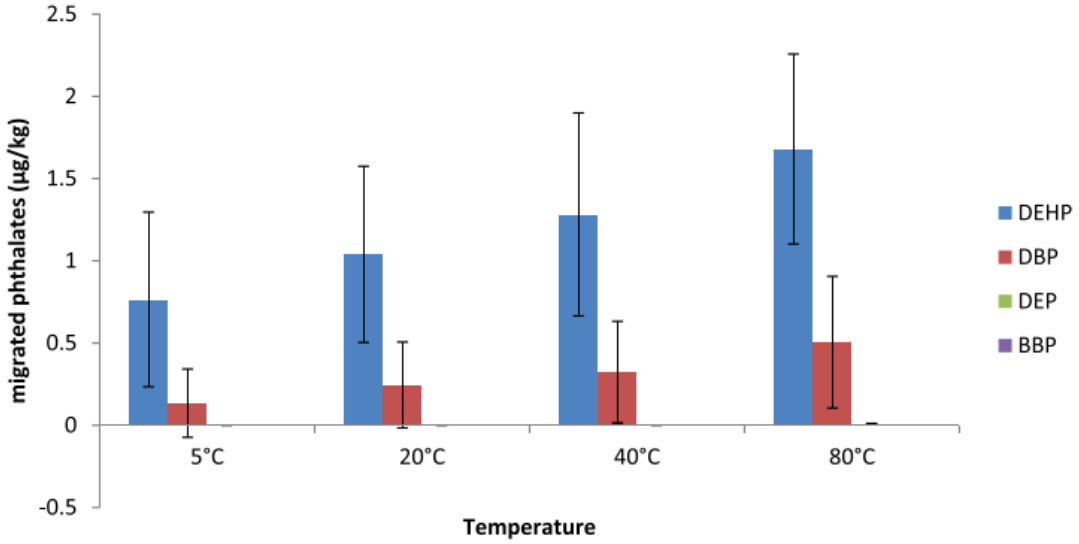


Figure 8: Migration of different phthalates from PET packaging material into water at varied temperatures (Ayamba et al. 2020, p. 6).

4.2 Impact of time span

The time of exposure is also one of the important factors influencing migration. Alp and Yerlikaya (2020) carried out a study investigating the migration of different phthalate esters from different materials (PP, PVC, tin cans, glass) to seafood. With a passing time, the concentrations of all phthalate esters were increasing, there was mostly a rapid rise in amount after one to two months reaching stagnation after three to four months of storage. DEHP was migrating in the highest amount in comparison with other phthalates and was found in all the samples, in some even at relatively high levels. These levels did not exceed the legal limits though (Alp and Yerlikaya 2020, pp. 425–432).

Luo et al. (2018) studied the impact of the storage period on the migration of phthalates into bottled water and have suggested, that phthalates may accumulate during the storage period and it is likely that the number of phthalates exceed the recommended limits after the long storage time. This may already happen during the quality guarantee period. Therefore, studies investigating long-term exposure are essential and the water guarantee period should be re-examined considering the phthalates migration into bottled water (Luo et al. 2018, p. 368).

In the study of Ayamba et al. (2020) the impact of time exposure, apart from the impact of temperature and food matrix, was taken into consideration. The samples from 5 different polyethylene packaging materials were used and the average concentrations of various phthalates after 30 minutes, 1, 2, and 4 hours of exposure were measured and counted (Ayamba et al. 2020, p. 3). The migration of DEHP, DBP, DEP and BBP into water used as a simulant of an aqueous environment was investigated. The amount of migrated DEHP was rising with the time of exposure, reaching the highest amount after 2 hours of exposure.

Average amount of migrated DEHP was 1.5 µg/kg of food simulant which was the highest amount of all the investigated phthalates. In case of DBP the amount was increasing with growing contact time and reached the highest average concentration of 0.5 µg/kg after 4 hours. DEP was detected only after 4 hours of exposure at very low concentrations and BBP was not detected at any contact time at all (Ayamba et al. 2020, p. 5). The specific migration limits set by EU legislation were not exceeded by any of the phthalates (Ayamba et al. 2020, p. 10).

4.3 Impact of pH

Another factor which may contribute to the migration is pH. It has also an impact on the migration of phthalates in bottled water. In most cases, alkaline pH is favourable for the migration of phthalates. On the contrary, acidic pH may also influence the migration of phthalates (Luo et al. 2018, p. 366). In case of BPA, increased pH increases the release from the polycarbonate packaging material. The degradation of the polymer is caused when exposed to alkalic or acidic pH which results in higher BPA migration. Increased pH can result for example from the use of hard water. Nevertheless, in the milk-based foodstuffs, the release of BPA from PC is low. This is caused by proteins which buffer a neutral pH (Vilarinho et al. 2019, p. 35).

In the study of Bošnir et al. (2007) the levels of phthalates present in bottled soft drinks and mineral water packed in PET were investigated. The levels of DMP, DBP, DEP, BBP and DEHP were measured. The soft drinks contained preservatives such as natrium benzoate, kalium sorbate and orthophosphoric acid and had a very low pH value of around 2.8. Mineral water contained no preservatives and had pH value of around 5.8. In soft drinks, the highest rate of migration was in case of DMP made up from 53 to 92% of the overall phthalate migration into soft drinks whereas in mineral water DMP was not present at all. DEHP was present in both soft drinks and mineral water. Nevertheless, the concentration of DEHP inmineral water was 8.78 µg/L which was significantly lower than in soft drinks where the DEHP levels ranged between 15 and 36.6 µg/L. A possible explanation of the difference in concentrations is that the very low pH below 3 in soft drinks has an impact on the intensity of phthalate migration and stimulates this phenomenon (Bošnir et al. 2007, pp. 92–93).

4.4 Impact of UV irradiation

Sunlight may also accelerate the migration because it might favour the degradation degree of additives such as phthalates (Luo et al. 2018, p. 366). In the study of Rastkari et al. (2020) plastic bottles of verjuice, lemon juice and vinegar were exposed to UV irradiation and the concentrations of migrating phthalates were measured. The presence of three main phthalates (DEP, DBP and DEHP) in two types of plastic materials (PET and HDPE) and the amount of these compounds that migrated to the fluid was researched. The samples were divided, poured into plastic bottles made of PET and HDPE and stored in a room

temperature of 25°C, exposed to natural sunlight for 2, 4 and 6 months. In case of vinegar, some concentrations of phthalates were measured at the beginning of the experiment before it came to contact with the plastic bottle. This could have been caused by the usage of plastics during vinegar production processes. DEHP and DEP showed the highest migration rate from both PET and HDPE bottles. After 2 months, the concentration of phthalates grew considerably, in case of DEHP the concentration continued to grow after 4 and 6 months whereas DEP and DBP concentrations have decreased after the 2nd month. The highest concentration of DEHP was measured in vinegar in the HDPE package exposed to sunlight after six months. This concentration was 0.6 µg/L. All the samples had levels of phthalates below 6 µg/L which is a limit established by the United States Environmental Protection Agency. It was suggested that natural sunlight may play a role in the drop of concentrations by causing degradation of phthalates which is slow and can be accelerated by the sunlight. The study came to the conclusion that the observed concentrations of phthalates in acidic juices are not a matter of concern and are not the main source of phthalate ingestion (Rastkari et al. 2018, pp. 28–32).

4.5 Impact of the character of food matrix

In the study carried out by Rastkari et al. (2018) it was found out that also the acidic character and composition of the packed foodstuff, in this case, fluid juices and vinegar, influence the migration rate. A significant difference in concentrations of all measured types of phthalates was observed. The highest concentrations showed vinegar and the lowest lemon juice under the same storage conditions (Rastkari et al. 2018, pp. 30–31).

Another study dealing with the impact of the food matrix on migration was done by Ayamba et al. (2020). Five different types of PET food containers were used as plastic materials from which the amounts of migrated phthalates were measured. Distilled water was used as an aqueous environment simulant and olive oil sold in glass bottles simulated a fatty environment. The small pieces of PET were immersed in 100 mL of distilled water, and the samples were exposed to different temperatures (5°C, 20°C, 40°C and 80°C) for 30 minutes, 1 hour, 2 and 4 hours. Samples with olive oil contained 20 mL of it and were exposed to the same conditions as the samples containing distilled water. The migrated amount of DEHP, DEP, DBP and BBP was investigated. In olive oil, trace amounts of DEHP were detected in all the blank samples. The detected concentrations of phthalates which migrated in the fatty environment were considerably higher than the concentrations under the same conditions in an aqueous environment. In the fatty food matrix, the concentrations of migrated DEHP were in the range from 0.69 mg/kg to 1.95 mg/kg at the highest temperature and longest contact time and for DEP the same applied with concentrations ranging from “not detected” to 1.77 mg/kg. The concentrations of DBP were in this case ranging from “not detected” to 1.43 mg/kg. Thus, at some of the concentrations, DEHP and DBP in fatty environment exceeded the specific migration limits set by the EU legislation at 1.5 mg/kg for DEHP and 0.3 mg/kg for DBP. All the levels of migrated phthalates

in the aqueous environment were below these specific migration limits (Ayamba et al. 2020, pp. 3–10).

The levels of DEHP detected in beverages containing lipids are significantly higher than those found in water. This could be due to the higher solubility of DEHP in presence of lipids. The concentrations of DEHP in milk were higher than in other beverages such as water, wine or beer. There is a correlation between increased levels of DEHP and increased content of fat in milk and milk products. In case of food, the fattiest foods contain generally the highest load of DEHP (Erythropel et al. 2014, pp. 9973–9974). Another proof that the fatty food matrix enables the migration of more phthalates is the migration of DEHP from the medical equipment. Concentrations of 17 to 25 mg/L of DEHP were detected in aqueous solutions in PVC bags whereas in lipid emulsions in infusion sets the detected amount was between 19.4 and 65.8 mg/L. In pure oils the concentration was even higher reaching values between 1,700 and 3,100 mg/L. This shows that the more lipophilic the stored solution in a plastic container or bag is the higher the amount of DEHP is which is. Higher solubility of DEHP in a fatty environment is the explanation for this phenomenon (Erythropel et al. 2014, p. 9974).

It seems that some preservatives may influence the migration of phthalates as well. In the study performed by Bošir et al. (2007) in soft drinks which contained kalium sorbate the concentrations of overall migrated phthalates were several times higher than in soft drinks containing orthophosphoric acid or natrium benzoate, in comparison with mineral water the difference was even higher and soft drinks containing kalium sorbate as preservative about 40 times higher levels of phthalates were detected. Specifically, soft drinks containing kalium sorbate had a total concentration of phthalates 819 µg/L, soft drinks with natrium benzoate 117 µg/L soft drinks with orthophosphoric acid 92 µg/L and mineral water only 20 µg/L. Soft drinks preserved with both natrium benzoate and kalium sorbate were also in the study and contained 543 µg/L of phthalates in total. The phthalate detected in the highest amounts was DMP followed by DEHP, DBP, DEP and the least detected was BBP which was only present in soft drinks containing kalium sorbate. According to the values measured in the study, it seems that the preservatives used in the manufacture have an impact on the migration of phthalates from PET bottles to the beverages inside. Kalium sorbate together with low pH favours migration of phthalates whereas Na-benzoate and orthophosphoric acid alone appear to be less aggressive regarding the phthalate migration from plastic bottles into drinks (Bošnir et al. 2007, pp. 92–93).

5. Possible health effects of bisphenols and phthalates

Plastics are used not only for food packaging but also in many other branches which makes them in the modern world ubiquitous and the exposure to potentially harmful additives is significant. The most important routes of exposure are through ingestion, inhalation and dermal contact (Meeker et al. 2009, p. 2098). Thus, there are two main groups of exposure sources, from both dietary sources which include food and drinks and non-dietary sources which include for example dust, air, personal care products and toys. However, the dietary sources represent the main source of exposure (Vilarinho et al. 2019, p. 34). The primary route of BPA exposure is oral from eating and drinking food and beverages that contain some amount of BPA which migrated from the package to food or the beverage. Nevertheless, exposure from the environment such as inhalation of dust particles also plays an important role in overall exposure to BPA (Robinson and Miller 2015, p. 380).

Another aspect that should be taken into consideration is that there are multiple chemicals able to migrate to food. Humans are daily exposed to various chemicals which have migrated from the food contact material to food. An array of these chemicals is called a chemical mixture and is present at different levels and in a different composition. Such a mixture of chemicals acting at the same time has in general higher toxicity (Muncke et al. 2020, p. 5). The toxicity of such a mixture of chemicals migrating from food packaging materials should be determined for hazards such as genotoxicity, endocrine disruption or mutagenicity (Muncke et al. 2020, p. 7). Furthermore, there can be non-intentionally added substances (NIAS) that can be impurities of additives or starting substances, products generated during the production and manufacturing and break-down product of intentionally added substances. Some of these substances have been revealed by modern analytical methods, but there are still some which remain unidentified (Muncke et al. 2020, p. 5).

5.1 Endocrine disruptors

Bisphenol A and its analogues and phthalates are in a group of chemicals called endocrine disruptors (EDs) (Yuan et al. 2020, p. 136; Vilarinho et al. 2019, p. 34). In some literature, they are also called estrogenic compounds (Luo et al. 2018, p. 368). These are exogenous chemical compounds which interfere with endogenous hormonal system and influence various hormonal processes in the body including the production of hormones, the release of hormones, their transport and metabolism (Escrivá et al. 2019, p. 4) . They have the effect of natural hormones, block their synthesis and bind to their receptors (Thent et al. 2018, p. 1). Endocrine disruptors can come from both natural and synthetical sources. Typical natural sources are phytochemicals present for example in soy, whereas compounds such as phthalates and BPA are synthetical and get into foodstuffs and beverages (Degen 2004, p. 849). Mostly, the synthetic EDs come from the production of plastics. Apart from phthalates and bisphenols, polychlorinated biphenyls, dioxins, vinclozolin,

di-chlorodiphenyltrichloroethane (known as DDT) and diethylstilbestrol are also in this group of chemicals (Thent et al. 2018, p. 1).

Endocrine disruptors bind to the molecular targets meant for hormones and intervene in hormonal functions (Vilarinho et al. 2019, p. 34). Mostly, EDs get to the body from food sources. The most attention attract such chemicals which resemble sexual hormones (estrogens, androgens) (Degen 2004, p. 848). They can take their place and block the receptors preventing the sexual hormones from fulfilling their role in the organism. Chemicals with estrogenic or androgenic activity may cause developmental and reproductive problems or contribute to the formation of tumours (Degen 2004, p. 850). These interfere with androgen or estrogen receptors and may trigger an either agonistic or antagonistic response. Furthermore, EDs might have an impact on the cell cycle, apoptotic mechanism and cause epigenic changes which can modify the activation and expression of genes (Cargnelutti et al. 2020). In the environment, EDs can affect animals and cause infertility, disruption of sexual behavior or mortality (Luo et al. 2018, p. 368). At both high and low dose concentrations relevant to human exposure the endocrine-disrupting effects were detected (Radwan et al. 2018, p. 2145).

5.2 Health effects of phthalates

Phthalates can potentially be toxic for humans so that the internal dose measurements are important for the assessment of exposure and risk assessment (Hauser and Calafat 2005, p. 808). They have been related to adverse health effects, especially in early-life exposure. Prenatal exposure to phthalates in pregnant women is linked to changes in labor, infant hormone levels and neurobehavioral changes of the infant and child. In men, phthalate exposure seems to decrease semen quality and impair testicular function in men (Serrano et al. 2014, p. 2). Furthermore, phthalates have been linked to obesity, type II diabetes asthma and allergy (Giuliani et al. 2020, p. 6). Acute toxicity of phthalates on the organism is rare, problematic is primarily subchronic and chronic exposure and their monoesters which arise during the metabolism (Leitz and Lachenmeier 2010, p. 531).

According to the reports, human exposure to phthalates that come from food is both from bioaccumulation in the food chain and from plastic material coating which the foodstuffs come in contact with (Alp and Yerlikaya 2020, p. 428). To assess the exposure and risk indirect measures of exposure which includes the monitoring of the environment should be carried out. Thanks to biomonitoring and advanced analytical methods it is possible to measure trace levels of phthalates. For human exposure detection, the most common is measuring the traces of phthalate metabolites in urine. These biomonitoring data are used in combination with indirect measures of exposure for the risk and exposure assessments. Individual exposure might vary over time and depends on a person´s diet, daily activities and the use of personal care products (Hauser and Calafat 2005, p. 808).

In female rodent studies the reproductive toxicity of DEHP was examined. The ovary appeared to be a target for DEHP and decreased estradiol production was observed. Furthermore, the dose of 2 mg/kg DEHP in adult rodents has decreased serum estradiol levels and prolonged the estrous cycle. There was no ovulation and as a consequence, no corpus luteum was made and the follicles became cystic. In DEHP treated rodents the granulosa cells were significantly smaller than control cells and they were suggested to be the target cells of DEHP in the ovary. Thus, the production of estradiol in granulosa cells was suppressed by DEHP and the low level of estradiol was not sufficient to trigger the production of luteinizing hormone (Lovekamp-Swan and Davis 2003, pp. 140–141). Testicular toxicity in pubertal animals has been reported in studies performed on animals and it also seems that some phthalates may have an impact on semen quality (Hauser and Calafat 2005, p. 812).

In the study of Su et al. (2019), high urinary MEHP levels were linked to some major cardiovascular risk factors such as Body Mass Index, triglycerides, fasting glucose, diastolic blood pressure and prevalence of hypertension and diabetes. The findings of this study suggested an association between increased urine levels of MEHP, a first phase metabolite of DEHP and MnBP, a metabolite of DIBP, to a concentration-dependent risk of subclinical atherosclerosis in young population (Su et al. 2019, pp. 588–591).

Phthalates have been linked to several types of cancer such as liver, skin, prostate, and breast cancer. In Mexico for instance, significantly higher MEP concentrations were detected in women with breast cancer (about 50% higher) than in healthy women (Giuliani et al. 2020, p. 9). DEHP and its urinary metabolite MEHP can activate a nuclear receptor which can modify protein and gene expression and can lead to increased cell proliferation or inhibition of apoptosis and oxidative stress. Apoptosis is a process which takes place in various tissues and it is responsible for maintaining the number of cells, removing old, damaged or unwanted cells and it prevents the formation of tumors. The suppression of apoptosis was observed in the rat liver and the number of cells removed by apoptosis decreased. These faulty cells can be further divided during mitosis and lead to the formation of tumors (Praveena et al. 2018, p. 11336). In the study of Seo et al. (2004) the doses of 50, 200 and 1,000 mg/kg were administered to rats orally for 14 days and the impact on the liver was observed. The rats were fed with corn oil containing the corresponding amount of phthalate. DEHP, DBP and BBP were used for the experiment. The enlargement of the liver occurred at all concentrations in case of DEHP and a significant impact on the liver size was observed at the concentration of 200 mg/kg and higher. In contrast, the significant increase in liver weight in the rats fed with corn oil with DBP and BBP appeared only at the concentration of 1,000 mg/kg (Seo et al. 2004, pp. 108–109). Already at the doses of 50 mg/kg/day, there is a possibility to develop liver tumors but the results were obtained only from the studies on rats and may not apply to humans the same way. Thus, the mechanism of phthalates may not be relevant to humans due to species differences (Praveena et al. 2018, p. 11337).

5.3 Health effects of BPA and its analogues

As an ubiquitous environmental contaminant, BPA is considered to be a potential threat to human health and there are concerns about its possible connection to cardiovascular diseases, metabolic disorders, infertility and cancer (Castellini et al. 2020, p. 2). Increased concentration values of BPs in urine in adults are associated with hypertension and obesity, decreased heart rate variability, increased blood pressure and increased incidence of cardiovascular diseases (Russo et al. 2019, p. 2).

BPA is a xenoestrogen due to its polycyclic phenolic structure which resembles 17-β estradiol and may have a similar effect as estrogen. Thus, BPA in its not glucurinated form is able to take place at the alpha and beta receptors (ERα and ERβ) for estradiol. There was a more evident dose dependence for ERβ to which the affinity of BPA was higher. Nevertheless, the affinity of 17-β estradiol to the alpha receptor is 10,000 times higher than that of BPA. This means that BPA acts as a weak estrogen and causes an endogenic disruption. This is problematic especially in males where such estrogenic disruption may lead to a reduction in the production of gonadotropins and reduced spermatogenesis. The testosterone level in BPA-treated animals was lower which could reflect the decreased expression of steroidogenic enzymes and has as a consequence the reduced testosterone biosynthesis (Castellini et al. 2020, p. 3). In addition, BPA may also evince an anti-androgenic activity by interfering with the androgen receptor. It acts as an antagonist and decreases the expression of the androgenic receptor in the testis. For spermatogenesis, a good functionality of androgen receptor, as well as high intratesticular levels of testosterone, are required which is the explanation why BPA affects testosterone biosynthesis and activity (Castellini et al. 2020, p. 3).

Studies on rodents with highly ranging doses from 2 µg BPA/kg body weight/day to 960 mg BPA/kg body weight/day with various time intervals ranging from five to eighty-four days have shown that BPA has an impact on the production of sperm and sperm quality. High doses of BPA caused significantly lower sperm counts, worse sperm motility, poor spermatogenesis and a higher rate of sperm DNA damage (Castellini et al. 2020, p. 3). The sperm production and along with it also male fertility were decreased when the daily intake of BPA exceeded 25 mg/kg of body weight (Thent et al. 2018, p. 3). In the study carried out by Radwan et al. (2018) the relation between BPA concentrations in urine and semen quality which is an indicator of male fertility was investigated. 315 men under 45 years of age in Poland took part in the study and provided semen and urine samples. Some concentration of BPA was detected in 98% of samples, in 95% of the urine samples, the concentration of BPA ranged from 1.84 µg/L to 8.19 µg/L. There was a positive association between BPA concentration in urine and percentage of immature sperm and the amount of sperm with abnormal morphology. Furthermore decreased motility and increased sperm sex chromosome disomy were observed (Radwan et al. 2018, pp. 2146–2149).

The alteration of the cholecalciferol (vitamin D_3) levels is also one of the impacts which the exposure to BPA has. Cholecalciferol circulating in the blood plays an important role in the prevention and reduction of chronic diseases such as cancer, autoimmune and cardiovascular diseases, and infections. In a study on rats performed by Kim et al., (2019) the impact of BPA on vitamin D_3 metabolism was examined. The results showed that the doses of 50 and 250 mg/kg of body weight which the rats were treated with for 13 weeks caused a significant decrease in levels of the active form of vitamin D_3. Thus, the plasma concentration of vitamin D_3 decreased whereas the urinary excretion increased (Kim et al. 2019, p. 6).

BPA is also linked to obesity and marked as a possible obesogen. It encourages both adipogenesis and lipid storage and by animals treated with low doses of BPA obesity-related disfunctions were observed (Castellini et al. 2020, p. 3). BPA levels which exceed 300 ng/L increased the fat mass and leptin level in serum and promoted obesity this way. In the study with obese middle-aged and elderly women the relation between obesity and BPA exposure was discovered. It was also found out that BPA has a positive effect on obesity even in non-obese women (Thent et al. 2018, p. 3). In addition, in the offspring of mother exposed to BPA during gestation, increased body weight has been observed (Haq et al. 2020, p. 1).

In a study of Haq et al. (2020) the diabetogenic effect of BPA in rodents was studied. The rodents were exposed to different concentrations of BPA (0; 50; 500; 2,500 and 5,000 μg/kg of body weight) in a solution. All the groups exposed to BPA showed significantly higher blood glucose levels. The effects were more apparent after three months of exposure, though. The level of serum insulin was also significantly high in groups treated with BPA. In addition, the effect of BPA on the level of triglycerides, free fatty acids and high-density lipoprotein (HDL) were investigated. The BPA treatment showed rising levels of triglycerides and free fatty acids levels with increasing doses and length of the time period. On the contrary, BPA caused a decreased serum level of HDL. There was a dose-dependent manner in all the tested biomarkers (Haq et al. 2020, pp. 2–4).

Estrogen, androgen and progesterone are also important regulators of bone metabolism. They are required in the regulation of osteoblasts and osteoclasts which are bone cells responsible for a balance between bone remodeling and bone resorption, respectively. Osteoblasts stimulate bone growth and replace bone tissue remover by osteoclasts. This mechanism can also be influenced by BPA because it interrupts the function of sex hormones. The estrogen receptors ERα and ERβ are present in osteoblasts and osteoclasts. Estrogen regulates the function of osteoclasts and reduces the expansion of osteoblasts. Through the endocrine disruption, BPA becomes an estrogen stimulator. BPA is believed to contribute to bone mass loss and osteoporosis (Thent et al. 2018, p. 3).

Regarding the carcinogenicity of BPA, there are not enough convincing studies that would provide an evidence that BPA is carcinogenic. BPA may contribute to some kinds of cancer such as breast cancer which could be caused by the impact of BPA on cell proliferation and differentiation in the prostate, testis or mammary gland but the evidence is not sufficient to claim that BPA plays a role in cancer development. A similar applies to genotoxicity.

There is no clear evidence that BPA would be mutagenic (EFSA 2015, p. 19). In the study of Haq et al. (2020) though, mRNA expression for glucose metabolism, cholesterol biosynthesis and fatty acid biosynthesis in the liver and insulin synthesis in the pancreas in connection with BPA exposure was investigated as an indicator of an impact on carbohydrate and lipid metabolism. At concentrations of 2,500 μg/kg and higher the mRNA expression, the significant changes were observed. The mRNA expression for cholesterol biosynthesis increased considerably at this concentration. On the contrary, in case of glucose metabolism and fatty acid biosynthesis the mRNA expression was decreased with the BPA exposure, more significantly at concentration of 2,500 μg/kg and higher. In all the investigated processes, a dose-dependent manners were observed. As a result, exposure to BPA may alter glucose and lipid metabolism in the liver (Haq et al. 2020, pp. 5–6).

High exposure to BPA may have an impact on human development. High prenatal exposure is linked to emotionally reactive and aggressive behaviour in boys whereas in girls the same was linked to behaviors related to depression and anxiety. Furthermore, BPA exposure is associated with the onset of puberty at a young age. In addition, Attention-Deficit/Hyperactivity Disorder (ADHD) was reported to be related to early-life exposure to BPA (Kim et al. 2019, p. 2). In a study on mice which were exposed to 5 μg/mL of BPA through contaminated water, the changes during development were observed which could lead to asthma or allergy. No significant differences in asthma or allergy development occurred in young mice which mothers were exposed to BPA in prenatal and perinatal period for 21 days. However, in mice exposed to BPA after birth till 9 weeks of age higher levels of airway eosinophils and increased airway hyperreactivity were observed (Robinson and Miller 2015, p. 382). In epidemiologic studies, high urinary levels of BPA were associated with increased risk of wheezing and with each doubling of BPA concentration in various age groups, the relative risk of wheeze, chest infection and the risk of bronchitis development increased (Robinson and Miller 2015, p. 383).

In case of BPA analogues, for some of them there is not enough data available regarding their toxicity. BPS and BPAF urinary concentrations were associated with higher risk of type II diabetes, BPAF was also associated with hypoglycaemia in elderly people (Pelch et al. 2019, p. 5). Regarding the impact of BPA analogues on pregnancy and reproduction, BPS urinary levels were in correlation with increased gestational age, increased risk of late term birth for girls and on the contrary to the preterm birth around 35 weeks of pregnancy (Pelch et al. 2019, p. 6). Also BPA analogues may be endocrine-disrupting chemicals. BPAF was found to be a quite strong estrogen receptor agonist and even more potent than BPA. In addition, some BPA analogues were found to be androgen receptor antagonists, in which BPAF, BPE, BPB and BPS with some other BPA analogue were included. Their anti-androgenic activity was weak though and in general, BPA analogues do not evince androgen receptor agonist activity (Pelch et al. 2019, p. 11).

As well as BPA, its substitutes decrease the neurite length and exert neural toxicity this way and apart from BPA, the possible neurotoxicity and impact on cell viability were tested

by other bisphenols. The human neural stem cells were incubated with BPS, BPF, BPE, BPB, BPZ and BPAF. For being able to assess the effect of human-relevant doses on the development of the neurons, the concentrations of 1, 10 and 100 nM for 16 days during differentiation of the cells. As well as BPA, other bisphenols showed a negative impact on the neurite length which has decreased after the treatment of the tissue with BPA analogues. BPS, BPF and BPAF had a significant effect on the neurite length already at concentrations of 1 nM. On the contrary, in treatment with BPE, BPB and BPZ the concentration of 100 nM was sufficient to decrease the total neurite length. The study showed that BPA and its substitutes may be slightly neurotoxic and lead to a reduction of the neurite length at the concentrations relevant to humans and the environment (Liang et al. 2020, p. 8).

6. Conclusion

Plastic materials are ubiquitous and as a result of the long-term use of plastic throughout industries where the packaging industry plays an important role also the additives in plastic materials such as plasticizers which make the material pliable and flexible and antioxidants which delay the degradation of the polymer became ubiquitous.

Phthalates are in the group of plasticizers and the most widely used one is DEHP followed by DEP, BBP, DBP or DINP. They are diesters of phthalic acid and are utilized mostly for manufacturing PVC. There are two main groups of phthalates that vary in their structure, metabolism and utilization. The group of low-molecular weight phthalates includes DEP and DBP, for instance. They have a shorter carbon chain containing 1-4 carbon atoms and are mostly used in personal care products. High-molecular weight phthalates such as DEHP, BBP and DINP have 8-10 carbon atoms in the carbon chain and are widely used for food packaging. Their metabolism is more complex in comparison with the low-molecular weight phthalates and after the hydrolysis and oxidation, conjugation takes place. Monoesters of the corresponding phthalates which are more hydrophilic are formed during the metabolism. This allows their elimination through urine and they are also excreted in faeces. The metabolites may be more toxic than the initial phthalate, though. Different SML and TDI were set for different phthalates. For DEHP, which can be found in foodstuffs often SML was set at 1.5 mg/kg of foodstuff and TDI was set at 50 µg/kg of body weight. In general, higher concentrations exceeding 0.3 mg/kg of foodstuff can often be measured in meat, cheese and oil whereas lower concentrations under 50 µg/kg of foodstuff are present in eggs, milk and grains. Thus, the exceeding of SML and TDI is rare.

Bisphenol A and its structural analogues such as BPF, BPB, BPM, BPAF or BPE are in the group of antioxidants. BPA is the most common bisphenol used in PC, epoxy resins, thermal paper and PVC. During the metabolism in the human body, BPA is excreted within 24 hours after ingestion in urine mostly in form of BPA glucuronide but it can also be metabolized in BPA monosulfate or BPA disulfate. The EU set the TDI for BPA which is 50 µg/kg of body weight. As well as in case of phthalates, there are some concentrations in foodstuffs but they are usually from nanograms to few micrograms per kilogram of foodstuff and do not exceed SML which wat set at 0.6 mg/kg of food. Furthermore, the TDI of 50 µg/kg of body weight is usually not exceeded as well. Regarding the BPA analogues, it seems they are not much better than BPA itself and may also have a negative impact on health in high doses.

The process during which the additives get from the package to the packed food or drinks is called migration. Phthalates and bisphenols are susceptible to migration because of their week bonds with the polymer. The intensity of migration is influenced by several environmental factors and by the factor of time. The temperature is one of the most important factors. With the rising temperature, the migration rate intensifies as well as with the time of exposure. For example, at the temperature of about 5°C, the migration of DEHP takes two

times longer than at 40°C and after exceeding 80°C the migration rate is even higher due to the hydrolysis of carbonate linkage. In addition, pH level, UV irradiation and the character of the food matrix also influence migration. The migration rate rises with very low or very high pH, UV irradiation contributes to the degradation of phthalates and in fatty foods, the concentration of migrated phthalates and bisphenols are higher than in aqueous foods because they are hydrophobic. Some additives such as kalium sorbate promote migration.

Bisphenols and phthalates are endocrine disruptors. They resemble sexual hormones such as estrogen, they can bind to their receptors and interfere in their function. This leads to worse spermatogenesis in men, it has a negative impact on sperm quality, reduces sperm concentration and imparts the fertility this way. In females, decreased estradiol production and prolongation of estrous cycle can be caused and high doses can lead to no ovulation. Sexual hormones play a role in the control of bone metabolism as well and high doses of BPA contribute to bone mass loss and osteoporosis. Similarly, BPA and phthalates contribute to obesity by encouraging adipogenesis and lipid storage. In case of BPA, regarding the carcinogenicity, increased cell proliferation and inhibition of cell apoptosis were observed but there is no clear evidence to declare phthalates or bisphenols carcinogenic although phthalates have already been linked to possibly contribute to the development of liver, prostate or breast cancer. Nevertheless, the impact was obvious at doses of 50 mg/kg of body weight which are a few orders of magnitude higher than human-related doses. Alteration of cholecalciferol metabolism occurred also at this dose and higher. Only the endocrine disruption seems to occur already at relatively low levels of BPA or phthalates and mostly, a dose-dependent manner applies.

In conclusion, it is necessary to mention that there have to be more studies done to better understand the possible health risks of phthalates and bisphenols and the consequences of the chronical exposure. Especially, ecotoxicological studies observing and examining the exposure to humans and its impact should be performed since the results of studies performed on animals may not be relevant to humans due to species-related diversity. The mixture of chemicals which migrate from the packaging at the same time and may increase the effect on heath also needs to be taken into consideration and examined thoroughly. In addition, an alternative packaging should be used more where it is possible and the size of plastic packages as well as the production of plastics in general should be reduced to avoid high levels of phthalates, bisphenols and other potentionally harmful substances in food, water and the environment.

7. List of abbreviations

BBP	Benzylbutyl phthalate
BPA	Bisphenol A
BPAF	Bisphenol AF
BPF	Bisphenol F
BPS	Bisphenol S
BPs	Bisphenols
BPZ	Bisphenol Z
DBP	Di-butyl phthalate
DEHP	Di-(2-ethylhexyl) phthalate
DEP	Di-ethyl phthalate
DIBP	Di-isobutyl phthalate
DIDP	Di-isodecyl phthalate
DINP	Di-isonoyl phthalate
EDCs	Endocrine-disrupting compounds
EFSA	European Food Safety Authority
FCCs	Food contact chemical
HDL	High density lipoprotein
HDPE	High-density polyethylene
LDPE	Low-density polyethylene
MCMHP	Mono(2-carboxymethylhexyl) phthalate
MECPP	Mono(2-ethyl-5-carboxypentyl) phthalate
MEHHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono(2-ethylhexyl) phthalate
MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
MEP	Monoethylphthalate
MHEHP	Mono2-(2-hydroxyethylhexyl) phthalate
NOAEL	No Observed Adverse Effect Level
PET	Polyethylene terephthalate
PP	Polypropylene
PS	Polystyren
PVC	Polyvinyl chloride
SML	Specific migration limit
SMLT	Total specific migration limit
TDI	Tolerable daily intake
US	United States

8. Publication bibliography

Alp, Ali Can; Yerlikaya, Pinar (2020): Phthalate ester migration into food: effect of packaging material and time. In *European Food Research and Technology (European Food Research and Technology)* 246 (3), pp. 425–435. DOI: 10.1007/s00217-019-03412-y.

Ayamba, Adongo Abdul-Malik; Agyekum, Akwasi Akomeah; Derick, Carboo; Dontoh, Derry (2020): Assessment of phthalate migration in polyethylene food contact materials sold on the Ghanaian market. In *Cogent Environmental Science* 6 (1), pp. 1–11. DOI: 10.1080/23311843.2020.1794242.

Bhunia, Kanishka; Sablani, Shyam S.; Tang, Juming; Rasco, Barbara (2013): Migration of Chemical Compounds from Packaging Polymers during Microwave, Conventional Heat Treatment, and Storage. In *Comprehensive Reviews in Food Science and Food Safety* 12 (5), pp. 523–545. DOI: 10.1111/1541-4337.12028.

Bošnir, Jana; Puntarić Dinko; Galić Antonia; Škes Ivo; Dijanic Tomislav; Klarić Maja et al. (2007): Migration of Phthalates from Plastic Containers into Soft Drinks and Mineral Water. In *Food Technology. Biotechnology* (45 (1)), pp. 91–95.

Braun, Joseph M.; Sathyanarayana, Sheela; Hauser, Russ (2013): Phthalate exposure and children's health. In *Current opinion in pediatrics* 25 (2), pp. 1–15. DOI: 10.1097/MOP.0b013e32835e1eb6.

Cargnelutti, Francesco; Di Nisio, Andrea; Pallotti, Francesco; Sabovic, Iva; Spaziani, Matteo; Tarsitano, Maria Grazia et al. (2020): Effects of endocrine disruptors on fetal testis development, male puberty, and transition age. In *Endocrine*. DOI: 10.1007/s12020-020-02436-9.

Castellini, Chiara; Totaro, Maria; Parisi, Antonio; D'Andrea, Settimio; Lucente, Liana; Cordeschi, Giuliana et al. (2020): Bisphenol A and Male Fertility: Myths and Realities. In *Frontiers in endocrinology* 11, pp. 1–10. DOI: 10.3389/fendo.2020.00353.

Degen, G. H. (2004): Endokrine Disruptoren in Lebensmitteln. In *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* 47 (9), pp. 848–856. DOI: 10.1007/s00103-004-0893-5.

EFSA (2015): Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. In *EFSA Journal* 13 (1), pp. 1–1040. DOI: 10.2903/j.efsa.2015.3978.

Erythropel, Hanno C.; Maric, Milan; Nicell, Jim A.; Leask, Richard L.; Yargeau, Viviane (2014): Leaching of the plasticizer di(2-ethylhexyl)phthalate (DEHP) from plastic containers and the question of human exposure. In *Applied microbiology and biotechnology* 98 (24), pp. 9967–9981. DOI: 10.1007/s00253-014-6183-8.

Escrivá, Laura; Hanberg, Annika; Zilliacus, Johanna; Beronius, Anna (2019): Assessment of the endocrine disrupting properties of Bisphenol AF according to the EU criteria and ECHA/EFSA

guidance. In *EFSA journal. European Food Safety Authority* 17 (Suppl 2), e170914. DOI: 10.2903/j.efsa.2019.e170914.

Giuliani, Angela; Zuccarini, Mariachiara; Cichelli, Angelo; Khan, Haroon; Reale, Marcella (2020): Critical Review on the Presence of Phthalates in Food and Evidence of Their Biological Impact. In *International journal of environmental research and public health* 17 (16). DOI: 10.3390/ijerph17165655.

Guerreiro, Tatiane Melina; Oliveira, Diogo Noin de; Melo, Carlos Fernando Odir Rodrigues; Oliveira Lima, Estela de; Catharino, Rodrigo Ramos (2018): Migration from plastic packaging into meat. In *Food research international (Ottawa, Ont.)* 109, pp. 320–324. DOI: 10.1016/j.foodres.2018.04.026.

Gundert-Remy, Ursula; Bodin, Johanna; Bosetti, Cristina; FitzGerald, Rex; Hanberg, Annika; Hass, Ulla et al. (2017): Bisphenol A (BPA) hazard assessment protocol. In *EFS3* 14 (12). DOI: 10.2903/sp.efsa.2017.EN-1354.

Hahladakis, John N.; Velis, Costas A.; Weber, Roland; Iacovidou, Eleni; Purnell, Phil (2018): An overview of chemical additives present in plastics: Migration, release, fate and environmental impact during their use, disposal and recycling. In *Journal of hazardous materials* 344, pp. 179–199. DOI: 10.1016/j.jhazmat.2017.10.014.

Haq, Muhammad Ejaz Ul; Akash, Muhammad Sajid Hamid; Rehman, Kanwal; Mahmood, Malik Hassan (2020): Chronic exposure of bisphenol A impairs carbohydrate and lipid metabolism by altering corresponding enzymatic and metabolic pathways. In *Environmental toxicology and pharmacology* 78, pp. 1–11. DOI: 10.1016/j.etap.2020.103387.

Hauser, R.; Calafat, A. M. (2005): Phthalates and human health. In *Occupational and environmental medicine* 62 (11), pp. 806–818. DOI: 10.1136/oem.2004.017590.

Heinemeyer, Gerhard; Sommerfeld, Christine; Springer, Andrea; Heiland, Astrid; Lindtner, Oliver; Greiner, Matthias et al. (2013): Estimation of dietary intake of bis(2-ethylhexyl)phthalate (DEHP) by consumption of food in the German population. In *International journal of hygiene and environmental health* 216 (4), pp. 472–480. DOI: 10.1016/j.ijheh.2013.01.001.

İyigündoğdu, İrem; ÜstÜndaĞ, Aylin; Duydu, Yalçın (2020): Toxicological Evaluation of Bisphenol A and Its Analogues. In *Turkish journal of pharmaceutical sciences* 17 (4), pp. 457–462. DOI: 10.4274/tjps.galenos.2019.58219.

Kim, Jae Kwan; Khan, Adnan; Cho, Seongha; Na, Jinhyuk; Lee, Yeseung; Bang, Geul et al. (2019): Effect of developmental exposure to bisphenol A on steroid hormone and vitamin D3 metabolism. In *Chemosphere* 237, pp. 1–9. DOI: 10.1016/j.chemosphere.2019.124469.

Leitz, Jenny; Lachenmeier, Dirk W. (2010): Phthalatkontaminationen in Lebensmitteln - Aktueller Wissensstand. In *Deutsche Lebensmittel-Rundschau: Zeitschrift für Lebensmittelkunde und Lebensmittelrecht* 5, pp. 530–533.

Liang, Xiaoxing; Yin, Nuoya; Liang, Shengxian; Yang, Renjun; Liu, Shuyu; Lu, Yuanping et al. (2020): Bisphenol A and several derivatives exert neural toxicity in human neuron-like cells by decreasing neurite length. In *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 135, pp. 1–10. DOI: 10.1016/j.fct.2019.111015.

Lopes, Alberto Joao; Tsochatzis, Emmanouil D.; Robouch, Piotr; Hoekstra, Eddo (2019): Influence of pre-heating of food contact polypropylene cups on its physical structure and on the migration of additives. In *Food packaging and shelf life* 20, pp. 1–8. DOI: 10.1016/j.fpsl.2019.100305.

Lovekamp-Swan, Tara; Davis, Barbara J. (2003): Mechanisms of phthalate ester toxicity in the female reproductive system. In *Environmental health perspectives* 111 (2), pp. 139–145. DOI: 10.1289/ehp.5658.

Luo, Qiong; Liu, Ze-Hua; Yin, Hua; Dang, Zhi; Wu, Ping-Xiao; Zhu, Neng-Wu et al. (2018): Migration and potential risk of trace phthalates in bottled water: A global situation. In *Water research* 147, pp. 362–372. DOI: 10.1016/j.watres.2018.10.002.

Martínez-Bueno, M. J.; Gómez Ramos, M. J.; Bauer, A.; Fernández-Alba, A. R. (2019): An overview of non-targeted screening strategies based on high resolution accurate mass spectrometry for the identification of migrants coming from plastic food packaging materials. In *TrAC Trends in Analytical Chemistry* 110, pp. 191–203. DOI: 10.1016/j.trac.2018.10.035.

Meeker, John D.; Sathyanarayana, Sheela; Swan, Shanna H. (2009): Phthalates and other additives in plastics: human exposure and associated health outcomes. In *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* 364 (1526), pp. 2097–2113. DOI: 10.1098/rstb.2008.0268.

Muncke, Jane; Andersson, Anna-Maria; Backhaus, Thomas; Boucher, Justin M.; Carney Almroth, Bethanie; Castillo Castillo, Arturo et al. (2020): Impacts of food contact chemicals on human health: a consensus statement. In *Environmental health : a global access science source* 19 (1), pp. 1–12. DOI: 10.1186/s12940-020-0572-5.

Pelch, Katherine; Wignall, Jessica A.; Goldstone, Alexandra E.; Ross, Pam K.; Blain, Robyn B.; Shapiro, Andrew J. et al. (2019): A scoping review of the health and toxicological activity of bisphenol A (BPA) structural analogues and functional alternatives. In *Toxicology* 424, pp. 1–17. DOI: 10.1016/j.tox.2019.06.006.

Plastics-the Facts 2019. An analysis of European plastics production, demand and waste data. Available from < https://www.plasticseurope.org/download_file/force/3183/181> (2019) 1-39.

Praveena, Sarva Mangala; Teh, Seoh Wei; Rajendran, Ranjith Kumar; Kannan, Narayanan; Lin, Chu-Ching; Abdullah, Rozaini; Kumar, Suresh (2018): Recent updates on phthalate exposure and human health: a special focus on liver toxicity and stem cell regeneration. In

Environmental science and pollution research international 25 (12), pp. 11333–11342. DOI: 10.1007/s11356-018-1652-8.

Radwan, Michał; Wielgomas, Bartosz; Dziewirska, Emila; Radwan, Paweł; Kałużny, Paweł; Klimowska, Anna et al. (2018): Urinary Bisphenol A Levels and Male Fertility. In *American journal of men's health* 12 (6), pp. 2144–2151. DOI: 10.1177/1557988318799163.

Rastkari, Noushin; Jeddi, Maryam Zare; Yunesian, Masud; Ahmadkhaniha, Reza (2018): Effect of sunlight exposure on phthalates migration from plastic containers to packaged juices. In *Journal of environmental health science & engineering* 16 (1), pp. 27–33. DOI: 10.1007/s40201-018-0292-8.

Robinson, Lacey; Miller, Rachel (2015): The Impact of Bisphenol A and Phthalates on Allergy, Asthma, and Immune Function: a Review of Latest Findings. In *Current environmental health reports* 2 (4), pp. 379–387. DOI: 10.1007/s40572-015-0066-8.

Russo, Giacomo; Barbato, Francesco; Mita, Damiano Gustavo; Grumetto, Lucia (2019): Occurrence of Bisphenol A and its analogues in some foodstuff marketed in Europe. In *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 131, pp. 1–14. DOI: 10.1016/j.fct.2019.110575.

Seo, Kyung Won; Kim, Kyu Bong; Kim, Yun Jung; Choi, Ju Young; Lee, Kyung Tae; Choi, Kwang Sik (2004): Comparison of oxidative stress and changes of xenobiotic metabolizing enzymes induced by phthalates in rats. In *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 42 (1), pp. 107–114. DOI: 10.1016/j.fct.2003.08.010.

Serrano, Samantha E.; Braun, Joseph; Trasande, Leonardo; Dills, Russell; Sathyanarayana, Sheela (2014): Phthalates and diet: a review of the food monitoring and epidemiology data. In *Environmental health : a global access science source* (1), pp. 1–14. DOI: 10.1186/1476-069X-13-43.

Silano, Vittorio; Barat Baviera, José Manuel; Bolognesi, Claudia; Chesson, Andrew; Cocconcelli, Pier Sandro; Crebelli, Riccardo et al. (2019): Update of the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP) for use in food contact materials. In *EFSA journal. European Food Safety Authority* 17 (12), pp. 1-85. DOI: 10.2903/j.efsa.2019.5838.

Stöven, Kirsten; Jacobs, Frank; Schnug, Ewald (2015): Mikroplastik: Ein selbstverschuldetes Umweltproblem im Plastikzeitalter. Journal für Kulturpflanzen 67(7) 2015. DOI: 10.5073/JFK.2015.07.01.

Su, Ta-Chen; Hwang, Jing-Shiang; Torng, Pao-Ling; Wu, Charlene; Lin, Chien-Yu; Sung, Fung-Chang (2019): Phthalate exposure increases subclinical atherosclerosis in young population. In *Environmental pollution (Barking, Essex : 1987)* 250, pp. 586–593. DOI: 10.1016/j.envpol.2019.04.006.

Thent, Zar Chi; Froemming, Gabriele Ruth Anisah; Muid, Suhaila (2018): Bisphenol A exposure disturbs the bone metabolism: An evolving interest towards an old culprit. In *Life sciences* 198, pp. 1–7. DOI: 10.1016/j.lfs.2018.02.013.

Traistaru, Elena; Rivis, Adrian; Moldovan, Raul Ciprian; Menalou, Antigoni; Georgescu, Cecilia (2013): Modelling migration from plastic packaging materials used in food industry. In *Journal of Agroalimentary Processes and Technologies*, p. 5.

Vilarinho, F.; Sendón, R.; van der Kellen, A.; Vaz, M. F.; Silva, A. Sanches (2019): Bisphenol A in food as a result of its migration from food packaging. In *Trends in Food Science & Technology* 91, pp. 33–65. DOI: 10.1016/j.tifs.2019.06.012.

Wyżga, Beata; Połeć, Karolina; Olechowska, Karolina; Hąc-Wydro, Katarzyna (2020): The impact of toxic bisphenols on model human erythrocyte membranes. In *Colloids and surfaces. B, Biointerfaces* 186, pp. 1–8. DOI: 10.1016/j.colsurfb.2019.110670.

Xu, Qian; Yin, Xueyan; Wang, Min; Wang, Haifeng; Zhang, Niping; Shen, Yanyan et al. (2010): Analysis of phthalate migration from plastic containers to packaged cooking oil and mineral water. In *Journal of agricultural and food chemistry* 58 (21), pp. 11311–11317. DOI: 10.1021/jf102821h.

Yuan, Hui; Hao, Qian; Su, Rongxin; Qi, Wei; He, Zhimin (2020): Migration of phthalates from polyvinyl chloride film to fatty food simulants: experimental studies and model application. In *Journal of Consumer Protection and Food Safety (Journal of Consumer Protection and Food Safety)* 15 (2), pp. 135–143. DOI: 10.1007/s00003-019-01249-x.

Plastics Europe (n. y.): Plastics: A story of more than 100 years of innovation, available from: https://www.plasticseurope.org/en/about-plastics/what-are-plastics/history, last seen: 02.04.2021

Plastics Europe (n.y.): How plastics are made, available from: https://www.plasticseurope.org/en/about-plastics/what-are-plastics/how-plastics-are-made, last seen: 02.04. 2021