



Chemical safety and risk assessment of bio-based and/or biodegradable polymers for food contact: A review[☆]

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ABSTRACT

Bio-based and/or biodegradable polymers are being developed and applied as a sustainable and innovative alternative to conventional petroleum-based materials for food packaging applications.

From the chemical standpoint, bio-based and/or biodegradable polymers present a complex chemical composition that includes additives, monomers, and other starting substances, but also, oligomers, impurities, degradation products, etc. All these compounds may migrate into the food and can be a hazard to the consumers' health. Thus, identifying potential migrants is crucial to assess the safety of these materials. The analytical methods applied to investigate migrants in bio-based and/or biodegradable polymers are reviewed and commented on. Mostly, gas chromatography or liquid chromatography coupled to mass spectrometry and specifically high-resolution mass spectrometry are the techniques of choice. In addition, a summary of recently published migration studies of chemicals from bio-based and/or biodegradable polymers into food simulants and food is provided. Moreover, current approaches to risk assessment of packaging materials are presented and illustrated with examples. Therefore, this review aims to highlight the chemical safety issues raised by biopolymers for food contact applications, that are often overlooked.

1. Introduction

Plastic packaging is present in our daily lives because it makes it more convenient, simplifying the distribution of products to the market. Nevertheless, when they reach the end of their useful life, these packaging materials are often not managed appropriately. Each year, Europe generates about 25.8 million tons of plastic waste. Despite recycling efforts, the reuse and recycling rate of plastics remains low compared to other materials. A percentage of plastic waste ends up in landfills and could enter into the food chain when ingested by animals and humans through food and water, and becoming a risk to human health (FoodPrint, 2020; Nesic, Castillo, Castaño, Cabrera-Barjas, & Serrano, 2020; European Commission, 2018).

Nearly 66 % of packaging waste comes from food packaging waste (Birania et al., 2022). Plastic food packaging materials, as well as food contact articles used to prepare and serve food, are mostly manufactured

from petroleum-based non-biodegradable polymers like polypropylene (PP), polyethylene (PE), polyethylene terephthalate (PET), etc. due to their wide availability at a relatively low cost, as well as its outstanding functional properties, including tensile and tear strength, heat sealability, and an effective barrier against oxygen, water vapor, carbon dioxide, anhydride and aromatic compounds, and so on. These characteristics are essential to preserve food freshness, prevent contamination and disease, delay food spoilage, and therefore reduce food waste. However, these plastic food packaging materials have some disadvantages, their widespread use, combined with low circularity, leads to the massive generation of waste, causing a negative effect on the environment and living organisms, as well as development from non-renewable resources that can lead to the depletion of petroleum feedstocks (Chakraborty, Bhagabati, & Katiyar, 2017; Siracusa, Rocculi, Romani, & Dalla Rosa, 2008; Lindström & Österberg, 2020).

The current management of plastics, from production to disposal,

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fails to capture the economic benefits of a more “circular” approach or minimize environmental impact. The need to rethink and improve this situation is evident, involving all key actors, from plastic producers to end consumers (European Commission, 2018). Indeed, replacing conventional plastics with sustainable materials is a priority of the European Union. The recent “Farm to Fork Strategy” published by the European Commission concerning food packaging states the revision of the current legislation “to improve the food safety and public health particularly in reducing the use of hazardous chemicals” and supporting the implementation of sustainable and innovative packaging. These actions are necessary to accomplish the strategy’s aim of “creating a fair healthy and environmentally friendly food system” as a central part of the European Green Deal (Communication from the Commission to the European Parliament, 2020). To mitigate these problems and improve the sustainability of technologies, great efforts have been made to explore alternatives to conventional petrochemical non-biodegradable plastics, such as the production and use of bio-based, renewable, compostable, and/or biodegradable raw materials using sustainable methods and greener processing solvents (Birania et al., 2022; Nesic et al., 2020). This review is focused and limited to the analysis and discussion of the chemical safety of bio-based and/or biodegradable materials for food contact applications.

Biodegradable and bio-based materials could be the future in the field of newer materials, with the potential to significantly transform the packaging sector. This sector offers great opportunities to reduce dependence on fossil resources and improve the sustainability of a particular field. It is generally accepted that the product’s sustainability is evaluated based on its beneficial, healthy, and safe impact on individuals and communities throughout its life cycle (Piergiorganni, Li, & Farris, 2013). In this context, bio-based plastics have a lower carbon footprint than other plastics reducing greenhouse gas emissions (FoodPrint, 2020; Spierling et al., 2018; Van den Oever, Molenveld, van der Zee, & Bos, 2017), which results in a substantial reduction in the environmental impact. Additionally, these materials increase acceptance by consumers, and maintain barrier properties and shelf-life of the packaged product, enabling a sustainable end of life (Reichert, Bugnicourt, Coltelli, Cinelli, Lazzeri, Canesi, Braca, Monje Martínez, Alonso, Agostinis, Verstichel, Six, De Mets, Cantos Gómez, Ißbrücker, Geerinck, Nettleton, Campos, Sauter, Pieczyk, & Schmid, 2020). There is a great interest in this area from a political, economic, and social perspective, which is reflected in several initiatives (Siracusa & Blanco, 2020).

According to the latest market data, the world production of bio-based and/or biodegradable polymers is expected to grow significantly in the next few years, from around 2 million tons (2022) to about 6 million tons (2027) (Bioplastics, 2020; Bioplastics, 2023), among which USA, Europe and Asia are the main regions in the bioplastic’s production (Siracusa & Blanco, 2020). Increased consumer awareness and government policy intervention are the driving force in the market towards greener packaging consumption and waste reduction (Reichert et al., 2020; Nesic et al., 2020).

However, the critical issue of food safety is often left behind, and it is essential to assure the safety of the food packaging materials with the ultimate goal of protecting the consumers’ health.

The aim of this review is to provide a comprehensive overview of the chemical safety and risk assessment of bio-based and/or biodegradable polymers for food contact applications. This review discusses the types of bio-based and/or biodegradable polymers used in food packaging. Additionally, analytical methods for detecting chemicals in these materials, migration studies, and approaches to risk assessment are examined. Finally, the review concludes with key findings and perspectives for future research in this field.

2. Types and classification of bio-based and biodegradable food packaging materials

The prefix “bio-” is generally associated with a good connotation, it is

often considered environmentally friendly, and associated with lower persistence and toxicity; especially when compared to the word or prefix “synthetic”, which often carries negative connotations. However, not all products and substances from the biological world are good and safe, so they can even be misleading. In relation to the terms “biopolymers” or “bioplastics”, there is some confusion because they are often used interchangeably. Nowadays, there is no consensus among the different sectors, e.g. industry, stakeholders, the scientific community, international organisms, etc., neither guidance nor regulations with a specific definition, although CEN has reported some standards on bio-based products (European Commission, 2024). For example, according to the European Bioplastics Association, bioplastic is defined as a material that is bio-based and/or biodegradable (Bioplastics, 2020). The first term refers to the origin/source and the second one to a property, the biodegradability. However, the IUPAC (International Union of Pure and Applied Chemistry) defines bio-based as “composed or derived in whole or in part of biological products issued from the biomass (including plant, animal, and marine or forestry materials)” and biodegradable as “qualifier for a substance or device that undergoes biodegradation”. Therefore, for IUPAC, a “bioplastic” is a bio-based polymer which is not necessarily biodegradable (Vert et al., 2012). Furthermore, there is still a false assumption that all bio-based polymers are biodegradable. However, it is interesting to note that although biomass is used as a raw material, the biodegradability of plastics is independent of the raw material employed in its manufacture, but by the composition and the environmental conditions required for its degradation (Sid, Mor, Kishore, & Sharanagat, 2021).

According to the European Bioplastic Association, there are two main groups of bioplastics: plastics based on renewable resources (bio-based) and biodegradable and/or compostable plastics (Peelman et al., 2013). Although there are two other categories that can be called bioplastics, for example, bio-nanocomposites and oxo-biodegradable plastics (Geueke, 2014), they will not be discussed in this article.

The term bio-based polymers refer to polymeric products, man-made or processed organic macromolecules, consisting of biological products produced or derived from biomass sources (from animals and plants) or by microorganisms using a carbon source through fermentative processes. However, bio-based products may also contain raw materials based on fossil fuels, their “biological” origin does not necessarily guarantee their biodegradation, and sometimes they can be returned to nature through the compounds process in the form of water, carbon dioxide, inorganic compounds, and biomass, leaving no distinguishable and/or toxic residues (Geueke, 2014; Siracusa & Blanco, 2020).

Biodegradable plastics, which can be made from fossil or natural fonts, refer to plastics that easily break down and biodegrade in the natural environment through the action of microorganisms and other living organisms, reducing the molar masses of macromolecules (Geueke, 2014; Lambert & Wagner, 2017).

The biological decomposition process (biodegradation) depends on numerous parameters, such as the surrounding environmental conditions, the type of material and the application (Piergiorganni et al., 2013). The degradation rate of the polymer is determined by the reactivity of the polymer with water and catalysts, as well as the nature of the functional groups. For example, ester bonds, oxygen atoms of hydroxyl groups, carboxylic acid, aldehyde, and ketones are generally considered to facilitate biodegradation (Siracusa et al., 2008; Lambert & Wagner, 2017). It is worth noting that most plastics currently labeled as biodegradable often break down under specific conditions that are not always readily found in the natural environment (European Commission, 2018).

In the context of the EU proposal regulation on packaging and packaging waste, the EU policy framework for biobased, biodegradable and compostable plastics is contemplated. Regarding the biodegradability of plastics in the open environment, it is recommended to limit the biodegradable plastics for specific applications for which the potential environmental benefits are clear. These include applications for

which collection from the environment is challenging and applications where separation of the plastic from other waste represents a challenge (European Commission, 2022; European Commission, 2021).

Concerning the classification, bio-based and/or biodegradable polymers could be classified into the following main groups (Fig. 1):

(I) Biodegradable bio-based polymers:

These materials are further divided into three categories based on their origin and production method:

- Category 1: biopolymers directly extracted or disposed of from agricultural waste, such as polysaccharides (cellulose, starch chitin, chitosan) and proteins (casein, whey protein). Lignin from plant waste and natural rubber from plant species are also included.
- Category 2: biopolymers produced by chemical synthesis or polymerization employing renewable monomers of agricultural origin, such as polylactic acid (PLA) from lactic acid.
- Category 3: biopolymers directly produced from natural or genetically modified microorganisms, such as polyhydroxyalkanoate (PHA), polyhydroxyvalerate (PHV), polyhydroxybutyrate (PHB), and their copolymers (PHBV) (Birania et al., 2022; Reichert et al., 2020).

II) Biodegradable petrochemical polymers: for instance, polybutylene succinate (PBS), polyethylene adipate (PEA), polyethylene succinate (PES), polybutylene adipate (PBA), aromatic copolyesters like poly(butylene adipate-co-terephthalate) (PBAT), polycaprolactone (PCL), aliphatic copolyesters (PBSA), thermoplastic polyvinyl alcohol (PVOH), etc.

III) Non-biodegradable bio-based polymers: synthesized as the current fossil fuel-based polymers, but initiated from bio-based raw materials. Some examples are bio-based polypropylene (bio-PP), polyethylene (bio-PE), polyvinyl chloride (bio-PVC), polyethylene terephthalate (bio-PET), polyethylene furanoate (PEF), etc. (Lambert & Wagner, 2017; Piergiovanni et al., 2013; Siracusa & Blanco, 2020).

Also, there is a consideration need to be done concerning the terms biodegradable/compostable. Thus, according to the European standard UNI EN 13432 (2002), for a product to be defined as compostable it must be biodegradable and disintegrable in a short time, or rather it must be transformed from microorganisms into aqueous compost, carbon dioxide and fertile. So that all compostable polymers are biodegradable, but not the other way around (Geueke, 2014). Hence, in this article only the term biodegradable will be considered.

Below a brief summary on bio-based and/or biodegradable polymers

that are expected to have high production capacity at an industrial level in the coming years and the materials that are expected to have greater growth and more applications in food packaging, according to data reported by the European Bioplastics organization (Bioplastics, 2023), is presented. Starch- and cellulose-based polymers, PLA and PHAs in the field of bio-based and biodegradable polymers; bio-PE, bio-PP, bio-PET, and PEF in the field of non-biodegradable bio-based polymers; and PBS and PBAT in the field of biodegradable petrochemical polymers are the materials considered in this review.

2.1. Starch-based polymers

Starch is a broadly available, low-cost biodegradable natural polysaccharide derived from plant sources such as rice, wheat, corn, potatoes, and tapioca. Depending on the source and geographical variations, starch consists of different proportions of amylopectin and amylose that affect its crystallinity and, therefore, the characteristics of packaging materials.

Starch-based films can act as a high oxygen barrier, being an effective edible coating for foods with high respiration rates (vegetables, fresh fruits, bakery, confectionery and meat products). They are usually tasteless, colorless, odorless films and compatible with various biopolymers.

The hygroscopicity and retrogradation of starch limit its application. To improve their processability, susceptibility to degradation, mechanical resistance and barrier against water vapor, it is common to combine starch with lipids and plasticizers (sorbitol, glycerol) that interact with inter/intramolecular hydrogen bonds in the chains of starch by reducing its melting temperature and processing temperature. For example, thermoplastic starch (TPS) is developed using mechanical or thermal energy and is a substitute for traditional PE and polystyrene (PS) plastic packaging.

Some examples are TPS/PBAT blend used as bags for carrots or potatoes, TPS/PLA blend as multi-layer candy packaging, or TPS used as a cellophane laminated layer for packaging cereals and cookies (Geueke, 2014; Birania et al., 2022; Peelman et al., 2013; Reichert et al., 2020; Nesic et al., 2020; Van den Oever et al., 2017).

2.2. Cellulose-based polymers

About 75 % of available biomass corresponds to carbohydrate polymers, and the most common is cellulose (Piergiovanni et al., 2013), which is a polysaccharide obtained from delignified cotton linters or wood pulp (Geueke, 2014).

Biodegradable cellulose films are flexible and resistant and tend to provide a barrier against oxygen, fats and oils, proving to be a good alternative to conventional polymers (LDPE, HDPE, PS and PP) for packaging various food products such as fresh products (lettuce shredded, cabbage, tomato, sweet corn, broccoli), cheeses, baked products, sweets, processed meats, among others (Birania et al., 2022; Peelman et al., 2013). It is important to highlight that regenerated cellulose-based polymers are explicitly regulated by European Commission Directive, 2007/42/EC (European Commission Directive, 2007/42/EC).

Due to their hydrophilic nature, these materials present a low water vapor barrier, resulting in poor mechanical properties, poor processability, brittleness, vulnerability to degradation, inadequate long-term stability, and high cost. To improve these properties, cellulose can be modified by adding plasticizing additives (diethyl phthalate, triacetin), surface modification (etherification or esterification), or coating and blending to improve printability, gloss, clarity, dimensional stability, rigidity, or water solubility (Geueke, 2014; Peelman et al., 2013; Reichert et al., 2020; Sid et al., 2021; Lindström & Österberg, 2020).

For example, cellulose acetate mixtures are biodegradable polymers approved for contact with food, classified by the FDA like GRAS (generally recognized as safe), and used to wrap fresh produce and

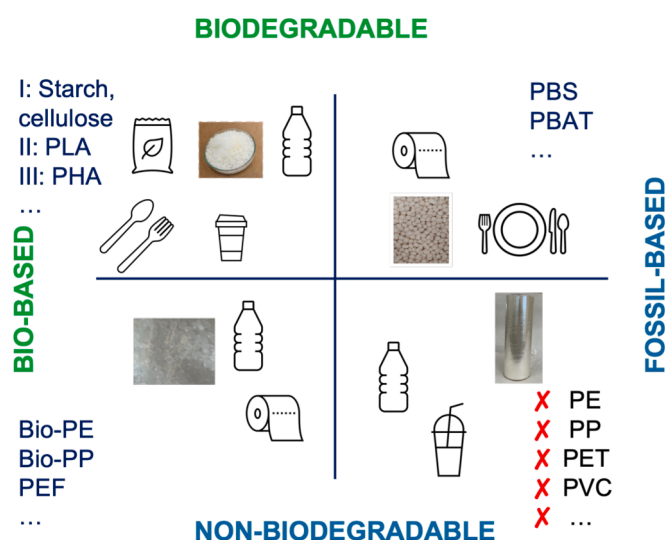


Fig. 1. Scheme of the classification of bioplastics and petroleum-based polymers.

baked products (FDA, 2024a). Another example is cellophane, formed from cellulose with glycerin to improve its flexibility, which is widely used to package baked products, processed meat, cheese, fresh products and sweets. As previously mentioned, nanocellulose is also used as a filler or coating to improve the properties of traditional packaging materials and help to obtain new materials (Sid et al., 2021).

With regard to safety issues of cellulose-based materials and starch-based materials, plasticizers such as propylene glycol, triethylene glycol, polyethylene glycol and triacetin are the main part of migrating substances; the monomer of these polymers is glucose and it is not a cause for concern (Bradley, 2010; Geueke, 2014). It is also interesting to mention that the presence of per- and polyfluorinated alkyl substances in the cellulose-based materials have received special attention due to their toxicity (Lerch, Fengler, Mbog, Nguyen, & Granby, 2023). On the other hand, in the case of regenerated cellulose, the total quantity of certain substances, e.g. toluene or isopropyl acetate (solvents), has a restriction (European Commission Directive, 2007/42/EC).

2.3. Polylactic acid (PLA)

PLA is one of the most recognized biopolymers produced through chemical synthesis from various renewable biomass sources, like corn, sugarcane, wheat, cassava and maize. Its exploration has expanded towards the use of second-generation raw materials, such as agricultural residues, wheat straw, bagasse, wood chips, corn stover, by-products and industrial waste, as well as the fermentation of methane for its production.

This aliphatic thermoplastic polyester is recyclable, biodegradable and compostable, produced by the chemical alteration of a carbohydrate source to dextrose, which is fermented into lactic acid by microorganisms and then subjected to polycondensation of lactic acid monomers or by ring-opening polymerization of lactide. It presents different stereochemical compositions: L-, D- and L,D-lactide, which determine the final properties of the polymer, such as its crystallinity and degradation.

Currently, PLA is considered a promising alternative to conventional polymers such as low-density PE (LDPE), high-density PE (HDPE), polystyrene (PS) and polyethylene terephthalate (PET), thanks to its attractive properties such as biocompatibility, bioabsorption capacity, transparency, water solubility resistance, good processability, rigidity, high tensile strength, printability, excellent organoleptic characteristics (aroma barrier), thermomechanical properties, and antimicrobial properties.

However, PLA also has some drawbacks, such as its high permeability to water vapor and oxygen, difficulty in heat-sealing, and low melt resistance, which restricts its use in packaging applications for gaseous and hot drinks, among others. Plasticization of PLA and its copolymerization are potential alterations to better its qualities, like permeability, stiffness, thermal stability and crystallinity (Geueke, 2014; Birania et al., 2022; Peelman et al., 2013; Nesic et al., 2020; Lambert & Wagner, 2017; Agarwal, Shaida, Rastogi, & Singh, 2023). Furthermore, it has been observed that the use of nanoparticles improves the stability of PLA in thermomechanical treatments (Dedieu, Peyron, Gontard, & Aouf, 2022).

Currently, it is used in America, Europe, and Japan mainly to package short self-life products such as fruits, vegetables and bread, due to its good respiratory properties. There are synthetic polymers produced from renewable resources (dextrose derived from corn) on an industrial scale for the fabrication of coffee capsules, cups and yogurt containers (Reichert et al., 2020; Nesic et al., 2020; Van den Oever et al., 2017; Sid et al., 2021; Agarwal et al., 2023; Dedieu et al., 2022).

2.4. Polyhydroxyalkanoates (PHA)

A composition 100 % bio-based and biodegradable thermoplastic aliphatic polyester produced synthetically or by bacteria aerobic fermentation using different carbon sources (sunflower, olive, soybean,

rapeseed oil, sugar cane, glycerol, starch, fructose, maltose, xylose, among others) (Birania et al., 2022; Lindström & Österberg, 2020; Agarwal, 2023). Today, there are more than 300 types of bacteria to produce PHA, including the genera *Alcaligenes*, *Bacillus*, and *Pseudomonas* (Nesic et al., 2020; Lambert & Wagner, 2017).

PHAs are based on hydroxyalkanoic acid as a monomer unit, and the carboxylic group is linked to the hydroxyl group of the contiguous monomer by an ester bond. According to the number of carbon atoms, PHAs are divided into three categories: short chain length (3–5 atoms), medium chain length (6–14 atoms), and long chain length (15 or more atoms) (Nesic et al., 2020). PHAs can be developed as homopolymers, composed of a single type of monomer, for instance, polyhydroxyvalerate (PHV), poly(3-hydroxybutyrate) (P3HB or PHB), poly(4-hydroxybutyrate) (P4HB), polyhydroxyhexanoate (PHH); or copolymers with different PHA monomers such as 3-hydroxybutyrate-co-3-hydroxyvalerate (PHBV), PHB copolymer (with a methyl group as a side chain) and PHV (with an ethyl group) (Reichert et al., 2020).

PHA polymers are isotactic, semi-crystalline, high molecular weight, water-insoluble thermoplastics with good thermomechanical characteristics, UV resistance and biodegradable. PHA copolymers degrade more rapidly than homopolymers. PHB shows a good gas barrier, high degree of crystallinity, melting point and glass transition temperature compared with other PHAs (Lambert & Wagner, 2017; Agarwal et al., 2023).

However, its stiffness, brittleness, poor processability and formability due to its thermal instability, poor impact resistance and high manufacturing process cost are factors that limit the industrial use of PHA/PHB as food packaging (Peelman et al., 2013; Nesic et al., 2020; Lindström & Österberg, 2020). PHBV copolymer has bettered physical characteristics and chemical stability but poor barrier properties (Birania et al., 2022). With the addition of plasticizers (4-nonylphenol, acetylated tributyl citrate, polyethylene glycol, dioctyl phthalate) it is feasible to reduce the glass transition temperature, improve elongation, impact resistance, toughness and processability avoiding thermal degradation (Nesic et al., 2020; Lambert & Wagner, 2017).

An example is a commercially available PHA called medium chain length polyhydroxyalkanoate (mcl-PHA), or Nodax® approved by the U. S. FDA for food contact use (Siracusa et al., 2008; Danimer Scientific, 2023). Currently, PHA is used in fast-food service products and biodegradable cheese coatings (Sid et al., 2021). Furthermore, PHAs can be used as additives to enhance polymer properties such as PLA, PBS, polycaprolactone, etc. (Reichert et al., 2020).

Oligomers have been reported to be the main migrants in both PLA and PHA polymers (Geueke, 2014; EFSA Cep Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2019). There is scarce knowledge about the toxicological properties of the oligomers. In the case of PHAs in a recent opinion of EFSA on the safety assessment of poly((R)-3-hydroxybutyrate-co-(R)-3-hydroxyhexanoate) was concluded that migrating oligomers do not give rise to concern for genotoxicity (EFSA Cep Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2019).

2.5. Polybutylene succinate (PBS)

PBS is an aliphatic polyester generally produced by the condensation of succinic acid and 1,4-butanediol. Synthesis is commonly based on fossil fuel-based materials, but also on bio-based materials such as the use of glucose to produce succinic acid, followed by chemical reduction to produce 1,4-butanediol. The ester bonds make it susceptible to biodegradation by various methods like enzymatic action, radiation, hydrolytic, and light-induced fission. PBS is a semi-crystalline polymer with good thermal properties, a high melting point (90–120 °C), mechanical properties like PP, and excellent processability. However, it has poor water resistance, and a limited gas barrier, and compared to conventional plastics, PBS is still very expensive. Its main use is the packaging industry, including primary and secondary packaging of meat and

dairy products using vacuum packaging. It can be processed in the form of bags, films, and boxes. In addition, PBS can also be employed as a plasticizer with other polymers like PLA (Geueke, 2014; Reichert et al., 2020; Lindström & Österberg, 2020; Rajgond, Mohite, More, & More, 2024).

2.6. Poly(butylene adipate co-terephthalate) (PBAT)

PBAT is a synthetic thermoplastic copolymer combining aliphatic and aromatic polyesters. It is produced by polycondensation of PTA, adipic acid, and 1,4-butanediol. It can be synthesized from renewable resources (sugarcane, corn starch), and degrades naturally in the environment. PBAT presents good mechanical properties and biodegradability because of the aromatic and aliphatic units, respectively. Its high flexibility makes it ideal for active food packaging applications. However, its manufacturing costs are high, since its mechanical resistance and barrier properties are lower than those of traditional plastics, limiting the production scale-up. Therefore, it is crucial to enhance its properties by mixing them with other biodegradable polymers (PLA, PHA or TPS, among others) or by adding fillers (Roy, Ghosh, Zhang, & Rhim, 2024; European Plastic Joint Stock Company, 2023). One example of commercially available PBAT is a biodegradable thermoplastic resin, which is used in food service ware markets for cutlery and single-use disposable packaging (Siracusa et al., 2008; Press Release Finder, 2004).

Concerning the safety of these biodegradable polyesters, in terms of hazards related to migrating substances, it has been demonstrated that oligomers and additives migrate into simulants and foods. In a recent study, plasticizers (e.g., triethylene glycol), slip agents (e.g., 13-docosenamide) and antioxidants (e.g., 2,4-di-*t*-butylphenol) have been reported to migrate from a PBS/PBAT based material into 50 % ethanol (v/v). It should be noted that some of the additives, e.g., 13-docosenamide, are class III according to the Cramer rules that means high toxicity (Zhao et al., 2024).

2.7. Bio-PE

A bio-based and non-biodegradable vinyl polymer synthesized from ethylene and obtained by dehydration of bioethanol from glucose (from sugar beet, sugar cane, starch crops and lignocellulosic materials). There are different types depending on the polymerization: bio-HDPE (low degree of short-chain branching), bio-LLDPE (high degree of short-chain branching), and bio-LDPE (high degree of short and long-chain branching). Its chemical, mechanical and physical properties are identical to those of fossil-based PE and can be treated using the same tools, without the need for an additional investment. However, its price is about 30 % higher than fossil-based PE (Siracusa & Blanco, 2020). Currently, there are commercial bio-PE yogurt bottles that can be recycled successfully (Plastics, 2012).

2.8. Bio-PP

A bio-based non-biodegradable vinyl polymer obtained from biological resources such as the fermentation of sugar cane, via a gasification approach from carbon-rich biomass sources (corn, grass, agricultural wastes, etc.) or hydro-treatment of vegetable or cooking oil. The polymerization technique is capable of produce high-molecular weight PP with similar properties as fossil-based PP. The main task for bio-PP producers is to obtain processing technologies cost-competitive with fossil-based PP. Since the bio-based PP large-scale production started in 2019, the market is still in its beginning, but its market presence is expected to increase to 5.9 % by 2028 (Bioplastics, 2023; Wang et al., 2023).

2.9. Bio-PET

A bio-based non-biodegradable aromatic polyester, synthesized from

monoethylene glycol (MEG) recovered from renewable biological resources (sugars source from agriculture by-products like bagasse, sugar beet) and terephthalic acid (PTA). Several researchers are working to develop a 100 % bio-based PET looking for bio-based solutions for PTA such as synthesis by the limonene method (Colonna et al., 2011), isobutanol method (Ryan, 2019), the furfural method (Agirrezabal-Telleria, Gandarias, & Arias, 2014) and the muconic acid method (Carraher, Pfennig, Rao, Shanks, & Tessonnier, 2017). Products made from this polymer have analogous weight, quality, functionality and appearance as conventional PET. Currently, bio-PET is used in the manufacture of a variety of products used in the food industry, such as drinking water bottles, and ketchup, among others. Since 2009, there have been commercialized bottles for soft drinks manufactured from 100 % bio-based MEG and petroleum-derived PTA (Geueke, 2014; Siracusa & Blanco, 2020).

2.10. Bio-PEF

A bio-based and non-biodegradable aromatic polyester that combined MEG synthesized from biomass and bio-based 2,5-furandicarboxylic acid (FDCA). FDCA is a monomer chemically produced by dehydration and oxidation from first-generation bio-feedstock (corn or wheat-based sugars), or second-generation feedstock (waste, bagasse, wood, corn stover, wheat-straw). This polymer gives twice the water vapor barrier of PET and could be recycled together with PET (Geueke, 2014; Reichert et al., 2020). The European Food Safety Authority (EFSA), which is in charge of evaluating the safety of a substance before authorizing its use in food contact materials (FCMs), established that “the substance furan-2,5-dicarboxylic acid as a monomer in the production of PEF polymer does not raise a safety concern for the consumer when the migration of the substance itself does not exceed 5 mg/kg food” (EFSA Cfe Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2014a). PEF is currently under development and is expected to reach commercial scale in 2024 (Bioplastics, 2023).

In these materials, the chemicals transferred—and consequently leading to consumer exposure—include additives and their degradation products, such as erucamide, Irganox 1076, and tris(2-nonylphenyl) phosphate, which have been reported in bio-PE. Additionally, cyclic and linear oligomers have been identified in PEF (Zimmermann, Dombrowski, Völker, & Wagner, 2020; Hoppe, De Voogt, & Franz, 2018b). No information on the toxicity of oligomers is available.

3. Trends in the development of bio-based and biodegradable materials

At present, bio-based packaging has entered the market for food products with short shelf-life as well as dry products that do not require water vapor barrier and/or high oxygen (like pasta and chips) as carrier bags, cutlery, films, transparent and rigid containers, bottles, dishes, pouches, trays, and so on (Peelman et al., 2013; Nesic et al., 2020).

Within the range of 20–100 % of the plastics could be replaced by bio-based substitutes. However, accomplishing a complete replacement of traditional plastic as food packing presents challenges due to economic issues linked to high-cost processing and production, technology scale-up, performance and versatility of the material, as well as the task of guaranteeing environmental benefits compared to conventional alternatives (Piergiovanni et al., 2013; Peelman et al., 2013; Nesic et al., 2020; Siracusa & Blanco, 2020; European Commission, 2018). Also, it should not be forgotten the safety issues of these new materials. Risk evaluations are necessary in order to protect consumers from the exposure to chemicals transferred from bio-based polymers.

These materials must exhibit similar or better barrier, mechanical, and processing properties than conventional plastics (Nesic et al., 2020). To overcome common challenges associated with bio-based polymers, it is recognized that a single strategy may not be sufficient to make these

materials commercially viable (Piergiovanni et al., 2013; Birania et al., 2022). Therefore, also the incorporation of nanoparticles, a variety of approaches were developed to improve its characteristics including coating bio-based films to improve their barrier properties (e.g., aluminium oxide coating to enhance the oxygen and water vapor barrier of polymers such as PLA film), blending two bio-based materials or with other additives (antioxidants, ultraviolet light absorbers, etc.) (e.g., blend of starch and PLA, plasticizers or other degradable polyesters reduce the brittleness of starch-based films; the incorporation of chitosan improves oxygen barrier, antimicrobial properties and moisture sensitivity of TPS composites), or combining novel bio-based materials with traditional flexible packaging (e.g., nanocellulose has proven to be an effective coating material for enhancing performance and reducing the environmental influence of traditional flexible packaging) (Peelman et al., 2013; Sid et al., 2021; Piergiovanni et al., 2013).

Some research studies evaluate consumer behavior towards these bio-based materials in products or packaging. For example, Koutsimanis, Getter, Behe, Harte, and Almenar (2012) concluded that sustainability criteria, recyclability, and ease of handling during use are issues that significantly influence consumers' purchasing decisions. The surveys show that, although bio-based materials are widely accepted, this does not always justify higher prices. Concern for food safety appears to be more significant than carbon emissions, indicating a slightly higher valuation of health compared to environmental protection (Friedrich, 2020). Consumer's preferences include agro-based materials to plastic because they raise awareness of the carbon footprints, are natural, ecological, biodegradable, renewable, and improve ecosystems, promoting the circular economy (Birania et al., 2022).

4. Sample preparation and analytical techniques

The expanding of polymer technology in the sector of FCMs requires continuous assessment with the use of advanced and sensitive analytical methodologies for the detection, identification, and determination of potential food contaminants from packaging, to ensure the food product quality and safety (Wrona & Nerín, 2020; Osorio, Dreolin, Aznar, Nerín, & Hancock, 2019).

In chemical safety, it is crucial to distinguish between direct material sample analysis and migration sample analysis. Material sample analysis may overestimate actual exposure, as it assesses the totality of compounds present in the polymer, including those that might not migrate into food under normal conditions of use. On the other hand, migration sample analysis better reflects actual exposure conditions, although it is subject to limitations related to the choice of food simulant, experimental conditions (temperature, time, etc.) and the sensitivity of analytical techniques. Therefore, a robust risk assessment should combine both perspectives to ensure the chemical safety of food contact materials.

Existing analytical methods and risk assessment processes to establish the transfer of chemicals from petrochemical polymers to food are foreseen to be suitable for bio-based FCMs (BSI Group, 2023). Some examples of analytical techniques employed to identify volatile and non-volatile substances in bio-based and/or biodegradable FCMs are summarized in Table 1.

Additives and oligomers are among the most common chemicals that migrate from the bioplastics. Thus, oligoesters composed by adipic acid, phthalic acid and butanediol, and PLA oligomers have been reported in a packaging material based on polyester and polylactic acid (Aznar, Úbeda, Dreolin, & Nerín, 2019). PLA cyclic oligomers and two series of linear oligomers with a hydroxyl group and an ethoxy group have been identified in PLA based materials. Moreover, new oligomers formed as a result of the interaction of PLA components and food simulants were also detected (Úbeda, Aznar, Alfaro, & Nerín, 2019a). For many of these migrants there is no information about their toxicity. Also, lactide, the cyclic dimer of lactic acid, has been reported as one of the most important migrating substances from PLA, and it is not listed in the

Regulation 10/2011 (Úbeda, Aznar, & Nerín, 2019b; Salazar, Domenech, Plessis, & Ducruet, 2017).

Likewise, additives such as lubricants, antioxidants, plasticizers, etc., and oligomers have been described as the main migrants from the biodegradable polyesters, PBA, PBAT and PBS (Zhang et al., 2023; Gies, Ellison, Chakraborty, Kwiecien, & Hercules, 2012; Lin et al., 2023).

It is also worth mentioning that, substances not included in the EU positive list, and classified as highly toxic (Class III) including 2-acetyl-2,3,5,6-tetrahydro-1,4-thiazine; 4-hydroxy-3,5-dimethyl-2-furanone and the oligomer TPA-AA-(BD)₂ composed by terephthalic acid, adipic acid and butane-1,4-diol have been identified in starch-based biopolymers (Osorio et al., 2019).

In the case of biodegradable multilayer films, components of the adhesives including intentionally added substances (e.g., 2,4,7,9-tetramethyl-5-decyne-4,7-diol) and non-intentionally added substances (NIAS) (e.g., 1,6-dioxacyclododecane-7,12-dione) have been described as the main migrants (Canellas, Vera, & Nerín, 2015).

As can be inferred from the literature, there is hardly any information about the toxicological properties of the substances that migrate from these new materials.

The main steps usually performed to evaluate the chemical safety of food packaging materials are presented in Fig. 2.

Established extraction methods such as dissolution/precipitation studies, Soxhlet extraction or ultrasonic-assisted solvent extraction have been suggested for analyzing volatile and non-volatile substances in bioplastic FCMs. The most commonly used techniques for the extraction of non-intentionally added substances (NIAS), defined as "impurities in the substances used, or reaction intermediates formed during the production process or decomposition or reaction products" are headspace (HS) extraction, purge and trap (P&T), direct thermal desorption for volatile organic compounds; liquid-liquid extraction for non-volatile compounds; solid phase extraction for semi-volatile and non-volatile compounds; solid phase microextraction (SPME), and fabric phase sorption extraction (FPSE) for the extraction of a wide variety of substances (Riboni et al., 2023; Nerín et al., 2022).

Regarding the analysis of volatiles and semi-volatiles present in FCMs, which can alter the flavor, smell and properties of the packaged foodstuff (Úbeda et al., 2019b), gas chromatography (GC) combined with mass spectrometry (MS) using electron impact ionization (EI) is normally used. It is a hard ionization technique, capable of ionizing virtually any organic compound robustly, producing highly reproducible fragmentation patterns, and allowing the acquired spectra to be compared with references from commercial mass spectra scientific libraries. Additionally, alternative approaches, like the use of normalized retention time index, may be utilized to enhance confidence in the identification.

However, the process of identification becomes difficult if the compound is not included in the library or if the sensitivity of the MS is inadequate for accurate mass verification. On the other hand, atmospheric pressure gas chromatography (APGC) and chemical ionization (CI) are viewed as gentle ionization methods that produce fewer fragments. High-resolution mass spectrometry (HRMS) stands as one of the most effective tools for examining unknown substances. Combining both APGC and HRMS techniques, accurate molecular ion mass can be obtained, even at low levels, to determine the structure of the molecule when not visible in the EI spectrum. APGC provides simplicity, flexibility, and the ability to form various adducts ($[M + H]^+$, $[M - H]^+$, $[M + N]^+$, $[M + O]^+$, among others), which enhance confidence in the elucidation of biopolymer composition. Hence, the APGC ionization method provides distinct structural details compared to EI, making them complementary approaches (Bradley, 2010; Úbeda et al., 2019b; Osorio et al., 2019; Riboni et al., 2023; Salazar et al., 2017).

This complementarity for non-targeted analysis was demonstrated by Osorio et al. (2019) for identification of solvent-extracted compounds from starch-based material, showing that glycerol, tetradecanoic acid, ethyl ester, 2-palmitoglycerol, and 9,12-octadecadienoic acid methyl

Table 1

Analytical techniques used in the investigation of migrants from bio-based and/or biodegradable materials.

Sample/Polymeric material	Extraction method	Analytical technique detection system	Potential migrants	Reference
Starch and PLA biopolymers (powder, pellets, cups and dishes)	Solvent extraction (MeOH) and ultrasonication (1 h/40 °C)	GC-EI-MS and APGC-Q/ToF	Degradation products of the material (alcohols and carbonyl compounds with lower MW, lactones and furanones such as 4-hydroxy-3,5-dimethyl-2-furanone), antioxidants, lubricants, slip agents, plasticizers, oligomers	Osorio et al., 2019
Blend of 18 % PLA and polyester (pellets and film)	Dissolution (DCM, ultrasonication) and precipitation (EtOH, magnetic stirring, freezing) of the polymer	GC-MS and APGC-QTOF	Lactide, oligomers (AA-BD, [AA-BD] ₂), emulsifiers, slips agents, antiblocking additives, slip agents and degradation products	Úbeda, Aznar & Nerín, 2019b
PLA-based pellets, films and retails (trays)	MHS-SPME	GC-EI-MS	Degradation products: lactides, alkanes, aldehydes (acetaldehyde), alcohols, acetone, acetic acid and 2,3-pentanedione	Salazar et al., 2017
Multilayer films: PLA, ecovio® EXP 0.5 SL® (ecoflex® and PLA), PVOH	Solvent extraction (MeOH)	GC-Q-MS and UPLC-ESI-Q-TOF-MS	Adhesive monomers, antioxidants, surfactants, plasticizers, degradation products, biocides and lactone structures	Canellas, Vera & Nerín, 2015
PLA retails (yogurt cup, vegetable tray, coffee cup lid)	Solvent extraction (MeOH) and ultrasonication (1 h)	GC-EI-QTOF-MS/MS	Acids (saturated and unsaturated fatty acids) and esters were identified	Zimmermann, Dierkes, Ternes, Völker, & Wagner, 2019
Blend of PLA and polyester (pellets and film)	Dissolution (DCM, ultrasonication) and precipitation (EtOH, magnetic stirring, freezing) of the polymer	ULPC-ESI-MS (QTOF) and ULPC-ESI-MS (QqQ)	Cyclic oligomers from the polyester component, PLA oligomers and additives (plasticizers and light stabilizers)	Aznar et al., 2019
PLA-based pellets and films	Dissolution (DCM, ultrasonication) and precipitation (EtOH, magnetic stirring, freezing) of the polymer	UPLC-QTOF-MS, with and without ion mobility (IM)	39 PLA oligomers (cyclic and linear), from n = 2 to n = 16, were identified	Úbeda, Aznar, Alfaro & Nerín, 2019a
PLA retails (yogurt cup, vegetable tray, coffee cup lid)	Solvent extraction (MeOH) and sonication (1 h)	UPLC-ESI-QTOF-MS	Compounds used as adhesive (mono(2-acryloyloxyethyl) succinate) and processing aid (pentaethylene glycol) were detected	Zimmermann et al., 2021
Bio-PBS and starch blend pellets	SPE	HPLC-ESI-QTOF-MS	Degradation products, stabilizers, plasticizers, organophosphorus compounds, antioxidants, benzoic acids, etc.	Klein et al., 2021
PBS resin Ecopond A200 and PBAT resin Ecopond A400	PBS: solvent extraction (EtOH/THF/acetone) by Soxhlet extractor PBAT: dissolution in chloroform, hexafluoroisopropanol, ACN	GPC, MALDI-FTICR-ESI-MS and UPLC-FTICR-ESI-MS	PBS: cyclic esters with repeating unit 2–8 PBAT: cyclic esters with repeating unit 1–10 (or more)	Zhang et al., 2023
PBA	Direct analysis	MALDI-TOF/TOF CID	The most prominent series of peaks were from the linear dibutanol-capped oligomers (2–39 repeat units), with cyclic oligomers being second, followed by species butanol-carboxyl and butanol-glycol terminated	Gies et al., 2012
PBAT pellet, PBAT/MFS pellet and PBAT/MFS blend film	HS-SPME	GC-MS	Several additives (surfactants, lubricants, adhesives, antioxidants, processing aids), by-products of processing (cyclopentanone, tetrahydrofuran and 2-sec-butylcyclopentanone) and oligomers (1,6-dioxacyclododecane-7,12-dione) were identified	Lin et al., 2023
Blend composition: PBAT-TPS, PBAT-PLA, PBAT-PHB	Solvent extraction (water) and derivatization	GC-EI-MS	Compounds regularly used in the formulation of biodegradable materials: dicarboxylic acids, hydroxyacids, diols, triols, glycerol dimers and trimers, terephthalic acid, etc.	Serrano-Ruiz, Eras, Martin-Closas, & Pelacho, 2020
PEF granulate	Solvent extraction (ACN/DCM)	UPLC-ESI-QTOF-MS and HPLC-UV	20 different oligomers below 1200 m/z were identified, being cyclic oligomers the most abundant oligomer group	Hoppe et al., 2018b
43 consumer products and raw materials: 27 bioplastics (PLA, PHA, PBS, PBAT, Bio-PE, Bio-PET) and 16 plant-based materials (starch, cellulose, bamboo)	Solvent extraction (MeOH) and ultrasonication (1 h)	UPLC-QTOF-MS/MS	343 compounds including monomers, oligomers, plastic additives, antioxidant degradation products, lubricants and NIAS	Zimmermann et al., 2020

Abbreviations: PLA, polylactic acid; MeOH, methanol; GC-EI-MS, gas chromatography-electron ionization-mass spectrometry; APGC-Q/ToF, atmospheric pressure gas chromatography with a quadrupole/time of flight mass analyzer; MW, molecular weight; DCM, dichloromethane; EtOH, ethanol; AA-BD, adipic acid-butanediol; MHS-SPME, multiple headspace – solid phase micro extraction; PVOH, polyvinyl alcohol; GC-Q-MS, gas chromatography-quadrupole-mass spectrometry; UPLC-ESI-Q-TOF-MS, ultra-high performance liquid chromatography coupled with electrospray ionization-quadrupole-time of flight-mass spectrometry; GC-EI-QTOF-MS/MS, gas chromatography-electron ionization- quadrupole-time of flight- tandem mass spectrometry; ULPC-ESI-MS (QqQ), ultra-performance liquid chromatography coupled with electrospray ionization-triple quadrupole mass spectrometry; PBS, polybutylene succinate; SPE, solid-phase extraction; HPLC-ESI-QTOF-MS, high-performance liquid chromatography coupled with electrospray ionization-quadrupole-time of flight-mass spectrometry; PBAT, poly(butylene adipate-co-terephthalate); THF, tetrahydrofuran; ACN, acetonitrile; GPC, gel permeation chromatography; MALDI-FTICR-ESI-MS, matrix-assisted laser desorption/ionization-Fourier transform ion cyclotron resonance-electrospray ionization-mass spectrometry; UPLC-FTICR-ESI-MS, ultra-high performance liquid chromatography coupled with Fourier transform ion cyclotron resonance-electrospray ionization-mass spectrometry; PBA, polybutylene adipate; MALDI-TOF/TOF CID, matrix-assisted laser desorption/ionization time-of-flight/time-of-flight collision-induced dissociation; MFS, modified starch; TPS, thermoplastic starch; PHB, polyhydroxybutyrate; PEF, polyethylene furanoate; HPLC-UV, high-performance liquid chromatography coupled with ultraviolet detection; PHA, polyhydroxyalkanoate; bio-PE, bio-based polyethylene; bio-PET, bio-based polyethylene terephthalate; NIAS, non-intentionally added substances.

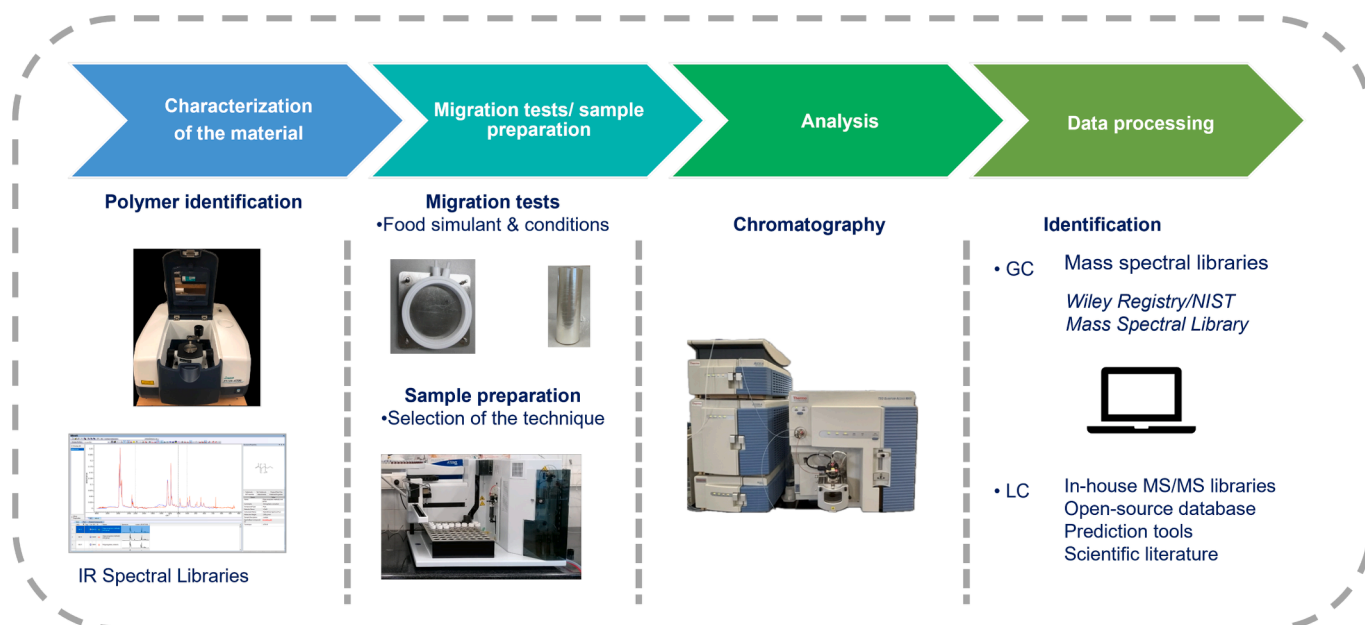


Fig. 2. Analytical strategy to evaluate the chemical safety of food packaging materials.

ester were only detected with EI; whereas tris(2,4-di-*tert*-butylphenyl) phosphite and two unidentified peaks were detected by APGC exclusively. Three oligomers, [AA-BD], [(AA)₂-(BD)₂], and [TPA-AA-(BD)₂] (AA: adipic acid, BD: butanediol), were also recognized as degradation products of polymeric resins. This complementarity was also observed by Úbeda et al. (2019b) when examining a combination of PLA and polyester, identifying fifteen distinct volatile compounds, including lactide (a cyclic form of lactic acid) not approved in Regulation (EU) 10/2011 (European Commission, 2011), or cyclopentanone by GC-MS. APGC-MS exclusively found the cyclic dimer [AA-BD]₂ likely originating from the polyester component.

In the work of Lin et al. (2023), volatile compounds in PBAT pellet, PBAT/MFS pellet, and PBAT/MFS blend film were analyzed using GC-MS and sixteen volatile substances were detected comprising several NIAS and additives, usually processing byproducts and oligomers such as 1,6-dioxacyclododecane-7,12-dione, an oligomer formed by the polymerization of the monomers BD, and AA through manufacturing of PBAT, which was detected in the raw materials and the final product with the highest contents. This last compound was also detected as one of the dominant peaks in the biodegradable multilayer materials analyzed by Canellas et al. (2015), along with monomers used in adhesives, antioxidants, surfactants, plasticizers, etc.

A technique applied for the quantification of the concentration of volatile organic compounds in solid matrices is multiple headspace – solid phase microextraction (MHS-SPME) GC, which allows to avoid the matrix effect, the use of solvent as well as the concentration like multiple headspace extraction as it was shown in the analysis of PLA based materials in diverse forms reported by Salazar et al. (2017).

Concerning the analysis of non-volatiles, liquid chromatography (LC), and in particular ultra-high pressure liquid chromatography (UHPLC), linked to HRMS, is the most utilized in the determination of non-volatile and thermolabile compounds in bioplastic materials (Aznar et al., 2019; Bradley, 2010). Electrospray (ESI) is the ionization source most commonly used, allowing for gentle ionization of the analytes. In this case, without reference libraries, more MS experiments must be conducted to increase the identification confidence. Although triple quadrupole (QqQ) analyzers are suggested for quantification, hybrid HRMS analyzers, like quadrupole time-of-flight (QToF) and Q-Orbitrap, are favored for non-targeted analysis due to their precise mass measurements of precursor ions and fragments (Riboni et al., 2023).

For example, in the research carried out by Aznar et al. (2019), non-volatile components extracted from pellets and films created using a PLA/bio-PE mixture were analyzed by UPLC-MS (QToF). The most intense compounds were found in the polyester section and consisted of cyclic oligomers made up of butanediol, adipic acid, and phthalic acid (PA). These compounds were represented by the formulas [AA-BD]₂, [PA-BD-AA-BD], [AA-BD]₃, and [PA-BD-AA-BD-AA-BD]. Three PLA cyclic oligomers consisting of lactic acid monomers were also identified, as well as plasticizers and light stabilizers; all of them were also identified in bio-based materials analyzed by Bradley (2010). Chromatographic peaks showing the same *m/z* interval step indicate the presence of non-volatile oligomers resulting from the appearance of monomer units (Wrona & Nerín, 2020). Also, in samples of PLA pellets and films analyzed by Úbeda et al. (2019a), 24 oligomers were detected, where half of them were cyclic and the other half linear. Each compound had the monomeric unit with molecular formula C₃H₄O₂ and shared fragmentation spectra (89.0600, 145.0503, and 217.0709 *m/z*, indicating C₃H₅O₃, C₆H₉O₄, and C₉H₁₃O₆ formulas respectively), which confirmed the similarity of their structures.

In 2020, Zimmermann et al. (2020) extracted a total of 43 bio-based and/or biodegradable consumer products and raw materials that mainly covered materials in contact with food and characterized the compounds present by non-target analysis using ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry/mass spectrometry (UPLC-QToF-MS/MS) finding a great variety of substances (>1000 chemical characteristics each in 80 % of the samples). The materials with the most compounds identified were those based on starch, cellulose and bio-PE. Three hundred forty-three substances could be tentatively identified including monomers (2-ethoxyethyl hexadecyl (2E)-2-butenedioate), oligomers (cyclic lactic acid oligomer), plastic additives (erucamide, N,N'-1,4-butanedioldihexadecanamide and Irganox 1076), lubricants (N,N'-ethylenebis(palmitamide)) and NIAS (tris(2-nonylphenyl) phosphate, degradation product of the antioxidant tris(nonylphenyl) phosphite). The most prevalent feature with *m/z* 641.6915 was detected in 37 samples but remained unidentified.

PEF polymer oligomers were also investigated by solvent extraction and HRLC-MS in a study by Hoppe et al. (2018b). A total of 20 oligomers were found, 87 % of which were cyclic oligomers formed by furandicarboxylic acid and monoethylene glycol units. MS fragmentation

experiments of the PEF oligomers presented similar fragmentation patterns with 277, 249, and 183 m/z , which support the suggested structures.

The release of chemical compounds from different plastic pellets after UV irradiation was evaluated through a screening via LC-QTOF by Klein et al. (2021), and the researchers discovered that UV irradiation favored the release of active compounds, being biodegradable pellets

(bio-PBS and starch blend) those that showed the highest intensities.

There are promising techniques as alternatives to chromatography based on direct desorption/ionization of analytes from the sample, for example, ambient techniques (AMS) such as direct analysis in real time coupled to mass spectrometry (DART-MS), the atmospheric solids analysis probe coupled to quadrupole time-of-flight mass spectrometry (ASAP-QTOF-MS), and the matrix-assisted laser ablation (MALDI). In

Table 2
Chemical structure of bio-based and biodegradable monomers and polymers.

Polymer Name	Monomer Name	Chemical Formula	Polymer Structure	Monomer Structure
PLA	Lactic acid	$(C_3H_4O_2)_n$		
PHB	3-Hydroxybutyric acid	$(C_4H_6O_2)_n$		
PBS	Succinic acid and 1,4-butanediol	$(C_8H_{12}O_4)_n$		
PBAT	Terephthalic acid, adipic acid, and 1,4-butanediol	$(C_{12}H_{12}O_4)_x(C_{10}H_{16}O_4)_y$		
Bio-PE	Ethylene	$(C_2H_4)_n$		
Bio-PP	Propene	$(C_3H_6)_n$		
Bio-PET	Monoethylene glycol and terephthalic acid	$(C_{10}H_8O_4)_n$		
Bio-PEF	Monoethylene glycol and 2,5-furandicarboxylic acid	$(C_8H_6O_5)_n$		
Bio-PA11	11-Aminoundecanoic acid	$(C_{11}H_{21}NO)_n$		
Bio-PTT	Terephthalic acid and 1,3-propanediol	$(C_{11}H_{10}O_4)_n$		

this case, the use of HRMS is required to obtain the unique identification of the compounds. They have the strengths of being quick analyses that do not require prior sample pretreatment, but they also present weaknesses because of a strong matrix effect, adduct formation, and complex spectra (Riboni et al., 2023). Very recently, Zhang's research group (Zhang et al., 2023) used MALDI-FTICR-MS to explore the substances present in PBS or PBAT materials by detecting cyclic esters with repeating units 2 to 8 in the solution extracted from PBS resin, while esters were found cyclic with repeating units 1 to 10 in PBAT derived from three monomers.

Inductively coupled plasma mass spectrometry (ICP-MS) is the primary method most frequently employed to detect and measure inorganic nanoparticles added to enhance the characteristics of bio-based and/or biodegradable packaging. Moreover, nanoparticles' size, shape and image can be determined through scanning electron microscopy (SEM), transmission electron microscopy (TEM), or atomic force microscopy (AFM) (Wrona & Nerín, 2020).

Often, analytical standards for individual monomers, oligomers, and polymers are not commercially available for quantification (Table 2). This is why several semi-quantitative approaches have been developed to quantify oligomers. Some of them are based on the use of an oligomeric substance as a calibration standard for all oligomers, such as bis(2-hydroxyethyl) terephthalate (BHET). Others are based on the use of a standard analogue (commercially available substance with similar structure and physicochemical properties) as an external standard, for example, BADGE·2H₂O to quantify BADGE derivatives, or dimethyl 2,5-furandicarboxylate to quantify PEF oligomers. However, these approaches have limitations and can lead to inappropriate quantification since it is usually assumed that all oligomers show the same ionization response or the same maximum UV absorption wavelength, but recent studies point out differences between the behavior of different oligomers. Another approach involves the synthesis of the oligomeric compounds themselves or their deuterium-labeled derivatives, which is more laborious and time-consuming. Therefore, alternative quantitative strategies need to be developed (Hoppe, de Voogt, & Franz, 2016; Tsochatzis, Lopes, Kappenstein, Tietz, & Hoekstra, 2020; Wrona & Nerín, 2020; Vázquez-Loureiro et al., 2023; Hayrapetyan et al., 2024; Hoppe et al., 2018b).

5. Migration studies from bio-based and/or biodegradable FCMs

The transfer of harmful chemical substances from FCMs to the environment or food, although it is often underestimated, is of concern to consumers, healthcare professionals, governments, and businesses.

It is critical to evaluate the process of migration of chemical substances from FCMs to food as it could alter the composition of food, modify the organoleptic properties, or even imply a hazard to the consumer's health (Aznar et al., 2019; Osorio et al., 2019; Agarwal et al., 2023). The goal of food safety is to identify and reduce or remove risks linked to materials utilized in packaging throughout the life cycle, with the ultimate goal of ensuring safety for human and environmental health (Coalition, 2011).

To ensure that food packaging materials can be managed safely, they must meet established standards. In European legislation, to ensure the protection of human health, all items intended to be in contact with food, no matter the material used (including those made from bio-based materials), must meet the requirements set by the Framework Regulation (EC) 1935/2004 (BSI Group, 2023; European Commission, 2004).

In Europe, bio-based and/or biodegradable polymers are also regulated by Commission Regulation (EU) 10/2011 of 14 January 2011, which establishes the list of approved monomers, starting substances, and additives for the production of plastic materials in contact with food, with its restrictions and specifications (European Commission, 2011). Furthermore, the substances used must not compromise the material biodegradability (Geueke, 2014). Migration tests can be performed by direct measurement in food (these results shall prevail) or

using food simulants permitted by Commission Regulation (EU) No 10/2011 (European Commission, 2011; EFSA, 2016; Van den Oever et al., 2017). Standardized testing conditions used for conventional fossil-derived plastics are expected to be adequate for bio-based and/or biodegradable plastic materials as well. There are two types of migration tests: overall migration, encompassing the sum of all moving packaging non-volatile substances released per unit packaging area under specific predetermined conditions, or specific migration, which relates only to specific known substance or family of substances (Van den Oever et al., 2017; Osorio et al., 2019). For example, Bucci, Tavares, and Sell (2007) evaluated the total migration of PHB packaging in different simulants (acetic acid 3 %, water, ethanol 15 % and heptane) obtaining values of 0.68 mg/dm², which was under the overall migration limit (OML) recommended by Agência Nacional de Vigilância Sanitária of the Ministry of Health of Brazil (8 mg/dm² or 50 mg/kg of food simulant) and by the Regulation EU 10/2011 (European Commission, 2011) (10 mg/dm² or 60 mg/kg of food simulant). However, information on the actual composition of materials used for polymer manufacturing is often confidential, and this, combined with the lack of commercially available analytical standards for confirmation, makes identification a very complex task and critical for a comprehensive evaluation (Hoppe et al., 2016; Karmaus, Osborn, & Krishan, 2018; Van den Oever et al., 2017; Osorio et al., 2019).

Bio-based and/or biodegradable packaging materials contain complex mixtures of chemicals, which include the intentionally added substances (IAS), used in the manufacture of the polymer, such as monomers, additives, and other starting substances, and the so-called NIAS, which may be present in the polymer due to various factors like impurities in the raw material, degradation and/or reaction processes. Both of them can migrate to food, and because of that, migration tests should be carried out for an adequate risk assessment of the materials (Zimmermann et al., 2020; Hoppe et al., 2018b; Aznar et al., 2019).

To date, little research has addressed the chemical safety of bio-based and/or biodegradable polymers for food contact applications. However, it is currently unknown if they present a safer alternative in terms of the chemicals they contain. Scientific literature suggests that migrating biodegradable and/or bio-based polymers have a toxicity comparable to that of traditional plastics (Zimmermann et al., 2020). However, Castle (2004) suggested that utilizing natural biological materials in packaging could increase the potential risks due various occurring contaminants in biomass resources like agri-food by-products. These risks may include inorganic contaminants, organic chemicals, heavy metals, residues such as pesticides, mycotoxins, plant toxins, allergens, etc. (BSI Group, 2023; Castle, 2004). In line with this, a recent study has demonstrated the migration of plant ingredients, pesticide residues and mycotoxins from a food contact material PBAT/modified starch blend film (MFS). The authors applied a non-targeted screening to investigate the chemicals transferred from the biodegradable material, and identified herbicides, pesticides fungicides and their oxides as well as three mycotoxins, specifically T-2 toxin, tentoxin and patulin. T-2 toxin migrated mainly to high ethanol content simulants and, on the contrary, tentoxin migrated to acidic and low ethanol content simulants, and patulin did not migrate into the food simulants. The authors highlight the high toxicity of these substances, therefore, in the risk assessment, in addition to the consumer's exposure to food contact substances, exposure to mycotoxins, pesticides, etc. as a consequence of the migration from these materials must be also considered (Lin et al., 2023). Moreover, the handling of these substances will also create a potential NIAS source that can transfer onto food upon contact (Castle, 2004). Furthermore, the possible migration of nanoparticles used in the manufacture of bio-nanocomposites, is another concern to consider for future packaging applications (Geueke, 2014; Naser, Deiab, & Darras, 2021). Due to increasing environmental worries and the necessity to lessen reliance on plastics made from petroleum, human exposure to chemicals migrating from bio-based polymers is expected to rise (Zimmermann et al., 2020).

Ultimately, as newer comonomers are being used in new materials formulation, it is imperative to highlight the potential occurring and migration of oligomers. Oligomers are made up of a few monomeric units and can be either cyclic or linear, forming during polymerization when it is incomplete or when polymer chains degrade during material processing (Hoppe et al., 2016; Hoppe, de Voogt, & Franz, 2018a; Paseiro-Cerrato, MacMahon, Ridge, Noonan, & Begley, 2016; Hoppe, Fornari, de Voogt, & Franz, 2017; Wrona & Nerín, 2020; Aznar et al., 2019; Hoppe et al., 2018b). They are often included within the group of NIAS, but their formation appears to be inevitable and even thermodynamically favored, so they could be considered as specific substances accompanying polymers (Hoppe et al., 2016; Lopes, Tsochatzis, Karasek, Hoekstra, & Emons, 2021). If the monomers used in the production of the polymer are known, possible oligomers may be predicted, and an oligomer database can be built, thus facilitating their identification (Hoppe et al., 2016). Their identification and quantification are considered of special interest by the EFSA and the European Commission (Tsochatzis et al., 2020). EFSA reported multiple opinions stating a specific migration limit (SML) of 0.05 mg/kg of food for the combined oligomeric fraction under 1000 Da that can migrate from new copolymers to foods (EFSA, 2014a; EFSA, 2014b; European Commission, 2011; Lopes et al., 2021).

In the absence of toxicity data, EFSA introduced the Threshold of Toxicological Concern (TTC) approach to classify the hazard of an individual substance (EFSA Scientific Committee, 2012; EFSA, 2016; Wrona & Nerín, 2020; Lopes et al., 2021). Theoretical toxicity levels may be determined for each compound by applying Cramer's rules based on the compound's molecular structure. The compounds can be categorized into three categories: class I (low toxicity), class II (medium toxicity), and class III (high toxicity) (Cramer, Ford, & Hall, 1976).

As can be seen in the literature, the transfer of migrants to food depends on the type of polymer material, and there are no exhaustive studies that compare the migration behavior of chemical compounds from bio-based packaging and packaging from fossil fuels. Therefore, research on the migration of particular chemical substances from various food packaging materials is necessary (Wrona & Nerín, 2020). Special focus is needed on low molecular weight chemical compounds, as it is generally recognized that molecules of molecular weight greater than 1000 Da have lower diffusion coefficients and are not physiologically absorbed from the gastrointestinal tract, except fluorocarbons (EFSA, 2016; EFSA, 2008; Osorio et al., 2019). Some examples of migration studies carried out in biodegradable and/or bio-based FCMs are shown in Table 3.

Global and specific migration tests were carried out on prototype cup samples of a biopolymer based on starch and PLA, filling the cups with the corresponding simulants. The global migration results were lower than the OML, except for ethanol 95 % and isooctane as vegetable oil substitutes, which may have caused an overestimation due to partially dissolving the polymer. This indicates a need to reformulate the material used with lipophilic foods. The compounds TPA-AA-(BD)₂, 2-acetyl-2,3,5,6-tetrahydro-1,4-thiazine, and 4-hydroxy-3,5-dimethyl-2-furanone, classified as Class III-substances following the Cramer rules, were found in the specific migration test carried out with ethanol 95 %. However, the findings indicated that repetitious use resulted in a decrease in the migration of volatile NIAS (Osorio et al., 2019).

Asensio, Montañés, and Nerín (2020) examined the migration of specific substances in disposable wheat pulp and wood dishes used in catering services with food simulants. In this research, SPME-GC-MS identified 67 compounds, most of which are commonly used in producing paper, adhesives, and food packaging, and they comply with legal standards, except nonanal (10.71 µg/kg) and docosanal (24.12 µg/kg), which exceed the limit of 10 µg/kg for not listed (no authorized) compounds in Regulation 10/2011 (European Commission, 2011).

Osorio et al. (2020) conducted a study analyzing migrants from bamboo-based biopolymer packaging through DART-SVP (direct real-time analysis coupled to standardized voltage and pressure), enabling

the simultaneous identification of volatile and non-volatile migrants quickly and effectively. This approach is presented as an effective way to assess the safety and legality of FCMs.

PLA has been thoroughly investigated as a bio-based and biodegradable material, and different studies have been published about the migration of oligomers from PLA (Wrona & Nerín, 2020). Generally, it was seen that PLA undergoes thermal degradation through the same proposed mechanistic pathways as polyesters (hydrolysis, intramolecular transesterification, intermolecular transesterification and intermolecular transesterification), giving rise to cyclic or linear oligomers (Dedieu et al., 2022).

In line with this, Conn et al. (1995) researched the migration of PLA polymer films using food simulants, reproducing the most severe conditions of temperature and time, and found lactic acid, lactide, and lactoylactic acid (lactic acid dimer). The US Food and Drug Administration (FDA) considers lactic acid as generally recognized as a safe (GRAS) substance and it is approved by the European Commission for food contact purposes, while lactide has demonstrated low intrinsic toxicity (FDA, 2024b; Geueke, 2014; Reichert et al., 2020; Siracusa et al., 2008).

In the study carried out by Úbeda et al. (2019b), after exposing the PLA blend film to the food simulants, only the presence of AA-BD and lactide were identified in ethanol 95 % using GC-MS, while none in aqueous simulants. Therefore, under the conditions studied, this material would be desirable to be used in water-based foods rather than oily foods (Úbeda et al., 2019b). However, linear PLA oligomers were found to be the predominant migratory components in ethanol 10 % analyzed by UPLC-QTOF-MS (Úbeda et al., 2019a). Opposite results were obtained by Gavril et al. (2019), as there was no migration of non-volatile compounds in the simulants with the highest percentage of water (acetic acid 3 % and ethanol 10 %), and no migration of volatile compounds was detected in ethanol 95 % in the GC-MS system. Gavril et al. (2019) demonstrated that the incorporation of sage leaves and lemon balm into a PLA structure reduced the migration of non-volatile compounds in ethanol at 95 % such as oligomers of polylactic acid, cyclic and linear (which belong to the Cramer's class I and class III, respectively), with sage showing a more pronounced effect; and volatile compounds in the simulants with the highest percentage of water.

Aznar et al. (2019) also investigated migration tests on their samples of a mixture of biodegradable fossil-based polyester and PLA by UPLC-MS(QTOF). They found that the maximum migration rates occurred in ethanol 95 %, with higher amounts of newly formed compounds detected in acetic acid 3 %. As well as in the study of Úbeda et al. (2019a), in no case were cyclic PLA oligomers detected in migration, likely due to their reaction with simulants, resulting in the opening of the cycle and formation of new linear compounds (Aznar et al., 2019; Úbeda et al., 2019a).

The migration of biodegradable multilayer teacups to a food sample as hot and cold tea was analyzed using UPLC-ESI-IMS-Q/TOF for the identification of non-volatile compounds and HS-SPME-GC-MS to analyze the migration of volatile compounds (Canellas, Vera, Nerín, Dreolin, & Goshawk, 2022). Six out of the eight migrants found in the tea were non-intentionally added oligomers. Apart from tributyl phosphate, which falls under Class III substances as per the Cramer rules, the NIAS identified were categorized as Cramer class I. In addition, the migration of five cyclic oligomers to hot tea varied from 2.56 to 4.68 mg/kg, surpassing the SML set for Cramer class I compounds (1.8 mg/kg) following the TTC (Kroes et al., 2004).

There is no information available regarding the study of the migration of specific components from PHA-based packaging. There is a study of the total migration of PHB films to different food simulants where a total migration lower than the recommended limit was demonstrated (Khosravi-Darani & Bucci, 2015; Bucci et al., 2007). The primary degradation procedure of PHB gives rise to degradation products, specifically crotonic acid and oligomers with a crotonate terminal group (Dedieu et al., 2022).

Table 3

Migration from bio-based and/or biodegradable materials into food and food simulants.

Sample	Simulants	Extraction method	Analytical technique detection system	Migrants	SML, NOAEL, TTC limits	Reference
Polysaccharide-based films made with pea starch, organocatalytic acetylated pea starch and pectin	EtOH 10 %, EtOH 50 %	Direct injection	UHPLC-TIMS-TOF-MS/MS	Several organic compounds, polysaccharide-related compounds, or lipids were detected (glycerol, monoacetylated maltose, dibutyl phthalate, PEG, 2,5-diketo-D-gluconic acid, 3-β-galactopyranosyl glucose)	From the <i>in silico</i> assessment, all identified compounds can be considered of no safety or health concern following the Kroes model	Tsochatzis et al., 2023
Starch and PLA biopolymers (cups)	EtOH 10 %, acetic acid 3 %, EtOH 95 %	Direct injection	GC-EI-MS	14 different compounds were found in EtOH 95 % such as furanone, oligomers, etc.	Migration values above the OML (60 mg/kg) were obtained in EtOH 95 %, as well as above the TTC value (1.8, 0.54 and 0.09 mg/kg) for many volatiles after the first use of this material	Osorio et al., 2019
Cups and dishes based on PLA and starch	EtOH 10 %, acetic acid 3 %, EtOH 95 %	Direct injection	UPLC-ESI-Q-TOF-MS, DART-MS, and ASAP-Q-TOF-MS GC-MS	Polyester oligomers, cyclic and linear, with a higher tendency to migrate to fat food	–	Osorio, Aznar, Nerín, Elliott, & Chevallier, 2022
Wheat and wood pulp dishes available in the market	EtOH 10 %, acetic acid 3 % and EtOH 95 %	SPME	GC-MS	The majority of identified migrants are used in the manufacture of paper, adhesives and in the food packaging industry. Compounds used in recycling paper/cardboard were also identified, as well as compounds related to the degradation of cellulose fiber	In general, migration values are very low and comply with the legislation (10 µg/kg for compounds not listed in EU Regulation 10/2011), except nonanal (10.71 µg/kg) and docosanal (24.12 µg/kg)	Asensio, Montañés & Nerín, 2020
Paper-based FCM (microwavable disposable paper plates and muffin cups)	EtOH 20 %, EtOH 50 % and food (oatmeal porridge, muffins and tomato soup)	For food: dSPE For food simulants: direct injection	LC-MS/MS	Migration of PFCAs and FTOHs to all food samples (to EtOH 50 % was higher than to real food samples). FTOHs did not migrate into EtOH 20 %	Estimated dietary PFAS exposure for children (1.06–5.67 ng/kg bw/day) exceeded EFSA's proposed safety threshold (0.63 ng/kg bw/day)	Lerch et al., 2022
Disposable FCM made of sugarcane bagasse or cellulose pulp derived from wood	EtOH 95 % and acetic acid 3 %	ASE and US	PFAS: HPLC-ESI-Q-Trap OPE: GC-EI-MS and HPLC-ESI-Q-Q-Q	PFAS mainly migrate towards aqueous acid foods (most abundant: PFBA and PFHxA), while OPE migrate towards hydrophilic and lipophilic foods.	TIBP and TCPPE exceeded the limit of 0.01 mg/kg	Simonetti et al., 2024
PLA sheets	Water, acetic acid 4 % and EtOH 20 %	Direct injection	LC-ESI-MS	Lactic acid and lactide were detected, as well as oligomers (from trimer to 13mer) were detected in EtOH 20 %	Lactic acid: 0.06–0.40 µg cm ⁻² (SML: 60 mg/kg) Lactide: not determined to 2.4 µg cm ⁻² (NOAEL: 100 mg/kg bw/day)	Mutsuga, Kawamura, & Tanamoto, 2008
Blend of 18 % PLA and polyester (pellets and film)	EtOH 10 %, acetic acid 3 %, EtOH 95 %	Liquid injection (EtOH 95 %) and HS-SPME (EtOH 10 %, acetic acid 3 %)	GC-EI-MS and APGC-QTOF	Only 3 compounds (lactide, AA-BD and [AA-BD] ₂) were identified in EtOH 95 %	–	Úbeda et al., 2019b
PLA-based pellets and films	EtOH 10 %, acetic acid 3 %, EtOH 95 %	Direct injection	UPLC-QTOF-MS	PLA linear oligomers and cyclic polyester oligomers	–	Úbeda et al., 2019a
Bioactive packaging based on PLA with powdered dry leaves of two medicinal plants (sage and lemon balm)	EtOH 10 %, acetic acid 3 %, EtOH 95 %	Direct injection (EtOH 95 %) and SPME (EtOH 10 %, acetic acid 3 %)	UHPLC-ESI-Q-TOF-MS and GC-MS	10 different PLA cyclic oligomers (n = 5–14) and one linear oligomer were observed in the EtOH 95 % migration by LC; while the volatile compounds originally present in plants were identified in EtOH 10 % and acetic acid 3 %	None of the films comply with (EU) No 10/2011 legislation in the case of migration in EtOH 95 %	Gavril et al., 2019
Blend of PLA and polyester (pellets and film)	EtOH 10 %, acetic acid 3 %, EtOH 95 %	Direct injection	ULPC-ESI-MS (QTOF) and ULPC-ESI-MS (QqQ)	Linear PLA oligomers and additives such as plasticizers	–	Aznar et al., 2019
Multilayer material for teacups: 40 % polyester + 60 % PLA	Hot and cold tea	Direct injection	UPLC-ESI-IMS-Q-TOF and HS-SPME-GC-MS	Benzisothiazolone (biocide), tributyl phosphate (plasticizer) and five polyester cyclic oligomers. Migration for hot tea (4.68 mg/kg) was higher than cold tea, exceeding the SML	–	Canellas, Vera, Nerín, Dreolin & Goshawk, 2022
PLA retails (yogurt cup, vegetable tray, coffee cup lid)	Ultrapure water	SPE	UPLC-ESI-QTOF-MS	Products made of PLA leached relatively few chemicals and most of the chemicals remain unknown	–	Zimmermann et al., 2021

(continued on next page)

Table 3 (continued)

Sample	Simulants	Extraction method	Analytical technique detection system	Migrants	SML, NOAEL, TTC limits	Reference
Multilayer films: PLA, ecovio® EXP 0.5 SL® (ecoflex® and PLA), PVOH	Tenax® (poly (2,6-diphenyl-p-phenylene oxide)	Extraction with MeOH	GC-Q-MS and UPLC-ESI-Q-TOF-MS	One IAS (2,4,7,9-tetramethyl-5-decyne-4,7-diol) and two NIAS coming from the adhesive were identified in this work, with migration values ranging from 0.81 to 2.07 mg/kg	The migration values and EDI were below the threshold established for this class of toxicity	Canellas et al., 2015
PBAT with 18 % of PLA	Acetic acid 3 % and pineapple juice	FPSE	UHPLC-ESI-MS-QTOF and UHPLC-ESI-MS-QqQ	21 oligomers were identified (cyclic and linear). The highest concentration value was found for cyclic [AA-BD] ₂ with 22.63 µg/g in 3 % acetic acid	–	Úbeda et al., 2021
PBAT/MFS blend film	EtOH 10 %, acetic acid 3 % and 4 %, EtOH 20 %, EtOH 50 %, EtOH 95 %	Direct injection	UPLC-HESI-Q-Orbitrap	134 non-volatile migrated compounds: additives, plant ingredients, synthetic by-products, oligomers (1,6-dioxacyclododecane-7,12-dione), pesticide residues, mycotoxins and solvent	Substances of great concern assigned (Risk I): pesticide residues, mycotoxins, surface modifiers, surfactants, compatibilizers, plasticizers, and adhesives	Lin et al., 2023

Abbreviations: NOAEL, no-observed-adverse-effect level; TTC, threshold of toxicological concern; EtOH, ethanol; SPME, solid-phase microextraction; GC-MS, gas chromatography-mass spectrometry; dSPE: dispersive solid phase extraction; LC-MS/MS: liquid chromatography followed by tandem mass spectrometric; PFCAs: perfluorinated carboxylic acids; FTOHs: fluorotelomer alcohols; PFAS: per- and polyfluorinated alkyl substances; EFSA: European Food Safety Authority; ASE: accelerated solvent extraction; US: ultrasonic; OPE: organophosphate ester; ESI-Q-q-Q: electrospray ionization triple quadrupole mass spectrometry; PFBA: perfluorobutanoic acid; PFHxA: perfluorohexanoic acid; TIBP: triisobutyl isomer; TCP: trichlorophenyl phosphate; SML, specific migration limit; UHPLC-TIMS-TOF-MS/MS, ultra-high performance liquid chromatography coupled to trapped ion mobility spectrometry and tandem mass spectrometry; PEG, polyethylene glycol; PLA, polylactic acid; GC-EI-MS, gas chromatography-electron ionization-mass spectrometry; UHPLC-ESI-Q-TOF-MS, ultra-high performance liquid chromatography coupled with electrospray ionization-quadrupole-time of flight-mass spectrometry; DART-MS, direct analysis in real time mass spectrometry; ASAP-Q-TOF-MS, atmospheric pressure solids analysis probe-quadrupole-time of flight-mass spectrometry; SPE, solid-phase extraction; PVOH, polyvinyl alcohol; MeOH, methanol; GC-Q-MS, gas chromatography-quadrupole-mass spectrometry; IAS, intentionally added substances; NIAS, non-intentionally added substances; EDI, estimated daily intake; UPLC-ESI-MS-Q/TOF, ultra-performance liquid chromatography-ion mobility separation-quadrupole time-of-flight mass spectrometry; HS-SPME-GC-MS, headspace solid-phase microextraction coupled with gas chromatography-mass spectrometry; LC-Q-Orbitrap-MS, liquid chromatography quadrupole-orbitrap mass spectrometry; GC-Q-Orbitrap-MS, gas chromatography quadrupole-orbitrap mass spectrometry; OML, overall migration limit; PBAT, poly(butylene adipate-co-terephthalate); FPSE, fabric phase sorptive extraction; UHPLC-ESI-MS-QqQ, ultra-high performance liquid chromatography coupled with electrospray ionization triple quadrupole mass spectrometry; AA-BD, adipic acid-butanediol; MFS, modified starch; HESI, heated electrospray ionization.

Vytejková et al. (2017) reported the global migration in PBS materials using the food simulant A. The results obtained were 1.7 mg/dm² for the PBSA/(90 % PBS with 10 % PBSA) film and 3.1 mg/dm² for the PBSA/(80 % PBS with 10 % PBSA and 10 % talc) film, which means that the global migration limit (OML) established in Regulation 10/2011 was not exceeded (European Commission, 2011).

So far, to the best of our knowledge, few studies carry out migration assays in real food samples. Úbeda, Aznar, Nerín, and Kabir (2021) performed migration assays of PBAT films in a real food sample (pineapple juice), as well as in acetic acid 3 % using FPSE with UHPLC-MS-QTOF. Twenty-one oligomers, including both cyclic and linear forms, were detected, with nine originating from PLA composed of [LA] (C₃H₄O₂) monomer units, and twelve from polyesters, composed of phthalic acid, adipic acid, and butanediol. Only two new cyclic compounds (PA-BD₄-AA₃ and PA₂-BD₃-AA), that were not found in acetic acid 3 %, were identified in the juice, which demonstrates the feasibility of the food simulant. The determined concentrations, semi-quantified using isolated oligomers, ranged from not detected to 22.63 µg/g (acetic acid 3 %) for the cyclic oligomer [AA-BD]₂, reaching a value of 19.64 µg/g in the pineapple juice sample.

Recently, Zhao et al. (2024) studied the migration of different additives, such as lubricants, plasticizers as well as degradation products of antioxidants from biodegradable packaging consisted of a mixture of PLA, PBAT and PBS into milk and the food simulant 50 % ethanol (v/v). The results showed that the migration occurs in a higher extension in the food simulants than in real food and only triethylene glycol exceeded the limits in the food simulant.

A PBAT/MFS composite film was evaluated under the most severe simulated migration conditions with six solutions, which were analyzed by LC-HRMS. Several non-volatile migrated substances, containing conventional additives, such as plasticizers, antioxidants, adhesives, lubricants, surfactants, surface modifiers, curing agents, flame

retardants, cross-linking agents, compatibilizers, production aids, preservatives, odorants, monomers, and anti-aging agent were identified. Some NIAS were also detected, such as plant ingredients, pesticide residues, mycotoxins, synthetic by-products, oligomers, and solvents. A more detailed discussion on contaminants of agri-food origin was commented above. As in the studies mentioned previously, the oligomers showed a greater affinity for alcoholic or fatty foods (Lin et al., 2023).

In cellulose-based food contact materials, special attention has been paid to per- and polyfluorinated alkyl substances (PFASs) due to the adverse effects they cause on human health and the negative impact on the environment (Barhoumi, Sander, & Tolosa, 2022). They are used in the FCMs to provide water and grease-repellent properties. Several studies have demonstrated that this class of compounds are able to migrate into food and food simulants.

Lerch, Nguyen, and Granby (2022) have reported the migration of perfluorinated carboxylic acids (PFCAs) and fluorotelomer alcohols (FTOHs) in all foods tested including oatmeal porridge, muffins, and tomato soup. Besides, the authors observed that the migration into 50 % ethanol (v/v) was considerably higher than into real foods.

More recently, Simonetti et al. (2024) analysed the presence of contaminants, specifically OPEs (organophosphorus phosphate esters) and PFASs, in bio-based and biodegradable food packaging materials. Using the HPLC-QTRAP-MS/MS technique, PFASs were quantified, while OPEs were analysed by HPLC-QqQ and GC-EI/MS. The results show that both contaminants are present in packaging materials, with baking papers being the most contaminated. PFASs migrate mainly towards acidic aqueous simulants, while OPEs migrate similarly towards hydrophilic and lipophilic simulants.

There is a rising interest in the food packaging sector in developing active packaging to interact with the content and thus improve its quality and safety. These active packaging are often designed using

biodegradable and bio-based materials combined with natural extracts. The purpose of this incorporation is to take advantage of their bioactive compounds, which have antioxidant and/or antimicrobial properties, so that they are released and extend the shelf-life of foods. For example, recently, Mellinas, García-Serna, Jiménez, and Garrigós (2024), developed and characterized active packaging based on bio-PE and natural extracts rich in tocopherols. Andrade et al. (2023) produced two PLA packaging materials incorporated with lemon by-products extract to retard the lipid oxidation of beef meat and almonds.

As noted in the literature, many migratory substances remain unknown, and limited toxicological data are available for many compounds. This lack of data, together with the lack of analytical standards, makes the quantification and then the human exposure assessment difficult (Tsochatzis, 2021). In addition, the behavior of these oligomers in the gastrointestinal system has been scarcely studied (Hoppe et al., 2018a). It is known that in the human body and animals, PLA is degraded and forms soluble oligomers that are then metabolized by cells (Nesic et al., 2020). Thus, this risk needs to be assessed, and specifications must be established according to source material (BSI Group, 2023).

6. Advances in safety evaluation and risk assessment of bio-based and/or biodegradable FCMs

The framework Regulation (EC) No 1935/2004 (2004) requires that all food-contact materials be safe, which means that they do not transfer their constituents in quantities that could represent a risk to human health. However, currently, there is no standardized protocol for its safety evaluation, which is particularly remarkable in the case of NIAS.

Following the European guidelines and those of the International Life Science Institute (ILSI) on food packaging materials, current approaches are focused on the combination of chemical analysis, especially using non-targeted screening analysis, *in vitro* bioassays, and *in silico* tools (Koster et al., 2015; Marin-Kuan et al., 2023a). The *in vitro* bioassays that are commonly performed are focused on genotoxicity, cytotoxicity, and endocrine activity (Groh & Muncke, 2017). Groh and Muncke (2017) presented an overview of *in vitro* cytotoxicity bioassays, *in vitro* genotoxicity bioassays, and *in vitro* endocrine activity tests used in FCMs studies. The review is illustrated with examples of evaluations of different packaging materials. The selection of a specific test or a battery of tests depends on the toxicological targets to be evaluated and the type of FCM (Koster et al., 2015).

These bioassays, however, present some limitations, such as sensitivity, thus/so some of them have been shown not to have sufficient sensitivity to detect genotoxic substances in the parts per billion (ppb) concentration range (Koster et al., 2015).

Lately, a testing protocol based on combining chemical analysis employing LC-MS and bioassays, specifically those including endocrine activity, genotoxicity, and metabolism-related targets, were developed to evaluate the safety of food contact coatings. The protocol provides guidance on sample preparation, migration, chemical analysis, and validated bioassays. An inter-laboratory study was conducted to apply the proposed protocol and, considering the results provided by the participants, some critical steps were identified. Regarding sample preparation and migration, different results of the laboratories may be attributed to the differences in the instrumentation and technique used and/or due to the contamination of the sample. In the case of the chemical analysis, the differences in the method and the instrument used can lead to different results, while concerning bioassays, the study suggests that standardization is needed. The authors concluded that harmonization between laboratories is crucial to reducing laboratory variability (Marin-Kuan et al., 2023a).

More recently, a novel approach, which combines HPTLC with genotoxicity bioassays, has been developed and successfully applied to evaluate the genotoxic potential of paper-based packaging materials (Marin-Kuan et al., 2023b).

There are very few studies collected in the literature on the risk assessment of FCMs, especially those on new bio-based and/or biodegradable materials.

Zimmermann et al. (2020) investigated the safety of a great variety of bio-based and/or biodegradable polymers and plant-based materials, including PLA, PHA, PBS, PBTA, starch, cellulose, bamboo, bio-PE, and bio-PET, by applying an approach based on chemical analysis and the *in vitro* toxicity. A non-targeted screening, using UPLC-QTOF-MS/MS, was used to identify of components and more than 300 priority compounds were tentatively identified, including both intentionally and non-intentionally added substances. The polymer extracts were subjected to several bioassays, namely baseline toxicity, oxidative stress response, and endocrine activity. Concerning the results of bioassays, the authors conclude that the extracts from cellulose and starch-based materials generally present a significant *in vitro* toxicity. The toxicity was less strong in raw materials than in final products and, compared with common petroleum plastics, bio-based and/or biodegradable polymers, and plant-based materials present similar toxicity regarding the chemicals that they contain.

7. Concluding remarks and future perspectives

The depletion of petroleum feedstocks and the environmental pollution caused by fossil fuel-based materials have prompted the industry of packaging to search for sustainable solutions. Bio-based and/or biodegradable polymers are being developed as an ecological alternative to petrochemical plastics. Among the bio-based and biodegradable materials, PLA is the polymer most extensively used in food packaging applications, and in recent years PHA has been promoted for their use as FCMs. Regarding bio-based non-biodegradable materials, PEF seems to be a promising polymer with improved barrier properties than PET, and its production is expected to increase considerably in the next years. The aliphatic biodegradable polyesters, such as PBS, and the aliphatic-aromatic (co) polyesters, such as PBST and PBAT, are currently being used in disposable cutlery and fast-food disposable packaging, respectively.

An important challenge is to develop polymers that comply with the regulations of FCMs and be environmentally friendly.

In relation to regulatory aspects, the current legislation is being reviewed and one of the issues addressed refers to the reduction of the use of hazardous chemicals, nevertheless the crucial aspect of safety is often disregarded, and more efforts have been devoted to the development of sustainable materials.

From the food safety point of view, it is foreseen that the growing number of novel co-monomers used to develop novel materials give rise to a growing number of possible oligomers. All these substances may migrate into the food. It is important to highlight that the identity of many of these substances is unknown and very limited toxicological data is available. Moreover, the lack of analytical standards hinders the migration quantification and migration limits cannot be enforced. Hence, special attention should be paid to the identification and quantification of these substances as an essential part of the risk evaluations.

Concerning the analysis, hyphenated techniques, namely GC-MS and LC-MS, have been widely applied to investigate potential migrants from bio-based and/or biodegradable polymers. High-resolution mass spectrometers, such as TOF and Orbitrap, are increasingly being employed since they provide a suitable combination of selectivity and sensitivity, giving more confidence in the identification of packaging chemicals. Non chromatographic techniques, such as ASAP-QToF-MS, DART-MS, or MALDI-TOF have been applied. However, notwithstanding the benefits in terms of time analysis and sample preparation, they present some limitations because of a strong matrix effect.

The current approaches in the risk assessment of packaging materials are focused on the combination of chemical analysis, particularly non-target analytical methodologies and *in vitro* bioassays, mostly genotoxicity, cytotoxicity, and endocrine activity. Standardization of the

protocols is necessary to achieve comparable results. Besides, due to the lack of toxicity data, *in silico* tools may be useful.

CRedit authorship contribution statement

Antía Lestido-Cardama: Writing – original draft, Methodology, Investigation, Conceptualization. **Leticia Barbosa-Pereira:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Raquel Sendón:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Juana Bustos:** Writing – review & editing, Methodology, Conceptualization. **Perfecto Paseiro Losada:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ana Rodríguez Bernaldo de Quirós:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

It is an article review

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