A review study of bisphenol A

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En översiktsstudie av Bisphenol A - som ett hormonstörande ämne i food contact materials tillverkat av polykarbonat och epoxyresin.

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Department of Molecular Sciences
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Abstract

Bisphenol A (BPA) is one of the worlds most produced chemicals. This compound is widely employed as an additive in polymers such as polycarbonates and epoxy resins in the manufacturing of plastics to provide transparency, rigidity and resistance to the resins. Because of the suitable properties of these polymers, they are commonly utilized in materials having contact with foods, so called Food Contact Materials (FCMs). Studies in which these materials have been exposed to different kinds of stress, such as heat and long time of exposure, reveal that plastic monomers and additives such as BPA, tend to migrate from the plastic package to the food. This theory, combined with the fact that BPA has been reported as an Endocrine Disrupting Chemical (EDC) with affinity for estrogen receptors (ER), has given rise to the debate regarding the potential adverse health effects of BPA exposure in humans.

The aim of this literature study was to examine the prevalence of BPA in FCMs manufactured from polycarbonates and epoxy resins and how this compound tends to migrate as a consequence of common use stress to these materials. Further, it also aimed to compile current research about the potential adverse health effects in humans as a result of exposure. Even though the researchers are divided, a lot of research suggests that high heat and long time of exposure have an impact on the migration of BPA from FCMs. Although, no measured concentrations have exceeded the tolerable daily intake (TDI) and the Specific Migration Limit (SML), which indicate that common use of plastic FCM not should constitute any health risks. Controversially, a lot of research has revealed adverse effects of BPA correlated to various important functions within the body, especially in pregnant women, fetal and young children. However, it should be considered that most documents that have been reviewed in this study are limited and that research on the long-term effects still is underinvestigated. Additionally, most studies have been performed on animals. To be able to draw any definitive conclusions regarding the possible detrimental effects of BPA in humans, more extensive research is needed.

Keywords: BADGE, Bisphenol A, Dietary Exposure, Endocrine Disrupting Chemicals, Epoxy Resins, Estrogenic Activity, Food Contact Material, Food Packaging, Migration, Plastic Food Containers, Polycarbonate.

Sammanfattning

Bisphenol A (BPA) är en av nutidens mest producerade kemikalier. Denna förening används i stor utsträckning som tillsats i polykarbonater och epoxyresiner vid tillverkning av plast för att tillföra transparens, spänst och styrka till resinerna. Till följd av dessa polymerers motståndskraftiga egenskaper återfinns de ofta i material som har kontakt med livsmedel, så kallade Food Contact Materials (FCMs). Studier där dessa material utsatts för olika typer av stress, så som värme och lång kontakttid, har visat att monomerer och tillsatser så som BPA, tenderar att migrera till maten de är i kontakt med. Detta faktum, i kombination med att BPA har visat sig vara ett hormonstörande ämne med affinitet för östrogenreceptorer, har väckt en debatt angående dess eventuella hälsorisker hos människan.

Syftet med denna litteraturstudie var att undersöka förekomsten av BPA i FCMs tillverkade av polykarbonater och epoxyresiner, samt hur denna förening tenderar att migrera vid vardagligt bruk av sådana material. Vidare syftade den även till att sammanfatta den forskning som finns gällande dess eventuella hälsorisker hos människan. Trots att forskarna är oeniga tyder mycket på att hög värme och lång kontakttid påverkar migrationen av BPA. Inga uppmätta koncentrationer av BPA i mat har däremot överskridit det tolerabla dagliga intaget (TDI) och den specifika migrationsgränsen (SML) vilket indikerar att ett vardagligt bruk av FCM inte bör utgöra några hälsorisker. Trots detta finns studier som pekar på negativa konsekvenser inom flera fysiologiska områden, framförallt i gravida, foster och små barn. I beaktande bör dock medtas att de flesta studier som granskats i denna rapport varit begränsade och därmed saknar belägg för effekterna som kan uppstå vid långvarig exponering. Majoriteten av studierna är dessutom utförda på djur. Av denna anledning krävs mer, extensiv forskning för att styrka påståendet om att BPA från FCMs utgör hälsofara för människan.

Nyckelord: BADGE, Bisphenol A, Dietary Exposure, Endocrine Disrupting Chemicals, Epoxy Resins, Estrogenic Activity, Food Contact Material, Food Packaging, Migration, Plastic Food Containers, Polycarbonate.

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Abbreviations

BPA	Bisphenol A
BPAP	Bisphenol AP
BPAF	Bisphenol AF
BPF	Bisphenol F
BPS	Bisphenol S
EA	Estrogenic Activity
EDC	Endocrine Disrupting Chemicals
EDI	Estimated Daily Intake
ER	Estrogen Receptor
FCM	Food Contact Material
OM	Overall Migration
PC	Polycarbonate
PE	Polyethylene
PET	Polyethylene terephtalate
PP	Polypropylene
PS	Polystyrene
SM	Specific Migration
SML	Specific Migration Limit
TDI	Tolerable Daily Intake

1. Introduction

Bisphenol A (BPA), also known as [2-2-bis(4hydroxyphenyl)propane], is regarded as a high production volume chemical (HPVC) and hence, one of the most produced synthetic compound in the world. In 1953 it was discovered that this substance could be crosslinked with phosgene or epichlorohydrin (ECH), giving rise to polymers known as polycarbonates (PC) and epoxy resins, respectively. The addition of BPA provided transparency, rigidity and resistance to the resins. Today, it is used as the most common additive in PCs and epoxy resins intended for production of various plastic products such as electronic equipment, thermal paper and toys as well as Food Contact Materials (FCMs) such as bottles, bowls and food containers.

The total worldwide production of BPA was in 2015 estimated at 7.7 million metric tons and expected to reach 10.6 million metric tons in 2022 (Industry Experts, 2016). As a consequence of the drastically increasing production and prevalence of BPA, the concern about its eventual health effects in humans has been raised (Bernardo *et al*, 2015). It has been reported that 90 % of the American population had measurable concentrations of BPA in their bodies (Calafat *et al*, 2008). A lot of investigating studies have been performed in this area; however, the results are shattered and vague regarding the migration and the eventual adverse effects of this compound.

1.1. Aim

The aim of this study was to examine the presence and migration of BPA in FCMs manufactured from polycarbonate and epoxy resins, respectively. Additionally, the potential adverse health effects of this molecule as an endocrine disrupting chemical (EDC) were investigated. Hence, following research questions were answered:

- What are EDCs and how is BPA linked to this concept?
- How is BPA transferred from plastic food packaging into the food and in what quantities?
- What are the potential health effects of BPA to humans?

1.2. Delimitations

There are many different kinds of EDCs present in FCMs, such as phtalates and styrene (Bhunia *et al*, 2013). However, to delimit the extent of this report, BPA was chosen to be the main focus. An important number of research publications about this synthetic compound have appeared over the years as it is one of the worlds most produced chemicals (Industry Experts. 2016).

For further delimitations, only FCMs manufactured from PC and epoxy resins have been considered in this study, since these are the most common polymers related to the addition of BPA in plastic products (Huang *et al.,* 2011).

1.3. Method

This literature study was conducted by searching for scientific articles and papers on web databases such as *Food Science and Technology Abstracts* (FSTA), *Aquatic Science and Fisheries Abstracts* (ASFA), *Web of Science* and *Google Scholar*.

Following keywords have been utilized in various combinations: “BADGE”, “Bisphenol A”, “Dietary Exposure”, “Endocrine Disrupting Chemicals”, “Epoxy Resins”, “Estrogenic Activity”, “Food Contact Material”, “Food Packaging”, “Migration”, “Plastic Food Containers”, “Polycarbonate”.

2. Background

To be able to answer the questions at issue, this chapter will present the results from the literature research. The first section is a review of plastic packaging in general; how it is produced and what kind of plastics that are most related to BPA. The following one presents information about the migration of monomers and additives from polymeric FCMs and how it can be affected by different factors. Section three introduce the concept EDC and describes how BPA is related to it, whereas section four provides information about the exposure of BPA and its regulations. Finally, information about the current research on potential adverse health effects of BPA in humans is presented. These five sections are followed by a discussion, analyzing the compiled information and concluded with a prediction about the prospects regarding this compound.

2.1. Plastic food packaging

Food packaging made of plastic exists in various forms such as trays, lids, bottles and pouches. Since the plastic material acts as a barrier against physical, chemical and microbiological deterioration, it serves a preservative function, both from quality and safety points of view (Bernardo *et al*, 2015). Plastics can be both utilized in pure plastic products or as additives in other FCMs to provide various enhancing properties such as reinforcing metals for lining closures and provide moisture resistance for paper products (Coles, McDowell & Kirwan*.,* 2003).

2.1.1. How is plastic packaging made?

The majority of today´s plastic packaging consists of multilayer polymerics that are based on two or more plastic films combined thorough co-extrusion, blending, lamination and coatings. These processes enable the achievement of desired qualifications of the food packaging such as ultraviolet- and visible light transmission, gas- and moisture permeability, flexibility, stretchability and other mechanical properties (Bhunia *et al*, 2013).

The macropolymers utilized in plastics can either be produced synthetically or synthesized from natural modified products, such as regenerated cellulose. The synthetically produced plastics are the most common ones utilized in FCMs and consist of a polymer incorporated with different kinds of additional chemicals to provide improvements such as flexibility, softness and color to the resin (Arvanitoyannis & Bosnea, 2004). The polymers which are utilized in plastic packaging are based on small hydrocarbon monomers that have been processed in different ways such as addition polymerization, condensation polymerization or copolymers synthesis. These plastic polymers can be divided into three major classes: thermoplastics, thermosets and elastomers (Bhunia *et al*, 2013). Thermoplastics and thermosets can be differentiated by their thermal behavior after being heated. Both of them become liquid at sufficiently high temperatures. However, thermoplastics can be melted and reshaped in repeated times whereas thermosets consist of strong cross-linking structures that prevent them from becoming liquid again. Elastomers, on the other hand, differ from the other two plastics since they consist of cross-linked structures that provide elastic properties (De Meulenaer & Huyghebaert, 2004).

Thermoplastics are the most utilized ones in the production of food packaging and food containers. To obtain desired properties such as flexibility, color and prevent oxidation, these polymers are mixed with small quantities of other chemicals known as additives. The mixture of thermoplastics and additives is then melted, mixed, extruded and pelletized resulting in a so called thermoplastic base resin. These base resins can be used for production of plastic devices either as they are or be mixed with other resins and additives (Begley, Dennison & Hollifield, 1990).

According to the Korea Food and Drug Administration (KFDA) the most common synthetic polymeric resins utilized in plastic food packaging are polyethylene (PE) (34.2%), polyethylene terephtalate (PET) (15.2%), polypropylene (PP) (11.5%), polycarbonate (PC) (7.1%) and polystyrene (PS) (3.5%) (KFDA, 2007). These statistics were confirmed by a similar study conducted in Japan; PE (26.8%), PET (13.8 %), PP (13.3 %) and PS (5.6%) (Bang *et al*, 2012). These two surveys indicate that PE is the most common synthetic resin used for plastic food containers over the world. However, the most common polymers related to addition of BPA as an additive are polycarbonates (PC) (64 %) and epoxy resins (34 %) (Huang *et al.,* 2011).

2.1.2. Polycarbonates

Polycarbonates (PC) are thermoplastic polymers consisting of linear polyesters. These can be synthesized through either (1) condensation or polymerization of BPA and carbonyl chloride molecules or (2) melt-transesterification between BPA and diphenyl carbonate (see figure 1) (Oliveira, 2015).

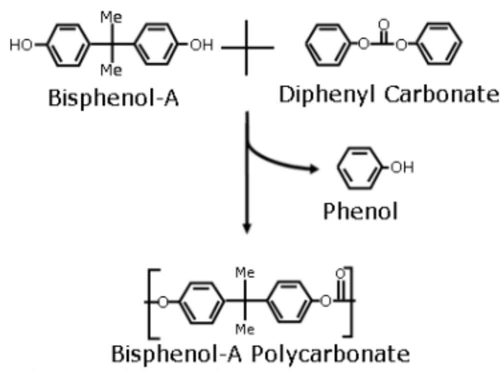

Figure 1. Reaction between BPA and diphenyl carbonate for production of polycarbonate (PC) (Yoganathan, Mammucari & Foster, 2010).

The addition of BPA to the polymer provide transparency, rigidity and resistance. Hence, these polymers are utilized in various products intended for technical and medical applications (Oliveira, 2015). As a result of its high glass transition temperature (Tg) of 150 °C and melt temperature (Tm) of 220-250 °C BPA is also commonly utilized in food containers exposed to high heat such as hot fillings or heat treatment. Such examples may be oven- and microwaveable products or boil-in bag packaging (Crompton, 2007).

2.1.3. Epoxy resins

Epoxy resins are thermosetting polymers produced by the condensation between epichlorohydrin (ECH) and liphatic amines or aromatic amines, thiols, polyamides, amidoamines, anhydrides or any kind of phenols such as BPA (Petrie, 2006). The use of BPA as starting material for epoxy resins results in polymers known as bisphenol A diglycidyl ether (BADGE), which are the most common kind of epoxy resins. However, there are also other bisphenol (BP) based epoxy resins such as BFDGE and NOGE (Berger & Oehme, 2000). Epoxy resins exhibit excellent mechanical and thermal stabilities and are hence utilized in nearly all drink and food cans on the market as a protecting inner layer against the metal (Lau and Wong, 2000). It is also widely utilized in other products such as adhesives, paints and in different engineering applications (Pulgar *et al.,* 2000).

2.1.4. Bisphenol A

BPA is a monomeric, organic compound which consist of two phenolic rings linked by a methyl bridge. This methyl bridge is in turn attached to two functional methyl groups (EURAR, 2003). In the presence of an acid catalyst, 1 mol of BPA is produced by the condensation of 2 mol of phenol with 1 mol of acetone,. The chemical formula of BPA is $C_{15}H_{16}O_2$ and its molecular weight 228.18 g/mol (Dodds & Lawson, 1996). The reactivity of BPA is determined by the presence of hydroxyl groups; hence it can easily be converted to ethers, esters and salts (Bernardo *et al*., 2015). Its melting- and boiling point are 156 ºC and 220 ºC, respectively (EURAR, 2003).

There are also other analogous compounds belonging to the BP family such as bisphenol B (BPB), bisphenol S (BPS), bisphenol F (BPF), bisphenol AP (BPAP) and bisphenol AF (BPAF) (EFSA, 2013). BPA belongs to the group of EDCs which have similar structures to natural occurring hormones and, if consumed, may have an impact on the homeostasis of animals and humans (Diamanti-Kandarakis *et al*., 2009). In 1938, different BPs, including BPA, were found to have an affinity for estrogen receptors and consequently to exhibit EA. This affinity was suggested to depend on the OH-groups in para position that are insufficiently hindered (Bernardo *et al*., 2015).

2.2. Migration of EDCs from FCM

It has been reported that not all monomers and additives utilized in plastic products are sufficiently polymerized and covalently bonded during the production. Some of these chemicals may leach and diffuse through the polymeric matrix of the product and into the foodstuff (Barnes, Sinclair & Watson 2007). In a study the leaching of chemical compounds with EA were observed from 455 commercial plastic items. The results revealed that almost all items that were tested tended to leach additives and monomers with EA, regardless of the lipophilic- or non-lipophilic property of the solvents that were used for the extraction (Yang *et al*, 2011).

A review article regarding the migration of chemical compounds from polymeric packaging the authors divided the migration process into four major steps:

> Diffusion of chemical compounds through the polymers, desorption of the diffused molecules from the polymer surface, sorption of the compounds at the plastic-food interface and desorption of the compounds in the food (Bhunia *et al*, 2013, p. 523).

The overall migration (OM) can be estimated by the performance of either monitoring of chemical compounds or by migration tests. Because of their simpler chemical structure, food simulants are commonly utilized in these tests. These food simulants usually occur in four different forms, representing properties of different foodstuff: water (aqueous food, PH > 4.5), 3 % aqueous acetic acid (acidic aqueous food, pH < 4.5), 10 % aqueous ethanol (alcoholic foods) and olive oil (fatty foods) (Barnes, Sinclair & Watson 2007).

A typical migration test can be split into two steps: Firstly, the polymer packaging and the food simulant are exposed to each other, letting the chemical compounds diffuse. Secondly, the OM of these chemical compounds is measured. In this context also the terms specific migration (SM) and specific migration limit

(SML) are commonly utilized. SM specifies the amount of a certain compound that has diffused from the plastic packaging into the food or food simulant, whereas the SML is a determined safety limit set for each migrating compound. This limit is based on the assumption that a person of 60 kg consumes 1 kg of food per day, with FCM as the only source of exposure. Another related concept is SML (T) which specifies the total migration limit, including the total moiety or substances related to SML. These values are specifically set for each potentially diffusing compound in all countries that have any kinds of regulatory guidelines for migration of chemical compounds in the production of FCMs. (Bradley *et al*., 2009).

2.2.1. Factors that affect the migration rate

The extent and rate of the SM are affected by several factors such as the food or food simulant itself (fatty, acidic or aqueous), contact time, surface contact area, contact temperature, chemical nature and concentration of the components in the packaging material (Barnes, Sinclair & Watson, 2007).

Polycarbonates

The migration of BPA from PC can occur in two possible ways: hydrolysis of the polymer or leaching of originally incomplete polymerized BPA molecules (Aschberger *et al*., 2010). It has been observed that temperature is the most critical factor when it comes to leaching of chemicals from plastic products made of PC (Kubwabo *et al*., 2009). At temperatures over 80 °C the carbonate linkages get hydrolyzed which increases the levels of migrating BPA (Maia *et al*., 2009). Another study showed that the migration of BPA was 55 times higher from plastic products exposed to boiling water (100 °C) than those exposed to water at 20 °C. Regarding microwave heating, some authors suggest that it seems to have very little impact on the migration level (Le, Besnard & Chagnon, 2015) and that it causes less migration than conventional heating (Bhunia *et al*, 2013).

However other authors reveal that the levels of migration increase by common use stresses such as microwave heating, boiling water and ultraviolet radiation (Yang *et al*, 2011). In a different study, the migration of BPA from PC containers into steamed hot rice and cooked hot pork respectively, was investigated. The experiment consisted of three different conditions: (A) hot steamed rice/cooked meat stored in a PC container at room temperature for 0, 10, 30 and 90 minutes, respectively, (B) hot steamed rice/cooked meat heated in a microwave for 3, 6 and 9 min, respectively, and (C) hot steamed rice/cooked meat stored in a 100 °C water bath for 10, 20 and 30 min, respectively. The results revealed that no concentrations of BPA could be detected for any of the samples exposed at room temperature and to boiling water. However, for the chicken and pork exposed to microwaving, BPA concentrations of 8-19 and 5-15 mg/L were obtained. It was also concluded that the migration increased with time (Lim *et al*, 2009).

Moreover, different studies suggest that solutions with acidic and alkali pH (such as dishwashing solutions and detergents) contribute to hydrolysis of polymers as well. This theory was reinforced by the observation of milk beverages with neutral pH where no increasement of BPA migration occurred (Onn,Woon & Leng 2005).

Epoxy resins

The effects of heat, storage and damage on the migration rate have also been observed in materials containing epoxy resins. However, the results are contradictory. In one survey the migration of free existing BPA molecules in can coatings were observed during sterilization. The authors found that about as much as 80-100 % of the BPA molecules diffused into the food in contact. The same authors also suggested that damages as well as prolonged storage time at different temperatures (5, 20 and 40°C) had no significant impact on the migration rate (Goodson *et al*., 2004). However, other researchers suggested that the storage time at different temperatures do affect the migration rate. According to a survey conducted by Munguia-López and Soto-Váldez in 2001, the highest level of migration occurred in acid and fatty food exposed at 121°C for 90 min. Additionally it was concluded that the migration also increased over time, in this case at least for the first 40 days (Munguia-Lópezand & Soto-Váldez, 2001). The impact of temperature during various times was also investigated in a different study in which it was concluded that the level of migrating BPA molecules from can coatings manufactured from epoxy resins into water was higher at 121 °C for 30 min (5 ng/mL) than at 105 °C for the same time (1 ng/mL). Additionally, it was also observed that the migration level was slightly higher from the cans exposed at 121°C for 60 min (see figure 2) (Almeida *et al*, 201).

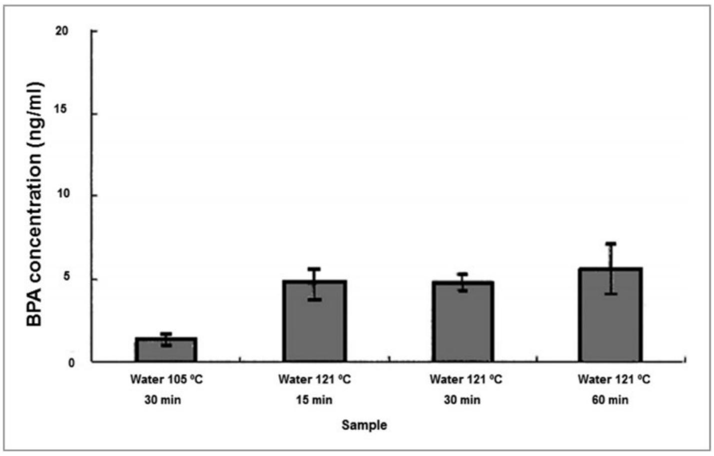

Figure 2. Migration of BPA molecules from can coatings into water during different temperatures and times (Kang et al, 2018).

2.3. Endocrine disrupting chemicals

EDCs are defined as exogenous compounds that are at first artificially produced for different purposes such as plasticizers, pesticides or solvents. However, studies from recent years showed that because of their similar structure to natural occurring hormones, these EDCs in very low concentrations are capable of mimicking or antagonizing the mode of action, transport or storage of these natural hormones in the body of animals and humans. Other surveys demonstrated that, due to the closely related properties of EDCs to natural hormones, there are no endocrine systems that these chemicals cannot interfere with. Hence, EDCs may be a problem for the interference of the homeostasis in all animals and humans (Diamanti-Kandarakis *et al*, 2009; Scholz & Klüver, 2009). In plastic food containers, phthalates, styrene and BPA have been suspected as major EDCs, exhibiting potential health risks to humans (Fisher *et al*., 2003).

2.3.1. Estrogen and estrogenic activity

The most studied EDCs are in particular estrogen, androgen and thyroid agonists and antagonists. Consequently, it has been suggested that compounds that mimic or antagonize the actions of estrogens are the most common kinds of EDCs (NRC, 1999). Estrogens are regarded as the primary sex hormones in females since they are responsible for the development and regulation of their sex characterizations and reproductive system. There are three types of naturally occurring estrogens in the female body: estrone (E1), estradiol (2) and estriol (E3). However, 17ßestradiol is considered as the most crucial one during the reproductive years. Further, estrogens belong to the group of steroids and are synthesized from cholesterol through enzymatic modification. They do exist in both natural and synthetic forms. The natural ones are synthesized within the body of all vertebrates and some insects as well as produced by plants (phytoestrogens) and fungi (mycoestrogen). However, synthetically produced estrogens with both intended as well as unintended use in the human body, are regarded as synthetic ones (Watson *et al*, 2007).

As previously described, the action of estrogens is facilitated by estrogen receptors (ER). These receptors can be divided into three different classes: nuclear estrogen receptors (ER), membrane bound estrogen receptors and estrogen G protein-coupled receptor (GPR30). The ERs work as transcription factors that control the gene expression and various downstream responses. Figure 3 illustrates the general pathway of a steroid hormone. This pathway is initiated with a hormone or hormone mimicking compound, that binds to either a membrane or cytosol receptor. The receptor migrates to the nucleus where it attaches to a response element (RE) which regulates the transcription and consequently the production of proteins. This pathway may be altered by EDCs through either the activation or inhibition of the transcriptional responses (Watson *et al*, 2007).

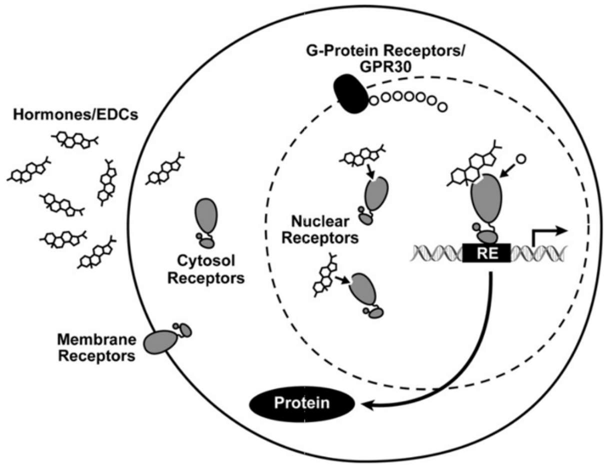

Figure 3. General signaling pathway of a steroid hormone (Schug et al, 2011).

2.3.2. Estrogenic activity of Bisphenol A

Studies suggest that BPA can be considered as a synthetic estrogen since it has affinity for estrogen receptors (ERα, ERß and membrane ER). Hence, it can interact with and alter the cellular pathways of true estrogens and is therefore defined as exhibiting EA. It has been demonstrated that this interaction can lead to various health problems in animals and humans (Watson *et al*, 2007), which will be described later in this thesis. However, the affinity of BPA to ERs is much lower than the affinity of estradiol (E2). Consequently, BPA is considered as a "weak estrogen" and it is suggested that there would be very small or even non effects in small doses (Wetherill *et al*., 2007). On the contrary, a different study reveals that these molecules may interact with membrane bound receptors and GPR30 as well, which induce cellular responses by lower doses such as picomolar to nanomolar concentrations (Watson *et al*., 2007).

2.4. BPA exposure in FCM

2.4.1. Food exposure

Detectable traces of BPA in the human body are widespread among the population. Studies suggest that measurable levels of BPA could be found in about 90 % of the American people (Calafat *et al*, 2008). However, the levels vary a lot between adults and children. If this variation depends on differences in metabolic activity or not is not known (Calafat *et al*, 2009). The exposure of BPA can take place in three different ways: the occupational pathway, through the environment or via food contact (Pielichowski & Michalowski, 2014). Additionally, it can be divided into two other different categories; dietary and non-dietary. The dietary source of exposure includes all food and drinks whereas the non-dietary includes air, dust, cosmetics, thermal paper, toys etc. However, researchers suggest that the dietary exposure is the most critical category since it affects most people (Cwiek-Ludwicka, 2015). Canned foods are regarded as the primary dietary source among adults and children, whereas breast milk and bottles made of PC are the two main sources among infants (von Goetz *et al*., 2010).

In an assessment of dietary exposure to BPA performed by EFSA, concentrations of BPA in plastic packed food and non-plastic packed food were compared. The food investigated in this study included cereals, meat, fish, spices, ready-to-eat food, ice cream and snacks. The results suggested that the plastic-packed food had on average significant higher concentrations (18.68 μg/kg) than the unpacked foods (1.5 μg/kg). As much as 30 μg/kg could be found in the plastic-packed foods while the highest concentrations among the unpacked ones were in meat and fish with 9.4 μg/kg and 7.4 μg/kg respectively (EFSA, 2015a). The relatively high concentrations of BPA in unpacked meat were suggested to depend on the contamination from plastic material used for post-mortem processing. The findings of BPA in fish were explained by the leaching of plastics in the oceans, particularly from plastic debris. Another explanation to the general discoveries of BPA in the unpacked food was contamination by the material used in the lab. This type of contamination is very difficult to handle when it comes to studies that include very low concentrations of chemicals (Deceuninck *et al*., 2019).

In 2011, a survey on the presence of BPA and BPB in canned beverages and powdered infant formulas available in the Portuguese market was performed. Thirty canned beverages and seven powdered infant formula samples were analyzed. Of these, 0.03 up to 4.70 μg BPA/L was found in twenty-one of the canned beverages and 0.23 and 0.40 μg BPA/L in two of the infant formula samples (Cunha *et al*., 2011). According to another study conducted in 2008 by the Canadian Total Diet Study, 154 samples of food composite samples were analyzed and 55 of these contained traces of BPA. The concentrations ranged from 0.20 to 106.00 ng/g and a recurring pattern was observed for canned foods which tended to have higher values (Cao *et al*., 2011).

The estimated level of BPA exposure from water was examined in a study in which volunteers drank water from PC bottles for one week. The results showed an increase of 69 % of BPA levels in their urine, however this exposure was suggested to depend on accidental or careless exposure of heat during transport and storage of the bottles, leading to the increased migration of BPA molecules. In addition, the study showed that the consumption of 2 L water from PC bottles only resulted in the ingestion of 6 ng/kg bw/day which is far below the TDI (Cao & Corrivau, 2008a, 2008b).

2.4.2. Regulations of BPA in FCM

When the concentration of a specific migrating chemical within a foodstuff is known, this data can be combined with statistics of how often and in what quantities that foodstuff is consumed (EDI), resulting in an exposure assessment (Cwiek-Ludwicka & Ludwicki, 2014). Another essential part of examining the potential health risks of EDCs is the performance of a risk assessment. The general procedure for conducting a risk assessment can be seen in figure 4. In the conduction of risk assessments of EDCs, the tolerable daily intake (TDI) is also included. This concept defines the maximum daily amount of exposure without receiving any adverse effects and is established by EFSA. However, its American equivalent is known as reference dose (RfD) and determined by U.S. EPA (EFSA, 2008).

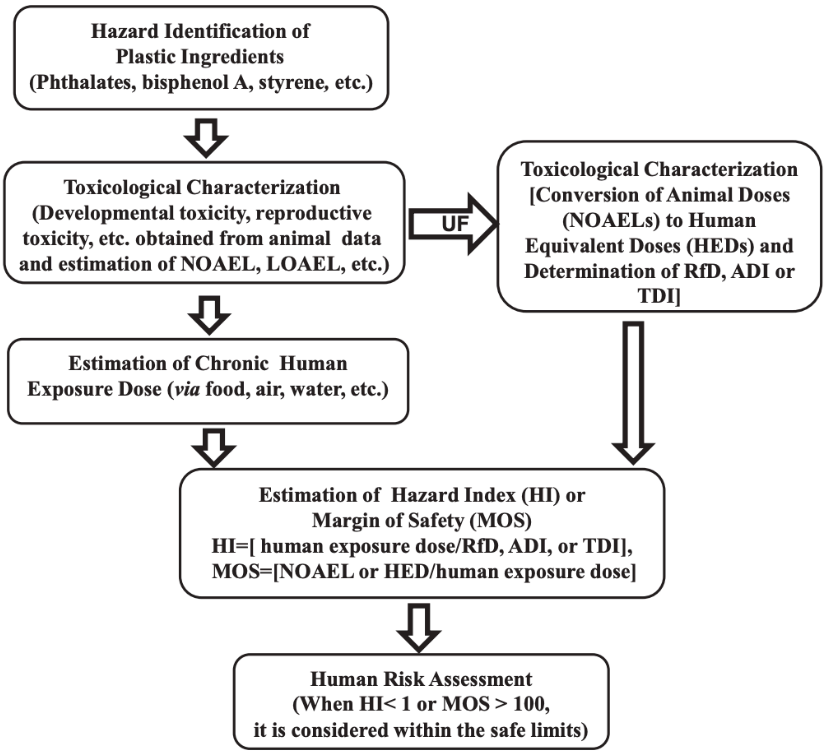

Figure 4. General scheme for performance of a human risk assessment in plastic products (Bang et al, 2012).

The very first BPA assessment was conducted in 1986 by the Scientific Commité on Food (SCF, 1986). The tolerable daily intake (TDI) was then estimated to be approximately 0.05 mg/kg body weight /day. It was also stated in the EC Directive No. 90/128 that the SML was 3 mg/kg of foodstuff (EC, 1990). However, since the middle of the twentieth century BPA has been more intensively discussed and considered as a more critical health risk to humans and animals. Several studies in 2006, 2008, 2010 and 2015 have been performed by EFSA to investigate this further. Today, the TDI is estimated at 4 µg/kg bw/day and the SML at 0.05 mg/kg food (Vilarinho *et al*, 2019). The history of the recommended TDI and SML can be seen in table 1.

Because of the endocrine disrupting properties of BPA, the European Chemicals Agency (ECHA) decided in January 2018 to add BPA to their candidate list over substances of very high concern (SVHC) (ECHA & ECA, 2018). In Europe, the addition of BPA is currently allowed in food packaging materials (Regulation [EU] No. 10/2011) but banned in feeding bottles for infants (EU Regulation No. 321/2011).

Table 1. Historical development of reference values of TDI and SML. Table compiled from Vilarinho et al, 2019.

Year	TDI (mg/kg bw/day)	SML (mg/kg food or food simulant)
1990	0.05	3.0
2004	0.01 (t-TDI)	0.6
2006	0.05	0.6 SML (T)
2011	0.05	0.6
2011	0.05	0.6 SML (T)
2015	4 µg/kg bw/day	0.6
2018		0.05 SML

2.5. Impacts of BPA on human health

Since it has been suggested that BPA exhibits endocrine disrupting properties, or more specifically EA, the concerns about how it could affect cellular pathways leading to disruption in growth and development have been raised. Consequently, the biological response and the toxicological effects of BPA exposure have been well documented in animals. However, the number of human studies is very limited and inconclusive (Chapin *et al*., 2008).

After ingestion, BPA molecules are quickly glucuronidated by the Phase II metabolism and secreted in the bile and the urine. The half-life of BPA in the human body is very short (about 5-6 hours) which makes the correlation between exposure and long-term effects complicated to examine (Volkel *et al*, 2002). The BPA metabolism is also affected by age, gender, physiological status and liver function (Bertoli, Leone & Battezzati, 2015). Following sections compile current research regarding several physiological functions in humans that may be disrupted by the exposure of BPA.

2.5.1. Breast cancer

In today´s society, breast cancer is regarded as the most common type of cancer among women. However, the incidence varies between different parts over the world, indicating that ethnicity and environment may have impact on the occurrence. In Korea the numbers of incidents have been only about 25 % of the reported numbers in the United States. However, between 1983 and 2005 the number of incidents increased sharply which gave rise to an investigation regarding risk factors. Consequently, a study of the association between BPA and breast cancer was performed (Yang *et al*, 2009). The results from the study showed no significant difference in mean serum BPA concentration between the controls and the cases. However, the median of the BPA serum concentration was higher for the women with breast cancer than for the healthy ones. Although, since the half time of BPA is very short (5-6 hours) no conclusion regarding the long-term toxicological effects could be drawn (Yang *et al*, 2009).

2.5.2. Reproductive system

Since BPA molecules have affinity for ERs it has been concluded that this molecule may have an impact on the reproductive system, particularly in pregnant and breast-feeding women (Caporossi & Papaleo, 2015). Its effects in the pediatric population are still very uncertain (Brown & Hauser, 2018). However, the most common reported targets for BPA molecules in adults are sex steroids, ovarian response and sex functions (Galloway *et al*, 2010). For instance, the onset of meiosis in the ovaries, interference with the germ cell nest disintegrations and accelerated development of follicles are revealed as possible targets of BPA exposure (Machtinger *et al*., 2013). However, other authors also observe more adverse effects such as reduced quality of oocytes for women undergoing IVF (Mok-Lin *et al*, 2009), altered serum reproductive hormones (Galloway *et al*, 2010), testicular dysgenic and premature breast development (Lang *et al*., 2008). Additionally, the case of recurrent miscarriage has also been examined. In a study in 2005, the BPA concentrations of 45 women with history of miscarriage in the first trimester were measured and compared to the concentrations of 32 healthy women. Interestingly, it was found that there was a relationship between high levels of serum BPA concentrations and antinuclear antibodies, which are related to miscarriages. However, the conclusion regarding this relationship was uncertain since other risk factors were not included (Sugiura-Ogasawara *et al*, 2005). Other authors suggest that there is a potential correlation between BPA and infertility. According to a study performed by the Danish Occupational Hospitalization Register an association between female plastic industry workers and increased infertility was reported. One hundred seven cases of treatment for infertility were obtained, whereas the expected number was 87.15 cases. However, this correlation was considered as very weak (Hougaard *et al*., 2009).

2.5.3. Metabolism

In 2003-2004 and 2005-2006 two studies were performed, in which the correlation between the presence of BPA concentration in the urine and metabolic disorders was examined respectively (Melzer *et al.*, 2010; Lang *et al*., 2008). The results claimed a relationship between high levels of BPA and cardiovascular disease (CVD) and diabetes. However, these studies were limited in their design (Melzer *et al.*, 2010; Lang *et al*., 2008). Additionally, since BPA has a short half time and CVD and diabetes are known to require decades to develop, it could not be concluded whether the etiologic window was relevant or not. However, the same authors revealed that the exposure of BPA to the prenatal phase of life is the most critical one when it comes to the development of metabolic diseases.

Since the number of obese people have increased remarkably over the past 30-40 years (Flegal *et al*, 2010), the relationship between environmental factors such as endocrine chemicals and overweight has been a subject of interest to the researchers (Grun & Blumberg, 2009). Consequently, BPA has been suggested as an obesogen. Even though the results have been contradictory most surveys indicate that there is a positive correlation between BPA exposure and overweight, especially when exposed to fetal. However, more research is required (Rubin, Schaeberle & Soto, 2019).

2.5.4. Puberty

Because of the EA of BPA, the pubertal development of young people may be affected. Some authors suggest that puberty could be accelerated by BPA, which in turn has been correlated to increased risk of breast cancer in rodents (Apter, 1996). However, this concern has not been confirmed by the National Toxicology Program Center for the Evolution of Risks to Human Reproduction (NTP-CERHR) which suggests that this correlation is minimal (Chapin *et al*, 2008). Other authors also suggest additional effects such as delayed breast development and accelerated pubic hair growth (Braun *et al*, 2018). However, most research in this area has limitations regarding the modelling of the studies. Additionally, the short half-life of BPA makes the correlation between childhood exposure and adverse effects difficult to determine. Hence, further research is required in this field (Braun *et al*, 2018).

2.5.5. Fetal and childhood development

Since fetuses and newborn children belong to two very critical and developing phases of life, they are especially sensitive to the exposure of EDCs. For this reason, these life stages have been in focus when it comes to the research of potential adverse effects as a consequence of BPA exposure. Additionally, children also tend to have higher concentrations of BPA in their urine. However, this is explained by their food proportions relative to their body weight is higher (Calafat *et al*, 2008). Hence, it has been reported that smaller doses are required to receive harmful effects in children than in adults (Newbold, Padilla-Banks & Jefferson, 2006). Some suggested explanations to the increased risks in these groups are that they have undeveloped and insufficient DNA-repair mechanisms, immune systems, detoxifying enzymes, liver metabolism and blood/brain barrier (Newbold *et al*., 2007).

2.5.6. Nervous system

It has been reported that the exposure of BPA may increase the risk of neurological disorders such as anxiety, autistics behavior, altered social behavior and impaired memory and ability to learn. However, these observations are very inconclusive and more extensive research is needed (EFSA CEF Panel, 2015). Although, most researchers are consent that prenatal and young childhood exposure are the most critical stages of life (Almeida *et al*., 2018). Some proposed theories about the effects of BPA on the nervous system are decreased levels of thyroxin (T4) in pregnant women and thyroid stimulating hormone (TSH) in newborn males, less prevalence of thyroid receptors in fetal and altered levels of dopamine (Elsworth *et al*., 2013).

3. Discussion

3.1. Migration of BPA from FCM

The migration of BPA from plastic items and its correlated health effects in humans are still broadly unexplored areas of research. The researchers are divided in many aspects and hence, more extensive research is still needed. Although, the studies that have been reviewed in this report are in agreement regarding the fact that food packed in plastic exhibits higher levels of BPA concentration than unpacked foodstuffs (EFSA, 2015a). Additionally, it has been concluded that most plastic products on the market also release chemical compounds that exhibit EA. Given that plastic FCMs are used by most people on a daily basis, this great extent of migration indicates that the exposure of EDCs to humans should be of concern. Further, the fact that 90 % of the American people showed measurable levels of BPA in their bodies indicates that FCMs may be an important contributor to these statistics (Calafat *et al*, 2008). This is reinforced by the research which suggests that dietary sources (especially canned foods, breast milk and bottles made of PC) are the most critical sources of exposure to humans (Cwiek-Ludwicka, 2015). However, to estimate the definitive migration and exposure of BPA are extremely complex questions since many factors can have an impact such as migration due to different kinds of stress, the composition of the foodstuff, the type of plastic material and the metabolic breakdown of the compound. Additionally, the non-dietary sources of exposure should be taken into account. Consequently, people working in extra exposed branches such as industry workers or cashiers exhibit greater risks when it comes to the accumulation of higher concentrations in their bodies (Cwiek-Ludwicka, 2015).

The factors and environmental circumstances that affect the SM of BPA is also an area that divide the researchers. Most studies indicate that conventional food processing (heating over 80 °C) increases the hydrolyzation of the polymers and thereby the migration of additives and monomers into the food. However, whether conventional heat treatment affects the migration or not is controversial. In the study where the migration of BPA from PC containers with steamed rice and cooked meat were investigated (Lim *et al*, 2009), only detectable levels of BPA could be found when the food was microwaved for 3, 6 and 9 min, respectively.

However, the traced levels (6-19 mg/L for steamed rice and 5-15 mg/L for cooked meat) from the microwaved food were far below the SML of 0.05 mg/kg and considered as safe. No traces of leaching BPA molecules could be detected from the food in boiling water bath and from storage in room temperature. However, the opinions regarding microwaving are controversial. Some authors suggest that it does affect the leaching of unbounded compounds (Yang *et al*, 2011), whereas others indicate that it is the safest technique in food processing and causes less migration than conventional heating (Le, Besnard & Chagnon, 2015; Bhunia *et al*, 2013). However, the researchers seem to be consent about that heat, and eventually extended time of contact, are the most critical factors when it comes to the impact on the migration of chemical compounds from FCMs. Further, according to the reviewed studies in this report no SM exceeded the legislated SML of 0. 0.05 mg/kg of food.

This report has been focusing most on FCMs prone to stress. However, there is evidence that even unstressed FCMs could release BPA. In the study in which plastic packed and unpacked foods were compared, measurable values of BPA could be obtained in both kinds (EFSA, 2015a). This also indicates that plastic FCM is not the only source of BPA contamination. To further investigate the prevalence of BPA in food, both unstressed FCMs as well as processing contamination should be taken into account.

Even though the process of producing plastic polymers has been described in detail in this report, the exact composition of most commercially plastic products are not known. A piece of plastic contains approximately 5-30 different chemicals, such as monomers and additives, whereas a whole item consequently consists of ≥ 100 chemicals. The probability that some of these are insufficiently polymerized or get hydrolyzed when exposed to stress, such as heat, is high. Hence, there is also an extensive risk that some of these chemicals, other than BPA, exhibit EA. This has been reinforced by a study in which polymers without any added additives were subjected to stress and no migration of chemicals with EA was obtained (Yang *et al*., 2011). As publications of the effects of BPA on health accumulate, legislation and demand of BPA-free PC products such as bottles manufactured by PET or PETG have been intensively promoted the last couple of years. However, it has been questioned whether these substitutes actually can be regarded as EA-free since the chemical structure of these compounds can be changed and consequently gives rise to EA. Sometimes these replacement resins are reported as releasing even more chemicals exhibiting EA than BPA containing PC products (Yang *et al*., 2011). The use of analogs to BPA such as BPS, BPF, BPAP and BPAF have also been utilized in many plastic products as substituents to BPA. Unfortunately, it has been proven that they exhibit EA as well, since they have similar chemical structures. Additionally, it has been reported that some of them also are more difficult for the body to biodegrade (EFSA, 2013).

3.2. Health effects from BPA exposure

The adverse effects correlated to BPA exposure are also an area of research that is controversial. Results from migration tests reveal concentrations as high as 1.5-30 µg BPA/kg in foodstuffs packed in plastic (EFSA, 2015a). Although, all reported levels are below the estimated TDI of 4 µg/kg bw/day which according to the latest report of EFSA (EFSA, 2015) will not contribute to any adverse effects in humans. Additionally, it is important to consider that the half-life of BPA is short, thus, it is quickly metabolized and excreted from the body. Hence, the bioaccumulation of the compound within tissues decreases (Yang, 2009). Although, there is evidence that membrane bound receptors and GPR30 may be stimulated by BPA in concentrations low as nano- to picomolar. Consequently, the cellular pathways of these may be altered (Watson *et al*., 2007). However, the short half-life of BPA also makes the long-term effects difficult to estimate, since the measured concentrations within the bodies of the tested people only display a temporary depiction. Additionally, the everyday life exposure of other EDCs also may have impact on the health. This report has been focusing on FCMs manufactured from PC and epoxy resins since BPA is most likely to occur as an additive in these. However, PE, PET, and PP are even more commonly utilized in FCMs (KFDA, 2007) and the probability that these release EDCs as well is very high. Consequently, the potential adverse health effects, or eventual cocktail effects, of these should not be dismissed in the debate regarding FCMs that release EDCs. Another problematic aspect to take into account is that hundreds of these studies have been performed on animals whereas only a few have been examining the outcomes in humans.

Despite all these limitations, various adverse effects from BPA exposure have been reported. The majority of these are correlated to the development of puberty, nervous system, metabolism and reproductive system. Additionally, it has been revealed that the risk of developing cancer is increasing as well. However, the results are divided in many aspects and consequently, more research is needed to be able to draw any definitive conclusions. In general, the researchers seem to be consent about considering pregnant women, fetal and children as the most vulnerable ones (Braun *et al*., 2018).

3.3. Conclusion

Even though the results from the studies performed on the correlation between BPA exposure and health are limited, the results should not be dismissed since they are of importance for further investigations in this area. The fact that 90 % of the American people have measurable levels of BPA in their bodies should be taken as a serious concern (Calafat *et al*, 2008). It has been determined that BPA is an EDC with EA that may alter the cellular pathway of many important functions within the human body, especially in pregnant women, fetal and young children. Even though the researchers are divided, there is evidence that common use stress could increase the migration of BPA from FCMs manufactured from PC and epoxy resins into the food. Additionally, dietary sources are considered as the most critical kind of BPA exposure. Even though the EDI not has been reported to exceed the TDI, the long-term effects are still uncertain. Hence, precautions, such as avoiding plastic FCMs, limiting the time of contact between the food and plastic packaging and proper storage of the FCM should be taken.

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