NIAS in Plastic Food Packaging

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Several food contact materials (FCMs) contain non-intentionally added substances (NIAS), and most of the substances that migrate from plastic food packaging are unknown. Food packaging can contain NIAS as a result of the interactions between different substances in the packaging materials, between food content and substances (for example, additives) in FCM, from degradation processes and mainly from the impurities present in the raw materials used for FCM production. (EU) nº 10/2011 defines that "non-intentionally added substance means an impurity in the substances used or a reaction intermediate formed during the production process or a decomposition or reaction product". Most NIAS are regularly detected when using high sensitivity analytical techniques, although the chemical structure of unknown compounds is often difficult to establish by conventional tools.

Keywords: food packaging additives ; food contact materials (FCMs) ; food safety ; additives in polymers ; migration study ; food contact articles (FCAs)

1. Migration of Substances from Packaging to the Food

The FCMs, depending on the circumstances, may transfer their constituents to the foodstuffs. This mass transfer phenomenon is called migration, leading to high human exposure to certain chemicals [1][2][3][4]. Considerable knowledge concerning the migration potential of FCMs has been accumulated recently, primarily in support of the FDA, European Commission and international food contact materials legislation and the scientific community [5][6][7][8][9][10][11]. The migration can occur from packaging to the food, where molecularly diffused substances of low molecular weight (e.g., oligomers or additives) can be transferred into foods [12] and from food to the packaging [13].

Migration is of significance for smaller size compounds (below 1000 Da) [14][15]; despite in terms of risk assessment, oligomers up to a molar weight of 1000 Da are evaluated to be relevant under the assumption of human gastrointestinal absorption [16][17]. The dimension to which migration occurs depends on several factors (**Figure 1**) listed below [18][19][20]:

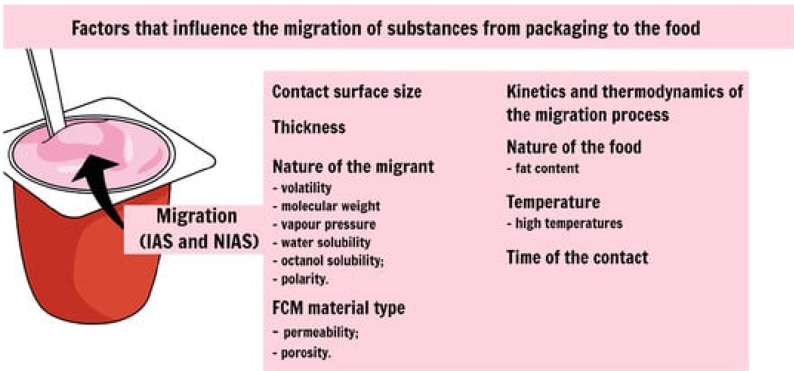

Figure 1. Main factors that influence the migration of substances from packaging to food.

- the contact surface size, since the more extensive the contact surface between packaging and food, the higher the migration rate [1];
- the nature of the migrant, since the more volatile and the lower the molecular weight, the greater the migration rate (also the vapour pressure, water solubility, octanol solubility and polarity) [21];
- FCM material type (e.g., impermeable, permeable, porous materials) [22];
- kinetics and thermodynamics of the migration process (how fast will a substance transfer from the FCM into food) [23][24];

- the nature of the food, since high-fat foods are reported with a high level of migration, for example [19][22];
- temperature, high temperatures demonstrate high migration rates [19][21];
- contact during serving and duration of the time of contact [19][22].

In the specific case of plastics, non-inert materials, the migration can occur from the inner side of the packaging and internal layers due to diffusion processes [25][26][27]. According to the deterministic model, the migration of substances from packaging to food occurs through diffusion, where there is a movement of molecular structures from the high concentration to the low concentration region until equilibrium is reached. Fick's second law can describe the diffusion rate [28][29][30][31][32]. Some studies describe precisely how to use this mathematical model [19][24][32]. In addition to diffusion, there is also desorption of diffuse polymer surface molecules, sorption of compounds at the plastic-food interface and desorption of compounds in the food that describe the migration stages [1].

Migration modelling can complement or substitute actual laboratory migration experiments that are expensive and time-consuming. Thus, it has become a popular tool for researchers, industry and regulators to predict migration. Efforts have been made to modify the standard "worst-case" deterministic models to reflect more realistic migration scenarios better. These approaches comprehend probabilistic and stochastic modelling that considers variability and uncertainty in the mass transfer parameters, mechanistic or empirical migration models that can be combined with food consumption data to estimate dietary exposure to the chemicals [33][34][35][36]. However, trained specialists should only use migration models with in-depth knowledge of chemical migration to make reliable predictions and correctly interpret the results. Gavriil et al. [35] published an extensive review to evaluate the migration models' efficiencies, concluding that these models cannot predict the total accurate migration from a different FCM to the food volume since the material might contain several completely unknown compounds. Thus, migration studies are still the traditional method for evaluating the migration of substances from packaging to food, despite analytical challenges and cost.

Two terms of high significance that should not be confused are the overall migration (OM) and the specific migration (SM). The OM refers to the sum of all mobile substances of packaging released per unit area of the package under the influence of specific predetermined conditions. On the other hand, SM is only related to a specific known substance [37].

In most cases, and as provided by legislation ((EU) n° 10/2011), the migration study is performed with food simulants in place of the food itself, due to the high complexity that food has typically as a matrix than foods [6][38][39]. They should represent the significant physicochemical properties exhibited by each food type. When using food simulants, temperature and standard testing time should replicate the migration from the FCM into the food [19][40]. Moreover, current legislation provides for the simulation of temperature and contact period situations in which migration tests performed according to the actual situation's food storage conditions.

In the US, according to The Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations) published by the FDA in 2007, sponsors should provide information sufficient to permit estimation of the daily dietary consumption of the food contact substances (FCS), e.g., consumer exposure. The FDA will calculate the FCS consumption or other components consumption that might migrate to food expected daily based on analyzed or estimated levels in food or food simulants. Still following the guidance, "Although the FDA always has accepted reliable analyses of FCS in real foods, many analytes are difficult to measure in food in practice. As an alternative, sponsors may submit migration data acquired with food simulants to reproduce the FCS's nature and migration into food. Because an FCS can contact many foods with different processing conditions and shelf lives, the submitted migration data should reflect the most severe temperature/time conditions to which the food contact article (FCA) containing the FCS will be exposed. The document brings a table with the respective recommended simulant according to the type of food. The recommendation for aqueous and acidic foods is 10% ethanol; low- and high-alcoholic foods, 10–50% ethanol; fatty food, food oil (e.g., corn oil), HB307, Miglyol 812 or others.

Two steps are involved in migration tests of substances from food packaging into food simulants: to expose the polymer packaging to the food simulant; to quantify the migrants transferred to a food simulant in terms of OM or SM. Determining OM is a regulatory requirement in EU countries with established migration limits for FCMs substances [1].

Most of the substances that migrate from packaging to food are unknown. A recent Scientific Opinion issued by the European Food Standard Authorization (EFSA) in 2016 comments that regarding identifying and evaluating all migrating substances, experience has shown that it is necessary to focus more on finished materials and articles used during the manufacturing process. Substances used in the manufacture of FCM or objects may contain impurities originating in their manufacture. Besides, during manufacture and use, reaction and degradation products may be formed, of which oligomers may be of the dominant class. These substances have become known as NIAS and referred to as such in the Commission Regulations. Regardless of whether they are intentional or unintended, all migrant substances' safety, not just initiating substances—e.g., monomers or additives only—needs to be assessed, and the guidelines should be updated to account for this broader approach fully. This change to the finished FCM and its use requires an adjustment of the current substance listing system. The present work will discuss the definition, different aspects and types of NIAS, analytical methods of determination and quantification and the next section's risk assessment task.

2. NIAS in Plastic Food Packaging

Inventory lists of plastic FCMs contain several thousands of chemicals, including starting substances like monomers, production aids and additives [41][42][43]. However, these chemicals often suffer transformations, and final FCAs and FCMs may contain novel compounds that can migrate into food [41][43][44]. **Figure 2** introduces the scientific terms for food contact articles (FCA), which are the combination of diverse food contact materials (FCMs) and food contact chemicals (FCCs) defined as substances used or present in the manufacture of FCMs or existing in the final FCMs or FCAs. Some FCCs are starting substances that no longer exist in the final FCM/FCA. Some FCCs are generated during the manufacture of an FCM/FCA or during the application of high temperatures, irradiation or the consumer's food packaging. FCCs comprehend intentionally added substances (IAS), such as monomers, additives, catalysts and production aids; and impurities and reaction products (oligomers, polymers, by-products and degradation products), be referred to as non-intentionally added substances (NIAS) [45].

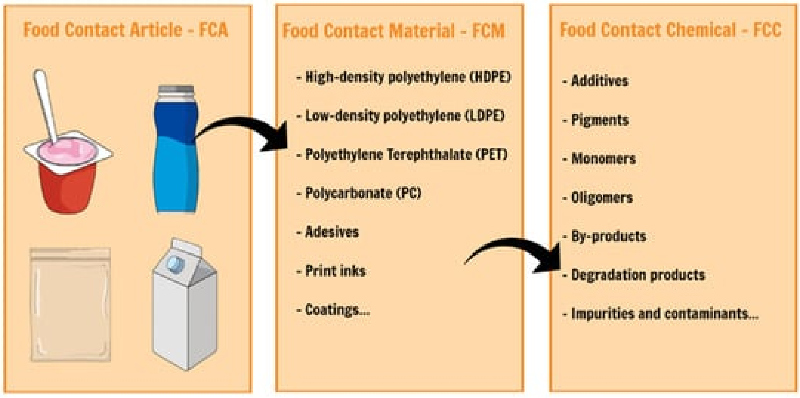

Figure 2. Illustration of key terms: FCA, FCM and FCC, and everything that makes up a food plastic packaging (adapted from Muncke et al. [46]).

The FDA classifies Food Contact Substance (FCS) as "any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting or holding food if such use of the substance is not intended to have any technical effect in such food". FCS could be "a single substance, such as a polymer or an antioxidant in a polymer. As a substance, it is reasonably pure". Although a polymer may be composed of diverse monomers, it has a well-defined composition. FCM is "made with the FCS and (usually) other substances. It is often (but not necessarily) a mixture, such as an antioxidant in a polymer. The composition may be variable".

It is impossible to know all substances that may be formed by the degradation of additives or plastics' polymerization [47][41]. Their presence is often not known by the consumer or by the manufacturer [48][41]. If, according to Regulation EC 1935/2004 on materials and articles intended to come into contact with food, the manufacturer must ensure the safety of food contact packaging, it is clear that it is necessary to know about the NIAS formed and also to assess the risk assessment (RA) of these new substances. Still, following EC (EU) n° 10/2011, unauthorized substances may be used in FCMs plastics behind a functional barrier, providing they do not migrate to the food at levels above 10 µg/kg. Thus, in Europe, NIAS could be within this approach [48].

In the United States, according to the FDA Code Federal Regulation Title 21 Sec. 170.39 on the threshold of regulation for substances used in food-contact articles, substances that may enter the diet at levels below 50 µg/kg and demonstrate that they are non-genotoxic, are exempt from need authorization indirect food additive [49]. The FDA uses the term "Indirect Food Additive", a food additive coming into contact with food as part of the packaging or processing but is not intended to be added directly to, become a constituent or have a technical outcome in/on the food. Indirect food additives cited in Title 21 of the US Code of Federal Regulations (21CFR) used in food-contact articles comprise adhesives and components of coatings (Part 175), paper and paperboard (Part 176), polymers (Part 177) and adjuvants and production aids (Part 178).

In this sense, the scientific community has been striving to define NIAS identification and determination strategies in FCMs and FCAs in general and strategies to predict the migration rate of these compounds from packaging to food and evaluate the health risks of each identified NIAS. A literature search was made using Medical Subject Headings (MeSH) terms on the Pubmed, Web of Science and Scopus databases. The initial screening process was performed from August to September 2020. Further directed searches were carried out by checking the reference lists of relevant articles. In this context, we defined a strategy composed of four phases to build the search strings: (i) identification of keywords considering the research question; (ii) synonyms based on relevant studies about non-intentionally added substances and plastic food packaging; and (iii) use of “AND” and “OR” Booleans operators.

- Search component 1 (SC1) was a population search: “food packaging” OR “food contact article” OR “food contact material” OR “packaging, food” OR “food containers” OR “plastic packaging materials” OR “multilayer food packaging” OR “multilayer packaging materials” OR “recycled plastic packaging” OR “acrylic adhesives” OR “recycled expanded polystyrene containers” OR “polyester-polyurethane” OR “food packaging polymer” OR “biodegradable food packaging” OR “nylons” OR “polyethylenes” OR “polypropylenes” OR “polystyrenes” OR “polyurethanes” OR “polyolefins” OR “acrylic adhesives” OR “recycled expanded polystyrene containers” OR “polyester-polyurethane” OR “polyvinyls” OR “polyesters” OR “polyethylene terephthalates” OR “polyhydroxy ethyl methacrylate” OR “silicones” OR “elastomers” OR “polyvinyl chloride” OR “silicone elastomers”.

- Search component 2 (SC2) was an intervention search: “non-intentionally added substances” OR “non-intentionally added compound” OR “NIAS” OR “breakdown products” OR “impurities” OR “side products” OR “neo-formed compounds” OR “degradation of polymers” OR “degradation of compounds” OR “degradation products” OR “non-volatile migrants” OR “volatile compounds” OR “non-volatile compounds” OR “volatile organic compound” OR “polymer additives” OR “oligomers” OR “additives” OR “plastic additives” OR “additive”.

- Because the ScienceDirect database only allows the use of a maximum of thirteen keywords in the search string, for this base it was used the following search components:

- SC1: (“food packaging” OR “food contact article” OR “food contact material” OR “plastic packaging materials”).

- SC2: (“non-intentionally added substances” OR “non-intentionally added compound” OR “NIAS” OR “additives”). **Table 1** presents published works that identified NIAS on different food plastic packaging, the techniques used in each work and the migration tests applied. Despite all efforts, there is much to discover and to do in this area. Below are the leading examples of possible NIAS formation, shown in **Figure 3**.

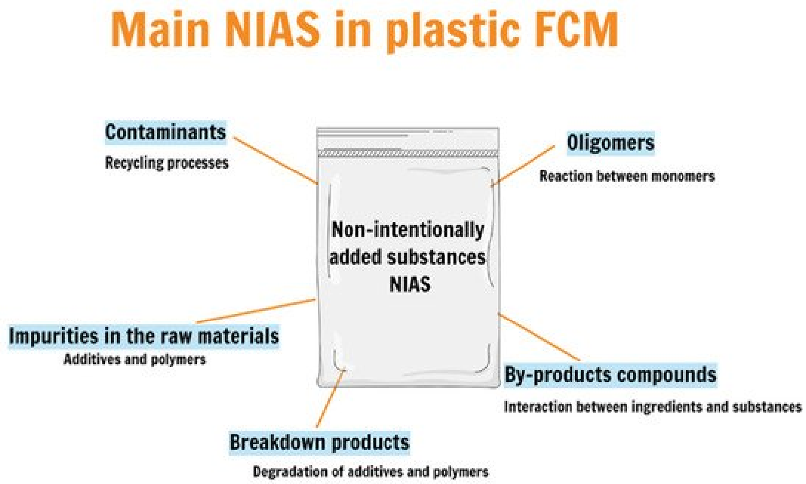

Figure 3. Mainly examples of NIAS formed during food plastic contact materials manufacturing, during the foodstuff’s shelf life, or during some processing (i.e., heating or irradiation).

Table 1. Studies published in the literature on NIAS Identification in different plastic food packaging.

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
Polyvinyl chloride PVC/polyethylene-PE multilayer film	Antioxidants derivatives: Triester analog of 1010; Plasticizers (contain glycerol): 1-oleoyl-3-linoleoyl-rac-glycerol; Slip agents (with an amide end group): Tetracosenamide, Docosanamide, Icosanamide; Others: 2-(2-hydroxyethyl-hexadecylamino)ethyl palmitate, Bis(2-ethylhexyl) 2,2′-disulfanediyldiacetate	UPLC-QTOF/MS	Stainless-steel migration cell, water, 40% ethanol or 95% ethanol	[28]
Multilayer plastic materials (the combination of aluminium (Al), polyethylene terephthalate (PET), polyamide (PA), polypropylene (PP) and polyethylene (PE)	Cyclic esters (AA-DEG and AA-DEG-IPA-DEG)	UPLC-MS-QTOF and UHPLC-MS-QqQ	Ultrapure water, ethanol 10% and 95% ethanol	[2]
Polyethylene terephthalate (PET)	Cyclic oligomers	LC-MS	50% ethanol at 80 °C	[5]
Polyester resins, tin plate sheets coated with polyester–phenolic lacquers and corresponding press-twist-closures (equipped with plasticized polyvinyl chloride [PVC] sealings)	Polyester oligomers (cyclic oligomers, dimers, trimers and tetramers)	HPLC–DAD, HPLC–DAD/MS, GC-MS, GC–MSD and RP-HPLC–DAD/MS	Mashed infant food and two types of homemade carrot puree, Acetonitrile, 50% Etanol, 20% Etanol	[6]
Rigid thermoformed containers and films made with Recycled polyethylene terephthalate-RPET	Chromium, nickel	CP-AES	Distilled water, 5% citric acid	[8]
Multilayer food packaging materials	Printing unknown ink compounds	GC-MS	Tenax, isooctane and etoh 95% and etoh 50%	[9]
Polyurethane adhesive	1,4,7-trioxacyclotridecane-8,13-dione; 1,6-dioxacyclododecane-7,12-dione dimer; 1,4-dioxacyclotridecane-5,13-dione; 1,4,14,19-tetraoxacyclopent acosene-5,13,20,25-tetra one and 1,4-dioxacyclotridecane-5,13-dione; by-product of the curing reaction: 1,1-(Methanediyldibenzene-4,1-diyl)bis[3-(2-hydroxyethyl)urea]; 4-(7-acetoxy-5-methoxy-8,8-dimethyl-2-oxo-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-3-yl)-1,3-phenylene diace-tate; Bis[2-(diethylamino)ethyl] 4,4′-[(2-methyl-1,3propanediyl)bis(oxycarbonylimino)] dibenzoate and Bis[2-(diethylamino)ethyl]4,4′-[1,5-p entanediylbis(oxycarbonylim ino)] dibenzoate; unknown compounds	UPLC–Q-TOF/MS	Tenax	[10]
Expanded polystyrene (EPS) (recycled material)	Styrene dimmers are observed, like cis-1,2-diphenylcyclobutane, 2,4-diphenyl-1-butene, trans-1,2-diphenylcyclobutane and 1-phenyltetralin. These compounds were reported as by-products during styrene polymerization or material processing	HS-SPME-GC–MS	10% (*v*/*v*) ethanol and 3%(*w*/*v*) acetic acid	[11]

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
Polyethylene-PE, low-density polyethylene-LDPE and HIGH-density polyethylene-HDPE	Dibutyl amine, *N*,*N*-bis(2-hydroxyethyl)alkylamines (impurity reaction or breakdown products), *N*,*N*-bis(2-hydroxyethyl) dodecylamine, tributylphosphine, tridodecylamine, Methyl (Ralox 35), ethyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propanoate (breakdown of Irganox 1010 or Irganox 1076), Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,1′-[2,2-bis(hydroxymethyl)-1,3-propanediyl] ester and benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,1′-[2-[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-2-(hydroxymethyl)-1,3-propanediyl] ester (degradation of Irganox 1010), alkylamides *N*,*N*′-1,2-ethanediylbis-(breakdown or impurity products of the additive octadecanamide, *N*,*N*′-1,2-ethanediylbis), Irgafos 168 OXO (oxo-derivative of Irgafos 168), 11-eicosenamide (derived from oleamide)	UPLC IMS QTOF	Ethanol 95%, ethanol 50%, Tenax, ethanol 10% and acetic acid 3%	[39]
Empty cans with lids coated with polyester resins	Oligomers	GC–MS, HPLC-DAD/MS, UHPLC-HRMS and DART-HRMS	--	[40]
Polyester coatings based on NAH	Oligomers	LC-MS/MS and LC-TOF-MS	Acetonitrile, Water, 10% Aqueous ethanol (*v*/*v*), 50% Aqueous ethanol (*v*/*v*) and diverse foodstuffs	[50]
Polyester can coating extracts	Linear and cyclic oligomers derived from the incomplete polymerization of polyester monomers, phthalic acids and diols	HPLC-MS, HPLC-ESI MS and HPLC-HRMS/MS	95/5 etoh/water (*v*/*v*-%) solution for 4 h at 60 °C and 50/50 etoh/water (*v*/*v*-%) solution for 10 days at 60 °C	[51]
Virgin and recycled Polyethylene terephthalate-PET pellets	Cyclic and linear oligomers: TPA-EG, (TPA-EG)2 + H_2O, (TPA-EG)2, (TPA-EG)3 + H20, (TPA-EG)3, (TPA-EG)4, and (TPA-EG)5, TPA2-EG-DEG + H_2O, TPA2-EG-DEG, TPA3-EG2-DEG + H_2O, TPA3-EG2-DEG, and TPA4-EG3-DEG, (TPA-DEG)2 and TPA4-EG2-DEG2	UPLC-MS-QTOF	Ethanol 10% *v*/*v*) and simulant B (acetic acid 3% *w*/*v*) as aqueous simulants and ethanol 95% *v*/*v* as a fat simulant	[52]
Baby food squeezes with multilayer materials (Polyethylene terephthalate-PET/aluminium-Al/polyethylene-PE)	Polyester oligomers, 29 cyclic and six linear oligomers. ε-caprolactam was tentatively identified as a heterogenic polyester oligomer combined with AA, DEG, PA and NPG; BHET and diethyl 5-(2-((2,4,5-trimethoxybenzoyl)oxy)acetamido)isophthalate, methoxyeugenol and Bis(2-methoxyethyl) sebacate	UHPLC-ESI-QTOF MS	Baby food: mixture of fruit purées (apple, banana, pear), fruit jelly, chocolate custard, acetic acid 3% (*w*/*v*) and ethanol 20% (*v*/*v*)	[53]
Polyurethane adhesives in multilayer packaging materials	Silane unknown compounds; degradation of antioxidants Irgafos and Irganox (2,6-Di-tert-butylbenzoquinone; isomer 2,5-di-tert-butylbenzoquinone; 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione; benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-methyl), by-product of the polyester-based urethane 91,6-Dioxacyclododecane-7,12-dione); cyclic adipate; unknown nitrogen-compounds; unknown phenolic compounds; 1,4,7-Trioxacyclotridecane-8,13-dione	HS-SPME-GC-MS	Tenax; isooctane	[54]

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
UV-curable varnishes over polypropylene	2-propenoic acid,1,1′-[2-[[3-[2,2-bis[[(1-oxo-2-propen-1-yl)oxy]methyl]butoxy]-1-oxopropoxy]methyl]-2-ethyl-1,3-propanediyl] ester is considered a NIAS, as it is a reaction product coming from the monomer TMPTA, 11-diethyl-7-oxo-4,6,10,12-tetraoxopentadecane-3,13-diyl diacrylate	GC-MS/Q and UHPLC-IMS/QTOF	Ethanol 95% (*v*/*v*) and Migracell® migration cells	[55]
Polyethylene terephthalate (PET), oriented polyamide (OPA), cast polypropylene (CPP), polyethylene (PE) and PE/ethyl vinyl alcohol PE(EVOH)	Primary aromatic amines-PAAs (1,8-diazacyclotetradecane-2,9-dione; caprolactam; 1,8,15-triazacycloheneicosane-2,9,16-trione; 1,3-bis(isocyanatomethyl)-cyclohexane, 1-cyanodecane and 1,4-bis(isocyanatomethyl)-cyclohexane; l-leucyl-l-leucyl-l-leucine; 1,4,7,18,21-pentaoxa-11,14,25,28-tetraazacyclohentriacontane (9CI); l-leucine; l-leucyl-l-leucyl-l-leucyl-l-leucyl-; butanediamide; *N*4-hydroxy-*N*1-[(1S)-2-methyl-1-(1-pyrrolidinylcarbonyl)propyl]-2-pentyl-, (2R)-; triethylamine, naphtylethylenediamine; 1,8,15,22-tetraazacyclooctacosane-2,9,16,23-tetrone; urea; *N*-cyclohexyl, urea, *N*-cyclohexy-*N*′-methyl and 1-(cyclohexycarbonyl)piperazine); Dimethyl phthalate	UHPLC–Q-TOF/MSE	3% (*w*/*v*) acetic acid	[56]
Polypropylene random copolymer composite films	Irgafos 168 and its two degradation products, 2,4-di-tert-butylphenol (DP1) and tris (2,4-di-tert-butylphenyl) phosphate (DP2)	GC-MS	Isooctane	[57]
Polypropylene (PP)	Degradation products derived from phenolic antioxidants, impurity/reaction product/breakdown product of the additives, Family 1: Family formed with the reference structure; was formed by the compounds that had a similar structure constituted by a group 3,5-di-tert-butyl-4-hydroxyphenyl; Family 2: With glycerol molecule (glyceryl monostearate, glyceryl palmitate and glyceryl dihexadecanoate, an ester of an acid chain bonded to a glycerol molecule); Family 3: Dihydroxy alquilamines (amine bonded to two ethanol molecules and also an alkyl hydrocarbon chain); Family 4: ceramide and dihydroceramide (a family of waxy lipid molecules which are composed of sphingosine (an 18 carbon amino alcohol with an unsaturated hydrocarbon chain) and a fatty acid); Family 5: amides bonded by ethylene (degradation products from a lubricant losing C_2H_4); Other compounds (amides come from the impurities or degradation products from erucamide and oleamide widely used as slip agents)	UPLC-MS-QTOF	Ethanol 95% and 10%, acetic acid 3% and Tenax	[58]
Hot melt adhesives (Ethylene-vinyl acetate-EVA and amorphous polyolefin APAO enriched in propene)	Degradation of Irganox 1010: 3,5-di-tert-butyl-4-hydroxybenzaldehyde	UPLC-ESI-MS/QTOF	Tenax	[59]
Polyethylene terephthalate (PET) pellets	The degradation product of the antioxidants Irgafos 168 and Irganox 1010: 2,4-bis(1,1-dimethyl ethyl) phenol; 2-methyl-1,3-dioxolane; linear aldehydes; residual monomers: ethylene glycol (EG); thermal degradation products: toluene, ethylbenzene and xylene; phthalates (DEP, DIBP)	HS-SPME/GC-MS	--	[60]
Polypropylene (PP) films	Degradation products from Irgafos 168, Tinuvin 326 and Irganox 1076	HPLC-DAD and GC-FID–MS	Distilled water/ethanol—50/50 *v*/*v*	[61]

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
Plastic films (with and without printing ink) including PE: polyethene. PET: polyethylene terephthalate. PA: Polyamide. PP: Polypropylene. EVA: Ethylene-vinyl acetate.	2,4-di-tert-butylphenol and 2,6-di-tert-butyl-1,4-benzoquinone. 2,4-di-tert-butylphenol is a degradation product of Irgafos 168 while 2,6-di-tert-butyl-1,4-benzoquinone is a degradation product of antioxidants such as Irganox 1010, Irgafos 168 and Irganox PS 802	purge and trap (P&T) coupled to GC–MS	Isooctane and Tenax	[62]
Polypropylene (PP)	2,4-di-tert-butylphenol (degradation product of Irgafos 168 and Irganox® 1010), tert-butyl-1-oxaspiro(4,5)deca-6-9-diene-2,8-dione (a by-product of the antioxidant Irganox 1010) and 2,6-di-tert-butyl-1,4-benzoquinone, a degradation product of antioxidants such as Irganox 1010, Irgafos 168 and Irganox PS 802	GC-MS	--	[63]
Polypropylene food storage containers	Degradation products: 2,4-di-tert-butylphenol and tris(2,4-di-tert-buthylphenyl)phosphate, methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate, a compound identified as product of degradation of Irganox 1076 and/or Irganox 1010; 2,6-di-tert-butylbenzoquinone (isooctane fraction) and 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione; different compounds have been identified as metabolites of bis-(2-ethylhexyl) phthalate (e.g., 2-ethylhexanoic acid, 2-ethylhexanol, phthalic acid, mono-2-ethylhexyl phthalate), and consequently suggested as possible degradation products of this phthalate; by-product Benzothiazole; degradation products *N*,*N*-bis-(2-hydroxyethyl)alkyl amine	GC × GC−ToF MS	3% (*w*/*v*) acetic acid, 10% (*v*/*v*) ethanol, and isooctane	[64]
Can coatings	Diisobutyl phthalate (DIBP), Degradation products formed from antioxidants (1,3-di-tert-butylbenzene and 2,4-di-tert-butylphenol degradation products from antioxidants Irgafos 168 or Irganox 1076, 2,6-di-tert-butyl-1,4-benzoquinone degradation products from antioxidants Irgafos 168 and Irganox 1010, 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione, a degradation product of Irganox 1010.	GC-MS and LC-MS/MS	--	[65]

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
Recycled pellets obtained from post-consumer low-density polyethylene (PC-LDPE) and high-density polyethylene (PC-HPDE)	**Polymer degradation products: octanal and nonanal (aldehydes); 3-decanone, 2-undecanone, 2,2,4,4,6,8,8-heptamethylnonanone and 3-dodecanone (ketones); hexane (others); Additives degradation products: 3,5-di-tert-butyl-4-hydroxybenzaldehyde (aldehyde); 2,6-di-tert-butyl-1,4-benzoquinone and 3,5-di-tert-butyl-4-hydroxyacetophenone (ketones); methyl tetradecanoate, ethyl tetradecanoate and ethyl palmitate(esters); 7,9-di-tert-butyl-1-oxaspiro (4,5)deca-6,9-diene-2,8-dione (others); Contaminants from external sources: methyl lactate, hexyl acetate and dimethyl butanedioate, α-methylionone, 3-(4-Isopropylphenyl)-2-methylpropionaldehyde, α-amylcinnamaldehyde, (phenylmethylene)octanal and dipropylene glycol amog others (cosmetic ingredients); alkylbenzenes (breakdown products produced by the degradation of alkylbenzene sulfonates); contamination related to food: the lactones, 5-methylfurfural, furfural and methyl hexanoate (can derive from food flavors as well as from cosmetics ingredients); furfuryl alcohol, methyl pyruvate and 2-acetyl pyridine (food flavors), methyl-2-ethylhexanoate, acetic acid, propanoic acid, pyridine and dimethyl trisulfide (rotten food products), 2,6-diisopropylnaphthalene (paper labels).**	**GC/MS and HS-SPME-GC/MS**	**--**	[66]
Plastic baby bibs (polyethylene vinyl acetate-PEVA, polyamide-PA and polyethylene-PE)	**Azocine, octahydro-1-nitroso-(Possible NIAS from printing ink); 1,6-Dioxacyclododecane-7,12-dione (NIAS from polyurethane adhesive); 1-Propene-1,2,3-tricarboxylic acid, tributyl ester (Tributyl aconitate)**	**GC-MS**	**Artificial saliva**	[67]
Polystyrene-PS cups and multilayer films	**Styrene monomer and oligomers; polyester urethane-based oligomers (PU) cyclic oligomers: α-methylstyrene; 1,1-diphenyl-ethylene; 2,4-diphenyl-1-butene; trans-1,2-diphenycyclobutane; 2,4,6-triphenyl-1-hexene;**	**GC-MS**	**10% *v/v* ethanol in water and 50% *v/v* ethanol in water**	[68]
Polyurethane adhesives	**1,4,7-trioxacyclotridecane-8,13-dione, a lactone**	**UPLC-TQMS and UPLC-QTOF-MS**	**Tenax and 3% acetic acid**	[69]
Polyvinylchloride (PVC)-coated cans	**6-(4-methylphenyl)-1,2,4,5-tetrazin-3-amine and BGA (6-phenyl-1,3,5-triazine-2,4-diamine)**	**UHPLC-HRMS**	**Water and 3% acetic acid**	[70]
Monolayer film with polylactic acid (PLA), polylimonene (PL) and zinc oxide nanoparticles (ZnO NPs)	**Tripropylene glycol diacrylate; 10-Heneicosene; α-Tocopherol acetate; *N*, *N*-Diethyldodecanamide; *N*-[(9Z)-9-Octadecen-1-yl]acetamide; 1-Palmitoylglycerol and Glycerol stearate**	**ICP-MS, GC–Q-Orbitrap-MS and LC–Q-Orbitrap-MS**	**10% ethanol, 3% acetic acid**	[71]
Flexible multilayer materials point by polyurethane (PU) layers	**Polyamide oligomers; Anhydride of monomethyl succinate, 3,5-di-tert-butyl-4-hydroxybenzaldehyde; Erythritol monopalmitate; PU oligomers (cyclic esters made up of phthalic acid (PA); diethylene glycol (DEG) in combination 1:1 (PA-DEG) or 2:2 (PA-DEG-PA-DEG0); adipic acid (AA) or phthalic acid (PA); and diols such as diethylene glycol (DEG), neopentyl glycol (NPG), dipropylene glycol (DPG), dihydroxyalkyl ethers (dHAE), ethylene glycol (EG), propylene glycol (PG), butylene glycol (BD) or hexanediol (HD).**	**UPLC MS–QTOF**	**Ethanol 10% *v*/*v*, acetic acid 3% *w*/*v*, and ethanol 95% *v*/*v***	[72]

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
Active packaging: Polypropylene (PP); PP + green tea; PP/poly (ethylene-co-vinyl alcohol) EVOH; PP/EVOH + oregano; PP/EVOH + citral; EVOH; Polyethylene terephthalate-PET/EVOH + citral; PET/EVOH + cinnamon; PP/EVOH/PP; PP/EVOH + oregano	Degradation of active compounds; impurities from the raw materials; additives used in the manufacture of the active polymer (citral thermal reaction products; oxidation product of citral; decomposition product of adipates used as plasticizers; impurity/reaction product/breakdown product for the additives used in the manufacture of PE materials; xanthenone derivates)	UPLC-QTOF-MS	Ethanol 10%; ethanol 95%	[73]
Polyethylene terephthalate (PET) film with an acrylic resin	Ethyl lauroyl arginate (LAE) impurities: *N*2-Dodecanoyl-*L*-arginine (LAS)	UPLC–MS(QTOF)	Ethanol 10%; ethanol 95%; sliced fresh chicken breasts	[74]
Multilayer materials	1,4,7-trioxacyclotridecane-8,13-dione, and diethylene glycol (DEG) [AA-DEG].	LC-HRMS	Ethanol 95% and Tenax	[75]
Silicone moulds and teats	Side reactions in the polymerization (cyclic and linear polydimethylsiloxanes; oligomeric dimethyl siloxanes)	H-NMR and GC-MS	Pizza	[76]
Polyurethane adhesives commonly used for food-contact laminated films	No NIAS detected.	GC–MS	Isooctane	[77]
Polyvinylchloride (PVC)—and polyethylene (PE)—based cling-films	2-ethyl hexanoic acid (2-EHA), triacetin	Solid-Phase Micro-Extraction and GC/MS	PDO Italian cheeses during cold storage under light or dark	[78]
Oriented polypropylene (OPP) and polyethylene terephthalate (PET) with printing inks	Printing unknown ink compounds	UPLC-QTOF-MS	Ethanol (95%) and Tenax	[79]
Polyurethanes (PURs)	Pyridine (NIAS, solvent); Dimethylacetamide (NIAS, solvent); 1,4-Dioxane (NIAS, reaction medium); Aniline NIAS, precursor, o-Toluidine NIAS, degradation product, Diaminotoluene NIAS, intermediate, o-Anisidine NIAS, intermediate, 1,4,7-trioxacyclotridecane-8,13-dione, Myristamide NIAS, contaminant, Palmitamide NIAS, contaminant, Oleamide NIAS, contaminant, Stearamide NIAS, contaminant.	GC-MS and DART-MS	--	[80]
Polycarbonate (PC)	Oligomers; PC-degradation products	UHPLC–ESI Q-orbitrap	--	[81]
Candy wrappers based on plastic and paper materials	2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadienone, a degradation product of BHT, Diethyl maleate, Triacetin, Propanoic acid, 2-methyl-, 3-Hydroxy-2,4,4-trimethylpentyl ester, Diethyl phthalate, Diisobutyl phthalate, 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6-9-diene-2,8-dione, Heneicosane, Tributyl aconitate, Docosane, Tricosane, Tetracosane, Pentacosane, Hexacosane, Heptacosane, Octocosane, Squalene, n-Nonacosane, Glycerol tricaprylate	GC-MS	--	[82]

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
Polyester-polyurethane lacquers	Impurities or degradation products of IPDI trimer IPDI and DPMDI, two cyclic oligoesters, 2EG + 2TPA and 2NPG + 2oPA	GC-(EI)qMS, GC-(EI)Orbitrap, GC-(APCI)TOFHRMS and GC(×GC)-(EI)TOFLRMS	--	[83]
Polybutylene terephthalate (PBT)	Cyclic oligomers from dimer to pentamer containing TPA and BD, cyclic oligomers, linear oligomers, dehydration products	HPLC-DAD/ESI-MS	--	[84]
Multilayer plastic materials (polyethylene (PE) and low-density polyethylene (LDPE) plus nylon)	Four cyclic oligomers of caprolactam (dimer, trimer, tetramer, and pentamer); by-products-cyclic ester oligomers made of the monomers adipic acid (AA), phthalic acid (PA), diethylene glycol (DEG), monoethylene glycol (MEG) and neopentilglycol (NPG); Nylon cyclic dimer, Caprolactam Cyclic Trimer, AA-DEG, Caprolactam Cyclic Tetramer, Caprolactam Cyclic Pentamer, PA-DEG, Cyclic ester made up of Phthalic acid and diethylene glycol in combination 1:2, AA-MEG-AA-MEG, AA-MEG-AA-DEG, AA-DEG-AA-DEG, PA-MEG-AA-DEG, PA-DEG-PA-DEG, PA-DEG-AA-NPG, AA-BD, AA-BD-AA-BD, AA-DEG + H_2O, AA-DEG-PA-DEG + H_2O, 3,6,9,12,15-pentaoxabicyclo(15.3.1)henicosa-1(21),17,19-triene-2,16-dione, 1,6-dioxacyclodecane-7,12-dione, 1,6-dioxacyclodecane-7,12-dione, 1,6,13,18-tetraoxacyclotetracosane-2,5,14,17-tetrone	LC-HRAMS and LC-ESI-Q-TOF-MS	3% acetic acid in water (*w*/*v*) and 20% of ethanol in water (*v*/*v*)	[85]
Low-Density Polyethylene (LDPE) films	Calcite ($CaCO_3$), calcium sulphate ($CaSO_4$), polystyrene (PS) and titanium dioxide (TiO_2), Ca and Ti	Raman spectroscopy and ICP-MS	--	[86]
Water-based acrylic adhesive	2-(12-(methacryloyloxy) dodecyl)malonic acid	GC-MS and UPLC-QTOF	Poly(2,6-diphenyl-p-phenylene oxide) (Tenax®)	[87]
High and low-density polyethylene(HDPE and LDPE)	Phthalic anhydride, phthalic acid, di-butyl phthalate (DBP) and bis(2-ethylhexyl) phthalate (DEHP)	FIA-MS, LTQ-Orbitrap	--	[88]
Multilayer materials with barrier properties	Acids (nonanoic acid), Alcohols (2-nonen-1-ol), Aldehydes (5-hydroxymethylfurfural), Aldehydes (5-hydroxymethylfurfural), Alkanes (n-dodecane), Alkenes (1-undecene), Antioxidants (2,6-di-tert-butyl-4-methylphenol), Aromatics (1,3-di-tert-butyl-benzene), Cyclics (*n*-propyl-cyclohexane), Esters (ethyl hydrogen sebacate), Ethers (1,1′-oxybis-octane), Ketones (2-undecanone), Oxidation Products (2,6-di-tert-butyl-1,4-benzoquinone)	SPME–GC–MS	--	[89]
Polyester Coatings	Oligomers	HPLC-DAD/CAD, HPLC-MS and HPLC-MS/MS	Water, 3% acetic acid, 10% ethanol, 50% ethanol, and isooctane	[90]

Food Contact Material	NIAS	Method/Technique	Migration Tests	Reference
Low-density polyethylen-LDPE and polyamide-PA added of NBBS, α-MSD, Irganox 1081, Irganox 1222, Santonox; LDPE 2/PA 6 2: Nonox A, Neozon D, Antioxidant 2246, Tinuvin P, TOTM	**Degradation products of TOTM, including DEHP, isophthalate bis(2-ethylhexyl)benzene-1,3-dicarboxylate (DOIP); decomposition product of NBBS was *N*-ethyl-*N*-methylbenzenesulfonamide; The formation of the cyclic saturated isomer (1,1,3-trimethyl-3-phenyl-2H-indene) is triggered by thermal impact, and so is the rearrangement of the carbon double bond to form isomer 2,4-diphenyl-4-methyl-2(E)-pentene). Decomposition product 2,3-dimethyl-3-phenylbutan-2-yl)benzene is formed by combining two cumyl radicals during pyrolysis of the pure additive and pyrolysis of LDPE entailing α-MSD. The degradation product of Neozon D and Nonox A identified in oxidative pyrolysis of the pure analyte was 10-methyl-benz[a]acridine; degradation products of Antioxidant 2246, Santonox, Irganox 1222/1081 and Tinuvin P: o-cresol, m-cresol or p-cresol, 2-tert-butyl-4-methylphenol and 2-tert-butyl-4,6-dimethylphenol, 3,5-di-tert-butyl-4-hydroxybenzaldehyde**	**Pyr-GC–MS and GC-EI-MS/MS**	**--**	**[91]**

DART-HRMS: direct analysis in real-time ionization coupled with high-resolution mass spectrometry; FIA-MS: low injection analysis (FIA) mass spectrometry; GC(×GC); (EI)TOFLRMS: two-dimensional gas chromatography-electron ionization time-of-flight high-resolution mass spectrometry; GC-(APCI)TOFHRMS: gas chromatography atmospheric-pressure chemical ionization time-of-flight high-resolution mass spectrometry; GC-(EI)Orbitrap: gas chromatography/electron ionization Orbitrap; GC-(EI)qMS: gas chromatography/electron ionization-quadrupole mass spectrometry; GC × GC−ToF MS: two-dimensional gas chromatography-time-of-flight mass spectrometry; GC-FID–MS: gas chromatography-mass spectrometry and flame ionization detector; GC-MS/Q: gas chromatography-quadrupole mass spectrometry; GC-MS: gas chromatography-mass spectrometry; GC–Q-Orbitrap-MS: gas chromatography and high-resolution mass spectrometry with Orbitrap analyzer; H-NMR: Proton nuclear magnetic resonance spectroscopy; HPLC-DAD/CAD: high-performance liquid chromatography coupled with diode array detector (DAD) and charged aerosol detector (CAD); HPLC-DAD/ESI-MS: high-performance liquid chromatography coupled to photodiode array detector and mass spectrometer; HPLC-DAD/MS: high-performance liquid chromatographic-mass spectrometry with diode-array detection; HPLC-DAD: high-performance liquid chromatographic method with diode-array detection; HPLC-ESI-MS: ultra-performance liquid chromatography-electrospray ionization mass spectrometry; HPLC-HRMS/MS: high-performance liquid chromatography high-resolution mass spectrometry; HPLC-MS/MS: high-performance liquid chromatography-tandem mass spectrometry; HPLC-MS: high-performance liquid chromatography-tandem mass spectrometry; HS-SPME-GC-MS: a combination of headspace solid-phase microextraction (HS-SPME) and gas chromatography-mass spectrometry; ICP-AES: inductively coupled plasma atomic emission spectrometry; ICP-MS: inductively coupled plasma mass spectrometry; LC-ESI-Q-TOF-MS: liquid chromatography-electrospray ionization mass spectrometer quadrupole time of flight; LC-HRMS: liquid chromatography high-resolution mass spectrometry; LC-MS/MS: Liquid chromatography-tandem mass spectrometry; LC-MS: liquid chromatography-mass spectrometry; LC–Q-Orbitrap-MS: liquid chromatography and high-resolution mass spectrometry with Orbitrap analyzer; LC-TOF-MS: liquid chromatography–quadrupole time of flight mass spectrometry; LTQ-Orbitrap Linear Trap Quadropole Orbitrap; Pyr-GC–MS: Pyrolysis gas chromatography-mass spectrometry; RP-HPLC–DAD/MS: Reverse phase-high performance liquid chromatography coupled with diode array absorption and mass spectrometry; UHPLC–ESI Q-orbitrap: ultra-high-performance liquid chromatography-electrospray ionization quadrupole Orbitrap mass spectrometry; UHPLC-HRMS: ultra-performance liquid chromatography high-resolution mass spectrometry; UHPLC-MS-QqQ: ultra-high-performance liquid chromatography coupled with triple quadrupole mass spectrometry; UHPLC–Q-TOF/MSE: ultra-performance liquid chromatography coupled with a hybrid quadrupole time-of-flight mass spectrometry; UPLC IMS QTOF: ultra-performance liquid chromatography-ion mobility separation-quadruple time-of-flight; UPLC-ESI-MS/QTOF: ultra-performance liquid chromatography-electrospray ionization mass spectrometer quadrupole time of flight; UPLC-QTOF-MS; UPLC–MS(QTOF): ultra-performance liquid chromatography–quadrupole time of flight mass spectrometry; UPLC-TQMS: ultra-performance liquid chromatography-tandem quadrupole mass spectrometry.

2.1. Oligomers

Monomers' reactions may cause oligomer formation during the polymerization processes due to incomplete polymerization, side reaction products like cyclic oligomers and subsequent thermal or hydrolytic degradation [92]. "Oligomers" are defined here as substances consisting of a small number (<20) of repeating units. Oligomers can also intentionally be used as “prepolymers”. These are reactive species that will be utilized as reacting blocks to manufacture polymers. When oligomers are not intentionally added, they are well within the scope of the NIAS definition, according to [45]. Oligomers do not come just from conventional polymers but also biodegradable polymers, and biopolymers also have a series of oligomers that can migrate to the food [48]. Despite this, according to other authors [92], the classification of oligomers as NIAS is still controversial due to similar properties of a homolog series of oligomers. Because the oligomer chemistry is linked to a polymer manufacturing process, it makes much sense to classify oligomers as polymer specific substances and not as NIAS. They are not explicitly regulated in the Regulation (EU) 10/2011. The extension of the EU positive list with new co-monomers as a consequence of industrial developments gives rise to an exponentially growing number of new oligomers present in food contact polymers as potential migrants.

However, according to a Scientific Opinion of EFSA (2016) [93], oligomers have become NIAS. Whether their presence is intended or not, it is needed to evaluate all migrating substances’ safety and not just the starting substances—e.g., the monomers or additives alone—and the guidelines should be updated. Importantly, oligomers are considered part of polymers in the US, with no impurities. Regulation (EU) No. 10/2011 does not explicitly regulate oligomers’ levels in general. However, two EFSA opinions concerning new co-monomers for polyester food-contact materials specified 50 µg kg^{-1} for total oligomer migration with less than 1000 Da [94][95]. The European Food Safety Authority (EFSA) states that the PA oligomers should not exceed 5 ppm (mg kg^{-1} food). **Table 2** listed scientific publications that determined oligomers in different types of plastic food packaging. Most of the FCMs studied are polyester coatings and resins [6][50][51][96] and polyethylene terephthalate materials [5][52][53].

Table 2. Studies published in the literature on oligomers (NIAS) Identification in different plastic food packaging.

Food Contact Material	NIAS	Method/Technique	Reference
Polycarbonate (PC)	**Oligomers**	**UHPLC–ESI Q-orbitrap**	[81]
Polyester Coatings	**Oligomers**	**HPLC-DAD/CAD, HPLC-MS and HPLC-MS/MS**	[40]
Polyester coatings based on NAH	**Oligomers**	**LC-MS/MS and LC-TOF-MS**	[50]
Polyester can coating extracts	**Linear and cyclic oligomers derived from the incomplete polymerization of polyester monomers, phthalic acids and diols**	**HPLC-MS, HPLC-ESI MS and HPLC-HRMS/MS**	[51]
Empty cans with lids coated with polyester resins	**Oligomers**	**GC–MS, HPLC-DAD/MS, UHPLC-HRMS and DART-HRMS**	[40]
Polyester resins, tin plate sheets coated with polyester–phenolic lacquers and corresponding press-twist-closures (equipped with plasticized polyvinyl chloride (PVC) sealings)	**Polyester oligomers (cyclic oligomers, dimers, trimers and tetramers)**	**HPLC–DAD, HPLC–DAD/MS, GC-MS, GC–MSD and RP-HPLC–DAD/MS**	[6]
Flexible multilayer materials point by polyurethane (PU) layers	**Polyamide oligomers, PU oligomers (cyclic esters made up of phthalic acid (PA)**	**UPLC MS–QTOF**	[72]
Polyethylene terephthalate (PET)	**Cyclic oligomers**	**LC-MS**	[5]
Virgin and recycled Polyethylene terephthalate-PET pellets	**Cyclic and linear oligomers: TPA-EG, (TPA-EG)2 + H_2O, (TPA-EG)2, (TPA-EG)3 + H20, (TPA-EG)3, (TPA-EG)4, and (TPA-EG)5, TPA2-EG-DEG + H_2O, TPA2-EG-DEG, TPA3-EG2-DEG + H_2O, TPA3-EG2-DEG, and TPA4-EG3-DEG, (TPA-DEG)2 and TPA4-EG2-DEG2**	**UPLC-MS-QTOF**	[52]

Food Contact Material	NIAS	Method/Technique	Reference
Baby food squeezes with multilayer materials (Polyethylene terephthalate-PET/aluminium-Al/polyethylene-PE)	**Polyester oligomers, 29 cyclic and six linear oligomers. ε-caprolactam was tentatively identified as a heterogenic polyester oligomer combined with AA, DEG, PA and NPG; BHET and diethyl 5-(2-((2,4,5-trimethoxybenzoyl)oxy)acetamido)isophthalate, methoxyeugenol and Bis(2-methoxyethyl) sebacate**	**UHPLC-ESI-QTOF MS**	[53]
Polybutylene terephthalate (PBT)	**Cyclic oligomers from dimer to pentamer containing TPA and BD, cyclic oligomers, linear oligomers, dehydration products**	**HPLC-DAD/ESI-MS**	[84]
Multilayer plastic materials (polyethylene (PE) and low-density polyethylene (LDPE) plus nylon	**Four cyclic oligomers of caprolactam (dimer, trimer, tetramer, and pentamer); by-products-cyclic ester oligomers made of the monomers adipic acid (AA), phthalic acid (PA), diethylene glycol (DEG), monoethylene glycol (MEG) and neopentilglycol (NPG); Nylon cyclic dimer, Caprolactam Cyclic Trimer, AA-DEG, Caprolactam Cyclic Tetramer, Caprolactam Cyclic Pentamer, PA-DEG, Cyclic ester made up of Phthalic acid and diethylene glycol in combination 1:2, AA-MEG-AA-MEG, AA-MEG-AA-DEG, AA-DEG-AA-DEG, PA-MEG-AA-DEG, PA-DEG-PA-DEG, PA-DEG-AA-NPG, AA-BD, AA-BD-AA-BD, AA-DEG + H_2O, AA-DEG-PA-DEG + H_2O, 3,6,9,12,15-pentaoxabicyclo(15.3.1)henicosa-1(21),17,19-triene-2,16-dione, 1,6-dioxacyclodecane-7,12-dione, 1,6-dioxacyclodecane-7,12-dione, 1,6,13,18-tetraoxacyclotetracosane-2,5,14,17-tetrone**	**LC-HRAMS and LC-ESI-Q-TOF-MS**	[85]
Polystyrene-PS cups and multilayer films	**Styrene monomer and oligomers; polyester urethane-based oligomers (PU) cyclic oligomers: α-methylstyrene; 1,1-diphenyl-ethylene; 2,4-diphenyl-1-butene; trans-1,2-diphenycyclobutane; 2,4,6-triphenyl-1-hexene;**	**GC-MS**	[68]

DART-HRMS: direct analysis in real-time ionization coupled with high-resolution mass spectrometry; GC-MS: gas chromatography-mass spectrometry; HPLC-DAD/CAD: high-performance liquid chromatography coupled with diode array detector (DAD) and charged aerosol detector (CAD); HPLC-DAD/ESI-MS: high-performance liquid chromatography coupled to photodiode array detector and mass spectrometer; HPLC-DAD/MS: high-performance liquid chromatographic-mass spectrometry with diode-array detection; HPLC-ESI-MS: ultra-performance liquid chromatography-electrospray ionization mass spectrometry; HPLC-HRMS/MS: high-performance liquid chromatography high-resolution mass spectrometry; HPLC-MS/MS: high-performance liquid chromatography-tandem mass spectrometry; HPLC-MS: high-performance liquid chromatography-mass spectrometry; HPLC-MS: high-performance liquid chromatography-tandem mass spectrometry; LC-ESI-Q-TOF-MS: liquid chromatography-electrospray ionization mass spectrometer quadrupole time of flight; LC-HRMS: liquid chromatography high-resolution mass spectrometry; LC-MS/MS: Liquid chromatography-tandem mass spectrometry; LC-MS: liquid chromatography-mass spectrometry; LC-TOF-MS: liquid chromatography–quadrupole time of flight mass spectrometry; RP-HPLC–DAD/MS: Reverse phase-high performance liquid chromatography coupled with diode array absorption and mass spectrometry; UHPLC–ESI Q-orbitrap: ultra-high-performance liquid chromatography-electrospray ionization quadrupole Orbitrap mass spectrometry; UPLC-ESI-MS/QTOF: ultra-performance liquid chromatography-electrospray ionization mass spectrometer quadrupole time of flight; UPLC–MS(QTOF): ultra-performance liquid chromatography–quadrupole time of flight mass spectrometry.

2.2. By-Products Compounds or Side Products

Side reactions occur during manufacturing the starting substances, materials, additives and the consumer's food packaging use, forming various novel products. Further, the close contact between the single materials can also lead to unwanted reaction products, often unknown [54][55]. An example of neo-formed NIAS is a primary aromatic amine (PAAs) in polyurethane (PU) adhesives formed by polyols and diisocyanate monomers' polymerization [97]. If the adhesive has not adequately cured or the ingredients have not adequately mixed, the polymerization reaction is not efficient enough, and the remaining non-polymerized aromatic isocyanates can produce PAAs in contact with water [56]. PU can often generate other by-products compounds, the cyclic adipate 1,4,7-trioxacyclotridecane-8,13-dione, likely to derive from a chemical reaction from the interaction between two common ingredients in the adhesive formula [47]. **Table 3** listed scientific publications that determined by-products in different types of plastic food packaging.

Table 3. Studies published in the literature on by-products/side reaction products (NIAS) Identification in different plastic food packaging.

Food Contact Material	NIAS	Method/Technique	Reference
Active packaging: Polypropylene (PP); PP + green tea; PP/poly (ethylene-co-vinyl alcohol) EVOH; PP/EVOH + oregano; PP/EVOH + citral; EVOH; Polyethylene terephthalate-PET/EVOH + citral; PET/EVOH + cinnamon; PP/EVOH/PP; PP/EVOH + oregano	**Degradation of active compounds; impurities from the raw materials; additives used in the manufacture of the active polymer (citral thermal reaction products; oxidation product of citral; decomposition product of adipates used as plasticizers; impurity/reaction product/breakdown product for the additives used in the manufacture of PE materials; xanthenone derivates)**	**UPLC-QTOF-MS**	[73]
Polyurethane adhesives in multilayer packaging materials	**By-product of the polyester-based urethane 91,6-Dioxacyclododecane-7,12-dione); cyclic adipate; unknown nitrogen-compounds; unknown phenolic compounds; 1,4,7-Trioxacyclotridecane-8,13-dione**	**HS-SPME-GC-MS**	[54]
Polyethylene terephthalate (PET), oriented polyamide (OPA), cast polypropylene (CPP), polyethylene (PE) and PE/ethyl vinyl alcohol PE(EVOH)	**Primary aromatic amines-PAAs (1,8-diazacyclotetradecane-2,9-dione; caprolactam; 1,8,15-triazacycloheneicosane-2,9,16-trione; 1,3-bis(isocyanatomethyl)-cyclohexane, 1-cyanodecane and 1,4-bis(isocyanatomethyl)-cyclohexane; l-leucyl-l-leucyl-l-leucine; 1,4,7,18,21-pentaoxa-11,14,25,28-tetraazacyclohentriacontane (9CI); l-leucine; l-leucyl-l-leucyl-l-leucyl-l-leucyl-; butanediamide; *N*4-hydroxy-*N*1-[(1S)-2-methyl-1-(1-pyrrolidinylcarbonyl)propyl]-2-pentyl-, (2R)-; triethylamine, naphtylethylenediamine; 1,8,15,22-tetraazacyclooctacosane-2,9,16,23-tetrone; urea; N-cyclohexyl, urea, *N*-cyclohexy-*N′*-methyl and 1-(cyclohexycarbonyl)piperazine); Dimethyl phthalate**	**UHPLC–Q-TOF/MSE**	[56]
Silicone moulds and teats	**Side reactions in the polymerization (cyclic and linear polydimethylsiloxanes; oligomeric dimethyl siloxanes)**	**H-NMR and GC-MS**	[76]
Multilayer plastic materials (polyethylene (PE) and low-density polyethylene (LDPE) plus nylon	**By-products-cyclic ester oligomers made of the monomers adipic acid (AA), phthalic acid (PA), diethylene glycol (DEG), monoethylene glycol (MEG) and neopentilglycol (NPG)**	**LC-HRAMS and LC-ESI-Q-TOF-MS**	[85]
Polypropylene food storage containers	**By-product Benzothiazole**	**GC × GC−ToF MS**	[64]
UV-curable varnishes over polypropylene	**2-propenoic acid,1,1′-[2-[[3-[2,2-bis[[(1-oxo-2-propen-1-yl)oxy]methyl]butoxy]-1-oxopropoxy]methyl]-2-ethyl-1,3-propanediyl] ester is considered a NIAS, as it is a reaction product coming from the monomer TMPTA, 11-diethyl-7-oxo-4,6,10,12-tetraoxopentadecane-3,13-diyl diacrylate**	**GC-MS/Q and UHPLC-IMS/QTOF**	[55]

GC(×GC)-(EI)TOFLRMS: two-dimensional gas chromatography-electron ionization time-of-flight high-resolution mass spectrometry; GC-MS: gas chromatography-mass spectrometry; H-NMR: Proton nuclear magnetic resonance spectroscopy; HS-SPME-GC-MS: a combination of headspace solid-phase microextraction (HS-SPME) and gas chromatography-mass spectrometry; LC-ESI-Q-TOF-MS: liquid chromatography-electrospray ionization mass spectrometer quadrupole time of flight; LC-HRMS: liquid chromatography high-resolution mass spectrometry; UHPLC–Q-TOF/MSE: ultra-performance liquid chromatography coupled with a hybrid quadrupole time-of-flight mass spectrometry; UPLC IMS/QTOF: ultra-performance liquid chromatography-ion mobility separation-quadruple time-of-flight; UPLC-QTOF-MS; UPLC–MS(QTOF): ultra-performance liquid chromatography–quadrupole time of flight mass spectrometry.

2.3. Breakdown Products or Degradation Products

During the polymers' manufacturer, processes like high temperatures or irradiation can cause the material's degradation, such as UV irradiation, gamma irradiation and microwave treatment [57]. Other factors like light exposure, oxidative damage or chemicals, in general, contribute to polymer degradation, causing changes in their physicochemical properties [98]. The same way is applied for the additives, e.g., antioxidants and light stabilizers since the purpose of these substances is to act as a scavenger when oxidizing conditions such as high temperatures or microwave exposure occur, and also exposure to UV light, and their mode of action is often to be oxidized earlier than the material [57][58]. Breakdown products are almost the primary source of NIAS in the FCMs. The degradation of additives and polymers leads to novel low molecular weight substances that can migrate to food [47]. Degradation products can be further divided into the degradation of polymers and additives' degradation [99].

Known cases of additives degradation breakdown products were reported by literature, as the degradation of common antioxidants like Irgafos 168 or Irganox 1010 results in NIAS's appearance in the polymers [47][98]. Another example of breakdown products is the azo initiators that can degrade and form recombination products without the azo group, e.g., tetramethyl-succinonitrile 2,2′-dimethyl-2,2′-azodipropiononitrile, chlorohydrins of epoxy compounds, that are considered NIAS [45]. **Table 4** listed scientific publications that determined breakdown products in different types of plastic food packaging. Most of the studies reported degradation products as NIAS, and most of the reported NIAS are degradation products from the antioxidants Irganox 1010 and Irgafos 168 [39][57][59][60][61][62][63][64][65].

Table 4. Studies published in the literature on degradation/breakdown products (NIAS) Identification in different plastic food packaging.

Food Contact Material	NIAS	Method/Technique	Reference
Active packaging: Polypropylene (PP); PP + green tea; PP/poly (ethylene-co-vinyl alcohol) EVOH; PP/EVOH + oregano; PP/EVOH + citral; EVOH; Polyethylene terephthalate-PET/EVOH + citral; PET/EVOH + cinnamon; PP/EVOH/PP; PP/EVOH + oregano	**Degradation of active compounds; impurities from the raw materials; additives used in the manufacture of the active polymer (citral thermal reaction products; oxidation product of citral; decomposition product of adipates used as plasticizers; impurity/reaction product/breakdown product for the additives used in the manufacture of PE materials; xanthenone derivates)**	**UPLC-QTOF-MS**	[73]
Polyurethane adhesives in multilayer packaging materials	**Silane unknown compounds; degradation of antioxidants Irgafos and Irganox (2,6-Di-tert-butylbenzoquinone; isomer 2,5-di-tert-butylbenzoquinone; 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione; benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-methyl)**	**HS-SPME-GC-MS**	[54]
Hot melt adhesives (Ethylene-vinyl acetate-EVA and amorphous polyolefin APAO enriched in propene)	**Degradation of Irganox 1010: 3,5-di-tert-butyl-4-hydroxybenzaldehyde**	**UPLC-ESI-MS/QTOF**	[59]
Polyethylene terephthalate-PET pellets	**The degradation product of the antioxidants Irgafos 168 and Irganox 1010: 2,4-bis(1,1-dimethyl ethyl) phenol; 2-methyl-1,3-dioxolane; linear aldehydes; residual monomers: ethylene glycol (EG); thermal degradation products: toluene, ethylbenzene and xylene; phthalates (DEP, DIBP)**	**HS-SPME/GC-MS**	[60]
Polycarbonate (PC)	**Oligomers; PC-degradation products**	**UHPLC–ESI Q-orbitrap**	[81]
Polypropylene (PP) films	**Degradation products from Irgafos 168, Tinuvin 326 and Irganox 1076**	**HPLC-DAD and GC-FID–MS**	[61]
Candy wrappers based on plastic and paper materials	**2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadienone, a degradation product of BHT, Diethyl maleate, Triacetin, Propanoic acid, 2-methyl-, 3-Hydroxy-2,4,4-trimethylpentyl ester, Diethyl phthalate, Diisobutyl phthalate, 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6-9-diene-2,8-dione, Heneicosane, Tributyl aconitate, Docosane, Tricosane, Tetracosane, Pentacosane, Hexacosane, Heptacosane, Octocosane, Squalene, n-Nonacosane, Glycerol tricaprylate**	**GC-MS**	[82]

Food Contact Material	NIAS	Method/Technique	Reference
Polypropylene (PP)	Degradation products derived from phenolic antioxidants, impurity/reaction product/breakdown product of the additives, Family 1: Family formed with the reference structure; was formed by the compounds that had a similar structure constituted by a group 3,5-di-tert-butyl-4-hydroxyphenyl; Family 2: With glycerol molecule (glyceryl monostearate, glyceryl palmitate and glyceryl dihexadecanoate, an ester of an acid chain bonded to a glycerol molecule); Family 3: Dihydroxy alquilamines (amine bonded to two ethanol molecules and also an alkyl hydrocarbon chain); Family 4: ceramide and dihydroceramide (a family of waxy lipid molecules which are composed of sphingosine (an 18 carbon amino alcohol with an unsaturated hydrocarbon chain) and a fatty acid); Family 5: amides bonded by ethylene (degradation products from a lubricant losing C_2H_4); Other compounds (amides come from the impurities or degradation products from erucamide and oleamide widely used as slip agents)	UPLC-MS-QTOF	[58]
Polypropylene (PP)	2,4-di-tert-butylphenol (degradation product of Irgafos 168 and Irganox® 1010), tert-butyl-1-oxaspiro(4,5)deca-6-9-diene-2,8-dione (a by-product of the antioxidant Irganox 1010) and 2,6-di-tert-butyl-1,4-benzoquinone, a degradation product of antioxidants such as Irganox 1010, Irgafos 168 and Irganox PS 802	GC-MS	[63]
Polypropylene random copolymer composite films	Irgafos 168 and its two degradation products, 2,4-di-tert-butylphenol (DP1) and tris (2,4-di-tert-butylphenyl) phosphate (DP2)	GC-MS	[57]
Plastic films (with and without printing ink) including PE: polyethylene. PET: Polyethylene terephthalate. PA: Polyamide. PP: Polypropylene. EVA: Ethylene-vinyl acetate.	2,4-di-tert-butylphenol and 2,6-di-tert-butyl-1,4-benzoquinone. 2,4-di-tert-butylphenol is a degradation product of Irgafos 168 while 2,6-di-tert-butyl-1,4-benzoquinone is a degradation product of antioxidants such as Irganox 1010, Irgafos 168 and Irganox PS 802	purge and trap (P&T) coupled to GC–MS	[62]
Polypropylene food storage containers	Degradation products, 2,4-di-tert-butylphenol and tris(2,4-di-tert-buthylphenyl)phosphate, methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate, a compound identified as product of degradation of Irganox 1076 and/or Irganox 1010, 2,6-di-tert-butylbenzoquinone (isooctane fraction) and 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione, 2-ethylhexanoic acid, 2-ethylhexanol, phthalic acid, mono-2-ethylhexyl phthalate), and consequently suggested as possible degradation products of this phthalate, by-product Benzothiazole, degradation products *N*,*N*-bis-(2-hydroxyethyl)alkyl amine	GC × GC−ToF MS	[64]
Polyethylene-PE, low-density polyethylene-LDPE and HIGH-density polyethylene-HDPE	Dibutyl amine, *N*,*N*-bis(2-hydroxyethyl)alkylamines (impurity reaction or breakdown products), *N*,*N*-bis(2-hydroxyethyl) dodecylamine, tributylphosphine, tridodecylamine, Methyl (Ralox 35), ethyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propanoate (breakdown of Irganox 1010 or Irganox 1076), Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,1′-[2,2-bis(hydroxymethyl)-1,3-propanediyl] ester and benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,1′-[2-[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-2-(hydroxymethyl)-1,3-propanediyl] ester (degradation of Irganox 1010), alkylamides *N*,*N*′-1,2-ethanediylbis-(breakdown or impurity products of the additive octadecanamide, *N*,*N*′-1,2-ethanediylbis), Irgafos 168 OXO (oxo-derivative of Irgafos 168), 11-eicosenamide (derived from oleamide)	UPLC IMS QTOF	[39]
Can coatings	Diisobutyl phthalate (DIBP), Degradation products formed from antioxidants (1,3-di-tert-butylbenzene and 2,4-di-tert-butylphenol degradation products from antioxidants Irgafos 168 or Irganox 1076, 2,6-di-tert-butyl-1,4-benzoquinone degradation products from antioxidants Irgafos 168 and Irganox 1010, 7,9-di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione, a degradation product of Irganox 1010.	GC-MS and LC-MS/MS	[65]

Food Contact Material	NIAS	Method/Technique	Reference
Low-density polyethylene-LDPE and polyamide-PA added of NBBS, α-MSD, Irganox 1081, Irganox 1222, Santonox; LDPE 2/PA 6 2: Nonox A, Neozon D, Antioxidant 2246, Tinuvin P, TOTM	**Degradation products of TOTM, including DEHP, isophthalate bis(2-ethylhexyl)benzene-1,3-dicarboxylate (DOIP); decomposition product of NBBS was *N*-ethyl-*N*-methylbenzenesulfonamide; The formation of the cyclic saturated isomer (1,1,3-trimethyl-3-phenyl-2H-indene) is triggered by the thermal impact, and so is the rearrangement of the carbon double bond to form isomer 2,4-diphenyl-4-methyl-2(E)-pentene). Decomposition product 2,3-dimethyl-3-phenylbutan-2-yl)benzene is formed by combining two cumyl radicals during pyrolysis of the pure additive and pyrolysis of LDPE entailing α-MSD. The degradation product of Neozon D and Nonox A identified in oxidative pyrolysis of the pure analyte was 10-methyl-benz[a]acridine; degradation products of Antioxidant 2246, Santonox, Irganox 1222/1081 and Tinuvin P: o-cresol, m-cresol or p-cresol, 2-tert-butyl-4-methylphenol and 2-tert-butyl-4,6-dimethylphenol, 3,5-di-tert-butyl-4-hydroxybenzaldehyde**	**Pyr-GC–MS and GC-EI-MS/MS**	[91]
Recycled pellets obtained from post-consumer low-density polyethylene (PC-LDPE) and high-density polyethylene (PC-HPDE)	**Polymer degradation products: octanal and nonanal (aldehydes); 3-decanone, 2-undecanone, 2,2,4,4,6,8,8-heptamethylnonanone and 3-dodecanone (ketones); hexane (others); Additives degradation products: 3,5-di-tert-butyl-4-hydroxybenzaldehyde (aldehyde); 2,6-di-tert-butyl-1,4-benzoquinone and 3,5-di-tert-butyl-4-hydroxyacetophenone (ketones); methyl tetradecanoate, ethyl tetradecanoate and ethyl palmitate(esters); 7,9-di-tert-butyl-1-oxaspiro (4,5)deca-6,9-diene-2,8-dione (others); Contaminants from external sources: methyl lactate, hexyl acetate, and dimethyl butanedioate, α-methylionone, 3-(4-Isopropylphenyl)-2-methylpropionaldehyde, α-amylcinnamaldehyde, (phenylmethylene)octanal and dipropylene glycol amog others (cosmetic ingredients); alkylbenzenes (breakdown products produced by the degradation of alkylbenzene sulfonates); contamination related to food: the lactones, 5-methylfurfural, furfural and methyl hexanoate (can derive from food flavors as well as from cosmetics ingredients); furfuryl alcohol, methyl pyruvate and 2-acetyl pyridine (food flavors), methyl-2-ethylhexanoate, acetic acid, propanoic acid, pyridine and dimethyl trisulfide (rotten food products), 2,6-diisopropylnaphthalene (paper labels).**	**GC/MS and HS-SPME-GC/MS**	[66]

GC × GC−ToF MS: two-dimensional gas chromatography-time-of-flight mass spectrometry; GC-FID–MS: gas chromatography-mass spectrometry and flame ionization detector; GC-MS: gas chromatography-mass spectrometry; HPLC-DAD: high-performance liquid chromatographic method with diode-array detection; HS-SPME-GC-MS: a combination of headspace solid-phase microextraction (HS-SPME) and gas chromatography-mass spectrometry; LC-MS/MS: Liquid chromatography-tandem mass spectrometry Pyr-GC–MS: Pyrolysis gas chromatography-mass spectrometry; UHPLC–ESI Q-orbitrap: ultra-high-performance liquid chromatography-electrospray ionization quadrupole Orbitrap mass spectrometry; UHPLC–Q-TOF/MSE: ultra-performance liquid chromatography coupled with a hybrid quadrupole time-of-flight mass spectrometry; UPLC IMS QTOF: ultra-performance liquid chromatography-ion mobility separation-quadruple time-of-flight; UPLC-ESI-MS/QTOF: ultra-performance liquid chromatography-electrospray ionization mass spectrometer quadrupole time of flight.

2.4. Impurities in the Raw Materials

Raw materials and additives may contain impurities, some of them known by the manufacturers, but minor impurities often are unknown and can persist in the final FCMs, consequently migrating to the foodstuffs [56][100]. Ink raw materials can be unique chemical substances or mixtures of many chemical substances. They comprise one or several main substances with a specific function in ink (IAS); besides these main components, the raw materials may contain other substances that will not have any specific function in ink, e.g., monomers or residues of catalysts, solvents or defoamers. Such substances are necessary to produce the raw material, but they are not needed in the printing inks. Nevertheless, such impurities are usually known due to the raw materials production process and should be specified in the supply chain to allow a risk assessment, as they should be considered “known NIAS” in the inks. However, it is not always possible to list and consider all impurities during the authorization.

2.5. Contaminants

There are multiple sources of contaminant residues in the supply chains, including presses (fountain solutions, lubricants and additives), substrates (plasticizers, surfactants, stabilizers, antioxidants, resins), inks and coatings (resins, polymers, adhesives, pigments, solvents, monomers, additives) and the environment (pesticides, cleaners, fumes) [101]. Toxic elements such as As, Cd, Hg, Pb are trace elements and environmental contaminants present in the raw materials and considered NIAS in the final FCA. When recycled materials are utilized for food packaging, often undefined mixtures of chemicals present during recycling can react and form additional substances that increase the list of potential NIAS. Furthermore, the accumulation of chemicals might occur when materials are recycled many times. Thus, the prediction, identification and control of NIAS in recycled materials are challenging because of their difficulty tracing their origin [47][8]. Packaging materials produced from recycled polyethylene terephthalate are applied for direct food contact in recycled rigid containers and films. Most recycled polyethylene terephthalate packaging materials contain metal catalysts, the most common antimony [8].

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