JAP&T
TPA-Timişoara

Available online at http://journal-of-agroalimentary.ro

Journal of Agroalimentary Processes and Technologies 2010, *16* (2), 265-275

Journal of Agroalimentary Processes and Technologies

In memoriam
Professor IOAN SILAGHI-DUMITRESCU, PhD
corresponding member of Romanian Academy
(June 1, 1950 – December 25, 2009)

Xenobiochemistry at the interface of packaging materials-food. Note I. Packaging materials and specific interactions in vivo

Z. Garban[1*] , Gabriela Garban[2], G.-D. Ghibu[3], C. Baltă[4], Adina-Elena Avacovici[1], Elisabeta-Mihaela Mitroi[5] , L. Miclău[1]

[1]Department of Biochemistry and Molecular Biology, Faculty of Food Products Technology, University of Agricultural Sciences and Veterinary Medicine, Calea Aradului Nr. 119, RO-300 645 Timişoara, Romania
[2]Laboratory of Environment and Nutrition, Institute of Public Health Timişoara, Bd. Dr. V. Babes Nr. 16, RO-300 226 Timisoara, Romania
[3]Medical Department, S.C. CaliVita International, Intrarea Fortăreţei Nr.4, RO-300 127 Timişoara,Romania
[4]Semiology Department, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, Calea Aradului Nr. 119, RO-300 645 Timişoara, Romania;
[5]Sanitary Veterinary and Food Safety Direction Timiş, Timişoara, Romania

Received: 15 June 2010; Accepted: 25 June 2010

Abstract

Issue related to xenobiochemistry at the begining of this millenium acquires new scientific connotations of theoretic and applicative interest by its ecological, nutritional, bio-medical and social implications. Reiterating the aspects which circumscribe the domain of biochemistry – metabolization of nutrients and that of xenobiochemistry – biotransformation of xenobiotics one can emphasize that physiological and physiopathological processes take place simultanously. Xenobiochemistry of food interest concerns not only with the xenobiotics resulted from initial food contamination but also with the xenobiotics derived from food packaging materials. Irrespective of their origin all xenobiotics attain into the organism together with foodstuffs.

In this context studies regarding the xenobiotics of food interest are of special importance. Certain food xenobiotics can come from deliberate contamination (food additivation) or from incidental contamination and from illicit contamination (food pollution). These are the xenobiotics accompanying ab initio (a priori) the food nutrients. Other xenobiotics can result from the food packaging materials and are considered as xenobiotics accompanying a posteriori the food nutrients (post-processing, post-handling, post-storage).

Studies regarding the effects caused by the substances originated from the packaging materials of foodstuffs must be performed by evaluating these effects at the interface of packaging-food, considering the migration of some xenobiotics from the packaging material into food nutrients. Also, the evaluation of the effects of some chemical derivatives of xenobiotics released from packaging materials may rise interest. In both situations the chemical xenobiotics appear a posteriori related to the processing period of foodstuffs. In case of plastic materials – discussed predilectly in this first note of the paper – the in vivo effects of xenobiotics are of interest. Usuall, the researches on food xenobiotics have in view three aspects: a) the role of chemical additives used in plastic materials for food packages; b) residual compounds resulting from organic synthesis of the food packages; c) monomers and their derivatives resulted from food packages in case of inadequate storage conditions and/or inadequate handling.

Keywords: xenobiotics from food packaging materials - in vivo effects

Corresponding author: *e-mail:* zgarban@yahoo.com

1. Introduction

Food is an important exposure route to various xenobiotics which can be classified in two groups. The first group of food xenobiotics includes the food additives and the contaminants like: mycotoxins, heavy metals, polycyclic aromatic hydrocarbons, biocides – substances capable to kill living organisms in a selective way (i.e. pesticides and antimicrobials). These food xenobiotics can be present in food ab initio together with the nutrients [14,15,17]. The second group of food xenobiotics comprises the substances released from certain packages intended to come into contact with foodstuff [9,23]. It is a known that some substances used in the composition of food packaging can migrate into food itself, becoming food xenobiotics which accompany a posteriori the food nutrients.

However, in the last decade, the role of food packages has received less attention they contribute significantly to human exposure to xenobiotics [16,20]. Therefore the monitoring of food packaging xenobiotics migration and the evaluation of the health risks posed by them has become an important part of ensuring food safety.

1. Materials used in food packages

The type of xenobiotics that can leach from the package and affect the food quality is closely related to the materials used in food packaging. The main materials that can be used in food packaging are: paper and board, metals, glass, ceramics and various plastic materials (having in their composition synthetic polymers and plasticizers). The characteristics of these materials will be discussed below.

Paper and board. Are made from different vegetable sources and composed mainly of cellulose and various additives. Additives used in this type of material include fillers, starch and derivatives, wet strength sizing agents, retention aids, biocides, fluorescent whitening agents and grease-proofing agents.

Cellulose-based materials. Are among the first modern packaging materials used in food industry. The original packaging film was regenerated cellulose film (RCF). Pure cellulose fiber derived from wood is dissolved and then regenerated by extrusion through a slot, casting onto a drum and following acid treatment, is wound up as film.

Cellulose is a high-molecular weight, naturally derived, polymer. To make it flexible, it is plasticised with humectants (glycol type). The degree of flexibility can be adjusted to suit the application. Cellulose acetate is also derived from cellulose. It has high transparency and gloss and it can be printed.

Xenobiochemical aspects. Paper and board were officially recognized as a source of contaminants in the Resolution of the Council of Europe (2002) for paper and board in contact with foods, which lists the following xenobiotics: diisopropylnaphthalenes (DIPN), benzophenone, partially hydrogenated terphenyls, solvents, phthalates, azo-colourants, primary aromatic amines and polycyclic aromatic hydrocarbons [54].

Metals. Are used in the fabrication of metal cans. Cans are made of tin-plate (steel coated with tin), tin-free steel (steel coated with chromium and chromium oxides) or aluminium. Together with metals there are used sometimes varmish. Most cans are internally coated with a polymeric layer, and thus the food contact layer is not the metal but the lacquer.

Xenobiochemical aspects. Therefore substances of concern in cans are not only the metals involved, but also components migrating from the coatings (e.g.: phenolic resins) – see Grob, 2002 [19].

Glass and ceramics. Glass is composed mainly of: silica, sodium and calcium oxides. These components have no significant effect on food safety. Ceramics is another important food contact material which is rarely found in packaging but is often found in dishes used to serve food. Clay, the major raw material of ceramics, is composed of alumina, silica and water. Substances of concern may, however, originate from glazes and printing inks.

Xenobiochemical aspects Thus lead and cadmium are frequently controlled in such materials since they may be present as contaminants [55].

Plastic materials. As packaging there can be used various synthetic polymers - compounds with high molecular weight and very low biological availability.

Among plastic materials used for food packaging one can mention: polyethylene, polypropylene, polyethylene terephthalate, polycarbonate, polyvinyl chloride, polyamide, polyacrylonitrile butadiene styrene a.o.

A detailed presentation of these plastics is making in the next pages. In case of plastic materials the xenobiotics of food interest, as it was shown, may be represented by: a) additives used in plastic packaging materials, e.g.: antioxidants, antistatics, antifoggings agents, palsticizers, heat stabilizers, dyes etc. ; b) residual compounds used in the manufacture of plastic materials, e.g.: solvents, catalizers, precursors used in the synthesis of plastics etc.; c) monomers resulting from the plastic materials which is released during inadequate preservation conditions or their derivatives, e.g. styrene, caprolactam, melamine and formaldehyde, acetaldehyde etc.

Xenobiochemical aspects. In plastic materials one can find in reduced amount ingredients some of the above mentioned ingredients: a) plastic additives; b) residues of some compounds from the raw materials used in the manufacture of plastics; c) monomers released in time from the own plastic materials (in some storage conditions , usage).

2.Chemical composition of the main plastic materials used in food package

The plastics materials used in food-packaging are: polyethylene (PE), polypropylene (PP), polyesters (PET, PEN, PC), ionomers, ethylene vinyl acetate (EVA), polyamides (PA), polyvinyl chloride (PVC), polyvinylidene chloride (PVdC), polystyrene (PS), styrene butadiene (SB), acrylonitrile butadiene styrene (ABS), ethylene vinyl alcohol (EVOH), polymethyl pentene (PMP), high nitrile polymers (HNP), fluoropolymers (e.g. polychlorotri - fluoroethylene - PCTFE; polytetrafluoroethylene - PTFE), polyvinyl acetate (PVA). In Europe, PE constitutes the highest proportion of consumption, followed by four others, PP, PET, PS (including expanded polystyrene or EPS) and PVC [9]. The other plastics listed meet particular niche needs, such as improved barrier, heat sealability, adhesion, strength or heat resistance. These materials are all thermoplastic polymers. Each is based on one, or more, simple compound or monomer. Their structural characteristics will be briefly discussed in the next subchapter.

2.1.Structural characteristics of the constituents

Polyethylene (PE). Is structurally the simplest plastic and is made by addition polymerisation of ethylene gas in a high temperature and pressure reactor.

Polyethylene is a thermoplastic polymer consisting of long chains of the monomer ethylene (CH_2=CH_2). The heat resistance of PE is lower than that of other plastics used in packaging, with a melting point of around 120°C, which increases as the density increases.

Polypropylene (PP). Is an addition polymer of propylene and has a linear structure with protruding methyl (CH_2) groups. Polypropylene is a harder and denser than PE and more transparent in its natural form and has the lowest density and highest melting point of all the high volume usage thermoplastics. The high melting point of PP (160°C) makes it suitable for applications where thermal resistance is needed.

Polyesters. Are condensation polymers formed from ester monomers, resulting from the reaction of a carboxylic acid with an alcohol.

a. The most used polyester in food packaging is *polyethylene terephthalate* (PET) which is obtained when terephthalic acid reacts with ethylene glycol and polymerises. Polyethylene terephthalate melts at a much higher temperature than PP, typically 260°C, and does not shrink below 180°C.
b. Another polyester used in food packaging is *polyethylene naphthalene dicarboxylate* (PEN), which is a condensation polymer of dimethyl naphthalene dicarboxylate and ethylene glycol. This polyester is UV resistant and has higher temperature resistance compared with PET.

Polycarbonate (PC). Is a polyester containing carbonate groups and bisphenol in its structure. It is formed by the polymerisation of the sodium salt of bisphenolic acid with phosgene.

It is glass clear, heat resistant and is mainly used as a glass replacement in processing equipment and for glazing applications. Its use in packaging is mainly for large water bottles. It is also used for sterilisable baby feeding bottles and as a replacement in food service. Bisphenols and their derivatives with epoxy or chlorohydrin groups are known to be endocrine disruptors in humans and also as having potentially carcinogenic effects [26,43].

Their migration from can coatings/varnishes, polycarbonate (PC) bottles and sealants have been studied intensively in the last decade [5,12,18,23,33].

Polyvinyl chloride (PVC). Is obtained by the addition polymerisation of vinyl chloride which is similar in structure with ethylene, but with a hydrogen atom substituted by a chlorine atom. It is used in the fabrication of bottles for vegetable oil and fruit drinks. PVC softens, depending on its composition, at relatively low temperatures (80–95°C).

Polyvinylidene chloride (PVdC). Is a polymer derived from vinylidene chloride (ethylene with two hydrogen atoms replaced by chlorine atoms). PVdC is a widely used component in the packaging of cured meats, cheese, snack foods, tea, coffee and confectionery.

Polystyrene (PS) is an addition polymer of styrene, a vinyl compound where a hydrogen atom is replaced with a benzene ring. Polystyrene is easily processed by foaming to produce a rigid lightweight material which has good impact protection properties. The blown PS foam can be extruded as a sheet and used to make trays for meat and fish, egg cartons etc.

Polyamides (PA). Are commonly known as nylon. Polyamide plastics are formed by a condensation reaction between a diamine and a diacid or a compound containing each functional group (amine). The different types of polyamide plastics are characterized by a number related to carbon atoms in the originating monomer. Such a compound is nylon 6.6 or polyamide 6.6 , having the chemical name of polyhexamethylen adipamide.

Ethylene vinyl acetate (EVA). Is a copolymer of ethylene with vinyl acetate. The weight percent of vinyl acetate usually varies from 10 to 40%, with the remainder being ethylene. It is a polymer that approaches elastomeric materials in softness and flexibility.

Polystyrene butadiene (PSB). Is also a packaging polymer which is tough and transparent. Blown film of PSB has high permeability to water vapour and gases. It is used to pack fresh produce.

Polyacrylonitrile butadiene styrene (PABS). Is a copolymer of acrylonitrile, butadiene and styrene, with a wide range of aplications which can be varied by altering the proportions of the three monomer components. It is a tough material with good impact and good flexing properties. PABS is either translucent or opaque.

A major use is in large shipping and storage containers (tote boxes), and it has been used for thin-walled margarine tubs and lids.

Ethylene vinyl alcohol (EVOH). Is a copolymer of ethylene and vinyl alcohol. It is a high-barrier material with respect to oil, grease, organic solvents and oxygen. It is moisture sensitive and, in film form, is water soluble. Ethylene vinyl alcohol is typically coextruded or laminated as a thin layer between cardboard, foil, or other plastics.

Polyvinyl acetate (PVA). Is a polymer which forms a highly amorphous material with good adhesive properties in terms of open time, tack and dry bond strength. The main use of PVA in food packaging is as an adhesive dispersion in water. PVA adhesives are used to seal the side seams of folding cartons and corrugated fibreboard cases and to laminate paper to aluminium foil.

Polymethyl pentene (PMP). Is a methyl pentene copolymer. It is based on 4-methyl-1-ene and has the lowest density of commercially available packaging plastics (0.83 cm^3). It is a clear, heat-resistant plastic which can be used in applications up to 200°C. The main food packaging use is as an extrusion coating onto paperboard for use in baking applications in the form of cartons and trays for bread, cakes and other cook-in-pack foods.

High nitrile polymers (HNP). Are copolymers of acrylonitrile. The nitrile component contributes to good gas and odour barrier properties and also to good chemical resistance. High nitrile polymers therefore offer very good flavour and aroma protection.

Fluoropolymers. Are high-performance polymers related to ethylene where all the hydrogen atoms are replaced only by fluorine or by fluorine and chlorine. From this group there are mentioned:

a) *polytetrafluoroethylene* (PTFE) which is known to have a high melting point (327°C), and is known to be extremely chemically resistant to a large variety of chemicals;

b) *polychlorotrifluoroethylene* (PCTFE) - material with the highest water vapour barrier of all the commercially available packaging polymers. It is a very good gas barrier and offers high resistance to most chemicals at low temperatures. In many applications, it is used as a replacement for aluminium foil.

Ionomers. Are polymers formed from metallic salts of acid copolymers and possess interchange ionic crosslinks which provide the characteristic properties of this family of plastics. One example of an ionomer is poly(ethylene-co-methacrylic acid). This polymer is a sodium or zinc salt (which provides the ions) of copolymers derived from ethylene and methacrylic acid.

2.2.Compositional peculiarities and the migration of certain ingredients from plastic packaging materials into foodstuff

Corroborated literature data referring to the compositional peculiarities of plastic packaging materials are presented in table 1. Approaching the problem of the migration of some chemical compounds or some of their derivatives - formed during storage or transport, from the packaging materials into foodstuffs, implies the knowledge of the chemical composition of the packages.

Also, there is important to know the conditions (temperature, pressure, pH) which contribute to the release of those substances from the packaging materials.

An other important aspect, from ecological point of view, is the knowledge of the degradation / biodegradation of these substances in the environment.

3. Effects in vivo induced by constituents of plastic food packaging materials

In the case of polymers used in food packaging it must be noted that the polymer itself has no significant toxicity. The problem arise form the potential of migration of various plastic additives (plasticizers and esters, antioxidants, initiators, stabilizers etc.), of various residues of unreacted compounds used in the polymer fabrication and also the polymer potential to release in certain conditions the monomers from its structure which can exert harmful effects.

It is a known fact nowadays that: a) additives used in the synthesis and manufacturing of plastic materials used in food packaging; b) residues of unreacted compounds used in the polymer fabrication; c) monomers from plastic materials can migrate in foodstuffs.

Tabel 1. Main food packages of plastic materials – chemical characteristics chimice, usage related to foodstuffs

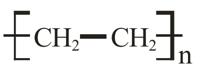
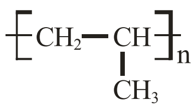
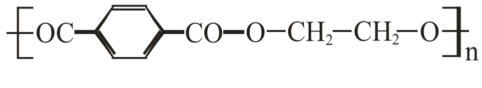
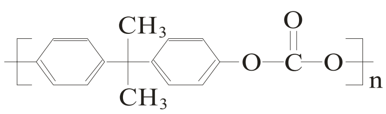
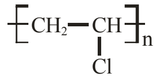
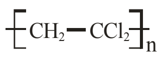
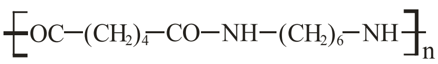
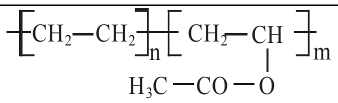
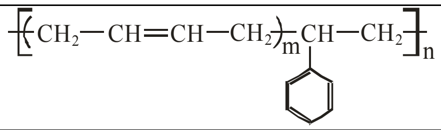
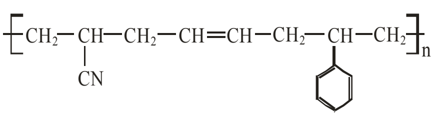
Nr. crt.	Compound denomination	Chain fragment (from macromolecule)	Chemical proprieties of general interest	Uses in packaging
1.	Polyethylene (PE)		- it can be utilized even at temperatures of 121-177°C - recommended sterilization temperatures: 100°C for packages with a over 0.5 mm thickness and 65.5°C for packages with 0.1-0.5 mm thickness	grocery bags, sandwich bags, squeeze bottles, freezer bags
2.	Polypropylene (PP)		- breaking temperature: -9.44°C - resists to water vapors, fats, acids, bases, solvents - maximum temperature of use: 37,18°C - corrugates at 45°C	containers for yogurt, margarine, syrups
3.	Polyethylene terephthalate (PET)		- maximum temperature of use: 100°C -at 82,2°C it starts to denaturate	bottles for various beverages, for vegetal oils, containers for mouthwashes, grocery bags, microwave trays

Table 1. Main food packages of plastic materials – chemical characteristics chimice, usage related to foodstuffs (*continue*)

Nr. crt.	**Compound denomination**	**Chain fragment (from macromolecule)**	**Chemical proprieties of general interest**	**Uses in packaging**
4.	Polycarbonate (PC)		- good resistance to acids and fats but poor resistance to bases and solvents - doesn't tolerate boiling in water - maximum temperature of use: 135°C	baby bottles, milk bottles, large water containers
5.	Polyvinyl chloride (PVC)		- maximum temperature of use: 65.5°C - resistant to water, acids, bases, some solvents, fats and oils	bottles for vegetable oils and fruits juices
6.	Polyvinylidene chloride (PVdC)		- resistant to water, oxygen, acids, bases, solvents	packages for meat, cheese, tea, coffee and baking products
7.	Polyamide (PA), e.g. Polyhexamethyleneadipamide (polyamide 6.6 or nylon 6.6)		- good barrier for water and oxygen	packages for food kept at room temperature
8.	Ethylene vinyl acetate (EVA)		- instable at high temperatures - resistant at low temperatures and to sterilization through irradiation	flexible packaging material for fatty foods,
9.	Polystyrene butadiene (PSB)		- temperature of use: from -40 to 100°C	packages for fresh products
10.	Polyacrylonitrile butadiene styrene (PABS)		- denaturizes at 93.33°C - maximum temperature of use: 74°C - resistant to acids, bases, oils - poor resistance to solvents and light	Packages for various food products with the exception of those containing alcohol and those designated to microwave or oven preparation

3.1.Chemical additives used in plastic materials for food packaging.

In the manufacturing process of plastic materials used in food packaging various chemical additives are used. These additives are agents with various functions: antioxidant, antistatic, antifogging, plasticizers, temperature stabilizers, flame retardants, UV stabilizers, colorants.

Among additives used in the production of plastic materials the most important through the impact on food safety are the *plasticizers*. Plasticizers or dispersants are known as additives that increase the plasticity or fluidity of the materials to which they are added. Plasticizers added to plastics increase the flexibility of the final product.

These plasticizers can be considered also as xenobiotics because they can migrate into the foodstuffs.

Diesters of phthalic acid (referred to often as phthalates) and other plasticizer are used mainly in plastic materials and are considered one of the most abundant man-made environmental pollutants. Humans can be exposed to these compounds through ingestion, inhalation and dermal exposure for their whole lifetime [30].

One of the most discussed plasticizers that migrate from plastic packages is phthalates. Phthalates are easily released into the food because there is no covalent bond between them and the plastics in which they are mixed. As the plastic material age and break down the release of phthalates accelerates.

Phthalates are considered to be endocrine disruptor compounds which have been shown to change hormone levels and cause birth defects [53].

Studies made on rodents and primates showed that some phthalates can suppresses steroidogenesis [22, 47] and may have the potential to alter androgen-responsive brain development in humans [46]. There are also studies that link the endocrine disruptor effect of phthalate with obesity and insulin resistance [21].

The most important plastic materials and the ones with the highest impact from this point of view are polyvinyl chloride (PVC) and polyvinylidene chloride (PVDC) which contain large amounts of plasticizers, having thus a higher degree of migration [24]. In the food products that come into contact with PVC or PVDC packages there are ten plasticizer which are commonly found as migrants: 4 phthalates – di-n-butylphthalate (DBP), n-butylbenzyl phthalate (BBP), di(2-ethylhexyl)phthalate (DEHP), diisononyl phthalate (DINP); 3 adipates – di-n-alkyl adipate (DAA), di(2-ethylhexyl)adipate (DEHA), diisononyl adipate (DINA) and 3 other compounds – dibutyl sebacate (DBS), O-acetyl tributyl citrate (ATCB) and diacetyllauroyl glycerol (DALG) – Tsumara et al., 2002. Lower molecular weight phthalates, including DBP and diethyl phthalate (DEP), are used as solvents and plasticizers for cellulose acetate.

There are limited information about the toxicity of adipates. Two adipates have especially raised concerns: DEHA and diethyl adipate. DEHA is considered to be a potential carcinogen and diethyl adipate shows reproductive toxicity in animal experiments [40].

Acetyl tributyl citrate (ATBC) is one of the most widely used plasticizers. It is used especially in PVC films that are the raw materials for a large variety of kitchen wraps used increasingly in microwave ovens to cover foods while cooking and heating. Studies in humans showed that ATCB is toxic to human KB cells, a subline of the ubiquitous keratin-forming tumor cell line HeLa and also ATCB can inhibit the proliferation of Lympho node T cells thus affecting immunity [37]. In the case of polyethylene terephthalate (PET) a study made on Salmonella strains grown directly in the plastic bottles with water stored for a period of 1 month shown leaching of mutagens. This activity was higher after storage in daylight [10].

Even if phthalates are not used as substrates or precursors in the manufacture of PET, there is evidence of phthalates leaching from PET bottles. Also recent studies shows that PET may yield estrogenic disruptors and the leached phthalate are the main compounds that can be incriminated for these efects [41].

Another important plastic additives class, which can migrate in foods and may affect human health are UV stabilizers. This class of plastic additives is used in food packages mainly to prevent polymer degradation and changes in the quality of the packed food due to UV rays. Some of the compounds used as UV stabilizers have been reported to have estrogenic activity. This is the case of 2-hydroxy-4-methoxybenzophenone and 2,2'-dihydroxy-4-methoxybenzophenone which exert estrogenic activity [25] and are potential carcinogens involved in breast cancer [36, 42].

Flame retardants are another class of plastic additives which is used in food packaging materials and poses health risks through migration and contamination of foods. Flame retardants are compounds that have an inhibitory effect on the ignition of combustible materials. Of the commercialized chemical flame retardants, the brominated variety is most widely used. They are very effective in plastics and also in textile as they reduce the flammability. One of the most discussed food contaminants from this category are polybrominated diphenyl ethers (PDBE). Additive flame retardants like PBDEs are not chemically but physically combined with polymers at levels ranging from 5 to 30 per cent by weight, creating the possibility for them to leach out of the treated materials into the food or into the surrounding environment. Polybrominated diphenyl ethers are known as endocrine disruptors which affects the thyroid function [29]. Animal studies have demonstrated that PBDEs are anti-androgenic compounds [45] and that the foetal period may be one of high sensitivity to PBDE exposure [32]. A recent study reported statistically significant associations between concentrations of PBDE congeners in breast milk and adverse birth outcomes, including reduced birth weight, birth length and reduced chest circumference [7].

Another flame retardant highly used in the plastic materials fabrication is tetrabromobisphenol A (TBBPA) which is a derivative of bisphenol A. As an additive flame retardant tetrabromobisphenol A it is used especially in acrylonitrile butadiene styrene.

In vitro studies have suggested a possible interference of TBBPA with thyroid hormone function and a potential of TBBPA as "endocrine disruptor" has been discussed [28]. Also recent studies have shown that TBBPA has also immunosuppressive effects on human natural killer cell [27].

3.2.Residual compounds derived from the manufacture of food packages

Various compounds used especially as catalyzers in the polymerization process may leave traces amounts in the structure of polymer. These compounds used in the packaging fabrication process may, in different conditions, migrate into food and influence the food safety.

Epidemiology studies have demonstrated measurable levels of perfluorochemicals in the serum of various individuals. One of the most encountered compound was perfluorooctanoic acid (PFOA), a processing aid in the manufacture of PTFE, which have been detected in the serum of elderly Americans as high as 175 and 16.7 ng ml^{-1}, respectively, with higher amounts being measured in production workers [38]. Toxicologically, PFOA is a peroxisome proliferator, a term used to describe a diverse group of non-genotoxic chemicals that target the liver, inducing peroxisomal β-oxidation and activation of the peroxisome proliferator activated receptor [1]. In rodents, peroxisome proliferators induce hepatomegaly, causing hypertrophy and hyperplasia of the liver, ultimately resulting in the formation of hepatic tumours. In addition, rodent studies indicate that some peroxisome proliferators, including PFOA, induce tumours in Leydig and pancreatic acinar cells [2]. Perfluorooctanoic acid has also been characterized as a developmental toxicant, causing increased mortality, reduced body weights and delayed sexual maturation in pups [56] and as having a long human half-life of 4.4 years [6]. Another compound that may contribute to the mutagenic and endocrine disruptor effect of PET is antimony (Sb) which is used in the form of antimony trioxide (Sb_2O_3) or antimony triacetate as a catalyst in the production of PET.

Though the estrogenic disruptor effect of antimony was not studied extensively, there are reports that indicate antimony to have "high estrogenicity" [8].

The PET resin typically contains antimony in concentrations between 100 and 300 mg/kg [11] and experimentally investigations have demonstrated significant levels of antimony in water bottled in PET containers [44], levels which increase with the raising of the ambient temperature [49].

3.3.Monomers and their derivatives resulted from food packages

Monomers and teir derivatives derived from various polymers used in plastic materials packages can be released in the conditions of inadequate handling and utilization. Important studies have been also made to determine the migration and toxicity of some monomers. In this context it can be reminded the following compounds: styrene [31], caprolactam [3], melamine and formaldehyde[4], acetaldehyde and other oligomers used in the composition of polyethylene terephthalate - PET [35].

An important monomer that can migrate from food packages is bisphenol A (BPA) which also can exert endocrine disruptor effects. Bisphenol A is found especially in the polycarbonate as monomer but it is also used as a plasticizer in other plastic materials. Bisphenol A presents both estrogenic and antiandrogenic activity and it is able to activate estrogen receptors at concentrations lower than 1μM, while it exhibits antiandrogenic activity at concentrations higher than 5μM. Moreover BPA has also a slight activity is on the pregnane X receptor [34]. Studies have shown that BPA induces also thyroid hormone mimicking effects [51]. Bisphenol A has been reported to induce aneuploidy and give rise to DNA adducts in cultured hamster embryo cells [48] and also to have potential carcinogenic effect, being associated with cancers of the hematopoietic system and with an increased incidence of interstitial-cell tumors of the testes. An, early life exposure to BPA may predispose to preneoplastic lesions of the mammary gland and prostate gland in adult life [26].

Bisphenol A is also used as an antioxidant in some plasticizers, and as a polymerization inhibitor in PVC. Also epoxy resins containing bisphenol A are used as coatings on the inside of almost all food and beverage cans [13]. In the case of polyacrylonitrile butadiene styrene (PABS), during the production of acrylonitrile copolymers, a small fraction of unreacted acrylonitrile monomer becomes physically entrapped in the polymer and can migrate slowly during storage or the contact with food or other materials.

Regarding its toxicity, acrylonitrile is a carcinogen and mutagen [39] Decreased fertility and birth defects have been observed in some laboratory animals exposed to high concentrations of acrylonitrile in air or drinking water [52]. Also studies revealed that exposure to acrylonitrile can induce DNA strand breakage and sex chromosome aneuploidy in human spermatozoa [50].

Concluding remarks

1. Thorough studies on xenobiotics originated from food packaging materials impose to reconsider the current problems related to food xenobiochemistry and food safety.
2. Food xenobiochemistry – dealing with the biotransformation of chemical xenobiotics and biochemistry - dealing with the metabolization of nutrients, are domains with synergistic evolution because chemical food xenobiotics accompany the food nutrients.
3. Xenobiotics of food interest which accompany ab initio the food nutrients can come from deliberate (additivation) or incidental and illicit contamination (pollution) of foodstuffs.
4. Xenobiotics derived from food packaging materials vary in accordance with the chemical composition of the packaging materials. In case of food packaging represented by "plastic materials" – the subject discussed in this paper - the in vivo effects are caused predilectly by: a) chemical additives introduced in the composition of the "plastic food packaging materials" like: antioxidants, plastifiers, heat stabilizers etc.; b) residual compounds resulted from the synthesis and manufacturing of the "plastic food packaging materials"; c) monomers and their derivatives present in the composition of "plastic food packaging materials" which, in some conditions (storage, handling etc.) can migrate into the foodstuffs. All the above mentioned xenobiotics coming from food packaging materials constitute the group of food xenobiotics accompanying a posteriori the food nutrients.
5. In the complex framework of food xenobiochemistry the specific analytical determinations must have in view the two groups of food xenobiotics, i.e. the "xenobiotics present ab initio in foodstuffs of animal and non-animal origin" and the "xenobiotics derived from food packaging materials". Only thus food safety and consumer protection will be guaranteed.

References

1. Begley T.H., White K., Honigfort P., Twaroski M.L., Neches R., Walker R.A.,Perfluorochemicals: potential sources of and migration from food packaging, *Food. Addit. Contam.*, **2005**, *22*(10), 1023-1031.
2. Biegel L.B., Hurtt M.E., Frame S.R., O'Connor J.C., Cook J.C., Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats, *Toxicological Science*, **2001**, *60*, 44–55.
3. Bradley E.L., Speck D.R., Read W.A., Castle L., Method of test and survey of caprolactam migration into foods packaged in nylon-6, *Food Addit, Contam*., **2004**, *21*(12), 1179-1185.
4. Bradley E.L., Boughtflower T.L., Smith L., Speck D.R., Castle L., Survey of the migration of melamine and formaldehyde from melamine food contact articles available on the UK market, *Food Addit, Contam*., **2005**, *22*(6), 597-606.
5. Bradley E.L., Read W.A., Castle L., Investigation into the migration potential of coating materials from cookware products, *Food Addit, Contam*., **2007**, *24*(3), 326-335.
6. Butenhoff J.L., Gaylor D.W., Moore J.A., Olsen G.W., Rodricks J., Mandel J.H., Zobel L.R., Characterization of risk for general population exposure to perfluorooctanoate, *Regulatory Toxicology and Pharmacology*, **2004**, *39*, 363–380.
7. Chao H.R., Wang S.L., Lee W.J., Wang Y.F., Papke O., Levels of polybrominated diphenyl ethers (PBDEs) in breast milk from central Taiwan and their relation to infant birth outcome and maternal menstruation effects, *Environ. Int.*, **2007**, *33*, 239-245.
8. Choe S-Y., Kim S-J., Hae-Gyoung K., Lee J.H., Choi Y., Lee H., Yangho K., Evaluation of estrogenicity of major heavy metals, *Sci. Total. Environ*., **2003**, *312*(1), 15-21.
9. Coles R., McDowell D., Kirwan M.J., *Food Packaging Technology*, Blackwell Publishing Ltd., Oxford, 2003.
10. de Fusca R., Monarca S., Biscardi D., Pasquini R., Fatigoni C., Leaching of mutagens into mineral water from polyethylene terephthalate bottles, *Sci. Total Environ*., **1990**, *90*, 241
11. Duh B.,Effect of antimony catalyst on solid-state poly-condensation of poly(ethylene terephthalate), *Polymer*, **2002**, *43*(11), 3147-3154
12. Dionisi G., Oldring P.K.T., Estimates of per capita exposure to substances migrating from canned foods and beverages, *Food Addit, Contam*., **2002**, *19*(9), 891-903.
13. Erickson B.E., Bisphenol A under scrutiny, *Chemical and Engineering News (American Chemical Society)*, **2008**, *86*(22), 36-39
14. Faber K., *Biotransformations*, Springer Verlag, Berlin-Heidelberg- New York, 1999.

15. Forbes V.E., Forbes T.L., *Ecotoxicologie - théorie et applications* (traduit en francaise), Edition de l'Institut National de la Recherche Agronomique, Paris, 1997.
16. Garban Z.,*Chemical xenobiotics of food interest* (in Romanian)*,*Editura Eurobit Timişoara, 2004
17. Garban Z., *Biochemistry: Comprehensive treatise. Vol. IV. Xenobiochemistry* (in Romanian), Editura Didactică şi Pedagogică R.A., Bucureşti, 2007.
18. Ghibu G.-D., Garban Gabriela, Avacovici Adina-Elena, Baltă C., Garban Z., Xenobiochemistry at the interface of packaging materials-food. Note II. Interactions and effects of bisphenol A from food packaging materials, **2010**, *in press*
19. Grob K., Comprehensive analysis of migrates from foodpackaging materials: a challenge, *Food Addit, Contam*., **2002**, *19*(Suppl.), 185-191.
20. Grob K., Biedermann M., Scherbaum E., Roth M., Rieger K., Food contamination with organic materials in perspective: packaging materials as the largest and least controlled source? A view focusing on the European situation, *Crit. Rev. Food. Sci. Nutr.*, **2006**, *46*, 529–535.
21. Grun F., Blumberg B., Endocrine disrupters as obesogens, *Mol. Cell. Endocr*., **2009**, *304*(1),19-29.
22. Hallmark N., Walker M., McKinnell C., Mahood I.K., Scott H., Bayne R., Coutts S., Anderson R.A., Greig I., Morris K., Sharpe R.M., Effects of Monobutyl and Di(n-butyl) Phthalate in Vitro on Steroidogenesis and Leydig Cell Aggregation in Fetal Testis Explants from the Rat: Comparison with Effects in Vivo in the Fetal Rat and Neonatal Marmoset and in Vitro in the Human, *Environ Health Perspect.*, **2007**, *115*(3), 390–396
23. HolmesM.J., HartA., Northing P.Oldring P.K.T., Castle L. Dietary exposure to chemical migrants from food contact materials: a probabilistic approach, *Food Addit, Contam*., **2005**, *22*(10), 907-919.
24. Kawamura Y., Tagai C., Maehara T., Yamada T., Additives in Polyvinyl Chloride and Polyvinylidene Chloride Products, *Journal of the Food Hygienic Society of Japan*, **1999**, *40*(4), 274-284
25. Kawamura Y., Nishimura T., Kikuchi Y., Nishikawa J., Nishihara T., Tanamoto K., Estrogenic Activities of UV Stabilizers Used in Food Contact Plastics and Benzophenone Derivatives Tested by the Yeast Two-Hybrid Assay, *J. Health. Sci.*, **2003**, *49*(3), 205-212.
26. Keri R.A., Ho S.M., Hunt P.A., Knudsen K.E., Soto A.M., Prins G.S., An evaluation of evidence for the carcinogenic activity of bisphenol A, *Reprod Toxicol.*, **2007**, *24*(2), 240-252.
27. Kibakaya E.C., Stephen K., Whalen M.M., Tetrabromobisphenol A has immunosuppressive effects on human natural killer cells, *J. Immunotoxicol*., **2009**, *6*(4), 285-292.
28. Kitamura S., Kato T., Iida M., Jinno N., Suzuki T., Ohta S., Fujimoto N., Hanada H., Kashiwagi K., Kashiwagi A., Anti-thyroid hormonal activity of tetrabromobisphenol A, a flame retardant, and related compounds: Affinity to the mammalian thyroid hormone receptor, and effect on tadpole metamorphosis, *Life Sci.*, **2005**, *76*, 1589-1601
29. Kuriyama S.N., Wanner A., Fidalgo-Neto A.A., Talsness C.E., Koerner W., Chahoud I., Developmental exposure to low-dose PBDE-99: tissue distribution and thyroid hormone levels, *Toxicology*, **2007**, *242*, 80–90
30. Latini G., Monitoring phthalate exposure in humans, *Clinica Chimica Acta*, **2005**, *361*, 20-29.
31. Lickly T.D., Breder C.V., Rainey M.L., A model for estimating the daily dietary intake of a substance from food-contact articles: styrene from polystyrene food-contact polymers, *Regulatory Toxicology and Pharmacology*, **1995**, *21*, 406-417.
32. Lilienthal H., Hack A., Roth-Harer A., Grande S.W., Talsness C.E., Effects of developmental exposure to 2,2, 4,4, 5-pentabromodiphenyl ether (PBDE-99) on sex steroids, sexual development, and sexually dimorphic behavior in rats, *Environ. Health Perspect*., **2006**, *114*, 194–201.
33. Lim D.S., Kwack S.J., Kim K.B., Kim H.S., Lee B.M., Potential risk of bisphenol A migration from polycarbonate containers after heating, boiling, and microwaving, *J. Toxicol. Environ. Health.* Part A., **2009**, *72*(21-22), 1285-129.
34. Mnif W., Pascussi J.M., Pillon A., Escande A., Bartegi A., Nicolas J.C., Cavaillès V., Duchesne M.J., Balaguer P. - Estrogens and antiestrogens activate hPXR, *Toxicol. Lett.*, **2007**, *170*(1), 19–29.
35. Mutsuga M., Tojima T., Kawamura Y., Tanamoto K., Survey of formaldehyde, acetaldehyde and oligomers in polyethylene terephthalate food-packaging materials, *Food Addit, Contam*., **2005**, *23*(2), 212-218
36. Nakagawa Y., Suzuki T., Metabolism of 2-hydroxy-4-methoxybenzophenone in isolated rat hepatocytes and xenoestrogenic effects of its metabolites on MCF-7 human breast cancer cells, *Chem. Biol. Interact*., **2002**, *139*(2),115-128.
37. Nara K., Nishiyama K., Natsugari H., Takeshita A., Takahashi H, Leaching of the Plasticizer, Acetyl. Tributyl Citrate: (ATBC) from Plastic Kitchen Wrap, Journal of Health Science, **2009**, *55*(2), 281-284.
38. Olsen G.W., Burris J.M., Burlew M.M., Mandel J.H., Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations, *Journal of Occupational and Environmental Medicine*, **2004**, *45*, 260–270

39. Poustková I., Poustka J., Babička L., Dobiáš J., Acrylonitrile in food contact materials – two different legislative approaches: comparison of direct determination with indirect evaluation using migration into food simulants, *Czech J. Food Sci*., **2007**, *25*, 265–271.
40. Remberger M., Andersson J., Cousins A.P., Kaj L., Ekheden Y., Dusan B., Brorstrom-Lunden E., IVL, Cato I., SGU, *Results from the Swedish National Screening Programme 2004. Subreport 1: Adipates*, 2005.
41. Sax L., Polyethylene Terephthalate May Yield Endocrine Disruptors, *Environ Health Perspect*. **2010** April, *118*(4), 445–448
42. Schlumpf M., Cotton B., Conscience M., Haller V., Steinmann B., Lichtensteiger W., In vitro and in vivo estrogenicity of UV screens, *Environ. Health. Perspect*., **2001**, *109*(3), 239-244
43. Sekizawa J. - Low-dose effect of bisphenol A: a serious threat to human health?, *J. Toxicol. Sci*., **2008**, *33*(4), 389–403
44. Shotyk S., Krachler M. - Contamination of bottled waters with antimony leaching from polyethylene terephthalate (PET) increases upon storage, *Environ. Sci. Technol*., 2007, 41(5), 1560-1563
45. Stoker T.E., Cooper R.L., Lambright C.S., Wilson V.S., Furr J., Gray L.E., In vivo and in vitro antiandrogenic effects of DE-71, a commercial polybrominated diphenyl ether (PBDE) mixture, *Toxicol. Appl. Pharmacol.*, **2005**, *207*, 78-88.
46. Swan S.H., Liu F., Hines M., Kruse R.L., Wang C., Redmon J.B., Sparks A., Weiss B., Prenatal phthalate exposure and reduced masculine play in boy, *International Journal of Andrology*, **2009**, *33*(2), 259 – 269
47. Tsumura Y., Ishimitsu S., Kaihara A., Yoshii K., Tonogai Y., Phthalates, Adipates, Citrate and Some of the Other Plasticizers Detected in Japanese Retail Foods: a Survey, *Journal of health science*, **2002**, *48*(6), 493-502
48. Tsutsui T., Tamura Y., Yagi E., Hasegawa K., Takahashi M., Maizumi N., Yamaguchi F., Barrett J.C., Bisphenol-A induces cellular transformation, aneuploidy and DNA adduct formation in cultured Syrian Hamster embryo cells, *Int. J. Cancer.*, **1998**, *75*, 290–294.
49. Westerhoff P., Prapaipong P. Shock E., Hillaireau A., Antimony leaching from polyethylene terephthalate (PET) plastic used for bottled drinking water, *Water. Res.*, **2008**, *42*(3), 551-556.
50. Xu D.X., Zhu Q.X., Zheng L.K., Wang Q.N., Shen H.M., Deng L.X., Ong C.N., Exposure to acrylonitrile induced DNA strand breakage and sex chromosome aneuploidy in human spermatozoa, *Mutat Res.*, **2003**, *537*(1), 93-100.
51. Zoeller R.T., Bansa R.l, Parris C., Bisphenol-A, an environmental contaminant that acts as a thyroid hormone receptor antagonist in vitro, increases serum thyroxine, and alters RC3/Neurogranin expression in the developing rat brain, *Endocrinology*, **2005**, *146*(2), 607–612.
52. ***Agency for Toxic Substances and Disease Registry (ATSDR) - *Acrylonitrile* CAS # 107-13-1, 2004.
53. ***Centers for Disease Control (CDC) - *Third National Report on Human Exposure to Environmental Chemicals*, U.S., 2005.
54. ***Council of Europe (CoE). - *Resolution AP (2002)1 on paper and board materials and articles intended to come in contact with foodstuffs.* Council of Europe, Committee of Ministers on 18 September 2002.
55. ***EFSA. - *Investigation of the significant factors in elemental migration from glass in contact with food.* Final Report Project Code A03029, Food Standards Agency, UK, 2002.
56. ***US Environmental Protection Agency - *Preliminary risk assessment of the developmental toxicity associated with exposure to perfluorooctanoic acid and its salts*, 10 April 2003, Washington, DC: US EPA Office of Pollution Prevention and Toxic Risk Assessment Division.