RECENT ADVANCES IN LC-MS ANALYSIS OF FOOD-PACKAGING CONTAMINANTS.

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Contents

Abstract

The supply of safe and high-quality foodstuffs relies on the efficient protection of food from deterioration. However, all food-packaging materials can release small amounts of their chemical constituents when they touch food, and any substance that migrates from the packaging into the food is of concern if it could pose health problems to the consumer.

The purpose of this review is to describe recent advances in the liquid chromatography-mass spectrometry (LC-MS) analysis of food-packaging contaminants since 2009, focusing on some relevant families of compounds (e.g., bisphenol A, bisphenol A diglycidyl ethers and related compounds, UV-ink photoinitiators, perfluorinated compounds, and phthalates).

1. Introduction

Food products are produced and distributed worldwide leading to very stringent regulations to guarantee food quality and safety. They are very complex mixtures consisting of naturally occurring compounds (lipids, carbohydrates, proteins, vitamins, organic acids, aromas), together with other substances generally originating from technological processes, agrochemical treatments, or packaging materials. Several of these compounds such as pesticide and veterinary drug residues, endocrine disruptors, food additives, environmental contaminants (including dioxins, chlorinated and brominated compounds, heavy metals), and contaminants of natural origin (mycotoxins and marine toxins) are of particular concern because although they are generally present in very small amounts they are nonetheless often dangerous to human health [1]. However, the comparison of the various sources of food contamination with organic chemicals suggests that in the public, but also among experts, the perception of risk is often distorted. As reported by Grob *et al.* [2], if you ask educated consumers about the principal source of food contamination they will list pesticides as the first item, then environmental chemicals such as the PCBs, and veterinary drugs, between others. Few would even mention food packaging materials although the amount of material migrating from food packaging into food may well be 100 times higher than the pesticides or environmental pollutants contribution. Moreover, it is difficult to compare the toxicity (primarily acute) of well-controlled pesticides with the potential (primarily chronic) toxicity of frequently not even identified compounds entering food from packaging materials. Despite the efforts on food legislation and regulation, food safety incidents occasionally occur and can originate from different sources such as both microbial and chemical contaminants. On the last decade, some food safety incidents have been directly related to packaging materials such as the alert for food contamination by UV ink photoinitiators on November 2005 in Europe [3]. The Italian Food Control Authority detected that the photoinitiator 2-isopropylthioxanthone (2-ITX) migrated into baby milk at concentrations ranging from 120 to 300 μg L^{-1}, resulting in the withdrawal from the market of more than 30 million liters of milk. In order to protect the consumer from potential food risk hazards risk analysis are mandatory, and for that purpose hazard identification, hazard characterization, exposure assessment and risk characterization are necessary. A very important prerequisite for performing risk assessment adequately is the presence of data generated by reliable and fit-for-purpose analytical methods to estimate the level of exposure and intake of the consumer

to contaminants and residues. Focusing on contaminants coming from packaging materials regulation must also be coherent. For instance, it should be avoided that for one type of contaminants strict rules are applied, while larger amounts of similar substances from another source are qualified or are not even required to be analyzed [2]. Commission Regulation EU No 10/2011[4] establish that plastic materials and articles shall not transfer their constituents to food simulants in quantities exceeding 10 milligrams of total constituents released per dm^2 of food contact surface (mg dm^{-2}). For instance, for a 100 g piece of cheese of 1 dm^2 top surface and 1 cm thickness, an overall migration of 240 mg kg^{-1} is legal; for individually packed slices of sandwich cheese, up to about 1050 mg kg^{-1} would be legal [2]. In addition plastic materials and articles intended to be brought into contact with food intended for infants and young children shall not transfer their constituents to food simulants in quantities exceeding 60 milligrams of total of constituents released per kg of food simulant. So, appropriate and reliable methodologies are crucial for both industrial and enforcement testing of compliance with the legislation. It is necessary to assess the concentration levels of contaminants migrating into food from the packaging and to evaluate the level of exposure according to the diet. For this purpose, several simulants (depending of type of food) specified in EU legislation are used in migration studies in order to evaluate the amount of non-desirable compounds migrating from food contact materials (FCM) [4-6].

In the analysis of contaminants and chemical residues in food, gas chromatography (GC) and liquid chromatography (LC) are the two main chromatographic methods employed in practice. However, the complexity of food matrices often requires not only extensive sample preparation, but also on-line coupling techniques, which are used for their superior automation and high-throughput capabilities. Moreover, the high sensitivity achieved using mass spectrometry or high resolution mass spectrometry (HRMS) as detection techniques allowed the simplification of sample-preparation procedures, thereby resulting in faster and low-handling methodologies [7]. The analysis of packaging material contaminants migrating into food is difficult because of the physicochemical properties of many of these compounds. First, the analytical methodologies used must achieve not only low detection limits but guarantee confirmation of the target analytes to prevent false positives or false negative results. The European Union established the 2002/657/EC directive [8] concerning the performance of analytical methods and the interpretation of results, where an identification point system was used for the confirmation of the identity of an analyte. Furthermore, the analysis of some food packaging contaminants is also complicated because of the difficulty to

obtain blank samples, such as in the case of perfluorinated compounds (PFCs), phthalates, and bisphenol A (BPA) and related compounds where materials used in sample treatment [9], or the own chromatographic system in the case of PFCs and phthalates, can be sources of contamination. Moreover, establishing concentration levels of food packaging contaminants migrating into food is not always easy as many of these compounds can be found in the food originating from other sources. For instance, PFCs can contaminate food by bioaccumulation of, especially, longer chain members in fish and shellfish, and not only for contact with packaging materials.

The aim of this review is to present current state-of-the-art in recent advances in LC-MS analysis of food packaging contaminants in food samples. It includes a selection of the most relevant papers recently published regarding instrumental and methodological aspects, as well as the newest applications. The number of publications in this field as well as the number of food packaging contaminants migrating into food is huge so we will present a selection of significant publications focused only on some relevant families with an increasing interest in their analysis during the last years, such as BPA and related compounds, UV ink photoinitiators, PFCs, and phthalates and their monoester metabolites. The structures, abbreviations and CAS numbers of all food packaging contaminants described in this review are summarized in Table 1. First, a description of each family of compounds regarding their presence in food, legislation and toxicological aspects will be presented. Then different aspects such as sample treatment, chromatographic separation and mass spectrometry techniques, sources of contamination and problems with blanks, as well as quantitation and confirmation strategies, will be generally addressed. Moreover, some relevant applications, food packaging migration studies and concentration levels found in the literature will also be discussed.

1.1. BPA, BADGEs and related compounds

BisphenolA (BPA) is widely used in the production of polycarbonate plastics and phenolic-epoxy resins, which have a variety of applications, such as plastic food containers and epoxy food-can coatings. Other applications of BPA include printed circuit boards, composites, adhesives, and tooling. Heat and contact with either acidic and basic foods, as the sterilization process in cans or polycarbonate plastic, increase the hydrolysis of the ester bond linking BPA molecules in the polycarbonate and epoxy resins and compounds are released to food [10]. Additionally, epoxy-based lacquers or vinylic organosol (PVC) materials are

commonly used for coating the inside of food cans, big storage vessels and food containers to reduce food spoilage and to prevent degradation of the food can. These lacquers are epoxy phenolic resins based on polymerization products of bisphenol A-diglycidyl ether (BADGE) and novolac glycidyl ether (NOGE, also known as epoxy novolac). NOGE, the technical reaction product of formaldehyde, phenol and epichlorohydrin, contain a mixture of compounds with two or more aromatic rings. The 2-ring product of NOGE, bisphenol F-diglycidyl ether (BFDGE), consists of the 3 isomers *p,p*-, *o,p*-, and *o,o*-BFDGE. So these coatings (epoxy-based lacquers and PVC) can release amounts of BADGE and BFDGE compounds as well as oligomers and derivatives which can migrate into the packaged foods. Chlorinated derivatives of BADGE and BFDGE may be generated during the thermal coating treatment, since BADGE and BFDGE are also used as additives to remove the hydrochloric acid formed during this process. Moreover, hydrolyzed derivatives such as BADGE·$2H_2O$, BADGE·H_2O, BFDGE·$2H_2O$ and BFDGE·H_2O can be produced during storage when the coating comes into contact with aqueous and/or acidic foodstuffs.

Exposure to BPA is thought to occur primarily through ingestion. Migration and leaching of BPA from metal cans and plastics to food and drinks is possible and evidences of this fact has been found around the world, including Japan, Europe, New Zeland and United States [11,12]. Currently, there is no US neither EU regulations nor limitations regarding to the amount of BPA in food or drink. BPA is permitted for use in food contact materials in the European Union (EU) under Regulation 10/2011/EU, relating to plastic materials and articles intending to come into contact with foodstuffs with a SML of 0.6 mg kg^{-1} or 100 µg dm^{-2} [4]. However, in January 2011, the European Union adopted Commission Directive 2011/8/EU, prohibiting the use of BPA for the manufacture of polycarbonate infant feeding bottles [13]. The US Environmental Protection Agency (EPA) and the European Food Safety Authority (EFSA) have set a BPA reference dose/tolerable daily intake (TDI) of 50 µg/kg/day, whereas Health Canada established a provisional TDI for BPA at 25 µg kg^{-1} of body weight/day [14]. Nowadays new bisphenol analogues such as bisphenol F (BPF), bisphenol B (BPB), bisphenol E (BPE) and bisphenol S (BPS) are also used in many industrial applications including polycarbonate plastics and resins [15,16]. Moreover, BPS is also used in curing fast-drying epoxy glues, and as an anticorrosive and it is the monomer of polyethersulphone (PES). Bisphenol-S is actually of a "comparable potency" to BPA. Also, it is "less biodegradable, and more heat-stable and photo-resistant" than its predecessor BPA. Because of that, a SML of 0.05 mg kg^{-1} have been established for BPS [4].

. Regarding toxicity, abundant data for BPA are available, although less information has been published on the other compounds. BPF, BPE and BPB have shown moderate to slight acute toxicity and an estrogenic activity similar to BPA [15], whilst BPS exhibited higher estrogenic activity, probably due to its polarity and the presence of sulfur in the structure [17]. In relation to BADGEs the European Union (EU) has set specific migration limits (SML) of 9 mg kg^{-1} for the sum of BADGE and its hydrolyzed derivatives and 1 mg kg^{-1} for the sum of BADGE·HCl, BADGE·2HCl and BADGE·HCl·H_2O [18]. While the use and/or presence of BFDGE in the manufacture of materials and articles intended to be in contact with food is prohibited and in consequence its presence in food is undesirable. On the other hand, on the basis of the available experimental data, a Tolerable Daily Intake (TDI) can be established for BADGE and its hydrolysis products. Considering the No-Observed-Adverse-Effect-Level (NOAEL) of 15 mg kg^{-1} body weight/day derived from the oral chronic toxicity/carcinogenicity study in the rat with BADGE, and applying an uncertainty factor of 100, a TDI of 0.15 mg kg^{-1} body weight can be established for BADGE. As BADGE is rapidly and extensively metabolized in vivo into the corresponding mono- and bis-diol derivatives BADGE·H_2O and BADGE·$2H_2O$, the Panel included them in the TDI. For the BADGE chlorohydrins BADGE·2HCl, BADGE·HCl, BADGE·HCl·H_2O, in view of the lack of genotoxicity in vivo, the Panel considers that the current restriction of 1 mg kg^{-1} of food remains appropriate [19].

The levels of BPA found in the literature did not reach concentrations which to date have been associated with adverse health effects. However, given the possibility of ingesting multiple foods with elevated BPA levels and the multiple sources of exposure to BPA, it is important to continue monitoring the presence of BPA in food and drinks as well as to investigate other potential pathways of exposure.

1.2. UV ink photoinitiators

Photoinitiators have been widely used in packaging materials as a main component of UV inks. These compounds contain photo sensible groups that start the polymerization process to cure the ink by UV radiation. UV inks are used to print packaging materials such as multilayer laminates, rigid plastic, cardboard and paper. Although intermediate aluminum layers are commonly used to prevent the migration of ink components into food products, the unintentional transfer of printing ink components from the outer printed surface onto the food

contact surface can occur when the printed material is rolled on spools or stacked during storage.

The alert for food contamination by UV ink photoinitiators arose in Europe in November 2005, when the Italian Food Control Authority detected that the photoinitiator 2-isopropylthioxanthone (2-ITX) migrated into baby milk at concentrations ranging from 120 to 300 μg L^{-1}, resulting in the withdrawal from the market of more than 30 million liters of milk [20]. Since then, residues of other photoinitiators such as 2-ethylhexyl-4-dimethylaminobenzoate (EHDAB), 4,4'-bis(diethylamino)-benzophenone (DEAB), 4-benzoylbiphenyl (PBZ), 2,4-diethyl-9*H*-thioxanthen-9-one (DETX), 1-hydroxycyclohexyl phenyl ketone (HCPK), 2-hydroxy-2-methylpropiophenone (HMPP), 2,2-dimethoxy-2-phenylacetophenone (DMPA) and benzophenone (BP) have also been controlled in packaged food [21,22]. Among these compounds BP is the most used UV-ink photoinitiator in UV-cured printing inks, with a final content in the printing ink of 5-10%. This compound is also added to the plastic packaging as a UV blocker. Its use allows manufacturers to package the product in clear glass or plastic. Without it, opaque or dark packaging would be required. Moreover BP is also used in other applications such as in soaps and perfumes because prevents ultraviolet (UV) light from damaging scents and colors, and also in sunscreen. Regarding the migration of BP, this is possible because BP is a fairly small molecule that is not chemically bound to the printing ink that can then transfer from the outer, printed carton into foods. Furthermore, BP have been also detected in recycle cartoon board even if it had not been printed, presumable due to previous material contamination [23]. Although the widely use of this family of compounds, there are no specific EU controls for migration from inks and their associated coatings, but there is a Group Tolerable Daily Intake (Group TDI) for BP and 4-hydroxybenzophenone of 0.01 mg kg^{-1} body weight/day. A SML for benzophenone of 0.6 mg kg^{-1} has been established in specific legislation for food contact plastics [4].

1.3. Perfluorinated compounds

Human exposure to perfluorinated compounds (PFCs) is currently receiving considerable attention from scientists and policy makers owing to the ubiquity of these substances in human blood and tissue samples worldwide, but particularly in industrialized areas. These compounds have been employed in textiles and food packaging due to their

unique properties as repellents of water and oils. The most abundant PFC in human samples is perfluorooctane sulfonate (PFOS), which was widely used; however, other perfluoroalkyl sulfonates (PFASs) and carboxylic acids (PFACs) are also frequently detected [24]. They are toxic, highly persistent and bio-accumulative. For these reasons, the industrial production of PFOS and some of its derivatives was phased out by the major producer 3M in 2002, and the European Union has banned most uses from the summer of 2008 [25]. However, hundreds of related chemicals such as homologues with shorter of longer alkyl chain, PFOA and telomers, which potentially may degrade to PFCAs are not regulated yet. Polytetrafluoroethylene (PTFE) is a fluoropolymer also widely utilized in recent decades for example as cooking utilities and packaging. PTFE is mostly well known by the DuPont brand name Teflon. The particular physical and chemical properties of various fluorinated chemicals make it difficult to replace them in a number of industries (textile, paper, chemical, fire-fighting, foam industry).

Human exposure to PFCs, mainly PFOS and PFOA, is due to a variety of environmental and product-related sources, although food (drinking water included) could be the dominant intake pathway. PFCs can contaminate food by bioaccumulation of, especially, longer chain members in fish and shellfish (a result of oceans acting as contaminant sinks) or contact with packaging materials. Few systematic investigations on PFC levels in food are conducted to date mostly in North America and Western Europe [26,27], and some dietary intakes of PFCs are being reported according to average consumption data [28]. EFSA has completed a risk assessment on PFOS and PFOA in the food chain and established a TDI of 150 and 1500 ng kg^{-1} body weight/day, respectively [29]. EFSA has noted an urgent need for data on PFC levels in various food items in order to better understand contamination routes and monitor trend in exposure levels.

Consequently, the number of works dealing with the analysis of PFCs in food matrices is considerably increasing during the last years. However, in this review, we will focus only on the publications that are reporting analysis of these compounds in packaged foods, although so far it is hard to tell if food contamination is due only to environmental exposure or also to migration from packaging, although some evidences of the later will be presented later.

1.4. Phthalates

1,2-Benzenedicarboxylic acid esters, also known as phthalate acid esters (PAEs), are industrial chemicals used as plasticizers in a variety of plastic products (especially PVC) because of their ability to increase flexibility, workability and durability. Other applications of PAEs include its use in paints, personal care products, films, pharmaceutical coatings, adhesives, insect repellent and food packaging materials. The worldwide annual production of PAEs is approximately 6.0 million metric tons per year and, even if the number of possible different phthalates is enormous, only few of them are commercially significant and produced at the industrial scale. Di-2-ethylhexyl phthalate (DEHP), which accounts for approximately 50% of the global production, di-n-butyl phthalate (DBP), di-isodecyl phthalate (DIDP) and di-isononyl phthalate (DINP) are among the toxic and most commonly used phthalates.

The widespread use and application of these compounds has resulted in their ubiquitous presence in the environment, and in view of the fact that they are classified by most countries (including the EU and the U.S.) as carcinogenic, mutagenic and toxic to reproduction, human exposure to PAEs is currently receiving considerable attention in both political and scientific circles. Phthalates are considered to be potential endocrine disrupters [30] because of their ability to interfere with androgen signaling/production, with foetal animals being particularly sensitive. Furthermore, exposure to these chemicals in male adults may cause alterations in pulmonary function and sperm properties with reduced sperm counts and mobility. In humans, phthalates are rapidly metabolized to their respective monoesters, which can be used as useful biomarkers of a specific phthalate exposure. The exposure of humans to phthalates takes place via inhalation, oral and skin absorption routes. From 16 January 2007, the EU Directive 2005/84/EC [31] banned DEHP, DBP and BBPfor use in PVC and other plasticized materials in all toys and childcare article. Likewise, DINP, DIDP, and DNOP were banned for those toys and child care articles which can be placed in the mouth of children. However, most studies have concluded that diet is the major route of exposure, and that environmental contamination is one of the sources of these chemicals in food at various levels. Current tolerable daily intakes range from 0.01 to 0.5 mg kg^{-1} body weight/day for DBP and BBP, respectively [32]. Food contamination with PAEs can occur during processing, handling, transportation and by migration from packaging. Indeed, despite the fact that the use of these compounds in food-packaging materials has decreased in the last years, there are still many products used for food packaging that contains PAEs as plasticizers representing important potential sources of food contamination during storage. Phthalates can migrate into foods from food-packaging films, PVC gaskets in metallic caps for glass jars, printing inks, paper and board packaging, PVC coatings on cookware [33] and

the rate of migration rises with increasing temperature. PAEs may also enter food chains during processing due to the common PVC materials used in food production, e.g. plasticized PVC tubing used in commercially milking process or PVC gloves used in catering. Thus, the ubiquity of these compounds and the potential impacts of PAEs exposures on public health have prompted the European Commission to regulate the usage of some phthalates (butylbenzyl phthalate (BBP), DEHP, DBP, DINP and DIDP) in food plastics. Some SML values into food simulants have been fixed in European Regulation 10/2011, for instance 0.3 mg kg^{-1} for DBP, 30 mg kg^{-1} for BBP and 1.5 mg kg^{-1} for DEHP. For compounds for which there are not SML, a restriction value of 60 mg kg^{-1} of food product must be applied [4].The Japanese government also has regulated the use of certain phthalates, prohibiting DEHP in gloves and in food containers and packages.

2. Sample preparation

The analysis of packaging contaminants migrating into food represents a challenging task because of the complexity of matrices and the low concentration levels expected for these compounds in food samples. Thus, efficient preconcentration and clean-up procedures are usually needed. Typical analytical procedure steps within sample preparation include sampling/homogenization, extraction, clean-up and concentration prior to instrumental analysis.

The most significant reported LC-MS methods for the analysis of the food packaging contaminants discussed in this review including sample treatment procedures are summarized in Table 2. Solvent extraction (SE) is the technique most commonly used for the extraction of packaging contaminants from food samples. Selection of solvents is based on the physicochemical properties of target compounds (mainly polarity and hydrophobicity). Methanol, sodium hydroxide in methanol solutions, acetonitrile, and ethyl acetate are usually employed for the extraction of polar or relatively polar contaminants such as PFCs [26,27,34-37] and BPA-related compounds [38-40] in milk, yoghurt, canned fish and cereal baby food samples. Frequently, mixture of solvents such as dichloromethane with cyclohexane, acetonitrile-hexane, methanol-hexane-methyl *tert*-butyl ether, hexane-acetone and tetrahydrofuran-water are also employed, for instance some of them for the extraction of phthalates [41,42] and BPA [43].

Liquid–liquid extraction (LLE) using acetonitrile [44-49] or hexane [50,51] has been reported for the analysis of UV ink photoinitiators in liquid and fatty food samples. However,

because of the limited selectivity of solvent-based extraction, a solid phase extraction (SPE) clean-up step is usually required before instrumental analysis [44,46,48,51]. To reduce solvent consumption and improve selectivity, SPE for the clean-up of sample extracts is also routinely used as an alternative to LLE (Table 2).

Other extraction techniques such as pressurized liquid extraction (PLE) [38,50,52-54] have also been used for sample treatment of BPA-related compounds and UV ink photoinitiators. Nowadays, QuEChERS (*Quick, Easy, Cheap, Effective, Rugged and Safe*) methodology is a frequent and attractive alternative for sample preparation in food analysis. QuEChERS method is particularly popular for the determination of polar, middle polar and non-polar pesticide residues in food matrices [7] but today is also being used for sample treatment of several families of compounds and for instance its application for the analysis of UV ink photoinitators in milk, fruit juice and baby foods has recently been reported [45].

Some of the problems that occur in the analysis of food packaging contaminants might be related to the extraction and clean-up steps, due to the fact that some of these compounds (PFCs, phthalates, especially DEHP and DBP, BPA and BPA-related compounds) often cause blank problems when analyzed al low concentration. For instance, BPA analysis in liquid samples generally starts with the preservation and filtration of the samples, two important steps of the analysis that can be the origin of some false positives and negatives. Filtration is frequently used as preliminary step to eliminate particulate matter but some errors can occur when membrane filters are used. It has been described that important loses of BPA up to 90% due to the adsorption of BPA on the nylon filters occurs [55]. To prevent this adsorption and increase the recoveries the addition of an organic solvent such as methanol (10%) to the water sample is recommended. Other types of filters such as those of regenerated cellulose are not affected by this phenomenon but it has been observed that sometimes they can introduce some interference compound that make difficult the chromatographic analysis of BPA. To overcome this problem the resolving power of the LC-MS system must be increased. Ultra-centrifugation as an alternative to filtration has been recommended to prevent both adsorptions and/or the introduction of interference compounds.

Another important problem in the analysis of such contaminants is that these compounds are inherently ubiquitous in the laboratory environment, and they can be introduced in the sample during sample treatment. Source of phthalates in the laboratory environment was investigated by Fankhauser-Noti and Grob [56]. A 1.5mL autosampler vial was shown to contain 10 ng of DBP and 4ng of DEHP, whereas the concentration of DBP and DEHP in the laboratory air was calculated to be 3 $\mu g\ m^{-3}$ and 2.4 $\mu g\ m^{-3}$, respectively.

Blank contaminations for PFCs were shown to be associated with fluoropolymer materials used in the laboratory, solvent PTFE caps and nitrogen blow down. In the same way background contamination of BPA can easily occur at ng L^{-1} level mainly arising from SPE cartridges, glassware, plastic ware and other reagents and laboratory tools. Another significant contamination source when high sensitive analytical methods are used to determine these compounds at low concentration levels is the quality of solvents. For instance, DEHP and DBP concentrations of 100 μg L^{-1} were found in commercially available hexane [2] whereas Fernández-Sanjuan *et al.* [57] found traces of PFOS, PFOA, and PFNA in solvent blanks. To solve this problem a reversed-phase column was successfully used as mobile phase residue trap to adsorb possible PFCs present in the solvent, the LC tubing and the valves, whereas hexane with lower levels of phthalates (<2pg μL^{-1}) was obtained by dispersive solid extraction using active aluminum oxide. BPA has been found at concentrations ranging from 20 to 200 ng L^{-1} in ultra high quality (UHQ) water because of plastics and epoxi-resins used in the water purifying equipment [9]. An additional problem is the daily variability of this contamination. As an example, Figure 1 shows the chromatograms of ultra high quality water obtained from a Milli-Q system in the morning after 12h of standby (Figure 1A) and after the production of ~5 liters of water (Figure 1B). A decrease in the concentration level of BPA (from 200 ng L^{-1} to 25 ng L^{-1}) is observed as ultra high quality water is produced along the day. To overcome this problem and to use this kind of water as a solvent, BPA can be eliminated by filtering the water through membrane filters where it is strongly retained as commented before. For instance, Watabe *et al.* [58] proposed to use C18 filters to obtain BPA-free water to prepare standard solutions.

Since different steps of sample treatment are potentially BPA, PFCs and phthalates contamination sources, procedural blanks have to be conducted for each batch of samples to ensure the minimal contamination. However, in the analysis of these compounds there are multiple sources of contamination difficult to be under control that can affect the robustness of the method. As an example, Sørensen [42] reported the impossibilities to obtain a zero method blanks for the analysis of phthalates in milk and milk-based products (Figure 2) even if it was shown that the contamination level could be reduced to a low level (from 2 μg Kg^{-1} for BBP to 6 μg Kg^{-1} for DEHP) by using high quality solvents combined with glassware rinsing with methanol, ethyl acetate and hexane just before use. Substraction of blank responses can improve in some cases the quantitation accuracy as the calculated concentration will be more similar to the real concentration. Concerning BPA analysis, BPA-

free UHQ water must be used for the preparation of standards and mobile phases and also for the different steps of sample treatment such as the conditioning of SPE cartridges, SPE washing steps, and to reconstitute dryed extracts. SPE preconcentration and clean-up cartridges and all laboratory tools and material (glassware, PLE cells, etc…) must be thoroughly washed with BPA-free UHQ water and organic solvents. Special care must be taken when filtration of both samples and injection extracts is performed to prevent BPA adsorption.

3. Liquid chromatography-mass spectrometry

Liquid chromatography-mass spectrometry conditions for the analysis of food packaging contaminants addressed in this review are also summarized in Table 2. In this table the LC column, mobile phase composition, ionization source, analyzer and acquisition mode are indicated.

Liquid chromatography

For the analysis of food packaging contaminants migrating into food reversed-phase liquid chromatography (RP-LC) using C8 or C18 columns with particle sizes of 3.5 – 5 μm were generally used (Table 2). However, nowadays sub-2 μm particle size columns have been also reported to improve chromatographic resolution and decrease analysis time. As an example, Yonekubo *et al*. [59] developed a fast LC-MS/MS method for the analysis of BPA and BADGEs in canned food using a reversed-phase column with 1.7 μm particle size, and Jogsten *et al.* [27] reported the use of a UHPLC separation using a 1.7 μm particle-size column for the analysis of 14 perfluorinated compounds in about 40 packaged foods. On the other hand, other authors proposed the use of fused-core (porous shell) columns in order to obtain fast LC methods and good chromatographic resolution under standard LC backpressures (<400 bar). This is because these particles with a 0.5 μm radius shell of porous stationary phase surrounding a 1.7 μm non-porous core exhibit reduced diffusion mass transfer, which allows working at high mobile phase flow-rates and achieving similar efficiency and peak capacity than those of sub-2 μm porous particle columns. For instance, Gallart-Ayala *et al*. [39] developed a fast LC-MS/MS method for the analysis of BADGEs and BFDGEs in canned food obtaining good chromatographic separation and resolution of the BFDGEs isomers in less than 5 minutes. In this case in order to improve the sensibility of

the method a methanol:ammonium formate/formic acid mobile phase was proposed since when acetonitrile was used instead of methanol the sensitivity of some of the analyzed compounds decrease drastically. However, better chromatographic separation of BFDGEs isomers was achieved using acetonitrile. The authors proposed then the use of methanol to improve method sensitivity although acetonitrile can be used in a second analysis if positive samples are detected in order to identify each isomer. The low backpressure provided by the use of fused-core columns in the chromatographic separation allowed the direct hyphenation of a conventional on-line SPE system with UHPLC obtaining fast analytical methods. For instance, a fast on-line solid phase extraction LC-MS/MS method for the direct analysis of bisphenols (BPA, BPF, BPE, BPB and BPS) in canned soft-drinks with a good chromatographic separation in less than 5 minutes has been reported in the literature [55]. In this case the use of a direct analysis using a SPE on-line method prevents false positives in the analysis of bisphenols, since as it was commented above these compounds are inherently ubiquitous in the laboratory environment, and they can be introduced during sample treatment.

As previously commented C8 and C18 columns are generally used for the chromatographic separation of food packaging contaminants discussed in this review. However, in some cases an orthogonal selectivity is demanded in order to improve the chromatographic separation. For instance, a C5 column has been described for the analysis of phthalate compounds in milk products and infant formulas [42], however partial co-elution between some of the analyzed compounds, DBP/BBP and DEHP/DINP405/DINP419 have been observed, while Mortensen *et al*. [41] used a Betasil Phenyl column for the analysis of phthalate monoesters in the same kind of matrices obtaining a good chromatographic separation. Gallart-Ayala *et al*. [44,45,60] proposed the use of a pentafluorophenyl propyl (PFPP) column for the analysis of photoinitiators in packaged food. This PFPP column allowed the chromatographic separation of the two ITX isomers (2- and 4-ITX) in less than 5 min [44], separation that could only be achieved until then by a zirconium column and with a very long analysis time (>30 min) [61]. The separation and simultaneous analysis of eleven UV ink photoinitiators in less than 6 min was also achieved by working at sub-ambient temperature (5ºC) with a PFPP column [45]. On the other hand, Jogsten *et al*. [27] used a Fluorosep RP C8 column for the analysis of PFCs in packaged spinaches since the presence of monomerically bonded perfluorooctyl groups in the stationary phase enhance the selectivity for the chromatographic separation of halogenated compounds. Moreover, as it has been commented above, in the analysis of this family of compounds a reversed phase

trapping column between the LC pump and the injection valve is generally used to retain the possible PFCs present in the solvent, the LC tubing and the valves reducing system contamination [57].

Mass spectrometry

Regarding ionization of food packaging contaminants, electrospray ionization (ESI) is the most commonly used technique. Positive ionization mode is usually employed to analyze BADGEs and BFDGEs, UV ink photoinitiators, and phthalate diesters, while negative ionization gives the best sensitivity for the detection of phthalate monoester metabolites, BPA, other bisphenols such as BPE, BPB, BPF and BPS, and PFCs (Table 2). In general, negative-ESI and positive-ESI are dominated by the deprotonated molecule, $[M-H]^-$, or the protonated molecule, $[M+H]^+$, respectively, and no further fragmentation is usually observed. However, in-source fragmentation can occasionally be observed such as in the case of some UV ink photoinitiators (HMPP, HCPK, DMPA, DEAB)[45]. This fragmentation was especially important for DMPA whose MS spectrum showed the in-source loss of a methoxy group as the base peak, yielding an ion at *m/z* 225 $[M-CH_3O]^+$ which was selected as precursor ion for tandem mass spectrometry experiments. In some cases, the formation of adduct ions with components of the mobile phase was also observed. BADGEs and BFDGEs showed a high tendency to form $[M+Na]^+$, $[M+K]^+$, $[M+NH_4]^+$ and $[M+ACN]^+$ clusters ions. However, some of these cluster ions such as $[M+Na]^+$ are very stable and no further fragmentation in tandem mass spectrometry was obtained, but on the other hand, efficient fragmentation occurred for ammonium adducts with a stable signal under tandem mass spectrometry [39,62]. In these cases to enable the formation of ammonium adducts and ensure signal reproducibility, formic acid/ammonium formate buffer are generally used as an additive in the mobile phase in positive ESI for the analysis of these compounds.

Ion suppression is one of the major problems in LC-MS with ESI sources. Ion suppression occurs due the presence of buffer additives, sample matrix components and poor chromatographic separation. Important ion suppression had been reported in the analysis of BPA and other bisphenols (BPF, BPB, BPE and BPS) caused by matrix effects since the co-elution of matrix components can interfere with the signal of the analytes [63]. In order to solve these problems different strategies could be carried out, such as improving sample treatment procedure and/or resolution of the chromatographic separation (i.e., using smaller particle size columns) or modifying the gradient elution as can be seen in Figure 3. In this

554 case, the gradient elution was modified by reducing the amount of organic solvent and the
555 gradient slope, which increased the retention of the studied analytes and forced them to elute
556 into a cleaner chromatographic area, thus minimizing the co-elution with matrix components
557 in the eluting front.

558 Tandem mass spectrometry (MS/MS) is generally used as acquisition mode for the
559 analysis of the food packaging contaminants addressed in this review (Table 2). Triple
560 quadrupole (QqQ) mass analyzers are the most popular instruments due to their higher
561 sensitivity and selectivity when operated in selected reaction monitoring (SRM) mode. For
562 the confirmation of the identity of the analytes the EU directive 2002/657/EC established that
563 two SRM transitions must be monitored to comply with a system of required identification
564 points [64]. In addition, the deviation of the relative intensity of the recorded transitions must
565 not exceed certain percentage of that observed with reference standards, and the retention
566 time must not deviate more than 2.5%. However, the application of these criteria did not
567 completely eradicate false positives and its application might even lead to the possibility of
568 reporting false negatives. The occurrence of a false positive in LC-MS/MS using a QqQ
569 analyzer implies the presence of interfering compounds that co-eluted with the analyte, and
570 have two transitions with a similar ion ratio [65,66]. But more problematic than false
571 positives is the possibility of reporting false negatives because the identification of relevant
572 compounds would be ignored. In this case when two transitions are monitored a false
573 negative might be reported if one of the transitions is affected by an interferent compound. In
574 some cases these problems can be solved by monitoring more than two selective transitions
575 or by using alternative confirmatory strategies. For instance, Llorca *et al.* [34] reported the
576 use of a quadrupole-linear ion trap (QqLIT) analyzer for the quantification of some
577 perfluorinated compounds by monitoring two SRM transitions for each compound. Moreover,
578 in order to achieve better confirmation the SRM mode was combined with Enhanced Product
579 Ion Scan (EPI) and MS^3 acquisition modes. Operating with the EPI mode, the first
580 quadrupole (Q1) filters the desired precursor ions which are fragmented in the Q2 trapping
581 the fragment ions in the LIT. As an example, Figure 4 shows the LC-MS/MS, MS/MS using
582 EPI mode and MS^3 spectra of PFOS and PFOA in real breast milk sample and the main
583 fragmentation pathways of these compounds. In other cases, however, the use of high
584 resolution mass spectrometry (HRMS) is mandatory. For instance, during the analysis of
585 benzophenone in packaged foods almost 50% of samples were reported as negative when
586 analyzed by LC-MS/MS using a triple quadrupole instrument because ion-ratios variations
587 higher than 20% were obtained due to an interferent signal in the confirmation transition. In

this case the studied compound only showed two product ions not being possible to monitor a third transition for confirmation [60]. For this reason an LC-HRMS method using an Orbitrap mass analyzer operating at a mass resolving power of 50,000 FWHM was then proposed for the analysis of BP in food packaged samples. Moreover, in this work, the full scan HRMS experiment was operated simultaneously with the "all ion fragmentation" (AIF) mode in order to obtain an unequivocal identification of the target analyte obtaining its product ion scan spectrum at high resolution mass spectrometry.

Finally, a somewhat different analytical approach has been given recently by Self *et al.* [67]. Their study reported an analytical method to rapidly qualitatively analyze seven phthalates compounds of interest in a wide variety of beverage/food and nutraceutical samples using direct analysis in real time (DART) ionization in positive mode coupled to an Orbitrap mass spectrometer. The method was shown to be capable of detecting selected PAEs, including BBP, DBP, DEHP, DINP, at level of 0.5-1 μg L^{-1} and 50 μg L^{-1} in beverage/food and nutraceutical samples, respectively. This has the potential for greatly facilitating qualitative screening food samples able to identify those who require further traditional chromatography methodology both for confirmation and for quantitation purposes.

4. Food packaging migration studies

In the analysis of food packaging contaminants, migration studies using food simulants are necessary in order to characterize new packaging materials and the amount of non-desirable contaminants than can migrate into food. EU Directives 82/711/EC [5] and 85/572/EEC [6] describe the migration tests and specify the use of food simulants depending on the type of food. Relating to FCMs, four liquid simulants are described: distilled water for aqueous foods with a pH above 4.5; acetic acid at 3% in distilled water for acidic aqueous food with pH below 4.5; ethanol at 15% for alcoholic food and oil for fatty food. Considering that the packaging, the storage temperature and the contact time between food packaging and food are the most important parameters for the migration of contaminants into food, the best migration test conditions are 40 ^{0}C for 10 days (extreme conditions or EC) concerning storage at room temperature for indefinite time [68]. Testing migration conditions are also described in EU Regulation 10/2011 [4] that is replacing old directives. For plastic materials and articles not yet in contact with food the simulants listed are: ethanol 10% (v/v) (simulant A), acetic acid 3% (v/v) (simulant B), ethanol 20% (v/v) (simulant C), ethanol 50% (v/v)

(simulant D1), vegetable oil (stimulant D2) and poly(2,6-diphenyl-p-phenylene oxide), particle size 60-80 mesh, pore size 200 nm (simulant E). Food simulants A, B and C have to be used for foods that have a hydrophilic character, food simulants D1 and D2 are assigned for foods that have a lipophilic character and food simulant E is assigned for testing specific migration into dry foods. However, the application of this Plastics Implementing Measure (PIM) is characterized by a specific phased implementation period and, in fact, these rules should be applied from 1 January 2016. Until then, rules described in earlier directives (Directives 82/711/EEC and 85/572/EEC) can also be applied. For instance, Fasano *et al.* [69] recently described migration studies of phthalates, alkylphenols, bisphenol A and di(2-ethylhexyl)adipate from food packaging using the food simulants (distilled water, acetic acid at 3% and ethanol at 15%) described in the earlier directives. The levels of these compounds in common FCMs (tuna cans, marmalade caps, yogurt packaging, polystyrene dish, teat, bags, films, baby's bottle, aseptic plastic laminate paperboard carton and plastic wine tops) were evaluated by migration tests. Additionally, to evaluate the potential migration of plasticizers and additives from plastic wine tops, two extraction methods were employed: incubation for 10 days at 40 ^{0}C and ultrasound extraction. All samples analyzed showed contaminant migration lower than SML and overall migration limits (OML) established in EU legislation. Moreover, the extraction carried out for 10 days at 40 ^{0}C showed to give better results than ultrasound extraction in order to detect all analyzed compounds.

Regarding BPA, many migration studies can be found in the literature during the last years. Of special interest are those performed from plastic baby bottles and baby bottle liners [69-73]. For instance, Kubwako *et al.* [70] studied the migration of BPA into water (used as food simulant) from polycarbonate baby bottles, non-polycarbonate baby bottles, baby bottle liners and glass baby bottles. They observed that residual BPA leaching from polycarbonate bottles increased with temperature and incubation time, observing a BPA migration of 0.11 μg L^{-1} into water incubated for 8 h. In contrast, only trace-levels of BPA were observed from non-polycarbonate plastic baby bottles and baby bottle liners, allowing to propose them, together with glass baby bottles, as good alternatives to the polycarbonate ones. Similar results were reported by Nam *et al.* [71] when they studied the migration of BPA from polycarbonate baby bottles after repeated uses, up to 100 times and at different temperatures. Again, BPA migration increased considerably at temperatures higher than 80 ^{o}C. The pattern of BPA level showed three steps; lag effect region (0.13–1.11 μg L^{-1} BPA), steady region (1.11 μg L^{-1} BPA) and aging region (1.11–3.08 μg L^{-1} BPA). When baby bottle was not washed, BPA level was 0.24 μg L^{-1}. However, after the procedure (extraction) was executed

656 once, the BPA level of bottle decreased to 0.13 μg L^{-1} (lag effect region). It was considered
657 that BPA remained on the surface of the bottle during the manufacturing process. BPA
658 migration level was increased up to 1.1 μg L^{-1} after the procedure was repeated 10 times, then
659 maintained at 1.1 μg L^{-1} level at up to 60 repetitions (steady region). BPA level rapidly
660 increased to 3.08 μg L^{-1} when the procedure was repeated 100 times (aging region). This was
661 attributed to the increase of the average inter-chain spacing of polycarbonate with the
662 repeated used of the bottle (from 0.499 nm in brand-new bottles to 0.511 nm in bottles used
663 more than 100 times), allowing a higher diffusion of BPA from the plastic material.
664 Moreover Guart *et al.* [12] investigated the potential migration of plasticizers and additives
665 from several plastic containers including polyethylene terephthalate (PET), polycarbonate
666 (PC), two types of high density polyethylene (HDPE), low density polyethylene (LDPE) and
667 polystyrene (PS) plastics.
668 Migration studies into food simulants have also been carried out with some UV ink
669 photoinitiators. As an example, Sanches-Silva *et al.* studied the migration of six UV ink
670 photoinitiators (including BP, EHDAB and ITX) into several food simulants (water, 3%
671 acetic acid *w/v* aqueous solution, and 10, 20, 30, 60 and 95% ethanol *v/v* aqueaous solution)
672 [74]. The migration levels of the six UV ink photoinitiators into the different food simulants
673 were compared after a 30 day contact period and a relationship between R (ratio between log
674 $K_{o/w}$ and photoinitiator molecular weight, M_w) and the total migration was found for
675 photoinitiators with a log $K_{o/w} < 5$. For ITX and EHDAB (with log $K_{o/w} > 5$), migration values
676 varied significantly among different simulants, being always higher for ITX (which has the
677 lower M_w).
678 Migration studies of non-intentionally added substances (NIAS) from plastics and
679 adhesives is one of the most studied topics in this field. Very recently, Felix *et al.* [75]
680 described the analytical tools for the identification of NIAS coming from polyurethane
681 adhesives in multilayer packaging materials and their migration into food simulants. In this
682 work Tenax®, used as solid adsorbent, and isooctane were used as food simulants and the
683 migrants were analyzed by GC-MS. More than 63 volatile and semivolatile compounds
684 (including some phthalates such as DBP) considered as potential migrants were detected
685 either in the adhesives or in the films. Cacho *et al.* proposed a method for the determination
686 of alkylphenols and phthalate esters in vegetables by stir bar sorptive extraction coupled to
687 GC-MS, and some migration studies from their packages were also performed [76]. DEP,
688 DBP and DEHP were found to have migrated from the bags to the simulants used and the

same compounds were then quantified in several vegetables (lettuce, salad, arugula, parsley and chard) at concentration levels in the 8-51 ng g^{-1} range.

Finally, it should be pointed out that GC-MS continues to be the technique of choice when performing food packaging migration studies.

5. Levels of food packaging contaminants in food

Several studies about the occurrence of packaging contaminants in food as well as their dietary intake have been reported [33,77]. However, in many of these studies one of the main problems is to correctly assess the source of contamination, which is especially difficult in the case of PFCs. Sensitive enough methods are required for the analysis of PFCs in food samples, especially when dealing with packaging contamination as low concentrations can be expected to be found being a handicap in some studies trying to correlate packaging with PFC food contamination. Tittlemier *et al.* analyzed food composites that were available in both polypropylene bottles and glass jars in order to examine if the type of sample container used for storage affected in the PFC food analysis [26]. Only six food composites were available in both kinds of containers but only in one of them (freshwater fish) concentrations were higher than the reported LOD or LOQ; PFOS was measured at 1.5 and 1.3 ng g^{-1} in the composite stored in polypropylene and glass containers, respectively. From the correlation of results obtained by the authors from samples stored in the different containers, and the lack of PFCs detected in composites stored in glass containers with PTFE lid liners, the authors suggested that PFOS was not adsorbing to the glass and that the PTFE lid liner was not a source of contamination. In contrast, PFC contamination from packaging was clearly observed in other studies. For instance, Wang *et al*. found no significant differences in the levels of PFCs when analyzing milk from various company brands [35]. No differences were either observed regarding the kind of milk (such as whole or skimmed milk), the tastes (such as chocolate and fruits) in both milk and yoghurt samples. However, significant differences among three kinds of packaging of milk in the concentration of PFHpA, PFNA and total PFC were found. Figure 5 shows the PFC levels in milk for three different packaging: Bailey (polyethylene; shelf-life: 30 days), Tetra Fino Aseptic (laminate of paper, polyethylene and aluminium foil; shelf-life: 30 days), and Tetra Brik Aseptic (laminate of paper, polyethylene and aluminum foil; shelf-life: 6-8 months). Among these packaging, the levels of PFCs in milk packaged with Bailey were notable higher than the levels with the other two packaging materials. The total PFC concentration in some samples exceeded 600 pg g^{-1}. PFC levels in

723 milk with Tetra Fino Aseptic were similar to the levels with Tetra Brik Aseptic, being the
724 total PFC concentrations in all samples with these two packaging lower than 300 pg g^{-1}.
725 Up to now there are some other studies suggesting that food packaging might serve as
726 a source of PFCs, used as repellents of water and grease, in food. For instance, Begley *et al.*
727 [78] demonstrated that perfluorochemicals would migrate into food simulants from food-
728 contact paper. As an example, PFOA migrated from a microwave popcorn bag into oil at a
729 concentration as high as 300 ng g^{-1}. However, in another study reported by Bradley *et al.* [79]
730 it was noted that the coating materials of cookware products containing
731 polytetrafluoroethylene (PFTE) were not considered as significant sources of PFCs, because
732 the levels of PFCs were too low to be detected. Jogsten *et al*. [27] also investigated the
733 influence of food packaging on the concentration of PFCs and from their results it was
734 uncertain whether some food packaging could contribute to an exposure to PFCs. Therefore,
735 further research needs to be carried out to verify which types of food packaging are correlated
736 with the concentrations of PFCs in food, as some evidences about packaging being one of
737 origins of food contamination with PFCs are appearing.
738 Another consideration to take into account is that once the packaging contaminant
739 migrated into food its concentration can change due to a number of factors. For instance,
740 recently Coulier *et al* .[40], showed that BADGE levels decay during food storage and new
741 reaction products are formed by the reaction with food ingredients such as amino acids and
742 sugars observing the formation of BADGE-glucose, BADGE-cysteine, BADGE-methyonine
743 and BADGE-lysine. Unlike other chemical contaminants, information on phthalates in food
744 is very limited, although their determination in foods began more than 3 decades ago,
745 probably due to the challenges in the methods or the high blank levels of phthalates caused by
746 the contamination of laboratory environments as previously commented.
747 Concentration levels reported in the literature of the packaging contaminants
748 migrating into food addressed in this review are summarized in Table 3. As can be seen, the
749 number of works dealing with the analysis of BPA, BADGES and related compounds as well
750 as UV Ink photoinitiators in food (taking into account only data related to contamination
751 from packaging) is considerably higher than those of PFCs and phthalates. In general,
752 concentrations of these contaminants are at the low ng g^{-1} or even pg g^{-1} level, although in
753 some cases much higher concentrations can be found. For instance, concentrations between 1
754 and 11.8 µg g^{-1} for some BADGEs or BFDGEs in canned fish, meat and vegetables
755 [43,59,80], or between 1.2 and 14.7 µg g^{-1} for some phthalates such as DEP and BBP in fruit
756 jellies [81] are reported.

About BPA, BADGEs, BFDGEs and related compounds their concentration is in general higher in canned fruits, vegetables, fish and meat, and lower concentrations are usually reported in baby food, and liquid samples (milk and milk-based products, soft drinks and sauces). But all of them have been reported at a certain concentration level in several foods. In contrast, although the number of UV Ink photoinitiators being analyzed in food is increasing, only few of them are usually found in food matrices, being ITX and BP those reported at higher concentrations. For instance, ITX have been found at concentration levels up to 439 ng g^{-1} in milk and milk-based products. Regarding PFCs levels in food Hráková *et al.* [36] reported PFOS concentrations up to 13 µg kg^{-1} in canned fish although probably the major origin of this PFOS contamination is due to the environment. Relatively high concentrations of PFCs were found in fast food (1-3.6 µg Kg^{-1}) [26] or in milk infant formulas and baby food cereals (0.04-1.3 µg kg^{-1}) [34]. About what concerns phthalates, although the number of manuscripts dealing with their analysis in food is reduced, it seems that their concentrations levels must be taken into account, being the packaging contaminants migrating into food at the highest concentrations (Table 3).

Conclusions

The huge variety of materials employed in packaging technology in order to maintain foodstuffs quality when the product arrives to the consumer has considerably increased the number of possible contaminants migrating into food. Some of the most relevant food packaging contaminant families such as BPA, BADGEs and related compounds, UV ink photoinitiators, perfluorinated compounds, and phthalates, have been addressed in this review.

The most recent approaches in the liquid chromatography-mass spectrometry analysis of food packaging contaminants have been discussed. Different aspects concerning all the steps of the analysis (sample treatment, chromatographic separation, mass spectrometry and quantitation and confirmation strategies) have been addressed by discussing recent LC-MS applications, as well as the problems arising from sources of contamination and blanks.

Solvent extraction and SPE are the techniques most commonly used for the extraction and preconcentration of packaging contaminants from food samples, but new sample treatment methods such as QuEChERS are appearing as a fast and simple alternative, and although few applications are described in the literature concerning food packaging contaminants it is a good alternative to explore in the future. Moreover, some of the problems

that occur in the analysis of food packaging contaminants might be related to the extraction and clean-up steps, due to the fact that many of these compounds (PFCs, phthalates, especially DEHP and DBP, BPA and BPA-related compounds) often cause blank problems when analyzed al low concentration. For instance, important loses of BPA after filtration are described which can be reduced by the addition of methanol before filtration. Another important problem in the analysis of such contaminants is that these compounds are inherently ubiquitous in the laboratory environment, and they can be introduced in the sample during sample treatment, together with the co-extraction of other interferences. Some examples discussing these problems and how to minimize them have been described in this review. In summary, sample treatment during food packaging contaminants analysis must be carried out very carefully and the control of method blanks is mandatory due to the important number of contamination sources. In order to prevent most of these problems, minimizing sample manipulation will be desirable and for this purpose on-line preconcentration, as well the use of direct analysis techniques such as DART and desorption electrospray ionization (DESI) procedures will be one of the recommended alternatives in the near future.

UHPLC technology using sub 2-µm columns and fused-core (porous shell) columns are the most convenient approach used today to achieve reliable and fast LC separations in the analysis of food packaging contaminants. Reversed-phase separations continues to be the chromatographic mode of choice for the analysis of many of these compounds, but in some cases other column selectivities are demanded in order to improve chromatographic separation, and some examples have been addressed in this review. Very relevant is the use of fluorinated stationary phases in the analysis of UV Ink photoinitiators. The use of PFPP columns allowed the separation even of both ITX isomers in a reduced analysis time.

Moreover the low backpressure provided by the use of fused-core columns in the chromatographic separation allowed the direct hyphenation of a conventional on-line SPE system with UHPLC obtaining fast analytical methods. But instrumentation can also be an important source of contamination when analyzing food packaging contaminants such as in the case of PFCs or phthalates. In this case a reversed phase trapping column is set between the LC pump and the injection valve to retain the possible PFCs present in the solvent, the LC tubing and the valves, and thus reducing system contamination.

ESI is the ionization source of choice in the analysis of food packaging contaminants. Several approaches such as the modification of gradient conditions to force the analytes to elute in a cleaner chromatographic area to solve or to minimize matrix effects and ion suppression characteristic of ESI sources have been addressed in this review. The use

atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) may be an alternative solution to minimize the matrix effects observed with ESI. On the other hand, the combination of the information provided by all API sources could be the key to detect new food packaging contaminants. Moreover, although triple quadrupole mass spectrometry monitoring two SRM transitions continues to be the method of choice in the analysis of food packaging contaminants, the use of different mass spectrometry acquisition strategies and high resolution mass spectrometry (HRMS) is one of the best alternatives in order to prevent false positives or even false negatives, and some relevant examples concerning the analysis of food packaging contaminants have been presented.

Finally, food packaging migration studies and reported levels of these contaminants in food have been discussed. Due to the huge variety of materials used for food packaging, migration studies using a variety of food simulants depending of the food type have been established in order to control the migration of non-desirable compounds from these food contact materials, and some examples have been presented. Regarding food packaging contaminant levels in food, although in general concentrations are in the range of low ng g^{-1} or even pg g^{-1}, higher concentrations for some of these contaminants are described, for instance levels up to 14.7 µg g^{-1} for some phthalates. But one of the main problems is not the concentration level but the huge variety of contaminants migrating into food that can be found, which is making the monitoring of these contaminants in food one of the main concerns in food quality and safety.

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Figure Captions

Figure 1. Chromatograms of BPA in ultra high quality water obtained from a Milli-Q system (a) in the morning after 12 h of standby and (b) after the production of ~5 liters of water.

Figure 2. LC/ESI-MS/MS chromatograms of a method blank during analysis of phthalates. The measured concentrations of phthalates were 5.1 μg kg^{-1} (DEHP), 2.4 μg kg^{-1} (DBP), 0.5 μg kg^{-1} (BBP), 2.9 μg kg^{-1} (DINP) and 3.1 μg kg^{-1} (DIDP). Reproduced from Ref. [42], with permission of John Wiley & Sons, Ltd.

Figure 3. On-line SPE LC-MS/MS and LC-UV at 228 nm chromatograms of a glass cola sample spiked at 10 μg L^{-1}. A) ESI at ambient temperature, gradient elution 0 min, 50:50 MeOH:water; from 0 to 1 min, linear gradient up to 100% MeOH and B) H-ESI at 300 ^{o}C, gradient elution 0 min 15% MeOH; from 0 to 3 min a linear gradient elution up to 80% MeOH, isocratic step (3.5 min). Compound identification: 1, BPS; 2, BPF; 3, BPE; 4, BPA and 5, BPB. Reproduced from Ref. [63], with permission of Elsevier.

Figure 4. Example of TIC chromatogram, MS/MS spectra using EPI mode and MS^3 spectra of PFOS and PFOA obtained for a breast milk sample. Reproduced from ref. [34], with permission of Elsevier.

Figure 5. Box plot of concentrations of PFHpA, PFOA, PFOS, PFNA, PFDA and total PFC in milk on the basis of different packaging. The data indicate significant differences ($P<0.001$) among three kinds of packaging of milk in the concentration of total PFCs. Reproduced from Ref. [35], with permission of Springer-Verlag.

Table 2. Analysis of food packaging contaminants in food samples by LC-MS/MS

Compound	Food product	LC conditions	Extraction	Clean-up	Recoveries	Ionization source	Analyzer	Quantiation	Confirmation	LODs	Ref.
BPA and related compounds											
BPA	Powdered milk and infant formulas	C18 (250x4.6 mm, 5 µm) MeOH:water	PLE Ethyl acetate	C18 matrix dispersant	92%	ESI(-)	QqQ	SRM (1 transition)	-	5 µgkg^{-1}	[38]
BPA, BPF, BPE, BPB and BPS	Soft-drinks	C18 (50x2.1 mm, 2.7 µm) MeOH:water	On-line SPE	-	-	H-ESI(-)	QqQ	SRM (1 transitions)	SRM (1 transition)	5 – 50 ng kg^{-1}	[63]
BADGEs and BFDGEs	Canned food and soft-drinks	C18 (150x2.1 mm, 2.7 µm) MeOH:Ammonium formate buffer 25 mM, pH 3.75	Liquid-Liquid extraction: Ethyl acetate SPE: OASIS HLB	-	60 – 95%	H-ESI(+)	QqQ	SRM (1 transitions)	SRM (1 transition)	0.13 – 4.0 µgkg^{-1}	[39]
NOGE-related and BADGE-related compounds	Canned food(fish, meat, fruit and congee)	C18 (100x2.1. mm, 1.7 µm) ACN:0.2% formic acid	Hexane:acetone (5:3).	ACN extraction and SPE PS-DVB	87 - 109%	ESI(+)	Q-Trap	SRM (1 transition)	SRM (1 transition)	10 – 197 ng kg^{-1}	[43]
BPA	Drinking water	DB Biphenylic (50x2.1 mm, 1.9 µm) ACN:water	Passive sample (POCIS), IsoluteENV+ Ambersorb 1500 Carbon	-	-	ESI(-)	QqQ Q-TOF	SRM (1 transition)	SRM (1 transition) and Accurate mass measurements	200 ng L^{-1}	[82]
BPA	Bottle water	C18 (50x2.1 mm, 2.2 µm) MeOH:water	Water	-	99%	APCI(-)	Q-Trap	SRM (1 transition)	SRM (1 transition)	40 ng L^{-1}	[83]
BADGE and reaction products	Canned food(tuna, apple puree) and Beer	C18 (150x2.1 mm, 3.5 µm) ACN:water both with ammonium acetate buffer (5 mM, pH 5)	ACN	-	-	ESI(+)	LTQ-FT-MS	Full scan	Accurate mass	-	[40]
BPA	Eggs and milk	C18 (150x2.1 mm, 3.5 µm) MeOH:0.1% ammonia	Dispersive-SPE (C18)	SPE (amino-propyl)	79 – 93%	ESI(-)	QqQ	SRM (1 transition)	-	100 ng kg^{-1}	[84]
BPA	Meat	C18 (150x2.1 mm, 3.5 µm) MeOH:0.1% ammonia	PLE Acetone	SPE (amino-propyl)	91 – 100%	ESI(-)	QqQ	SRM (1 transition)	-	300 ng kg^{-1}	[52]
BPA and BPF	Honey	C18 (250x2.0 mm, 5 µm) ACN:water	Water and HCl	SPE-Polysteryrenedininylbe	94 - 116%	ESI(-)	Q	SIM (1 Precursor ion)	-	500 – 2000 ng kg^{-1}	[85]

				nzene							
BPA, BADGEs	Canned food(fish, vegetables, sauces and others)	C18 (50x2.1 mm, 1.7 µm) ACN:water	ACN	SPE OASIS HLB	69 – 98%	ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	390 – 690 ng kg^{-1}	[59]
BPA	Milk	C18 (250x4 mm, 5 µm) MeOH:water	Water	SPE C18	83 – 106%	ESI(-)	Q	SIM (1 Precursor ion)	-	1700 ng kg^{-1}	[86]
BADGEs	Canned food (fish, meat and baby food)	C18 (100x2.1 mm, 3.5 µm) ACN:water	PLE Hexane:acetone	SPE C18+Aminopropyl bonded silica (NH_2)	85 – 96%	APCI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	800 – 1750 ng kg^{-1}	[53]
BPA	Beverages (water, puree, soda)	C18 (150x2.1 mm, 3.5 µm) MeOH:0.1% ammonia	OASIS HLB	SPE GCD	82 – 97%	ESI(-)	QqQ	SRM (1 transition)	SRM (2 transition)	10 – 600 ng kg^{-1}	[87]
BPA	Canned food (soup, meat, vegetables, fish, pasta)	C18 (150x2.1 mm, 3 µm) C8 (150x2.1 mm, 3 µm) MeOH:water	ACN	-	94 – 110%	ESI(-)	Q-Trap	SRM (1 transition)	SRM (1 transition)	2 ng g^{-1}	[88]
UV Ink Photoinitiators											
11 photoinitiators	Baby food, Fruit juice, gazpacho, water, wine	PFPP (150x2.1 mm, 3 µm) ACN:ammonium formate buffer	ACN	QuEChERS	81-98%	ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	0.07-220 µg kg^{-1}	[45]
2-ITX and 4-ITX	Baby food, milk, fruit juice, soy milk, vegetable and broth.	PFPP (150x2.1 mm, 3 µm) ACN:ammonium formate buffer	ACN	SPE (OASIS HLB)	85%	ESI(+)	QqQ	H-SRM (1 transition)	H-SRM (1 transition)	2-13 ng kg^{-1}	[44]
ITX, EHDAB, EDAB, BP, HCPK	Fruitjuice, milk, wine	C18 (250x4.6 mm, 5 µm) MeOH:water	n-Hexane	SPE (DSC-Si)	42-100%	ESI(+)	Ion trap	SRM (1 transition)	_	2-100 µg L^{-1}	[51]
ITX	Fruit juice	C18 (150x4.6 mm, 5 µm) MeOH:water	PLE n-hexane:acetone (1:1)	-		ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	0.01 µgL^{-1}	[50]
ITX, BP, HCPK, EHDAB, TPO, Irgacure 369, Irgacure 907	Milk	C18 (150x2.0 mm, 3 µm) MeOH:0.1%HCOOH	ACN	SPE (OASIS HLB)	45-84%	ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	0.05-2.5 µg kg^{-1}	[46]

2-ITX, EHDAB	Milk	C18 (50x2.1mm, 3.5 µm) MeOH:ammonium formate buffer	PLE Ethyl acetate	-	56-89%	ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	ITX: 0.1 µg L^{-1} EHDAB: 40 µg L^{-1}	[54]
HCPK, BP, ITX, EHDAB	Beverages	C18 (150x4.0mm, 5 µm) ACN:water	ACN	-	84-93%	-	-	-	-	20 to 30 µg L^{-1}	[47]
ITX	Milk, fruit jice, tea, yoghurt and drinks	C18 (100x2.1 mm, 5 µm) MeOH:0.1% HCOOH	ACN:water containing Carrez I and II	SPE (OASIS HLB)	97-103%	ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	0.15 µg kg^{-1}	[48]
ITX	Milk, yoghurt and pudding	C18 (100x2.0 mm, 5 µm) MeOH: ammonium formate buffer	ACN	-	50-105%	ESI(+)	Q	SIM	In-source fragmentation	6.2 µg kg^{-1}	[49]
Perfluorinated compounds											
PFOA, PFOS, i,p-PFNA, PFNA, PFDA, PFDS	Milk infant formulas Cereals baby food	C18 LiChroCART Purosphere Star-18e (125x4mm, 5µm) MeOH/ammonium acetate solution	10 mMNaOH in MeOH	SPE: C18 Sep-Pack	61-106%	ESI(-)	QqQ	SRM (1 transition)	SRM (1-2 transitions) MS^3	5-167 ng kg^{-1}	[34]
PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTA, FOEA, FOUEA, PFHxS, PFOS	Milk Milk powder Yoghurt	Dionex Acclaim 120 C18 (4.6x150mm, 5µm) MeOH/ammonium acetate solution	MeOH or MeOH + acidic MeOH	SPE: Oasis WAX	80-118%	ESI(-)	QqQ	SRM (1 transition)	--	2-31 ng kg^{-1}	[35]
PFOA PFOS FOSA	Canned fish	Atlantis T3 (2.1x100mm, 3µm) MeOH/ammonium acetate solution	MeOH	Activated charcoal	104-116%	ESI(-)	QqQ	SRM (1 transitions)	SRM (1 transition)	0.05-0.1 µg kg^{-1}	[36]
PFBA, PFBS, PFPeA, PFHxA, PFHxS, PFHpA, PFOA, PFOS, PFNA, PFDA, PFUdA, PFDoA, PFTrA, PFTeA	Packaged spinaches	Fluorosep RP C8 (2.1x150mm, 5µm) MeOH/ammonium formate solution	THF:water (75:25 v/v)	SPE: Oasis WAX and EnviCarb	70-104%	ESI(-)	QqQ	SRM (1 transition)	SRM (1 transition)	1-30 ng kg^{-1}	[89]
PFBuS, PFHxS, PFOS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA	40 Packaged foods (pork liver, duck foie grass, Frankfurt,	UPLC: Acquity BEH C18 (2.1x50mm, 1.7 µm) MeOH/ammonium acetate solution	0.2 M NaOH + MeOH	SPE: Oasis WAX and EnviCarb	17-83%	ESI(-)	QqQ	SRM (1 transition)	SRM (1 transition) (less for 4 compounds)	1-63 ng kg^{-1}	[27]

	lettuce, salt)										
PFBuS, PFHxS, PFOS, PFDS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA	Canned fish Milk Yoghurt	Waters Symmetry C18 (2.1x150mm, 5µm) ACN/ammonium acetate solution	0.2 M NaOH + MeOH	SPE: Oasis WAX and EnviCarb	60-130%	ESI(-)	QqQ	SRM (1 transition)	SRM (2 transitions)	1-650 ng kg^{-1}	[37]
PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoA, PFTeDA,	Fast food Preprepared foods	Genesis C18 (2.1x50 mm, 3 µm) ACN-MeOH/ammonium formate solution	MeOH	--	71-120%	ESI(-)	QqQ	SRM (1 transition)	SRM (1 transition) (less for two compounds)	0.5-6 µg kg^{-1}	[26]
Phthalates											
5 phthalate compounds (DBP, BBP, DEHP,DINP, DIDP)	Milk, milk products and infant formulas	C5 Luna 100A (2x50mm, 5µm) Water/MeOH/ACN solution	Methanol,*tert*-butyl methyl ether, hexane	ACN (DBP,BBP, DEHP); Deactivated silica (DINP,DIDP)	92-105%	ESI(+)	QqQ	SRM (1 transition)	SRM (1transitions)	4-9 µg kg^{-1}	[42]
6 phthalate monoesters compounds (mMP, mEP, mBP, mBzP, mEHP, mNP)	Human milk, consumer milk and infant formula	BetasilPhenylcolumn (2.1x100mm, 3µm) Acetic acid/water/ACN solution	Ethylacetate: cyclohexane (95:5 v/v)	Two-step SPE: Oasis HLB	93-104%	ESI(-)	QqQ	SRM (1 transition)	--	0.01-0.50 µg L^{-1}	[41]
5 phthalate compounds (DEP, DMP, BBP,DPP, DcHP)	Fruit jellies	Inertsil C8-3 column (2.1x150 mm, 5µm) MeOH/Water	ACN	QuEChERS	83-103%	ESI(+)	Q	SIM	--	0.09–3.68 ngmL^{-1}	[81]
5 phthalate compounds	Beverage/food samples (n.13), nutraceutical samples (n.4)	--	--	--	--	DART (+)	ExactiveOrbitrap	-- (Screening)	-- (Screening)	s/n>3: 0.5-50µgg^{-1}	[67]

Table 3. Levels of food packaging contaminants reported in different food matrices.

Food	Contaminant	Levels	Ref.
BPA, BADGEs, BFDGEs and related compounds			
Fruits and vegetables	BPA	5 – 317 ng g^{-1}	[90,91]
	BPB	27.1 – 85.7 ng g^{-1}	[92]
	BPS	11.5 – 175 ng g^{-1}	[91]
	BADGE	0.1 – 106.4 ng g^{-1}	[59]
	BADGE·HCl	1.3 ng g^{-1}	[39,59]
	BADGE·H_2O	35 – 53 ng g^{-1}	[39]
	BADGE·2H_2O	1.2 – 860 ng g^{-1}	[39,59,93]
	BADGE·HCl·H_2O	0.8 – 480 ng g^{-1}	
	BADGE·2HCl	0.8 – 140 ng g^{-1}	
	BFDGE·2H_2O	n.d. – 420 ng g^{-1}	[93]
	BFDGE·2HCl	0.15 – 0.7 ng g^{-1}	
Fish	BPA	2.1 – 109 ng g^{-1}	[90]
	BADGE	0.1 – 11800 ng g^{-1}	[43,59]
	BADGE·2H_2O	0.6 – 142 ng g^{-1}	[59]
	BADGE·HCl·H_2O	0.2 – 133.8 ng g^{-1}	[43,59]
	BADGE·2HCl	1.2 – 155.2 ng g^{-1}	
	BADGE·HCl	0.3 – 68.8 ng g^{-1}	
	BFDGE	20 – 4200 ng g^{-1}	[43,94,95]
	BFDGE·2H_2O	n.d. – 1060 ng g^{-1}	[93]
	BFDGE·2HCl	1120 ng g^{-1}	[96]
Meat	BPA	9.6 – 98 ng g^{-1}	[90]
	BADGE	25 – 113 ng g^{-1}	[43,80]
	BADGE·HCl·H_2O	20.47 – 1085 ng g^{-1}	
	BADGE·HCl	74.42 – 477 ng g^{-1}	
	BADGE·2H_2O	458 – 590 ng g^{-1}	[80]
	BADGE·2HCl	476 – 751 ng g^{-1}	
Baby food	BPA	0.27 – 11.0 ng g^{-1}	[11,97,98]
Soft drinks	BPA	0.032 – 4.5 ng mL^{-1}	[63,90,99]
	BPF	0.14 – 0.22 ng mL^{-1}	[63]
	BADGE·2H_2O	2.1 – 5.1 ng g^{-1}	[39]
Sauces	BPA	0.9 – 235.4 ng g^{-1}	[90]
	BADGE	0.1 – 3.4 ng g^{-1}	[59]
	BADGE·2H_2O	1.2 – 106.4 ng g^{-1}	
	BADGE·HCl·H_2O	0.8 – 28.2 ng g^{-1}	
	BADGE·2HCl	0.8 – 13.7 ng g^{-1}	
	BADGE·HCl	1.3 ng g^{-1}	
Milk and milk products	BPA	7.11 – 27.0 ng g^{-1}	[59,90]
UV Ink Photoinitiators			
Fruit Juices	BP	2.1 – 90 ng mL^{-1}	[45,51,60]
	EHDAB	0.14 – 0.8 ng mL^{-1}	[45,51]
	ITX	0.05 – 80.9 ng mL^{-1}	[45,48,51]
	DEAB	0.7 ng mL^{-1}	[45]
	DETX	0.07 ng mL^{-1}	
	EDMAB	0.5 – 2.5 ng mL^{-1}	
Baby food	BP	2.3 – 40 ng g^{-1}	[45,60]
	EHDAB	0.3 – 0.6 ng g^{-1}	[45]
	ITX	0.4 – 0.8 ng g^{-1}	[44,45]
	DETX	0.1 ng g^{-1}	[45]
	EDMAB	0.15 – 0.5 ng g^{-1}	
	DMPA	0.2 ng g^{-1}	
Milk and milk products	BP	2.84 – 39 ng g^{-1}	[46,51,60]
	EHDAB	0.13 – 120 ng g^{-1}	[46,51,54]
	ITX	0.81 – 439 ng g^{-1}	[44,46,48,51,54]

Wine	BP	1.8 – 217 ng mL^{-1}	[45,51]
	ITX	0.06 – 0.24 ng mL^{-1}	
	HCPK	1.2 ng mL^{-1}	[51]
Perfluorinated compounds			
Canned Fish and Seafood products	PFOS	0.7 – 12.8 ng g^{-1}	[36]
	PFOA	1.1 – 1.7 ng g^{-1}	
	FOSA	1.2 – 5.1 ng g^{-1}	
Packaged spinaches	PFBA, PFBS, PFPeA, PFHxA, PFHxS, PFHpA, PFOA, PFOS, PFNA, PFDA, PFUdA, PFDoA, PFTrA, PFTeA	0.045 – 0.075 ng g^{-1}	[89]
Canned meat	PFOS	0.003 – 0.054 ng g^{-1}	[27]
	PFOA	0.179 – 0.440 ng g^{-1}	
	PFHxS	0.003 – 0.250 ng g^{-1}	
	PFHxA	0.004 – 0.080 ng g^{-1}	
Milk and milk products	PFOA	0.018 – 0.482 ng g^{-1}	[35]
	PFOS	0.005 – 0.695 ng g^{-1}	
	PFHpA	0.013 – 0.312 ng g^{-1}	
	PFNA	0.027 – 0.476 ng g^{-1}	
	PFDA	0.015 – 0.100 ng g^{-1}	
	PFUnDA	0.015 – 0.040 ng g^{-1}	
	PFTA	0.031 – 0.144 ng g^{-1}	
Baby food	PFOA	0.166 – 0.723 ng g^{-1}	[34]
	PFOS	0.162 – 1.098 ng g^{-1}	
	PFNA	0.044 – 0.219 ng g^{-1}	
	i,p-PFNA	0.166 – 0.723 ng g^{-1}	
	PFDA	0.236 – 1.289 ng g^{-1}	
	PFDS	0.055 – 0.719 ng g^{-1}	
Phthalates			
Milk, milk products and infant formulas	mBP	0.6 – 3.9 ng mL^{-1}	[41]
	mEHP	5.6 – 9.9 ng mL^{-1}	
	DEHP	7 – 138 ng g^{-1}	[42]
Fruit jellies	DEP	490 – 1200 ng g^{-1}	[81]
	BBP	2900 – 14700 ng g^{-1}	

Figure 1

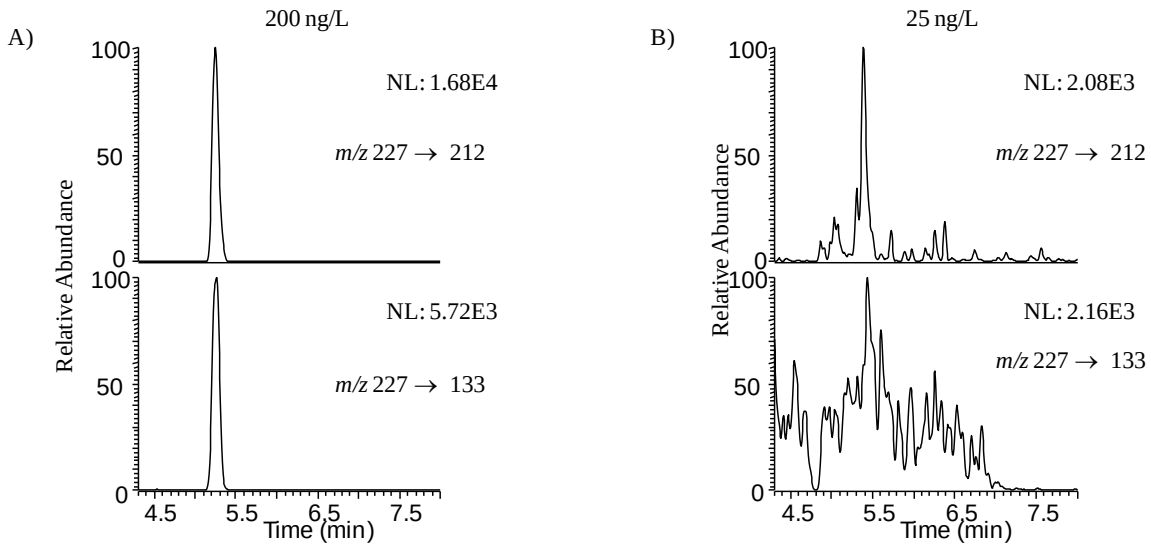

A)
200 ng/L
100
50
0
NL: 1.68E4
m/z 227 → 212
100
50
0
NL: 5.72E3
m/z 227 → 133
Relative Abundance
4.5
5.5
6.5
7.5
Time (min)
B)
25 ng/L
100
50
0
NL: 2.08E3
m/z 227 → 212
100
50
0
NL: 2.16E3
m/z 227 → 133
Relative Abundance
4.5
5.5
6.5
7.5
Time (min)

Figure 2

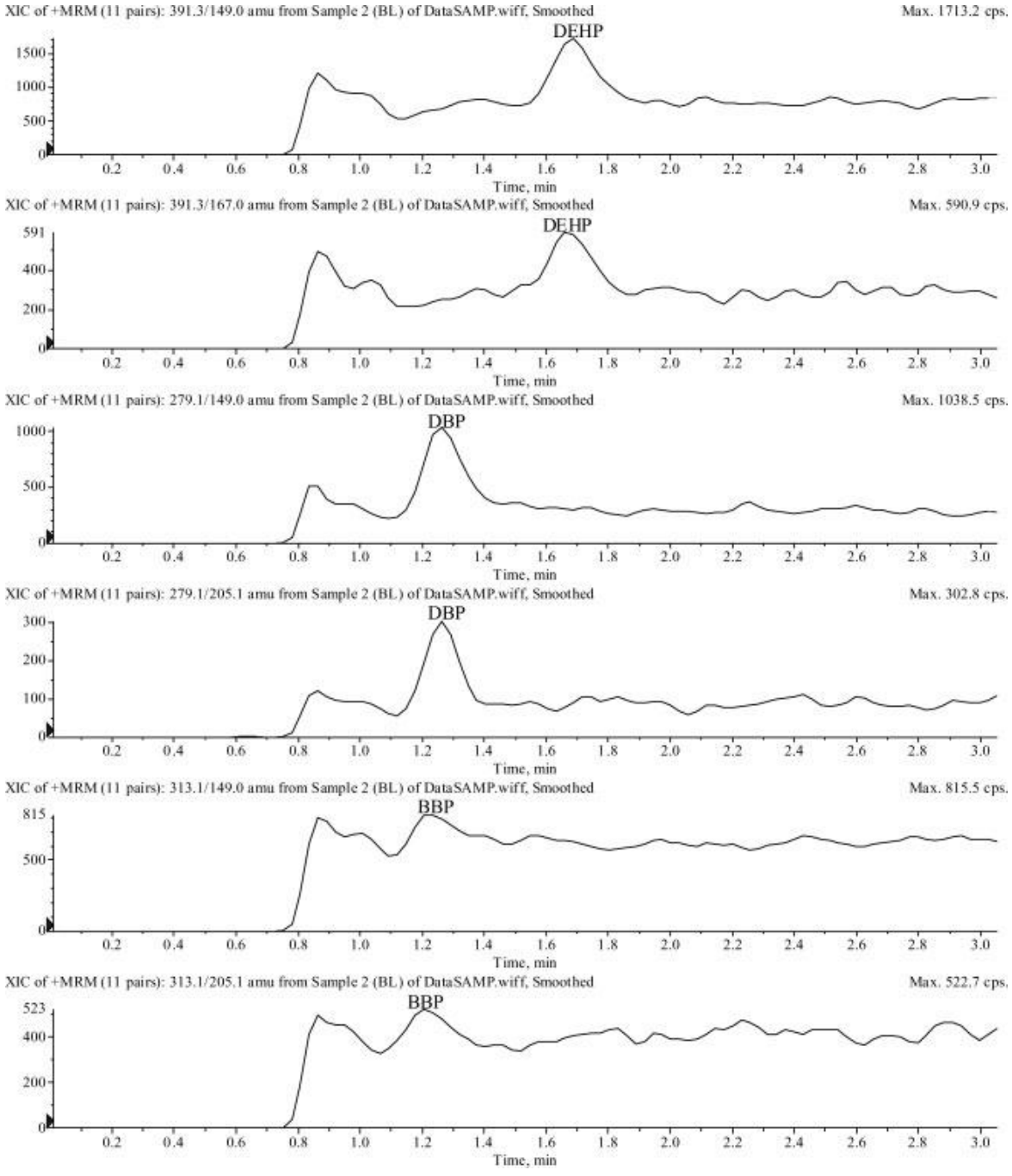

XIC of +MRM (11 pairs): 391.3/149.0 amu from Sample 2 (BL) of DataSAMP.wiff, Smoothed
Max. 1713.2 cps.
DEHP
Time, min
XIC of +MRM (11 pairs): 391.3/167.0 amu from Sample 2 (BL) of DataSAMP.wiff, Smoothed
Max. 590.9 cps.
DEHP
Time, min
XIC of +MRM (11 pairs): 279.1/149.0 amu from Sample 2 (BL) of DataSAMP.wiff, Smoothed
Max. 1038.5 cps.
DBP
Time, min
XIC of +MRM (11 pairs): 279.1/205.1 amu from Sample 2 (BL) of DataSAMP.wiff, Smoothed
Max. 302.8 cps.
DBP
Time, min
XIC of +MRM (11 pairs): 313.1/149.0 amu from Sample 2 (BL) of DataSAMP.wiff, Smoothed
Max. 815.5 cps.
BBP
Time, min
XIC of +MRM (11 pairs): 313.1/205.1 amu from Sample 2 (BL) of DataSAMP.wiff, Smoothed
Max. 522.7 cps.
BBP
Time, min

Figure 3

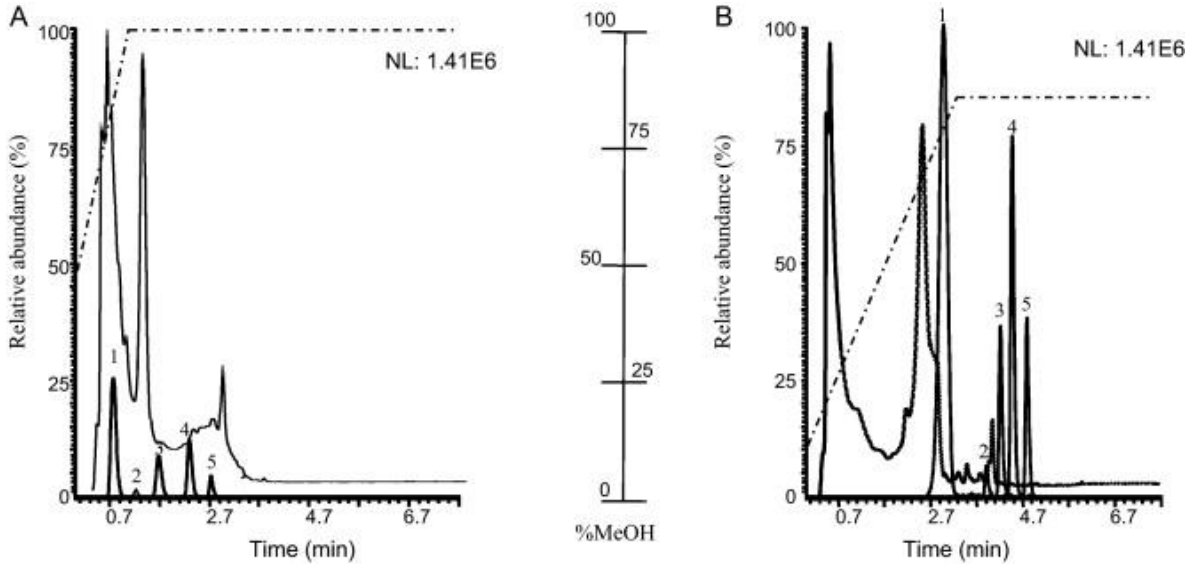

A
NL: 1.41E6
Relative abundance (%)
Time (min)
%MeOH
B
NL: 1.41E6
Relative abundance (%)
Time (min)

Figure 4

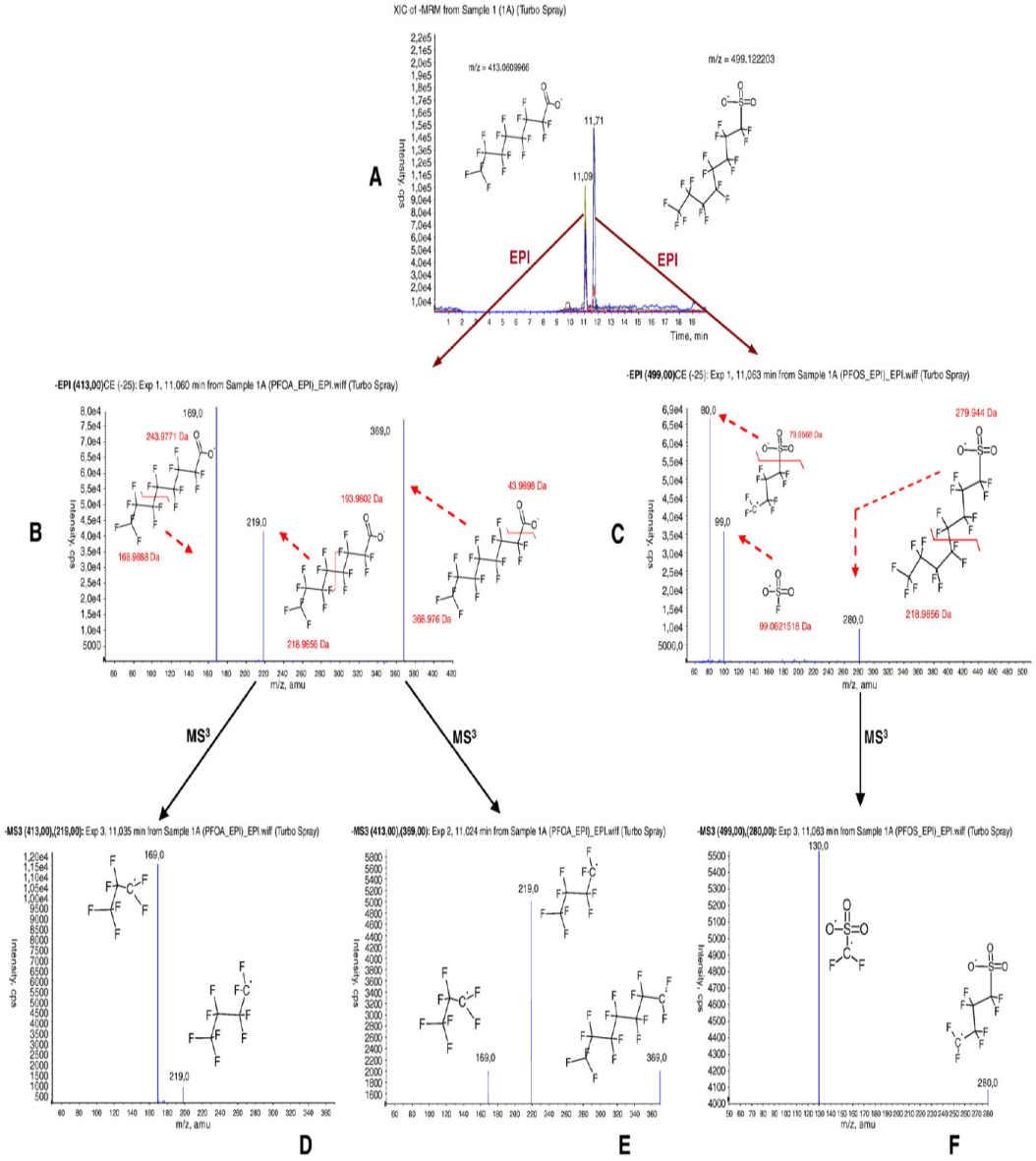
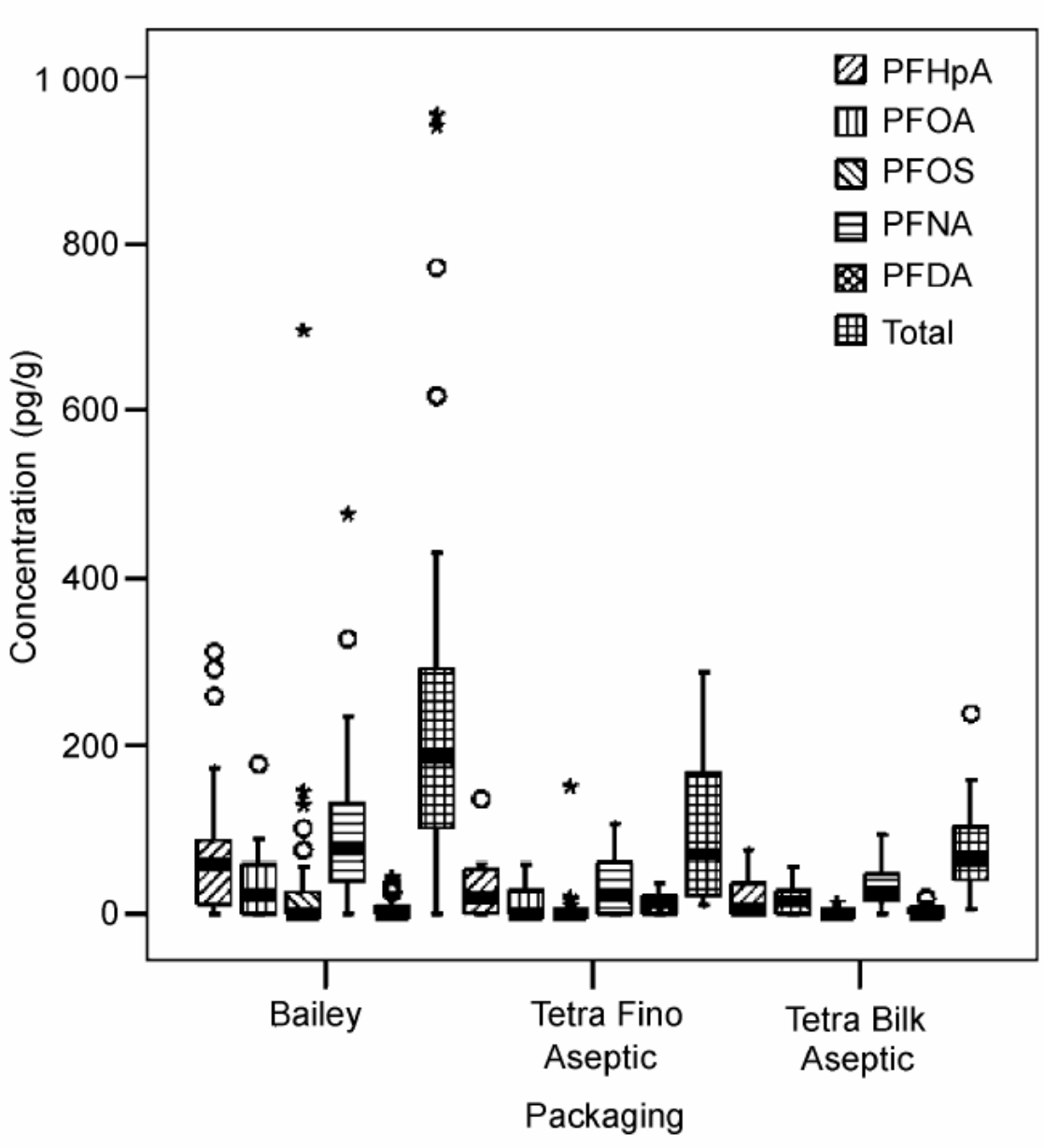

XIC of -MRM from Sample 1 (1A) (Turbo Spray)
A
m/z = 413.0609966
m/z = 499.122203
11,71
11,09
EPI
EPI
Intensity, cps
Time, min
-EPI (413,00)CE (-25): Exp 1, 11,060 min from Sample 1A (PFOA_EPI)_EPI.wiff (Turbo Spray)
B
169,0
243.9771 Da
369,0
193.9902 Da
43.9898 Da
219,0
168.9888 Da
368.976 Da
216.9856 Da
m/z, amu
-EPI (499,00)CE (-25): Exp 1, 11,063 min from Sample 1A (PFOS_EPI)_EPI.wiff (Turbo Spray)
C
80,0
79.9568 Da
279.944 Da
99,0
99.0621518 Da
280,0
218.9856 Da
m/z, amu
MS3
MS3
MS3
-MS3 (413,00),(219,00): Exp 3, 11,035 min from Sample 1A (PFOA_EPI)_EPI.wiff (Turbo Spray)
169,0
219,0
m/z, amu
D
-MS3 (413,00),(369,00): Exp 2, 11,024 min from Sample 1A (PFOA_EPI)_EPI.wiff (Turbo Spray)
219,0
169,0
369,0
E
-MS3 (499,00),(280,00): Exp 3, 11,063 min from Sample 1A (PFOS_EPI)_EPI.wiff (Turbo Spray)
130,0
280,0
m/z, amu
F

Figure 5


1 000
800
600
400
200
0
Concentration (pg/g)
PFHpA
PFOA
PFOS
PFNA
PFDA
Total
Bailey
Tetra Fino Aseptic
Tetra Bilk Aseptic
Packaging