JAP&T TPA-Timişoara

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Journal of Agroalimentary Processes and Technologies 2012, *18*(4), 318-323

*Journal of Agroalimentary Processes and Technologies*

# Xenobiochemistry at the interface of packaging materials-food. Note II. Interactions and effects of bisphenol A from food packaging materials

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**Received: 07 November 2012; Accepted: 16 November 2012**

***Abstract***

Interactions between food packaging materials and chemical compounds of food are of interest for human nutrition, physiology, biochemistry and xenobiochemistry. In certain situations the chemical constituents of the packaging materials may interact with food nutrients and/or non-nutritive ingredients of food. Such situations are dependent on storage conditions, storage duration, processing technologies etc. The chemical constituents of packaging materials which migrate in food may cause after the consumption pathophysiological and pathobiochemical problems. From this point of view is important to know their interaction mechanisms with nutrients are more specifically with tissular bioconstituents.

Biotransformation aspects, specific for xenobiochemistry, of bisphenol A used to manufacture "polycarbonate" plastic and epoxy resin lignins of food and beverage cans (packaging materials) are evidenced in this paper. In this context details on the biotransformation, i.e. xenobiosynthesis of bisphenol A in the organism are given.

Bisphenol A released from polycarbonates of packaging materials and introduced mainly by food intake in the human organism can interact with various substances. Thus, bisphenol A first is glucuronidated (i.e. conjugated with glucuronic acid and/or sulphonic derivatives) and then after may be adducted (DNA is implied by the guanine component). Knowledge of these specific interactions and the consecutive harmful effects and allow to understand the pathobiochemical mechanisms.

***Keywords***: xenobiochemistry-bisphenol A; interactions and biological effects of bisphenol A

## 1. Introduction

Issues related to chemical xenobiotics of food interest are of importance not only for the food composition but also for the materials used in food packaging [7,9,11]. In the case of food it is known that nutrients are sometimes accompanied by xenobiotics. In the case of food packaging, the action of external agents (temperature, humidity etc) and sometimes even the action of food itself (due to long preservation periods) can alter the structure of the packaging material which can release xenobiotic compounds into the food [6,8,12].

The xenobiotics resulted from food packaging materials can be represented by various metals or metallic compounds and/or by organic substances having various composition [4,10]. One of those organic substances is bisphenol A (BPA). Data regarding that substance were reported first by A.P. Dianin in 189 [28]. It is obtained by the condensation of acetone (hence the suffix A in the name) with two equivalents of phenol.

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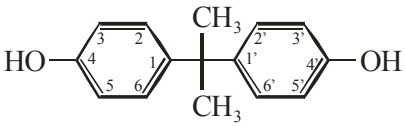
Bisphenol A is one of the highly produced chemicals worldwide, used in various plastic materials. And such plastics, made from bisphenol, are used in the manufacturing of food packaging materials from which, in certain conditions, can enter into foods or beverages exerting biological effects. Bisphenol A is known as an estrogen-mimicking compound or a xenoestrogen. Another issue regarding BPA is its genotoxic and carcinogenic activities. Bisphenol A was first discussed as a possible genotoxic due to its chemical structure which resembles that of diethylstilbestrol, a well-known carcinogen in humans.

## 1. Structural characteristics of bisphenol A from food packaging materials

Bisphenol A (BPA) is a diphenyl compound, important in food xenobiochemistry, which has the following chemical denomination: 4,4'-isopropylidendidiphenol, CAS No. 80-05-7 [5].




Bisphenol A (BPA)

Bisphenol A used in the manufacturing of epoxy, polycarbonate, and polyester-styrene resins which are the raw materials for many products, such as baby feeding bottles, plastic food containers and tableware, recycled cardboard and paper used for food packaging, and also to line food and beverage cans. The plastic material which contains bisphenol A and mostly used in food packaging is polycarbonate.

Polycarbonates are, from the technologic point of view, a special category of thermoplastic polymers. These polymers can be processed in various geometric forms and used as food packages.

The chemical denomination of "polycarbonates" derives from the fact that these polymers contains functional groups (monomers) linked together by carbonate groups –O–(C=O)–O– which are found in the macromolecular chain (fig. 1.).

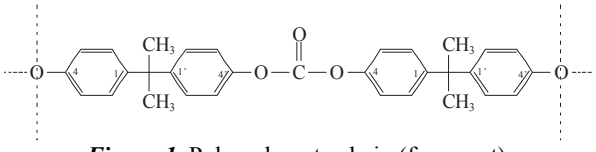



***Figure 1***. Polycarbonate chain (fragment)

In the structure of the polycarbonate chain can be found bisphenol A which is a monomer (a constitutive repetitive fragment).

Polycarbonates are synthesized starting from bisphenol A and NaOH which leads to a deprotonation of hydroxyl groups. Further on, through a reaction with phosgene, a chlorinated intermediary compound is formed from which the polycarbonate synthesis starts.

## 2. Specific interactions in the biotransformation of bisphenol A

Problems regarding the nutrients metabolism are of interest for biochemistry, while problems regarding the chemical xenobiotics biotransformation are of interest for xenobiochemistry [2,9].

Having in view the concepts of xenobiochemistry the biotransformation of bisphenol A arouses a special importance. From food packages, in certain conditions, polycarbonates release into the food bisphenol A and its derivatives. The quantity released directly depends on the temperature, the package integrity, the nature of food (solid or liquid), food pH, hardness of the water etc [3]. However bisphenol A may be released into water and foods even at room temperature.

An animal study showed that bisphenol A is released from polycarbonate animal cages into water at room temperature and it may be responsible for enlargement of the reproductive organs of female mice [14].

Once entered into various tissues of the organism, BPA undergoes different biotransformation processes. It may be noted the fact that in xenobiochemistry, the xenobiotransformation reactions can take place in the form of conjugation reactions and/or adduction reactions. Adduction are realised with DNA from nucleoproteins [22, 18]. These reactions are part of the xenobiosynthesis process. In the case of BPA, unlike other xenobiotics, both types of reactions are found. The conjugation reactions, regarding the interaction with glucuronic acid (GlcA) and with sulfonic derivatives affects directly BPA and/or the hydroxylated derivative of BPA in the position $C_3$ of the phenolic [30].

The adduction reaction concerns the 3,4-quinonic derivative of BPA. In this case and deoxyribonucleic acid adduct is formed (a DNA-BPA type of adduct). The binding of BPA

derivative is made between the $C_6$ of BPA 3,4-quinone and the $N_7$ of guanine from DNA macromolecule [5].

### 2.1. Conjugation reactions of bisphenol A

Studies on BPA biotransformation in mice have identified up to ten metabolites including the glucuronic acid conjugates of BPA, several double conjugates and conjugated methoxylated compounds, demonstrating the formation of potential reactive intermediates [30,17]. There are biotransformation reactions (more exactly xenobiosynthesis reactions) through conjugation/adduction which yield xenobioderivatives of bisphenol A. The structures of the main xenobioderivatives resulted in the biotransformation process are given in figure 2.

As it can be seen in the figure 2, the main routes of biotransformation in the case of BPA are sulfonation and glucuronidation which exerts the sulfonated and glucuronated metabolites of BPA. These are considered to be detoxification processes. Another pathway is the bisphenol bioactivation which leads to the formation of 3-hidroxy-bisphenol (3-OH BPA) which can be detoxified through a mixed process of sulfonation and glucuronidation.

### 2.2. Reactions with adducts formation of bisphenol A

One of the most controversial issues regarding BPA is the presence of genotoxic and carcinogenic effects in animals and humans.

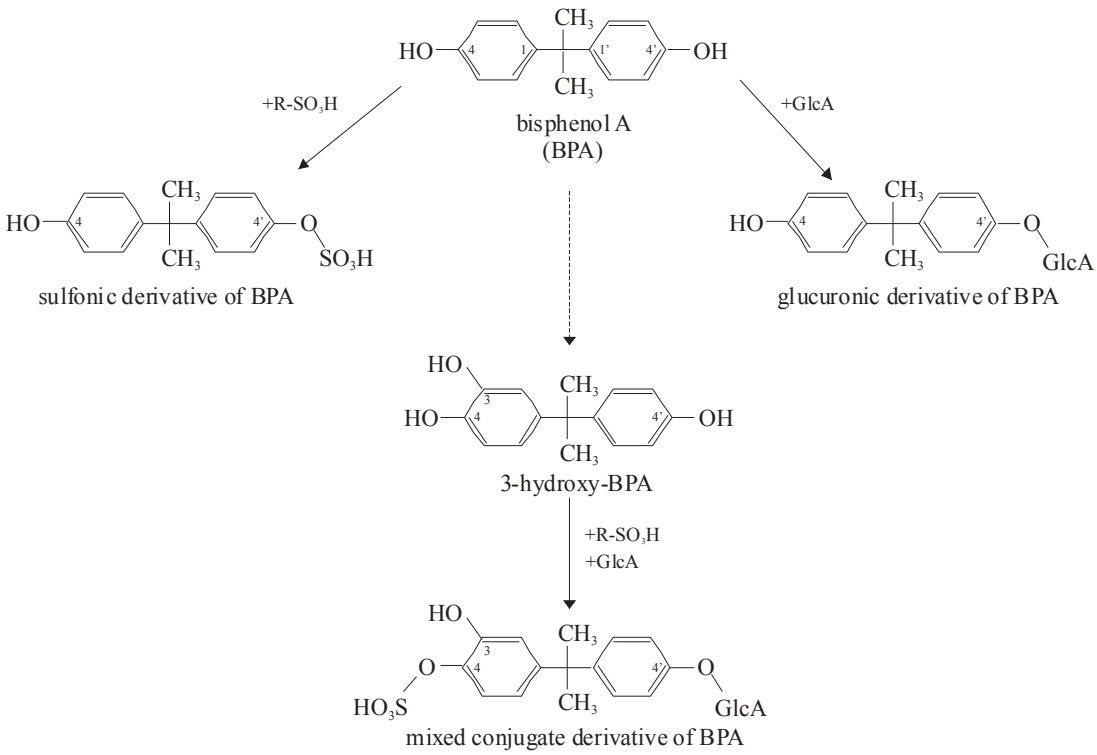



***Figure 2.*** Biotransformation of BPA by conjugation reactions

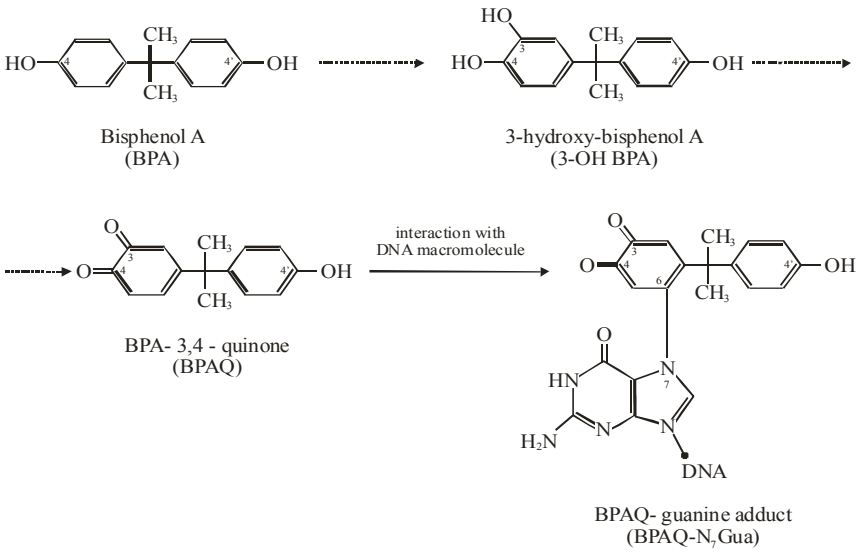



***Figure 3.*** Formation of DNA-BPA adduct from interaction of guanine from DNA and BPA

Studies on BPA carcinogenicity made on rodents led to the conclusions that this compound can induce carcinomas in prenatally exposed rats and also, in the case of an early exposure, BPA can sensitize the mammary gland and lead to development of carcinomas later in life [28]. The carcinogenic effects of BPA are the result of the interaction between BPA metabolites and the DNA macromolecule, interaction which leads to DNA adducts.

The ability of BPA to bind DNA was demonstrated in a cell system, in the presence of a metabolic activation system [5], in cultured Syrian hamster embryo cells [27] and in vivo in the liver of CD-1 rats [1]. In addition, recent studies provided evidence that the oral administration of BPA to mice causes the formation of DNA adducts also in mammary epithelial cells, which represent a major target of BPA [16].

Bisphenol A undergoes a process of biotransformation, both in humans and in experimental animals, which lead either to detoxification by glucuronidation or sulfonation or to bioactivation through hydroxylation. The hydroxylated derivatives, and mainly to 3-hydroxy-BPA (3-OH-BPA or BPA catechol) can be further detoxified through trough glucuronidation and sulfonation or it can be then oxidized to its ortho-quinone, i.e., BPA-3,4-quinone (BPAQ) which react with DNA or deoxyguanosine (dG) to form a guanine-$N_7$ adduct (BPAQ-$N_7$-Gua) - Edmonds et al, 2004 [5]. In figure 3 are shown the reactions leading to the DNA adduct formation.

## 3. Biological effects of bisphenol A

The most documented biological effect exerted by BPA is the disruption of endocrine function. Bisphenol A is mainly considered to be a xenoestrogen, however other hormone receptors might also be targets for BPA. Studies have shown that BPA induces estrogen and thyroid hormone mimicking effects, estrogen and thyroid hormone independent effects, as well as altered expression of the receptors themselves [31,21,20]. Recent studies have shown that BPA can disrupt the endocrine function of pancreas, thus interfering with blood glucose homeostasis. Bisphenol A exerts rapid non-genomic effects on insulin releasing β-cells and glucagon releasing α-cells within freshly isolated islets of Langerhans [25]

Bisphenol A has been shown to affect chromosome segregation and induce nondisjunction in cultured cells and in vivo in mammalian oocytes [15,26]. Other animal studies have reported that BPA exposure affects brain morphology, neuroanatomy and behavior in rodents [24]. Also BPA has shown the capacity to modulate the metabolic pathways stimulating 3T3-L1 cells to differentiate into adipocytes [23]. The 3T3-L1 are cells with a fibroblast-like morphology which, under appropriate conditions, can differentiate into adipocyte-like phenotype.

Sensitivity to endocrine disruptors, like BPA, varies extensively with the organism life stage. The effects are more severe if the exposure occurs in the first stages of life. Bisphenol A alters the so called "epigenetic programming" of genes which results in persistent effects that are expressed later in life [13]. Prenatal and/or neonatal exposure to low doses of BPA results in organizational changes in the prostate, breast, testis, mammary glands, body size, brain structure and chemistry, and behavior of laboratory animals [29].

Another concern related to BPA is the carcinogenic potential of this compound. Studies have shown that BPA is associated with cancers of the hematopoietic system and with a increased incidence of interstitial-cell tumors of the testes. Also, an early life exposure to BPA may predispose to pre-neoplastic lesions of the mammary gland and prostate gland in adult life [19].

Nowadays the use of plastic materials and articles in contact with foods are established by the Commission Regulation (EU) No. 11/2011. Also, by the Commission Directive (EU) 2011/8 the use of Bisphenol A in plastic infant feeding bottles is restricted [32,33].

## 4. Conclusions

1. Food packaging containing «polycarbonates» obtained by the polycondensation of bisphenol A derivatives, by degradation may release into the environment bisphenol A which may enter into the organism together with food.

2. Once entered into the organism bisphenol A can interact with tissular bioconstituents during the phase of xenobiosynthesis by:

a. conjugation interactions in vivo with glucuronic acid (GlcA) and/or with sulphonic derivatives (R-$SO_3H$)

b. adduction interactions in vivo with nucleic acid macromolecules - predilectly with DNA (and targeted to guanine residue from DNA)

3. Knowledge of mechanisms of interactions of residual products resulted from packaging with bisphenol A content may bring information related to pathobiochemical aspects and useful for preventive medicine.

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