Recent advances in LC-MS analysis of food-packaging contaminants

Héctor Gallart-Ayala, Oscar Núñez, Paolo Lucci

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).

Keywords: Bisphenol A (BPA); Bisphenol A diglycidyl ether (BADGE); Contaminant; Food packaging; LC-MS; Liquid chromatography (LC); Mass spectrometry (MS); Perfluorinated compound (PFC); Photoinitiator; Phthalate

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1. Introduction

Food products are produced and distributed worldwide, so leading to very stringent regulations to guarantee food quality and safety. Food products are very complex mixtures consisting of naturally-occurring compounds (lipids, carbohydrates, proteins, vitamins, organic acids, and aromas) and other substances generally originating from technological processes, agrochemical treatments, or packaging materials. Several of these compounds [e.g., 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, comparison of the various sources of food contamination with organic chemicals suggests that among 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 (e.g., PCBs and veterinary drugs, among others). Few would even mention food-packaging materials, although the amount of material migrating from food packaging into food may well be 100 times greater than the contribution of pesticides or environmental pollutants. 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 (e.g., microbial and chemical contaminants). In the past decade, some food-safety incidents have been directly related to packaging materials {e.g., the alert for food contamination by UV-ink photoinitiators on November 2005 in Europe [3]}. The Italian Food Control Authority detected that photoinitiator 2-isopropylthioxanthone (2-ITX) migrated into baby milk at concentrations of 120–300 μg/L, resulting in the withdrawal from the market of more than 30 million liters of milk.

In order to protect the consumer from potential food hazards, risk analysis is mandatory, and, for that purpose, hazard identification, hazard characterization, exposure assessment and risk characterization are necessary. A very important

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prerequisite for performing risk assessment adequately is the presence of data generated by reliable, 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 example, it is necessary to avoid that, for one type of contaminant, strict rules are applied, while larger amounts of similar substances from another source are accepted or do not even need to be analyzed [2]. Commission Regulation EU No 10/2011[4] established that plastic materials and articles should not transfer their constituents to food simulants in quantities exceeding 10 mg of total constituents released per dm^2 of food contact surface (mg/dm^2) {e.g., for a 100 g piece of cheese of 1 dm^2 top surface and 1 cm thickness, an overall migration of 240 mg/kg is legal; for individually packed slices of sandwich cheese, up to about 1050 mg/kg would be legal [2]}. In addition, plastics materials and articles intended to be brought into contact with food intended for infants and young children should not transfer their constituents to food simulants in quantities exceeding 60 mg of total of constituents released per kg of food simulant.

Appropriate, reliable methodologies are therefore 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 on the type of food) specified in EU legislation are used in migration studies in order to evaluate the amount of undesirable compounds migrating from food-contact materials (FCMs) [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 (MS) or high-resolution MS (HRMS) as detection techniques allowed the simplification of sample-preparation procedures, thereby resulting in faster methodologies requiring less handling [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 limits of detection (LODs) but guarantee confirmation of the target analytes to prevent false positives or false negative results. The European Union (EU) 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 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 [e.g., perfluorinated compounds (PFCs), phthalates, and bisphenol A (BPA) and related compounds], where these materials are used in sample treatment [9], or the chromatographic system itself (e.g., for PFCs and phthalates) can be the source 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 food originating from other sources (e.g., PFCs can contaminate food by bioaccumulation of, especially, longer chain members in fish and shellfish, and not only through contact with packaging materials).

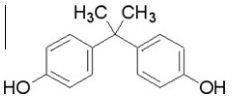
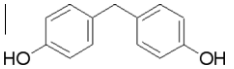
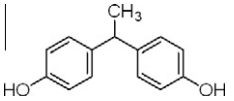
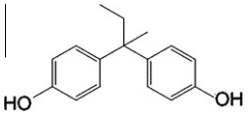
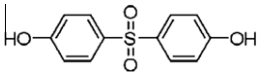
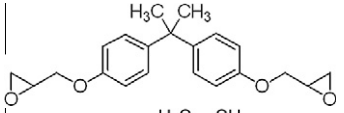
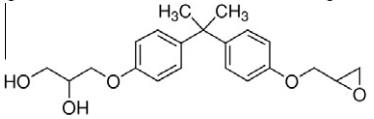
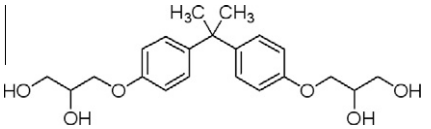
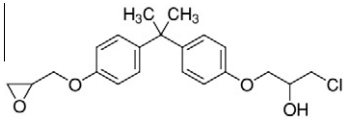
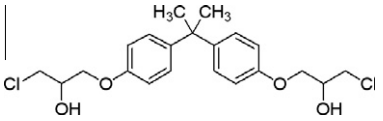
The aim of this review is to present the current state of the art in recent advances in LC-MS analysis of food-packaging contaminants in food samples. It includes a selection of the most relevant papers recently published regarding instrumental and methodological aspects, and the newest applications. The number of publications in this field and the number of food-packaging contaminants migrating into food are huge, so we present a selection of significant publications focused on some relevant families where there has been increasing interest in their analysis in recent years (e.g., BPA and related compounds, UV-ink photoinitiators, PFCs, and phthalates and their monoester metabolites). Table 1 summarizes the structures, abbreviations and CAS numbers of all food-packaging contaminants described in this review.

First, we present a description of each family of compounds regarding their presence in food, legislation and toxicological aspects. Then, we address different aspects {e.g., sample treatment, chromatographic separation and MS techniques, sources of contamination and problems with blanks, and quantitation and confirmation strategies). Moreover, we discuss some relevant applications, food-packaging migration studies and concentration levels found in the literature.

1.1. BPA, BADGEs and related compounds

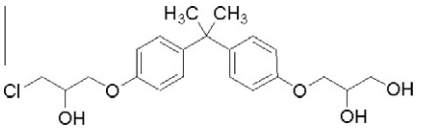
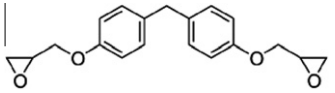
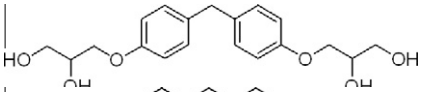
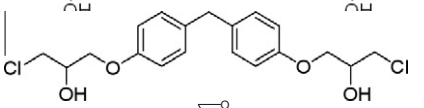
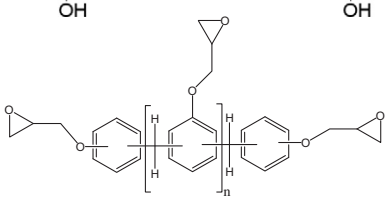
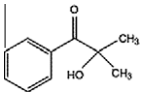
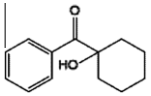
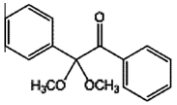
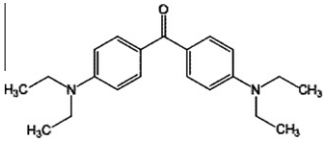
Bisphenol A (BPA) is widely used in the production of polycarbonate plastics and phenolic-epoxy resins, which have a variety of applications (e.g., plastics food containers and epoxy food-can coatings). Other applications of BPA include printed circuit boards, composites, adhesives, and tooling. Heat and contact with acidic and basic foods, like the sterilization process in cans or polycarbonate plastics, increase the hydrolysis of the ester bond linking BPA molecules in the polycarbonate, and epoxy resins and compounds are released to food [10]. Also, 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

Table 1. Contaminants migrating into food from packaging materials

Compound	Abbreviation	Structure	CAS-number
Bisphenols, BADGEs and related compounds			
Bisphenol A 2,2-bis(4-hydroxyphenyl)propane	BPA		80-05-7
Bisphenol F bis(4-hydroxyphenyl)methane	BPF		620-92-8
Bisphenol E bis(4-hydroxyphenyl)ethane	BPE		2081-08-5
Bisphenol B bis(4-hydroxyphenyl)butane	BPB		77-40-7
Bisphenol S bis(4-hydroxyphenyl)sulfonate	BPS		80-09-1
Bisphenol A diclycidyl ether	BADGE		1675-54-3
Bisphenol A (2,3-dihydroxypropyl) glycidyl ether	BADGE·H_2O		76002-91-0
Bisphenol A bis(1,2-dihydroxypropyl) ether	BADGE·$2H_2O$		5581-32-8
Bisphenol A (3-chloro-2-hydroxypropyl) glycidyl ether	BADGE·HCl		13836-48-1
Bisphenol A bis(3-chloro-2-hydroxypropyl) ether	BADGE·2HCl		4809-35-2

(*continued on next page*)

Table 1 (*continued*)

Compound	Abbreviation	Structure	CAS-number
Bisphenol A (3-chloro-2-hydroxypropyl) (2,3-dihydrocypropyl) ether	BADGE·HCl·H_2O		227947-06-0
Bisphenol F diglycidyl ether Novalic glycidyl ether 2-ring (mixture of 3 isomers: o,o-, o,p-, p,p-)	BFDGE 2R-NOGE		2095-03-6
Bisphenol F bis(2,3-dihydroxypropyl) ether (mixture of 3 isomers: o,o-, o,p-, p,p-)	BFDGE·2H_2O		72406-26-9
Bisphenol F bis(3-chloro-2-hydroxypropyl) ether (mixture of 3 isomers: o,o-, o,p-, p,p-)	BFDGE·2HCl		Not available
n-Ring Novalic glycidyl ether (n=3, 4, 5, 6) (mixture of isomers, chain-like or branched)	3R-NOGE 4R-NOGE 5R-NOGE 6R-NOGE		158163-01-0 (3R-NOGE)
UV ink photoinitiators			
2-Hydroxy-2-methylpropiophenone	HMPP		7473-98-5
1-Hydroxycyclohexyl phenyl ketone	HCPK		947-19-3
2,2-dimethoxy-2-phenylacetophenone	DMPA		24650-42-8
4,4'-Bis(diethylamino)-benzophenone	DEAB		90-93-7

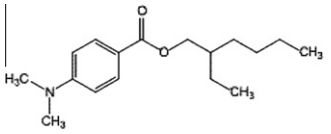
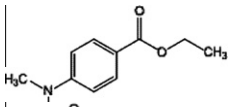
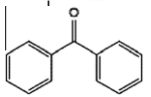
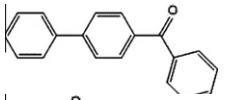
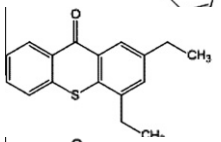
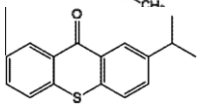
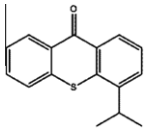
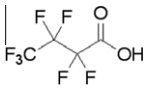
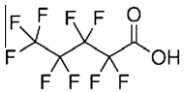
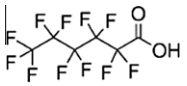
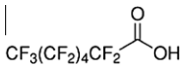
2-Ethylhexyl 4-(dimethylamino)benzoate	EHDAB		21245-02-3
Ethyl 4-dimethylaminobenzoate	EDMAB		10287-53-3
Benzophenone	BP		119-61-9
4-Benzoylbiphenyl	PBZ		2128-93-0
2,4-Diethyl-9H-thioxanthen-9-one	DETX		82799-44-8
2-Isopropylthioxanthone	2-ITX		5495-84-1
4-Isopropylthioxanthone	4-ITX		83846-86-0
Perfluorinated compounds			
Perfluorobutanoic acid	PFBA		375-22-4
Perfluoropentanoic acid	PFPeA		2706-90-3
Perfluorohexanoic acid	PFHxA		307-24-4
Perfluoroheptanoic acid	PFHpA		375-85-9

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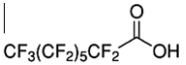
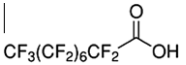
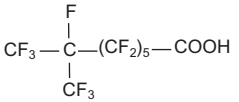
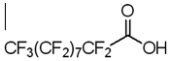
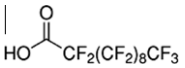
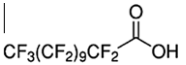
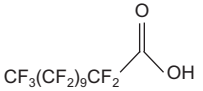
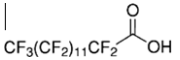
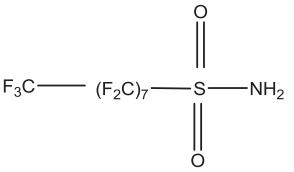
Table 1 (*continued*)

Compound	Abbreviation	Structure	CAS-number
Perfluorooctanoic acid	PFOA		335-67-1
Perfluorononanoic acid	PFNA		375-95-1
Perfluro-7-methyl octanoic acid	i,p-PFNA		15899-31-7
Perfluorodecanoic acid	PFDA		335-76-2
Perfluoroundecanoic acid	PFUnDA		2058-94-8
Perfluorododecanoic acid	PFDoDA		307-55-1
Perfluorotridecanoic acid	PFTrDA		72629-94-8
Perfluorotetradecanoic acid	PFTA PFTeDA		376-06-7
Perfluoro-1-butansulfonate	PFBS PFBuS	CF_3-$(CF_2)_3$-SO_3H	29420-49-3
Perfluorohexane sulfonate	PFHxS	CF_3-$(CF_2)_5$-SO_3H	355-46-4
Perfluorooctane sulfonate	PFOS	CF_3-$(CF_2)_7$-SO_3H	1763-23-1
Perfluorodecane sulfonate	PFDS	CF_3-$(CF_2)_9$-SO_3H	67906-42-7
Perfluorooctane sulfonamide	FOSA PFOSA		754-91-6

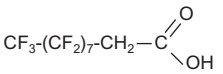
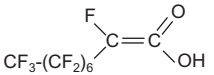
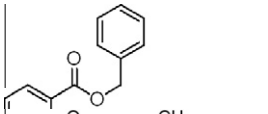
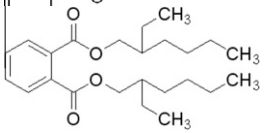
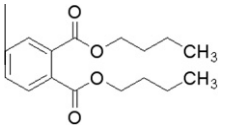
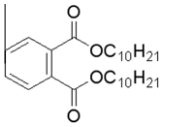
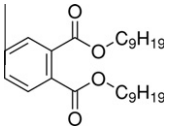
2-Perfluorooctyl ethanoic acid	FOEA		
2H-perfluoro-2-decenoic acid	FOUEA		67-56-1 (solution in methanol)
Phthalates			
Benzyl butyl phthalate	BBP		85-68-7
di-2-ethylhexyl phthalate	DEHP		117-81-7
di-n-butyl phthalate	DBP		84-74-2
di-isodecyl phthalate	DIDP		26761-40-0
di-isononyl phthalate	DINP		68515-48-0

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	Quantitation	Confirmation	LODs	Ref.
BPA and related compounds											
BPA	Powdered milk and infant formulas	C18 (250 × 4.6 mm, 5 µm) MeOH:water	PLE Ethyl acetate	C18 matrix dispersant	92%	ESI(-)	QqQ	SRM (1 transition)	-	5 µg/kg	[38]
BPA, BPF, BPE, BPB and BPS	Soft-drinks	C18 (50 × 2.1 mm, 2.7 µm) MeOH:water	On-line SPE	–	–	H-ESI(-)	QqQ	SRM (1 transitions)	SRM (1 transitions)	5–50 ng/kg	[61]
BADGEs and BFDGEs	Canned food and soft-drinks	C18 (150 × 2.1 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 transitions)	0.13–4.0 µg/kg	[39]
NOGE-related and BADGE-related compounds	Canned food(fish, meat, fruit and congee)	C18 (100 × 2.1. 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	[43]
BPA	Drinking water	DB Biphenylic (50 × 2.1 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	[79]
BPA	Bottle water	C18 (50 × 2.1 mm, 2.2 µm) MeOH:water	Water	–	99%	APCI(-)	Q-Trap	SRM (1 transition)	SRM (1 transition)	40 ng/L	[80]
BADGE and reaction products	Canned food(tuna, apple puree) and Beer	C18 (150 × 2.1 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 (150 × 2.1 mm, 3.5 µm) MeOH:0.1% ammonia	Dispersive-SPE (C18)	SPE (amino-propyl)	79–93%	ESI(-)	QqQ	SRM (1 transition)	–	100 ng/kg	[81]
BPA	Meat	C18 (150 × 2.1 mm, 3.5 µm) MeOH:0.1% ammonia	PLE	SPE (amino-propyl) Acetone	91–100%	ESI(-)	QqQ	SRM (1 transition)	–	300 ng/kg	[51]
BPA and BPF	Honey	C18 (250 × 2.0 mm, 5 µm) ACN:water	Water and HCl	SPE-Polysteryrenedi-ninylbenzene	94–116%	ESI(-)	Q	SIM (1 Precursor ion)	–	500 –2000 ng/kg	[82]
BPA, BADGEs	Canned food(fish, vegetables, sauces and others)	C18 (50 × 2.1 mm, 1.7 µm) ACN:water	ACN	SPE OASIS HLB	69–98%	ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	390–690 ng/kg	[57]
BPA	Milk	C18 (250 × 4 mm, 5 µm) MeOH:water	Water	SPE C18	83–106%	ESI(-)	Q	SIM (1 Precursor ion)	–	1700 ng/kg	[83]
BADGEs	Canned food (fish, meat and baby food)	C18 (100 × 2.1 mm, 3.5 µm)	PLE Hexane:acetone	SPE C18+Aminopropyl bonded silica (NH_2)	85–96%	APCI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	800–1750 ng/kg	[52]
BPA	Beverages (water, puree, soda)	C18 (150 × 2.1 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	[84]
BPA	Canned food (soup, meat, vegetables, fish, pasta)	C18 (150 × 2.1 mm, 3 µm) C8 (150 × 2.1 mm, 3 µm) MeOH:water	ACN	–	94–110%	ESI(-)	Q-Trap	SRM (1 transition)	SRM (1 transition)	2 ng/g	[85]

UV Ink Photoinitiators											
11 photoinitiators	Baby food, Fruit juice, gazpacho, water, wine	PFPP (150 × 2.1 mm, 3 μm) ACN:ammonium formate buffer	ACN	QuEChERS	81–98%	ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	0.07–220 μg/kg	[45]
2-ITX and 4-ITX	Baby food, milk, fruit juice, soy milk, vegetable and broth.	PFPP (150 × 2.1 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	[44]
ITX, EHDAB, EDAB, BP, HCPK	Fruit juice, milk, wine	C18 (250 × 4.6 mm, 5 μm) MeOH:water	n-Hexane	SPE (DSC-Si)	42–100%	ESI(+)	Ion trap	SRM (1 transition)	–	2–100 μg/L	[22]
ITX	Fruit juice	C18 (150 × 4.6 mm, 5 μm) MeOH:water	PLE n-hexane:acetone (1:1)	–		ESI(+)	QqQ	SRM (1 transition)	SRM (1 transition)	0.01 μg/L	[50]
ITX, BP, HCPK, EHDAB, TPO, Irgacure 369, Irgacure 907	Milk	C18 (150 × 2.0 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	[46]
2-ITX, EHDAB	Milk	C18 (50 × 2.1 mm, 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 EHDAB: 40 μg/L	[21]
HCPK, BP, ITX, EHDAB	Beverages	C18 (150 × 4.0 mm, 5 μm) ACN:water	ACN	–	84–93%	–	–	–	–	20 to 30 μg/L	[47]
ITX	Milk, fruit juice, tea, yoghurt and drinks	C18 (100 × 2.1 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	[48]
ITX	Milk, yoghurt and pudding	C18 (100 × 2.0 mm, 5 μm) MeOH: ammonium formate buffer	ACN	–	50–105%	ESI(+)	Q	SIM	In-source fragmentation	6.2 μg/kg	[49]
Perfluorinated compounds											
PFOA, PFOS, i,p-PFNA, PFNA, PFDA, PFDS	Milk infant formulas Cereals baby food	C18 LiChroCART Purosphere Star-18e (125 × 4 mm, 5 μm) MeOH/ammonium acetate solution	10 mM NaOH in MeOH	SPE: C18 Sep-Pack	61–106%	ESI(-)	QqQ	SRM (1 transition)	SRM (1–2 transitions) MS^3	5–167 ng/kg	[34]
PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTA, FOEA, FOUEA, PFHxS, PFOS	Milk Milk powder Yoghurt	Dionex Acclaim 120 C18 (4.6 × 150 mm, 5 μm) MeOH/ammonium acetate solution	MeOH or MeOH + acidic MeOH	SPE: Oasis WAX	80–118%	ESI(-)	QqQ	SRM (1 transition)	–	2–31 ng/kg	[35]
PFOA PFOS FOSA	Canned fish	Atlantis T3 (2.1 × 100 mm, 3 μm) MeOH/ammonium acetate solution	MeOH	Activated charcoal	104–116%	ESI(-)	QqQ	SRM (1 transitions)	SRM (1 transition)	0.05–0.1 μg/kg	[36]
PFBA, PFBS, PFPeA, PFHxA, PFHxS, PFHpA, PFOA, PFOS, PFNA, PFDA, PFUdA, PFDoA, PFTrA, PFTeA	Packaged spinaches (2.1 × 150 mm, 5 μm) MeOH/ammonium formate solution	Fluorosep RP C8	THF:water (75:25 v/v)	SPE: Oasis WAX and EnviCarb	70–104%	ESI(-)	QqQ	SRM (1 transitions)	SRM (1 transitions)	1–30 ng/kg	[86]
PFBuS, PFHxS, PFOS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA	40 Packaged foods (pork liver, duck foie gras, Frankfurter, lettuce, salt)	UPLC: Acquity BEH C18 (2.1 × 50 mm, 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	[27]

(*continued on next page*)

Table 2 (*continued*)

Compound	Food product	LC conditions	Extraction	Clean-up	Recoveries	Ionization source	Analyzer	Quantitation	Confirmation	LODs	Ref.
PFBuS, PFHxS, PFOS, PFDS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA	Canned fish Milk Yoghurt	Waters Symmetry C18 (2.1 × 150 mm, 5 μm) 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	[37]
PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoA, PFTeDA,	Fast food Pre-prepared foods	Genesis C18 (2.1 × 50 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	[26]
Phthalates											
5 phthalate compounds (DBP, BBP, DEHP,DINP, DIDP)	Milk, milk products and infant formulas	C5 Luna 100A (2 × 50 mm, 5 μm) 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 (1 transition)	4–9 μg/kg	[42]
6 phthalate monoesters compounds (mMP, mEP, mBP, mBzP, mEHP, mNP)	Human milk, consumer milk and infant formula	Betasil Phenyl column (2.1 × 100 mm, 3 μm) Acetic acid/water/ACN solution	Ethyl acetate: cyclohexane (95:5 v/v)	Two-step SPE: Oasis HLB	93–104%	ESI(-)	QqQ	SRM (1 transition)	–	0.01–0.50 μg/L	[41]
5 phthalate compounds (DEP, DMP, BBP,DPP, DcHP)	Fruit jellies	Inertsil C8–3 column (2.1 × 150 mm, 5 μm) MeOH/Water	ACN	QuEChERS	83–103%	ESI(+)	Q	SIM	–	0.09–3.68 ng/mL	[78]
5 phthalate compounds	Beverage/food samples (n.13), nutraceutical samples (n.4)	–	–	–	–	DART (+)	Exactive Orbitrap	– (Screening)	– (Screening)	s/n>3: 0.5–50 μg/g	[64]

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, contains a mixture of compounds with two or more aromatic rings. The two-ring product of NOGE, bisphenol F-diglycidyl ether (BFDGE), consists of three isomers (i.e. *p,p*-, *o,p*-, and *o,o*-BFDGE), so these coatings (epoxy-based lacquers and PVC) can release amounts of BADGE and BFDGE compounds and oligomers and derivatives that can migrate into the packaged foods. Chlorinated derivatives of BADGE and BFDGE may be generated during thermal coating treatment, since BADGE and BFDGE are also used as additives to remove the hydrochloric acid formed during this process. Moreover, hydrolyzed derivatives (e.g., 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 are possible, evidence of which has been found around the world, including Japan, Europe, New Zealand and USA [11,12].

Currently, there are no US or EU regulations or limitations regarding the amount of BPA in food or drink. BPA is permitted for use in FCMs in the EU under Regulation 10/2011/EU, relating to plastics materials and articles intended to come into contact with foodstuffs with a specific migration limit (SML) of 0.6 mg/kg or 100 μg/dm^2 [4]. However, in January 2011, the EU 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 of body weight/day [14].

New bisphenol analogues [e.g., 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]. BPS is also used in curing fast-drying epoxy glues, is an anticorrosive and is the monomer of polyethersulfone (PES). BPS is of a ''comparable potency'' to BPA. Also, it is ''less biodegradable, and more heat-stable and photoresistant'' than its predecessor, BPA. Because of that, an SML of 0.05 mg/kg has 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 EU has set SMLs of 9 mg/kg for the sum of BADGE and its hydrolyzed derivatives and 1 mg/kg for the sum of BADGE·HCl, BADGE·2HCl and BADGE·HCl·H_2O [18]. The use and/or the presence of BFDGE in the manufacture of materials and articles intended to be in contact with food is prohibited, so its presence in food is undesirable. However, on the basis of the available experimental data, a TDI can be established for BADGE and its hydrolysis products. Considering the No-Observed-Adverse-Effect-Level (NOAEL) of 15 mg/kg 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 body weight can be established for BADGE. As BADGE is rapidly and extensively metabolized *in vivo* into the corresponding mono-diol and bis-diol derivatives, BADGE·H_2O and BADGE·$2H_2O$, the EU Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) 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 AFC Panel considered that the current restriction of 1 mg/kg of food remains appropriate [19].

The levels of BPA found in the literature did not reach concentrations so far 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 to monitor the presence of BPA in food and drinks and 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 (e.g., multilayer laminates, rigid plastics, 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 photoinitiator 2-isopropylthioxanthone (2-ITX) migrated into baby milk at concentrations of 120–300 μg/L, resulting in the withdrawal from the market of more than 30 million liters of milk [20]. Since then, residues of other photoinitiators [e.g., 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 plastics packaging as a UV blocker. Its use allows manufacturers to package the product in clear glass or plastics. Without it, opaque or dark packaging would be required. Moreover BP is also used in other applications such as in soaps and perfumes because it 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 has also been detected in recycled cartoon board, even when not printed, presumably due to contamination of the previous material [23]. Although UV-ink photoinitiators are widely used, there are no specific EU controls for migration from inks and their associated coatings, but there is a Group TDI for BP and 4-hydroxybenzophenone of 0.01 mg/kg body weight/day. An SML for benzophenone of 0.6 mg/kg has been established in specific legislation for food-contact plastics [4].

1.3. Perfluorinated compounds (PFCs)

Human exposure to PFCs is currently receiving considerable attention from scientists and policy makers due 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 3 M in 2002, and the EU banned most uses from the summer of 2008 [25]. However, hundreds of related chemicals (e.g., homologues with shorter or longer alkyl chains, PFOA and telomers, which potentially may degrade to PFCAs) are not regulated. Polytetrafluoroethylene (PTFE) is a fluoropolymer, also widely utilized in recent decades (e.g., cooking utensils and packaging). PTFE is most well known by 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 (e.g., textile, paper, chemical, fire-fighting, and 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. To date, there have been few systematic investigations on PFC levels – 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 TDIs of 150 ng/kg body weight/day and 1500 ng/kg body weight/day, respectively [29]. EFSA has noted an urgent need for data on PFC levels in various food items in order to improve understanding of contamination routes and to monitor trends in exposure levels.

Consequently, the number of works dealing with the analysis of PFCs in food matrices has increased considerably in recent years. However, in this review, we focus on the publications reporting analysis of these compounds in packaged foods, although so far it is hard to tell if food contamination is due to only environmental exposure or migration from packaging, although we present some evidence of the latter.

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 plastics products (especially PVC) because of their ability to increase flexibility, workability and durability. Other applications of PAEs include use in paints, personal-care products, films, pharmaceutical coatings, adhesives, insect repellents 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 a few of them are commercially significant and produced on an industrial scale. Di-2-ethylhexyl phthalate (DEHP), which accounts for ~50% of global production, di-n-butyl phthalate (DBP), di-isodecyl phthalate (DIDP) and di-isononyl phthalate (DINP) are among the toxic, most commonly used phthalates.

The widespread use and the application of these compounds has resulted in their ubiquitous presence in the environment, and, because they are classified by most countries (including EU and USA) as carcinogenic, mutagenic and toxic to reproduction, human exposure to PAEs is currently receiving considerable attention in political and scientific circles. Phthalates are considered to be potential endocrine disrupters [30] because of their ability to interfere with androgen signaling and production, with fetal animals being particularly sensitive.

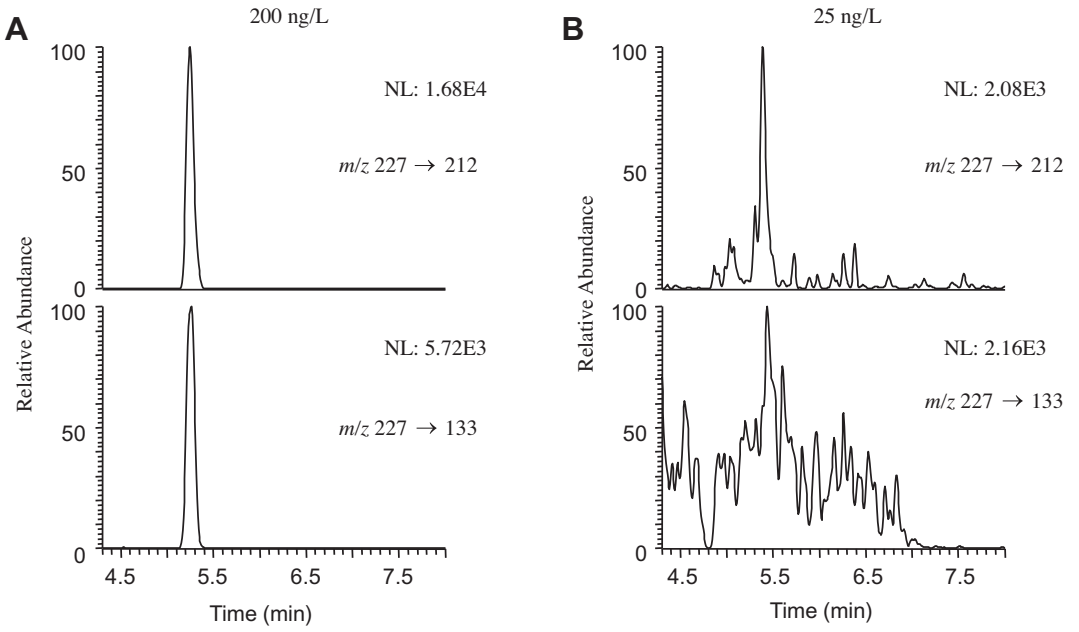


Figure 1. Chromatograms of BPA in ultra-high-quality water obtained from a Milli-Q system (A) in the morning after standing for 12 h, and (B) after the production of ~5 L of water.

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.

Since 16 January 2007, the EU Directive 2005/84/EC [31] has banned DEHP, DBP and BBP for use in PVC and other plasticized materials in all toys and childcare articles. Likewise, DINP, DIDP, and DNOP were banned for toys and childcare articles that may be placed in the mouths 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 TDIs are 0.01 mg/kg body weight/day and 0.5 mg/kg 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 recent years, there are still many products used for food packaging that contains PAEs as plasticizers, which are 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, and 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 commercial milking processes or PVC gloves used in catering). The ubiquity of these compounds and the potential impacts of PAE exposures on public health therefore prompted the European Commission to regulate the usage of some phthalates [i.e. butylbenzyl phthalate (BBP), DEHP, DBP, DINP and DIDP] in food plastics. Some SML values for food simulants have been fixed in European Regulation 10/2011 (e.g., 0.3 mg/kg for DBP, 30 mg/kg for BBP and 1.5 mg/kg for DEHP). For compounds for which there are not SML, a restriction value of 60 mg/kg of food product must be applied [4]. The Japanese government has also 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, so efficient preconcentration and clean-up procedures are needed. Typical steps in analytical procedures for sample preparation include sampling, homogenization, extraction,

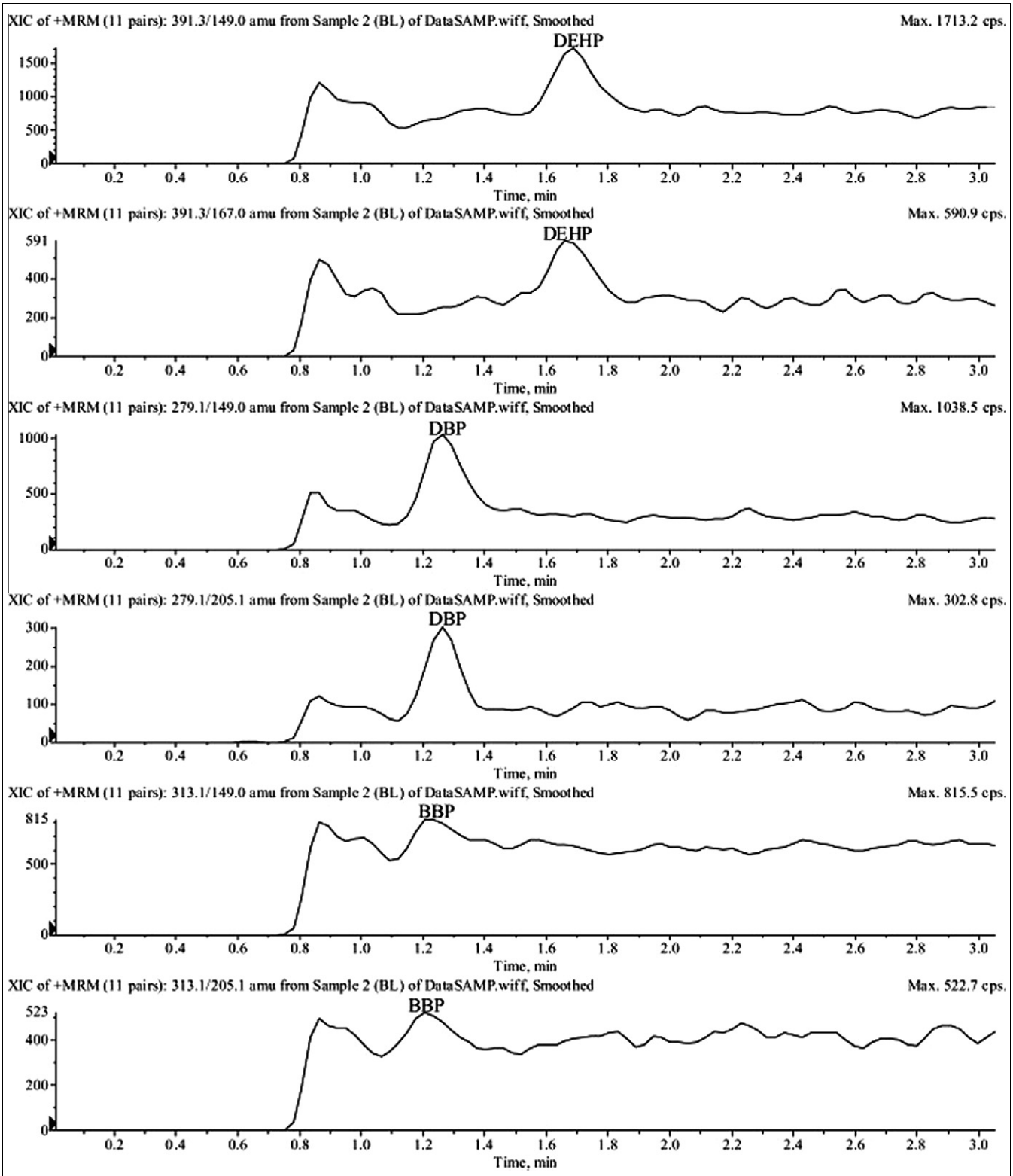


Figure 2. LC/ESI-MS/MS chromatograms of a method blank during analysis of phthalates. The measured concentrations of phthalates were 5.1 μg/kg (DEHP), 2.4 μg/kg (DBP), 0.5 μg/kg (BBP), 2.9 μg/kg (DINP) and 3.1 μg/kg (DIDP) (reproduced from [42], with permission of John Wiley & Sons, Ltd.).

clean up and concentration prior to instrumental analysis.

Table 2 summarizes the most significant reported LC-MS methods for the analysis of the food-packaging contaminants discussed in this review including sample treatment procedures.

Solvent extraction (SE) is the most common technique for extracting packaging contaminants from food samples. The 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 {e.g., PFCs [26,27,34–37] and BPA-related compounds [38–40]} in milk, yoghurt, canned fish and cereal-baby-food samples. Frequently, a mixture of solvents (e.g., dichloromethane with cyclohexane, acetonitrile–hexane, methanol–hexane–methyl *tert*-butyl ether, hexane–acetone and tetrahydrofuran–water) are also employed {e.g., for the extraction of phthalates [41,42] and BPA [43]}.

Liquid–liquid extraction (LLE) using acetonitrile [44–49] or hexane [22,50] 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 [22,44,46,48]. 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 {e.g., pressurized liquid extraction (PLE) [21,38,50–52]} 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, attractive option for sample preparation in food analysis. The QuEChERS method is particularly popular for the determination of polar, middle polar and non-polar pesticide residues in food matrices [7], but it is also being used for sample treatment of several families of compounds {e.g., its application to 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, because some of these compounds (e.g., PFCs, phthalates, especially DEHP and DBP, BPA and BPA-related compounds) often cause blank problems when analyzed al low concentration (e.g., 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. Important losses of BPA up to 90% have occurred due to the adsorption of BPA on the nylon filters [53]. To prevent this adsorption and to increase the recoveries, the addition of an organic solvent [e.g., methanol (10%)] to the water sample is recommended. Other types of filters (e.g., those of regenerated cellulose) are not affected by this phenomenon, but sometimes they can introduce some interference compound that makes the chromatographic analysis of BPA difficult. 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 adsorption and 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 into the sample during sample treatment. Sources of phthalates in the laboratory environment were investigated by Fankhauser-Noti and Grob [54]. A 1.5-mL autosampler vial was shown to contain 10 ng of DBP and 4 ng of DEHP, whereas the concentrations of DBP and DEHP in the laboratory air were estimated 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 the ng/L level, mainly arising from SPE cartridges, glassware, plastics ware, and other reagents and laboratory tools.

Another significant contamination source when highly sensitive analytical methods are used to determine these compounds at low concentration levels is the quality of solvents {e.g., DEHP and DBP concentrations of 100 μg/L were found in commercially-available hexane [2] and Fernández-Sanjuan et al. [55] found traces of PFOS, PFOA, and PFNA in solvent blanks}. To solve this problem, a reversed-phase (RP) column was successfully used as the 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 (<2 pg/μL) was obtained by dispersive solid extraction using active aluminum oxide.

BPA has been found at concentrations of 20–200 ng/L in ultra-high-quality (UHQ) water because of plastics and epoxy-resins used in the water-purifying equipment [9]. An additional problem is the daily variability of this contamination. As an example, Fig. 1 shows the chromatograms of ultra-high-quality water obtained from a Milli-Q system in the morning after standing for 12 h (Fig. 1A) and after the production of ~5 L of water (Fig. 1B). A decrease in the concentration level of BPA (from 200 ng/L to 25 ng/L) is observed as ultra-high-quality water is produced during the day. To overcome this problem and to use this kind of water as a solvent, BPA can be elimi-

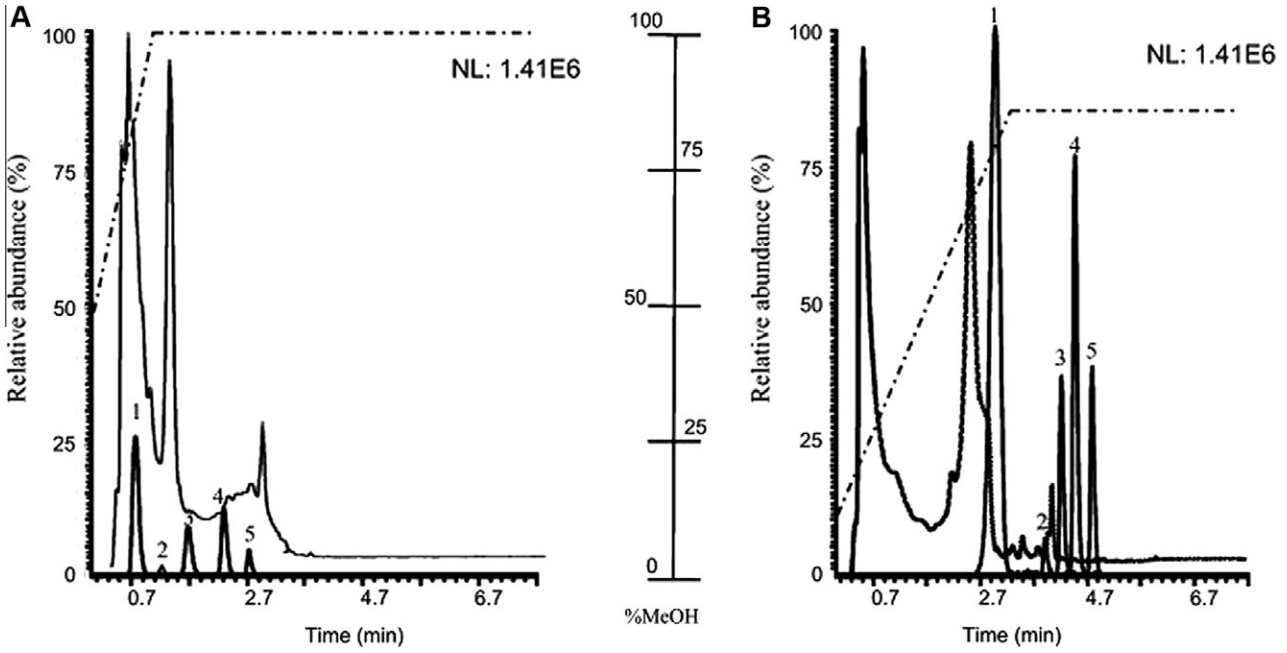


Figure 3. On-line SPE LC-MS/MS and LC-UV at 228 nm chromatograms of a cola sample spiked at 10 μg/L. (A) ESI at ambient temperature, gradient elution 0 min, 50:50 MeOH:water; from 0 to 1 min, linear gradient up to 100% MeOH; and, (B) H-ESI at 300°C, gradient elution 0 min 15% MeOH; from 0 to 3 min a 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 [61], with permission of Elsevier).

nated by filtering the water through membrane filters where it is strongly retained, as mentioned above {e.g., Watabe et al. [56] proposed to use C18 filters to obtain BPA-free water to prepare standard solutions}.

Since different steps of sample treatment are potential sources of contamination by BPA, PFCs and phthalates, procedural blanks have to be made for each batch of samples to ensure minimal contamination. However, in the analysis of these compounds, there are multiple sources of contamination, which are difficult to control and which can affect the robustness of the method. As an example, Sørensen [42] reported it impossible to obtain zero method blanks for the analysis of phthalates in milk and milk-based products (Fig. 2) even if it was shown that the contamination level could be reduced to a low level (from 2 μg/kg for BBP to 6 μg/kg for DEHP) by using high-quality solvents and rinsing glassware with methanol, ethyl acetate and hexane just before use. Subtraction of blank responses can improve in some cases the accuracy of quantitation, as the concentration calculated will be nearer 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 (e.g., conditioning SPE cartridges, SPE washing steps, and reconstituting dried extracts). SPE preconcentration and clean-up cartridges and all laboratory tools and material (e.g., glassware and PLE cells) 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 (LC-MS)

Table 2 also summarizes the LC-MS conditions for the analysis of food-packaging contaminants addressed in this review. Table 2 indicates LC column, mobile phase composition, ionization source, analyzer and acquisition mode.

3.1. Liquid chromatography

For the analysis of food-packaging contaminants migrating into food, RP-LC using C8 or C18 columns with particle sizes of 3.5–5 μm were generally used (Table 2). However, sub-2-μm particle size columns have also been reported to improve chromatographic resolution and decrease analysis time. As an example, Yonekubo et al. [57] developed a fast LC-tandem MS (LC-MS/MS) method for the analysis of BPA and BADGEs in canned food using a RP column with 1.7-μm particle size, and Jogsten et al. [27] reported the use of a ultra-

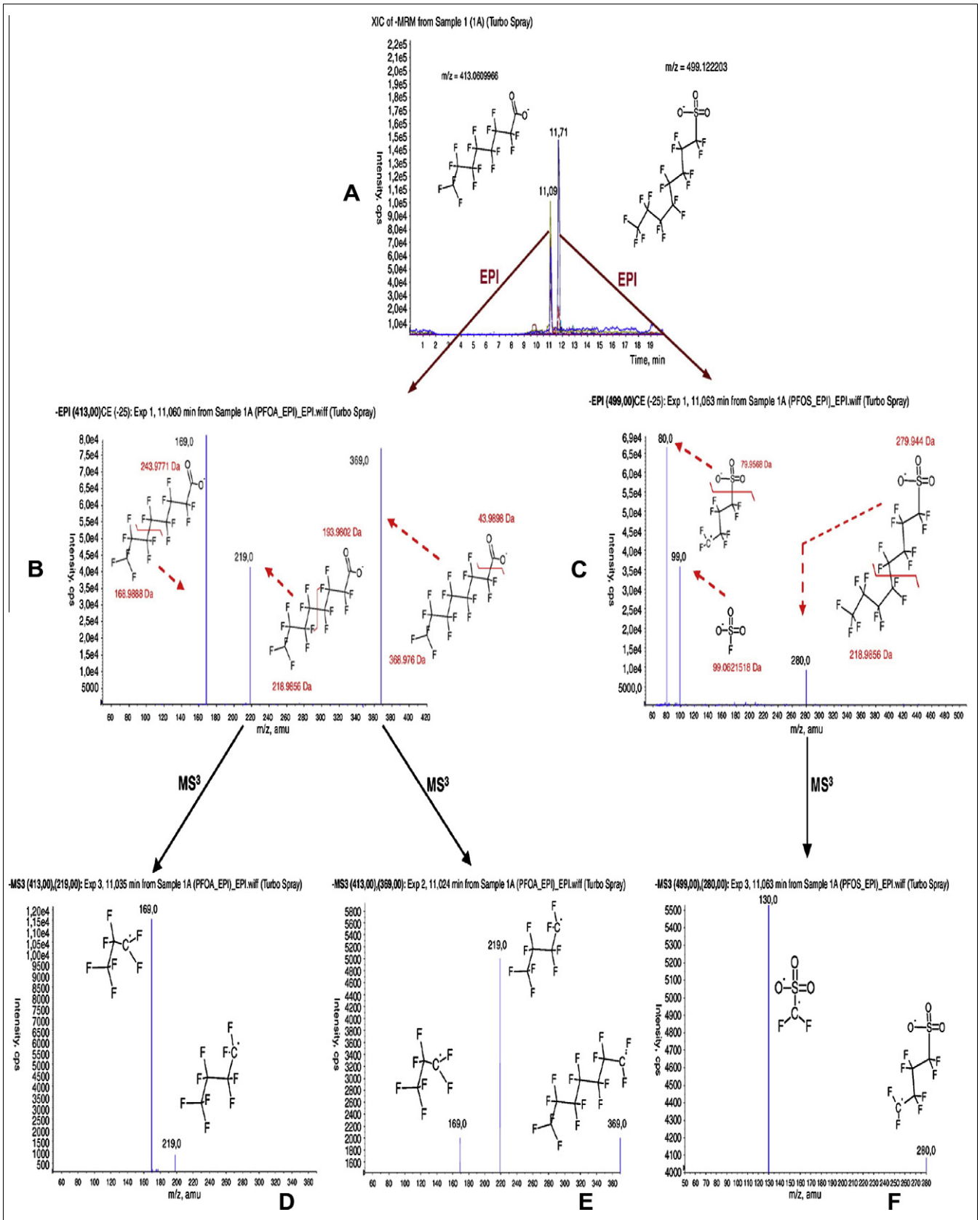


Figure 4. Example of TIC chromatogram, MS/MS spectra using EPI mode and MS^3 spectra of PFOS and PFOA obtained for a breast milk sample (reproduced from [34], with permission of Elsevier).

high-performance LC (UHPLC) separation using a 1.7-μm particle-size column for the analysis of 14 PFCs in about 40 packaged foods. However, 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 allowed working at high mobile-phase flow-rates and achieved similar efficiency and peak capacity to those of sub-2 μm porous particle columns. For example, Gallart-Ayala et al. [39] developed a fast LC-MS/MS method for the analysis of BADGEs and BFDGEs in canned food, and obtained good chromatographic separation and resolution of the BFDGE isomers in less than 5 min. 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 decreased dramatically. However, better chromatographic separation of BFDGEs isomers was achieved using acetonitrile. The authors then proposed 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 coupling of a conventional on-line SPE system with UHPLC, so obtaining fast analytical methods. For example, a fast on-line SPE 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 min was reported [53]. In this case, the use of a direct analysis using the SPE on-line method prevented false positives in the analysis of bisphenols, since, as mentioned above, these compounds are inherently ubiquitous in the laboratory environment, and they can be introduced during sample treatment.

As mentioned above, C8 and C18 columns are generally used for the chromatographic separation of food-packaging contaminants discussed in this review. However, in some cases, orthogonal selectivity is demanded in order to improve the chromatographic separation. For example, a C5 column was described for the analysis of phthalate compounds in milk products and infant formulas [42], but partial co-elution between some of the analyzed compounds, DBP/BBP and DEHP/DINP405/DINP419, was observed, while Mortensen et al. [41] used a Betasil Phenyl column for the analysis of phthalate monoesters in the same kind of matrices, and obtained a good chromatographic separation.

Gallart-Ayala et al. [44,45,58] 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-ITX and 4-ITX) in less than 5 min [44] – a separation that could only be achieved before then by a zirconium column and with a very long analysis time (>30 min) [59]. The separation and the simultaneous analysis of 11 UV-ink photoinitiators in less than 6 min was also achieved by working at sub-ambient temperature (5°C) with a PFPP column [45]. However, Jogsten et al. [27] used a Fluorosep RP C8 column for the analysis of PFCs in packaged spinach, since the presence of monomerically-bonded perfluorooctyl groups in the stationary phase enhanced the selectivity for the chromatographic separation of halogenated compounds. Moreover, as mentioned above, in the analysis of this family of compounds, an RP 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, thereby reducing system contamination [55].

3.2. Mass spectrometry

Regarding ionization of food-packaging contaminants, electrospray ionization (ESI) is the most commonly used technique. The positive-ionization mode is usually employed to analyze BADGEs and BFDGEs, UV-ink photoinitiators, and phthalate diesters, while the negative-ionization mode gives the best sensitivity for the detection of phthalate-monoester metabolites, BPA, other bisphenols (e.g., 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 {e.g., with 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 MS/MS 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 clusters of $[M+Na]^+$, $[M+K]^+$, $[M+NH_4]^+$ and $[M+ACN]^+$ ions. However, some of these cluster ions {e.g., $[M+Na]^+$} are very stable and no further fragmentation in MS/MS was obtained, but efficient fragmentation occurred for ammonium adducts with a stable signal under MS/MS [39,60]. In these cases, to enable the formation of ammonium adducts and ensure signal reproducibility, formic acid/ammonium formate buffer is 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 to the presence of buffer additives, sample-matrix components

and poor chromatographic separation. Significant ion suppression was 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 [61]. In order to solve these problems, different strategies could be carried out [e.g., improving sample-treatment procedures and/or resolution of the chromatographic separation (i.e. using smaller particle-size columns) or modifying the gradient elution, as can be seen in Fig. 3]. In this case, the gradient elution was modified by reducing the amount of organic solvent and the gradient slope, which increased the retention of the studied analytes and forced them to elute into a cleaner chromatographic area, thus minimizing the co-elution with matrix components in the eluting front.

MS/MS is generally used as acquisition mode for the analysis of the food-packaging contaminants addressed in this review (Table 2). Triple quadrupole (QqQ) mass analyzers are the most popular instruments, due to their higher sensitivity and selectivity when operated in selected-reaction monitoring (SRM) mode. For confirmation of the identity of the analytes, the EU directive 2002/657/EC established that two SRM transitions must be monitored to comply with a system of required identification points [8]. In addition, the deviation of the relative intensity of the recorded transitions must not exceed a certain percentage of that observed with reference standards, and the retention time must not deviate more than 2.5%. However, the application of these criteria did not completely eradicate false positives and their application might even lead to the possibility of false negatives. The occurrence of a false positive in LC-MS/MS using a QqQ analyzer implies the presence of interfering compounds that co-eluted with the analyte, and have two transitions with a similar ion ratio [62,63]. But more problematic than false positives is the possibility of reporting false negatives because the identification of relevant compounds would be ignored. In this case, when two transitions are monitored, a false negative might be reported if one of the transitions is affected by an interferent compound. In some cases, these problems can be solved by monitoring more than two selective transitions or by using alternative confirmatory strategies. For example, Llorca et al. [34] reported the use of a quadrupole-linear ion trap (QqLIT) analyzer for the quantification of some PFCs by monitoring two SRM transitions for each compound. Moreover, in order to achieve better confirmation, the SRM mode was combined with enhanced product ion (EPI) scan and MS^3 acquisition modes. Operating with the EPI mode, the first quadrupole (Q1) filters the desired precursor ions, which are fragmented in the Q2 trapping the fragment ions in the LIT. As an example, Fig. 4 shows the LC-MS/MS, MS/MS using EPI mode and MS^3 spectra of PFOS and PFOA in a real breast-milk sample and the main fragmentation pathways of these compounds.

In other cases, the use of HRMS is essential. For example, during the analysis of benzophenone in packaged foods, almost 50% of samples were reported as negative when analyzed by LC-MS/MS using a QqQ instrument because ion-ratio variations greater than 20% were obtained, due to an interferent signal in the confirmation transition. In this case, the studied compound only showed two product ions and it was impossible to monitor a third transition for confirmation [58]. 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 samples of packaged food. Moreover, in this work, the full-scan HRMS experiment was operated simultaneously with the ''all-ion fragmentation'' (AIF) mode in order to obtain unequivocal identification of the target analyte by obtaining its product ion-scan spectrum with HRMS.

Finally, a somewhat different analytical approach was given recently by Self et al. [64]. Their study reported an analytical method to analyze rapidly and qualitatively seven phthalate compounds of interest in a wide variety of beverage/food and nutraceutical samples using direct analysis in real time (DART) ionization in positive-ion mode coupled to an Orbitrap mass spectrometer. The method could detect selected PAEs, including BBP, DBP, DEHP, DINP, at levels of 0.5–1 μg/L and 50 μg/L in beverage/food and nutraceutical samples, respectively. This method has the potential for greatly facilitating qualitative screening of food samples, being able to identify those that require further traditional chromatography methodology for the purposes of both confirmation and quantitation.

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:

(1) distilled water for aqueous foods with a pH above 4.5;
(2) acetic acid at 3% in distilled water for acidic aqueous food with pH below 4.5;
(3) ethanol at 15% for alcoholic food; and,
(4) 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

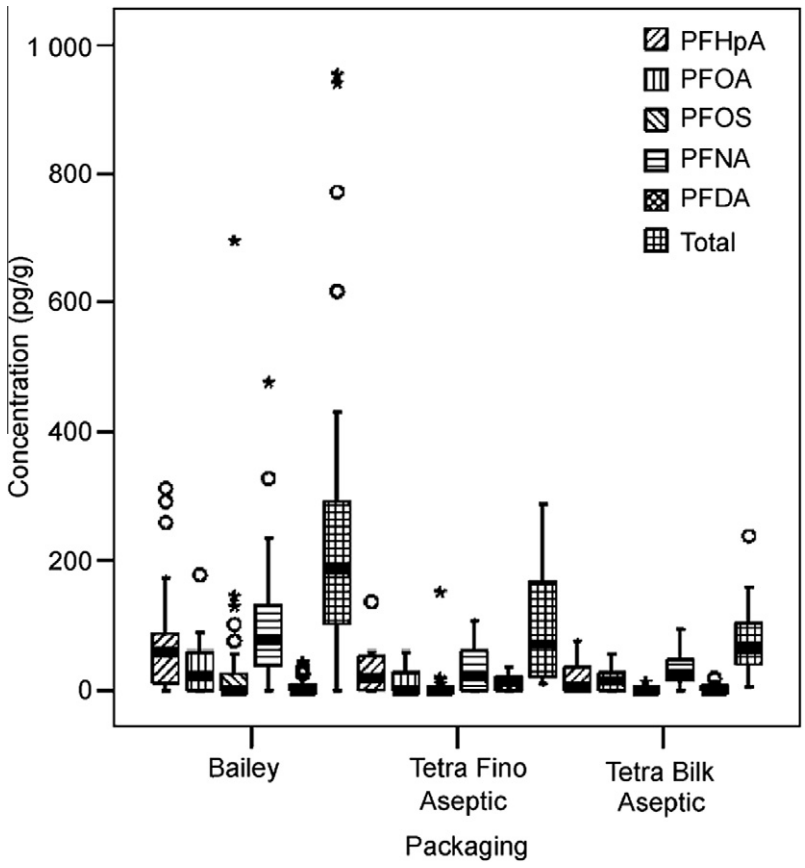


Figure 5. Box plot of concentrations of PFHpA, PFOA, PFOS, PFNA, PFDA and total PFC in milk on the basis of different packaging. The data indicate significant differences ($P < 0.001$) among three kinds of packaging of milk in the concentration of total PFCs (reproduced from [35], with permission of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

conditions are 40°C for 10 days [extreme conditions (EC)] concerning storage at room temperature for indefinite time [65]. Migration-test conditions are also described in EU Regulation 10/2011 [4], which is replacing old directives. For plastics materials and articles not yet in contact with food, the simulants listed are:

(1) ethanol 10% (v/v) (simulant A);
(2) acetic acid 3% (v/v) (simulant B);
(3) ethanol 20% (v/v) (simulant C);
(4) ethanol 50% (v/v) (simulant D1);
(5) vegetable oil (stimulant D2); and,
(6) 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, D1 and D2 are assigned to foods that have a lipophilic character, and E is assigned to testing specific migration into dry foods. However, the application of this Plastics Implementing Measure (PIM) is characterized by a specific phased implementation period, with these rules needing to 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 example, Fasano et al. [66] 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 (e.g., tuna cans, marmalade caps, yogurt packaging, polystyrene dish, teats, bags, films, baby bottles, aseptic plastics-laminated paperboard carton and plastics wine tops) were evaluated by migration tests. Also, to evaluate the potential migration of plasticizers and additives from plastics wine tops, two extraction methods were employed: incubation for 10 days at 40°C and ultrasound extraction. All samples analyzed showed contaminant migration below the SMLs and the overall migration limits (OMLs) established in EU legislation. Moreover, the extraction carried out for 10 days at 40°C gave better results than ultrasound extraction in order to detect all analyzed compounds.

Regarding BPA, many migration studies can be found in the literature. Of special interest are those performed on plastics baby bottles and baby bottle liners [66–70]. For example, Kubwako et al. [67] studied the migration of BPA into water (used as food simulant) from poly-

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	[87,88]
	BPB	27.1–85.7 ng/g	[89]
	BPS	11.5–175 ng/g	[88]
	BADGE	0.1–106.4 ng/g	[57]
	BADGE·HCl	1.3 ng/g	[39,57]
	BADGE·H_2O	35–53 ng/g	[39]
	BADGE·2H_2O	1.2–860 ng/g	[39,57,90]
	BADGE·HCl·H_2O	0.8–480 ng/g	
	BADGE·2HCl	0.8–140 ng/g	
	BFDGE·2H_2O	n.d. –420 ng/g	[90]
	BFDGE·2HCl	0.15–0.7 ng/g	
Fish	BPA	2.1–109 ng/g	[87]
	BADGE	0.1–11800 ng/g	[43,57]
	BADGE·2H_2O	0.6–142 ng/g	[57]
	BADGE·HCl·H_2O	0.2–133.8 ng/g	[43,57]
	BADGE·2HCl	1.2–155.2 ng/g	
	BADGE·HCl	0.3–68.8 ng/g	
	BFDGE	20–4200 ng/g	[43,91,92]
	BFDGE·2H_2O	n.d. –1060 ng/g	[90]
	BFDGE·2HCl	1120 ng/g	[93]
Meat	BPA	9.6–98 ng/g	[87]
	BADGE	25–113 ng/g	[43,77]
	BADGE·HCl·H_2O	20.47–1085 ng/g	
	BADGE·HCl	74.42–477 ng/g	
	BADGE·2H_2O	458–590 ng/g	[77]
	BADGE·2HCl	476–751 ng/g	
Baby food	BPA	0.27–11.0 ng/g	[11,94,95]
Soft drinks	BPA	0.032–4.5 ng/mL	[61,87,96]
	BPF	0.14–0.22 ng/mL	[61]
	BADGE·2H_2O	2.1–5.1 ng/g	[39]
Sauces	BPA	0.9–235.4 ng/g	[87]
	BADGE	0.1–3.4 ng/g	[57]
	BADGE·2H_2O	1.2–106.4 ng/g	
	BADGE·HCl·H_2O	0.8–28.2 ng/g	
	BADGE·2HCl	0.8–13.7 ng/g	
	BADGE·HCl	1.3 ng/g	
Milk and milk products	BPA	7.11–27.0 ng/g	[57,87]
UV Ink Photoinitiators			
Fruit Juices	BP	2.1–90 ng/mL	[22,45,58]
	EHDAB	0.14–0.8 ng/mL	[22,45]
	ITX	0.05–80.9 ng/mL	[22,45,48]
	DEAB	0.7 ng/mL	[45]
	DETX	0.07 ng/mL	
	EDMAB	0.5—2.5 ng/mL	
Baby food	BP	2.3–40 ng/g	[45,58]
	EHDAB	0.3–0.6 ng/g	[45]
	ITX	0.4–0.8 ng/g	[44,45]
	DETX	0.1 ng/g	[45]
	EDMAB	0.15–0.5 ng/g	
	DMPA	0.2 ng/g	
Milk and milk products	BP	2.84–39 ng/g	[22,46,58]
	EHDAB	0.13–120 ng/g	[21,22,46]
	ITX	0.81–439 ng/g	[21,22,44,46,48]
Wine	BP	1.8—217 ng/mL	[22,45]
	ITX	0.06–0.24 ng/mL	
	HCPK	1.2 ng/mL	[22]

(*continued on next page*)

Table 3. (*Continued*)

Food	Contaminant	Levels	Ref.
Perfluorinated compounds			
Canned Fish and Seafood products	PFOS	0.7–12.8 ng/g	[36]
	PFOA	1.1–1.7 ng/g	
	FOSA	1.2–5.1 ng/g	
Packaged spinaches	PFBA, PFBS, PFPeA, PFHxA, PFHxS, PFHpA, PFOA, PFOS, PFNA, PFDA, PFUdA, PFDoA, PFTrA, PFTeA	0.045–0.075 ng/g	[86]
Canned meat	PFOS	0.003–0.054 ng/g	[27]
	PFOA	0.179—0.440 ng/g	
	PFHxS	0.003–0.250 ng/g	
	PFHxA	0.004–0.080 ng/g	
Milk and milk products	PFOA	0.018–0.482 ng/g	[35]
	PFOS	0.005–0.695 ng/g	
	PFHpA	0.013–0.312 ng/g	
	PFNA	0.027—0.476 ng/g	
	PFDA	0.015–0.100 ng/g	
	PFUnDA	0.015–0.040 ng/g	
	PFTA	0.031–0.144 ng/g	
Baby food	PFOA	0.166–0.723 ng/g	[34]
	PFOS	0.162–1.098 ng/g	
	PFNA	0.044–0.219 ng/g	
	i,p-PFNA	0.166–0.723 ng/g	
	PFDA	0.236–1.289 ng/g	
	PFDS	0.055–0.719 ng/g	
Phthalates			
Milk, milk products and infant formulas	mBP	0.6–3.9 ng/mL	[41]
	mEHP	5.6–9.9 ng/mL	
	DEHP	7–138 ng/g	[42]
Fruit jellies	DEP	490–1200 ng/g	[79]
	BBP	2900–14700 ng/g	

carbonate 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, and observed BPA migration of 0.11 μg/L into water incubated for 8 h. By contrast, only trace levels of BPA were observed from non-polycarbonate plastics baby bottles and baby-bottle liners, allowing them to be proposed, with glass baby bottles, as good alternatives to the polycarbonate ones.

Similar results were reported by Nam et al. [68], when they studied the migration of BPA from polycarbonate baby bottles after repeated use, up to 100 times, and at different temperatures. Again, BPA migration increased considerably at temperatures above 80°C. The pattern of BPA level showed three regions:

- lag effect (0.13–1.11 μg/L BPA);
- steady (1.11 μg/L BPA); and,
- aging (1.11–3.08 μg/L BPA).

When the baby bottle was not washed, BPA level was 0.24 μg/L. However, after the procedure (extraction) was executed once, the BPA level of bottle decreased to 0.13 μg/L (lag-effect region). BPA was considered to remain on the surface of the bottle during the manufacturing process. The BPA migration level increased up to 1.1 μg/L after the procedure was repeated 10 times, then maintained at 1.1 μg/L level at up to 60 repetitions (steady region). The BPA level rapidly increased to 3.08 μg/L when the procedure was repeated 100 times (aging region). This was attributed to the increase of the average inter-chain spacing of polycarbonate with repeated used of the bottle (from 0.499 nm in brand-new bottles to 0.511 nm in bottles used more than 100 times), allowing greater diffusion of BPA from the plastics material. Moreover, Guart et al. [12] investigated the potential migration of plasticizers and additives from several plastics containers, including polyethylene terephthalate (PET), polycarbonate (PC), two types of high-density polyethylene (HDPE), low-density polyethylene (LDPE) and polystyrene (PS) plastics.

Migration studies into food simulants were also carried out with some UV-ink photoinitiators. For example, Sanches-Silva et al. studied the migration of six UV-ink photoinitiators (including BP, EHDAB and ITX) into several food simulants (water, 3% acetic acid *w*/*v* aqueous solution, and 10%, 20%, 30%, 60% and 95% ethanol *v*/*v* aqueous solution) [71]. The migration levels of the six UV-ink photoinitiators into the different food simulants were compared after a 30-day-contact period and a relationship between R (ratio between log $K_{o/w}$ and photoinitiator molecular weight, M_w) and the total migration was found for photoinitiators with a log $K_{o/w} < 5$. For ITX and

EHDAB (with log $K_{o/w} > 5$), migration values varied significantly among different simulants, always being higher for ITX (which has the lower M_w).

Migration of non-intentionally added substances (NIASs) from plastics and adhesives is one of the most studied topics in this field. Very recently, Felix et al. [72] described the analytical tools for the identification of NIASs coming from polyurethane adhesives in multilayer packaging materials and their migration into food simulants. In this work Tenax, a solid adsorbent, and isooctane were used as food simulants and the migrants were analyzed by GC-MS. More than 63 volatile and semi-volatile compounds, including some phthalates (e.g., DBP), considered as potential migrants were detected in the adhesives or the films. Cacho et al. proposed a method for the determination of alkylphenols and phthalate esters in vegetables by stir-bar sorptive extraction (SBSE) coupled to GC-MS, and some migration studies from their packages were also performed [73]. DEP, 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 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 and their dietary intake have been reported [33,74]. However, in many of these studies, one of the main problems is to assess correctly 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, that being a handicap in some studies trying to correlate packaging with PFC contamination of food.

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 the PFC food analysis [26]. Only six food composites were available in both kinds of containers, but only in one of them (freshwater fish) were concentrations higher than the reported LOD or limit of quantitation (LOQ); PFOS was measured at 1.5 ng/g and 1.3 ng/g 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.

By contrast, PFC contamination from packaging was clearly observed in other studies. For example, Wang et al. found no significant differences in the levels of PFCs when analyzing milk from various company brands [35]. No differences were observed regarding the kind of milk (e.g., whole or skimmed milk), the tastes (e.g., 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. Fig. 5 shows the PFC levels in milk for three different packaging materials:

- Bailey (polyethylene; shelf-life: 30 days);
- Tetra Fino Aseptic (laminate of paper, polyethylene and aluminum foil; shelf-life: 30 days); and,
- Tetra Brik Aseptic (laminate of paper, polyethylene and aluminum foil; shelf-life: 6–8 months).

Among these packaging materials, the levels of PFCs in milk packaged with Bailey were notably higher than the levels with the other two packaging materials. The total PFC concentration in some samples exceeded 600 pg/g. PFC levels in milk with Tetra Fino Aseptic were similar to the levels with Tetra Brik Aseptic, the total PFC concentrations in all samples with these two packaging being below 300 pg/g.

Some other studies suggested that food packaging might serve as a source of PFCs, used as repellents of water and grease, in food. For example, Begley et al. [75] demonstrated that perfluorochemicals would migrate into food simulants from food-contact paper. As an example, PFOA migrated from a microwave popcorn bag into oil at a concentration as high as 300 ng/g. However, in another study, Bradley et al. [76] noted that the coating materials of cookware products containing polytetrafluoroethylene (PFTE) were not considered as significant sources of PFCs, because the levels of PFCs were too low to be detected. Jogsten et al. [27] also investigated the influence of food packaging on the concentration of PFCs, and, from their results, it was uncertain whether some food packaging could contribute to exposure to PFCs, so further research needs to be carried out to verify which types of food packaging correlated with the concentrations of PFCs in food, as there appears to be some evidence about packaging being one of origins of food contamination with PFCs.

Another consideration to take into account is that, once the packaging contaminant migrates into food, its concentration can change due to a number of factors. For example, recently Coulier et al. [40] showed that BADGE levels decay during food storage and new reaction products are formed by the reaction with food ingredients (e.g., amino acids and sugars), by observing the formation of BADGE-glucose, BADGE-cysteine, BADGE-methyonine and BADGE-lysine. Unlike other chemical contaminants, information on phthalates in

food is very limited, although their determination in foods began more than three decades ago, probably due to the challenges of the methods or the high blank levels of phthalates caused by the contamination of laboratory environments, as mentioned above.

Table 3 summarizes concentration levels of packaging contaminants migrating into food, as addressed in this review. As can be seen, the number of works dealing with the analysis of BPA, BADGES and related compounds, and UV-ink photoinitiators in food (taking into account only data related to contamination from packaging) is considerably greater than those on PFCs and phthalates. In general, concentrations of these contaminants are at the low ng/g level, or even the pg/g level, although, in some cases, much higher concentrations can be found {e.g., 1–11.8 μg/g for some BADGEs or BFDGEs in canned fish, meat and vegetables [43,57,77], or 1.2–14.7 μg/g for some phthalates (e.g., DEP and BBP) in fruit jellies [78]}.

With respect to BPA, BADGEs, BFDGEs and related compounds, their concentration is generally greater in canned fruits, vegetables, fish and meat, and lower concentrations are usually reported in baby food and liquid samples (e.g., milk and milk-based products, soft drinks and sauces). But all of them have been reported at a certain concentration level in several foods. By contrast, although the number of UV-ink photoinitiators being analyzed in food is increasing, only a few of them are usually found in food matrices, ITX and BP being those reported at higher concentrations. For example, ITX has been found at concentration levels up to 439 ng/g in milk and milk-based products.

Regarding PFC levels in food, Hráková et al. [36] reported PFOS concentrations up to 13 μg/kg in canned fish, although probably the major source of this PFOS contamination was the environment. Relatively high concentrations of PFCs were found in fast food (1–3.6 μg/kg) [26] or in infant-milk formulas and baby-food cereals (0.04–1.3 μg/kg) [34].

With respect to phthalates, although the number of papers dealing with their analysis in food has reduced, it seems that their concentration levels must be taken into account, with packaging contaminants migrating into food at the highest concentrations (Table 3).

6. Conclusions

The huge variety of materials employed in packaging technology in order to maintain the quality of foodstuffs when the product arrives at the consumer has considerably increased the number of possible contaminants migrating into food. In this review, we have addressed some of the most relevant food-packaging-contaminant families (e.g., BPA, BADGEs and related compounds, UV-ink photoinitiators, PFCs, and phthalates).

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

SE and SPE are the techniques most commonly used for extraction and preconcentration of packaging contaminants from food samples, but a new sample-treatment method (QuEChERS) appears to be a fast, simple option, and, although there are few applications in the literature concerning food-packaging contaminants, QuEChERS is a good option to explore in the future.

Also, some of the problems that occur in the analysis of food-packaging contaminants might be related to the extraction and clean-up steps, because many of these compounds (PFCs, phthalates, especially DEHP and DBP, BPA and BPA-related compounds) often cause blank problems when analyzed at low concentration. For example, we described significant losses of BPA after filtration, which can be reduced by adding methanol before filtration.

Another significant problem in the analysis of such contaminants is that these compounds are inherently ubiquitous in the laboratory environment, and they can be introduced into the sample during sample treatment, together with the co-extraction of other interferences. In this review, we gave some examples of these problems and how to minimize them.

In summary, sample treatment during analysis of food-packaging contaminants must be carried out very carefully and the control of method blanks is essential due to the significant number of sources of contamination. In order to prevent most of these problems, it is desirable to minimize sample manipulation, so we recommend on-line preconcentration and use of direct analysis techniques [e.g., DART and desorption electrospray ionization (DESI)] as options for the near future.

UHPLC technology, using sub 2-μm columns and fused-core (porous shell) columns, is the most convenient approach to achieve reliable, fast LC separations in the analysis of food-packaging contaminants. RP separations continue 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 we gave some examples in this review. The use of fluorinated stationary phases is very relevant to the analysis of UV-ink photoinitiators. The use of PFPP columns even allowed the separation 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 has allowed the direct coupling of a conventional on-line

SPE system with UHPLC, obtaining fast analytical methods. But instrumentation can also be a significant source of contamination when analyzing food-packaging contaminants (e.g., PFCs or phthalates). In this case, an RP 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, thus reducing system contamination.

ESI is the ionization source of choice in the analysis of food-packaging contaminants. In this review, we have described several approaches (e.g., modification of gradient conditions) to force the analytes to elute in a cleaner chromatographic area to resolve or to minimize matrix effects and ion suppression characteristic of ESI sources. The use atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) may be options to minimize the matrix effects observed with ESI. However, the combination of the information provided by all API sources could be the key to detect new food-packaging contaminants. Moreover, although QqQ monitoring two SRM transitions continues to be the method of choice in the analysis of food-packaging contaminants, the use of different MS-acquisition strategies and HRMS is one of the best ways to prevent false positives or even false negatives, and we presented some relevant examples concerning the analysis of food-packaging contaminants.

Finally, we discussed food-packaging-migration studies and reported levels of these contaminants in food. Due to the huge variety of materials used for food-packaging, migration studies, using a variety of food simulants, depending on the food type, were established to control the migration of undesirable compounds from these FCMs, and we gave some examples. Regarding the levels of food-packaging contaminants in food, although generally concentrations are at low ng/g or even pg/g levels, higher concentrations for some of these contaminants were described (e.g., levels up to 14.7 μg/g for some phthalates). But one of the main problems is not the concentration level, but the huge variety of contaminants that can be found migrating into food, and that makes their monitoring in food one of the main concerns in food quality and safety.

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