Review

Mass Spectrometry-Based Techniques for the Detection of Non-Intentionally Added Substances in Bioplastics

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Abstract: The safety of food contact materials is a hot topic since chemicals can migrate from packaging into food, thus raising health concerns about and/or producing changes in the organoleptic properties of foodstuffs. Migration tests are required to demonstrate the compliance with current regulations and to investigate the transferred compounds. In this context, mass spectrometry is the analytical technique of choice for the detection and quantitation of both intentionally added substances, such as antioxidants, stabilizers, processing aids, and non-intentionally added substances (NIAS). Untargeted strategies represent a major analytical challenge, providing a comprehensive fingerprinting of the packaging material and migrating components, allowing for NIAS identification. Hyphenated mass spectrometry-based techniques have been devised for screening the presence of migrating contaminants and for quantitation purposes. Both low-resolution (LRMS) and high-resolution (HRMS) methods were screened, with a special emphasis on the latter because of its capability to directly characterize food contact materials with minimal/no sample preparation, avoiding chromatographic separation, and reducing sample handling, analysis costs, and time. Examples related to the migration of contaminants from existing or newly developed bioplastic materials will be discussed, providing an overview of the most used MS-based methods, covering the state-of-the-art approaches from 2012 up to 2022.

Keywords: bioplastics; non-intentionally added substances; mass spectrometry; biopolymers; food contact materials

1. Bioplastics

Due to the ease of production, versatility, low cost, and excellent mechanical and chemical properties, plastics have become one of the most important manufactured materials in the 20th and 21st century [1,2], reaching a production of 390 million tons in 2021.

Petroleum-based polymers, and in particular polyethylene (PE), polypropylene (PP), and polyethylene terephthalate (PET), are today the most commonly used materials for food contact applications. Despite some valuable advantages, the main issue of plastics spread is their deleterious impact on both the environment and ecological systems; in fact, most disposable products end up in landfills or worse yet, are released into the environment, where it takes several centuries to be degraded, leading to serious health concerns on local ecosystems [1,3]. Alternative end-life perspectives of common plastics are recycling or incineration for energy recovery. Recycling is one of the most important matters from the early 2000s: In EU, plastics recycling reached more than 10 million tons in 2021, leading to the reintroduction of more than 5.5 million tons of recycled products, with

an increase rate of 15% compared to the previous year [2]. However, chemical deterioration of plastics during recycling has been demonstrated [4], introducing novel potential sources of contamination [5], which represent a particularly challenging issue especially for food contact applications.

To reduce the use of polymers deriving from fossil sources and provide more sustainable solutions, a transition to a circular economy approach is demanded: in this context, the Directive (EU) 2019/904 has banned the use of single use plastics [6], thus driving research towards the development of novel sustainable materials and production technologies. Biodegradability of products, use of monomers from renewable resources, and development of energy-effective production processes are the key points of this new vision [7].

In this scenario, the term bioplastics has been often misunderstood, being erroneously perceived by the general public as more sustainable, less persistent, and less toxic compared to conventional petrochemical polymers [1,3,8–10]. Actually, bioplastics is an umbrella term used to indicate plastics that can be bio-based, biodegradable or both [11], thus covering a wide range of materials. Therefore, bioplastics include both bio-based materials obtained from renewable carbon sources (but possibly non-biodegradable), allowing for a more sustainable manufacturing, and biodegradable plastics, which can be degraded when accidentally dispersed into the environment, regardless of the carbon sources from which they derive [1,8,9]. A schematic representation of bioplastics is summarized in Figure 1.
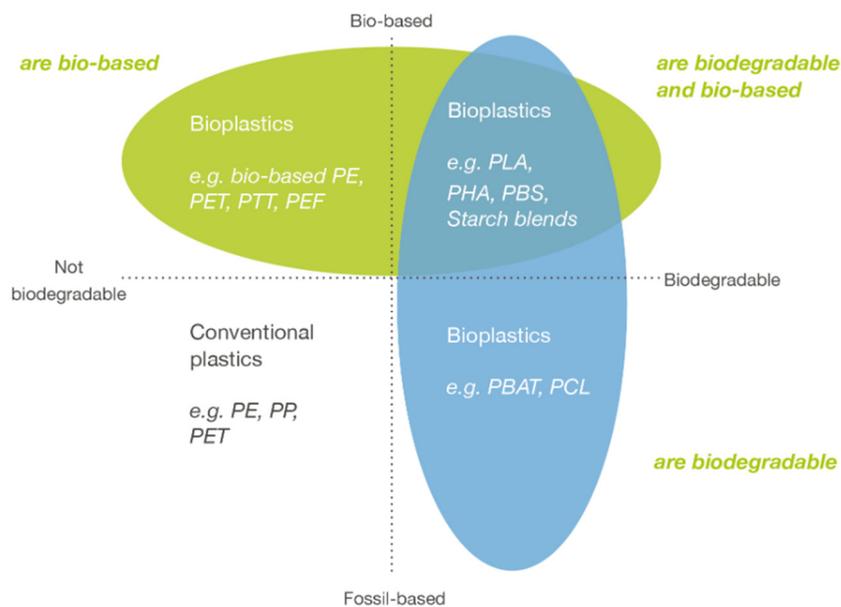

Figure 1. Schematic representation of bioplastics: on the *x*-axis is the biodegradability feature, on the *y*-axis is the origin of the monomer; reprinted with permission from ref. [11].

Despite representing a small percentage of the total plastics production, bioplastics manufacturing is growing at a rate of 10% per year [1], with Western Europe the largest market for biodegradable polymers (52%), followed by Asia and Oceania (25%), and the US (22%) [8]. The most common bioplastics include: (i) polylactic acid (PLA), a bio-based thermoplastic aliphatic polyester with properties similar to polystyrene, obtained by the polymerization of lactic acid (LA); (ii) polybutylene adipate terephthalate (PBAT), a copolyester of adipic acid (AA), 1,4-butanediol (BD), and terephthalic acid (THP), which is a fully biodegradable alternative to low-density PE; (iii) polybutylene succinate (PBS), a fully biodegradable thermoplastic polyester polymer resin with properties comparable to PP; (iv) starch-based materials, i.e., bio-based and biodegradable polymers often modified by cross-linking or by using additives to improve their physical and chemical properties [9,12]; and (v) polyhydroxyalkanoates (PHAs), a class of biodegradable polyesters produced by the bacterial fermentation of sugars and lipids, having characteristics close to PE and PP.

Recently, the research interest has been focused on the development of materials based on the use of easily available, cheap, and environmentally friendly feedstock, such as food wastes, non-edible parts of food crops, agricultural residues, and seaweed [7,13]. Novel processing techniques, such as electrospinning and stereocomplexation of enantiomeric polymers, together with novel post-production treatments, have been proposed to improve the material properties [1].

The impact of bioplastics on the environment is a matter of great concern [14]: it has been demonstrated that commercially available bioplastics do not easily biodegrade in the natural environment and can exert harmful effects to the ecosystems comparable to conventional plastic materials [9,15–21]. It has been observed that biodegradable bioplastics can require several years to be fully degraded under environmental conditions; in addition, a high degree of fragmentation in micro- and nanoplastics has been highlighted [21,22]. Another challenging point is the conditions under which degradation takes place: anaerobic or aerobic degradation, degree of humidity, temperature, and the presence of specific microorganisms can result in very different processing rates. As an example, PLA presents very limited degradation in an anaerobic landfill or a soil medium. Furthermore, bio-based materials pose other emerging safety concerns related to the risk associated to the possible release of allergenic proteins from food contact materials [23].

Finally, the presence of potentially toxic compounds, including both intentionally added substances (IAS) and non-intentionally added substances (NIAS), has sparked an important debate on the safety of bioplastics used as food contact materials (FCMs). NIAS are compounds of various origins deriving from impurities contained in monomers and additives used for polymer production, or being generated as side-products during the production process, or by the decomposition of polymers or IASs [24,25]. Unlike IAS, it is not possible to detect and identify all NIAS in industrially produced FCMs because, to date, there is no comprehensive untargeted method with sufficient sensitivity [26]. A database reporting extractable substances detected in FCMs was prepared by Geueke et al. with as many as 2881 identified compounds migrating from plastic, glass, paper, metal, composite, and other materials [27]. This database is named FCCmigex (https://www.foodpackagingforum.org/fccmigex, accessed on 6 March 2023), is open access, and is continuously updated.

Owing to the different physiochemical properties of these compounds, different analytical approaches are required for their determination. Being able to provide both molecular weight and structural information, mass spectrometry (MS) is one of the most powerful techniques for the detection and identification of these compounds. Gas (GC) and liquid chromatography (LC)-coupled to MS, and more recently to high-resolution mass spectrometry (HRMS), as well as ambient techniques (AMS) have been successfully applied for the determination of intentionally and non-intentionally added compounds, both from extracts and directly from the plastic material [25,28–31].

The aim of this survey is to cover the recent studies regarding the application of MS-based techniques for the determination of NIAS in bioplastics. The terms bioplastics, biopolymers, NIAS, mass spectrometry, high resolution mass spectrometry and FCMs were used as keywords for the literature search. This survey will attempt to cover the state-of-the-art methods from 2012 up to 2022.

2. Intentionally and Non-Intentionally Added Substances

One of the most important fields of application of bioplastics is the production of FCMs, defined as "all materials and articles intended to come into contact with food, such as packaging and containers, kitchen equipment, cutlery and dishes, whose components could be transferred into food" [32]. To ensure a high level of food safety, EU requires that plastic FCMs comply with the specific conditions described in the EU Regulation 10/2011 [33]. This regulation reports a list of more than 850 compounds authorized to be used in plastic formulations, the so-called IAS, including monomers and additives such as plasticizers, strengtheners, UV stabilizers, flame retardants, matting agents and

pigments. In addition, substances which are present in a FCM even if not included in this list, shall be evaluated in accordance with internationally recognized scientific principles on risk assessment.

Migrating substances from FCMs can be classified as IAS, known or predictable NIAS, and unexpected NIAS [29]. To date, some different approaches suitable for most abundant NIAS in conventional FCMs were published but an official guidance for assessing their detection and quantitation of NIAS is still missing. NIAS identification is mainly focused on compounds having molecular weight below or equal to 1000 Da, with the exception of fluorochemicals presenting a cut-off of 1500 Da [34], since substances having higher molecular weight are not expected to exert harmful effects. The main challenges in the determination of these compounds are related to their unpredictable release, different properties, and origin [25,29]. In fact, one of the most common sources of NIAS is the degradation of polymers and additives used for the manufacturing of the final product: exposition to high temperatures or high irradiation energies during polymer manufacturing can also increase the formation of compounds having low molecular weights and high diffusion coefficients, with higher migration potentials [25,29,30,35]. Oligomers deriving from incomplete polymerization processes or side reactions can also be formed and transferred to foodstuffs [28,29]. The lack of information regarding the exact composition of each FCM, which can include different layers, adhesives, IAS, as well as synthetic by-products, catalyzers residues, contaminants, etc., increases the difficulty in the determination of NIAS present in the final retail product [25,29,30]. In addition, multiple sources of contamination alongside the supply chain, including lubricants, residues from machineries, substrates, inks, or environmental contaminants should be considered. Furthermore, recycling often leads to the accumulation of these contaminants, posing an even more challenging issue. In this framework, the determination of NIAS in bioplastics is a top priority, requiring the use of advanced analytical techniques, powerful software, updated databases and cutting-edge tools for data processing [25,29,30,35,36].

3. Migration Tests and Extraction Techniques

Migration is the diffusion-driven phenomenon related to the transfer of substances present in FCMs into foodstuff [12,33]. Different parameters can affect migration, namely, the area of the contact surface, the properties of the migrant compounds, the nature of the polymeric material, the type of food, temperature and contact time. Migration tests usually require the use of food simulants that are placed in contact with the plastic material at a definite temperature for a precise amount of time: these conditions should represent the worse-case scenario for product shelf-life and are supposed to slightly overestimate the amount of substances transferred into real food [12,25,29,33]. The use of simulants decreases the complexity of the analytical matrix, while maintaining the physicochemical properties of the original foodstuff. Since migration tests usually require prolonged analysis time and are quite expensive, migration modelling has been proposed [37]; however, these approaches are very limited since they cannot predict the migration of NIAS. Considering that most biobased materials are intended to be biodegradable or compostable, they have an intrinsic sensitivity to water; therefore, despite the functional properties that should not change, an alteration of the chemical substances present in the bioplastics at high humidity and temperature must be forecasted, leading to the formation of novel compounds that could more easily migrate into the simulant [12].

As stated in the EU Regulation 10/2011, two different kinds of migrations could be performed to ensure that FCMs do not pose a risk to human health: overall migration, intended as the maximum permitted amount of non-volatile substances released from a material into the food simulant under defined conditions, and specific migration, i.e., the maximum permitted amount of a substance that can migrate into food or food simulants [33]. In the US, the FDA requires that producers need to estimate the daily dietary consumption of migrating substances using food simulants [38].

However, migration tests are dedicated to IAS and NIAS eligible to transfer from the polymer to the simulant over a limited range of time and composition. These experiments mostly focus on the food safety topic but are not suitable to determine all IAS/NIAS and the ones in trace amounts. Thus, to have a more comprehensive overview, conventional extraction techniques, such as ultrasound-assisted solvent extraction [39–41], Soxhlet extraction [42] or dissolution/precipitation studies, requiring the complete dissolution of the polymeric matrix [43–46], have been proposed for the analysis of volatile and non-volatile compounds in bioplastic food materials. Pre-concentration steps can be required for both IAS and NIAS analysis, considering that low concentration levels are forecasted [25,28–30]. The most exploited techniques used for NIAS extraction are: (i) headspace extraction (HS-static or dynamic) and purge and trap (P&T) of the plastic material/food simulant for the analysis of volatile organic compounds (VOCs) [4,12,47]; (ii) direct thermal desorption (TD) of the FCM for VOCs determination [48]; (iii) liquid–liquid extraction (LLE) for the analysis of non-volatile compounds [35]; (iv) solid phase extraction (SPE) for the analysis of semi- and non-volatile compounds [26,49]; and (v) solid phase microextraction (SPME) either in HS [31,43,50–54] or direct immersion (DI) [55] mode and fabric phase sorptive extraction (FPSE) [56] for the extraction of a broad range of compounds.

Obviously, the selection of the correct pre-treatment procedure is of pivotal importance to obtain analyte extraction and enrichment, while avoiding contamination and degradation phenomena. Several parameters need to be considered, including the nature of the migrating compounds, the extracted matrix, the partition coefficients between phases, and the thermodynamics and kinetics of the processes. A schematic representation of the possible approaches for NIAS investigation, sample preparation strategies, and MS-based techniques in association with compound nature is reported in Figure 2.
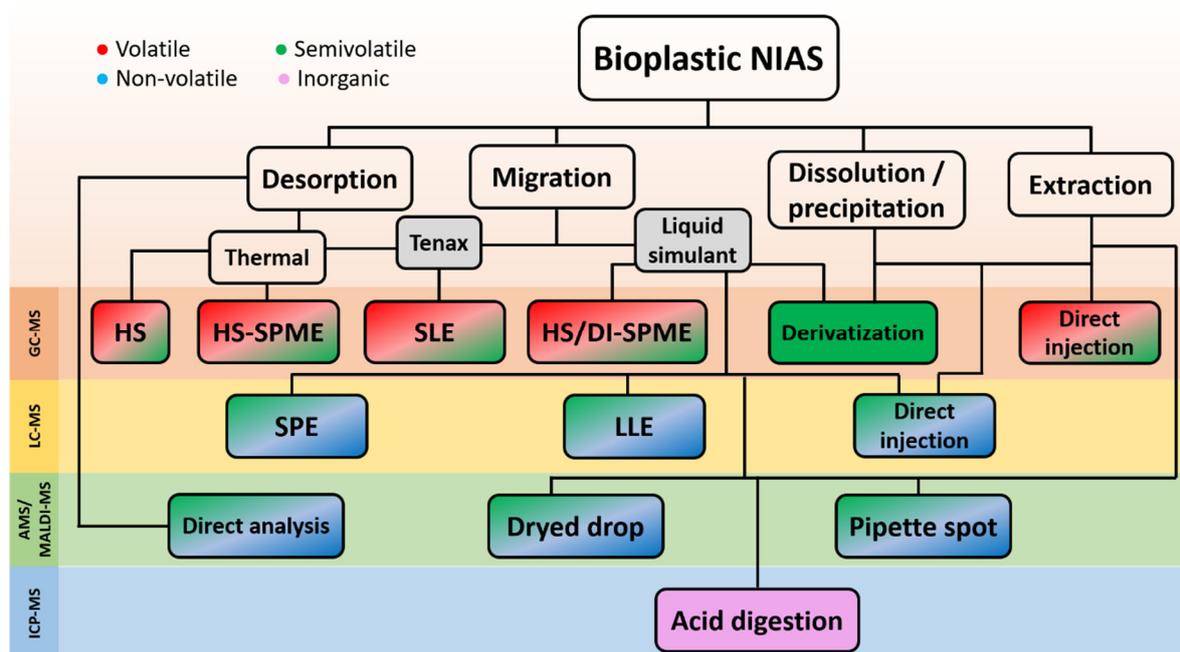

Figure 2. Schematic representation of MS-based analytical approaches for NIAS investigation.

4. Untargeted Analysis of NIAS

After migration experiments and sample preparation have been carried out, the migrating compounds need to be identified and quantified. Although IAS and predictable NIAS can be analyzed by target approaches, untargeted analysis is required to obtain the most complete coverage of the migrating substances [28,57]. Standard protocols and official guidelines are still missing, and the identification and quantitation of the compounds released from FCMs is an open challenge. Generally, hyphenated analytical techniques are

used including both GC-MS and LC-MS [12,28–30]. Nuclear magnetic resonance (NMR) has also been proposed for the analysis of NIAS [58], but limitations in terms of sensitivity and complexity of the obtained spectra are still a great challenge.

HRMS is the technique of choice for untargeted analysis, providing accurate mass measurements of both precursor and fragment ions with high sensitivity [25,28–30]. Generally, identification of the analytes can be summarized as follows: (i) determination of the elemental composition of the analyte based on the accurate mass of the precursor ion; (ii) identification of possible candidates based on mass error and isotopic ratios; (iii) identification of the fragmentation pattern associated to the precursor ion; (iv) comparison of both precursor and fragmentation pattern with online databases to obtain the structural elucidation of the detected molecule. Currently, no specific identification criteria for NIAS are available so, when it comes to dealing with unknown compounds, a general strong-established approach such as the 5 levels purposed by Schymanski et al. should be followed [59].

Hybrid analyzers such as tandem quadrupole-time of flight (QToF), quadrupole-Orbitrap (Q-Orbitrap), and linear ion trap-Orbitrap (LTQ-Orbitrap) are becoming the golden standard for NIAS analysis, allowing for the analysis of both precursor and fragment ions with enhanced mass accuracy and sensitivity [28–30,35].

Two different acquisition modes are used for untargeted NIAS analysis, namely, data-dependent (DDA) and data-independent (DIA) acquisition. In DDA, the instrument switches between total ion and product ion acquisition based on selected criteria, such as intensity of precursor ions, defined isotope pattern, charge state or specific m/z values; in DIA all the precursor ions are detected and fragmented, allowing for the analysis of all the detectable ions within a defined m/z range during the same run, without an a priori filtering procedure [28]. In particular, elevated energy (MS^E) is one of the most important DIA modes for QToF instruments: it is based on the alternate scanning of ions generated by low and high collision energy ramps, with the simultaneous acquisition of spectra related to the precursor and fragment ions, respectively [60]. Sequential Window Acquisition of all Theoretical MS (SWATH) is another noticeable DIA mode, in which the full mass scan range is divided into segments to produce MS/MS data, obtaining the complete fragmentation map and reducing the complexity of the fragmentation spectra [61]. As for Q-Orbitrap and LTQ-Orbitrap, precursor ions can be fragmented multiple time (MS^n), obtaining multiple fragmentation events, thus increasing structural information. In this context, full scan/all ion fragmentation (AIF) is the preferred DIA mode, allowing for the fragmentation of all the precursor ions without a preselection in the quadrupole [35]. Regardless of the instrumental platform used, untargeted HRMS produces thousands of data to be analyzed [28] and, therefore, features filtering to reduce the number of peaks that have to be identified is a critical step. The first point is the removal of signals related to noise. This process can be based on thresholds in terms of count intensity, signal/noise ratio or on the comparison of the analyzed FCM with controls or blank materials. In this case, multivariate statistics is required to select only the most significant features related to clusters separation. Other filters based on group variability and statistical power can be applied.

Recently, ion mobility (IM) spectrometry has become an important tool for untargeted analysis [28,62]: this technique allows for the separation of the ions based on their collision cross section (CCS), which is an intrinsic property of a compound. In fact, CCS is related to the 3D conformation of a molecule and is useful to discriminate between isobaric and isomeric species; therefore, CCS libraries dedicated to migrating substances are in the development stage [62]. The combination of IM with platforms coupling chromatographic techniques and hybrid HRMS analyzers has been successfully applied to increase the detection capabilities of untargeted analysis [31,45]. In the next section, examples related to the MS-based determination of volatile and non-volatile NIAS will be discussed.

5. Chromatographic Techniques for NIAS Identification

5.1. GC-MS Determination of Volatile and Semivolatile NIAS

GC-MS is the most commonly used platform for the analysis of volatile migrating substances [39,40,43,50–53,58]. One of the main advantages is the possibility to use electron ionization sources (EI) to produce broad and repeatable fragmentation patterns; then, identification is performed by comparing the experimental spectra with reference databases. In addition, other strategies such as those based on the use of normalized retention time indexes, can be applied to increase the identification confidence. Unfortunately, NIAS being mainly degradation products, reference spectra are often missing, so HRMS is required for univocal identification purposes [35,63]. Table 1 provides a summary of the GC-MS methods used in the last years for the investigation of volatile and semi-volatile NIAS in bioplastics.

Table 1. GC-MS methods for the investigation of volatile and semi-volatile NIAS in bioplastics.

Bioplastic Material	Extraction/Migration NIAS	Sample Pretreatment	MS Analyzer	Ref.
Wheat pulp and wood dishes	Migration test using 3% acetic acid, 10% ethanol, 95% ethanol	HS-SPME	Q	[50]
Bamboo, wheat pulp, and palm leaf dishes	Migration using Tenax®	HS-SPME	Q	[51]
Starch-based biopolymers	Direct analysis of pellets and films	HS-SPME	Q	[52]
Biopolymers based on starch and PLA	Ultrasonication in MeOH/migration using acetic acid 3%, ethanol 10%, ethanol 95%, isooctane, sunflower oil	Direct injection	Q/APGC-QtoF	[39]
Biodegradable blend (polyester + 18% PLA)	Dissolution/precipitation/direct analysis/migration using acetic acid 3%, ethanol 10%, ethanol 95%	Direct injection/HS-SPME	Q/APGC-QtoF	[43]
PLA-based pellets, film, and retails	Direct analysis of bioplastics	MHS-SPME	Q	[53]
PLA-based final product	Ultrasonication in MeOH	Direct injection	QtoF	[40]
Biodegradable mulch (PBAT, TPS, PLA, PHB and cereal flour)	Extraction using ultrapure water	Lyophilization-derivatization	Q	[58]

Very recently, Asensio et al. analyzed disposable dishes made by wood and wheat pulp, developed for being used at room temperature with food by means of HS-SPME-GC-MS [50] using divinylbenzene/carboxen/polydimethylsiloxane (DVB-CAR/PDMS) fibers. Migration tests were performed using three different simulants (acetic acid 3%, ethanol 10%, ethanol 95%): a total of 67 compounds were identified, including aldehydes, alcohols, carboxylic acids, hydrocarbons and aromatic compounds, mostly related to the manufacturing of paper, adhesives, and packaging production. Thirteen analytes listed in Regulation EU No. 10/2011 [33] with a specific migration limit were identified, among which 2,6-ditert-butyl-4-methylphenol (BHT), dibutyl phthalate, and erucamide were the compounds commonly detected in conventional plastics, and their presence into the investigated FCMs was explained taking into account their processing into a packaging industry. In this context the detected NIAS acted as environmental contaminants and were embedded into the produced biomaterials. Considering that the use of biomaterials at high temperatures could promote the release of NIAS, the same research group evaluated the migration of VOCs from bamboo, wheat pulp, and palm leaf-based dishes using Tenax® as a solid food simulant [51]. The same analytical method previously developed [50] was applied with slight modification, performing the extraction with both PDMS and DVB/CAR/PDMS SPME fibers. Using the PDMS fiber a total of 50, 22, and 26 compounds were identified in bamboo, palm leaf, and wheat pulp, respectively, whereas 38, 31, and 29 analytes were detected using the DVB/CAR/PDMS fiber in the 3 different matrices.

The identified compounds were mostly substances naturally present in plant materials, belonging to alkanes (C_{12}–C_{32}), alkenes (C_{13}–C_{29}), aldehydes (C_{12}–C_{30}) and carboxylic acids. Ethyl and methyl esters were also identified abeing used as additives, plasticizers, or lubricants in packaging and FCM industry. Semi-quantitation was also performed using model compounds and the concentration of all the detected compounds complied with the EU limits. An interesting finding was related to the VOCs detected in the analyzed plant-based FCMs: once again the VOCs identified in the biomaterials were the same as those observed in conventional plastic.

The aroma of starch-based polymers was investigated by Osorio and coworkers who studied the release of VOCs from starch-based biopolymer samples intended for food packaging using different GC-MS approaches [39,52]. In the first study, the key odorant compounds released by PLA-starch resins and films were investigated by means of HS-SPME and gas chromatography coupled to both mass spectrometry and a sniffing port (GC-(EI)MS-O) [52]. In total, 35 odorant compounds were detected as being aldehydes, the odorants with the highest impact on the aroma in starch-based films. Trimethylamine, 1-octen-3-one, sotolon, (Z) and € nonenal, eugenol or p-vinyguiacol were identified as aroma impact compounds, highlighting the role of the initial starch in the final aroma of the packaging material. In a different study, untargeted analysis of volatile and semi-volatile compounds was carried out by GC-MS, using both EI with a single quadrupole (Q) mass analyzer, and atmospheric pressure gas chromatography (APGC) with a QToF mass analyzer [39]. The capability of APGC ionization in multi-adducts formation proved to be useful for increasing the GC(EI)-MS confidence in the structural elucidation of the unknown compounds. GC-(EI)MS and APGc-QToF-MS demonstrated to be complementary techniques for identifying extractables and leachable NIAS. APGc-QToF-MS provided the accurate mass of the molecular ions, as well as their fragments and adducts formed at the GC–MS interface, whereas quantitation was performed by using Q analyzer by external standard calibration. NIAS were identified by comparing the GC-(EI)MS experimental spectra with those stored in the NIST Standard Reference Database, whereas HRMS data were elaborated to obtain in silico fragmentation of the most significant candidates present in the ChemSpider database. Twenty-one compounds were detected in the pellets extracted with methanol using ultrasound assisted extraction, including glycerol, oligomers, fatty acids, esters and amides. Most of the identified compounds were related to the degradation of the polymeric material or to the presence of plasticizers, lubricants, and antioxidants. The results showed that migration was below the overall migration limit (OML) for all the simulants except for ethanol 95% and isooctane, as these solvents wer able to interact with the polymeric materials, leading to their partial dissolution. Finally, consecutive experiments simulating repeated use showed a decrease in migration along the time.

Similarly, GC–(EI)MS and APGc–QToF-MS were used by Ubeda et al. to provide complementary and accurate information on VOCs released by biomaterials composed of polyester with 18% PLA [43]. A total of 15 compounds were identified in PLA pellets (13 compounds) and films (12 compounds) by GC–(EI)MS-O, with 10 common compounds, mostly related to bioplastics manufacturing. Olfactory analysis resulted in a total of 10 odorant compounds in PLA-based biopolymer, mostly ketones and aldehydes. Although common compounds identified by both techniques showed more sensitivity by GC–(EI)MS than APGC–QTOF, the advantages provided by APGC, such as the presence of the molecular ion or the coupling to HRMS, facilitate the identification of oligomers such as the AA-BD dimer or compounds that cannot be identified by standard GC–(EI)MS.

Salazar et al. studied the volatile profile of PLA samples by multiple headspace SPME (MHS-SPME)GC-(EI)MS [53]. Each step of the production process was investigated: an increase in the concentration levels of both acetaldehyde and 2,3-pentanedione was assessed after extrusion, followed by a decrease in VOCs after thermoforming as a consequence of evaporation due to process temperature, positively influencing the sensorial quality of the packaging. The effect of aging on the VOCs profile for both extruded and thermoformed plastics was also evaluated by analyzing samples stored for six months at

ambient conditions: interesting results were achieved from the commercial point of view since a decrease in the VOCs content along the time was observed, thus demonstrating that the formation of volatile NIAS was not affected by the aging of the material. The identified VOCs lactides were obtained by degradation processes such as depolymerization by intramolecular ester exchange, whereas the presence of aldehydes, alcohols, ketones and acetic acid was ascribed to transesterification and side-reactions. The presence of 2,4-dimethyl-2-pentanol was explained considering the hydrolysis of ester groups, whereas the formation of 2,3,4-trimethyl-hexane was related to degradation processes.

In 2019, Zimmermann et al. studied the in vitro toxicity and chemical composition of many plastic consumer products, including PLA-based plastics [40]. Untargeted Gc-QToF-MS analyses were performed onto methanolic extracts: a total of 1411 features were detected and 260 compounds were tentatively identified. Most of these compounds were classified as food additives and contaminants, intermediates, solvents, process regulators and aids, surfactants, lubricants, and lubricant additives. Baseline toxicity for 3 out of 4 PLA-based FCMs was demonstrated, resulting in higher toxicity compared to most of the investigated plastics. PLA contained 7 estrogenic compounds, 5 anti-androgenic substances, and 16 chemicals inducing oxidative stress or cytotoxicity. The evaluation of the toxicological signatures of the investigated products highlighted that all PLA-based materials were able to induce a baseline toxicity similar to that exerted by polyvinylchloride and polyurethanes, thus suggesting that bio-based and biodegradable materials are not necessarily safer than conventional plastics.

Since biodegradable plastics are considered a greener and economical alternative to the use of PE agricultural mulches, the compounds released by these materials were studied by Serrano-Ruiz et al. [58]: four commercial mulching films, three experimental biodegradable plastics, one paper-based material and one non-biodegradable PE were tested. Biodegradable plastics were composed of blends of PBAT with thermoplastic starch, PLA, polyhydroxybutyrate (PHB) and cereal flour. The migration was studied using ultrapure water and the extracts were lyophilized. The identification of the migrating compounds was performed by means of both GC-(EI)MS and NMR. GC-(EI)MS analysis was performed after derivatization with methoxylamine hydrochloride, pyridine, and N-methyl-N-(trimethylsilyl)trifluoroacetamide. PE displayed a low VOCs profile in which only a few additives such as hexadecenoic, octadecanoic, and the bis(2-ethylhexyl) ester of 1,10-decanedioic acid could be identified. On the opposite, the analysis of biodegradable mulches showed the presence of different compounds, namely, dicarboxylic acids, hydrox-yacids, diols, triols, glycerol dimers and trimers, monosaccharides, disaccharides and THP, commonly used in the formulation of biodegradable mulch materials, either as structural components or additives. After identification, the most abundant compounds, namely, AA, LA, BD and THP, were quantified by means of both ultra-high performance liquid chromatography triple quadrupole-mass spectrometry (UHPLC-(QqQ)MS) in multiple-reaction monitoring mode and GC coupled to a flame ionization detector. The use of selective detectors allowed to reach detection limits in the low μg/kg range thus allows us to assess the presence of NIAS in all the investigated bioplastics.

5.2. LC-MS Determination of Non-Volatile NIAS

LC, and in particular UHPLC, coupled to HRMS have been used for the analysis of non-volatile migrants and thermally labile compounds from plastic materials [26,41,44,45,49,56,64]. Considering that the most common ionization source in LC-MS is electrospray (ESI), which provides a soft ionization of the analytes, and no reference libraries are available, additional MS experiments are required to increase the identification confidence. Despite QqQ analyzers are proposed for quantitation purposes, hybrid HRMS analyzers such as QToF and Q-Orbitrap are preferred for untargeted analysis as they provide accurate mass measurements of both precursor and fragment ions. As reported in Table 2, a QToF mass analyzer operating in MS^E acquisition mode are the most used analytical platforms for studying NIAS in bioplastics.

Table 2. LC-MS methods for the investigation of non-volatile NIAS in bioplastics.

Bioplastic Material	Extraction/Migration NIAS	Sample Pretreatment	MS Analyzer	Acquisition Mode	Ref.
Biodegradable polyester + PLA	Dissolution/precipitation/ migration using acetic acid 3%, ethanol 10%, ethanol 95%	Direct injection	QToF/QqQ for quantitation	MS^E/SIR (selected ion recording)	[44]
PLA and PLA-polyester	Total dissolution/migration using acetic acid 3%, ethanol 10%, ethanol 95%	Direct injection	QToF/IM-QToF	MS^E/HDMS^E	[45]
PLA and starch-based biopolymers	Migration using acetic acid 3%, ethanol 10%, ethanol 95%	Direct injection	QTOF	MS^E	[64]
27 biobased plastic material and 16 plant-based materials	Ultrasonication using MeOH	Direct injection	QToF	MS^E	[41]
PLA-based final product	Migration using water	SPE	QToF	MS^E	[26]
PBAT + 18% PLA	Migration using acetic acid 3%, pineapple juice	FPSE	QToF/QqQ	MS^E/SIR	[56]
Bio-PBS and a starch blend	Artificial weathering	SPE	QToF	DIA MS^1 scans and MS^2 scans of the most intense ion	[49]

Recently, Aznar et al. developed a UHPLC-QToF-MS method for the determination of non-volatile migrants from a biodegradable PLA-polyester blend using a dissolution/precipitation approach [44]. The migration from PLA-based pellets and films using three different food simulants, namely, acetic acid 3%, ethanol 10%, ethanol 95% was also investigated. Untargeted analysis was carried out by operating in sensitivity MS^E mode, resulting in the detection of 23 compounds in the pellets and 19 in the films, mostly identified as cyclic or linear PLA oligomeric species. Since all the compounds detected in films were also present in the pellets, no new compound was formed during the extrusion process. As for migration studies, 28 compounds were identified, of which 14 were already detected in the films, whereas 14 new analytes were ascribed to the reaction of the simulant with the plastic components. Cyclic oligomers mainly composed by AA, phthalic acid (PHT), and BD were the most abundant compounds in all the analyzed samples. Three cyclic oligomers composed by LA monomers were detected only in the pellets but not in simulants after the migration tests, suggesting a cycle opening and the formation of linear oligomeric species. Plasticizers and antioxidants were also identified, but at low intensity. A similar study was performed by Ubeda et al. [45], who investigated the migration of oligomers from bioplastic materials based on PLA and PLA-polyester to be used for FCMs production. Total dissolution and migration tests using different simulants were performed. Both UHPLC-QToF-MS and UHPLC-IM-QToF-MS analyses were carried out and a total of 39 different oligomers made of repeated monomer units were identified. Twenty-four oligomers (50% linear and 50% cyclic) were identified by total dissolution, whereas 25 linear oligomers were detected after the migration studies. It was observed that 10 of the compounds identified after migration tests were also present when dissolution experiments were carried out, whereas 15 new oligomeric species were obtained by the reaction between PLA components and the food simulants. No significant change in the oligomer profile was obtained between pellets and films, thus proving that the manufacturing process was not able to affect the material composition. Cyclic oligomers with 5–11 repeating units were present in the pellets at a higher concentration compared to linear oligomers (5–8 repeating units). UHPLC-IM-QToF-MS analyses showed a good correlation between the CCS values of the oligomers and their molecular weight. Interestingly, the CCS values of linear and cyclic oligomers were not significantly different, thus suggesting that the linear species could be present in a folded form, resulting in CCS values close to the cyclic components.

Oligomers migrating from biopolymers based on PLA and starch were analyzed by Osorio et al. using UHPLC-QToF-MS and AMS techniques [64]. Migration tests using acetic acid 3%, ethanol 10%, and ethanol 95% as simulants were performed. By the UHPLC-HRMS

analysis operating in MS^E mode, 14 cyclic and 5 linear oligomers with AA, three different polyols, and isobutanol as repeating units were identified in all the analyzed samples. Different dimers, trimers, tetramers and combinations of the repeating units were also observed. As for the starch-based material, a total of 14 oligomers, 12 cyclic, and 2 linear, were identified as having BD, AA, and THP as repeating units. Dimers, trimers, tetramers, or different combinations of AA-BD and THP-BD were observed. For both bioplastics, the highest number of oligomers was detected in the ethanol 95% simulant. The same samples were also analyzed by two different AMS techniques to evaluate the detection capability of these techniques towards the main oligomers present in biopolymers in a very rapid way. A more detailed explanation on the use of AMS is illustrated in Section 6.

The release of chemicals from retail products made of bioplastic materials was investigated by Zimmermann et al. by applying an ultrasound-assisted methanol extraction followed by UHPLC-QToF-MS/MS analysis [41]. In particular, 43 consumer products and raw materials (preproduction pellets) were analyzed, covering bio-based and biodegradable materials (PLA, PHA), petroleum-based and biodegradable plastics (PBS, PBAT), bio-based non-biodegradable polymers (Bio-PE, Bio-PET) and plant-based materials (starch, cellulose, bamboo). A total of 41,395 features were detected, ranging from 5811 to 31,727 per material, with only 1% of common features. Three hundred forty-three priority compounds including monomers, oligomers, plastic additives, lubricants and unpredicted NIAS were tentatively identified. In addition, in vitro toxicity was assessed for the different plastic products: 29 out of 43 extracts induced baseline toxicity, 18 induced oxidative stress response, 4 compounds were cytotoxic, 1 product activated the human estrogen receptor and 10 produced antiandrogenic activity. These findings demonstrated that bioplastics and plant-based materials were able to induce baseline toxicity and endocrine activity in a slightly higher percentage than conventional plastics, and therefore did not result in enhanced eco-compatibility and health safety compared to traditional products. The same analytical approach was followed to study the migration of chemicals in ultrapure water from retail products made of either petroleum-based plastics or PLA [26]. SPE was performed to extract and pre-concentrate the migrating compounds prior to an untargeted UHPLC-QToF-MS analysis in MS^E mode. Between 17 and 8681 relevant chemical features were present in the migrates: approximately 8% of all detected features was tentatively identified for a total of 2979 unique compounds, highlighting the need of more complete databases to better assess NIAS migration from plastic materials. Once again, the results achieved in this study confirmed that humans are exposed to more plastic chemicals than those currently considered in public health science and policies.

In 2021, Ubeda and coworkers reported the use of FPSE for the extraction and pre-concentration of oligomers migrating from a bioplastic made of PBAT with 18% of PLA [56]. Both UHPLC-QToF-MS and UHPLC-(QqQ)MS analyses were carried out using acetic acid 3% and pineapple juice as food simulant and real matrix, respectively. UHPLC-QtoF-MS analyses carried out in MS^E mode resulted in the identification of 10 cyclic and 11 linear oligomers. Nine oligomers were made by repeated LA monomeric units, with both cyclic and linear oligomers, whereas 6 cyclic and 6 linear oligomers composed by AA, PHT, and/or BD could be identified and ascribed to the polyester components. Compared to the direct injection of the acetic acid 3% solution, FPSE increased the area of the detected peaks up to 30 times and allowed the identification of 3 and 2 oligomers related to the polyester component in the simulant and pineapple juice, respectively. Finally, semi-quantitative analysis was performed by means of UHPLC-(QqQ)MS obtaining about 30 µg/g as the total amount oligomers in simulant and real food, with a higher concentration of cyclic oligomers compared to the linear ones.

The release of chemicals from both bioplastics and petroleum-based pellets was investigated by Klein et al. in a study dealing with the effect of UV-weathering on NIAS migration [49]. Two different bioplastics were investigated, namely, Bio-PBS and a starch blend, containing PBAT, thermoplastic starch, glycerin and PLA. Artificial weathering was performed for 24 h using both UV-C and UV-A/B irradiation. The samples were leached

in ultrapure water either during or after the irradiation, then the leachate was acidified, extracted by SPE, and submitted to UHPLC-QToF-MS/MS analysis in data-dependent MS^2 acquisition mode. Only 42 compounds were detected in the control, whereas almost 2900 chemicals including stabilizers, organophosphorus compounds, plasticizers and antioxidants were present after sample irradiation, thus proving the pivotal role of UV irradiation in promoting both plastic degradation and toxicity in terms of oxidative stress, baseline toxicity, antiestrogenicity and antiandrogenicity.

5.3. Complete Profiling of NIAS

To obtain the most complete coverage of the compounds released from bioplastics, the combined used of GC-MS and LC-MS has been proposed (Table 3).

Table 3. Combined GC-MS and LC-MS methods for the investigation of NIAS in bioplastics.

Bioplastic Material	Extraction/Migration NIAS	GC-MS	LC-MS		Ref.
		MS Analyzer	MS Analyzer	Acquisition Mode	
Multilayers (containing PLA, PVA, ecovio® EXP 0.5 SL®)	Adhesive dissolution in MeOH/migration using Tenax TA®-MeOH elution	Q	QToF	MS^E	[46]
Bamboo-based biopolymer	Migration using acetic acid 3%, ethanol 10%, ethanol 95%	Q	QToF	MS^E	[55]
Multilayer biodegradable polymer (40% polyester + 60% PLA)	Migration using cold and hot tea	Q	IM-QToF	$HDMS^E$	[31]
Bioactive packaging based on PLA	Migration using 3% acetic acid acid, 10% ethanol, 95% ethanol	Q	QToF	MS^E	[54]
Monolayer film with PLA, polylimonene PL, and ZnO NPs	Migration using 3% acetic acid acid, 10% ethanol	Q-Orbitrap	Q-Orbitrap	AIF	[35]

Different multilayer materials containing PLA, polyvinyl alcohol (PVA), and ecovio® EXP 0.5 SL® (a biodegradable material) and the adhesive used for their assembling were analyzed by Canellas and his research group using both GC-(EI)MS and UHPLC-QToF-MS [46]. The adhesive was dissolved in methanol, whereas migration tests on the final multilayer materials were performed using Tenax TA™ as the food simulant. As for the adhesive extract, untargeted GC-MS analysis allowed the identification of 6 volatile components (5 constituents of the adhesive formulation and 1,6-dioxacyclododecane-7,12-dione, a NIAS related to the degradation of the resin), whereas 3 non-volatile components were identified by UHPLC-HRMS by operating in MS^E acquisition mode, including AA, a common monomer used in adhesive formulation, and two biocides used in water-based adhesives. Four additional unknown compounds were also detected as neoformed compounds obtained by the reaction of volatile and non-volatile compounds: the authors reported a tentative identification of these compounds based on the fragmentation spectra and considering the reactions between the other 7 identified compounds. Migration of the final multilayers in dry food was also investigated: all the components identified in the adhesive were detected in the PLA-paper multilayer below the detection limits, whereas 3 compounds migrated from ecovio- and ecovio-PVA based multilayers, namely, 2,4,7,9-tetramethyl-5-decyne-4,7-diol, 1,6-dioxacyclododecane-7,12-dione, and 1,6,13,18-tetraoxacyclotetracosane-7,12,19,24-tetraone. In particular, the last two substances were considered as neoformed NIAS deriving from the reaction between BD and AA.

In 2020 Osorio et al. reported the migration of volatile, semi-volatile, and non-volatile compounds from bamboo-based biopolymer FCM. Identification was performed by both GC-(EI)-MS and UHPLC-QToF-MS [55]. Acetic acid 3%, ethanol 10%, and ethanol 95% were used as food simulants. Twenty-five volatile and semi-volatile compounds were detected by GC-(EI)MS, mostly in the acetic acid simulant (15) compared to those identified in the ethanolic extracts (6 each). Despite the fact that most of the compounds (16) were

identified as alkanes, multiple compounds classified as class II and III (medium and high toxicity) were observed, among which included different phytosterols. As for UHPLC-QToF-MS analysis, the MS^E acquisition mode allowed the identification of 12 compounds, including valine, triethanolamine, melamine and melamine derivatives. Both melamine and melamine derivatives were found at concentration levels above the limits established by European legislation [33], especially when migration tests were carried out under acidic conditions, thus demonstrating that the analyzed material could not be identified as bamboo, but as melamine with bamboo filler. The same material was also studied by direct analysis using the real time mass spectrometry (DART-MS) as described in Paragraph 6.

Very recently, the detection and elucidation of oligomers migrating to tea from a biodegradable multilayer material (40% polyester + 60% PLA) was studied by Canellas et al. [31]. Migration tests were performed using both cold and hot tea as a real food matrix: the samples were submitted to UHPLC-IM-QToF-MS in a data-independent analysis using high definition MS^E mode for the untargeted screening of the non-volatile migrating NIAS, whereas HS-SPME-GC-(EI)MS analysis was performed to identify VOCs. The CCS values were used as an additional identification point providing an increased identification capability due to the simultaneous information deriving from retention time, drift time, accurate mass of precursor and product ions. A chemometric approach based on the use of orthogonal partial least square discriminant analysis allowed for the identification of 7 markers of migration, among which only the identification of benzisothiazolone used as biocide in adhesive and plastic industry and tributyl phosphate used as plasticizer or flame retardant in plastic and paper industry were feasible by performing a database search. By exploiting the capabilities of the Fragment Match tool in the UNIFI software, 5 additional components were identified as cyclic oligomers obtained from the combination of AA, BD, neopentyl glycol and 1,6 hexanediol. Among these substances, only the volatile AA-BD cyclic oligomer was detected as a migrating compound by using the HS-SPME-GC-(EI)MS method. Results achieved by migration tests using hot tea demonstrated high contents of the 5 oligomers, all exceeding the SML established for Cramer class I compounds, whereas a decrease in more than an order of magnitude in their concentration was observed in cold tea. The obtained findings proved that the biomaterial can be used only for cold beverages, thus highlighting the importance of NIAS detection and quantitation to assess the safety of food contact material.

The use of hybrid MS analyzers coupled to both GC and UHPLC instruments proved to be a useful choice also for the identification of NIAS released from active packaging materials [35,54]. In the research study carried out by Gavril et al. [54], different migration tests on a new biodegradable antioxidant active packaging, based on herbal antioxidants incorporated into a PLA matrix were carried out. Three different simulants were tested: ethanol 95% extracts were directly analyzed by GC-MS, whereas a SPME extraction using a DVB/CAR/PDMS fiber was carried out for the analysis of ethanol 10% and acetic acid 3% migrating solutions. The results proved that the use of active biobased material in packaging formulations was able to decrease the migration of both volatile and non-volatile compounds compared to the neat PLA film, demonstrating the absence of non-volatile migrating substances in ethanol 10% and acetic acid 3% extracts, whereas 10 cyclic (5–14 repeating units) and one linear (n = 2) PLA oligomer were identified when ethanol 95% was used. By contrast, when SPME-GC-MS analyses were carried out, 16 and 8 VOCs were identified in ethanol 10% and acetic acid 3% extracts, respectively, including fatty acids, fatty acid derivatives, and alcohols. Similarly, Martinez-Bueno and coworkers developed a monolayer film made of PLA, polylimonene (PL), and zinc oxide nanoparticles (ZnO NPs), acting as an antimicrobial agent and tested NIAS migration using acetic acid 3% and ethanol 10% as food simulants [35]. The solution was directly analyzed by UHPLC-Q-Orbitrap-MS in AIF mode, whereas LLE using hexane was carried out before GC-(EI)Q-Orbitrap-MS analysis. N,N-diethyldodecanamide, 1-palmitoylglycerol, glycerol stearate, and N-[(9Z)-9-octadecen-1-yl]acetamide were the non-volatile compounds identified as the amides with the most abundant compounds in the developed films (Figure 3). The highest migration

was observed in films containing PL, especially under acidic conditions. As for VOCs, tripropylene glycol diacrylate, 10-heneicosene, and α-tocopherol acetate were identified. The migration of Zn²⁺ from ZnO NPs was also assessed by inductively coupled plasma-mass spectrometry (ICP-MS) as described in Section 7.
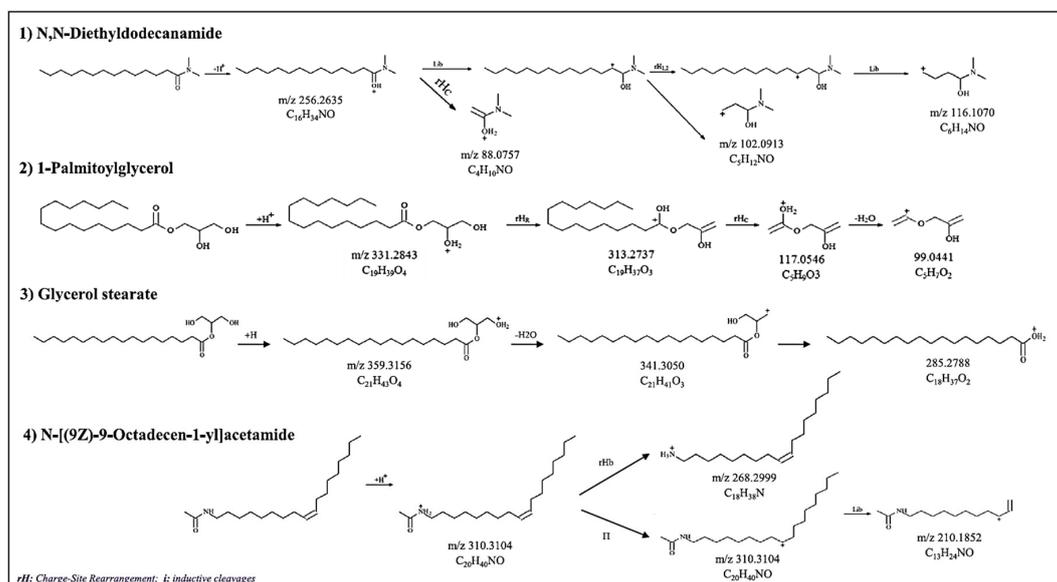

Figure 3. Tentative proposal fragmentation mechanism for the compounds detected by LC-Q-Orbitrap-MS. Reprinted with permission from ref. [35].

6. Non-Chromatographic Techniques for NIAS Investigation

Based on the direct desorption/ionization of the analytes from the sample, and requiring no or very limited sample pre-treatment, AMS techniques [55,64] and matrix-assisted laser ablation (MALDI) [42,65] have been proposed for the direct analysis of plastic materials or migrating solutions. Not providing any chromatographic separation, the use of HRMS is required to obtain the univocal identification of the compounds. However, despite the noteworthy advantages in terms of rapid analysis time, several limitations due to the presence of a strong matrix effect, adduct formation, and complex spectra need to be considered.

Very recently, MALDI-HRMS was used by the research groups of Zhang [42] and Gies [65] to investigate the compounds present in PBS or PBAT materials, as well as in aged PLA/PBA FCMs. In the study promoted by Zhang et al. [42], gel permeation chromatography (GPC), UHPLC-FTICR-MS, and MALDI-FTICR-MS analyses were carried out to analyze the oligomeric species extracted from PBS or PBAT, by applying a Soxhlet extraction and different dissolution procedures. GCP allowed for rough molecular weight information, not determining the specific structure of the oligomers, that was assessed by using MALDI-FTICR-MS and UPLC-FTICR-MS. Cyclic esters with repeating units 2–8 were detected from the extracted solution of PBS resin, whereas cyclic esters with repeating units 1–10 were found in PBAT deriving from three monomers with multiple possible random combinations. Although the tested conditions were different from those prescribed for migration studies, the high amounts of compounds extracted from PBS material raised concerns regarding its use as FCM. The capability of MALDI-ToF/ToF collision-induced dissociation (CID) fragmentation was exploited by Gies et al. [65] for the characterization of major degradation products of PBA aging under environmental conditions. CID fragmentation using low and high kinetic energies, proved to be a powerful tool to both determine the major degradation pathways and identify different end-groups within PBA samples. The results highlighted that under low kinetic energy conditions unique fragment ions were obtained, which were not routinely observed under high-energy conditions. This study proved that PBA oligomers can undergo different low-energy degradation pathways, in-

cluding proton transfer reactions, remote hydrogen abstraction reactions, and combinations of these reactions: 1,5-hydrogen shift reactions were considered as the major low-energy fragmentation pathway. It should be noted that high-energy conditions complicate the interpretation of CID spectra and PBA degradation pathways: MS/MS data were more complicated and revealed the prevalence of multiple fragmentation reactions occurring in concert. PBA structures terminating with butanediol, adipic acid, and buteneol as well as cyclic architectures with no terminal groups were observed. Side-products were also identified containing terminal groups such as glycol, propenyl, methanol, and aldehydes.

As previously anticipated in Section 5.2, AMS techniques, namely, DART-MS and Atmospheric Solids Analysis Probe (ASAP)-QToF-MS were proposed by Osorio et al. to screen NIAS in bamboo-, PLA-, and starch-based biopolymers [55,64]. In both cases, AMS was applied to screen for target compounds already identified by using hyphenated techniques. DART-MS resulted in a promising tool to determine the presence of the main migrants from bamboo-based biopolymers in a very short analysis time [55]. A total of 26 compounds were identified in ethanol 95%, completely matching the compounds already identified by the previously mentioned hyphenated techniques. Five compounds were detected and identified only by DART-MS, namely, paracoumaryl alcohol, protocatechuic acid, histidine, caffeic acid and trans-coniferyl alcohol. It was highlighted that both polarity and volatility are important parameters to be considered in the formation of adducts: a higher number of interactions with the different reactive species were obtained in the case of small and high volatile compounds. The same research group analyzed the migrating compounds from PLA and starch-based bioplastics using both DART-MS and ASAP-Q-ToF-MS [64], evidencing the capability of ASAP in the ionization of small molecules, whereas DART-MS was proposed as the technique of choice for the determination of high molecular weight oligomers. In addition to the oligomers already identified by UHPLC-HRMS (see Section 5.2), 5 linear and 1 cyclic adducts were detected by DART-MS in the starch-based material using ethanol 95% as simulant. The structure and molecular formula of the 6 candidates were calculated based on the detected *m/z* ratios and the possible combination of AA, BD, and THP monomers. As for ASAP analysis, results similar to those achieved by DART-MS were obtained when the PLA-based material was analyzed, whereas high intensity peaks at low *m/z* ratios not identified by using DART-MS or UHPLC-HRMS were detected in the starch-based sample. These results suggested the use of AMS as a promising non-laborious alternative to assess the legal compliance of food packaging materials. All discussed non-chromatographic techniques are listed in Table 4.

Table 4. MALDI and AMS methods for the investigation of NIAS in bioplastics.

Bioplastic Material	Extraction/Migration NIAS	MS Ionization Technique	Sample Injection	Mass Analyzer	Ref.
PBAT and PBS resins	Soxhlet extraction (ethanol/THF/acetone)/ dissolution in CHCl$_3$, hexafluoroisopropanol/alcoholysis using MeOH	MALDI	Direct injection	FTICR	[42]
PBA	Direct analysis	MALDI	Dried droplet method	ToF/ToF	[65]
Bamboo-based biopolymer	Migration using acetic acid 3%, ethanol 10%, ethanol 95%	DART	Pipette-spotted onto quick strip	Q	[55]
PLA and starch-based biopolymers	Migration using acetic acid 3%, ethanol 10%, ethanol 95%	DART/ASAP	Pipette-spotted onto quick strip/dipping capillary/direct injection	Q/QToF	[64]

7. ICP-MS Determination of NIAS in Bioplastics

Metal contamination caused from FCMs is one of the significant concerns in food safety. Thus, an accurate determination of metal migration is required to assess the potential health

hazards to humans. Both ICP-MS and optical emission spectroscopy are the techniques of choice for metal determination [35,66], ICP-MS being a powerful tool to investigate the metal migration form food packaging material due to its high sensitivity, selectivity, and multi-element analysis capability.

In the study carried out by Martinez-Bueno et al., ICP-MS was applied to evaluate the migration of Zn^{2+} from ZnO NPs used as antimicrobial agents to produce active food contact materials [35]. Both ethanol 10% and acetic acid 3% were used as food simulants to mimic potential migration in hydrophilic foods having pH > 4.5 and pH < 4.5, respectively. A different migration was observed: Zn^{2+} concentration values of 2.1 and 2.0 mg/L for the PLA/ZnONPs and PLA/PL/ZnONPs films, respectively, were obtained when ethanol 10% was used, whereas higher concentrations, i.e., 39.0 and 49.5 mg/L, respectively, were observed for the acidic simulant. Dissolution of ZnO NPs was increased by the addition of PL additive thus suggesting that only the PLA/ZnONPs film could be used as FCM.

An interesting study was carried out by Astolfi et al. to evaluate the migration potential of heavy metals and other elements in PHA samples having different sources and produced following different process steps [66]. The contents of 40 elements in different PHA samples produced under six different conditions were investigated by means of ICP-MS. Water and acetic acid 3% were used as simulants. Microwave-assisted digestion using nitric acid was performed to dissolve the plastic samples and assess the elemental composition of the bioplastic materials. The feedstock type, PHA stabilization, and extraction procedures affected the element migration. The concentration of inorganic elements in crop-based PHA was generally lower than that of waste-based PAHs, whereas PHA materials deriving from municipal waste were characterized by the highest contents of environmentally relevant elements. Seven out of 40 elements were not detected, whereas the total content of the remaining metals was in the 0.0001 (Be)–49.5 mg/kg (Na) range. As for the heavy metals, Zn presented the highest concentration (300 mg/kg), whereas toxic metals such as Ni and Cd were below 10 mg/kg. Zn, Cu, Pb, As, and Cr, presented concentration values higher than the migration limits set by EU regulation 10/2011 [33]. Among the different production conditions based on the use of waste-feedstock, only PHA samples obtained after extraction from wet biomass (acid storage) with aqueous-phase extraction were in accordance to the EU regulation 10/2011 and could be used as FCMs for food (water)-contact under frozen and refrigerated conditions [33]. On the contrary, commercial PHAs produced using crop-based feedstock were characterized by lower elemental contents compared to the legislation limits for all the tested conditions. Both these bioplastics also comply with European standard EN 71e3, and therefore are safe for toys production [67].

8. Conclusions

The migration of NIAS from bioplastics for food contact applications is a matter of great interest since the migration of unpredictable substances into food can raise new health concerns. There is still a long way to go: MS-based techniques play a key role in the identification of NIAS, but difficulties in identifying all the unknowns are still present. AMS is emerging as a very promising alternative tool to quickly assess the safety and legal compliance of food packaging materials, but efforts are required to increase the sensitivity required for migrating NIAS screening analysis. New experiments able to evaluate the safety and applicability of bioplastics as FCM need to be planned: in fact, despite extraction tests being arguably more effective than migration tests, they could extract more substances than those migrating in foodstuff. In addition, the use of alternative simulants and migration test conditions, especially those for high temperature applications is required, since the use of actual simulants could overestimate migration into real foods or generate artifacts. Finally, the development of harmonized analytical protocols, certified standard materials, and updated comprehensive databases is required for confirmation and quantitation purposes, together with a correct risk assessment evaluation.

Author Contributions: Conceptualization: N.R. and F.B.; original draft Preparation: N.R. and F.B.; literature review: N.R.; review and editing: A.C., M.M., M.P. and M.C.; funding acquisition: M.C. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AA	adipic acid
AIF	all ion fragmentation
AMS	ambient mass spectrometry
APGC	atmospheric pressure gas chromatography
ASAP	atmospheric solids analysis probe
BD	1,4-butanediol
CCS	collision cross section
CID	collision-induced dissociation
DART	direct analysis in real time
DDA	data-dependent acquisition
DIA	data-independent acquisition
DI	direct immersion
DSPE	dispersive solid phase extraction
DVB/CAR/PDMS	divinylbenzene/carboxen/polydimethylsiloxane
EI	electron ionization sources
ESI	electrospray ionization
FCM	food contact material
FPSE	fabric phase sorptive extraction
FTICR	Fourier transformed ion cyclotron resonance
GC-MS	gas chromatography-mass spectrometry
GPC	gel permeation chromatography
HRMS	high-resolution mass spectrometry
HS	headspace extraction
IAS	intentionally added substances
ICP-MS	inductively coupled plasma-mass spectrometry
IM	ion mobility
LA	lactic acid
LC-MS	liquid chromatography-mass spectrometry
LRMS	low-resolution mass spectrometry
LTQ-Orbitrap	linear ion trap-Orbitrap
LLE	liquid-liquid extraction
MALDI	matrix assisted laser ablation
MHS	multiple headspace
NIAS	non-intentionally added substances
NMR	nuclear magnetic resonance
OML	overall migration limit
PBAT	polybutylene adipate terephthalate

PBS	polybutylene succinate
PDMS	polydimethylsiloxane
PE	polyethylene
PET	polyethylene terephthalate
PHA	polyhydroxyalkanoates
PHB	polyhydroxybutyrate
PHT	phthalic acid
PL	polylimonene
PLA	polylactic acid
PP	polypropylene
P&T	purge and trap
PVA	polyvinyl alcohol
Q	single quadrupole
Q-Orbitrap	quadrupole-Orbitrap
QqQ	triple quadrupole
QToF	quadrupole-time of flight
SPE	solid phase extraction
TD	direct thermal desorption
THP	terephthalic acid
VOC	volatile organic compound
SPME	solid phase microextraction
SWATH	sequential windowed acquisition of all theoretical MS
UHPLC	ultra-high pressure liquid chromatography
ZnO NP	zinc oxide nanoparticle

References

1. Abrha, H.; Cabrera, J.; Dai, Y.; Irfan, M.; Toma, A.; Jiao, S.; Liu, X. Bio-Based Plastics Production, Impact and End of Life: A Literature Review and Content Analysis. *Sustainability* **2022**, *14*, 4855. [CrossRef]
2. Plastics Europe; European Association of Plastics Recycling and Recovery Organisations. *Plastics—The Facts 2022*; PlasticsEurope AISBL: Brussels Belgium, 2022.
3. Merino, D.; Quilez-Molina, A.I.; Perotto, G.; Bassani, A.; Spigno, G.; Athanassiou, A. A Second Life for Fruit and Vegetable Waste: A Review on Bioplastic Films and Coatings for Potential Food Protection Applications. *Green Chem.* **2022**, *24*, 4703–4727. [CrossRef]
4. Horodytska, O.; Cabanes, A.; Fullana, A. Non-Intentionally Added Substances (NIAS) in Recycled Plastics. *Chemosphere* **2020**, *251*, 126373. [CrossRef] [PubMed]
5. Gerassimidou, S.; Lanska, P.; Hahladakis, J.N.; Lovat, E.; Vanzetto, S.; Geueke, B.; Groh, K.J.; Muncke, J.; Maffini, M.; Martin, O.V.; et al. Unpacking the Complexity of the PET Drink Bottles Value Chain: A Chemicals Perspective. *J. Hazard. Mater.* **2022**, *430*, 128410. [CrossRef] [PubMed]
6. European Council. Directive (Eu) 2019/904 of the European Parliament and of the Council of 5 June 2019 on the Reduction of the Impact of Certain Plastic Products on the Environment. *Off. J. Eur. Union* **2019**, *155*, 1–19.
7. Falua, K.J.; Pokharel, A.; Babaei-Ghazvini, A.; Ai, Y.; Acharya, B. Valorization of Starch to Biobased Materials: A Review. *Polymers* **2022**, *14*, 2215. [CrossRef]
8. Ghosh, K.; Jones, B.H. Roadmap to Biodegradable Plastics-Current State and Research Needs. *ACS Sustain. Chem. Eng.* **2021**, *9*, 6170–6187. [CrossRef]
9. Lambert, S.; Wagner, M. Environmental Performance of Bio-Based and Biodegradable Plastics: The Road Ahead. *Chem. Soc. Rev.* **2017**, *46*, 6855–6871. [CrossRef]
10. Rujnić-Sokele, M.; Pilipović, A. Challenges and Opportunities of Biodegradable Plastics: A Mini Review. *Waste Manag. Res.* **2017**, *35*, 132–140. [CrossRef]
11. European Bioplastics What Are Bioplastics. Available online: https://www.european-bioplastics.org/bioplastics/ (accessed on 20 February 2023).
12. Bradley, E.L. *Report FD 10/04 FSA PROJECT A03070 Biobased Materials Used in Food Contact Applications: An Assessment of the Migration Potential*; The Food and Environment Research Agency: London, UK, 2010.
13. Mora-Sandí, A.; Ramírez-González, A.; Castillo-Henríquez, L.; Lopretti-Correa, M.; Vega-Baudrit, J.R. Persea Americana Agro-Industrial Waste Biorefinery for Sustainable High-Value-Added Products. *Polymers* **2021**, *13*, 1727. [CrossRef]
14. Gao, Z.; Yu, H.; Li, M.; Li, X.; Lei, J.; He, D.; Wu, G.; Fu, Y.; Chen, Q.; Shi, H. A Battery of Baseline Toxicity Bioassays Directed Evaluation of Plastic Leachates—Towards the Establishment of Bioanalytical Monitoring Tools for Plastics. *Sci. Total Environ.* **2022**, *828*, 154387. [CrossRef]
15. Curto, M.; Le Gall, M.; Catarino, A.I.; Niu, Z.; Davies, P.; Everaert, G.; Dhakal, H.N. Long-Term Durability and Ecotoxicity of Biocomposites in Marine Environments: A Review. *RSC Adv.* **2021**, *11*, 32917–32941. [CrossRef] [PubMed]

16. Ferreira-Filipe, D.A.; Paço, A.; Duarte, A.C.; Rocha-Santos, T.; Silva, A.L.P. Are Biobased Plastics Green Alternatives?—A Critical Review. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7729. [CrossRef]

17. Liao, J.; Chen, Q. Biodegradable Plastics in the Air and Soil Environment: Low Degradation Rate and High Microplastics Formation. *J. Hazard. Mater.* **2021**, *418*, 126329. [CrossRef] [PubMed]

18. Manfra, L.; Marengo, V.; Libralato, G.; Costantini, M.; De Falco, F.; Cocca, M. Biodegradable Polymers: A Real Opportunity to Solve Marine Plastic Pollution? *J. Hazard. Mater.* **2021**, *416*, 125763. [CrossRef] [PubMed]

19. Uribe-Echeverría, T.; Beiras, R. Acute Toxicity of Bioplastic Leachates to Paracentrotus Lividus Sea Urchin Larvae. *Mar. Environ. Res.* **2022**, *176*, 105605. [CrossRef]

20. Wei, X.F.; Bohlén, M.; Lindblad, C.; Hedenqvist, M.; Hakonen, A. Microplastics Generated from a Biodegradable Plastic in Freshwater and Seawater. *Water Res.* **2021**, *198*, 117123. [CrossRef]

21. Wei, X.F.; Capezza, A.J.; Cui, Y.; Li, L.; Hakonen, A.; Liu, B.; Hedenqvist, M.S. Millions of Microplastics Released from a Biodegradable Polymer during Biodegradation/Enzymatic Hydrolysis. *Water Res.* **2022**, *211*, 118068. [CrossRef]

22. Yu, W.; Chen, J.; Zhang, S.; Zhao, Y.; Fang, M.; Deng, Y.; Zhang, Y. Extraction of Biodegradable Microplastics from Tissues of Aquatic Organisms. *Sci. Total Environ.* **2022**, *838*, 156396. [CrossRef]

23. Cavazza, A.; Mattarozzi, M.; Franzoni, A.; Careri, M. A Spotlight on Analytical Prospects in Food Allergens: From Emerging Allergens and Novel Foods to Bioplastics and Plant-Based Sustainable Food Contact Materials. *Food Chem.* **2022**, *388*, 132951. [CrossRef]

24. Bignardi, C.; Cavazza, A.; Laganà, C.; Salvadeo, P.; Corradini, C. Release of Non-Intentionally Added Substances (NIAS) from Food Contact Polycarbonate: Effect of Ageing. *Food Control* **2017**, *71*, 329–335. [CrossRef]

25. Kato, L.S.; Conte-Junior, C.A. Safety of Plastic Food Packaging: The Challenges about Non-Intentionally Added Substances (NIAS) Discovery, Identification and Risk Assessment. *Polymers* **2021**, *13*, 2077. [CrossRef] [PubMed]

26. Zimmermann, L.; Bartosova, Z.; Braun, K.; Oehlmann, J.; Völker, C.; Wagner, M. Plastic Products Leach Chemicals That InduceIn VitroToxicity under Realistic Use Conditions. *Environ. Sci. Technol.* **2021**, *55*, 11814–11823. [CrossRef]

27. Geueke, B.; Groh, K.J.; Maffini, M.V.; Martin, O.V.; Boucher, J.M.; Chiang, Y.T.; Gwosdz, F.; Jieh, P.; Kassotis, C.D.; Łańska, P.; et al. Systematic Evidence on Migrating and Extractable Food Contact Chemicals: Most Chemicals Detected in Food Contact Materials Are Not Listed for Use. *Crit. Rev. Food. Sci. Nutr.* **2022**, 1–11. [CrossRef]

28. Martínez-Bueno, M.J.; Gómez Ramos, M.J.; Bauer, A.; Fernández-Alba, A.R. An Overview of Non-Targeted Screening Strategies Based on High Resolution Accurate Mass Spectrometry for the Identification of Migrants Coming from Plastic Food Packaging Materials. *TrAC—Trends Anal. Chem.* **2019**, *110*, 191–203. [CrossRef]

29. Nerín, C.; Bourdoux, S.; Faust, B.; Gude, T.; Lesueur, C.; Simat, T.; Stoermer, A.; Van Hoek, E.; Oldring, P. Guidance in Selecting Analytical Techniques for Identification and Quantification of Non-Intentionally Added Substances (NIAS) in Food Contact Materials (FCMS). *Food Addit. Contam. Part A* **2022**, *39*, 620–643. [CrossRef] [PubMed]

30. Nerin, C.; Alfaro, P.; Aznar, M.; Domeño, C. The Challenge of Identifying Non-Intentionally Added Substances from Food Packaging Materials: A Review. *Anal. Chim. Acta* **2013**, *775*, 14–24. [CrossRef]

31. Canellas, E.; Vera, P.; Nerin, C.; Dreolin, N.; Goshawk, J. The Detection and Elucidation of Oligomers Migrating from Biodegradable Multilayer Teacups Using Liquid Chromatography Coupled to Ion Mobility Time-of-Flight Mass Spectrometry and Gas Chromatography–Mass Spectrometry. *Food. Chem.* **2022**, *374*, 131777. [CrossRef]

32. EFSA Food Contact Materials. Available online: https://food.ec.europa.eu/safety/chemical-safety/food-contact-materials_en (accessed on 5 January 2023).

33. European Commission. European Union Commission Regulation (EU) No 10/2011 of 14 January 2011. *Off. J. Eur. Union* **2011**, *12*, 1–89.

34. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Recent Developments in the Risk Assessment of Chemicals in Food and Their Potential Impact on the Safety Assessment of Substances Used in Food Contact Materials. *EFSA J.* **2016**, *14*, 4357. [CrossRef]

35. Martínez-Bueno, M.J.; Hernando, M.D.; Uclés, S.; Rajski, L.; Cimmino, S.; Fernández-Alba, A.R. Identification of Non-Intentionally Added Substances in Food Packaging Nano Films by Gas and Liquid Chromatography Coupled to Orbitrap Mass Spectrometry. *Talanta* **2017**, *172*, 68–77. [CrossRef]

36. US Food & Drug Administration. *CFR—Code of Federal Regulations Title 21*; US Food & Drug Administration: Silver Spring, MD, USA, 2022.

37. Gavriil, G.; Kanavouras, A.; Coutelieris, F.A. Food-Packaging Migration Models: A Critical Discussion. *Crit. Rev. Food Sci. Nutr.* **2018**, *58*, 2262–2272. [CrossRef]

38. US Food & Drug Administration. *Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations)*; Center for Food Safety and Applied Nutrition: College Park, MD, USA, 2007.

39. Osorio, J.; Dreolin, N.; Aznar, M.; Nerín, C.; Hancock, P. Determination of Volatile Non Intentionally Added Substances Coming from a Starch-Based Biopolymer Intended for Food Contact by Different Gas Chromatography-Mass Spectrometry Approaches. *J. Chromatogr. A* **2019**, *1599*, 215–222. [CrossRef] [PubMed]

40. Zimmermann, L.; Dierkes, G.; Ternes, T.A.; Völker, C.; Wagner, M. Benchmarking the in Vitro Toxicity and Chemical Composition of Plastic Consumer Products. *Environ. Sci. Technol.* **2019**, *53*, 11467–11477. [CrossRef] [PubMed]

41. Zimmermann, L.; Dombrowski, A.; Völker, C.; Wagner, M. Are Bioplastics and Plant-Based Materials Safer than Conventional Plastics? In Vitro Toxicity and Chemical Composition. *Environ. Int.* **2020**, *145*, 106066. [CrossRef] [PubMed]

42. Zhang, C.; Chen, C.; Ouyang, C.; Zeng, X.; Guo, Z.; Lai, F.; Li, J. Analysis of Oligomers in Poly (Butylene Succinate) and Poly (Butylene Adipate-Co-Terephthalate). *Polym. Bull.* **2022**, *80*, 4487–4502. [CrossRef]

43. Ubeda, S.; Aznar, M.; Nerín, C. Determination of Volatile Compounds and Their Sensory Impact in a Biopolymer Based on Polylactic Acid (PLA) and Polyester. *Food Chem.* **2019**, *294*, 171–178. [CrossRef]

44. Aznar, M.; Ubeda, S.; Dreolin, N.; Nerín, C. Determination of Non-Volatile Components of a Biodegradable Food Packaging Material Based on Polyester and Polylactic Acid (PLA) and Its Migration to Food Simulants. *J. Chromatogr. A* **2019**, *1583*, 1–8. [CrossRef]

45. Ubeda, S.; Aznar, M.; Alfaro, P.; Nerín, C. Migration of Oligomers from a Food Contact Biopolymer Based on Polylactic Acid (PLA) and Polyester. *Anal. Bioanal. Chem.* **2019**, *411*, 3521–3532. [CrossRef]

46. Canellas, E.; Vera, P.; Nerín, C. UPLC–ESI-Q-TOF-MSE and GC–MS Identification and Quantification of Non-Intentionally Added Substances Coming from Biodegradable Food Packaging. *Anal. Bioanal. Chem.* **2015**, *407*, 6781–6790. [CrossRef]

47. García Ibarra, V.; Rodríguez Bernaldo de Quirós, A.; Paseiro Losada, P.; Sendón, R. Non-Target Analysis of Intentionally and Non Intentionally Added Substances from Plastic Packaging Materials and Their Migration into Food Simulants. *Food Packag. Shelf Life* **2019**, *21*, 100325. [CrossRef]

48. Okoffo, E.D.; Chan, C.M.; Rauert, C.; Kaserzon, S.; Thomas, K.V. Identification and Quantification of Micro-Bioplastics in Environmental Samples by Pyrolysis-Gas Chromatography-Mass Spectrometry. *Environ. Sci. Technol.* **2022**, *56*, 13774–13785. [CrossRef]

49. Klein, K.; Hof, D.; Dombrowski, A.; Schweyen, P.; Dierkes, G.; Ternes, T.; Schulte-Oehlmann, U.; Oehlmann, J. Enhanced in Vitro Toxicity of Plastic Leachates after UV Irradiation. *Water Res.* **2021**, *199*, 117203. [CrossRef] [PubMed]

50. Asensio, E.; Montañés, L.; Nerín, C. Migration of Volatile Compounds from Natural Biomaterials and Their Safety Evaluation as Food Contact Materials. *Food Chem. Toxicol.* **2020**, *142*, 111457. [CrossRef] [PubMed]

51. Asensio, E.; Nieves, S.; Nerín, C. Migration Studies from Food Contact Natural Biomaterials in High Temperature Applications. *SSRN Electron. J.* **2022**. [CrossRef]

52. Osorio, J.; Aznar, M.; Nerín, C. Identification of Key Odorant Compounds in Starch-Based Polymers Intended for Food Contact Materials. *Food Chem.* **2019**, *285*, 39–45. [CrossRef] [PubMed]

53. Salazar, R.; Domenek, S.; Plessis, C.; Ducruet, V. Quantitative Determination of Volatile Organic Compounds Formed during Polylactide Processing by MHS-SPME. *Polym. Degrad. Stab.* **2017**, *136*, 80–88. [CrossRef]

54. Gavril, G.L.; Wrona, M.; Bertella, A.; Świeca, M.; Râpă, M.; Salafranca, J.; Nerín, C. Influence of Medicinal and Aromatic Plants into Risk Assessment of a New Bioactive Packaging Based on Polylactic Acid (PLA). *Food Chem. Toxicol.* **2019**, *132*, 110662. [CrossRef]

55. Osorio, J.; Aznar, M.; Nerín, C.; Birse, N.; Elliott, C.; Chevallier, O. Ambient Mass Spectrometry as a Tool for a Rapid and Simultaneous Determination of Migrants Coming from a Bamboo-Based Biopolymer Packaging. *J. Hazard. Mater.* **2020**, *398*, 122891. [CrossRef]

56. Ubeda, S.; Aznar, M.; Nerín, C.; Kabir, A. Fabric Phase Sorptive Extraction for Specific Migration Analysis of Oligomers from Biopolymers. *Talanta* **2021**, *233*, 122603. [CrossRef]

57. Wrona, M.; Nerín, C. Analytical Approaches for Analysis of Safety of Modern Food Packaging: A Review. *Molecules* **2020**, *25*, 752. [CrossRef] [PubMed]

58. Serrano-Ruíz, H.; Eras, J.; Martín-Closas, L.; Pelacho, A.M. Compounds Released from Unused Biodegradable Mulch Materials after Contact with Water. *Polym. Degrad. Stab.* **2020**, *178*, 109202. [CrossRef]

59. Schymanski, E.L.; Jeon, J.; Gulde, R.; Fenner, K.; Ruff, M.; Singer, H.P.; Hollender, J. Identifying Small Molecules via High Resolution Mass Spectrometry: Communicating Confidence. *Environ. Sci. Technol.* **2014**, *48*, 2097–2098. [CrossRef] [PubMed]

60. Mattarozzi, M.; Riboni, N.; Maffini, M.; Scarpella, S.; Bianchi, F.; Careri, M. Reversed-Phase and Weak Anion-Exchange Mixed-Mode Stationary Phase for Fast Separation of Medium-, Long- and Very Long Chain Free Fatty Acids by Ultra-High-Performance Liquid Chromatography-High Resolution Mass Spectrometry. *J. Chromatogr. A* **2021**, *1648*, 462209. [CrossRef] [PubMed]

61. Gómez Ramos, M.J.; Lozano, A.; Fernández-Alba, A.R. High-Resolution Mass Spectrometry with Data Independent Acquisition for the Comprehensive Non-Targeted Analysis of Migrating Chemicals Coming from Multilayer Plastic Packaging Materials Used for Fruit Purée and Juice. *Talanta* **2019**, *191*, 180–192. [CrossRef] [PubMed]

62. Song, X.C.; Canellas, E.; Dreolin, N.; Goshawk, J.; Nerin, C. A Collision Cross Section Database for Extractables and Leachables from Food Contact Materials. *J. Agric. Food. Chem.* **2022**, *70*, 4457–4466. [CrossRef] [PubMed]

63. Miralles, P.; Yusà, V.; Pineda, A.; Coscollà, C. A Fast and Automated Strategy for the Identification and Risk Assessment of Unknown Substances (Ias/Nias) in Plastic Food Contact Materials by Gc-q-Orbitrap Hrms: Recycled Ldpe as a Proof-of-Concept. *Toxics* **2021**, *9*, 283. [CrossRef]

64. Osorio, J.; Aznar, M.; Nerín, C.; Elliott, C.; Chevallier, O. Comparison of LC-ESI, DART, and ASAP for the Analysis of Oligomers Migration from Biopolymer Food Packaging Materials in Food (Simulants). *Anal. Bioanal. Chem.* **2022**, *414*, 1335–1345. [CrossRef]

65. Gies, A.P.; Ellison, S.T.; Chakraborty, A.K.; Kwiecien, N.W.; Hercules, D.M. MALDI-TOF/TOF CID Study of Poly(Butylene Adipate) Fragmentation Reactions. *RSC Adv.* **2012**, *2*, 4135–4151. [CrossRef]

66. Astolfi, M.L.; Marconi, E.; Lorini, L.; Valentino, F.; Silva, F.; Ferreira, B.S.; Canepari, S.; Majone, M. Elemental Concentration and Migratability in Bioplastics Derived from Organic Waste. *Chemosphere* **2020**, *259*, 127472. [CrossRef]
67. *ISO 8124-3:2020*; Safety of Toys—Part 3: Migration of Certain Elements. British Standards Institution: London, UK, 1994.